CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211746Orig1s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality

New Drug Application (NDA) 211746 - Resubmission

Integrated Quality Assessment Template

TABLE OF CONTENTS

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 211746
Assessment #2

Drug Product Name	Olopatadine hydrochloride and mometasone furoate (MF)/nasal spray; proposed proprietary name: Ryaltris
Dosage Form	Nasal spray
Strength	665 mcg olopatadine HCl and 25 mcg mometasone furoate per actuation
Route of Administration	intranasal
Rx/OTC Dispensed	Rx
Applicant	Glenmark Specialty SA
US agent, if applicable	Glenmark Pharmaceuticals, Inc.

Submission(s) Assessed	Document Date	Discipline(s) Affected
Resubmission	13-JUL-2021	All
Amendment	05-AUG-2021	Manufacturing
Amendment	10-SEP-2021	Microbiology
Amendment	17-NOV-2021	Drug Product
Amendment	22-NOV-2021	Manufacturing/Drug Product
Amendment	07-DEC-2021	Drug Product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Friedrich Burnett	Donna Christner
Drug Product	Jizhou Wang	Julia Pinto
Manufacturing	Lane Christensen	Frank Wackes/Ying Zhang
Microbiology	Yan Zheng	Jesse Wells
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Craig M. Bertha	
Laboratory (OTR)	N/A	
Environmental	N/A	

APPEARS THIS WAY ON ORIGINAL

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II	(b) (4)		Inadequate	28-FEB-2019	Last reviewed by Xingding Hu
	II			Adequate	28-SEP-2018	Last reviewed by Friedrich. Burnett
	III					The NDA applicant has provided adequate leachables and extractables data. A completed review of this DMF is not necessary for approval.
	III					As above
	III					As above
	III			adequate	24-JUN-2013	Yanning Lin
	III			adequate	30-OCT-2013	Erika E. Englund
	III			adequate	05-FEB-2015	Craig M. Bertha
	III			adequate	28-OCT 2013 for (b) (4) testing 20-Jun-2019 (b) (4) extractables	Erika E. Englund Jizhou Wang

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	123164	Supporting IND for NDA 211746

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other				

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

N/A – The application is recommended for approval.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The olopatadine hydrochloride/mometasone furoate (MF) nasal spray is indicated for treatment of seasonal allergic rhinitis in patients 12 years and older. The quality standards and approaches outlined in the final Agency CMC guidance for nasal sprays are appropriate for this product. Both drugs are already approved as single entity nasal spray drug products for SAR, so this dosage form is merely for convenience and perhaps to improve compliance for patients that are using both products. Thus, the overall benefit is likely limited, such that allowance of undue risk to quality is not warranted.

The nasal spray was developed under IND 123164 and uses common device components from well-known manufacturers, and the formulation is a suspension due to the fact that MF is practically insoluble in aqueous solution (olopatadine is formulated as a hydrochloride salt, which is in solution).

Proposed Indication(s) including Intended Patient Population	Seasonal allergic rhinitis (SAR) in patients 12 years of age and older
Duration of Treatment	Seasonally
Maximum Daily Dose	5.32 mg olopatadine HCl and 200 mcg MF

Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

This NDA 211746 was originally submitted on 28-MAY-2018. A Complete Response Letter (CRL) by the Agency was issued for this NDA on 21-JUN-2019 and a request for a Type A Meeting regarding the Sponsor's proposed response to the CRL was granted by the Agency and the Preliminary FDA Comments were received on 09-SEP-2019. An Extension Request was requested on 28-APR-2020 and granted by the Agency for a 1- year with a due date of 20-JUN-2021. Due to the COVID-19 pandemic a Second Extension Request was requested on 26-MAY-2021 and granted by the Agency for 6- months with a due date of 20-DEC-2021.

Glenmark has addressed the CRL in the resubmission cover letter and via the updated Reviewer's Guide, which includes an outline of the NDA Sections that have been updated in response to the CRL as well as a summary of the pertinent regulatory correspondences (i.e., the Type A Meeting Responses from the Agency, 09-SEP-2019).

The CRL did not have any drug substance CMC comments since the NDA was recommended for approval from the drug substance perspective on 27-FEB-2019; F. Burnett, OPQ Review Platform.

The resubmission includes the unchanged drug substance specification (differences between the Drug Product manufacturer's Specification and the Drug substance manufacturer have been indicated below for each drug substance) and satisfactory test results on three validation batches.

The available stability data for three olopatadine hydrochloride registration stability batches manufactured at (b) (4) support the **proposed** (b) (4) **retest period** when the bulk drug substance is stored at (b) (4) °C/ (b) (4) % RH.

The available stability data for three mometasone furoate monohydrate registration stability batches manufactured at (b) (4) support the proposed (b) (4) retest period when the bulk drug substance is stored at (b) (4) °C.

The drug substance CMC remains adequate, and the NDA remains recommended for approval from the drug substance perspective.

Drug Product: Adequate

The drug product GSP 301 NS is a (b) (4) suspension containing 665 µg of olopatadine hydrochloride and mometasone furoate monohydrate equivalent to 25 µg per actuation, (b) (4) and is packaged in a HDPE bottle which is crimped with a metering pump manufactured by (b) (4), with a nasal spray actuator and a cap.

In this resubmission, the sponsor has adequately provided the validation data for the routine HDPE bottle extractables method and a description of the development of extractables acceptance criteria for the HDPE bottle.

