CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205832Orig1s000

CHEMISTRY REVIEW(S)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 205832/000	**Sponsor:**	BOEHRINGER PHARMS
C de:	570		900 RIDGEBURY RD
F	1		RIDGEFIELD, CT 06877
Stamp Date:	02-MAY-2014	**Brand Name:**	NINTEDANIB (BIBF 1120)
PDUFA Date:	02-JAN-2015	**Estab. Name:**	
Action Goal:		**Generic Name:**	NINTEDANIB (BIBF 1120)
District Goal:	02-SEP-2014		

Product Number; Dosage Form; Ingredient; Strengths

001; CAPSULE, SOFT GELATIN; NINTEDANIB; 100MG
002; CAPSULE, SOFT GELATIN; NINTEDANIB; 150MG

FDA Contacts:	E. JAO	Prod Qual Reviewer		3017961684
	J. METCALFE	Micro Reviewer	(HFD-805)	3017961576
	Y. LIU	Product Quality PM		3017961926
	J. LEE	Regulatory Project Mgr		3017963769
	C. BERTHA	Team Leader		3017961646

Overall Recommendation:	ACCEPTABLE	on 22-AUG-2014	by T. SHARP	()	3017963208
	PENDING	on 20-MAY-2014	by EES_PROD		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** 9610492 **FEI:** 3002806556		
	BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG BINGER STREET 173		
	INGELHEIM AM RHEIN, RHEINLAND-PFALZ, GERMANY		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE RELEASE TESTER		
	DRUG SUBSTANCE STABILITY TESTER		
	FINISHED DOSAGE LABELER		
	FINISHED DOSAGE PACKAGER		
	FINISHED DOSAGE RELEASE TESTER		
	FINISHED DOSAGE STABILITY TESTER		
Profile:	CAPSULES, SOFT GELATIN	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	21-MAY-2014		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	05-JUN-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		
Profile:	(b) (4)	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	04-JUN-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** 1510690 **FEI:** 1510690

BOEHRINGER INGELHEIM ROXANE INC

COLUMBUS, , UNITED STATES 432289579

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Profile: CAPSULES, SOFT GELATIN **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-JUL-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Profile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-JUL-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

E ment: (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE RELEASE TESTER

Profile: CAPSULES, SOFT GELATIN **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-JUN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: (b) (4)

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-JUN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: (b) (4)

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-AUG-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: (b) (4)

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY

OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-JUN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER

Profile: CAPSULES, SOFT GELATIN **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-JUL-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER

Profile: CAPSULES, SOFT GELATIN **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-MAY-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Final Risk Analysis for the drug product

DP attribute/ CQA	Factors that can impact the CQA	FMECA RPN #	IQA Comment	Final conclusion

(b) (4)

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/s/

ARTHUR B SHAW
09/12/2014

CRAIG M BERTHA
09/16/2014
I concur.

MEMORANDUM TO FILE

DATE: September 4, 2014

NDA: 205832

SUBJECT: Revised Carton and Container Labels

The applicant has submitted revised carton and container labels to reflect the recommendations in Appendix B of MAPP 5021.1 "Naming of Drug Products Containing Salt Drug Substances." The strength is now expressed as the "Each capsule contains [Active strength] equivalent to [salt strength]" on the side panel, compared with the original. (b) (4)

Examples
Original
(b) (4)

Revision

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

These revisions were submitted for both strengths for cartons and container labels.
ACCEPTABLE

1 Page Draft Labeling has been Withheld in Full as B4(CCI/TS) Immediately Following this Page

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/s/

ARTHUR B SHAW
09/04/2014

Chemistry Review Cover Sheet

NDA Number 205832
Ofev (nintenanib) Oral Capsules
Edwin Jao, Ph.D. (drug substance)
Arthur B. Shaw, Ph.D. (drug product)
ONDQA/DNDQIII/Branch VIII

Table of Contents

Chemistry Review Data Sheet

1. NDA 205832
2. REVIEW #1
3. REVIEW DATE: September 2, 2014
4. REVIEWER: Arthur B. Shaw, Ph.D. (drug product) and Edwin Jao (drug substance)
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Comment
Original	2014-05-02	
IR	2014-05-23 (not in DARRTS)	request clarification on ID of manufacturing sites
Quality amendment	2014-05-30	Response to IR
CMC Filing Review	2014-06-05	Acceptable for filing
IR Letter	2014-06-13	Info about reaction between ethane sulfonate and glycerol, receiving specs for excipient (b) (4)
IR Letter	2014-06-18	Questions about materials in drug substance synthesis.
Quality amendment	2014-06-26	Response to 6-13 IR
IR Letter	2014-06-25	Microbiology Testing in specs
Quality amendment	2014-07-01	Response to 6-25 IR
IR Letter	2014-07-02	Drug product questions
Quality amendment	2014-07-07	Response to 6-18 IR
Quality amendment	2014-07-22	Response to 7-02 IR
IR Letter	2014-07-29	Recommend change in dissolution specs
Quality amendment	2014-08-06	Response to 7-29 IR and follow-up to 6-18 IR
IR Letter	2014-08-11	Drug product questions
Quality amendment	2014-08-20	Response to 8-11 IR
Biopharm review	2014-08-14	Recommend approval
Micro review	2014-08-22	Recommend approval

7. NAME & ADDRESS OF APPLICANT:

Name:	BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
Address:	900 Ridgebury Road P.O. Box 368 Ridgefield CT 06877
Representative:	Ann Cherian, Senior Associate Director, Regulatory Affairs
Telephone:	(203) 791-6759
Fax	(203) 791-6262
Email	ann.cherian@boehringer-ingelheim.com

