CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216903Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	216903		
Applicant Name	Slayback Pharma LLC		
Drug Product Name	Neostigmine Methylsulfate and Glycopyrrolate Injection		
Dosage Form.	Injection		
Proposed Strength(s)	1.0 mg and 0.2 mg per 1 mL (3.0 mg and 0.6 mg per 3 mL)		
Route of Administration	Intravenous		
Maximum Daily Dose	5 mg/day neostigmine, (b) (4)		
Rx/OTC Dispensed	Rx		
Proposed Indication	Neostigmine Methylsulfate and Glycopyrrolate Injection, a fixed dose combination (b) (4)		
Drug Product Description	a clear colorless solution supplied in a pre-filled syringe		
Co-packaged product information	N/A		
Device information:	3 mL (b) (4) luer-lock prefilled syringe with luer lock & tipcap closed with (b) (4) grey (b) (4) elastomeric (b) (4) stopper, and assembled with translucent plunger rod		
Storage Temperature/ Conditions	°C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Zhixing Shan	Gaetan Ladouceur
	Drug Product/ Labeling	Grace Chiou	Julia Pinto

	Manufacturing	Paul Dexter	David Anderson
	Biopharmaceutics	Hansong Chen	Ta-Chen Wu
	Microbiology	George Arhin	Paul Dexter
	Other (specify):	N/A	M/A
	RBPM	Anika Lalmansingh	
	ATL	Valerie Amspacher	
Consults			

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: Based on the data provided, a shelf life of 18 months is acceptable when stored at 20-25 ºC.

b. Additional Comments for Action

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation: The CMC recommendation is for approval based on reviews by drug substance, drug product, process/ facilities, biopharmaceutics and microbiology. A shelf life of 18 months is acceptable when stored at 20-25 ºC.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance - Adequate

Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: N/A

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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: The carton and container labels were accessed from eCTD 0004. The PI was accessed from eCTD 0002.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name Established name(s) Route(s) of administration	NEOSTIGMINE METHYLSULFATE AND GLYCOPYRROLATE Injection, for intravenous use	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Injection: 1.0 mg/mL of Neostigmine Methylsulfate and 0.2 mg/mL of Glycopyrrolate in 3 mL Prefilled Syringe (3)	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
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.		Inadequate Revise to include single-dose

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

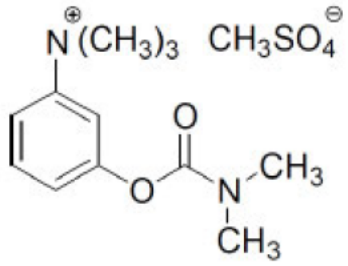
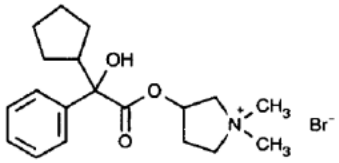
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted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

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)	Neostigmine methylsulfate and Glycopyrrolate Injection is available as: • Injection: 1.0 mg of neostigmine methylsulfate and 0.2 mg of glycopyrrolate per mL, 3 mg of neostigmine methylsulfate and 0.6 mg of glycopyrrolate in 3 mL prefilled syringe.	Adequate
Strength(s) in metric system		
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		
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.		Inadequate Revise to include single-dose

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Neostigmine methylsulfate and Glycopyrrolate Injection is a clear colorless solution available as a prefilled syringe that contains a fixed dose combination of neostigmine methylsulfate, a cholinesterase inhibitor and glycopyrrolate, an anticholinergic agent, for intravenous administration.	Adequate
Dosage form(s) and route(s) of administration		
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.		
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Neostigmine methylsulfate and glycopyrrolate Injection is available as a 3 mL Prefilled Syringe. Each mL contains Neostigmine Methylsulfate USP (1 (b) (4) mg), Glycopyrrolate USP (0.2 mg), edetate disodium dihydrate USP, sodium chloride USP in water for injection. The pH is adjusted, when necessary, with Hydrochloric acid/sodium hydroxide to achieve a value of 3.6.	Inadequate Revise to include quantities of inactive ingredients
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.		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)		Inadequate Revise to include sterile statement.
Pharmacological/ therapeutic class	See above	Adequate