In addition, the sponsor has provided additional leachables study data to demonstrate the risk of leachable (b) (4) in the drug product is minimal. (b) (4)

(b) (4)

The sponsor has updated the stability studies by providing 24/36 month long term stability data for three (3) registration batches of the 240 MD presentation and three (3) registration batches of 56 MD presentation manufactured in Glenmark facility in this resubmission. All the data are well within the specification and support a shelf life of 24 months for the drug product. Note that the Glenmark drug product manufacturing facility has been withdrawn from the application and is replaced by (b) (4).

In addition, two (2) registration batches of 56 MD presentation and three (3) registration batches of 240 MD presentation manufactured in (b) (4) a proposed new facility comparable to Glenmark facility, have been introduced into the stability study program. The available 3 months/6 long term (25ºC/60%RH) and accelerated stability (40ºC/75%RH) data from the batches manufactured (b) (4) fall into the specification after multiple additional testing or correction of OOS results. The regression analysis supports a **shelf life of 24 month for the drug product** manufactured (b) (4).

While the performance related key attributes of spray content uniformity (SCU) and pump delivery (PD) are well within the specification for the

Glenmark batches throughout 24/36 months, these attributes barely fall into the second tier specification for [redacted] batches after additional testing or extra care for sample handing during 3 to 6 month long term and accelerated stability studies. The sponsor has performed OOS investigations for abnormal SCU and PD OOS and attributed inappropriate sample handing methods and defective [redacted] pumps to be the root causes. These batches will not cause any risks for patient since *the sponsor has committed that the two (2) 56 registration batches and three (3) 240 registration batches manufactured* [redacted] *will not be released for patient use* (*see TSR/SOMFN-01/21/038-00: OOS investigation for batch 201141 and TSR/SOMFN-01/21/042-00: OOS investigation for batch 201139)*. In addition, the Sponsor has committed to perform a full stability program for these 56 MD and 240 MD presentation and to inform the Agency immediately in case of out-of-specification results. The manufacturing reviewer has flagged the [redacted] drug product manufacturing site for a post approval inspection for further quality assurance.

Considering the demonstrated minimal leachables risk for the container closure system, that there were no trending stability data for 12 Glenmark batches, and the committed full time stability studies for the batches from new manufacture site, we recommend the approval of this NDA from CMC perspective.

Labeling: Inadequate

From the first review cycle (see IQA dated 21-MAY-2019), minor revisions are recommended for the package insert and container and carton labels.

Manufacturing: Adequate

The drug product, olopatadine hydrochloride, USP and mometasone furoate nasal spray, is manufactured [redacted]. The drug product is packaged in two presentations: a 240-spray presentation, which is the commercial product, and a 56-spray presentation, which is the professional sample. The drug product manufacturer and packager in the original submission, Glenmark Pharmaceuticals Limited (FEI 3005757050) was out of compliance and recommended for a withhold. Due to restrictions on travel due to the pandemic, the NDA holder decided to withdraw the original manufacturing site where the current submission proposes a new manufacturer and packager, [redacted]. Information provided within the resubmission confirms the manufacturing processes are similar and equipment used is of the same design and have the same operating principles as used in the original submission batches. Both the facility and process assessment recommendations are that the application is Adequate.

Biopharmaceutics: N/A

Microbiology (if applicable): Adequate

The applicant has provided sufficient information to assure that the drug product will not be contaminated with *Burkholderia cepacia* and the specification includes testing and appropriate acceptance criteria as per USP <60> *Microbiological Examination of Nonsterile Products Tests for* Burkholderia Cepacia *Complex* in addition to standard microbial limits testing as per USP <61> and <62>, (b) (4) (b) (4) content.

C. Risk Assessment

DP attribute/ CQA	Factors that may impact the CQA	O[1]	S[1, 2]	D[1]	Initial RA FMECA RPN #	Comment & considerations for risk assessment	Final RA	Lifecycle considerations
Description	• Suspension (b) (4)	1	3	1	3	(b) (4)	3	
pH	• (b) (4) capacity of formulation • formulation component degradation	2	3	2	12		12	
Related Substances	• purity of both APIs • degradation of APIs as formulated • compatibility of APIs with formulation and device components	2	3	2	12		12	
Assay	• degradation of APIs as formulated • purity of both APIs • incorrect amounts of APIs formulated • uniformity of MF in suspension during manufacturing	2	3	1	6		6	

[1] O = Probability of Occurrence; S = Severity of Effect; D = Detectability
[2] Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs (thus a median value of "3" will be used throughout)

	• compatibility of APIs with formulation and device components					(b) (4)	
(b) (4)		2	3	1	6		6
Spray Content Uniformity (SCU)	(b) (4) • pump delivery variability or defect • initial viscosity variable or changes over time • lower than target fill and/or leakage leading to end-of-unit SCU failures	2	3	3	18		18
Droplet Size Distribution (DSD)	• viscosity of MCC/CMC Na and CMC Na • actuator variability • pump defect (b) (4)	2	3	2	12		12
Viscosity	• viscosity of MCC/CMC Na and CMC Na • initial viscosity variable or changes over time (b) (4)	2	3	2	12		12