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ofev (acceptable per Proprietary Name Review in IND 74683, April 5, 2014)
b) Non-Proprietary Name (USAN): ..... Nintedanib esylate
c) Code Name/# BIBF 1120
d) Chem. Type/Submission Priority
   - Chem. Type: 1
   - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: Orphan

10. PHARMACOL. CATEGORY: vascular endothelial growth factor receptor (VEGFR) 1-3, platelet-derived growth factor receptor (PDGFR) α and β, fibroblast derived growth factor receptor (FGFR) 1-3 tyrosine kinase inhibitor

11. DOSAGE FORM: soft gel capsule

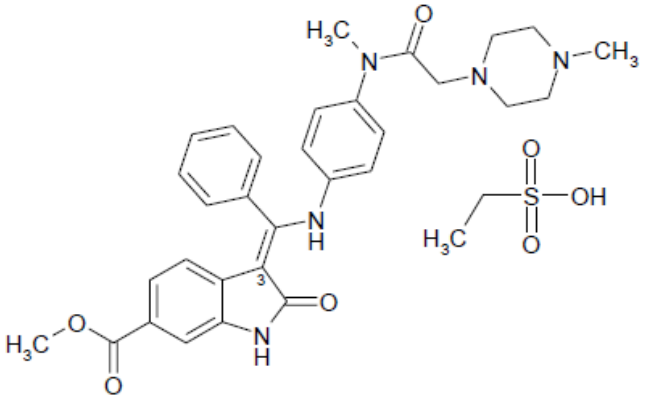
12. STRENGTH/POTENCY: 100 and 150 mg ((b) (4)

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): None

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



$C_{31}H_{33}N_5O_4 \cdot C_2H_6O_3S$
649.76 g/mol (ethanesulfonate)
539.62 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:
Reviewed: **None**
Not reviewed since there is sufficient information in the NDA. See Section P Container Closure and Excipients below

DMF	Holder	DMF Subject	Item Referenced
(b) (4)			

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	74683	Development of drug

18. STATUS:
CONSULTS/ CMC RELATED REVIEWS:

	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	2014-08-22	N/A
Biopharm review	Acceptable	2014-08-14	Kareen Riviere
EA	Categorical Exclusion granted	No review needed	N/A
Microbiology	Acceptable	2014-08-22	John Metcalfe
Statistics	Not applicable		
Methods Validation	Pending		N/A

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability: The application is recommended for approval from a Quality perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance (E. Jao)

The drug substance BIBF 1120 ethanesulfonate is a vascular endothelial growth factor receptor (VEGFR) 1-3, platelet-derived growth factor receptor (PDGFR) α and β, fibroblast derived growth factor receptor (FGFR) 1-3 tyrosine kinase inhibitor. It is a new molecular entity (NME), and an ethyl sulfonate salt. It is a bright yellow powder, (b) (4) . The drug substance is manufactured by Boehringer Ingelheim in Germany (b) (4). The site received acceptable recommendation from the Office of Compliance. Adequate material and in-process controls are in place for the manufacturing of the drug substance, such that the quality and purity are ensured. Comprehensive investigation of the impurities/degradants was conducted, and their structures, sources, toxicology, and fate are well understood. All genotoxic impurities (b) (4) are adequately controlled through the manufacturing process. The proposed drug substance specification is acceptable from quality risk management perspective. Release data from 99 batches of drug substance (used for non-clinical, clinical, primary stability studies, and market supply) are provided and met the specification. All batches used in the phase III clinical trials and for market supplies were manufactured using the synthetic route and at the site also for future commercial production. The drug substance is very stable at room temperature. The proposed re-test period of (b) (4) months is supported by full shelf data and granted.

2. Drug Product (A. Shaw)

The drug product is a soft gelatin capsule for oral use at 100 mg (peach-colored) and 150 mg (brown-colored) strengths. The active ingredient is mixed with lecithin, (b) (4) triglycerides (b) (4) and hard fat (b) (4). (b) (4) filled into a soft gelatin capsule comprised of gelatin, glycerol, and colorants (titanium dioxide, red and yellow ferrous oxide). The different strengths are (b) (4) 100 mg and (b) (4) 150 mg). The finished capsule is printed with black printing ink.

All of the excipients are compendial. (b) (4) (b) (4)

The applicant has provided a list of Critical Quality Attributes (CQAs) that support the Quality Target Product Profile. They then assessed the potential Critical Process Parameters (CPPs) and the likelihood that they would affect the CQAs. The drug substance (b) (4) is compatible with the excipients. The choice of excipients and the operating parameters (b) (4) are based on extensive experience at the manufacturer, (b) (4) Although the Pharmaceutical Development report contains a number of experiments designed to assess the effects of varying operating parameters and excipient levels. The net effect was to confirm the choice of parameters and excipients. The applicant is not requesting (b) (4).

(b) (4)

The specifications measure the appearance, identity, assay, impurities, dissolution, content uniformity and microbial limits. The applicant provided reasonable justifications for not testing dimensions, residual solvents, hardness, water content, polymorphism, and (b) (4). The latter, which are genotoxic, (b) (4) were tested on stability using a validated assay (LOQ (b) (4) = (b) (4) and were not found under any storage conditions. No degradants have been observed and they are controlled as "single unidentified impurities" in the

Specification. The dissolution test and the microbial limits test were found acceptable by the respective reviewers.

The results of batch testing and stability testing show that the drug products conformed to the specifications at release and throughout the proposed expiration date of 36 months. All sites were found satisfactory on inspection.

