CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207923Orig1s000

CHEMISTRY REVIEW(S)

Quality Recommendation: Approval

NDA 207923
Review # 1
Review Date 28-OCT-2015

Drug Name/Dosage Form	Glycopyrrolate (Glycopyrronium bromide)/inhalation powder
Strength	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	15-MAY-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	11-SEP-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
Laboratory (OTR)	N/A	

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

Table of Contents

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 (approved) Referenced for Concept1 Inhaler.
NDA 207930	Utibron (glycopyrronium bromide/indacaterol maleate) inhalation powder (pending approval)

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

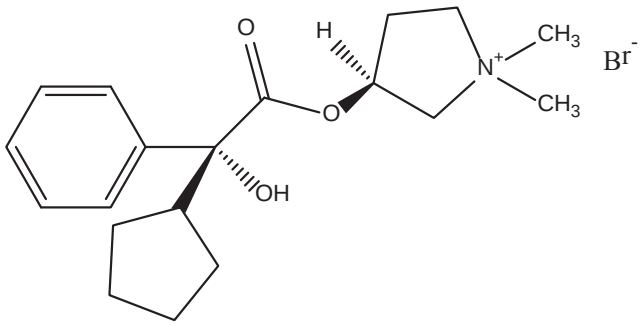
1. Summary of Complete Response issues : None
2. Action letter language, N/A
3. Benefit/Risk Considerations: N/A

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 [Glycopyrrolate or Glycopyrronium Bromide] Quality Summary

1. Chemical Name or IUPAC Name/Structure



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

2. Properties/CQAs Relevant to Drug Product Quality
   The identity, purity (organic related, inorganic, residual solvents), moisture content, and the physical form of the drug substance 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)

4. Suppliers of starting materials (site)
   Suppliers not indicated

5. Summary of Synthesis

(b) (4)

6. Process
   a. (b) (4), as applicable
      N/A
   b. Critical equipment
      None identified

7. Container Closure
   The drug substance is stored in (b) (4)
   .

8. Retest Period & Storage Conditions
   A retest period is (b) (4).

B. Drug Product Quality Summary

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

(b) (4)

6. Container Closure: Foil-foil blisters
7. Expiration Date & Storage Conditions: 18 months at 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	Seebri Neohaler

Non Proprietary Name of the Drug Product	glycopyrrolate inhalation powder
Non Proprietary Name of the Drug Substance	Glycopyrrolate
Proposed Indication(s) including Intended Patient Population	Anticholinergic 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 twice daily (*BID*) by oral inhalation
Alternative Methods of Administration	None

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 B)

Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

Applicant's Response:

(b) (4)

[redacted]

ASSESSMENT OF MICROBIOLOGY

22. 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.

2.3.P.6 Reference Standards or Materials

23. 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

24. 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

25. 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

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
ADEQUATE. – Brian Rogers 8/18/2015

Supervisor Comments and Concurrence:

Concur. – Zhigang Sun, 8/19/2015

Note: additional reviewers can be added, as appropriate

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

Labeling & Package Insert

1. **Package Insert**

Labeling & Package Insert

2. **Package Insert**

Labeling & Package Insert

3. **Package Insert**

QUALITY ASSESSMENT
NDA # 207923

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

(Proposed text from 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	*SEEBRI™ NEOHALER® (glycopyrrolate) inhalation powder, for oral inhalation use*	**ACCEPTABLE**
Dosage form, route of administration	*inhalation powder, for oral inhalation use*	**ACCEPTABLE**
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	*Inhalation powder: SEEBRI capsules contain 15.6 mcg of glycopyrrolate inhalation powder for use with the NEOHALER device*	**ACCEPTABLE**