						(b) (4)		
Spray Pattern	• actuator dimensional variability • actuator clogging (b) (4)	1	3	2	6		6	(b) (4)
Particle size distribution (PSD)	• particle size of MF • solubility of MF in formulation • viscosity of MCC/CMC Na and CMC Na • initial viscosity variable or changes over time	2	3	2	12		12	
Microbial enumeration test	(b) (4)	2	3	2	12		12	
(b) (4)		2	3	1	6		6	
Osmolality	• incorrect formulation	1	3	2	6		6	
Leachables	• compounds leached from pump and bottle	2	3	4	24		12	(b) (4)


(b) (4)

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

N/A

2. Drug Substance Deficiencies

N/A

3. Drug Product Deficiencies

N/A

4. Labeling Deficiencies

There are minor labeling deficiencies that will be addressed at future OND led labeling meetings:

- Section 3 of the package insert (PI) should be revised to provide a more detailed description of the dosage form.
- The labels for the container and the carton labels should be revised to indicate the placement of the expiration date, the lot number, and the bar code.

5. Manufacturing Deficiencies

N/A

6. Biopharmaceutics Deficiencies

N/A

7. Microbiology Deficiencies

N/A

8. Other Deficiencies *(Specify discipline, such as Environmental)*

N/A

Application Technical Lead Name and Date:

Craig M. Bertha, Chemistry Reviewer, 16-DEC-2021

CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	211746
Assessment Cycle Number	02
Drug Product Name/ Strength	GSP301 nasal spray (olopatadine hydrochloride and mometasone furoate)
Route of Administration	Nasal Spray
Applicant Name	Glenmark Specialty SA
Therapeutic Classification/ OND Division	OND/OII/DPACC
Manufacturing Site	(b) (4)
Method of Sterilization	N/A for non-sterile

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
Resubmission	07/13/2021
IR response	09/10/2021

List Submissions being assessed (table):

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: NDA 211746 was originally submitted on 05/21/2018. It was reviewed and found adequate in N211746MR01 on 03/06/2019. A Complete Response Letter was issued on 06/21/2019 due to inadequacy from other disciplines. The current resubmission is provided on 07/13/2021 with response to the CRL. The applicant also proposes a new DP manufacturing site, (b) (4) The previously reviewed manufacturing site is withdrawn due to the delays in scheduling a facility re-inspection. Submission dated 09/10/2021 is provided in response to the Agency's information request dated 08/31/2021.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): N/A

Supporting Documents: N/A

S DRUG SUBSTANCE

The manufacturing process for the drug substance is not reviewed because the drug substance is non-sterile.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of the drug product—no change. The product is a (b) (4) aqueous suspension packaged in a 20mL or 30mL HDPE bottle. This is a multiple dose product with two presentations: a 240-spray commercial presentation (9 (b) (4) g fill/20mL) and a 56-spray professional presentation (29 (b) (4) g fill/30mL).

DP composition—no change.

DP Container closure system—no change for both presentations.

Assessment: Adequate

(b) (4)

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

R REGIONAL INFORMATION

Executed Batch Records
Batch records for (b) (4) registration batches of 56 MD (201141) and 240 MD (201139) are provided.

Assessment: Adequate

MICROBIOLOGY LIST OF DEFICIENCIES

N/A

Primary Microbiology Assessor Name and Date: Yan Zheng, Ph.D. , 09/17/2021

Secondary Assessor Name and Date (and Secondary Summary, as needed): Jesse Wells, Ph.D. 09/17/2021

Yan Zheng

Digitally signed by Yan Zheng
Date: 9/20/2021 11:38:08AM
GUID: 58ca9ce301e697996a209b08cf0d70b6

Jesse Wells

Digitally signed by Jesse Wells
Date: 9/20/2021 11:43:46AM
GUID: 508da70b00028ea901ac6652677f7d00

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/s/

CRAIG M BERTHA
12/16/2021 01:01:03 PM

Recommendation: Complete Response

NDA 211746
Review #1

Drug Name/Dosage Form	olopatadine hydrochloride and mometasone furoate/nasal spray
Strength	665 mcg olopatadine HCl and 25 mcg mometasone furoate per actuation
Route of Administration	intranasal
R_x/OTC Dispensed	R_x
Applicant	Glenmark Specialty SA
US agent, if applicable	Glenmark Pharmaceuticals, Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	*21-MAY-2018*	*all*
Amendment	*31-OCT-2018*	*Drug product*
Amendment	*03-DEC-2018*	*Process/facilities*
Amendment	*22-JAN-2019*	*Drug product*
Amendment (labeling)	*25-JAN-2019*	*Drug product*
Amendment	*01-FEB-2019*	*Drug product*
Amendment	*11-FEB-2019*	*Microbiology*
Amendment	*15-FEB-2019*	*Drug product*
Amendment	*03-APR-2019*	*Drug product*
Amendment	*25-APR-2019*	*Drug product*
Amendment	*10-MAY-2019*	*Drug product*
Amendment (labeling)	*14-MAY-2019*	*Drug product*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Friedrich Burnett	Donna Christner
Drug Product	Jizhou Wang	Craig M. Bertha
Process	Ying Zhang	Christina Capacci-Daniel
Microbiology	Yan Zheng	Elizabeth Bearr
Facility	Ying Zhang	

Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Florence Aisida Anika Lalmansingh	
Application Technical Lead	Craig M. Bertha	
Laboratory (OTR)	N/A	
ORA Lead	Zhihao Peter Qiu	
Environmental	N/A	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II		(b) (4)	**Inadequate**	28-FEB-2019	Last reviewed by Xingding Hu
	II			**Adequate**	28-SEP-2018	Last reviewed by Friedrich. Burnett
	III					The NDA applicant has provided adequate leachables and extractables data. A completed review of this DMF is not necessary for approval.
	III					As above
	III					As above
	III			**adequate**	24-JUN-2013	Yanning Lin
	III			**adequate**	30-OCT-2013	Erika E. Englund
	III			**adequate**	05-FEB-2015	Craig M. Bertha
	III			**adequate**	28-OCT 2013 for (b) (4) testing 20-Jun-2019 for (b) (4) extractables	Erika E. Englund Jizhou Wang

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	123164	supporting IND for development of N211746 drug product

2. CONSULTS

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

Executive Summary

I. Recommendations and Conclusion on Approvability

The OPQ/CMC recommendation is **complete response (CR)**. There is a facility assessment recommendation of cGMP Withhold from the Office of Regulatory Affairs. In addition, the type II drug master file [redacted] (b) (4) for the olopatadine drug substance is currently inadequate and the holder has been notified of the deficiencies. Two additional comments are reminders to the applicant of pending information, data, and reports regarding some aspects of the control strategy for extractables/leachables from the container closure system.

The following comments are to be included in the CR letter from OPQ/CMC:

- **During recent inspections of the Glenmark Pharmaceuticals Ltd (FEI 3005757050) manufacturing facility and [redacted] (b) (4) testing facility for this NDA, our field investigator observed objectionable conditions at the facilities and conveyed that information to the representatives of the facilities at the close of the inspections. Satisfactory resolution of the observations is required before this NDA may be approved.**

- **Supporting drug master file [redacted] (b) (4) has been reviewed and is currently inadequate. Deficiency comments have been forwarded to the holder of this file.**

- **Provide the stability results for the 30 month (25°C/60% RH) time-point for your registration batches to assure that all acceptance criteria are met all potential leachables, [redacted] (b) (4), are absent or below levels of safety concern. Provide an updated extractable and leachable correlation, if applicable.**

- **Provide the validation data for the routine HDPE bottle extractables method and a description of the development of extractables acceptance criteria for the HDPE bottle.**

II. Summary of Quality Assessments

A. Product Overview

The olopatadine hydrochloride/mometasone furoate (MF) nasal spray is indicated for treatment of seasonal allergic rhinitis in patients 12 years and older. The quality standards and approaches outlined in the final Agency CMC guidance for

nasal sprays are appropriate for this product.[1] Both drugs are already approved as single entity nasal spray drug products for SAR, so this dosage form is merely for convenience and perhaps to improve compliance for patients that are using both products. Thus, the overall benefit is likely limited, such that allowance of undue risk to quality is not warranted.

The nasal spray was developed under IND 123164 and uses common device components from well-known manufacturers, and the formulation is a suspension.

Proposed Indication(s) including Intended Patient Population	***seasonal allergic rhinitis***
Duration of Treatment	***Seasonally***
Maximum Daily Dose	***5.32 mg olopatadine HCl & 200 mcg MF***
Alternative Methods of Administration	***N/A***

B. Quality Assessment Overview

Both olopatadine and mometasone furoate (MF) are APIs previously approved for the nasal inhalation route of administration and for the same indication sought by this application. Olopatadine is formulated as its hydrochloride salt and is in solution. However, MF is a lipophilic molecule and is in suspension in the aqueous-based nasal spray formulation. As a result, the applicant has specific requirements for the particle size of MF prior to formulation, due to the potential that variability in this parameter could impact local bioavailability. Most of the other supportive information for both APIs is provided by reference to the respective suppliers type II drug master files (DMF) (b) (4) (olopatadine hydrochloride) and (b) (4) (MF). Both DMFs were initially reviewed and found to be adequate to support this NDA. However, subsequently and recently, DMF (b) (4) for olopatadine was reviewed in support of four abbreviated NDAs and deemed **inadequate**. Thus, the initial approval recommendation from the API review team is reversed (**not approvable**) due to this change in DMF (b) (4) status. An associated deficiency comment will be included in the CR letter (see above).

The drug product GSP 301 NS is a (b) (4) suspension containing 665µg of olopatadine hydrochloride and mometasone furoate monohydrate equivalent to 25µg per actuation, and is packaged in a HDPE bottle with crimp attached nasal spray metering pump with actuator/nosepiece and a protective cap. The trade presentation of the nasal spray product includes 240 actuations; however, the applicant will also have a 56 actuation physician sample. The applicant's proposed expiry periods of (b) (4) months for the 56 actuation professional sample and 24 months for the 240 actuation trade presentation are acceptable (storage at 25°C (77°F).

[1] See *Guidance for Industry, Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation* (July 2002).

Several issues were noted during the drug product evaluation that required additional follow-up information and mitigating action from the applicant, some of which are still unresolved. The most concerning issue was the potential contamination of the drug product formulation with (b) (4) leachables from the nasal spray pump (b) (4) (b) (4). Note that this assessment has been made by the pharmacology/toxicology team. Since all batches (b) (4) released are analyzed (b) (4), this assures all drug product will have sufficiently low levels (b) (4) However, this applicant had erroneously identified several of the peaks in the chromatograms from their leachables test samples from the registration stability batches. (b) (4). This issue was of particular concern as the (b) (4) nasal spray pump used for the applicant's drug product is common and is currently in use in multiple other approved nasal spray drug products. However, with further examination, the applicant has now provided sufficient data demonstrating that these peaks were not actually due to (b) (4). Note that due to multiple information requests and amendments, this issue was resolved, but one major amendment resulted in a 3 month PDUFA clock extension.

