CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214919Orig1s000

PRODUCT QUALITY REVIEW(S)

Table of Contents

RECOMMENDATION

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

NDA 214919
Assessment 1

Drug Product Name	Glycopyrrolate Injection
Dosage Form	Solution for injection
Strength	0.6mg/3mL (0.2 mg/mL)
Route of Administration	Intraventous or intramuscular
Rx/OTC Dispensed	Rx
Applicant	Fresenius Kabi USA, LLC
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 4; eCTD 0004	21 Jun 21	All, original resubmission after refuse-to-file
Supporting document 6; eCTD 0006	8 Oct 21	Microbiology, drug substance, process, biopharmaceutics
Supporting document 8; eCTD 0008	30 Dec 21	Drug product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Fred Burnett	Donna Christner
Drug Product	Eric Bow	Julia Pinto
Manufacturing	Erika Pfeiler	Bethanie Lee
Microbiology	Erika Pfeiler	Bethanie Lee
Biopharmaceutics	Assad Noory	Hansong Chen
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	Eric Bow	Julia Pinto

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	1	11 Feb 21	Reviewed by Wei Song
(b) (4)	III	(b) (4)	(b) (4)	4		
029178	V	Fresenius Kabi USA, LLC	sterility assurance and process validation	1	13 Dec 21	Reviewed by Hemlata Tamta
(b) (4)	III	(b) (4)	(b) (4)	4		
(b) (4)	V	(b) (4)	(b) (4)	1	13 Jan 22	Reviewed by Kellyann Miller
(b) (4)	III	(b) (4)	(b) (4)	1	22 Jul 21	Reviewed by Aditi Das

Action codes for DMF Table:
1 – DMF Reviewed.
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

Document	Application Number	Description
NDA	017558	LD – Robinul

2. CONSULTS

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

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The CMC recommendation for this application is approval based on drug substance, drug product, process/facilities, biopharmaceutics and microbiology reviews. Drug product will have a PMC.

The proposed expiry of 24 months is acceptable when stored at 20°–25°C (68°–77° F).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Glycopyrrolate Injection USP, 0.6mg/3mL is a sterile, ready-to-use solution in a prefilled syringe and is used either for IV or IM injection. The syringe system is comprised of a transparent (b) (4) glass barrel assembled with a plastic luer lock (b) (4), a (b) (4) (b) (4) tip cap, (b) (4), and a plastic plunger rod.

The proposed expiry of 24 months is acceptable when stored at 20°–25°C (68°–77° F).

This NDA was originally submitted 30 Dec 20 and a refuse-to-file letter dated 25 Feb 21 was sent. This review is of the resubmission received 21 Jun 21.

Proposed Indication(s) including Intended Patient Population	Anesthesia - indicated for use as a preoperative antimuscarinic to reduce salivary, tracheobronchial and pharyngeal secretions; to reduce the volume and free acidity of gastric secretion; and to block cardiac vagal inhibitory reflexes during induction of

	anesthesia and intubation. May be used intraoperatively to counteract surgically or drug-induced or vagal reflexes associated arrhythmias. Glycopyrrolate protects against the peripheral muscarinic effects (e.g., bradycardia and excessive secretions of cholinergic agents such as neostigmine and pyridostigmine given to reverse the neuromuscular blockade to due non-depolarizing muscle relaxants. Peptic Ulcer - adjunctive therapy for the treatment of peptic ulcer when rapid anticholinergic effect is desired or when oral medication is not tolerated
Duration of Treatment	acute
Maximum Daily Dose	(b) (4)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The impurities (process and degradants) have been adequately described with respect to the origin, identification, source, and characterization of the actual and potential impurities for the drug substance.
The drug substance specifications are adequate (consistent with ICH Q3A, Q3C, and Q6A) to ensure the quality of glycopyrrolate as it relates to the safety and efficacy of the eventual drug product.

The synthetic scheme, control of materials, control of critical steps and intermediates, process validation studies, manufacturing process and development, characterization, impurities/degradant characterization, specifications, the analytical procedures, reference standards, container closure system, and stability data have all been cross-referenced to DMF (b) (4) and all have been determined to be adequate as per the last review dated 11-FEB-2021 by W. Song.

Information in the DMF supports a retest period of (b) (4) months.

