CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210997Orig1s000
210997Orig2s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 210997

Review #1

Drug Name/Dosage Form	**Glycopyrrolate Injection, USP Injection**
Strength	**0.2 mg / mL**
Route of Administration	**Intravenous or Intramuscular**
Rx/OTC Dispensed	**Rx**
Applicant	**Exela Pharma Sciences, LLC**
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	*9/5/17*	*OPQ*
2	*9/22/17*	*OPQ*
4	*10/11/2017*	*OPQ*
5	*10/25/17*	*OPQ*
8	*1/17/2018*	*OPQ*
9	*2/8/18*	*OPQ*
10	*2/12/18*	*OPQ*
11	*2/12/18*	*OPQ*
12	*2/26/18*	*OPQ*
13	*3/29/18*	*OPQ*
14	*4/3/18*	*OPQ*
15	*4/5/18*	*OPQ*
22	*5/25/18*	*OPQ*
23	*6/1/18*	*OPQ*
24	*6/4/18*	*OPQ*
25	*6/7/18*	*OPQ*

Quality ReviewTeam

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Martin Haber	Donna Christner
Drug Product	Chris Hough	Julia Pinto
Process	Yongming Lu/Haitao Li	
Microbiology	Denise Miller/Jason God	Bryan Riley
Facility	Wenzheng Zhang/Christina Capacci-Daniel	Derek Smith
Biopharmaceutics	Sandra Suarez/Kelly Kitchens	Tapash Ghosh
Regulatory Business Process Manager	Steven Kinsley	
Application Technical Lead	Ciby Abraham	
Laboratory (OTR)		
ORA Lead	Caryn McNab	
Environmental		

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	4/16/2018	
	Type II			Adequate	4/15/2018	
	Type III			Adequate	6/1/2018	
	Type III			Adequate	6/1/2018	
	Type III			Adequate	6/1/2018	
	Type III			Adequate	6/1/2018	
	Type III			Adequate	6/1/2018	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	17558	Reference for 505(b)(2)

2. CONSULTS – N/A

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

Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

Based on the recommendations from drug substance, process, microbiology, facilities, and drug product, CMC recommends the approval of Glyrx-PF (Glycopyrrolate Injection, USP) 0.2 mg/mL in 1 mL and 2 mL vials.

II. Summary of Quality Assessments

A. Product Overview

Glyrx-PF (0.2 mg/mL) is indicated for preoperative antimuscarinic during anesthesia and as adjunctive therapy for the treatment of peptic ulcer. The drug product is preservative free and the route of administration is intramuscular and intravenous.

Proposed Indication(s) including Intended Patient Population	GLYCOPYRROLATE INJECTION, USP (0.2 mg/mL) is indicated for the following: • As a preoperative antimuscarinic during anesthesia • As adjunctive therapy for the treatment of peptic ulcer
Duration of Treatment	**Adults** *Preanesthetic Medication:* 0.004 mg/kg IM, given 30 to 60 minutes prior to the anticipated time of induction of anesthesia *Intraoperative Medication:* single doses of 0.1 mg IV and repeated, as needed, at intervals of 2 to 3 minutes *Reversal of Neuromuscular Blockade:* 0.2 mg for each 1 mg of neostigmine or 5 mg of pyridostigmine *Peptic Ulcer:* 0.1 mg at 4-hour intervals, 3 or 4 times daily IV or IM **Pediatric patients** *Infants (1 month to 2 years of age):* may require up to 0.009 mg/kg *Peptic Ulcer:* Not recommended for the treatment of peptic ulcer in pediatric patients.

Maximum Daily Dose	***See above***
Alternative Methods of Administration	***N/A***

B. Quality Assessment Overview

The drug substance, Glycopyrrolate, USP is manufactured by (b) (4) (b) (4) and is referenced in DMF# (b) (4) (found adequate for this NDA and last reviewed 4/16/2018). The second supplier for Glycopyrrolate, USP drug substance is (b) (4) and is referenced in DMF# (b) (4) (found adequate for this NDA and last reviewed 4/15/2018). Glycopyrrolate is an odorless white crystalline powder. From the (b) (4) supplier, the drug substance has a (b) (4) month retest period when packaged in (b) (4) (b) (4) (b) (4) From the (b) (4) (b) (4) supplier, the retest period is (b) (4) months when packaged in (b) (4)

The drug product is a clear colorless solution for injection intended for intravenous or intramuscular use with a labeled content of 0.2 mg/mL Glycopyrrolate, USP in (b) (4) (b) (4) vials of the following pack sizes:

