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April 5, 2019

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, Maryland 20852

CITIZEN PETITION

Exela Pharma Sciences, LLC ("Exela") submits this Petition to the Food and Drug Administration ("FDA") in accordance with 21 C.F.R. § 10.25(a) and § 10.30,[1] and pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act ("FDC Act"). For the reasons discussed below, Exela respectfully requests that FDA assign a Therapeutic Equivalence Evaluation Code ("TE Code") for the company's GLYRX-PF (glycopyrrolate injection), 0.2 mg/mL and 0.4 mg/2 mL, which FDA approved on July 11, 2018 under New Drug Application ("NDA") 210997. NDA 210997 was submitted by Exela to FDA pursuant to FDC Act § 505(b)(2). GLYRX-PF was approved for use in pre-anesthesia, intraoperative use, reversal of neuromuscular blockage, and adjunctive use in peptic ulcers.

I. FDA ACTION REQUESTED

In its Citizen Petition dated December 16, 2018[2], Exela previously requested that FDA assign in the Agency's Orange Book a TE Code of "AP" to GLYRX-PF with respect to West-Ward Pharmaceuticals Ltd's ("West-Ward") Robinul® (glycopyrrolate injection), 0.2 mg/mL, which FDA approved under NDA 017558 prior to January 1, 1982. In addition to this request, Exela also requests that FDA assign in the Agency's Orange Book a TE Code of "AP" to GLYRX-PF with respect to Somerset Therapeutics LLC's ANDA 207639 (glycopyrrolate injection, 0.2

[1] In the Preface to FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book"), the Agency states that "[a] person seeking to have a therapeutic equivalence rating for a drug product approved in a 505(b)(2) application may petition the Agency through the citizen petition procedure (*see* 21 CFR 10.25(a) and 21 CFR 10.30)." Orange Book Preface (37th ed., 2017), at xxiv.

[2] Exela Citizen Petition Dated December 16, 2018, Docket ID: FDA-2018-P-4769-001.

mg/mL and 0.4 mg/2 mL) ("Somerset ANDA Product"). As Robinul® is currently listed in the discontinued section of the Orange Book, a TE Code of "AP" with respect to a product that is currently in the active section, such as the Somerset ANDA Product, is necessary, under current FDA guidance[3], so that Exela will be exempt from, or can otherwise obtain a refund of, any Prescription Drug User Fee Act ("PDUFA") program fees that FDA assessed with respect to NDA 210997 for Fiscal Year 2019, and also for purposes of qualifying for an exemption from the annual program fee that might be assessed in future fiscal years under proposed legislation to reauthorize PDUFA.[4] As demonstrated below, Exela's GLYRX-PF, meets all applicable requirements for a TE Code with respect to the Somerset ANDA Product. There is no basis for FDA to deny this request. Accordingly, the assignment of a TE Code of "AP" is warranted.

II. STATEMENT OF GROUNDS

A. Factual and Regulatory Background

The Orange Book Preface explains that there are "two basic categories into which multisource drugs have been placed": (1) "A-rated" drug products (i.e., "Drug products that FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products"; and (2) "B-rated" drug products (i.e., "Drug products that FDA at this time, considers not to be

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[3] *Assessing User Fees Under the Prescription Drug User Fee Amendments of 2017 Guidance for Industry* dated May 2018. https://www.regulations.gov/document?D=FDA-2017-D-5913-0005 FDA Guidance dated

[4] Under the FDC Act, as amended by PDUFA, a prescription drug product is not assessed a product fee under FDC Act § 736(a)(3)(A) if such product qualifies for an exception under FDC Act § 736(a)(3)(B) (i.e., if such product is "the same as another product" approved under an NDA or Abbreviated NDA ["ANDA"] and that is listed in the Prescription Drug Product List section of the Orange Book). A sponsor's product that is excepted from the prescription drug product user fee is also exempt from assessment of any associated establishment user fee. See *id.* § 736(a)(2)(A). In 2016, FDA communicated a new policy in correspondence to another drug manufacturer that "once a determination is made that products are the same for purposes of the user fee exception [at FDC Act § 736(a)(3)(B)], such determination applies retroactively to the date of approval." Letter from Donal Parks, FDA, to Robert A. Dormer and Kurt R. Karst, at 4 (Aug. 23, 2016). As such, provided a request for refund of PDUFA user fees is timely made within the 180-day statutory deadline, *see* FDC Act § 736(i), FDA will refund previously paid user fees once the Agency determines that two drug products are the "same" as one another, and will not assess fees on an ongoing basis provided the two "same" drug products remain in the Prescription Drug Product List section of the Orange Book.

therapeutically equivalent to other pharmaceutically equivalent products"). Orange Book Preface (37th ed., 2017), at xiii (emphasis in original).