A risk analysis by the review team is included as an attachment at the end of this review.

B. Description of How the Drug Product is Intended to be Used: The drug product, an immediate release capsule, is intended to be used to treat idiopathic pulmonary fibrosis, with the drug being administered twice daily. Patients will be started on the 150 mg capsules, with doing cut back to the 100 mg capsules if the 150 mg dose is not tolerated. The capsules cannot be divided into smaller doses.

C. Basis for Approvability or Not-Approval Recommendation: The application is recommended for approval because the applicant has provided sufficient data to show that the manufacturing of the drug product is under control and that the specifications are adequate to support the clinical use of the drug.

III.Administrative

See DARRTS signatures and ccs

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/s/

ARTHUR B SHAW
09/02/2014

EDWIN JAO
09/03/2014

CRAIG M BERTHA
09/03/2014
I concur.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION CONSULT REQUEST FORM

TO: **FDA**
Division of Pharmaceutical Analysis
Attn: Michael Trehy, Ph.D.
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: Arthur Shaw, Ph.D.
Craig Bertha, Ph.D.
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: Arthur.Shaw@fda.hhs.gov
Phone: (301)-796 1460
Fax.: (301)-796 4777

Through: Craig Bertha, Ph.D.
Phone: (301)-796-1646
And Youbang Liu, Ph.D.
ONDQA Methods Validation Project Manager
Phone: (301)-796-1926

SUBJECT: Methods Validation Request

Application Number: NDA 205832
Name of Product: Ofev (nintenanib) Code name BIBF 1120 Ethanesulfonate
Applicant: BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

Applicant's Contact Person: Ann Cherian, Senior Associate Director, Regulatory Affairs

Address: 900 Ridgebury Road P.O. Box 368
Ridgefield CT 06877-0368
Telephone: (203) 791-6759 Fax: (203) 791-6262
Email: ann.cherian@boehringer-ingelheim.com

Date NDA Received by CDER: **05/02/2014**

Submission Classification/Chemical Class: 1P

Date of Amendment(s) containing the MVP: **05/02/2014**

Special Handling Required: No

DATE of Request: **06/24/2014**

DEA Class: N/A

Requested Completion Date: **08/01/2014**

Format of Methods Validation Package (MVP)

PDUFA User Fee Goal Date: **1/2/2015 (See Comment below)**

☐ Paper X☐ Electronic ☐ Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as descr bed in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

ATTACHMENT(S): *Methods Validation Request Sheet*, NDA Methods Validation Package (if not available in the EDR).

MVP Reference #	**METHODS VALIDATION REQUEST**	NDA # 205832

⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT

ITEM	QUANTITY	BATCH Number
BIBF 1120 Ethanesulfonate	(b) (4)	1051764
BIBF 1120 Capsules, 100 mg		304543A
BIBF 1120 Capsules, 150 mg		304542A
BIBF 1120 Ethanesulfonate Reference Standard		0004
(b) (4) Impurity Reference Standard		0002
Impurity Reference Standard		0002
Impurity Reference Standard		0002
(b) (4) BS Impurity Reference Standard		0002
(b) (4) Impurity Reference Standard		0001
(b) (4) Impurity Reference Standard		00002

⇒ ITEM 2: **Contents of Attached Methods Validation Package**	Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)	P.1
Specifications/Methods for New Drug Substance(s)	S.4.1
Specifications/Methods for Finished Dosage Form(s)	P.5.1
Supporting Data for Accuracy, Specificity, etc.	S.4.3 AND p 5.3
Applicant's Test Results on NDS and Dosage Forms	S.4.4 AND p.5.4

⇒ ITEM 3: **REQUESTED DETERMINATIONS**
Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.

Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
A143073	Assay of BIBF 1120 ES	s.4.2	**0**	
A143067	Impurities in BIBF 1120 ES	s.4.2	**0**	
q00215543 -01	Assay, Degradation Products, Uniformity of Content and Identification of BIBF 1120 capsules, 100 mg and 150 mg/capsule	P.5.2	**0**	

Additional Comments: This drug has received a breakthrough designation and is expected to be acted on well before the PDUFA date.

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method
6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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/s/

ARTHUR B SHAW
06/25/2014

CRAIG M BERTHA
06/26/2014

YOUBANG LIU
06/26/2014

Addendum - IQA Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: N205832
2. DATES AND GOALS:

Letter Date: 02-MAY-2014	Submission Received Date : 02-MAY-2014
PDUFA Goal Date: 02-JAN-2015	Planned DPARP Goal Date: 02-SEP-2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	None provided (however "Ofev" was proposed and granted under the I74683
Established or Non-Proprietary Name (USAN):	Nintedanib
Dosage Form:	Capsules
Route of Administration	Oral
Strength/Potency	100 and 150 mg/capsule
Rx/OTC Dispensed:	Rx X OTC

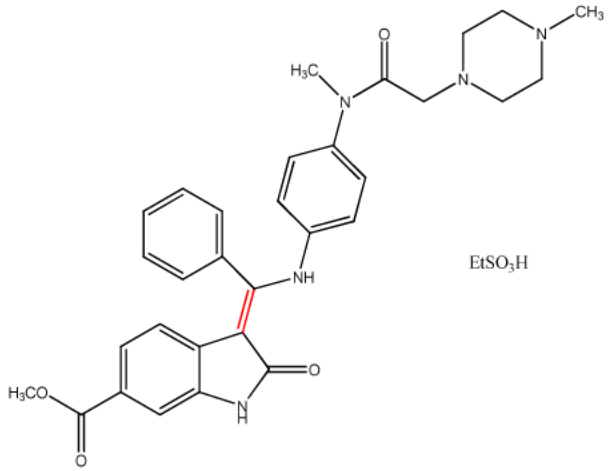
4. INDICATION: Treatment of Idiopathic Pulmonary Fibrosis (IPF)

