

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207930Orig1s000

CHEMISTRY REVIEW(S)

Facility Alerts

This report displays the Alerts associated with facilities on the selected applications.

No active OAI / POAI Alerts are present against the facilities on selected Projects

[Refresh](#)

Facility Status View for NDA 207930 Original 1

Displays information for the facilities that are associated to NDA 207930 Original 1. It also shows the Overall Manufacturing Inspection Recommendation for the application and the associated OPF Facility Recommendations.

Time run: 10/28/2015 5:01:30 PM

Overall Manufacturing Inspection Recommendations for NDA 207930 Original 1

Project Name	Sponsor Name	Overall Manufacturing Inspection Recommendation	Overall Manufacturing Inspection Task Status	Overall Manufacturing Inspection Recommendation Task Completion Date
NDA 207930-Orig- New NDA(s)	NOVARTIS PHARMACEUTICALS CORP	Approve	Complete	10/27/2015

OPF Facility Recommendations for Facilities on NDA 207930 Original 1

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/s/

MARY GRACE LUBAO
11/10/2015

**QUALITY ASSESSMENT****Quality Recommendation: Approval**

NDA 207930
Review # 1
Review Date 28-OCT-2015

Drug Name/Dosage Form	Indacaterol/Glycopyrrolate (Glycopyrronium Bromide)/inhalation powder
Strength	27.5 mcg indacaterol/15.6 mcg glycopyrrolate/capsule
Route of Administration	Oral inhalation
Rx/OTC Dispensed	Rx
Applicant	Novartis
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATES
Original submission	29-DEC-2014
Quality Amendment	07-APR-2015
Quality Amendment	23-APR-2015
Quality Amendment	29-APR-2015
Quality Amendment	22-JUN-2015
Quality Amendment	29-JUN-2015
Quality Amendment	09-JUL-2015
Quality Amendment	27-JUL-2015
Quality Amendment	04-AUG-2015
Quality Amendment	12-AUG-2015
Quality Amendment	25-AUG-2015
Quality Amendment	28-AUG-2015
Quality Amendment	25-SEP-2015
Labeling Amendment	15-OCT-2015
Labeling Amendment	19-OCT-2015
Labeling Amendment	26-OCT-2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Martin Haber, Ph.D.	NDBII/DNDAPI
Drug Product	Arthur Shaw, Ph.D.	NDPBIV/DNDPII
Process	Brian Rogers, Ph.D.	PABIV/DPAII
Microbiology	Vinayak Pawar, Ph.D.	MABI/DMA
Facility	Steve Hertz	IABI/DIA
Biopharmaceutics	N/A	
Project/Business Process Manager	Don Henry	OPRO
Application Technical Lead	Craig M. Bertha	NDPBIV/DNDPII



CHEMISTRY REVIEW



Laboratory (OTR)	N/A	
ORA Lead	Paul Perdue	MDTP/DMPTPO
Environmental Assessment (EA)	N/A	



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**QUALITY ASSESSMENT
NDA # 207930**



Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION:

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS ¹	DATE REVIEW COMPLETED
(b) (4)	III		(b) (4)	ACCEPTABLE	7/23/2015
	IV		ACCEPTABLE	09/16//2015	
	IV		No review necessary, Sufficient information in NDA		
	IV				

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

APPLICATION NUMBER	DESCRIPTION
IND 76377	Clinical trials for INDACATEROL MALEATE GLYCOPYRRONIUM BROMIDE
NDA (b) (4)	Arcapta (indacaterol maleate) inhalation powder Referenced for indacatoerl maleate and Concept 1 InhalerApproved
NDA 207923	Seebri (glycopyrronium bromide) inhalation powder Pending

3. 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: Approve

A. Recommendation and Conclusion on Approvability

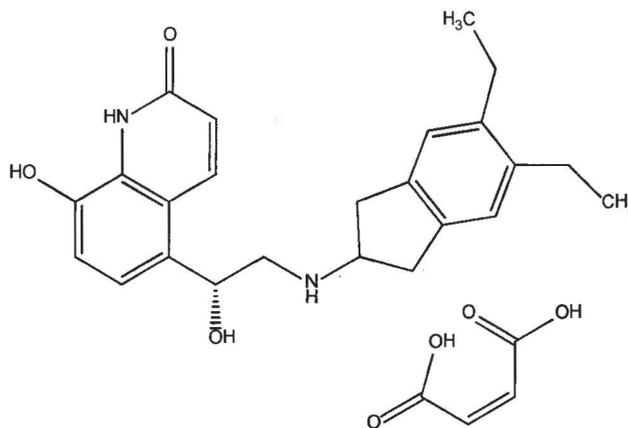
1. Summary of Complete Response issues : None
2. Action letter language, N/A
3. Benefit/Risk Considerations: N/A

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable N/A

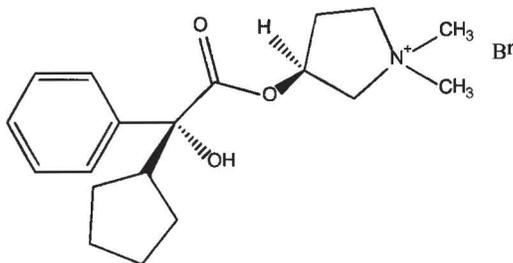
II. Summary of Quality Assessments

A. Drug Substance [Indacaterol/Glycopyrrolate or Glycopyrronium Bromide] Quality Summary

1. Chemical Names or IUPAC Names/Structures



(b) (4)



Glycopyrronium Bromide [(S)-3-((R)-2-cyclopentyl-2-hydroxy-2-phenylacetoxyl)-1,1-dimethylpyrrolidinium bromide and enantiomer]

2. Properties/CQAs Relevant to Drug Product Quality



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The identity, purity (organic related, inorganic, residual solvents, metals, etc.), moisture content, and the physical form (b) (4) of the drug substances are important to the attainment of the quality of the drug product.