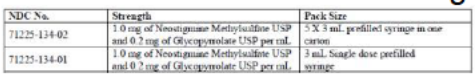
Chemical name, structural formula, molecular weight	Neostigmine Methylsulfate USP Neostigmine methylsulfate, a cholinesterase inhibitor, is (m-hydroxyphenyl) trimethylammonium methylsulfate dimethylcarbamate. The molecular formula is $C_{13}H_{22}N_2O_6S$, a molecular weight is 334.39 g/mol and the following structural formula is:  Glycopyrrolate USP Glycopyrrolate is a quaternary ammonium salt (anticholinergic agent) with a chemical name of 3[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl pyrrolidinium bromide. The molecular formula is $C_{19}H_{28}BrNO_3$ and the molecular weight is 398.33 and the structural formula is: 	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)		Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	Adequate
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug		

Company X," "structurally unique molecular entity"		

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) Strength(s) in metric system Available units (e.g., bottles of 100 tablets) Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Neostigmine methylsulfate and Glycopyrrolate Injection is a clear colorless solution available in the following:  Neostigmine Methylsulfate and Glycopyrrolate Injection should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light. Store in carton until time of use.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
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.	See above	Adequate

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.)	NA	Adequate
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.”	NA	NA
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	See above	Adequate
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.”	NA	NA
Include information about child-resistant packaging	NA	NA

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	Manufactured for: Slayback Pharma LLC Princeton, NJ 08540.	Inadequate Revise to include street address

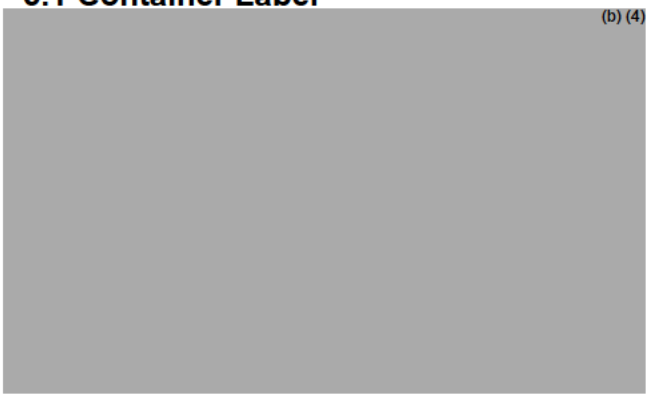
2.0 PATIENT LABELING

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

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

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label



3.2 Carton Labeling

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence Dosage strength Route of administration	Neostigmine Methylsulfate and Glycopyrrolate Injection (b) (4)	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance		Inadequate Revise to include equivalency statement for glycopyrrolate
Net contents (e.g. tablet count) "Rx only" displayed on the principal display NDC number Lot number and expiration date	(b) (4) (b) (4)	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15° C to 30°C (59°F to 86°F). [see USP Controlled Room Temperature]. Protect from light. Store in carton until time of Administration. (b) (4)	Inadequate Remove "Protect from light" statement as the proposed product is not photosensitive.
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 which require "Not for direct infusion" statement.	See above	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Bar code	(b) (4)	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	(b) (4)	Adequate
Medication Guide (if applicable)	NA	NA
No text on Ferrule and Cap overseal		
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.		
And others, if space is available		

Assessment of Carton and Container Labeling: *Adequate*

The carton and container labeling is adequate, pending the Applicant's acceptance of the revisions noted above in red.

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

ITEMS FOR ADDITIONAL ASSESSMENT

Adequate. Pending the Applicant's acceptance of the revisions noted above in red, the labeling information is adequate.

Overall Assessment and Recommendation:

This application is recommended for approval per labeling/labels perspective once the following changes have been made to the label.

Grace Chiou

Digitally signed by Grace Chiou
Date: 11/30/2022 12:06:25PM
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Julia Pinto

Digitally signed by Julia Pinto
Date: 11/30/2022 12:10:54PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA 216903-ORIG-1
Assessment Cycle Number	1
Drug Product Name/ Strength	Neostigmine Methylsulfate and Glycopyrrolate Injection, 1.0 mg and 0.2 mg per mL (3 mL Prefilled Syringe)
Route of Administration	IV injection
Applicant Name	Slayback Pharma LLC
Therapeutic Classification/ OND Division	Fixed dose combination of cholinesterase inhibitors/DAAP
LD/RS Number	NDA 204078, NDA 017558/RS ANDA 090963
Proposed Indication	For reversal of the effects of non-depolarizing neuromuscular blocking agents (NMBAs) after surgery, (b) (4) (b) (4)
Primary Reviewer	Hansong Chen, PharmD, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.