There were also some noted complaints of actuator orifice blockage in the nasal spray supplies used in supportive clinical studies, however the sponsor has addressed this with an improved actuator cap which provides a better seal for the actuator orifice between doses. In addition, various test acceptance criteria have been tightened to more closely reflect the historical data and system suitability requirements for test methods have been enhanced to assure methods continue to meet validation requirements. One remaining issue that we would like the applicant to address in the response to the CR action, is the provision of the validation data for the routine extractables method applied to the incoming HDPE bottles. This is not considered an approvability issue and could have been accepted post-approval if an approval action were to have been taken in this review cycle.

The application has provided sufficient description of the manufacturing process and included drug product batch results that support the process parameter operating ranges for commercial scale production. However, facilities deficiencies for this application have been classified as MAJOR because one or more facilities were found inadequate due to inspectional deficiencies. Once these deficiencies are said to be resolved, the Agency must reevaluate these during the next review cycle. It is expected that this assessment, upon receipt of an amendment responding to this deficiency, will require substantial expenditure of Agency resources. It is also noted that in terms of the device components of this nasal spray drug product, CDRH has determined that they do not need to conduct a compliance investigation for this application.

C. Special Product Quality Labeling Recommendations (NDA only)

D. Final Risk Assessment (see Attachment)

(b) (4)

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

Labeling & Package Insert

1. Package Insert

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

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: RYALTRIS Established Name:	Acceptable
Dosage form, route of administration	(b) (4) Route: nasal spray	Acceptable
Controlled drug substance symbol (if applicable)	N/A	Acceptable
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	(b) (4)	Acceptable

Conclusion: : Acceptable with the required data elements as summarized above

(b) "Full Prescribing Information" Section

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

(b) (4)

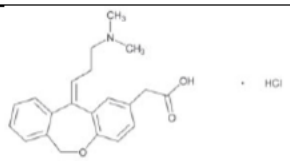
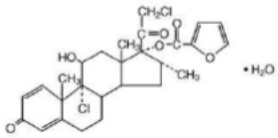
Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Nasal spray	Acceptable
Strengths: in metric system	(b) (4)	Acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.		Not acceptable

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

APPEARS THIS WAY IN ORIGINAL

QUALITY ASSESSMENT
NDA # 211746

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	RYALTRIS	Acceptable
Dosage form and route of administration	nasal spray	Acceptable
Active moiety expression of strength with equivalence statement for salt (if applicable)	containing an isotonic aqueous suspension of olopatadine hydrochloride (equivalent to 0.6% w/v olopatadine base) and mometasone furoate monohydrate (equivalent to 0.025% w/w mometasone furoate on the anhydrous basis	Acceptable
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	benzalkonium chloride, carboxymethyl cellulose sodium, dibasic sodium phosphate heptahydrate, edetate disodium, hydrochloric acid, microcrystalline cellulose, polysorbate 80, sodium chloride, sodium hydroxide, and water	Acceptable
Statement of being sterile (if applicable)	N/A	Acceptable
(b) (4)		Acceptable

Chemical name, structural formula, molecular weight	 2-[(11Z)-11-[3-(dimethylamino)-propylidene]-6H-benzo[c][1]-benzoxepin-2-yl]acetic acid hydrochloride Molecular formula: C21H23NO3•HCl Molecular weight: 373.88  [(8S,9R,10S,11S,13S,14S,16R,17R)-9-chloro-17-(2-chloroacetyl)-11-hydroxy-10,13,16-trimethyl-3-oxo-6,7,8,11,12,14,15,16-octahydro-cyclopenta[a]phenanthren-17-yl] furan-2-carboxylate;hydrate Empirical formula: C27H30Cl2O6•H2O Molecular weight: 539.45.	Acceptable
If radioactive, statement of important nuclear characteristics.	N/A	Acceptable
Other important chemical or physical properties (such as pKa, solubility, or pH)	(b) (4)	Acceptable

Conclusion: Acceptable with the required data elements as summarized above

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

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form		
Available units (e.g., bottles of 100 tablets)	Each bottle contains a net fill weight of 29 g and will deliver 240 metered sprays after priming *for 240 MD.*	Not acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	metered—dose spray	Acceptable
Special handling (e.g., protect from light, do not freeze)	N/A	Acceptable
Storage conditions	Store RYALTRIS upright with the dust cap on at room temperature (see USP Controlled Room Temperature, between (b) (4) °C and 25°C, or between (b) (4) °F and 77°F, with excursions permitted between 15°C to 30°C or between 59°F to 86°F). Do not store in a freezer or refrigerator.	Acceptable

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)	Not provided	Not acceptable