3. List of starting materials

The starting materials for the synthesis of glycopyrrolate are

(b) (4)
(for more detail see reviews of NDA 22383).

4. Suppliers of starting materials (site)

Suppliers not specified for either drug substance, but requirements for (b) (4) are part of the drug substance control for indacaterol (see NDA 22383).

5. Summary of Syntheses

For glycopyrrolate:

(b) (4)

For indacaterol:

(b) (4)

6. Process

- a. (b) (4) as applicable
N/A
- b. Critical equipment
None identified

7. Container Closure



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The drug substances are stored in [redacted] (b) (4)

8. Retest Period & Storage Conditions

Re-test periods are [redacted] (b) (4) for both glycopyrrolate and [redacted] (b) (4) indacaterol maleate.

B. Drug Product Quality Summary

1. Strength: 15.6 mcg glycopyrronium bromide (glycopyrrolate) and 27.5 mcg of indacaterol/capsule
2. Description/Commercial Image: Capsules with yellow color coding in blister package combined with a relatively small off-white inhaler device with yellow color coded buttons for capsule piercing
3. Summary of Product Design: [redacted] (b) (4) inhalation powder product
4. List of Excipients:
Lactose
Magnesium Stearate
5. Process Selection (Unit Operations Summary)

[redacted] (b) (4)

6. Container Closure: Foil-foil blisters
7. Expiration Date & Storage Conditions: 16 months at Controlled Room Temperature
8. List of co-packaged components: Concept1 inhaler device

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Utibron Neohaler
Non Proprietary Name of the Drug Product	glycopyrrolate and indacaterol inhalation powder
Non Proprietary Name of the Drug Substance	glycopyrrolate and indacaterol
Proposed Indication(s) including Intended Patient Population	Anticholinergic and beta ₂ adrenergic agonist (respectively) indicated for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema
Duration of Treatment	Maintenance treatment (chronic)
Maximum Daily Dose	15.6 mcg/27.5 mcg, respectively, twice daily by oral inhalation
Alternative Methods of Administration	None



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D. Biopharmaceutics Considerations

N/A

E. Novel Approaches

N/A

F. Any Special Product Quality Labeling Recommendations

N/A

G. Process/Facility Quality Summary (see Attachment A)

H. Life Cycle Knowledge Information (see Attachment C)



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Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE



(b) (4)



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(b) (4)



ASSESSMENT OF THE BIOPHARMACUETICS

N/A

ASSESSMENT OF MICROBIOLOGY

8. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:

Since the drug product is not a sterile product and is not conducive to bacterial growth owing to the necessarily dry nature of the formulation, the total aerobic microbial count (TAMC) and the total combined yeasts/moulds count (TYMC) are determined according to the harmonized methods of Ph. Eur. 2.6.12, USP <61> and JP <4.05 I> "Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests" by the pour-plate method.

For the absence of specified microorganisms *Pseudomonas aeruginosa*, *Staphylococcus aureus* and bile-tolerant gramnegative bacteria proceed according to the harmonized methods of Ph. Eur. 2.6.13, USP <62> and JP <4.05 II> "Microbiological Examination of Non-Sterile Products: Test for Specified Micro-Organisms".



Reviewer's Assessment: Satisfactory

The drug product is not a sterile product. Manufacturing of the inhalation powder hard capsule takes place in (b) (4). The inhalation powder hard capsules are submitted to microbiological release testing.

The microbial attributes of the drug product were assessed through development studies and as part of the long-term registration stability testing. All microbial attributes are consistently met to date on all batches as provided in [3.2.P.8.1].

The firm's compliance with the cGMP requirements will be critical to the control of microbial contamination in the product.

9. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Reviewer's Assessment: Not Applicable

This is not a sterile product.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

10. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Reviewer's Assessment: Not Applicable

11. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Reviewer's Assessment: Not Applicable



**QUALITY ASSESSMENT
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OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

Primary Reviewer: Vinayak B. Pawar 03/10/2015

Secondary Reviewer: Stephen E. Langille 03/10/2015

Satisfactory – Brian Rogers 8/18/2015

Supervisor Comments and Concurrence:

Concur. – Zhigang Sun, 8/18/2015

Note: additional reviewers can be added, as appropriate.

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1



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Labeling & Package Insert

The information reviewed below was submitted in the October 15, 2015 amendment in response to our comments dated October 7, 2015

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

Proposed text in October 26, 2015 amendment is in *italics*

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	<i>UTIBRON™ NEOHALER® (indacaterol and glycopyrrolate)</i>	ACCEPTABLE Utibron ACCEPTABLE per DMEPA review 7/6/2015
Dosage form, route of administration	<i>inhalation powder, for oral inhalation use</i>	ACCEPTABLE
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	<i>Inhalation powder: UTIBRON capsules contain 27.5 mcg of indacaterol and 15.6 mcg glycopyrrolate inhalation powder for use with the NEOHALER device (3)</i>	ACCEPTABLE



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Conclusion: ACCEPTABLE

“Full Prescribing Information” Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms	<i>Inhalation powder</i>	ACCEPTABLE
Strengths:	<i>27.5 mcg/15.6 mcg of indacaterol/glycopyrrolate</i>	ACCEPTABLE
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	<i>a hypromellose capsule with yellow transparent cap and uncolored transparent body with black “” logo on the cap and black product code “IGP27.5_15.6” under the black bar on the body.</i>	ACCEPTABLE