Drug Product: Adequate

The applicant has provided release data for three batches, and twelve months of stability data for those same three batches. All the release and stability data met the set specifications for all tested parameters. An expiry of 24 months has been granted based on the totality of the stability data. The analytical methods used are appropriate for control of the drug product, and all methods have been validated. Sufficient extractable and

leachables data was provided to conclude this represents a low safety risk, however the studies were not sufficient to fully characterize the extractable and leachable profile of the container closure system. A postmarketing commitment will be sent to the applicant to address these issues.

Postmarketing commitment 4242:

PMC 4242-1:
Perform an extractables study on the container closure with an AET of (b) (4) ppm.

PMC 4242-2
Perform a leachables stability study with testing at timepoints consistent with the recommendations in ICH Q1A (R2) Stability Testing of New Drug Substances and Products.

Labeling: Adequate

Manufacturing: Adequate

The drug product is (b) (4) and the pH is adjusted. The drug product has a pH range of (b) (4) and is adjusted with (b) (4) HCl and (b) (4) NaOH. No PAIs or 704(a) requests were performed in support of the subject application. All facilities are approved.

Biopharmaceutics: Adequate

The biopharmaceutics review focuses on the scientific bridge of the listed drug (LD) and proposed drug product based on the supporting data. Sufficient data were provided and a bridge between the Reference drug and the proposed drug is established.

Microbiology (if applicable): Adequate

The drug product is (b) (4) in a syringe system.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
		H, M, or L		Acceptable or Not Acceptable	

			(b) (4)		
Sterility	• Formulation • Container closure • Process parameters • Scale/equipments • Site	H		Acceptable	
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M		Acceptable	
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
Uniformity of Dose (Fill Volume/deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L		Acceptable	
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
pH- (Low)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M		Acceptable	
Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
Appearance (Color/turbidity)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	

D. List of Deficiencies for Complete Response

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

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

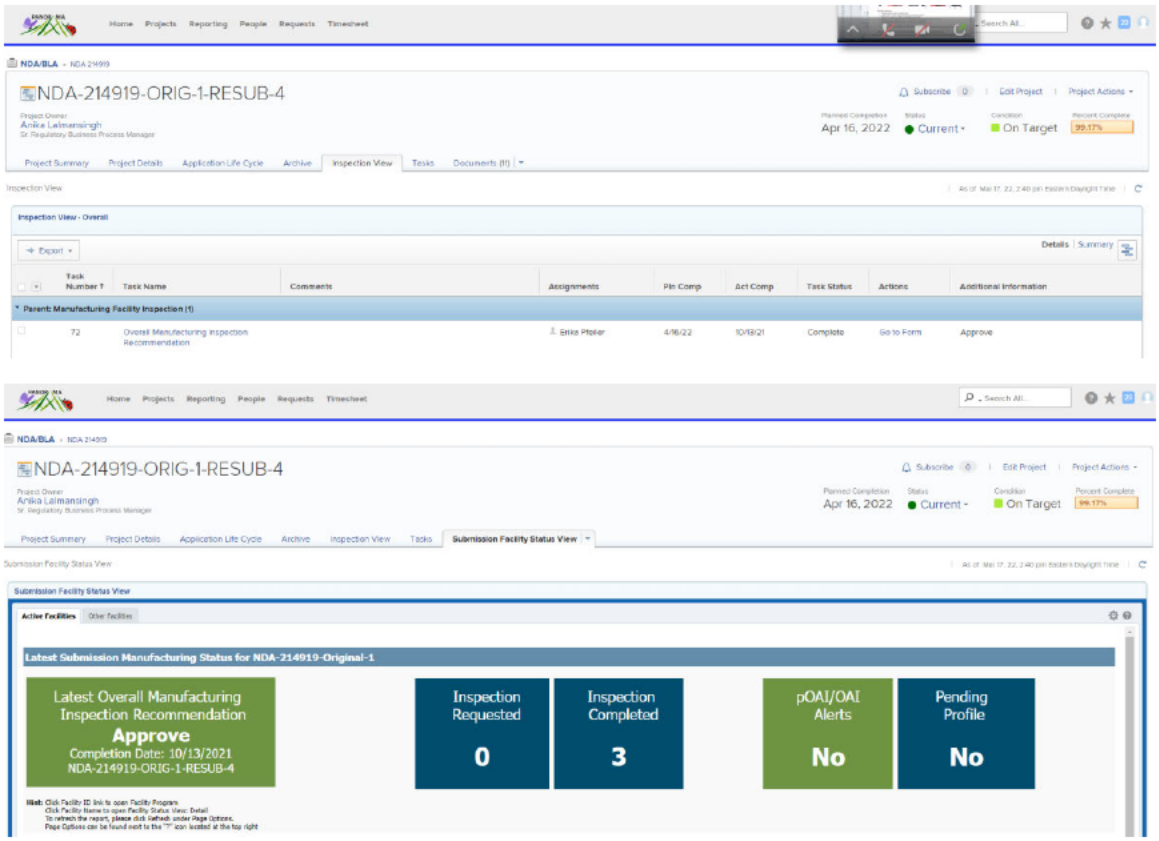
5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