5. NAME OF APPLICANT (as indicated on Form 356h): Boehringer Ingelheim Pharmaceuticals, Inc.

Initial Quality Assessment

Nintedanib soft gelatin capsules ("Ofev" had been proposed and granted as the proprietary name under IND 74683) from Boehringer Ingelheim (BI) are formulated in two strengths, 100 and 150 mg, and are to be taken orally. The recommended dose is 150 mg BID. Nintedanib is an NME and a tyrosine kinase inhibitor, which is said to include "the receptors platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, and vascular endothelial growth factor receptor (VEGFR) 1-3…for the treatment of Idiopathic Pulmonary Fibrosis (IPF)" (b) (4). The drug is said to bind "competitively to the ATP binding pocket of these receptors and blocks the intracellular signaling which is crucial for the proliferation, migration and transformation of fibroblasts representing essential mechanisms of the IPF pathology." The applicant states that the drug also inhibits Flt-3, Lck, Lyn, and Src kinases.

The drug substance is achiral and is an ethyl sulfonic acid salt with the structure shown below (b) (4)



This addendum has been written to provide a more formal risk assessment to the reviewer regarding the drug product. The table below captures the associated risk analysis for each drug product CQA and is meant to help focus the reviewer on the higher risk aspects of the application during review.

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ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

See appended electronic signature page}
Craig M. Bertha, PhD
Acting CMC-Lead
Division III
Office of New Drug Quality Assessment

{See appended electronic signature page}
Eric Duffy, PhD
Division Director, Acting Branch Chief
Division III
Office of New Drug Quality Assessment

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/s/

CRAIG M BERTHA
06/12/2014

ERIC P DUFFY
06/13/2014

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: N205832

2. DATES AND GOALS:

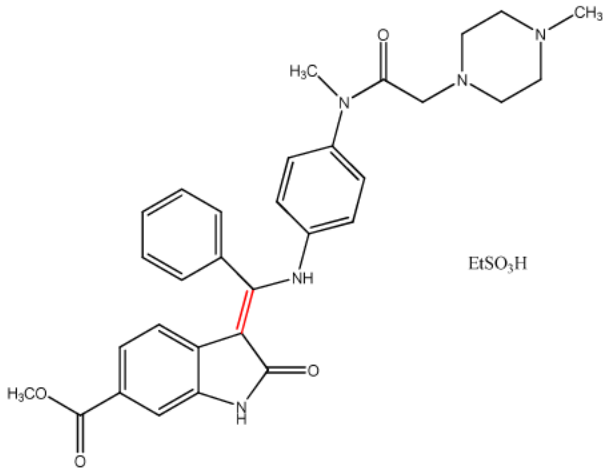
Letter Date: 02-MAY-2014	Submission Received Date : 02-MAY-2014
PDUFA Goal Date: 02-JAN-2015	

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	None provided (however "Ofev" was proposed and granted under the I74683
Established or Non-Proprietary Name (USAN):	Nintedanib
Dosage Form:	Capsules
Route of Administration	Oral
Strength/Potency	100 and 150 mg/capsule
Rx/OTC Dispensed:	Rx X OTC

4. INDICATION: Treatment of Idiopathic Pulmonary Fibrosis (IPF)

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



6. NAME OF APPLICANT (as indicated on Form 356h): Boehringer Ingelheim Pharmaceuticals, Inc.

7. SUBMISSION PROPERTIES:

Review Priority:	Priority Review Requested
Submission Classification (Chemical Classification Code):	Although there is no formal policy, the chemistry classification codes for the drug product (see draft of MaPP 7500.3) would appear to be type 1 (**New Molecular Entity or NME)**.
Application Type:	505(b)(1)
Breakthrough Therapy	No
Responsible Organization (Clinical Division):	DPARP

8. CONSULTS:

9.

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics	☐	X	The applicant has not provided a statistical analysis of the stability data, however they provide full term data (i.e., 36 months long-term data and a 36 month expiry request). It is unlikely that the reviewer will need to consult with the biometrics team and request formal statistical analyses of the data, unless undue variability is noted for any of the parameters than might call into question the ability of the product to routinely meet the specification acceptance criteria during the planned shelf life.
Clin Pharm	☐	X	
EES	X	☐	A request was sent to the ONDQA PM on 07-MAY-2014, to enter the EER into EES.
Pharm/Tox	X	☐	As noted above, hard fat does not appear to have been used as an excipient in any approved oral dosage forms. The pharmacologist should be made aware of this observation from review of the inactive ingredient guide. A formal consult is not deemed necessary for this issue. There are many compounds that present a potential toxicological risk (e.g., compounds containing structural alert functions, known genotoxic/mutagenic compounds, positive computational toxicology results, positive Ames test, etc.) beyond the common impurities limited by the requirements of ICH Q3A and B. See table 2 in S.3. The applicant presents their control strategy for

			assuring that these myriad impurities remain sufficiently low. If, after evaluation of the control strategy and supporting data, the reviewer concludes it unlikely that the applicant will be able to maintain the level of any of these impurities below the threshold of toxicological concern (b) (4)), he/she should consult the pharmacologist for assessment.
Methods Validation	X	☐	As nintedanib is an NME, it is recommended that we send a method assessment request to the Agency laboratory. Once the reviewer evaluates the methods and the associated validation reports, he/she can identify the methods most appropriate to forward for assessment. For an oral dosage form, it is typical that drug substance and drug product impurities methods are forwarded for assessment.
EA	☐	X	Applicant claims a calculated expected environmental introduction concentration and the level is below the (b) (4) cut-off. Therefore their request for a categorical exclusion under 21 CFR 25.31(b), not requiring submission of an environmental assessment or impact statement, is appropriate. However, the reviewer should confirm that the calculations meet the Agency guidance for EAs (July 1998). If there are questions, the OPS EA expert can be consulted (R. Bloom, PhD).
New Drug Micro	☐	X	As per the microbiology pilot, the microbiology team has been notified of the application. John Metcalfe, PhD is the assigned microbiology reviewer.
CDRH	☐	X	N/A
Other	☐	X	N/A