Conclusion: ACCEPTABLE

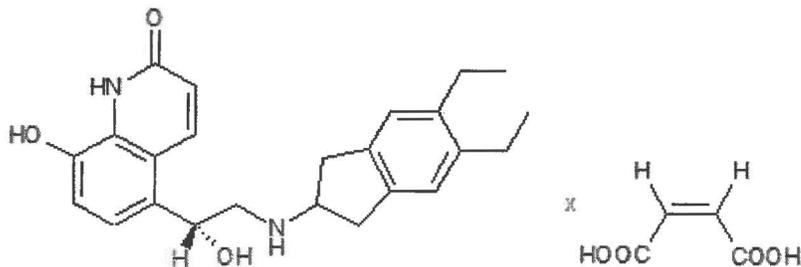
#11: Description (21CFR 201.57(c)(12))

(Attach proposed text)

Item	Information Provided in NDA	Reviewer’s Assessment
Proprietary name and established name	<i>UTIBRON NEOHALER</i>	ACCEPTABLE
Dosage form and route of administration	<i>(b) (4) powder (b) (4), for oral inhalation (b) (4) NEOHALER device. (b) (4). (b) (4) in hypromellose (HPMC) capsules with yellow transparent cap and uncolored transparent body.</i>	ACCEPTABLE
Active moiety expression of strength	<i>27.5 mcg/15.6 mcg of indacaterol/glycopyrrolate</i>	ACCEPTABLE
Inactive ingredient information listed by USP/NF names.	<i>lactose monohydrate (which contains trace levels of milk protein) and 0.03 mg of magnesium stearate</i>	ACCEPTABLE
Chemical name, structural formula, molecular weight	<i>See below</i>	ACCEPTABLE
Other important chemical or physical properties (such as pKa, solubility, or pH)	<i>white powder that is freely soluble in water and sparingly soluble in absolute ethanol</i>	ACCEPTABLE

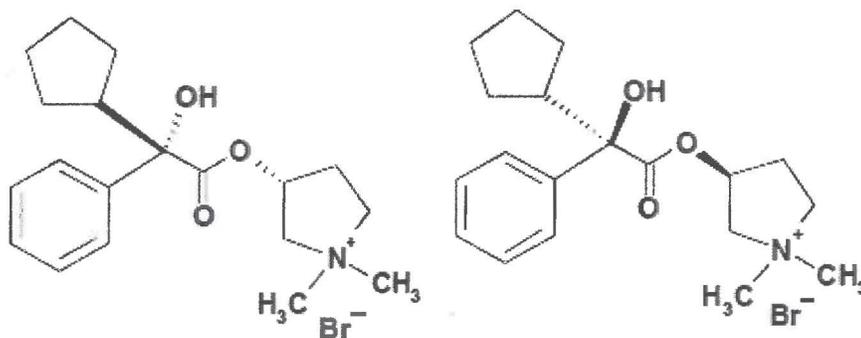
Active ingredients

One active component of UTIBRON NEOHALER is indacaterol maleate, a (R) enantiomer. Indacaterol maleate is a selective beta2-adrenergic agonist. Its chemical name is (R)-5-[2-(5,6-Diethylindan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one maleate; its structural formula is



Indacaterol maleate has a molecular weight of 508.56, and its empirical formula is $C_{24}H_{28}N_2O_3 \cdot C_4H_4O_4$. Indacaterol maleate is a white to very slightly grayish or very slightly yellowish powder. Indacaterol maleate is slightly soluble in ethanol and very slightly soluble in water.

The other active component of UTIBRON NEOHALER is glycopyrrolate, which, is chemically described as (3RS)-3-[(2SR)-(2-cyclopentyl-2-hydroxy-2-phenylacetyl) oxy]-1,1-dimethylpyrrolidinium bromide. This synthetic quaternary ammonium compound acts as a competitive antagonist at muscarinic acetylcholine receptors, also referred to as anticholinergic. Glycopyrrolate, $C_{19}H_{28}BrNO_3$, is a white powder that is freely soluble in water and sparingly soluble in ethanol. It has a molecular mass of 398.33. The structural formula is:



ACCEPTABLE

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

(Proposed text in italics)



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Item	Information Provided in NDA	Reviewer's Assessment
<p>Strength of dosage form</p> <p>Available units (e.g., bottles of 100 tablets)</p> <p>Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number</p>	<p><i>UTIBRON NEOHALER contains UTIBRON (indacaterol/glycopyrrolate, (27.5 mcg, 15.6 mcg) inhalation powder) capsules packaged in aluminum blister cards, 1 NEOHALER device, and an FDA approved Medication Guide.</i></p> <p><i>Unit Dose (blister pack), Box of 60 (10 blister cards with 6 yellow transparent capsules each)</i> <i>NDC 0078-0664-19</i></p> <p><i>Unit Dose (blister pack), Box of (b) (4) blister cards with 6 yellow transparent capsules each)</i> <i>(b) (4)</i></p> <p><i>The NEOHALER device consists of a white protective cap and a base with mouthpiece, capsule chamber and 2 yellow push buttons.</i></p>	ACCEPTABLE
<p>Special handling (e.g., protect from light, do not freeze)</p>	<ul style="list-style-type: none"> • <i>UTIBRON capsules should be used with the NEOHALER device only. Do not use the NEOHALER device with any other capsules.</i> • <i>Store UTIBRON capsules in the blister protected from light and moisture. Remove the UTIBRON capsules from the blister immediately before use.</i> • <i>Always use the new NEOHALER inhaler provided with each new prescription.</i> <p><i>Keep out of the reach of children.</i></p>	ACCEPTABLE
<p>Storage conditions</p>	<p><i>Store in a dry place at 77°F (25°C); excursions permitted to 59°F to 86°F (15°C to 30°C) [see USP Controlled Room Temperature].</i></p>	ACCEPTABLE

Conclusion: ADEQUATE

Amend the Full Prescribing Information, "How Supplied" section of the label as follows:
UTIBRON NEOHALER contains UTIBRON (indacaterol/glycopyrrolate, 27.5 mcg/15.6 mcg) inhalation powder) in yellow transparent capsules packaged in aluminum blister cards, 1 NEOHALER device, and an FDA approved Medication Guide.