Conclusion: ACCEPTABLE

(b) "Full Prescribing Information" Section

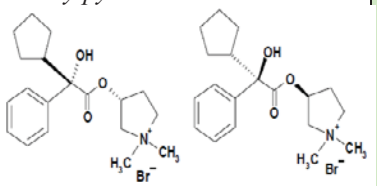
 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	*Inhalation powder*	**ACCEPTABLE**
Strengths:	*15.6 mcg of glycopyrrolate*	**ACCEPTABLE**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	*Inhalation powder: SEEBRI NEOHALER consists of SEEBRI capsules containing glycopyrrolate powder for oral inhalation and the NEOHALER device. SEEBRI capsules contain 15.6 mcg of glycopyrrolate in a transparent, orange hypromellose (HPMC) capsule with the product code "GPL15.6" printed in black and the logo ( ) printed with two radial black bars.*	**ACCEPTABLE**

Conclusion: ACCEPTABLE

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

(Proposed text in italics)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	*SEEBRI NEOHALER*	**ACCEPTABLE**
Dosage form and route of administration	*SEEBRI NEOHALER consists of SEEBRI capsules and a NEOHALER device. Each SEEBRI capsule contains a dry powder formulation of glycopyrrolate packaged in transparent orange hypromellose (HPMC) capsules for oral inhalation only with the NEOHALER device.* *Each transparent orange HPMC capsule contains 15.6 mcg of glycopyrrolate blended with approximately 25 mg of lactose monohydrate (which contains trace levels of milk protein) and 0.04 mg of magnesium stearate.*	**ACCEPTABLE**
Active moiety expression of strength	*15.6 mcg of /glycopyrrolate*	**ACCEPTABLE**
Inactive ingredient information listed by USP/NF names.	*Lactose monohydrate (which contains trace levels of milk protein)* (b) (4) *and 0.03 mg of magnesium stearate* (b) (4) .	**ACCEPTABLE**
Chemical name, structural formula, molecular weight	*(3RS)-3-[(2SR)-(2-cyclopentyl-2-hydroxy-2-phenylacetyl) oxy]-1,1-dimethylpyrrolidinium bromide*  *398.33*	**ACCEPTABLE**
Other important chemical or physical properties (such as pKa, solubility, or pH)	*white powder that is freely soluble in water and sparingly soluble in absolute ethanol*	**ACCEPTABLE**

Conclusion: Inadequate see above

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

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form Available units (e.g., bottles of 100 tablets) Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	*SEEBRI NEOHALER contains SEEBRI (glycopyrrolate (15.6 mcg) inhalation powder) orange transparent capsules packaged in aluminium blister cards, one NEOHALER device, and FDA approved Patient Labeling.* *Unit Dose (blister pack), Box of 60 (10 blister cards with 6 orange transparent capsules each) NDC 0078-0662-19* *The NEOHALER device consists of a white protective cap and a base with mouthpiece, capsule chamber and 2 orange push buttons.*	**ACCEPTABLE**
Special handling (e.g., protect from light, do not freeze)	• *SEEBRI capsules should be used with the* (b) (4) *NEOHALER device only. Do not use the* (b) (4) *NEOHALER device with any other capsules.* • *Store SEEBRI capsules in the blister protected from moisture. Remove the SEEBRI capsules from the blister immediately before use.* • *Always use the new NEOHALER inhaler provided with each new prescription*	**ACCEPTABLE**
Storage conditions	*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].*	**ACCEPTABLE**

Conclusion: INADEQUATE See above

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

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

Conclusion:

4. Labels

1) Immediate Container Label

(b) (4)

Reviewer's Assessment:

APPEARS THIS WAY ON ORIGINAL

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	*Do not push the capsule through foil* *For use with Neohaler® only* *Do not swallow capsule* These are critical instructions and are appropriately on the immediate blister	

ACCEPTABLE

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

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

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

B. 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****
AN	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 14:34:47 -04'00'

B. Endorsement Block

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

Regulatory and Business Project Manager Name/Date:

M E M O R A N D U M

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 207923**

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 "NVA237 15.6 mcg (glycopyrrolate)".**
[Submission Date: December 29, 2014]

The Microbial Limits specification for "NVA237 (glycopyrrolate 15.6 mcg)" 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: NVA237 (glycopyrrolate 15.6 mcg), 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 6002278 023 R01.