Other Applications or Submissions to note (if any):

DOCUMENT NAME	DATE	APPLICATION NUMBER	DESCRIPTION
IND	Submitted 15-MAR-2011, currently active	74683	Nintedanib capsules for IPF

Previous Communications with the Applicant to note (see module 1.6.3 for complete detail):

DOCUMENT NAME	DATES	APPLICATION NUMBER	DESCRIPTION
Correspondence	19-AUG-2011	IND 74683	Unsolicited Agency CMC-related comments sent to sponsor
Correspondences	29&31-OCT-2013	IND 74683	CMC-related responses sent to sponsor for questions in 30-SEP-2013, meeting package

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes X No
CMC Filing Issues:
1.

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? Yes No X
CMC Comments for 74-Day Letter:
1.

Biopharmaceutics:

NDA Number	NDA 205-832
Submission Date	5/2/2014
Product name, generic name of the active	Nintedanib soft gelatin capsules
Dosage form and strength	IR soft gelatin capsules; 100 mg and 150 mg
Applicant	Boehringer Ingelheim
Clinical Division	DPARP
Indication	treatment of idiopathic pulmonary fibrosis (IPF)
Type of Submission	505(b)(1) Original
Biopharmaceutics Reviewer	Kareen Riviere, Ph.D.
Biopharmaceutics Team Leader	Tapash Ghosh, Ph.D.
Biopharmaceutics Supervisor (acting)	Richard Lostritto, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
2.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	-	-	
3.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		x	

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? Yes No
Microbiology Filing Issues:
See Microbiology Filing Review for details and for any potential Microbiology review issues.

Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
No	No	No	N/A

Is a team review recommended?	Yes	No X
Suggested expertise for team:		

Summary of Critical Issues and Complexities

In addition to the issues discussed during development under I74683 (see below) the following items are notable:

- Under accelerated storage conditions, there were some failures in the stability parameter of dissolution (drop in dissolution [redacted] (b) (4) testing as well as failures with Q = [redacted] (b) (4) at 60 minutes). There was also unacceptable adhesion (sticking) of the capsules to each other. However, the applicant indicates that "in case of sticking of some capsules these could be easily separated from each other by shaking the bottle. No negative impact of adhesion of capsules is found." Notwithstanding any bioavailability concern associated with dissolution failure, the applicant is not requesting to extrapolate the stability data to extend the expiry beyond the available long term data as per ICH Q1E, thus the dissolution failures under the accelerated conditions are of lesser importance in terms of that aspect of quality.

- Excessive storage time [redacted] (b) (4) resulted in [redacted] (b) (4), thus there should be a limit on the length of time capsules are stored [redacted] (b) (4).

- As the solution is a suspension, it is noted that the applicant is not proposing to routinely check the uniformity of the fill mix prior to encapsulation (analogous to blend uniformity for a solid oral dosage form).
- The drug substance specification does not include tests (with acceptance criteria) to confirm [redacted] (b) (4) for microbial limits. The application should be evaluated to assure that these exclusions are justified.

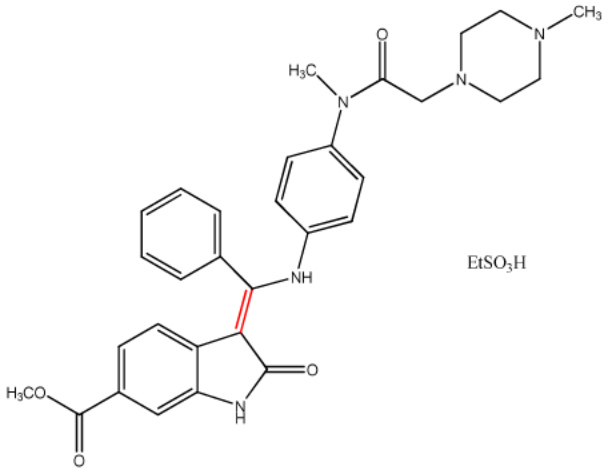
- The drug product specification does not include a test with acceptance criterion [redacted] (b) (4) of the dosage form. The reviewer should evaluate that this is justified with data or other information.

Description of Facility Related Risks or Complexities (i.e. foreign sites, large number of sites involved, etc.)
See EES for complete list of facilities related to this application.
The drug substance and product are manufactured at foreign sites. The drug substance is manufactured by Boehringer Ingelheim Pharma GmbH & Co. KG in Germany. The drug product is also manufactured internationally, (b) (4) .