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
<p>Manufacturer/distributor name (21 CFR 201.1)</p>	<p><i>Distributed by:</i> <i>Novartis Pharmaceuticals Corporation</i> <i>East Hanover, New Jersey 07936</i></p>	ACCEPTABLE

Conclusion: ACCEPTABLE

2. Labels



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1) Immediate Container Label



(b) (4)

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	No comments	ACCEPTABLE
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		
Net contents (21 CFR 201.51(a))		
Lot number per 21 CFR 201.18		
Expiration date per 21 CFR 201.17		
"Rx only" statement per 21 CFR 201.100(b)(1)		
Storage (not required)	N/A	
NDC number	No comments	
Bar Code per 21 CFR 201.25(c)(2)**	N/A	
Name of manufacturer/distributor	"Mfd. by: Novartis Pharma Stein AG Stein, Switzerland" Note that this is the manufacturer not the distributor	
Others	<i>Do not push the capsule through foil</i> <i>For use with Neohaler® only</i> <i>Do not swallow capsule</i> These are critical instructions and are appropriately on the immediate blister	

ACCEPTABLE

The applicant has also provided blisters for samples and for the placebo used for demonstrations:



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(b) (4)



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	No comments	ACCEPTABLE
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		
Net contents (21 CFR 201.51(a))		
Lot number per 21 CFR 201.18		
Expiration date per 21 CFR 201.17		
Name of all inactive ingredients (except for oral drugs);		
Sterility Information (if applicable)	N/A	
“Rx only” statement per 21 CFR 201.100(b)(1)	No comments	
Storage Conditions	No comments	
NDC number	No comments	
Bar Code per 21 CFR 201.25(c)(2)**	N/A	
Name of manufacturer/distributor	“Manufactured by: Novartis Pharma Stein AG Stein, Switzerland Distributed by: Novartis Pharmaceuticals Corp. East Hanover, NJ 07936”	
“See package insert for dosage information” (21 CFR 201.55)	No comments	
“Keep out of reach of children” (optional for Rx, required for OTC)		
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))		

Conclusion: ACCEPTABLE

II. List of Deficiencies To Be Communicated

- A. Drug Substance
- B. Drug Product



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- C. Process/Facility
- D. Biopharmaceutics
- E. Microbiology
- F. Label/Labeling



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Attachments

A. Facility

OVERALL RECOMMENDATION:				
DRUG SUBSTANCE				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
DRUG PRODUCT				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION

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C. Lifecycle Knowledge Management

a) Drug Substance

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Initial Risk Ranking*	Justification	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments**
NA	H, M, or L			Acceptable	No concerns.

b) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Deliver Dose Uniformity (DDU)	Multiple. See IQA	L	DDU and CU tested in specs	Acceptable	None
Aerodynamic Particle Size Distribution (APSD)		M	APSD tested in specs	Acceptable	None
Purity (impurities/degradants)		L	Degradants tested in specs	Acceptable	None



III. Administrative

A. ATL: Craig M. Bertha

Signature/Date

**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: 2015.10.28 15:12:18 -04'00'

B. Endorsement Block

Reviewers' Names/Dates: See above for reviewers and secondary reviewers' concurrence

Regulatory and Business Project Manager Name/Date:

MEMORANDUM



DEPARTMENT OF HEALTH AND HUMAN SERVICES
 PUBLIC HEALTH SERVICE
 FOOD AND DRUG ADMINISTRATION
 CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 5, 2015

TO: NDA 207930

FROM: Vinayak B. Pawar, Ph.D., Sr. Review Microbiologist, CDER/OPQ/DMA

THROUGH: Stephen E. Langille, Ph.D., Acting Chief, Branch III CDER/OPQ/DMA
cc: Christine Ford, Sr. Regulatory Project Manager, CDER/OND/ODEII/DPA

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for “QVA149 27.5/12.5 mcg (Indaceterol/glycopyrrolate)”.
 [Submission Date: December 29, 2014]

The Microbial Limits specification for “QVA149 27.5/12.5 mcg (Indaceterol/glycopyrrolate)” Hard Capsule is acceptable from a Product Quality Microbiology perspective. Therefore, this non-sterile drug product submission is recommended for approval from the standpoint of product quality microbiology.

Drug Product: QVA149 27.5/12.5 mcg (Indaceterol maleate/glycopyrrolate), a Hard Capsule for oral inhalation administration.

The drug product is tested for Microbial Limits at release using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The Microbial Limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use).

The Microbial Limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapter <61> and <62>. The following drug product specifications were provided in Document DP 6001565 022 R01.

Test -70161.01	Limit	Test Methodology
Total Aerobic Microbial Count	NMT (b) (4) CFU/g	USP <61>
Total Yeasts and Molds Count	NMT (b) (4) CFU/g	USP <61>
Test for Specified Micro-organisms: <i>Pseudomonas aeruginosa</i> <i>Staphylococcus aureus</i> <i>Bile-tolerant gram negative bacteria</i>	Absence in (b) (4) Absence in (b) (4) Absence in (b) (4)	USP <62>

The drug product will also be tested for Microbial Limits annually as part of the post-approval stability

MEMORANDUM

protocol.

ADEQUATE

Reviewer Comments – The microbiological quality of the drug product is controlled via a suitable testing protocol. The inhalation powder hard capsule delivered via ‘Concept1’ oral inhalation device is currently used in marketed product Arcapta® Neohaler® in the US.