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

M E M O R A N D U M

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

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: N207923

2. DATES AND GOALS:

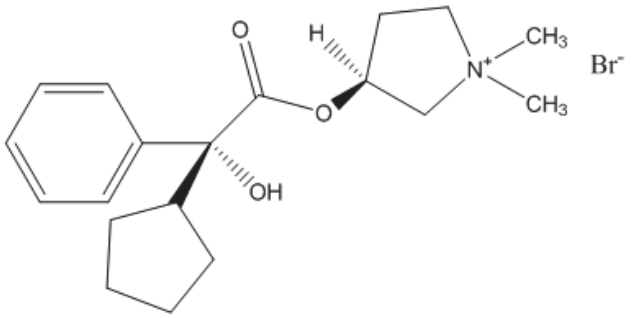
Letter Date: 29-DEC-2014	Submission Received Date : 29-DEC-2014
PDUFA Goal Date: 29-OCT-2015 (from Panorama)	

3. PRODUCT PROPERTIES:

Trademark or Proprietary Name Proposed:	Seebri™ Neohaler®
Established or Non-Proprietary Name (USAN):	Glycopyrrolate
Dosage Form:	Inhalation powder
Route of Administration	Oral inhalation
Strength/Potency	**15.6 mcg glycopyrrolate/capsule** (equivalent to 12.5 mcg of glycopyrronium cation)[1]; dosage is 15.6 mcg BID
Rx/OTC Dispensed:	Rx X 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:



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

[1] Although for NMEs the Agency will have applicants express the strength of quaternary salt drugs in terms of the cation, the USP has stated that this policy will not be applied to the already marketed anticholinergic compounds, like glycopyrrolate. Glycopyrrolate is synonymous with glycopyrronium bromide, thus the strength for this application is to be presented in terms of the pre-metered amount of glycopyrrolate per capsule, i.e., 15.6 mcg.

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
Application Type:	505(b)(1) (not an NME)
Breakthrough Therapy	Yes No X
Responsible Organization (Clinical Division):	DPARP

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	Drug product expiration of 18 months is based on 12 months of real time stability data and no statistical analyses are provided; Although not an NME, it is recommended that the reviewer consider the principles outlined in ICH Q1E when evaluating the applicant's proposed expiration dating period and stability data.
Clinical Pharmacology		X	
Establishment Evaluation Request (EER)	X		The ONDP PM was informed of the application on 30-DEC-2014, and asked to enter the facilities.

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Pharmacology/Toxicology	X		The lactose and Mg stearate used is already approved for use in the applicant's inhalation powder product of N22383, thus no consult to pharm/tox 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 pharm/tox team if there has been changes made that would impact the impurity profile of this excipient. 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). 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. However, the pharmacologist should be made aware of the allowance of two degradants ((b) (4)) to be above the Q3B qualification threshold of 1.0% (neither have structural alerts).
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.

(b) (4)

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
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

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:
N/A

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 (assuming filing):

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective?
Yes X No
Biopharmaceutics Filing Issues:
1. None

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter?
Yes No x
Biopharmaceutics Comments for 74-Day Letter:
None

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective?
Yes No
Microbiology Filing Issues:
See separate filing review from the microbiology team.

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. The drug is not an NME, but has not been approved, as of yet, for the inhalation route of administration.