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

Facilities screenshot showing approval (taken on 17 Mar 22)



Valerie Amspacher

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	n/a	
Established name(s)	Yes	
Route(s) of administration	Yes	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Yes	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	No	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	n/a	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	n/a	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	n/a	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	No	

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Yes	
Dosage form(s) and route(s) of administration	Yes	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	n/a	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Yes	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Yes	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	
Statement of being sterile (if applicable)	No	
Pharmacological/ therapeutic class	Yes	
Chemical name, structural formula, molecular weight	Yes	
If radioactive, statement of important nuclear characteristics.	n/a	
Other important chemical or physical properties (such as pKa or pH)	n/a	

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	n/a	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	n/a	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
Available units (e.g., bottles of 100 tablets)	Yes	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	n/a	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	No	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Yes	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	n/a	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Yes	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	n/a	
Include information about child-resistant packaging	n/a	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Yes	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): Adequate

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Yes	
Dosage strength	Yes	
Route of administration	Yes	
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	n/a	
Net contents (e.g. tablet count)	Yes	
"Rx only" displayed on the principal display	Yes	
NDC number	Yes	
Lot number and expiration date	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Yes	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	n/a	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	
Bar code	Yes	

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes	
Medication Guide (if applicable)	n/a	
No text on Ferrule and Cap overseal	n/a	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	n/a	
And others, if space is available	n/a	

Assessment of Carton and Container Labeling: ***Adequate***

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date: Eric Bow

Secondary Assessor Name and Date (and Secondary Summary, as needed): Julia Pinto

Eric Bow

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Julia Pinto

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BIOPHARMACEUTICS

Product Background:

NDA: 214919-ORIG-1-RESUBMISSION

Drug Product Name / Strength: Glycopyrrolate Injection, USP, Sterile Liquid, 0.6 mg per 3 mL syringe

Route of Administration: IV/ IM Injection

Applicant Name: Fresenius Kabi USA, LLC

Review recommendation: Adequate

Review Summary:

The original NDA was submitted on December 30, 2020. On February 25, 2021, a refusal to file letter (RTFL) was issued to this NDA; the Biopharmaceutics deficiencies in the RTFL are included in Section "Highlighted Key Outstanding Issues from Last Cycle:".

On 6/18/2021, the Applicant resubmited this NDA. The biopharmaceutics review focuses on the scientific bridge of the listed drug (LD) and proposed drug product based on the supporting data. Sufficient data were provided and a bridge between the Reference drug and the proposed drug is established.

Conclusion and recommendation:

From a Biopharmaceutics perspective, this Reviewers conludes that 214919-ORIG-1-Resubmission for Glycopyrrolate Injection, USP, 0.6 mg per 3 mL syringe is adequate.

List Submissions being reviewed:

Original submission	12/30/2020
RESUBMISSION	6/18/2021
Response to IR	10/8/2021

Highlighted Key Outstanding Issues from Last Cycle:

- The Applicant should provide sufficient supporting data for the biowaiver.

- The Applicant should provide a detailed justification that the (b) (4) formulation has no impact to the safety or efficacy of the proposed drug product.

Concise Description Outstanding Issues Remaining:

None

Bridging of Formulations

Reviewer's Assessment: N/A

Biowaiver Request

The Applicant requested a biowaiver based on 21 CFR § 320.22(b), which states that for certain drug products, the in-vivo bioavailability or bioequivalence of the drug product may be self-evident. Comparative formulations of the proposed drug product and listed drug (LD) are provided below:

Table 1.12.15- 1 Comparison of FK USA's and Innovator's Formulation

Ingredients	Robinul® Hikma Pharmaceuticals International Ltd.	Glycopyrrolate Injection, USP FK USA
Glycopyrrolate, USP	0.2 mg/mL	0.2mg/ mL
Benzyl Alcohol	0.9%	Not applicable
Hydrochloric Acid	(b) (4)	(b) (4)
Sodium Hydroxide	(b) (4)	(b) (4)
Water for Injection	Q.S	Q.S.