Initial Quality Assessment

Nintedanib soft gelatin capsules ("Ofev" had been proposed and granted as the proprietary name under IND 74683) from Boehringer Ingelheim (BI) are formulated in two strengths, 100 and 150 mg, and are to be taken orally. The recommended dose is 150 mg BID[1]. Nintedanib is an NME and a tyrosine kinase inhibitor, which is said to include "the receptors platelet-derived growth factor receptor (PDGFR) α andβ, fibroblast growth factor receptor (FGFR) 1-3, and vascular endothelial growth factor receptor (VEGFR) 1-3…for the treatment of Idiopathic Pulmonary Fibrosis (IPF)" to slow the progression of the disease. The drug is said to bind "competitively to the ATP binding pocket of these receptors and blocks the intracellular signaling which is crucial for the proliferation, migration and transformation of fibroblasts representing essential mechanisms of the IPF pathology." The applicant states that the drug also inhibits Flt-3, Lck, Lyn, and Src kinases.

The drug substance is achiral and is a ethyl sulfonic acid salt with the structure shown below. Note however, that there is a potential for an *E* isomer about the exocylic double bond (in red). Single crystal X-ray structure determination confirms the presented isomer configuration. Note that the structure has both arylamine and acylarylamine functions, both being structural alert moieties on the lists provided by ONDQA. The nintedanib ethanesulfonic acid salt is slightly soluble in water (2.8 mg/mL) and is not demonstrated (by Dynamic Vapor Sorption) to be hygroscopic.



The synthesis is [redacted] (b) (4)

[1] Thus, the ICH Q3A identification and qualification thresholds for the drug substance are 0.10% and 0.15%. The Q3B identification and qualification thresholds for the drug product are both 0.2%.

The 100 mg capsules are peach colored and opaque soft gelatin capsules imprinted with "100" and the BI company symbol, and they contain a bright yellow viscous suspension. The 150 mg capsules are brown colored and opaque soft gelatin capsules imprinted with "150" and the BI symbol, and they also contain a bright yellow viscous suspension formulation. The two formulations are listed in the two tables reproduced below:

Start of Applicant Material

Table 1 Qualitative and quantitative composition of BIBF 1120 capsules, 100 mg

	Ingredient	[mg / capsule]	Function	Reference to Standards
Fill Material	BIBF 1120 ethanesulfonate	(b) (4)	Drug substance	Company standard
	(b) (4) triglycerides		(b) (4)	NF
	Hard fat			NF
	Lecithin			NF
	Subtotal (Fill)			
Capsule Shell	Gelatin	(b) (4)	(b) (4)	NF
	Glycerol (b) (4)			Company standard
	Titanium dioxide			USP, C.I.[4] 77891
	Red ferric oxide [2]			NF, C.I.[4] 77491
	Yellow ferric oxide [3]			NF, C.I.[4] 77492
	(b) (4)			USP
Black Ink	(b) (4)	(b) (4)	Printing ink	DMF No. (b) (4)
Subtotal (Shell)		(b) (4)		
Total				

1 Equivalent to 100 mg BIBF 1120 base.

(b) (4)

Table 1 Qualitative and quantitative composition of BIBF 1120 capsules, 150 mg

	Ingredient	[mg / capsule]	Function	Reference to Standards
Fill Material	BIBF 1120 ethanesulfonate	180.60[1]	Drug substance	Company standard
	(b) (4) triglycerides	(b) (4)	(b) (4)	NF
	Hard fat			NF
	Lecithin			NF
	Subtotal (Fill)			
Capsule Shell	Gelatin	(b) (4)	(b) (4)	NF
	Glycerol (b) (4)			Company standard
	Titanium dioxide			USP, C.I.[2] 77891
	Red ferric oxide [2]			NF, C.I.[4] 77491
	Yellow ferric oxide [3]			NF, C.I.[4] 77492
	(b) (4)			USP
Black Ink	(b) (4)		(b) (4) ink	DMF No (b) (4)
Subtotal (Shell)		(b) (4)		
Total				

1 Equivalent to 150 mg BIBF 1120 base.

(b) (4)

End of Applicant Material

Note that the gelatin, of NF grade, used to prepare the soft gel capsules is said by BI to be obtained (b) (4) "poses no TSE risk." Information for the (b) (4) is referenced to DMF (b) (4) and a letter of authorization is provided to allow our review of that file. All three excipients in the formulation filled into the soft gel capsules are of NF grade. Lecithin has been used in another oral soft gel capsule in a much larger quantity (b) (4) than is used here. It does not appear, according the FDA inactive ingredient guide that hard fat has been used in other approved oral dosage forms, only a rectal suppository. The reviewer should inform the pharmacologist of this fact. Lastly, (b) (4) triglycerides (b) (4) have been used in another oral capsule, but at a slightly lower quantity per unit (b) (4)

(b) (4)

Under the associated IND 74683 for the IPF indication, the DPARP provided solicited and unsolicited responses to BI for some CMC-related issues:

- The sponsor was asked to monitor levels of (b) (4) as impurities in the drug substance (19-AUG-2011, letter). See below.

- In the responses to a meeting request of 29- and 31-OCT-2013, we agreed that any CTD sections of the application for which there was no information, could be omitted from the submission.

- We agreed that the sponsor would include the executed drug product batch records (EBRs) for one primary stability batch of each strength of the drug product in the NDA, but that they would also include the EBR for a phase 3 clinical batch as well if there were significant differences from the primary stability batches. It would be unusual to allow a firm to designate stability batches as "primary" if there were significant differences from these as compared to the phase 3 clinical batches, but nonetheless, that is what was agreed. The application provides the executed batch records for the clinical/primary stability batches 1363940001 (100 mg) and 1363980001 (150 mg), consistent with our request.

- In addition the sponsor was provided additional comments:

  - The sponsor was requested to include a test for (b) (4) in the drug substance specification or to justify the absence of such a test. The proposed specification does not include such a test and the applicant provides a justification for its absence in S.4.5.