0.2 mg of Glycopyrrolate, USP drug substance as 1mL fill in (b) (4) vial
0.4 mg of Glycopyrrolate, USP drug substance as 2 mL fill in 2 mL vial

All single dose (1 mL and 2 mL) vials of Glycopyrrolate Injection, USP contain drug substance, 0.2 mg/mL Glycopyrrolate, USP and excipients, 9 mg/mL sodium chloride (tonicity agent), sodium hydroxide and/or hydrochloric acid, NF (pH adjuster) and Water for Injection, USP. The product is (b) (4) packaged in (b) (4) (b) (4) vials with (b) (4) rubber stoppers. Extractables/leachables were conducted on the container closure system and was found adequate. Additional details can be found in the drug product and pharmacology/toxicology reviews.

An expiry of 24 months is granted for Glyrx-PF (Glycopyrrolate Injection, USP) 0.2 mg/mL in 1 mL and 2 mL vials when stored at 25°C (77°F); (b) (4) (b) (4)

(b) (4)

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation Approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, stability	• Formulation • Raw materials • Process parameters •Scale/equipment • Site	L	-	-	-
Physical stability (API)	• Formulation • Raw materials • Process parameters •Scale/equipment • Site	L	-	-	-
Content uniformity	• Formulation • Raw materials • Process parameters •Scale/equipment • Site	L	-	-	-
Microbial Limits	• Formulation • Raw materials • Process parameters •Scale/equipment	H	-	L	Appropriate risk mitigation strategy was set in place to mitigate sterility issues. See microbiology review for additional details.

In Vitro Dissolution	• Formulation • Raw materials • Process parameters •Scale/equipment • Site • Exclude major reformulations • Alcohol dose dumping	L	-	-	-

*Risk ranking applies to product attribute/CQA

**For example, post marketing commitment, knowledge management post approval, etc.

BIOPHARMACEUTICS

Product Background:

NDA: 210997 ORIG-1

Drug Product Name / Strength: Glycopyrrolate Solution for Injection USP (0.2 mg/mL vial (0.2 mg/1 mL and 0.4 mg/2 mL))

Route of Administration: Intraveous or intramuscular injection

Applicant Name: Exela Pharma Sciencies, LLC

The Applicant is seeking approval of Glycopyrrolate Solution for injection 0.2 mg/mL per vial under two presentations, 0.2 mg/1 mL and 0.4 mg/2 mL. This 505b2 submission relies of the efficacy and safety findings of Robinul Injection. Rubinol was approved by the FDA under NDA 017558 (currently discontinued[1]) and is indicated for use as a preoperative antimuscarinic to reduce salivary, tracheobronchial, and pharyngeal secretions. Exela's products will be labeled for the same indications, dosage, and administration as was approved for Robinul Injection.

Review Summary:

The proposed product is an injectable solution which protects against the peripheral muscarinic effects (e.g., bradycardia and excessive secretions) of cholinergic agents. The formulation (components and composition) of the drug product under this NDA is very similar to Robinol (see Appendix).

A biowaiver request is included in this NDA submission as per 21 CFR 320.22b. Specifically, the Applicant claims that the proposed product meets the following requirements listed under the CFR:

1. BA is self-evident;
2. Glycopyrrolate Injection, USP is a parenteral drug product intended for administration by injection; and
3. Contains the same active ingredient, dosage form, route of administration, and indications as the reference listed drug, Robinul Injection (Glycopyrrolate Injection, USP) that is the subject of an approved new drug application, NDA 017558;
4. The inactive ingredients are different between the two products, however, the differences are not expected to adversely impact the efficacy or safety of Exela's product.

However, Exela's proposed drug product does not meet the requirements under 21 CFR 320.22b (i.e., having the same active and inactive ingredients). The proposed product has different osmolarity (b) (4) (Table 1, Appendix). Of note,

[1] Drugs at the FDA

solutions differing greatly in osmolarity from the normal range may cause tissue irritation, pain on injection, and electrolyte shifts. When solutions with extremes of tonicity are infused, fluids shift into or out of cells leading to phlebitis and thrombophlebitis.

