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September 25, 2020

Re: Docket No. FDA-2020-P-1236

Dear Mr. Rosen:

This letter responds to your citizen petition received on March 30, 2020 (Petition), requesting that the Food and Drug Administration (FDA or Agency) designate Acetylcysteine Injectable, 6 grams (g)/30 milliliters (mL), approved under abbreviated new drug application (ANDA) 200644 held by Fresenius Kabi USA LLC, as a reference listed drug (RLD) and reference standard in the *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book).[1]

You state that the current RLD listed in the Orange Book, Cumberland Pharmaceuticals Inc's Acetadote (acetylcysteine) injectable, 6 g/30 mL (new drug application (NDA) 021539), obtained patent protection for a formulation of acetylcysteine injection that does not include the inactive ingredient edetate disodium (Petition at 2). You state that "[p]revious formulations of the reference product did include edetate disodium", but you indicate that it was subsequently reformulated to exclude this inactive ingredient (Petition at 2). You also state that all the currently approved ANDAs for acetylcysteine injectable, 6 g/30 mL, contain edetate disodium, and you say that "[t]here is no indication that the previous formulation of the reference product was withdrawn for reasons relating to safety or efficacy" (Petition at 2). Therefore, you request that FDA designate ANDA 200644 as an RLD (Petition at 1) and "reference standard for purposes of comparison testing in support of filing and acceptance of an ANDA" (Petition at 2).

We have carefully considered the Petition. For the reasons described below, your Petition is denied. As further explained below, an applicant may seek approval in an ANDA of a drug product whose formulation includes edetate disodium as an inactive ingredient and that relies on Acetadote (acetylcysteine) injectable, 6 g/30 mL (NDA 021539) as the RLD if the requirements are met.

I. BACKGROUND

A. Acetadote

Acetadote (acetylcysteine) Injection 6 g/30 mL is an intravenous medication indicated to prevent or lessen hepatic injury after ingestion of a potentially hepatotoxic quantity of acetaminophen in patients with acute ingestion or from repeated supratherapeutic ingestion.[2]

[1] The Orange Book is available at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

[2] See labeling for Acetadote, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021539s017lbl.pdf.

The original formulation of Acetadote, approved on January 23, 2004 (NDA 021539), contained the chelating agent edetate disodium. The NDA approval included a postmarketing commitment to "evaluate the potential benefit of edetate disodium on the stability of the drug product."[3] In January 2011, FDA approved a reformulation of Acetadote that removed the edetate disodium.[4] Following this approval, Cumberland Pharmaceuticals Inc., the holder of the NDA for Acetadote, stopped marketing the original formulation.[5]

B. ANDAs and Regulatory Background

Section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)) allows the submission of an ANDA to market a generic version of a previously approved drug product. To obtain approval, the ANDA applicant must show, among other things, that the generic drug product (1) has the same active ingredient(s), dosage form, route of administration, strength, conditions of use, and, with certain exceptions, labeling as the listed drug; and (2) is bioequivalent to the listed drug.

A *listed drug* is a new drug product: (1) that has been approved under section 505(c) of the FD&C Act for safety and effectiveness or has been approved under section 505(j) of the FD&C Act; (2) whose approval has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(6) of the FD&C Act; and (3) that has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness.[6] Listed drug status is reflected by the drug product's identification in the current edition of FDA's Orange Book as an approved drug.[7] An *RLD* is the listed drug identified by FDA as the drug product on which an applicant relies in seeking approval of its ANDA.[8] Generally, an RLD is a drug product approved in an NDA under section 505(c) of the FD&C Act.

A *reference standard* is the drug product selected by FDA that an applicant seeking approval of an ANDA must use in conducting an in vivo bioequivalence study required for approval.[9] FDA generally selects a single reference standard that ANDA applicants must use in any in vivo bioequivalence testing required for approval. A single reference standard ensures the greatest level of consistency between a generic drug and its RLD and among generic drugs. Generally, the RLD will be the drug product selected by the Agency as the reference standard for

[3] See Approval Letter dated January 23, 2004, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-539_Acetadote_Approv.pdf.

[4] See Cumberland Pharmaceuticals Inc. v. Food & Drug Administration, et al., 981 F. Supp. 2d 38, 44 (D.D.C. 2013).