  - The sponsor was asked to justify the lack of microbial testing for the drug product. Currently the applicant proposes to include microbiological testing in

[2]Observe below from the IND phase of development that the Agency informed the sponsor that they should provide data confirming the physical (in addition to chemical) stability of the suspended drug substance in the soft gel formulation.

the drug product specification, however, regarding the testing frequency, the specification states that, for both strengths, this is "not a routine test" and that the drug product will comply if tested. The reviewer will need to evaluate the applicant's justification for this proposed strategy for microbial testing of the drug product (see P.5.6). Also, if the parameter is listed on the drug product specification, the lack of routine testing may be considered by the investigator to be contrary to cGMPs.

- The sponsor was requested to investigate the potential for [redacted] (b) (4) in the soft gelatin capsule [redacted] (b) (4) and asked to include information about this in the NDA. The applicant has examined the [redacted] (b) (4). Note that X-ray powder diffraction data were also obtained for the drug substance in the drug product on stability, to address any potential change in the crystalline form of the suspended nintedanib ethanesulfonate.

- The sponsor was informed that their conclusion that there is no impact of the drug substance particle size on the performance of the drug product in terms of dissolution, depends on the Agency acceptance of the dissolution method in terms of its ability to discriminate and detect particle size change. The sponsor was asked to provide a tabular presentation of the available data for batches of the drug product that were used in the clinical/pharmacokinetic studies and to identify their ages, dissolution results, and the PK data to "determine if stability of drug product plays a role in bioavailability." The biopharmaceutics team will need to address this point.

- The sponsor was asked to confirm in the NDA that the gelatin of the soft gelatin capsule drug product dosage form meets the requirements for assurance of the absence of bovine sphongiform encephalopathy (BSE). As noted above, the gelatin is said to be obtained from [redacted] (b) (4) a BSE-free source.

The applicant is proposing a 36 month shelf life based on the stability data for both strengths of the drug product. Data from three primary stability batches for each strength are provided and the applicant states that the "manufacturing process…simulates the production of the proposed commercial product." Note that 36 months of long-term (25°C/60%RH) stability data are provided in the application for the 6 primary stability batches.

CMC RECOMMENDATION:
From a CMC perspective, the Applicant has submitted a reviewable submission.

INITIAL BIOPHARMACEUTICS ASSESSMENT

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of the proposed dissolution method and acceptance criterion.

The proposed dissolution method is:

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	100 rpm	900 ml	37 °C	0.1 M HCl

The proposed dissolution acceptance criterion is:

Acceptance Criterion
Q = (b) (4)% at 60 min

BIOPHARMACEUTICS RECOMMENDATION:
The ONDQA Biopharmaceutics team has reviewed NDA 205-832 for filing purposes. We found this NDA **fileable** from a Biopharmaceutics perspective. The Applicant has submitted a reviewable submission.

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
4.	Is the CMC section organized adequately?	X	☐	☐	
5.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X	☐	☐	
6.	Are all the pages in the CMC section legible?	☐	☐		All pages examined for production of this IQA were legible.
7.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X	☐	☐	The adequacy of the provided data will be determined during review. See summary above.

B. FACILITIES*					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
8	Is a single, comprehensive list of all involved facilities available in one location in the application?	X	☐	☐	See form 356h
9	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? **This question is not applicable for synthesized API.**	☐	☐	X	

1(	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	☐	X	☐	The site is identified in S.2.1 and is listed on the Form 356h (for the drug product-related responsibilities)

1	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X	☐	☐	

1	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X	☐	☐	
1	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X	☐	☐	See Form 356h

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
14.	Has an environmental assessment or claim of categorical exclusion been provided?			Exclusion requested as per 21 CFR 25.31(b)

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
15.	Does the section contain a description of the DS manufacturing process?	X		
16.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
17.	Does the section contain information regarding the characterization of the DS?	X		
18.	Does the section contain controls for the DS?	X		
19.	Has stability data and analysis been provided for the drug substance?	X		
20.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
21.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
22.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
23.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
24.	Is there a batch production record and a proposed master batch record?		X	Executed batch records are provided as described above. No master batch record is provided, but that is not a requirement for a 505(b)(1) application as long as there is a "comparably detailed description of the product process" as per 21 CFR 314.50(d)(ii)(*c*). The reviewer should evaluate whether sufficient detail is included in the manufacturing description.
25.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		The applicant used the planned to-be-marketed formulations [redacted] (b) (4) in the phase III clinical studies. The determination of adequate linkage between various investigational product formulations is beyond the scope of the CMC quality review.
26.	Have any biowaivers been requested?		X	
27.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		There are 60 and 150 cc HDPE bottles with child-resistant closures.
28.	Does the section contain controls of the final drug product?	X		See notes above regarding the justification of the exclusion of certain parameters.
29.	Has stability data and analysis been provided to support the requested expiration date?	X		As indicated above, the applicant has provided 36 months of stability data and propose a 36 month expiry.
30.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	

31.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
32.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
33.	If appropriate, is a separate microbiological section included assuring sterility of the drug product		X	The drug product is not sterile. The microbiology team has been informed of the submission of this application and will make a determination of any review necessary, as per the pilot.