END

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

/s/

VINAYAK B PAWAR
03/10/2015

STEPHEN E LANGILLE
03/10/2015

OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: N207930

2. DATES AND GOALS:

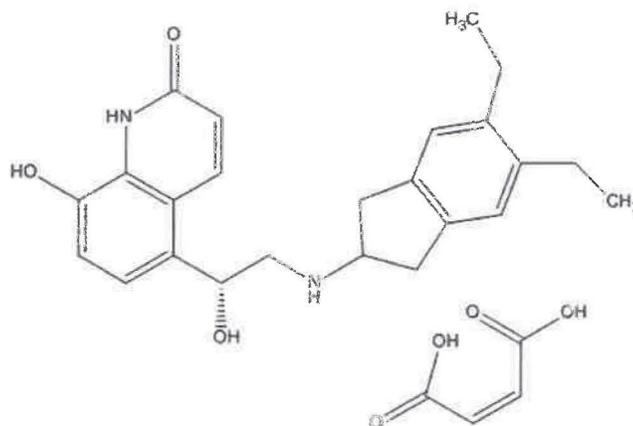
Letter Date: 29-DEC-2014	Submission Received Date : 29-DEC-2014
PDUFA Goal Date: 29-OCT-2015 (from Panorama)	

3. PRODUCT PROPERTIES:

Trademark or Proprietary Name Proposed:	Ultibro™ Neohaler®
Established or Non-Proprietary Name (USAN):	Indacaterol/glycopyrrolate
Dosage Form:	Inhalation powder
Route of Administration	Oral inhalation
Strength/Potency	27.5 mcg indacaterol (b)(4) mcg indacaterol maleate)/15.6 mcg glycopyrrolate (12.5 mcg of glycopyrronium (b)(4)/capsule; dosage is one capsule by inhalation BID
Rx/OTC Dispensed:	Rx <u>X</u> OTC

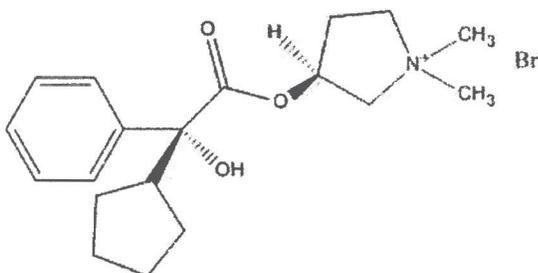
4. INDICATION: For the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



(b) (4)

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FILING REVIEW**



Glycopyrronium Bromide [(*S*)-3-((*R*)-2-cyclopentyl-2-hydroxy-2-phenylacetoxy)-1,1-dimethylpyrrolidin-1-ium bromide and enantiomer]

6. NAME OF APPLICANT (as indicated on Form 356h): Novartis
Pharmaceuticals Corporation

7. SUBMISSION PROPERTIES:

Review Priority:	Standard Priority
Submission Classification (Chemical Classification Code):	Based on draft MaPP 7500.3, Type 3: New Dosage Form (for glycopyrrolate) and Type 4: New Combination
Application Type:	505(b)(1) (no NMEs)
Breakthrough Therapy	Yes No <input checked="" type="checkbox"/>
Responsible Organization (Clinical Division):	DPARP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
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**OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW**

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics			Drug product expiration of 16 months ¹ is based on 12 months of real time stability data and a statistical evaluation; Although not an NME, reviewer should consider the principles outlined in ICH Q1E when evaluating the applicant's proposed expiration dating period and stability data. The reviewer may consult the biometrics team if deemed necessary after evaluation of the stability data.
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		The ONDQA PM was informed of the application on 30-DEC-2014, and asked to enter the facilities.
Pharmacology/Toxicology	X		<p>The lactose and Mg stearate used is already approved for use in the applicant's inhalation powder product of N22383, thus no consult to pharmacology/toxicology is likely to be necessary. Although the Mg stearate from (b) (4) (DMF (b) (4)) was already approved for use in another of the applicant's (b) (4) products (b) (4), that product was never launched, thus it is not certain that the DMF is up to date. Therefore, there may need to be some consultation with the pharmacology/toxicology team if there has been change that would impact the impurity profile of this excipient.</p> <p>Indacaterol maleate was the drug substance first approved for inhalation under the applicant's NDA 22383, and the bulk of the related CMC information is referenced to that application. The specification acceptance criteria for related impurities of this approved NDA are applied to the indacaterol used for the current application. The limits for individual unidentified indacaterol drug-related impurities are currently set at the Q3B identification threshold. It is not anticipated that a pharmacology/toxicology consult will be necessary regarding the indacaterol related impurities. Also, drug product foreign particulate acceptance criteria (b) (4) for the drug product of</p>

¹ Sixteen (16) months is not a time-point consistent with the recommendations of ICH Q1A, thus this may need further discussion from a policy perspective.

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FILING REVIEW**

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
			<p>NDA 22383.</p> <p>Although glycopyrrolate is not an NME and it is a monographed drug substance, it has not been approved for the inhalation route of administration. Generally, the concern for impurities is greater for inhalation versus oral drugs, but doses are typically much lower for the former route. Nevertheless, the applicant provides a substantive list of potential impurities, and some of these include structural alert groups (i.e., (b) (4)). It is noted that no individual drug-related impurities are to be greater than the 0.10% identification threshold of Q3A. (b) (4).</p> <p>There are also relatively low limits on individual metal impurities that, when combined with the very low daily dose of the drug, would not pose a concern that would need to be addressed by the pharmacology/toxicology team. Any consult for glycopyrrolate drug substance related issues can be handled via NDA 207923, as this is the repository for the glycopyrrolate drug substance information.</p>
Methods Validation			It will be left to the reviewer to decide if it is warranted to send any methods for assessment by the Agency laboratory, based on evaluation of the method and the associated validation data provided.
Environmental Assessment			The applicant claims categorical exclusion as per 21 CFR 25.31(b). The reviewer can consult with the OPS EA expert (R. Bloom, PhD) if the calculations related to the expected introduction concentration are determined to be questionable.
CDRH			From a purely CMC-perspective, it is not necessary at this point to request CDRH to evaluate any of the quality-related information for the device, since it has already been approved for use under NDA 22383.
Other			N/A

(b) (4)

**OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW**

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>
CMC Filing Issues: N/A

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>
CMC Comments for 74-Day Letter (assuming filing):

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes <input checked="" type="checkbox"/>
Biopharmaceutics Filing Issues: 1. NONE

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? Yes <input type="checkbox"/> No <input type="checkbox"/>
Biopharmaceutics Comments for 74-Day Letter: Refer to page 16 of this document.