2. Labels

1) Immediate Container Label

56 MD:

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))	RYALTRIS	
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	665 mcg/25 mcg* per spray	
Net contents (21 CFR 201.51(a))	Yes	
Lot number per 21 CFR 201.18	240 MD or 56 MD	
Expiration date per 21 CFR 201.17	**Not provided**	
"Rx only" statement per 21 CFR 201.100(b)(1)	Yes	
Storage (not required)	Yes	
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Yes	
Bar Code per 21 CFR 201.25(c)(2)**	**Not provided**	
Name of manufacturer/distributor	Yes	
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

2) Cartons

56 MD

QUALITY ASSESSMENT
NDA # 211746

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))	RYALTRIS	
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	665 mcg/25 mcg* per spray	
Net contents (21 CFR 201.51(a))	Yes	
Lot number per 21 CFR 201.18	No	
Expiration date per 21 CFR 201.17	No	
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	Yes	
Sterility Information (if applicable)	N/A	
"Rx only" statement per 21 CFR 201.100(b)(1)	Yes	
Storage Conditions	Yes	
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Yes	
Bar Code per 21 CFR 201.25(c)(2)**	No	
Name of manufacturer/distributor	Yes	
"See package insert for dosage information" (21 CFR 201.55)	Yes	
"Keep out of reach of children" (optional for Rx, required for OTC)	Yes	
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	Yes	

Overall Conclusion/summary for labeling: there are some deficiencies but considering that the application is not recommended by the OPQ/CMC team for approval, these can be addressed during the next review cycle.

Comments on Drug product:

1. Provide the leachables results for the 30 months (25°C/60% RH) time point to demonstrate that the levels of all the extractables [redacted] (b) (4) meet the acceptance criteria. In addition, demonstrate the absence of the peak at ~ [redacted] (b) (4) minutes originally appeared in leachables Study 9957D. Provide updated extractable and leachable correlation if applicable.
2. Provide the validation of the routine extractables method and development of extractables acceptance criteria for the HDPE bottle as committed.

II. Administrative

A. Reviewer's Signature

B. Endorsement Block

Reviewer Name/Date: [*Same date as draft review*]
Secondary Reviewer Name/Date:
Project Manager Name/Date:

Jizhou Wang

Digitally signed by Jizhou Wang
Date: 5/20/2019 03:57:24PM
GUID: 53160853000083c4052c25f3a3cf964a

Craig Bertha

Digitally signed by Craig Bertha
Date: 5/21/2019 05:18:55AM
GUID: 50841a65000098a9383c817879a6a84d

MICROBIOLOGY

IQA Review Guide Reference

Product Background:

NDA: 211746

Drug Product Name / Strength: GSP301 nasal spray (Olopatadine hydrochloride, USP and mometasone furoate). 665 mcg/25mcg

Route of Administration: Nasal spray

Applicant Name: Glenmark Specialty SA

Manufacturing Site: Glenmark Pharmaceuticals Limited
Village Kishanpura Baddi Nalagarh Rd., Baddi, Solan, Himachal Pradesh 173205, India

Method of Sterilization: N/A for non-sterile

Review Recommendation: **Adequate**

Theme (ANDA only): Choose an item.

Justification (ANDA only): Choose an item.

Review Summary: The submission is **recommended** for approval on the basis of sterility assurance.

List Submissions Being Reviewed: 05/21/2018; 01/22/2019; 02/11/2019

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: This is eCTD submission. Submission dated 01/22/2019 is provided in response to the Agency's information request dated 01/14/2019. Submission dated 02/11/2019 is provided in response to the Agency's information request dated 01/28/2019.

Concise Description Outstanding Issues Remaining: N/A

Supporting Documents: N/A

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance

No review was conducted on the drug substance as the drug substance is non-sterile.

P.1 Description of the Composition of the Drug Product

- **Description of drug product –**The product is a (b) (4) aqueous suspension packaged in a 20mL or 30mL HDPE bottle. The bottle is crimped with a metering pump, a nasal spray actuator and a cap. This is a multiple dose product with two presentations: a 240-spray commercial presentation (9 (b) (4) g fill/20mL) and a 56-spray professional presentation (29 (b) (4) g fill/30mL).
- **Drug product composition –**

Component	Quality Standard	Amount per Batch
Active Ingredient		
Olopatadine hydrochloride	USP	(b) (4)
Mometasone furoate monohydrate (equivalent to mometasone furoate)	In-house	
Inactive Ingredients		
Microcrystalline cellulose / (b) (4)	USP-NF	
Carboxymethylcellulose sodium (b) (4)	USP-NF	
Sodium chloride	USP	
Edetate disodium	USP	
Dibasic sodium phosphate heptahydrate	USP	
Polysorbate 80	USP-NF	
Benzalkonium chloride solution (b) (4)	USP-NF	
Hydrochloric acid	USP-NF	
Sodium hydroxide	USP-NF	
Water for Injection	USP	
Total batch size	--	

(Table reproduced from the submission, 3.2.P.3.2)