Although the drug product does not meet the requirements under 21 CFR 320.22b, as per 21 CFR 320.24(b)(6) the FDA may consider additional information in supporting the relative BA or BE of the drug product to the Listed Drug and a scientific bridge can be established to the Agency's finding of safety and effectiveness for the Listed Drug. In this regard, the difference in osmolarity ***is considered of no clinical relevance*** due to the following reasons:

- Normal osmolarity of blood/serum is about 300-310 mOsm/L. Hypotonic and hypertonic solutions may be infused in small volumes and into large vessels, where dilution and distribution are rapid. The osmolarity of the proposed product is 300 mOs/kg.
- The generally accepted upper limit for a peripheral IV is 900 mOsm/L. When the osmolarity exceeds 900 mOsm/L, the ability of the peripheral veins to dilute parenteral infusions sufficiently is compromised, and chemical irritation of the vein intima occurs.
- In a brief review of the literature[2], it seems that 154 mOsm/L, is the lowest osmolarity that should be used via any IV route. Very hypotonic IV solutions such as 1/4 NS (NaCl 0.2%) cause red blood cells to swell and burst.
- In an email correspondence with the Clinical Review Team dated 2/07/18, Dr. Crisafi confirmed that the differences in osmolarity are of no clinical relevance.

There were no major changes implemented through drug product development. The manufacturing site for the clinical and commercial product is Exela Pharma Sciences, Lenoir, NC. The drug product is in solution. Therefore, the assurance of the quality of the drug product relies on drug product specifications (other than in vitro release testing) and in process controls characteristic of injectable drug product formulations.

List Submissions being reviewed (table):

SUBMISSION(S) DATE	SEQUENCE NO.
09/05/17	0001
12/20/17	0007

Highlight Key Outstanding Issues from Last Cycle:

[2] http://www.rxkinetics.com/iv_osmolarity.html

– ***Submit a formal request for a biowaiver, citing the appropriate CFR section and the data supporting the request.***

Concise Description Outstanding Issues Remaining: NONE

From Biopharmaceutics perspective, NDA 21099, Glycopyrrolate for Injection USP (0.2 mg/mL vial (0.2 mg/1 mL and 0.4 mg/2 mL)), is recommended for Approval.

Primary Biopharmaceutics Reviewer Name and Date:

Sandra Suarez Sharp, Ph.D. (Branch 2DB\ONDP\OPQ), 04/30/18

Secondary Reviewer Name and Date:

Kelly M. Kitchens, Ph.D., Acting Team Lead (Branch 2\DB\ONDP\OPQ), May 1, 2018

APPENDIX

Table 1. Comparison of Exela's Glycopyrrolate Injection, USP with RLD product, Robinul Injection

Exela's Formulation		RLD Product[1]	
Ingredients	**Composition**	**Ingredients**	**Composition**
Glycopyrrolate, USP	0.2 mg/mL	Glycopyrrolate, USP	0.2 mg/mL
Sodium chloride, USP	9 mg/mL	Sodium chloride, USP	Not present
Benzyl alcohol, NF*	Not Present	Benzyl alcohol, NF	9 mg/mL
Sodium hydroxide, NF and/or Hydrochloric acid, NF	pH adjusted to 2.5	Sodium hydroxide, NF and/or Hydrochloric acid, NF	pH adjusted to 2.0 to 3.0
Water for Injection, USP	q.s to 1.0 mL	Water for Injection, USP	q.s to 1.0 mL
Osmolality	About 300 mOsm/kg	Osmolality	Less than 50 mOsmol/kg

[1]Information regarding RLD formulation was obtained from the approved label of the RLD product, Robinul Injection.

MICROBIOLOGY

Product Background: The drug product is a (b) (4) solution indicated for use in pre-anesthesia, intraoperative use, reversal of neuromuscular blockade and in peptic ulcers.

NDA: 210997

Drug Product Name / Strength: Glycopyrrolate Injection / 0.2 mg/mL

Route of Administration: IV or IM

Applicant Name: Exela Pharma Sciences, LLC

Manufacturing Site:
Exela Pharma Sciences, LLC
1325 William White Place
Lenoir, NC 28645

Method of Sterilization: (b) (4)

Review Recommendation: Adequate.

Review Summary: Drug product is (b) (4) (b) (4). This review covers the validation of the (b) (4) process and the (b) (4) related components. (b) (4) (b) (4)

List Submissions Being Reviewed:
09/05/2017 (original)
01/17/2017 (validation of analytical procedures)
02/26/2018
03/29/2018

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: An initial Information Request was submitted by the Agency, dated 2/12/2018. The applicant's responses, received 2/26/2018, are covered in the appropriate sections of this review. A second information request was submitted by the Agency, dated 22 March 2018. The applicant's responses, received 29 March 2018, are covered in the appropriate sections of this review.