Benzyl Alcohol is a preservative in LD but not present in the proposed drug product, which is considered to have no impact on the safety or efficacy of the proposed drug product.

The Applicant also provided the following comparative physicochemical property data (i.e., pH and osmolarity) of the proposed drug product and Reference Standard:

Table 3.2.P.2- 1 Comparison Results of FK USA Product with Reference Standard

Test	Fresenius Kabi Glycopyrrolate Injection, USP Lot 6400670.25H 12 Month stability	Westward (Hikma Farmaceutica Portugal SA) Reference Standard					
pH	2.6	2.7	2.7	2.7	2.7	2.7	2.7
		Tested on 3/2021 Lot 1905178.1 Exp 09/2021			Tested on 3/2021 Lot 2001095.1 Exp 5/2022		
Osmolality (mOsm/kg)	5	86	98	86	86	85	86
		Tested on 3/2021 Lot 1905178.1 Exp 09/2021			Tested on 3/2021 Lot 2001095.1 Exp 5/2022		
Glycopyrrolate Assay (%)	99.2	98.5 Tested in 6/2020 Lot 1905178 Exp 09/2021			NT [1]		
USP Related Compound C (%)	(b) (4)	Tested on 6/2020 Lot 1905178 Exp 09/2021			NT [1]		
Total Degradation Product (%)	(b) (4)	Tested on 6/2020 Lot 1905178 Exp 09/2021			NT [1]		
Largest Individual Unknown Degradation Product	(b) (4)	Tested on 6/2020 Lot 1905178 Exp 09/2021			NT [1]		

[1] Not Tested

The Applicant did not provide sufficient supporting information for the biowaiver. On 08/27/2021 an information request (IR) (see Appendix for details) was sent to the Applicant.

In response to the IR, the Applicant stated "The physicochemical properties of FK USA's Glycopyrrolate Injection, USP are equivalent to the Orange Book reference standard (RS) for Glycopyrrolate Injection, USP. Robinul® has been discontinued from the market according to the FDA Orange Book; therefore, the physicochemical properties were compared to the Orange Book designated reference standard (RS) - 0.2mg/mL Glycopyrrolate Injection, USP (Hikma Farmaceutica Portugal SA). Fresenius Kabi tested physicochemical properties of 3 batches of reference standard product manufactured by Westward (Hikma Farmaceutica Portugal SA) and compared them to 3 batches of Fresenius Kabi drug product. The testing was performed in triplicate and results are provided in Table below:

Table 1: Results of physicochemical properties of Fresenius Kabi drug product and Reference Standard

Test	Fresenius Kabi Glycopyrrolate Injection, USP Lot 6400569.25H ~22 Month stability			Fresenius Kabi Glycopyrrolate Injection, USP Lot 6400670.25H ~22 Month stability			Fresenius Kabi Glycopyrrolate Injection, USP Lot 6400571.25H ~22 Month stability			Westward (Hikma Farmaceutica Portugal SA) Reference Standard								
pH	2.4	2.4	2.4	2.5	2.5	2.5	2.4	2.4	2.4	2.7	2.7	2.7	2.7	2.7	2.7	2.6	2.6	2.6
										Tested on 3/2021 Lot 1905178.1 Exp 09/2021			Tested on 3/2021 Lot 2001095.1 Exp 5/2022			Tested 9/2021 Lot 2005195.1 Exp 10/2022		
Osmolality (mOsm/kg)	7	7	7	6	6	6	7	7	7	86	98	86	86	85	86	87	87	87
										Tested on 3/2021 Lot 1905178.1 Exp 09/2021			Tested on 3/2021 Lot 2001095.1 Exp 5/2022			Tested 9/2021 Lot 2005195.1 Exp 10/2022		
Glycopyrrolate Assay (%)	96.8	96.9	96.8	97.7	97.7	97.6	97.6	97.7	97.6	98.6	98.8	98.7	98.6	98.7	98.7	98.7	98.8	98.9
										Tested 9/2021 Lot 1905178.1 Exp 09/2021			Tested 9/2021 Lot 2001095.1 Exp 5/2022			Tested 9/2021 Lot 2005195.1 Exp 10/2022		
USP Related Compound C (%)	(b) (4)									(b) (4)								(b) (4)
										Tested 9/2021 Lot 1905178.1 Exp 09/2021			Tested 9/2021 Lot 2001095.1 Exp 5/2022			Tested 9/2021 Lot 2005195.1 Exp 10/2022		
Total Degradation Product (%)										(b) (4)								
										Tested 9/2021 Lot 1905178.1 Exp 09/2021			Tested 9/2021 Lot 2001095.1 Exp 5/2022			Tested 9/2021 Lot 2005195.1 Exp 10/2022		
Largest Individual Unknown Degradation Product (%)										(RRT	(RRT		RRT	RRT	RRT	(RRT	(RRT	(RRT
										(b) (4)								
										Tested 9/2021 Lot 1905178.1 Exp 09/2021			Tested 9/2021 Lot 2001095.1 Exp 5/2022			Tested 9/2021 Lot 2005195.1 Exp 10/2022		