[5] Id.

[6] § 314.3(b) (21 CFR 314.3(b)).

[7] Id.

[8] Id.

[9] Id.

conducting in vivo bioequivalence testing.[10] In certain circumstances, however, the Agency may select a generic drug product as the reference standard for bioequivalence testing. For instance, if the RLD has been discontinued from marketing, FDA may select a therapeutically equivalent[11] generic drug product as the reference standard.[12] Finally, even if FDA selects a reference standard that is a drug product other than the RLD for use in conducting in vivo bioequivalence studies, an ANDA applicant must demonstrate that its proposed generic drug meets the sameness requirements in section 505(j) of the FD&C Act and Agency regulations in relation to the RLD.

II. DISCUSSION

As noted, you state that the current RLD[13] listed in the Orange Book, Cumberland Pharmaceuticals Inc's Acetadote (acetylcysteine) injectable, 6 g/30 mL (NDA 021539), has a formulation that does not include the inactive ingredient edetate disodium (Petition at 2). In the Petition, you state that all the currently approved ANDAs for Acetylcysteine Injection, 6 g/30 mL, including Acetylcysteine Injectable, 6 g/30 mL, approved under ANDA 200644 held by Fresenius Kabi USA LLC, contain edetate disodium. (Petition at 2.) Therefore, you are requesting that Fresenius Kabi USA LLC's product be designated as an RLD and reference standard that can serve as the basis for the filing of ANDAs (Petition at 1-2).

Section 505(j)(4)(H) of the FD&C Act provides that FDA shall approve an ANDA unless, among other things:

> ... information submitted in the application or any other information available to the Secretary shows that (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included

Consistent with the statute, FDA has issued implementing regulations on inactive ingredients in products proposed in ANDAs. In general, a drug product approved in an ANDA may have different inactive ingredients from the RLD as long as the ANDA demonstrates that the different inactive ingredients do not affect the safety or efficacy of the proposed drug product.[14] However, for ANDAs for parenteral drug products, the only difference in excipients that are routinely permitted are changes in preservatives, buffers, or antioxidants. FDA's regulation at § 314.94(a)(9)(iii) concerning the content and format of an ANDA states the following:

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[10] Id.

[11] "Therapeutic equivalents are 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" (§ 314.3(b)).

[12] "Abbreviated New Drug Applications and 505(b)(2) Applications," 81 FR 69580 at 69619 (Oct. 6, 2016).

[13] As a preliminary matter, we note that an RLD generally is a drug product approved under section 505(c) of the FD&C Act based on full reports of investigations of safety and effectiveness. Acetadote is listed as the RLD and also the reference standard in the current edition of the Orange Book.

[14] § 314.94(a)(9)(ii) (21 CFR 314.94(a)(9)(ii)).

> Generally, a drug product intended for parenteral use must contain the same inactive ingredients and in the same concentration as the [RLD] identified by the applicant…However, an applicant may seek approval of a drug product that differs from the [RLD] in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

The corresponding provision that addresses the refusal to approve an ANDA, 21 CFR 314.127(a)(8)(ii)(B)[15], provides the following:

> FDA will consider an inactive ingredient in, or the composition of, a drug product intended for parental use to be unsafe and will refuse to approve the ANDA unless it contains the same inactive ingredients, other than preservatives, buffers, and antioxidants, in the same concentration as the listed drug, and, if it differs from the listed drug in preservative, buffer, or antioxidant, the ANDA contains sufficient information to demonstrate that the difference does not affect the safety or efficacy of the drug product.

The regulations governing inactive ingredients were issued to address particular safety concerns posed by parenteral drug products. In addressing comments on proposed § 314.127 regarding changes in preservatives, buffers, and antioxidants, the Agency noted in the preamble of the final rule that under the statute, the inquiry is whether these inactive ingredients are "safe under the conditions prescribed, recommended, or suggested in the labeling" and that the regulation "reflects this concern, which is particularly acute for parenteral drug products" (57 FR 17950 at 17970; April 28, 1992).