- **Description of container closure system –**

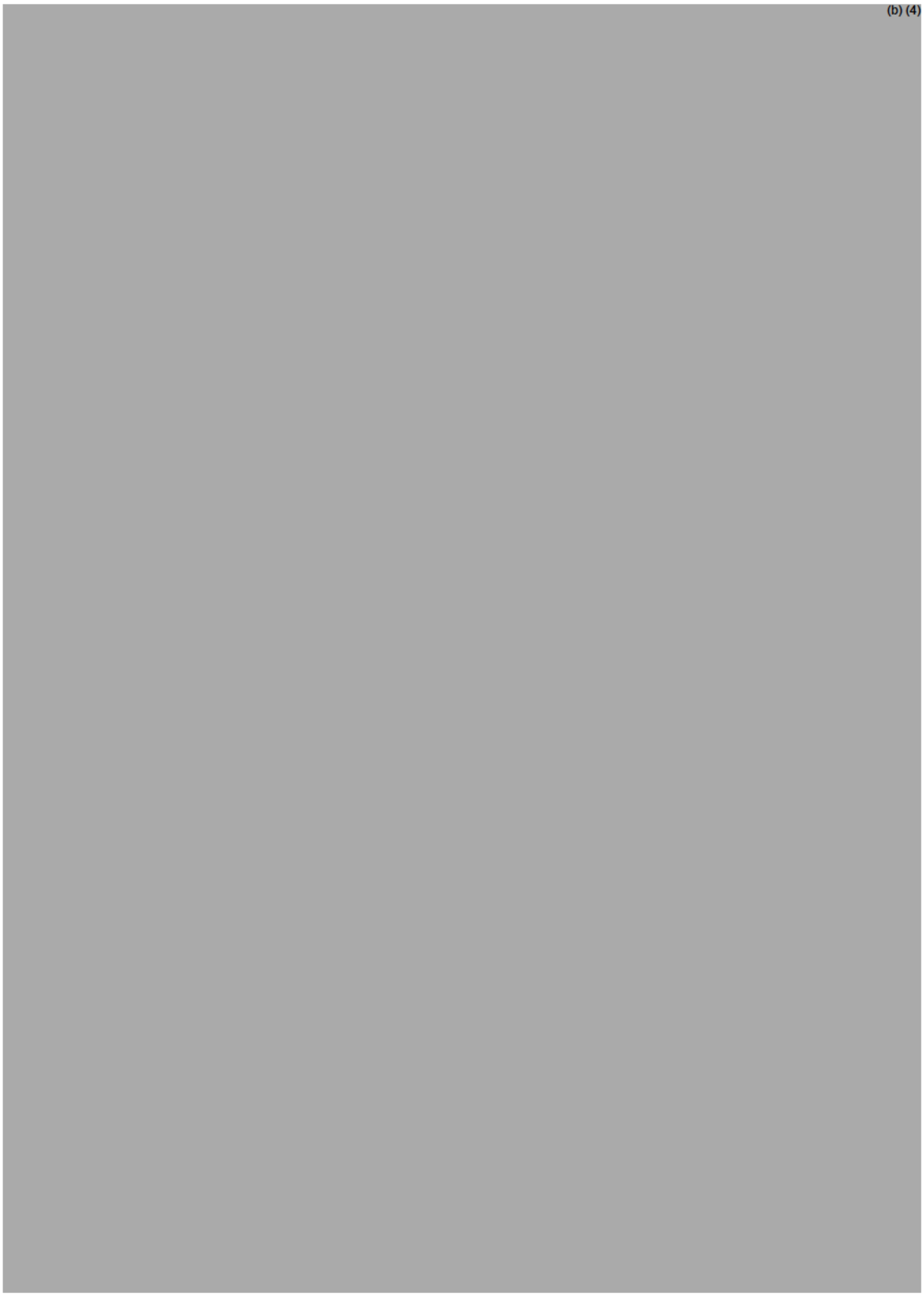
	56-spray	240-spray	Supplier
Bottle	20mL/20mm white opaque, round HDPE bottle	30mL/20mm white opaque, round HDPE bottle	(b) (4)
Pump	Pump (b) (4) pump	(b) (4)	
Actuator	Actuator (b) (4)		
Cap	(b) (4) cap		