Assessment Recommendation: **Adequate**

Assessment Summary:

The Applicant proposes a fixed dose combination product, Neostigmine Methylsulfate and Glycopyrrolate Injection, 1.0 mg and 0.2 mg/mL for intravenous administration. With the current submission, the Applicant seeks approval through 505(b)(2) regulatory pathway relying on the Agency's findings of efficacy and safety of two Listed Drugs (LDs), BLOXIVERZ® and ROBINUL®.

NDA 204078 for BLOXIVERZ® (Neostigmine Methylsulfate) Injection 1.0 mg/mL, held by Exela Pharma Sciences LLC was approved on 05/31/2013, indicating for the reversal of the effects of non-depolarizing neuromuscular blocking agents (NMBAs) after surgery. NDA 017558 for ROBINUL® (Glycopyrrolate) Injection USP 0.2 mg/mL, held by Hikma Pharmaceuticals USA Inc was approved on 02/06/1975 for use as a preoperative antimuscarinic to reduce salivary, tracheobronchial, and pharyngeal secretions; to reduce the volume and free acidity of gastric secretions; and to block cardiac vagal inhibitory reflexes during induction of anesthesia and intubation.

By citing 21 CFR 320.22(b)(1) and 21 CFR 320.24(b)(6), the Applicant requests a waiver of the requirement to conduct in-vivo bioavailability/bioequivalence studies for the proposed drug product. However, 21CFR § 320.22(b)(1) is not applicable because the proposed drug product is a fixed dose combination of two listed drugs (LD) and has different excipients from those presented in two LDs. The Applicant has provided an

adequate scientific justification to establish a scientific bridge between the proposed drug product and LDs, BLOXIVERZ® and ROBINUL®, permitting reliance on the Agency's findings of efficacy and safety of both LDs, in accordance with 21 CFR 320.24(b)(6) given the following consideration:

1) The LDs were approved for IV and/or IM administration but this proposed drug product is proposed for the IV route only for the same respective indication.
2) The proposed drug product contains different excipients from those presented in individual LDs. The differences in formulation are not expected to affect the drug disposition of Neostigmine Methylsulfate and Glycopyrrolate in humans.
3) The proposed drug product and LD/Reference Standard (RS) have different osmolarities and pHs; however, the differences are not expected to bring any additional safety issues
4) There is no drug-drug interaction potential between neostigmine and glycopyrrolate that could potentially alter the drug absorption and pharmacokinetics profile of each drug substance.

***Recommendation and conclusion**:*
From a Biopharmaceutics perspective, NDA 216903-Orig-1 for Neostigmine Methylsulfate and Glycopyrrolate Injection, 1.0 mg and 0.2 mg per mL (3 mL Prefilled Syringe) is **adequate.**

Document(s) Assessed	Date Received
Original submission (eCTD-0002)	4/23/2022

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

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

B. 13 BIOWAIVER REQUEST

1. <u>Comparison in formulation between the LDs and proposed drug product</u>

Table 1. A Comparison of the Active and Inactive Ingredients between the LDs, proposed drug, and other similar drug products

Ingredient(s)	Quality Standard	Pharmaceutical Function	Quantity					
			Proposed Drug Product[7]		BLOXIVERZ[1]	ROBINUL[5,3]	GLYRX-PF[6,4]	Glycopyrrolate Injection[5,5]
			mg/mL	% w/v	mg/mL	mg/mL	mg/mL	mg/mL
Neostigmine Methylsulfate	USP	Active Pharmaceutical Ingredient	1.0 mg	(b) (4)	1.0 mg	--	--	--
Glycopyrrolate	USP	Active Pharmaceutical Ingredient	0.2 mg		--	0.2 mg	0.2 mg	0.2 mg
Disodium Edetate Dihydrate	USP	(b) (4)	0.5 mg		--	--	--	--
Sodium Chloride	USP		8 mg		--	--	(b) (4)	--
Sodium Acetate Trihydrate	USP		--		0.2 mg	--	--	--
Benzyl Alcohol	NF	Preservative	--		--	0.9%	--	0.9%
Phenol	USP	Preservative	--		4.5 mg	--	--	--
Acetic Acid	NF	pH Adjuster	--		q.s to adjust pH	--	--	--
Hydrochloric Acid	NF	pH Adjuster	q.s to adjust pH		--	q.s to adjust pH	q.s to adjust pH	q.s to adjust pH
Sodium Hydroxide	NF	pH Adjuster	q.s to adjust pH		q.s to adjust pH	q.s to adjust pH	q.s to adjust pH	q.s to adjust pH
Water for Injection	USP	(b) (4)	(b) (4)		(b) (4)	(b) (4)	(b) (4)	(b) (4)