FDA defines "therapeutic equivalents" to mean "approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." 21 C.F.R. § 314.3(b). FDA defines "pharmaceutical equivalents" to mean:

> drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

Id. Drug products designated with an "A" TE Code fall under one of two main policies:

> (1) for those active ingredients or dosage forms for which no in vivo bioequivalence issue is known or suspected, the information necessary to show bioequivalence between pharmaceutically equivalent products is presumed and considered self-evident based on other data in the application for some dosage forms (e.g., solutions) or satisfied by a showing that an acceptable in vitro dissolution standard is met. A therapeutically equivalent rating is assigned to such products so long as they are manufactured in accordance with Current Good Manufacturing Practice regulations and meet the other requirements of their approved applications (these are designated AA, AN, AO, AP, or AT, depending on the dosage form, as described below); or
>
> (2) for those Drug Efficacy Study Implementation (DESI) drug products containing active ingredients or dosage forms that have been identified by FDA as having actual or potential bioequivalence problems, and for post-1962 drug products in a dosage form presenting a potential bioequivalence problem, an evaluation of therapeutic equivalence is assigned to pharmaceutical equivalents only if the approved application contains adequate scientific evidence establishing through in vivo and/or in vitro studies the bioequivalence of the product to a selected reference product (these products are designated as AB).

Orange Book Preface at xiii-xiv.

The Orange Book also defines and explains FDA's policies for various "A" sub-codes. Specifically, the TE Code "AP" is defined as "Injectable aqueous solutions and, in certain instances, intravenous non-aqueous solutions." Orange Book Preface at xvi. The Electronic Orange Book entry for the Somerset ANDA Product[5] is shown below:

Mkt.Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	GLYCOPYRROLATE	GLYCOPYRROLATE	A207639	INJECTABLE	INJECTION	0.2MG/ML	AP			SOMERSET THERAPEUTICS LLC

Exela's GLYRX-PF is available in two presentations: 0.2 mg/mL and 0.4 mg/2mL. The current Electronic Orange Book listing for GLYRX-PF is shown below:

Mkt.Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	GLYCOPYRROLATE	GLYRX-PF	N210997	SOLUTION	INTRAMUSCULAR, INTRAVENOUS	0.2MG/ML (0.2MG/ML)				EXELA PHARMA SCIENCES LLC
RX	GLYCOPYRROLATE	GLYRX-PF	N210997	SOLUTION	INTRAMUSCULAR, INTRAVENOUS	0.4MG/2ML (0.2MG/ML)				EXELA PHARMA SCIENCES LLC

According to FDA's approval letter, dated June 23, 2017 and attached as Exhibit A to this petition, the Somerset ANDA Product also has 0.2 mg/mL and 0.4 mg/2mL presentations:

> We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is **approved**, effective on the date of this letter. The Office of Bioequivalence has determined your Glycopyrrolate Injection USP, 0.2 mg/1 mL and 0.4 mg/2 mL (0.2 mg/mL) Single-dose Vials and 1 mg/5 mL (0.2 mg/mL) and 4 mg/20 mL (0.2 mg/mL) Multiple-dose Vials to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Robinul Injection, 0.2 mg/mL, of West-Ward Pharmaceuticals International Limited (West-Ward).

In addition, as with Exela's GLYRX-PF, the Somerset ANDA Product designated West-Ward's Robinul® as the RLD and also claimed therapeutic equivalence to Robinul®. In the case

[5] Orange Book as of March 31, 2019.

of the Somerset ANDA Product, FDA granted an "AP" rating on approval, as shown by Exhibit A.

B. Request for TE Code Assignment for Exela's GLYRX-PF

According to FDA's website, FDA considers drug products to be pharmaceutical equivalents if they meet these three criteria:

- they contain the same active ingredient(s)
- they are of the same dosage form and route of administration
- they are identical in strength *or* concentration.

https://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm (emphasis added).