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? Yes <input type="checkbox"/> No <input type="checkbox"/>
Microbiology Filing Issues: See separate filing review from the microbiology team.

**OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW**

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: N/A			

Summary of Critical Issues and Complexities:

This is a relatively straightforward inhalation powder application from Novartis that utilizes the same device that we recently approved for use with their long acting beta agonist drug product of NDA 22383. In addition, the lactose used is from the same source as for that approved application, and the Mg stearate is from a source found acceptable for another inhalation powder drug product approved for Novartis. The capsules in this case are hypromellose, not hard gelatin capsules, as were used in the similar NDA 22383. Neither drug is an NME, but glycopyrrolate has not been approved for the inhalation route of administration. Nevertheless, the application is a 505(b)(1) according to the applicant.

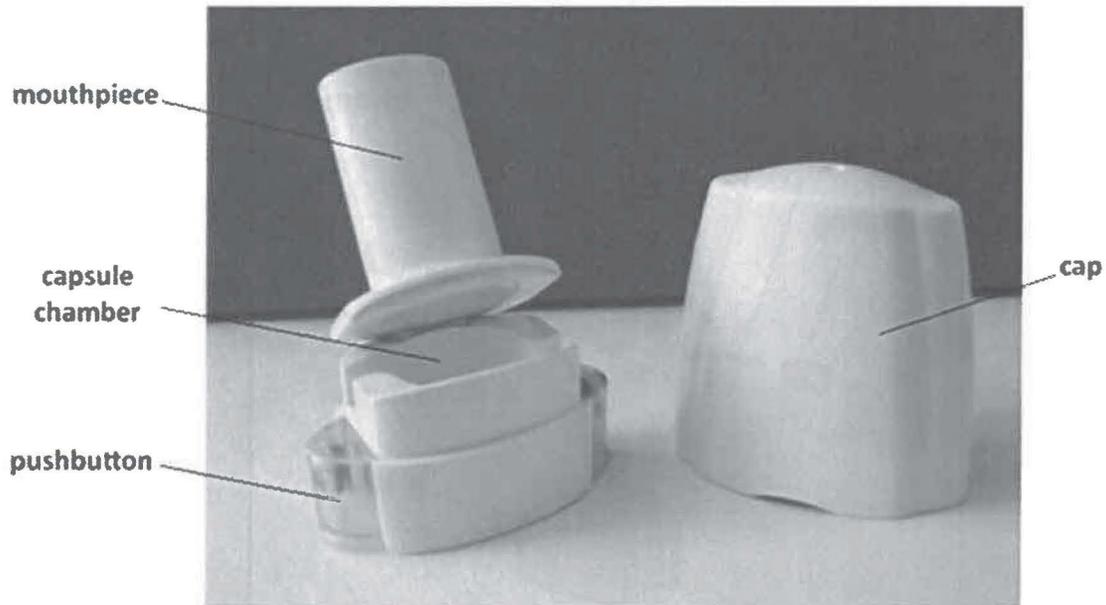
However, there is one major critical unresolved issue that requires evaluation is the *in vitro* comparability between the two monotherapy DPI products and the combination drug product of this application. As requested, the applicant has provided these comparative data in the P.2.1.2.2 section for evaluation. If these data (DDU and APSD) are not determined to be comparable, this could impact the evaluation of the clinical data and the clinical team should be notified as soon as feasible.

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FILING REVIEW**

INITIAL QUALITY ASSESSMENT

The application is submitted in support of an indacaterol/glycopyrrolate inhalation powder drug product for the treatment of COPD. If approved, this would be the first inhalation powder that includes glycopyrrolate for the inhalation route of administration. As already indicated, the device has already been approved for use with another inhalation powder drug product for this applicant. A schematic drawing of the device and exploded view are reproduced below from the application:

Figure 4-1 **Start of Applicant Material
Picture of the Concept1 device**



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FILING REVIEW

Figure 4-2 **Exploded view of Concept1 device**



End of Applicant Material

During development it is worth noting that the clinical Division had a concern regarding the use of the capsules from this drug product (b) (4) and the the potential impact on the associated drug product performance. This issue may be brought up again for this application. The reviewer should refer to the CMC memorandum dated 14-JAN-2011, under NDA 22383 for pertinent evaluation of related *in vitro* performance data. The Division also raised the concern regarding (b) (4)

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[REDACTED] (b) (4)

At the 13-JUN-2007, pre-IND meeting, the Division made note of *in vitro* APSD differences between this combination product and the associated monotherapy drug products. The firm was cautioned that the interpretation of the clinical study results may be compromised considering these differences. The sponsor was strongly encouraged to sort out these differences prior to proceeding with clinical studies. Also at this meeting, the firm divulged that they planned to use

[REDACTED] (b) (4) for collection of APSD data and that they would use [REDACTED] (b) (4)

[REDACTED]

An EoP2 meeting was held on 27-SEP-2011, as well as a follow-up meeting on 07-MAR-2012, and again the issue of pharmaceutical comparability between the monotherapy comparators and the combination drug product was a major issue of discussion, but remained unresolved. The response to the questions posed by the sponsor at the 19-MAR-2014, pre-NDA meeting also included the following reminder from the CMC team regarding this issue:

We remind you to submit in vitro CMC-related data (e.g., dose delivery, aerodynamic particle size distribution by cascade impaction) clearly demonstrating that, for the duration of the clinical studies, each strength of the combination drug product is pharmaceutically similar to the single ingredient monotherapy drug products, in terms of the delivery performance for each drug. Typically these data should be provided for our evaluation via the IND, prior to the commencement of your phase 3 clinical studies. In addition, we expect these data to be included in the pharmaceutical development section (P.2) of the NDA for the inhalation combination drug product.