Concise Description Outstanding Issues Remaining: (None)

Supporting Documents:
DMF (b) (4) LOA dated 18 June 2013. The DMF was reviewed on 3 February 2017 (see (b) (4)), and found adequate for the endotoxin (b) (4) (b) (4).

DMF (b) (4) LOA dated 27 March 2018. The DMF was reviewed on 09 April 2018 (see (b) (4)) and found adequate for endotoxin (b) (4) (b) (4)

List Number of Comparability Protocols (ANDA only): (None)

S Drug Substance

N/A. Drug substance is supplied non-sterile.

P.1 Description of the Composition of the Drug Product

- **Description of drug product –**
  Clear, colorless solution for injection.

- **Drug product composition –**

Table 1: Composition of Glycopyrrolate Injection

Glycopyrrolate Injection , USP	Proposed Commercial Batch
Glycopyrrolate, USP	(b) (4)
Sodium Chloride, USP	
Hydrochloric Acid, NF	q.s. to pH 2.5
Sodium Hydroxide, NF	If necessary to q.s. pH
Water for Injection, USP	q.s. to (b) (4)

Table 1 was compiled from date presented in the table on page 4/7 in "__cdsesub1_evsprod_nda210997_0001_m3_32-body-data_32p-drug-prod_glyc-exel-inje_32p3-manuf_batch-formula.pdf," located in Module 3.2.P.3.2

- **Description of container closure system –**

Table 2: Container-closure components for Glycopyrrolate Injection

(b) (4) (b) (4)	(b) (4)
(b) (4) (b) (4)	
(b) (4) (b) (4)	
(b) (4) (b) (4)	

Table 2 was reproduced from the table on page 3/11 in "container-closure-summary.pdf," located in Module 3.2.P.7

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Container/Closure and Package Integrity**

  Container-closure integrity testing is performed (b) (4)

  (b) (4)

- **Antimicrobial Effectiveness Testing**

  N/A. Drug product is non-preserved and labeled as single-dose.

Reviewer's Assessment: ***Adequate.***

Description of drug product and pharmaceutical development information were consistent with the FDA Guidances for Industry: (1) Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, and (2) Q8(R2) Pharmaceutical Development.

P.3 Manufacture

P.3.1 Manufacturers

Exela Pharma Sciences, LLC
1325 William White Place
Lenoir City, NC

P. 3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

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(b) (4)

[redacted]

Reviewer's Assessment: ***Adequate.***
The drug product specification (sterility and bacterial endotoxins testing) and validations comply with USP <1> Injections, <71> Sterility Test, and <85> Bacterial Endotoxins Test, as well as FDA Guidance for Industry: Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.

P.8 Stability

P. 8.1 Stability Summary and Conclusion

Stability testing was performed at accelerated (40°±2°C/75±5%RH) and long term (25°±2°C/60±5%RH) on 4 batches each for both drug product presentations. Endotoxin and sterility were tested at 0, 3 and 6 months of accelerated samples and at 0, 12 and 24 months on long-term samples. All testing was performed on vials stored in the inverted position. Based on preliminary stability data, a shelf-life of 24 months is proposed.

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

The applicant commits to placing the first 3 commercial batches on stability. (b) (4) thereafter, one batch will be placed on stability, provided that batches are manufactured.

P.8.3 Stability Data

Data are provided through 18 months of testing and show no excursions for sterility. No results are provided for endotoxin testing on stability samples. This information will be requested via IR.

Reviewer's Assessment: ***Adequate.***

The applicant has met regulatory expectations with regard to the design of the stability testing program to support the drug product's microbiological quality throughout its shelf life. In addition, the stability data submitted to date support the microbiological quality of the subject drug product.

R Regional Information

- **Executed Batch Records**

(b) (4)

[redacted]

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(b) (4)

[redacted]

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

- **2.A. Package Insert**
  Drug product is labeled as single dose, to be stored at 20-25°C.

Reviewer's Assessment: ***Adequate.***
The applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling.

List of Deficiencies: (None)

Primary Microbiology Reviewer Name and Date: Jason M. God, Ph.D., 19 April 2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Denise A. Miller, Senior Microbiologist, 19 April 2018

Jason God

Digitally signed by Jason God
Date: 4/19/2018 02:42:44PM
GUID: 56e1bae0001680fc58a5ce226a4481ab

Denise Miller

Digitally signed by Denise Miller
Date: 4/19/2018 03:17:49PM
GUID: 508da7280002a5d546459b998253d1aa

Ciby Abraham

Digitally signed by Ciby Abraham
Date: 6/10/2018 07:38:05PM
GUID: 512518c000026e22966a3bf7c15f7809