Q.S = Quantity Sufficient; USP = United States Pharmacopeia; NF = National Formulary

[6]GLYRX-PF (Glycopyrrolate) Injection, 0.2 mg/mL, 0.4 mg/2 mL, (b) (4) is a 505(b)(2) NDA # N210997 held by Exela Pharma Sciences LLC in solution dosage form for intramuscular & intravenous administration and it is approved against 505(b)(1) ROBINUL as RLD. GLYRX-PF differs from the Reference Listed Drug (ROBINUL) in osmolality, absence of benzyl alcohol and presence of sodium chloride.

[5]ROBINUL (NDA # N017558) is identified as RLD for Glycopyrrolate and has been discontinued. The Federal Register determination says that the product was not discontinued or withdrawn for safety or efficacy reasons. Subsequently, an approved Glycopyrrolate Injection, 0.2 mg/mL; ANDA # A090963 held by Hikma Farmaceutica (Portugal) SA has been designed as RS (Reference Standard) by the FDA.

As shown in Table 1, the proposed product is different form two listed drugs in formulation as the former is the fixed-dose combination of two LDs. Additionally, the proposed drug product does not have the same excipients (i.e., preservative (b) (4)) as presented the formulations of the LDs. Specifically, an optimized concentration of Disodium Edetate Dihydrate is added to the proposed drug as (b) (4). Sodium Chloride USP is added to the proposed formulation for (b) (4) Hydrochloric acid and/or sodium hydroxide is used as a pH adjuster.

The Applicant provided the following justifications for the excipient differences in the formulation of the proposed drug:

a) No novel excipients have been proposed in the proposed formulation and all the excipients used are of compendial grade (i.e., meets the respective USP Monographs). They are well within the levels suggested by the FDA's IID database and routinely used for parenteral dosage forms.
b) The excipients, Disodium Edetate and Sodium Chloride, are (b) (4) excipients and do not have property to alter the availability of the drugs upon intravenous administration.
c) Sodium Acetate Trihydrate, phenol, Benzyl Alcohol, and Acetic Acid are presented in the formulation of both LDs as (b) (4) preservative, and pH adjuster, respectively. Their absence in the proposed drug will not alter the disposition of both active ingredients.

Reviewer's comment:

The function of NaCl is (b) (4) Disodium Edetate Dihydrate acts as (b) (4) This Reviewer agrees that differences in excipients between the LDs and the proposed drug product are not expected to affect the disposition of Neostigmine Methylsulfate and Glycopyrrolate.

2. Comparison of physicochemical properties of the LDs, RS, and proposed drug product

Table 2. The drug products used for comparison of physicochemical properties

Drug Product	Proposed Drug Product	BLOXIVERZ	ROBINUL[5]	Glycopyrrolate Injection[5]	Combination of RLD/RS
	Neostigmine Methylsulfate and Glycopyrrolate Injection	BLOXIVERZ (Neostigmine Methylsulfate) Injection	ROBINUL (Glycopyrrolate) Injection	Glycopyrrolate Injection	(BLOXIVERZ & Glycopyrrolate Injection USP[5] in 1:1 Ratio)
Application #	--	NDA # 204078	NDA # 017558	ANDA # 090963	NDA # 204078 & ANDA # 090963
Strength / Fill Used	1.0 mg & 0.2 mg/mL (3 mL PFS)	10 mg/10 mL (1 mg/mL) (10 mL Vial)	Not Available	0.2 mg/mL (2 mL)	Mix of 1.0 mg & 0.2 mg/mL
Number of Lots Tested	3	3	--	3	3

ROBINUL (NDA N017558) is identified as RLD for Glycopyrrolate and has been discontinued. The Applicant used Glycopyrrolate Injection, 0.2 mg/mL, held by Hikma Farmaceutica and approved under ANDA 090963 as Reference Standard (RS) to conduct physicochemical property comparison.

