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**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**

Hyman, Phelps & McNamara, P.C. submits this Petition to the Food and Drug Administration (“FDA”) on behalf of Xellia Pharmaceutical ApS and Xellia Pharmaceuticals USA, LLC (“Xellia”), and in accordance with 21 C.F.R. § 10.25(a) and § 10.30,<sup>1</sup> and pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (“FDC Act”). For the reasons discussed below, Xellia respectfully requests that FDA assign a Therapeutic Equivalence Evaluation Code (“TE Code”) for the company’s Vancomycin Injection, 500 mg/100 mL and 1 g/200 mL, which FDA approved on February 15, 2019 under New Drug Application (“NDA”) 211962, and that was submitted to the Agency pursuant to FDC Act § 505(b)(2).<sup>2</sup>

Xellia requests that FDA assign in the Agency’s Orange Book a TE Code of “AP” to the 500 mg/100 mL and 1 g/200 mL drug products under NDA 208562 for Xellia’s Vancomycin Injection. A TE Code is necessary so that Xellia will be exempt from, or can otherwise obtain a refund of, any Prescription Drug User Fee Act (“PDUFA”) program user fees that FDA may assess with respect to NDA 211962 for Fiscal Year 2020 and in

<sup>1</sup> 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 (39th ed., 2019), at xxiv.

<sup>2</sup> FDA approved two additional strengths under NDA 211962—1.5 g/300 mL and 2 g/400 mL—that are not relevant to this Citizen Petition because FDA has not approved another drug product that is a pharmaceutical equivalent of either strength.

future fiscal years. As demonstrated below, Xellia’s Vancomycin Injection, 500 mg/100 mL and 1 g/200 mL, meet all applicable requirements for a TE Code with respect to Baxter Healthcare Corporation’s (“Baxter’s”) Vancomycin Injection, 500 mg/100 mL and 1 g/200 mL, which are approved under NDA 050671. Accordingly, the assignment of a TE Code 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 therapeutically equivalent to other pharmaceutically equivalent products”). Orange Book Preface (39th ed., 2019), at xiii (emphasis in original).

An FDA regulation defines the term “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).<sup>3</sup> FDA further explains in the Orange Book Preface that:

FDA classifies as therapeutically equivalent those drug products that meet the following general criteria:

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<sup>3</sup> Another FDA regulation defines the term “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.

21 C.F.R. § 314.3(b).

- (1) they are approved as safe and effective;
- (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the identical active drug ingredient in the identical dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity;
- (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard;
- (4) they are adequately labeled; and
- (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations.

Orange Book Preface (39th ed., 2019), at vii (reformatted).

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 either presumed and considered self-evident (based on other information in the application for some dosage forms (e.g., solutions)), or satisfied by a showing that an acceptable in vitro approach is met. A therapeutically equivalent rating is assigned 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 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 xiv. The Orange Book also defines and explains FDA's policies for various "A" sub-codes. In particular, the TE Code "AP" is defined as "Injectable aqueous solutions and, in certain instances, intravenous non-aqueous solutions." Orange Book Preface at xvii.

**B. Vancomycin Injection, 500 mg/100 mL and 1 g/200 mL**

FDA has approved two NDAs for pharmaceutically equivalent versions of Vancomycin Injection, 500 mg/100 mL and 1 g/200 mL: (1) Xellia's Vancomycin Injection, 500 mg/100 mL and 1 g/200 mL (NDA 211962); and (2) Baxter's Vancomycin Injection, 500 mg/100 mL and 1 g/200 mL (NDA 050671). Both NDAs appear as follows in the electronic version of the Orange Book:

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength
RX	VANCOMYCIN HYDROCHLORIDE	VANCOCIN HYDROCHLORIDE IN PLASTIC CONTAINER	N050671	INJECTABLE	INJECTION	EQ 500MG BASE/100ML
RX	VANCOMYCIN HYDROCHLORIDE	VANCOCIN HYDROCHLORIDE IN PLASTIC CONTAINER	N050671	INJECTABLE	INJECTION	EQ 1GM BASE/200ML
RX	VANCOMYCIN HYDROCHLORIDE	VANCOCIN HYDROCHLORIDE IN PLASTIC CONTAINER	N211962	SOLUTION	INTRAVENOUS	EQ 500MG BASE/100ML
RX	VANCOMYCIN HYDROCHLORIDE	VANCOCIN HYDROCHLORIDE IN PLASTIC CONTAINER	N211962	SOLUTION	INTRAVENOUS	EQ 1GM BASE/200ML

Although Xellia's Vancomycin Injection drug products appear, based on their listing in the Orange Book, to differ in dosage form vis-à-vis Baxter's Vancomycin Injection drug products, in fact, both the Xellia and Baxter drug products are in the identical dosage form. Indeed, the Prescribing Information for each drug product describes each as a "solution":

Vancomycin Injection is supplied as a ready to use clear, colorless to light brown **solution** in single-dose flexible bags containing 500 mg, 1 g, 1.5 g, and 2 g vancomycin in 100 mL, 200 mL, 300 mL, and 400 mL of liquid (consists of water and PEG together with the excipients NADA and lysine)

Vancomycin Injection (NDA 211962; Xellia), Prescribing Information, Section 16.1 (How Supplied) (Feb. 2019) (emphasis added).