Although this is not expected to not impact any decisions about the quality control of the combination drug product of this application, regardless of outcome, it is a critical unresolved issue for the clinical team that will require evaluation by the CMC reviewer (team). The outcome may impact the review of the clinical team if it is found that there is a lack of comparability. Note too that the sponsor was also informed via the pre-NDA meeting minutes that they should use glycopyrrolate with a strength of 15.6 mcg for the drug product.

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

DP attribute/ CQA	Factors that can impact the CQA ³	O ⁴	S ^{4,5}	D ⁴	FMECA RPN #	Comment & considerations
Delivered Dose Uniformity (DDU for glycopyrrolate and indacaterol)	<ul style="list-style-type: none"> • Inhomogeneity or low formulation assay (e.g., from manufacturing; result of shipping) • Lower than target fill of capsules • Failure of packaging (foil-foil blister) • Patient mis-use of dosage form in terms of storage • Particle size/ (b) (4) content of lactose, (b) (4) indacaterol • Device malfunction (e.g., failure to puncture capsule, capsule fails to spin) • Static charge of formulation 	2	2	3	[REDACTED]	(b) (4)

³ Patient mis-use can impact performance on device but human factors are beyond scope of CMC evaluation.

⁴ O = Probability of Occurrence; S = Severity of Effect; D = Detectability

⁵ Severity of effect can only be estimated; input from clinical or pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs.

**ONDP Initial Quality Assessment (IQA) and Filing Review
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Aerodynamic Particle Size Distribution (APSD)	<ul style="list-style-type: none"> • Inhomogeneity or low formulation assay (e.g., from manufacturing; result of shipping) • Lower than target fill of capsules • Failure of packaging (foil-foil blister) • Patient mis-use of dosage form in terms of storage • (b) (4) content of (b) (4) • Particle size of (b) (4) • Particle size (b) (4) content of lactose • Device malfunction (e.g., failure to puncture capsule, capsule fails to spin) • Static charge of formulation/device • Composition of device air flow path components • Device flow resistance variation • High dependence of performance on flow rate 	3	3	3	27

(b) (4)

**ONDP Initial Quality Assessment (IQA) and Filing Review
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						(b) (4)
Purity (impurities/degradants)	<ul style="list-style-type: none"> • degradation of either API as formulated • input purity of APIs • input purity of lactose & Mg stearate 	1	2	2	4	

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

BIOPHARMACEUTICS INITIAL ASSESSMENT		
Biopharmaceutics Summary		
Submission:		
<p>Novartis is seeking approval of QVA149 (indacaterol/glycopyrrolate) Inhalation Powder Hard Capsules for long-term maintenance twice a day treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. QAB149 (Arcapta® Neohaler®) was approved in the United States in 2011 as a once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD (NDA 22-383). A NDA for NVA237 (glycopyrrolate) is being submitted to FDA (NDA 207-923) with the same indication that is proposed for QVA149. Both monotherapy products are presented as inhalation powder hard capsules delivered via the Concept1 inhalation device.</p>		
Drug Product:		
<p>Novartis has developed QVA149 as a dry powder in hard capsules that are inserted into a single-dose, dry powder inhalation device (Concept1). One QVA149 inhalation powder hard capsule contains 27.5 mcg of indacaterol maleate and 15.6 mcg of glycopyrrolate (glycopyrrolate), corresponding to 12.5 mcg of glycopyrrolate.</p>		
<p>NVA237 (glycopyrrolate) drug substance requires (b) (4)</p> <div style="background-color: gray; height: 40px; width: 100%;"></div>		
<div style="background-color: gray; height: 250px; width: 100%;"></div> (b) (4)		
<p>An overview of QVA149 formulations used in clinical development is shown in the table below.</p>		
Clinical Study	QVA149 dosage strengths	Device

**ONDP Initial Quality Assessment (IQA) and Filing Review
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Phase I	27.5/12.5 mcg, 55/50 mcg, 110/50 mcg, 300/100 mcg	Concept1
Phase II	150/50 mcg, 300/50 mcg, 300/100 mcg	Concept1
Phase III	27.5/12.5 mcg, 27.5/25 mcg, 110/50 mcg	Concept1

The compositions of QVA149 inhalation powder hard capsules and the capsule weight of the inhalation powder (b) (4)

Relevant Biopharmaceutics Information

Several clinical pharmacology and biopharmaceutics studies [e.g., Study QVA149A2106 – Relative bioavailability of indacaterol and glycopyrronium from QVA149 (110/50 µg) versus QAB149 (150 µg) and NVA237 (50 µg) monotherapy products and the corresponding free combination (QAB149 150 µg and NVA237 50 µg)] were conducted to determine the impact of changes in dosing/formulation. These studies will be reviewed by OCP.

Currently, dissolution testing is not being implemented as part of the quality control tests of orally inhaled products (OIPs). This Reviewer acknowledges that dissolution testing is not currently being implemented as part of the quality control testing of orally inhaled products (OIPs) and therefore, it is not a required parameter for QC purposes at this time.

Review Issues Identified:

(b) (4)

Biopharmaceutics Review:

The biopharmaceutics review will be focused on ensuring that 1) appropriate bridging has been established throughout the phases of drug product development; 2) Changes (b) (4) do not impact the in vitro and in vivo drug release rate and/or that appropriate monitoring and control strategy is implemented to ensure consistent in vitro/in vivo release.