Table 3. Comparison of physicochemical properties of the LDs, RS, and proposed drug product

Physicochemical properties	BLOXIVERZ® (Neostigmine Methylsulfate) Injection, USP, 1.0 mg/mL			Glycopyrrolate Injection, USP 0.2 mg/mL (RS)			Neostigmine Methylsulfate and Glycopyrrolate Injection, 1.0 mg and 0.2 mg per mL		
	Batch No.: AM3066D	Batch No.: AM6214B	Batch No.: AM8220B	Batch No.: 2005094.1	Batch No.: 2005095 1	Batch No.: 2105022.1	Batch No.: ATY101	Batch No.: ATY102	Batch No.: ATY103
pH	5.50	5.57	5.56	2.61	2.61	2.63	3.5	3.5	3.5
Osmolality mOsmol/Kg	55	56	55	86	86	87	267	267	267
Viscosity (cps)	1.31	1.35	1.35	1.34	1 33	1.31	1.32	1.39	1.38

Table 3 shows that the proposed drug product has comparable viscosity as BLOXIVERZ® and glycopyrrolate injection (RS). However, it has different pH and higher osmolality compared to BLOXIVERZ® and RS.

Table 4. Mixture of BLOXIVERZ® (Neostigmine Methylsulfate) Injection, USP and Glycopyrrolate Injection, USP

physicochemical properties	BLOXIVERZ® (Neostigmine Methylsulfate Injection, USP) and Glycopyrrolate Injection, USP 1.0 mg per mL and 0.2 mg per mL (1:1 ratio mixture)			Neostigmine Methylsulfate and Glycopyrrolate Injection, 1.0 mg and 0.2 mg per mL (the proposed drug)		
	Batch No.: AM3066D and 2005094 1	Batch No.: AM6214B and 2005095.1	Batch No.: AM8220B and 2105022.1	Batch No.: ATY101	Batch No.: ATY102	Batch No.: ATY103
pH	3 37	3.37	3.34	3.5	3.5	3.5
Osmolality mOsmol/Kg	71	70	69	267	267	267
Viscosity (cps)	1 36	1.34	1.37	1.32	1.39	1.38

Additionally, the Applicant mixed BLOXIVERZ® and RS with 1:1 ratio and compared the mixture's physicochemical properties against the proposed drug, as shown in Table 4. The results show that the proposed drug product has similar pH as the mixture, but the latter has much lower osmolality.

The Applicant justified the differences in pH and osmolality between the proposed drug and LD/RS as follows:

a) The pH Value of the proposed formulation is similar, when compared against the mixture of both LD/RS (1:1 ratio) prepared in line to dosage recommended in labelling of Glycopyrrolate Injection. The pH values are well within the range of observed pH Values of LD/RS i.e., 2.6 for Glycopyrrolate Injection and (b) (4) for BLOXIVERZ® (Neostigmine Methylsulfate) Injection. Thus, the pH value of the proposed drug product does not pose any risk of irritation or phlebitis or any other safety challenges.

b) LD/RS formulations and BLOXIVERZ® /RS mixture were found to be hypotonic solutions and observed Osmolality values are around 55 mOsmol/Kg for BLOXIVERZ® Injection, around 86 mOsmol/Kg for Glycopyrrolate Injection and around 70 for BLOXIVERZ® /RS mixture. The proposed drug product is found to be isotonic solution with osmolality values of 267 mOsmol/Kg, which is desirable for IV administration of injectable products.