Justification for low osmolality of the proposed drug

The following is the justification provided by the Applicant for the low osmolality of the proposed drug prodouct:

"Osmolality evaluation of Fresenius Kabi's Glycopyrrolate Injection with comparison to Glycopyrrolate Injection, USP (West-Ward Pharmaceutical)" as well as in the paragraphs below. Overall, it was concluded that Fresenius Kabi drug product with the given osmolality level will not have any significant in-vivo effect in terms of safety and efficacy compared to the RLD based on the following assessment:

A healthy human body maintains serum osmolality within range by employing various physiological defense mechanism act via release of antidiuretic hormone, atrial natriuretic peptide and renin-angiotensin-aldosterone system. As per the drug product indications and calculated maximum daily dose, the Glycopyrrolate injection drug volume would be 0.5 to 10 mL for intravenous and 0.5 to 1 mL for intramuscular administration for specific indications. Moreover, Glycopyrrolate injection may be administered via the tubing of a running infusion of normal saline. In addition, Hassin et al, reported that large volume (about 2.5 liters) of hypotonic solution can be administered intravenously without harmful effect.

Considering small dose volume and subsequent rapid distribution into the general blood circulation and normal osmolality is maintained by various physiological defense mechanisms in the human body, it is not expected that this hypo-osmolality difference in such small drug volumes will have any effect on normal antimuscarinic properties of Glycopyrrolate Injection, USP drug product.

Justification for absence of benzyl alcohol

The Applicant also provided a detail justification for the absence of the benzyl alcohol preservative in the proposed drug product as follows:

The Fresenius Kabi drug product is [redacted] (b) (4) during the manufacturing process and further sterility confirmation is performed throughout the shelf life of the product. Glycopyrrolate 3 mL is presented in a pre-filled syringe that is to be administered as a single dose and not as a multi-dosed product; therefore, use of preservative is not required for this product.

Fresenius Kabi had confirmed that except being a preservative per common knowledge, benzyl alcohol does not provide other critical functionality, i.e., solubilizer nor stabilizer, in this product formulation. Fresenius Kabi product, containing no benzyl alcohol, is stable and does not have additional degradation when compared to the designated reference standard (RS) 0.2mg/mL Glycopyrrolate Injection, USP (Hikma Farmaceutica Portugal SA) which contains 0.9% Benzyl alcohol. Overall, the absence of benzyl alcohol has no impact on the safety or efficacy of the proposed drug product.

Reviewer's Assessment:

Overall, the Applicant's justification for the differences in formulaition and physicochemical properties between the proposed drug and LD/RS is acceptable. A scientific bridge between two drugs have been established per 21 CFR 320.24(b)(6) due to the following reasons:

1) *The LD and proposed drug product are for both IV and IM administration.*
2) *The proposed drug contains the same concentration of active ingredient as the LD. Although benzyl alcohol is not included in the proposed drug product, its absence does not affect the in vivo performance of the proposed drug.*
3) *The proposed drug product and LD/RS have comparable physicochemical properties including osmolality and pH.*

Appendix:

Biopharmaceutics IR and the Applicant's response

IR

We acknowledge that you submitted a biowaiver request with some supporting data for your proposed drug product; however, the data you provided in this resubmission are not sufficient to support the biowaiver request. Specifically, you should provide the following:

a) You should test **at least 3 batches** of each drug product (i.e. the LD vs the proposed drug) for physicochemical property comparison. The measurements should be done in triplicate for each batch tested.

b) You should justify that the differences in osmolality between your proposed drug and the LD do not affect the in vivo performance of glycopyrrolate.