Reviewer's Assessment: Adequate

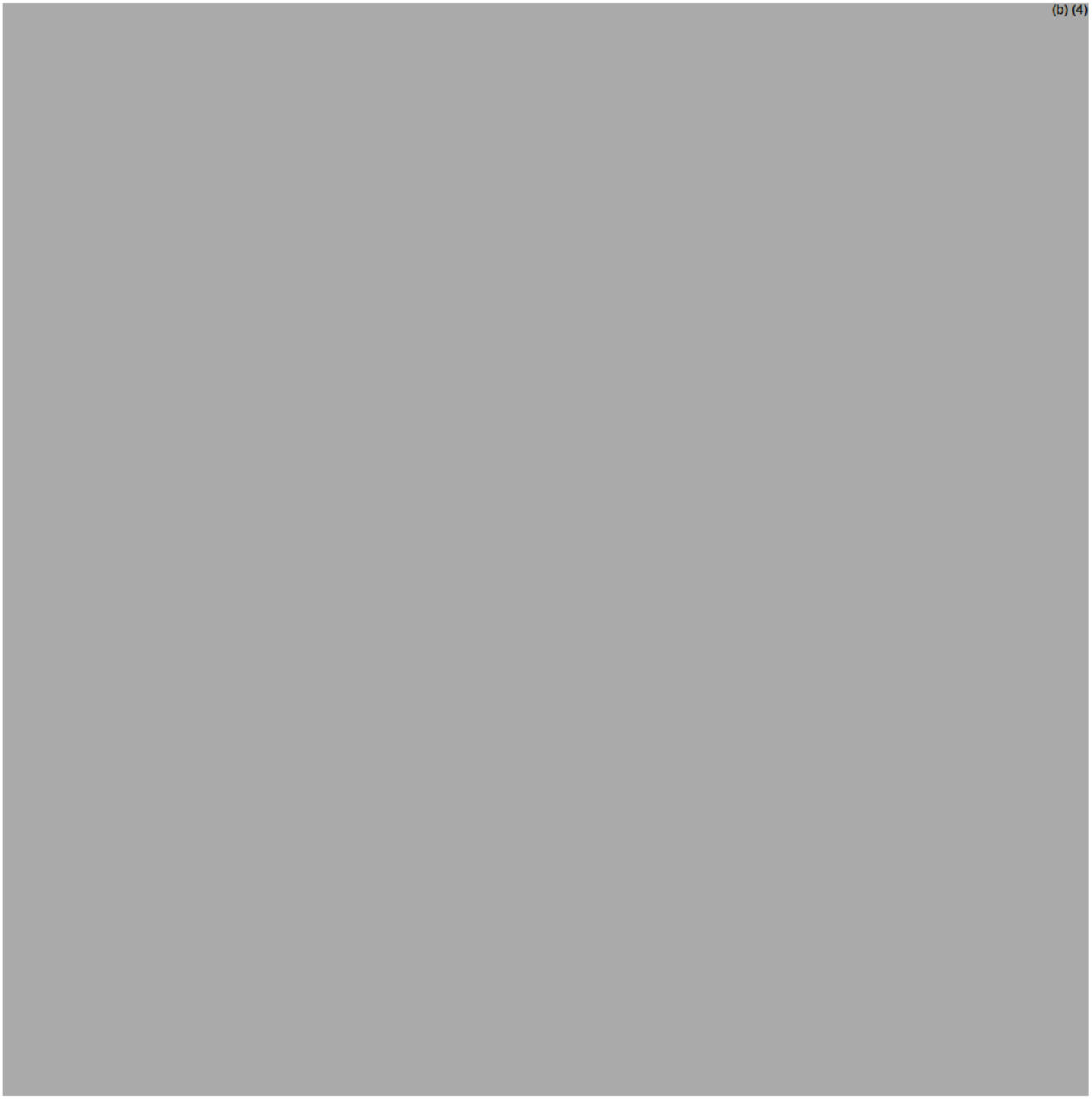
The product description is acceptable.

P.2 Pharmaceutical Development

(b) (4)



(b) (4)



Primary Microbiology Reviewer Name and Date:

Yan Zheng, Ph.D. 03/06/2019

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

Elizabeth Bearr, Ph.D. 03/06/2019

Yan Zheng

Digitally signed by Yan Zheng
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Elizabeth Bearr

Digitally signed by Elizabeth Bearr
Date: 3/06/2019 11:09:00AM
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OPQ/CMC Review - NDA 211746

Final Risk Assessment for Drug Product CQAs

DP attribute/ CQA	Factors that may impact the CQA	O[1]	S[1, 2]	D[1]	Initial RA FMECA RPN #	Comment & considerations for risk assessment	Final RA	Lifecycle considerations
Description	• Suspension (b) (4) (b) (4)	1	3	1	3	(b) (4)	3	
pH	• (b) (4) capacity of formulation • formulation component degradation	2	3	2	12		12	
Related Substances	• purity of both APIs • degradation of APIs as formulated • compatibility of APIs with formulation and device components	2	3	2	12		12	
Assay	• degradation of APIs as formulated • purity of both APIs • incorrect amounts of APIs formulated • uniformity of MF in suspension during manufacturing • compatibility of APIs with formulation and device components	2	3	1	6		6	

[1] O = Probability of Occurrence; S = Severity of Effect; D = Detectability
[2] Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs (thus a median value of "3" will be used throughout)

OPQ/CMC Review - NDA 211746

Final Risk Assessment for Drug Product CQAs

(b) (4)		2	3	1	6	(b) (4)	6	
Spray Content Uniformity (SCU)	(b) (4) • pump delivery variability or defect • initial viscosity variable or changes over time • lower than target fill and/or leakage leading to end-of-unit SCU failures	2	3	3	18		18	
Droplet Size Distribution (DSD)	• viscosity of MCC/CMC Na and CMC Na • actuator variability • pump defect (b) (4)	2	3	2	12		12	
Viscosity	• viscosity of MCC/CMC Na and CMC Na • initial viscosity variable or changes over time (b) (4)	2	3	2	12		12	

OPQ/CMC Review - NDA 211746

Final Risk Assessment for Drug Product CQAs

Spray Pattern	• actuator dimensional variability • actuator clogging (b) (4)	1	3	2	6	(b) (4)	6	(b) (4)
Particle size distribution (PSD)	• particle size of MF • solubility of MF in formulation • viscosity of MCC/CMC Na and CMC Na • initial viscosity variable or changes over time	2	3	2	12		12	
Microbial enumeration test	(b) (4)	2	3	2	12		12	
(b) (4)		2	3	1	6		6	
Osmolality	• incorrect formulation	1	3	2	6		6	
Leachables	• compounds leached from pump and bottle	2	3	4	24		12	(b) (4)

OFFICE OF PHARMACEUTICAL QUALITY

IQA – Signature Page

Craig M. Bertha, ATL (DNDPII, CMC Lead for DPARP)

Craig Bertha

Digitally signed by Craig Bertha
Date: 5/21/2019 07:48:05AM
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