Critical Review Issues

Critical review issues identified during filing are as follows.

- The need for monitoring drug substances (b) (4) at release and stability will be evaluated.

Comments for Day 74-Letter

- Provide information on the solubility, hygroscopicity, and intrinsic dissolution differences between (b) (4) (if any) of indacaterol and glycopyrrolate.
 - o Explain how these differences (if any) could impact the drug product mean

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

residence time in the lungs and the rate and extend of absorption

APPEARS THIS WAY ON ORIGINAL

**ONDP Initial Quality Assessment (IQA) and Filing Review
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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	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		For the pages that were examined for this IQA review.
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		Seven site are listed in the form 356h
6.	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.			NA

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

	Parameter	Yes	No	Comment
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • 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		Two Novartis sites are responsible for the synthesis of the glycopyrrolate drug substance in Cork, Ireland and Stein, Switzerland; Four Novartis sites are responsible for the synthesis of the indacaterol drug substance in Cork, Ireland, and Stein, Basel, and Pratteln, Switzerland
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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		One Novartis site is responsible for the manufacture of the drug product in Stein, Switzerland

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

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • 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		
10.	Is a statement provided that all facilities are ready for inspection at the time of submission?	X		

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

STOP!

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

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		By reference to NDAs 22383 and 207923
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		By reference to NDAs 22383 and 207923
14.	Does the section contain information regarding the characterization of the DS?	X		By reference to NDAs 22383 and 207923
15.	Does the section contain controls for the DS?	X		Including reference to NDAs 22383 and 207923
16.	Has stability data and analysis been provided for the drug substance?	X		By reference to NDAs 22383 and 207923
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

**ONDP Initial Quality Assessment (IQA) and Filing Review
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E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	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		
21.	Is there a batch production record and a proposed master batch record?	X		There are single executed batch records provided for the preparation of the (b) (4) and the drug product. A proposed MBR is not required for a 505(b)(1) application.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		See P.2 document 6001565_P2_CTFO_840_1.
23.	Have any biowaivers been requested?			To be addressed by biopharmaceutics team.
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	X		Concept1 device is already approved for use with the drug product of NDA 22383.
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		There are also stability studies reported for the (b) (4).
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

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

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

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product		X	

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

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b)(4)	4	(b)(4)	(b)(4)	17-JUN-2013	
	4			21-NOV-2014	Reviewed for approved NDA (b)(4)
	4			17-NOV-2014	No approved inhalation powder products use hypromellose capsules
	3			20-JUL-2013	
	3			07-AUG-2012	Reviewed for approved NDA 22383

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

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

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).

ONDQA-BIOPHARMACEUTICS				
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING				
	PARAMETER	YES	NO	COMMENT
34.	Does the application contain dissolution data?		x	Currently, dissolution testing is not being implemented as part of the quality control tests of orally inhaled products (OIPs); therefore, it is not a required attribute for QC purposes at this time.
35.	Is the dissolution test part of the DP specifications?		x	NA
36.	Does the application contain the dissolution method development report?		x	NA
37.	Is there a validation package for the analytical method and dissolution methodology?		x	NA
38.	Does the application include a biowaiver request?		x	
39.	Does the application include an IVIVC model?		x	
40.	Is information such as BCS classification mentioned, and supportive data provided?		x	
41.	Is information on mixing the product with foods or liquids included?		x	
42.	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? (Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)		x	The to-be-marketed product is the same product used in the pivotal clinical studies. One site was responsible for the manufacture of the drug product (Novartis, Stein, Switzerland)
43.	Is there any in vivo BA or BE information in the submission?	x		Several studies were conducted to assess the relative BA among the fix-dose combination product and the monoproducts for different strengths/doses developed during formulation development. These studies will be reviewed by OCP. <u>\\CDSESUB1\evsprod\NDA207930\0000\m2\27-clin-sum</u>

**ONDP Initial Quality Assessment (IQA) and Filing Review
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ONDQA-BIOPHARMACEUTICS				
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING				
	PARAMETER	YES	NO	COMMENT
44.	<p>Is there a modified-release claim? If yes, address the following:</p> <p>a.) Is there information submitted to support the claim in accordance with 320.25(f)?</p> <p>b.) Is there information on the potential for alcohol-induced dose dumping?</p>		x	<p>NA One Novartis site is responsible for the manufacture of the drug product in Stein, Switzerland</p>

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

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
45.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	x		
46.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			
47.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?			Refer to page 15 of this document.

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

{See appended electronic signature page}

Craig M. Bertha, PhD
Quality Assessment Lead
Office of New Drug Products

{See appended electronic signature page}

Sandra Suarez, PhD
Quality Assessment Lead (biopharmaceutics)
Office of New Drug Products

{See appended electronic signature page}

John Duan, PhD
Acting Branch Chief (biopharmaceutics)
Office of New Drug Quality Assessment

{See appended electronic signature page}

Julia Pinto, PhD
Acting Branch Chief
Office of New Drug Quality Products

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

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=13001
03470, cn=Craig M. Bertha -S
Date: 2015.01.26 14:16:31 -05'00'

Sandra
Suarez -A

Digitally signed by Sandra Suarez -A
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Sandra Suarez -A,
0.9.2342.19200300.100.1.1=130014
7809
Date: 2015.01.26 14:23:10 -05'00'

John Z. Duan -S

Digitally signed by John Z. Duan -S
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ou=People, cn=John Z. Duan -S,
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Date: 2015.01.26 14:27:31 -05'00'

Julia C. Pinto -A

Digitally signed by Julia C. Pinto -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, cn=Julia C. Pinto -A,
0.9.2342.19200300.100.1.1=1300366849
Date: 2015.02.03 10:24:52 -05'00'