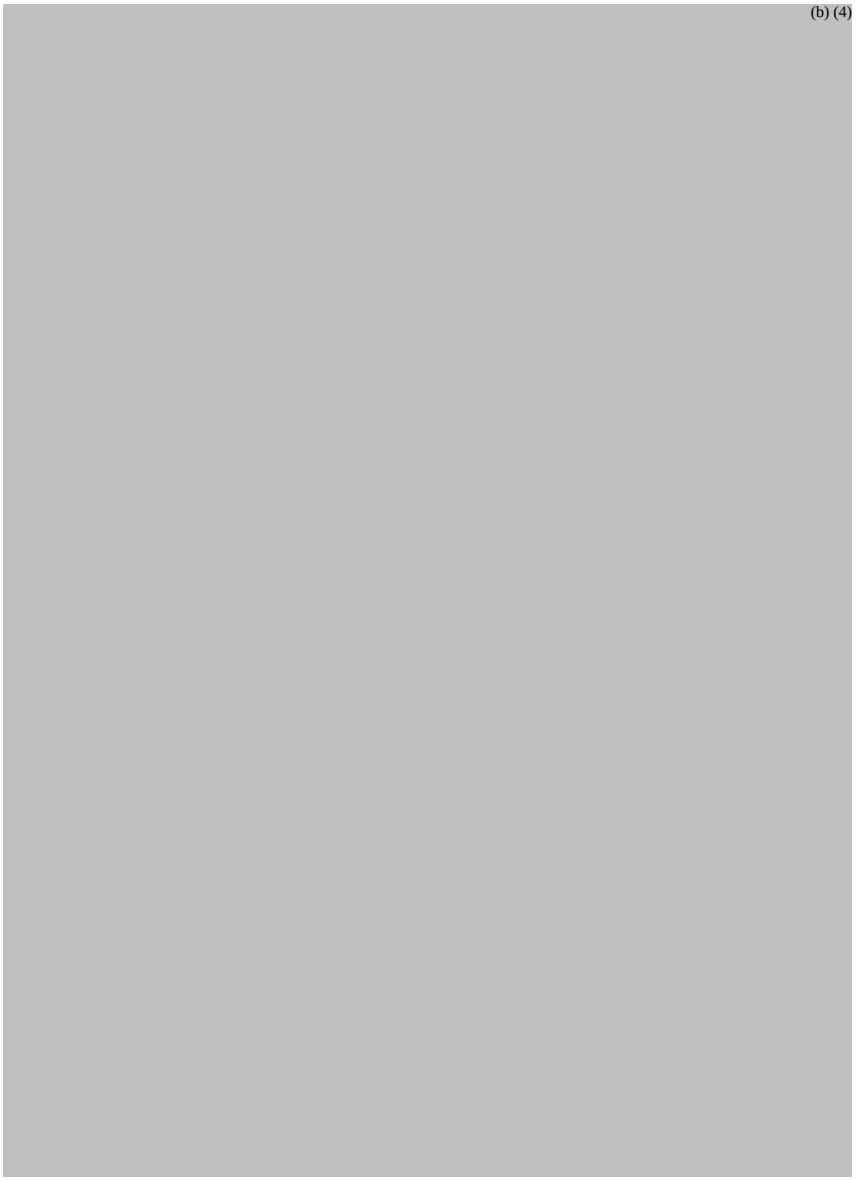
INITIAL QUALITY ASSESSMENT

The application is submitted in support of a glycopyrrolate inhalation powder drug product for the treatment of COPD. If approved, this would be the first inhalation powder for 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:

Start of Applicant Material

Figure 7-1 Picture of the Concept1 device

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 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 clinical Division also raised the concern (b) (4) .

The Agency agreed with the applicant that (b) (4) could be considered a designated regulatory starting material for the synthesis of glycopyrrolate., assuming there are no related issues with associated impurities in the final drug substance.

The Agency also agreed that the starting point of the shelf-life of the drug product would be from the date at which time the (b) (4) as long as the applicant provided stability data for drug product manufactured with (b) (4) for support.

The Agency agreed that (b) (4) would be considered to be (b) (4) as opposed to a starting material for the synthesis.

The Agency agreed that the applicant use "glycopyrrolate" for labeling purposes (established name). For all future submissions for NVA237 applications, the Agency stated that the applicant should use "glycopyrrolate 15.6 mcg" for glycopyrronium 12.5 mcg.

ONDQA 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)	• 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 and (b) (4) • Device malfunction (e.g., failure to puncture capsule, capsule fails to spin) • Static charge of formulation	2	2	3	12	(b) (4)

[3] Patient mis-use can impact performance of 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

						(b) (4)
Aerodynamic Particle Size Distribution (APSD)	• 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 • Variable composition of device air flow path components • Device flow resistance variation • High dependence of performance on flow rate	3	3	3	27	

						(b) (4)
Purity (impurities/degradants)	• degradation of API as formulated • input purity of API • input purity of lactose & Mg stearate	1	2	2	4	

BIOPHARMACEUTICS INITIAL ASSESSMENT

Biopharmaceutics Summary

Submission:

Novartis is seeking approval of NVA237 (glycopyrrolate) Inhalation Powder Hard Capsules for the long term maintenance, twice daily bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Drug Product:

Novartis has developed NVA237 as a dry powder in hard capsules that are inserted into a single-dose, dry powder inhalation device (Concept1). One NVA 237 inhalation powder hard capsule contains 15.6 mcg of glycopyrronium bromide (glycopyrrolate), corresponding to 12.5 mcg of glycopyrronium.