Vancomycin Injection, USP is supplied as a frozen, iso-osmotic, premixed **solution** in a 100 mL, 150 mL, or 200 mL single dose GALAXY plastic container (PL 2040). . . .

Vancomycin Injection (NDA 050671; Baxter), Prescribing Information, How Supplied/Storage and Handling (Sept. 2017) (emphasis added).

Similarly, although Xellia's Vancomycin Injection drug products appear, based on their listing in the Orange Book, to differ in route of administration vis-à-vis Baxter's Vancomycin Injection drug products, in fact, both the Xellia and Baxter drug products are administered by the identical route. Indeed, the Prescribing Information for each drug product describes the route of administration as "for intravenous use only." Vancomycin Injection (NDA 050671; Baxter), Prescribing Information, Description (Sept. 2017); Vancomycin Injection (NDA 211962; Xellia), Prescribing Information, Section 2.1 (Important Administration Instructions) (Feb. 2019).

The Orange Book identification of Baxter's Vancomycin Injection in an "injectable" dosage form and with an "injection" route of administration appears to be a vestigial remnant of a nomenclature system that FDA no longer applies to a drug product identified in labeling as a ready-to-use solution for injection. As such, the Orange Book dosage form and route of administration identification for Baxter's Vancomycin Injection (NDA 050671) should be updated to contemporary nomenclature to accurately portray the drug and Xellia's Vancomycin Injection as pharmaceutical equivalents.

Xellia's Vancomycin Injection, 500 mg/100 mL and 1 g/200 mL (NDA 211962), which were determined to be bioequivalent to, and are otherwise the same as Baxter's Vancomycin Injection, 500 mg/100 mL and 1 g/200 mL (NDA 050671), were submitted to FDA pursuant FDC Act § 505(b)(2). Xellia would have been required to submit a 505(b)(2) NDA instead of an Abbreviated New Drug Application ("ANDA") for the 500 mg/100 mL and 1 g/200 mL strengths because of a so-called "non-exception

excipient” formulation change in the company’s drug product vis-à-vis the listed drug, Baxter’s Vancomycin Injection (NDA 050671), that otherwise precludes the submission of an ANDA. See 21 C.F.R. § 314.94(a)(9)(iii).<sup>4</sup> Specifically, Xellia’s Vancomycin Injection formulation differs qualitatively from Baxter’s Vancomycin Injection (NDA 050671) in two excipients. Whereas Baxter’s Vancomycin Injection contains approximately 5 g of Dextrose Hydrous, or 0.9 g of Sodium Chloride per 100 mL, Xellia’s Vancomycin Injection omits these excipients and contains 1.8 mL polyethylene glycol 400 (“PEG 400”), 1.36 g N-acetyl-D-alanine (“NADA”), and 1.26 g L-lysine hydrochloride (monochloride) per 100 mL.

As a result of the use of PEG 400 and NADA in Xellia’s Vancomycin Injection drug products, the Prescribing Information includes the following warning:

**WARNING: RISK OF EMBRYO-FETAL TOXICITY DUE TO EXCIPIENTS**

*See full prescribing information for complete boxed warning.*

**This formulation of Vancomycin Injection is not recommended for use during pregnancy because it contains the excipients polyethylene glycol (PEG 400) and N-acetyl D-alanine (NADA), which caused fetal malformations in animal reproduction studies. If use of vancomycin is needed during pregnancy, use other available formulations of vancomycin. (5.1, 8.1)**

Vancomycin Injection (NDA 211962; Xellia), Highlights of Prescribing Information, (Feb. 2019) (emphasis in original); see also Vancomycin Injection (NDA 211962; Xellia), Prescribing Information, Section 5.1 (Risk of Embryo-Fetal Toxicity Due to PEG 400 and NADA Excipients) and 8.1 (Pregnancy) (Feb. 2019).

<sup>4</sup> Xellia’s drug product is also available in new strengths—1.5 g/300 mL and 2 g/400 mL—that further supported the submission of a 505(b)(2) NDA.