The Applicant's response:

The Applicant provided the requested supporting data, which were assessed in the review.

Lifecycle Management Considerations

List of Deficiencies: None

Primary Biopharmaceutics Reviewer Name and Date:

Assadollah Noory, Ph, D.

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

Hansong Chen, PharmD. Ph. D.

Assadollah Noory

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	214919
Assessment Cycle Number	01
Drug Product Name/ Strength	Glycopyrrolate Injection, USP/0.6 mg per 3 mL syringe
Route of Administration	Intravenous (IV) or Intramuscular (IM)
Applicant Name	Fresenius Kabi USA, LLC
Therapeutic Classification/ OND Division	Division of Anesthesiology, Addiction and Pain Medicine (DAAP)
Manufacturing Site	5200 Corporate Parkway, West Wilson, North Carolina, USA, 27893
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
eCTD sequence 0001	12/30/2020
eCTD sequence 0005	06/21/2021
eCTD sequence 0006	10/08/2021

List Submissions being assessed: See table

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

Remarks: The drug product is (b) (4) in a syringe system.

This assessment was started by Avital Shimanovich as primary but taken over by Erika Pfeiler when Avital left the Agency.

Concise Description of Outstanding Issues: N/A

Supporting Documents:

- Type III DMF (b) (4), (b) (4)
- Microbiology review, (b) (4) M79R01.docx, dated 12/18/2020, and found adequate for the depyrogenation of the subject container closure system.

- Type V DMF 029178 (Holder: Fresenius Kabi USA LLC, Subject: (b) (4) (b) (4) subject drug product.
- Microbiology reviews: D29178M03R01.doc, dated 04/13/2017, D29178M04R01.docx, dated 02/21/2018/D29178M04R01.docx, dated 08/03/2018, and D29178M10R01.docx, dated 07/16/2021, for the DP manufacturing process found adequate.
- Type V DMF (b) (4): (b) (4).
- Microbiology review, D (b) (4) M16R01.docx, dated 6/18/2020, and found adequate (b) (4)
- Type III DMF (b) (4) (b) (4)
- Microbiology review, (b) (4) M049R01.docx, dated 06/03/2020, and found adequate (b) (4).

S DRUG SUBSTANCE

The drug substance is manufactured as non-sterile and the drug product is (b) (4) in the container closure system. Therefore, a product quality microbiology assessment of the drug substance will not be performed.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

12/30/2020 submission, Section 3.2.P.1, Description and Composition of the Drug Product

- **Description of the drug product** – The drug product (DP) is a sterile, clear solution.

- **Composition of the drug product** – The DP composition is as follows:

Ingredient	Content per unit	Function
Glycopyrrolate	0.6 mg	Active
Hydrochloric Acid, NF	q.s. for pH 2-3	pH adjustor
Sodium Hydroxide, NF	q.s. for pH 2-3	pH adjustor
Water for Injection, USP	3 mL	Solvent

- **Description of the container closure system** – The container closure system (CCS) is as follows:

Component	Description	Supplier
Syringe Barrel* (b) (4)	(b) (4)	(b) (4)
Cap*		
Plunger stopper*		
Plunger rod*		

*All of the CCS components are supplied ready to use.

Assessment: *Adequate*

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APPENDICES

Assessment: *N/A*

R REGIONAL INFORMATION

Executed Batch Records

Three batch records were provided. (b) (4) (b) (4)

Assessment: ***Adequate***

The applicant provided batch records for the three exhibit batches which were (b) (4) per the commercial settings.

Comparability Protocols

Assessment: *N/A, there were no CPs associated with the submission.*

2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Prescribing Information

- **Post-dilution/constitution hold time**

Assessment: *N/A, the drug product is delivered without dilution.*

Post-Approval Commitments

Assessment: *N/A*

MICROBIOLOGY LIST OF DEFICIENCIES

N/A

Primary Microbiology Assessor Name and Date:
Avital Shimanovich, PhD, 07/16/2021
Erika Pfeiler, Ph.D., 10/13/2021
Secondary Assessor Name and Date: Bethanie Lee, PhD, 10/13/2021

Erika Pfeiler

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Bethanie Lee

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