NVA237 (glycopyrrolate) drug substance requires (b) (4) .

An overview of NVA237 formulations used in clinical development is shown in the table below. The TBM formulation/device has been used since Phase I clinical study.

Clinical study	Dosage form	Capsule dosage strengths (µg) [1)]	Device
Phase I and II [2)]	Vectura inhalation powder hard capsule	16, 24, 48, 96, 100, 192, 200, 320 [3)]	(b) (4)
Phase I and II	Inhalation powder hard capsules	12.5, 25, 50, 100, 200	Concept1
Phase III [4)]	Inhalation powder hard capsules	50	Concept1
Phase III [5)]	Inhalation powder hard capsules	12.5	Concept1

The compositions of the clinical formulations of NVA237 inhalation powder hard capsules used in phases II and III are described in the table below (b) (4) . The qualitative and quantitative composition of 12.5 mcg dose formula for clinical usage is identical with the proposed commercial formula. (b) (4)

Ingredient	Theoretical amount per capsule [mg]				
	12.5 mcg	25 mcg	50 mcg	100 mcg	200 mcg
Capsule fill					(b) (4)
NVA237 (b) (4)					
Lactose monohydrate					
Magnesium stearate					
Capsule fill weight					
Empty capsule shell					
Capsule shell (theoretical weight)					
Total weight (approx.)	**74.00**	**74.00**	**74.00**	**74.00**	**74.00**

Relevant Biopharmaceutics Information
Several clinical pharmacology and biopharmaceutics studies were conducted to determine the impact of changes in dosing/formulation. These studies will be reviewed by OCP.

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.

NVA237 bromide consists of (b) (4)

Review Issues Identified:
None

Biopharmaceutics Review:
The biopharmaceutics review will be focused on ensuring that 1) appropriate bridging has been stablished throughout the phases of drug product development.

Critical Review Issues

Critical review issues identified during filing are as follows.

- None

Comments for Day 74-Letter

- None

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 *potential* filing issue or a *potential* 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 sites 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

	Parameter	Yes	No	Comment
7.	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		Two Novartis sites are responsible for the synthesis of the drug substance in Cork, Ireland and Stein, Switzerland
8.	Are drug product 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		Two Novartis sites are responsible for the manufacture of the drug product (b) (4) in Stein, Switzerland and Pratteln, Switzerland, respectively

	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: • 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).

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		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
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	

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 6002278_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	

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)	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		

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. There is only one site that is responsible for the manufacturing of the drug product (Novartis, Stein, Switzerland)
43.	Is there any in *vivo* BA or BE information in the submission?	x		Two studies (Study NVA237A2108 and Study P-AD237-004) were conducted to assess the absolute and relative bioavailability. These studies will be reviewed by OCP. \\CDSESUB1\evsprod\NDA207923\0000\m2\27-clin-sum

ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING				
	PARAMETER	**YES**	**NO**	**COMMENT**
44.	Is there a modified-release claim? If yes, address the following: a.) Is there information submitted to support the claim in accordance with 320.25(f)? b.) Is there information on the potential for alcohol-induced dose dumping?		x	NA

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?			

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}
Ge Bai, PhD
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

{See appended electronic signature page}
Sandra Suarez, PhD
Quality Assessment Lead (Biopharmaceutics)
Office of New Drug Products

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

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: 2015.02.03 08:02:21 -05'00'

Ge Bai -S

Digitally signed by Ge Bai -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ge Bai -S, 0.9.2342.19200300.100.1.1=2001255807
Date: 2015.02.03 10:00:06 -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=1300147809
Date: 2015.02.03 10:21:57 -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 10:31:18 -05'00'