**C. Request for TE Code Assignment for Xellia's Vancomycin Injection, 500 mg/100 mL and 1 g/200 mL**

Xellia's Vancomycin Injection, 500 mg/100 mL and 1 g/200 mL, meet all applicable requirements for a TE Code with respect to Baxter's Vancomycin Injection, 500 mg/100 mL and 1 g/200 mL (NDA 050671).

***First***, both Xellia's Vancomycin Injection and Baxter's Vancomycin Injection drug products are approved as safe and effective.

***Second***, both Xellia's Vancomycin Injection and Baxter's Vancomycin Injection drug products are pharmaceutical equivalents in that both drug products contain identical amounts (*i.e.*, 500 mg/100 mL and 1 g/200 mL) of the identical active drug ingredient (*i.e.*, vancomycin HCl), and are in identical dosage forms (*i.e.*, solution) for the same route of administration (*i.e.*, intravenous).

***Third***, both Xellia's Vancomycin Injection and Baxter's Vancomycin Injection drug products are equivalent to one another and "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).

***Fourth***, both Xellia's Vancomycin Injection and Baxter's Vancomycin Injection drug products are manufactured in compliance with Current Good Manufacturing Practice regulations.

***Fifth***, both Xellia's Vancomycin Injection and Baxter's Vancomycin Injection drug products are adequately labeled vis-à-vis one another. Although the Prescribing Information for Xellia's Vancomycin Injection includes a Black Box Warning, as well as other labeling information in Sections 5.1 and 8.1 concerning the risk of embryo-fetal toxicity due to the PEG 400 and NADA excipients in Xellia's vancomycin formulation, such differences do not preclude a determination that the two drug products should be AP-rated. Indeed, FDA has approved myriad A-rated therapeutic equivalents under ANDAs with labeling changes because of excipient differences.

FDA's regulations implementing the statutory ANDA "same labeling" requirement set forth examples of permissible differences in labeling that may result because a generic drug product and the Reference Listed Drug ("RLD") are produced or distributed by different manufacturers. These differences include "differences in expiration date, ***formulation***, bioavailability, or pharmacokinetics, labeling revisions made to comply with

current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under [the FDC Act].”  
21 C.F.R. § 314.94(a)(8)(iv) (emphasis added).

FDA has interpreted the difference-due-to-differences-in-manufacturer exception above to apply when the generic drug product differs in an aspect that is not required by the statute or regulation to be the same as the RLD, such as a difference in inactive ingredients. To that end, FDA has permitted the addition of warnings and related information in generic drug labeling that does not appear in the RLD labeling and, notwithstanding such differences, has still granted an “A” therapeutic equivalence rating among such drug products.<sup>5</sup> In this case, the labeling between Xellia’s Vancomycin Injection and Baxter’s Vancomycin Injection drug products differ because of formulation differences; however, those differences should not preclude FDA’s assignment of an AP TE Code.

For all of the reasons above, Xellia’s Vancomycin Injection, 500 mg/100 mL and 1 g/200 mL (NDA 211962) and Baxter’s Vancomycin Injection, 500 mg/100 mL and 1 g/200 mL (NDA 050671) 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).

<sup>5</sup> See Zeneca, Inc. v. Shalala, 213 F.3d 161 (D.C. Cir. 2000) (upholding an FDA decision to allow a generic product to include a different, permissible inactive ingredient and, therefore, to include in its labeling a warning consistent with Agency regulations for products containing that ingredient); FDA, Petition Response, Docket No. FDA-1999-P-0027 (Legacy No. 1999P-1654), at 4 (Apr. 19, 2005) (“[FDA’s] regulations do not prohibit approval of a proposed generic product whose labeling includes a warning (or, as in this case, cautionary statements) about a preservative that differs from that of the [RLD].”); FDA, Petition Response, Docket Nos. FDA-2005-P-0003, FDA-2006-P-0019, FDA-2006-P-0331, and FDA-2006-P-0391 (Sept. 15, 2009) (FDA permitted the generic product to contain a previously approved formulation of the drug product and carry labeling different from the reformulated RLD product).

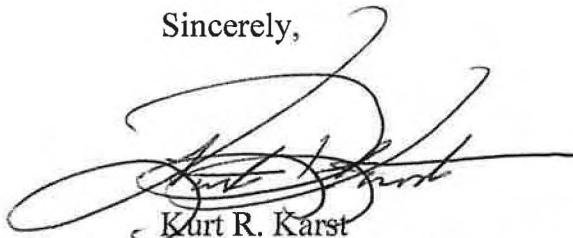
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**V. CERTIFICATION**

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,



Kurt R. Karst

Counsel to Xellia Pharmaceutical ApS and  
Xellia Pharmaceuticals USA, LLC