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
34.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		Refer to table of DMF information below.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	3	(b) (4)	(b) (4)	07-JUN-2011	(b) (4)
(b) (4)	3	(b) (4)	(b) (4)	20-SEP-2011	
(b) (4)	3	(b) (4)	(b) (4)	06-SEP-2012	

					(in addition to the introduction of new formulations)
(b) (4)	3	(b) (4)	HDPE bottles	14-APR-2014	The file was last reviewed 13-APR-2009, (b) (4)
(b) (4)	3	(b) (4)	(b) (4)	02-JAN-2013	The file was last reviewed to support an application for a (b) (4) (adequate; see review dated 21-MAR-2012)

[1]Note that the application references the master files of (b) (4) for the HDPE bottles and CR caps, respectively, but does not provide any letters of authorization (LOAs) for the materials of composition used by these drug product component suppliers. The DMFs (b) (4) should be reviewed for such LOAs if there is not sufficient information in the NDA or the two CCS component master files as per MaPP 5015.5.

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
35.	Has the draft package insert been provided?	X		
36.	Have the immediate container and carton labels been provided?	X		

ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	**Yes**	**No**	**Comment**
37.	Does the application contain dissolution data?	x		
38.	Is the dissolution test part of the DP specifications?	x		
39.	Does the application contain the dissolution method development report?	x		
40.	Is there a validation package for the analytical method and dissolution methodology?	x		
41.	Does the application include a biowaiver request?		x	
42.	Is there information provided to support the biowaiver request?		x	
43.	Does the application include a IVIVC model?		x	
44.	Is information such as BCS classification mentioned, and supportive data provided?	x		Applicant reports that the drugs substance is either a BCS Class 2 or 4 compound

45.	Is information on mixing the product with foods or liquids included?		x	
46.	Is there any in *vivo* BA or BE information in the submission?	x		The Applicant conducted BA studies 1199.17, 1199.21, and 1199.75 that will be evaluated by the Clinical Pharmacology reviewer.

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

See appended electronic signature page}
Craig M. Bertha, PhD
Acting CMC-Lead
Division III
Office of New Drug Quality Assessment

See appended electronic signature page}
Kareen Riviere, PhD
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

See appended electronic signature page}
Tapash Ghosh, PhD
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

{See appended electronic signature page}
Eric Duffy, PhD
Division Director, Acting Branch Chief
Division III
Office of New Drug Quality Assessment

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

/s/

CRAIG M BERTHA
05/30/2014

KAREEN RIVIERE
05/30/2014

TAPASH K GHOSH
05/30/2014

ERIC P DUFFY
06/05/2014

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre-Marketing Applications (Original)

I. Review Cover Sheet

1. OMPQ Reviewer:

2. NDA/BLA Number: 205-832
   Submission Date: May 2, 2014
   21st C. Review Goal Date: September 2, 2014
   PDUFA Goal Date: November 2, 2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	To be determined by Sponsor
Established or Non-Proprietary Name (USAN) and strength:	Nintedanib capsules, 100 mg and 150 mg
Dosage Form:	Soft gelatin Capsules

4. SUBMISSION PROPERTIES:

Review Priority :	PRIORITY
Applicant Name:	Boehringer Ingelheim
Responsible Organization (OND Division):	DPARP

II. Application Detail

1. INDICATION: Treatment of idiopathic pulmonary fibrosis (IPF) t (b) (4)

2. ROUTE OF ADMINISTRATION: Oral

3. STRENGTH/POTENCY: 100 mg & 150 mg

4. Rx/OTC DISPENSED: X☐Rx ☐OTC

5. ELECTRONIC SUBMISSION (yes/no)? Yes

6. PRIORITY CONSIDERATIONS: Yes

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V	X			
2.	Breakthrough Therapy Designation	X			
3.	Orphan Drug Designation		X		
4.	Unapproved New Drug		X		
5.	Medically Necessary Determination	X			
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		X		
7.	Rolling Submission		X		
8.	Drug/device combination product with consult		X		
9.	Complex manufacturing		X		
10.	Other (e.g., expedited for an unlisted reason)		X		

III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	**Yes**	**No**	**Comment**
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		
12.	Do all sites indicate they are ready to be inspected (on 356h)?	X		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?		X	ONDQA sent IR for missing CSN site; added to EER
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	X		
15.	Additional notes (non-filing issue) 1. Are all sites registered or have FEI #?	X		
	2. Do comments in EES indicate a request to participate on inspection(s)?		X	
	3. Is this first application by the applicant?		X	

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
16.	Have any Comparability Protocols been requested?		X	Could not locate. Not likely.

IMA CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
17.	Does this application fit one of the EES Product Specific Categories?	X		New molecular entity
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	X		Drug product profile should be CSG, soft gelatin capsules (b) (4). CDER EES_Questions was informed.
19.	**From a CGMP/facilities perspective, is the application fileable?** If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements? No			
Nanotechnology	RTRT Proposal	PAT	Drug/Device Combo
☐	☐	☐	☐
PET	Design Space	Continuous Mfg	Naturally derived API
☐	☐	☐	☐
Other (explain):			

Manufacturing Highlights

1. Drug Substance

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	

Include process flow chart/diagram (see eCTD Section 2.3.S.1)

2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	

Include process flow chart/diagram (see eCTD Section 2.3.P.1)

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3. **Facility-Related Risks (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.). Describe any potential 21CFR 211 compliance issues.** None expected.

4. **Drug Product Facility Inspectional History that could impact the manufacturing of this product.** None at this time.

Additional information not covered above

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V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no, Yes to questions 11-12) Yes
Based on Section IV, is a KTM warranted for any PAI? (yes/no). If yes, please identify the sites in the above chart. No
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no) No
Comments for 74 Day Letter
1.
2.
3.

REVIEW AND APPROVAL
(DARRTS)

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

/s/

LINDA L NG
06/03/2014

MAHESH R RAMANADHAM
06/03/2014