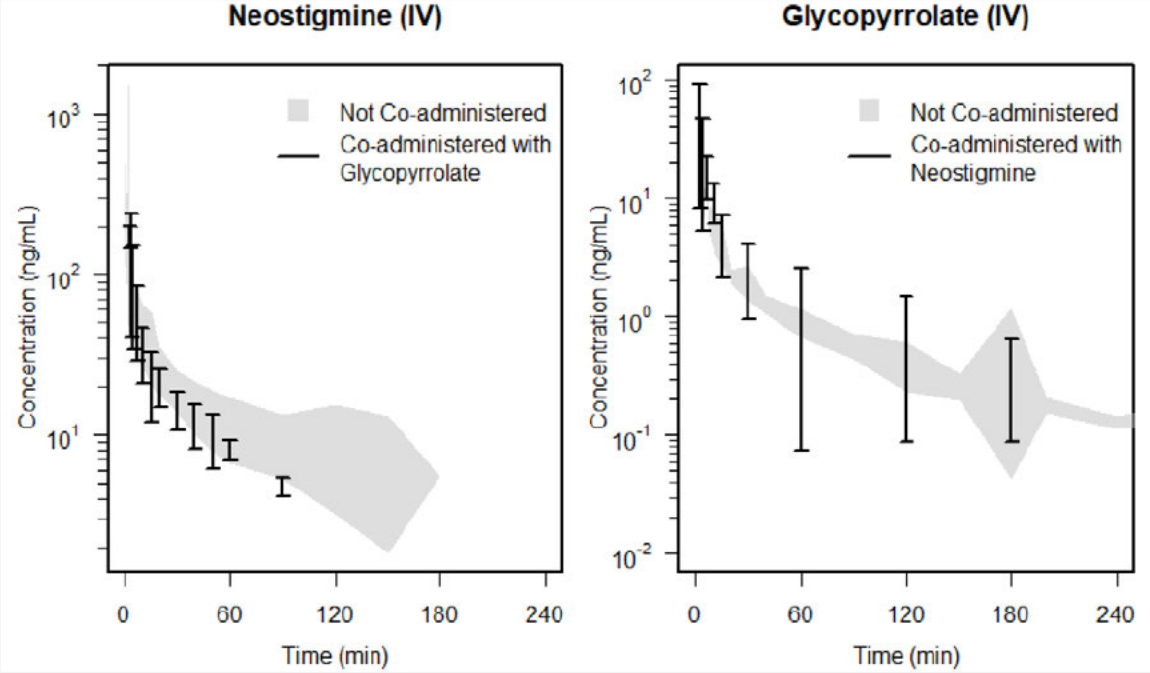
Reviewer's comment:
The Applicant's justification for the differences in physicochemical properties is acceptable. The pH value of the proposed drug product is within the range of BLOXIVERZ® and RS, which is not expected to bring additional safety issue. Although the proposed drug product has higher osmolality than the individual LD/RS and mixture of LD and RS, its value is close to being isotonic.

3. Drug-drug interaction between Neostigmine Methylsulfate and Glycopyrrolate

Since the proposed drug is a fixed-dose combination of Neostigmine Methylsulfate and Glycopyrrolate injection, concern would arise whether any drug-drug interaction between these two APIs can occur. According to the Applicant, simultaneous administration of neostigmine and glycopyrrolate as a mixture in the same syringe has been reported as early as 1972. The broad use of the combination of the two actives within the same syringe for over 50 years and the availability of these approved combination products indicate the compatibility and safety of two active ingredients when used as a fixed-dose combination.

The Applicant summarized the literature data and concluded that the plasma concentration-time profiles for neostigmine were similar when administered with atropine or glycopyrrolate (Figure 1). The Applicant also found that plasma concentration-time profiles for glycopyrrolate are similar regardless of whether it is co-administered with neostigmine (Figure 1).

Figure 1. Dose-Normalized Concentration-time Profiles of Neostigmine and Glycopyrrolate Administered Separately or Co-administered as Reported in the Literature



Reviewer's comment:
The provided information indicates a lack of drug-drug interaction potential between neostigmine and glycopyrrolate. This fixed-dose combination product has been approved by EMA. Additionally, the OCP reviewer for this NDA (i.e., Dr. Srikanth Nallani) also confirmed the Applicant's conclusion.

4. Biowaiver request

By citing 21 CFR 320.22(b)(1) and 21 CFR 320.24(b)(6), the Applicant requests a waiver of the requirement to conduct in-vivo bioavailability/bioequivalence studies for the proposed drug product.

Reviewer's comment:
The LDs and the proposed drug product do not have the same concentrations of active and inactive ingredients, it does not meet requirements of 21 CFR. 320.22(b)(1). Therefore, 21 CFR § 320.22(b)(1) is not applicable to this case.