Exela's GLYRX-PF product is pharmaceutically equivalent to the Somerset ANDA Product. This product has the same: active ingredient (glycopyrrolate). As discussed above, FDA defines a pharmaceutical equivalent as one that has the same strength *or* concentration. Both the Somerset ANDA Product and Exela's GLYRX-PF have a concentration of 0.2 mg/mL. In terms of the strength, Exela's GLYRX-PF and the Somerset ANDA Product are sold in the same size vials. The Somerset ANDA Product is available in 2 mL and 1 mL vials for the 0.4 mg and 0.2 mg products respectively.[6] The same is the case for GLYRX-PF.[7] Therefore, both products contain the same total drug content. Finally, regarding the dosage form and route of administration, Exela notes that the Somerset ANDA Product was granted an AP rating with respect to the RLD Robinul® even though its dosage form is listed in the Orange Book as an "INJECTABLE" and its route of administration is listed as "INJECTION." In contrast, the RLD's dosage form in the Orange Book is listed as "SOLUTION" and its route of administration is listed as "INTRAMUSCULAR, INTRAVENOUS." As such, the fact that the route of administration for GLYRX-PF listed in the Orange Book is "INTRAMUSCULAR, INTRAVENOUS" and the dosage form is listed as "SOLUTION" should not preclude pharmaceutical equivalence. In addition, it is clear from the approved labeling, that both products are solutions for injection, as is the RLD. Therefore, Exela submits that the difference in listing in the Orange Book with respect to dosage form and route of administration reflects a change in the nomenclature used in the Orange Book as opposed to a substantive difference in dosage form or route of administration.

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[6] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a46c5ec1-a1b4-46fc-9b37-8da7f0c983d6

[7] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2189f3f5-39dc-4e85-b7c6-9515ded59686

Therefore, Exela's GLYRX-PF should be deemed a pharmaceutical equivalent to the Somerset ANDA Product.

Exela's GLYRX-PF should be assigned a therapeutic equivalence code of "AP" because it has already been deemed bioequivalent to Robinul®, the RLD designated by the Somerset ANDA Product, by FDA. Specifically, both presentations (0.2 mg/mL and 0.4 mg/2mL) of Exela's GLYRX-PF product qualified for a bioequivalence waiver, pursuant to 21 C.F.R. § 320.22. Moreover, both GLYRX-PF and West-Ward's Robinul® "can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." 21 C.F.R. § 314.3(b) (defining "therapeutic equivalents"). Considering that GLYRX-PF qualified for a bioequivalence waiver with respect to the RLD, GLYRX-PF is "expected to have the same clinical effect and safety profile [as the RLD] when administered to patients under the conditions specified in the labeling", both products designate the same RLD, and the Somerset ANDA Product was deemed therapeutically equivalent to the RLD, Exela's product should also be deemed bioequivalent to the Somerset ANDA Product. *Id*.

As such, Exela's GLYRX-PF and Somerset ANDA product are pharmaceutical and therapeutic equivalents and Exela's GLYRX-PF should be identified in the Orange Book with an "AP" TE Code.

III. ENVIRONMENTAL IMPACT

Petitioner claims a categorical exclusion under 21 C.F.R. § 25.31.

IV. ECONOMIC IMPACT STATEMENT

Petitioner will, upon request by the Commissioner, submit economic impact information, in accordance with 21 C.F.R. § 10.30(b).

V. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner that are unfavorable to the Petition.

Sincerely,

Aruna Koganti Digitally signed by Aruna Koganti
Date: 2019.04.05 15:52:47 -04'00'

Aruna Koganti, Ph.D., MBA
Vice President, Regulatory Affairs and Clinical Programs
Exela Pharma Sciences, LLC

Exhibit A

ANDA 207639

ANDA APPROVAL

Somerset Therapeutics, LLC
475 Bernardsville Road
Mendham, NJ 07945
Attention: Veerappan Subramanian
President and CEO

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on June 13, 2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Glycopyrrolate Injection USP, 0.2 mg/1 mL and 0.4 mg/2 mL (0.2 mg/mL) Single-dose Vials and 1 mg/5 mL (0.2 mg/mL) and 4 mg/20 mL (0.2 mg/mL) Multiple-dose Vials.[1]

Reference is also made to the complete response letter issued by this office on October 20, 2016, and to your amendments received on December 13, 2016; and February 16 and May 2, 2017.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is **approved**, effective on the date of this letter. The Office of Bioequivalence has determined your Glycopyrrolate Injection USP, 0.2 mg/1 mL and 0.4 mg/2 mL (0.2 mg/mL) Single-dose Vials and 1 mg/5 mL (0.2 mg/mL) and 4 mg/20 mL (0.2 mg/mL) Multiple-dose Vials to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Robinul Injection, 0.2 mg/mL, of West-Ward Pharmaceuticals International Limited (West-Ward).

Under section 506A of FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

[1] We note that the RLD upon which you have based this ANDA, West-Ward's Robinul Injection, 0.2 mg/mL, is no longer being marketed in the United States and is currently listed in the discontinued section of FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"). The Agency has determined that West-Ward's Robinul Injection, 0.2 mg/mL, was not withdrawn from sale for reasons of safety or effectiveness. FDA published this determination in (81 FR 61220; September 6, 2016). This determination allows the Agency to approve ANDAs for the discontinued drug product.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur

by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

Sincerely yours,

{See appended electronic signature page}

Priya Shah, PharmD
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research