However, a scientific bridge between the LDs and proposed drug product has been established per 21 CFR 320.24(b)(6) given the following consideration:

1) *The LDs were approved for IV and/or IM administration but this proposed drug product is proposed for the IV route only for the same indications.*
2) *The proposed drug product contains different excipients from those presented in individual LDs. The differences in formulations are not expected to affect the disposition of Neostigmine Methylsulfate and Glycopyrrolate.*
3) *The proposed drug product and LD/RS have different osmolarities and pHs; however, the differences are not expected to bring any additional safety issues.*
4) *There is no drug-drug interaction between neostigmine and glycopyrrolate.*

5. Conclusion

The Applicant provided adequate supporting data to establish a scientific bridge between the LDs and proposed drug product per 21 CFR 320.24(b)(6).

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

Hansong Chen

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Ta-Chen Wu

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U.S. FOOD & DRUG ADMINISTRATION

MICROBIOLOGY

Product Information	
NDA Number	216903
Assessment Cycle Number	1
Drug Product Name / Strength	Neostigmine Methylsulfate and Glycopyrrolate Injection, 1.0 mg/mL and 0.2 mg/mL (3 mL fill in 3 mL COC luer-lock prefilled syringe)
Route of Administration	Intravenous injection
Applicant Name	Slayback Pharma LLC
Manufacturing Site	Gland Pharma Limited (b) (4) (b) (4) (b) (4) Hyderabad, (b) (4) 500043 India
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Theme:

☐ N/A	☒ Depyrogenation Validation Data
☒ Product Sterility Assurance	☒ Product Release and/or Stability Specifications
☒ Media Fill Data	☒ Validation for Product Release and/or Stability Test Method
☒ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: N/A

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

List Submissions Being Assessed (table):

Submit	Received	Review Request	Assigned to Reviewer
April 23, 2022	April 25, 2022	N/A	May 12, 2022

(eCTD Sequence #0002)			
August 3, 2022 (eCTD Sequence #0005)	August 3, 2022	N/A	August 4, 2022

August 3, 2022 submission is response to Agency July 21, 2022 IR letter

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

Concise Description of Outstanding Issues: See IR on last page.

Supporting Documents:

- DMF [redacted](Type III; Title: [redacted], [redacted] LOA dated 08/16/2021. Reviewed in Microbiology review [redacted].docx dated 3/11/2022. Recommended.
- DMF [redacted] (Type V, [redacted] LOA dated 08/13/2021. Reviewed in Microbiology review [redacted].docx dated 3/8/2022.
- DMF [redacted](DMF Type V, [redacted] LOA dated 0/13/2021.Reviewed in Microbiology review [redacted].docx, dated 01/29/2022 Recommended.
- [redacted].doc dated 03/18/2022 for the [redacted]

Select Number of Approved Comparability Protocols: 0

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –**
  The subject drug product is a clear, colorless sterile, [redacted] preservative free solution filled as [redacted](1.0 mg/mL Neostigmine Methylsulfate + 0.2 mg/mL Glycopyrrolate); 3 mL fill in 3 mL [redacted]luer-lock prefilled single-dose syringe

- **Drug product composition** –

Ingredient	Quantity per mL (mg/mL)	Quantity per vial (mg/3 mL)	Function
Neostigmine Methylsulfate, USP	1,0 mg	3.0 mg	Active Pharmaceutical Ingredient
Glycopyrrolate, USP	0.2 mg	0.6 mg	Active Pharmaceutical Ingredient

Disodium Edetate Dihydrate, USP	0.5 mg	1.5 mg	(b) (4)
Sodium Chloride, USP	8.0 mg	24.0 mg	
Hydrochloric Acid, NF	q.s.	q.s.	pH Adjuster
Sodium Hydroxide, NF	q.s.	q.s.	pH Adjuster
Water for Injection, USP			(b) (4)
			(b) (4)

- **Description of container closure system –**

Component	Description	Manufacturer/Supplier
Container	3 mL (b) (4) syringe barrel with integrated Luer Lock and Elastomeric Rubber Tip Cap	(b) (4)
Closure	(b) (4) elastomeric plunger stopper, (b) (4) with plunger rod; (b) (4)	
Plunger Rod	(b) (4) plunger rod	

Reviewer's Assessment: Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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Valerie Amspacher

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