However, when an ANDA applicant seeks approval for a parenteral formulation that is qualitatively and quantitatively[16] the same as a previously approved version of the RLD it references, FDA has determined that, in appropriate circumstances, it may waive the requirement in the regulation that the inactive ingredients in a parenteral drug product approved under an

[15] See also 21 C.F.R. §314.127(a)(8)(i) ("FDA will refuse to approve an ANDA…for any of the following reasons, unless the requirement has been waived under §314.99:…Information submitted in the ANDA or any other information available to FDA shows that: (A) The inactive ingredients of the drug product are unsafe for use, as described in paragraph (a)(8)(ii) of this section, under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug product; or (B) The composition of the drug product is unsafe, as described in paragraph (a)(8)(ii) of this section, under the conditions prescribed, recommended, or suggested in the proposed labeling because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included.").

[16] See FDA's guidance for industry *ANDA Submissions – Refuse-to-Receive Standards* at 8, n. 46 (December 2016, Rev.2) ("[Quantitative sameness generally is interpreted by OGD to mean a concentration that is within 95-105% of the RLD concentration.") We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/default.htm.

ANDA be the same as those in the currently approved formulation of the RLD,[17] insofar as the statutory requirement regarding safety of inactive ingredients has been met (21 CFR 314.99).[18]

FDA's regulations also require an ANDA for a product that refers to a listed drug that has been voluntarily withdrawn from sale to be accompanied by a citizen petition seeking a determination whether the listed drug was withdrawn for safety or effectiveness reasons (21 CFR 314.122(a)). The regulations further require FDA to determine whether a listed drug that has been voluntarily withdrawn from sale was withdrawn for safety or effectiveness reasons prior to approving an ANDA that refers to the listed drug (21 CFR 314.161(a)(l)). Where an applicant proposes a generic parenteral drug formulation that differs from its RLD in inactive ingredients other than preservatives, buffers, and antioxidants, but is the same as a previously approved formulation of the RLD (other than preservatives, buffers, and antioxidants), FDA conducts this same type of analysis to determine whether the previously approved formulation was discontinued from sale for reasons of safety or effectiveness.[19]

As explained in our response dated November 7, 2012, to citizen petitions in Docket Nos. FDA-2011-P-0339 and FDA-2012-P-0507, we reviewed the relevant scientific data and determined that the original formulation of Acetadote containing edetate disodium was not withdrawn from sale for reasons of safety or efficacy.[20] We stated that, consequently, FDA intends to approve ANDAs for acetylcysteine injection that duplicate that original formulation if they meet all applicable requirements for approval.[21]

Therefore, FDA can accept and approve ANDAs for Acetadote proposing to duplicate the original formulation of Acetadote that meet all requirements and include a request to waive the requirements of § 314.94(a)(9)(iii) under § 314.99(b). The Acetadote NDA 021539 would continue to be the RLD and the reference standard for any ANDAs that seek to duplicate the

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[17] As noted above, 21 CFR 314.94(a)(9)(iii) and 314.127(a)(8)(ii)(B) include an exception that permits ANDAs to differ from their RLDs in preservatives, buffers and antioxidants, under certain circumstances.

[18] See, e.g., March 25, 2005, letter from Steven K. Galson, Acting Director, Center for Drug Evaluation and Research, to Molly Ra pp and Anthony Celeste, Docket Nos. 2001-P-0574 and 2005-P-0061; September 15, 2009, letter from Janet Woodcock, Director Center for Drug Evaluation and Research, to Beth Brannan, Geoffrey M. Levitt, William A. Rakoczy, Christine J. Siwik, and Imtiyaz Basade, Docket Nos. FDA-2005-P-0003, FDA-2006-P-0019, FDA-2006-P-0331, and FDA-2006- P-0391.

The waiver provision states that "[a]n applicant may ask FDA to waive under this section any requirement that applies to the applicant under §§ 314.92 through 314.99. The applicant must comply with the requirements for a waiver under §314.90." 21 CFR 314.99(b). The waiver provision also states that "[i]f FDA grants the applicant's waiver request with respect to a requirement under §§314.92 through 314.99, the waived requirement will not constitute a basis for refusal to approve an ANDA under §314.127." Id; see also §314.127(a).

[19] See. e.g. Docket No. FDA-2001-P-0154 (01P-0333) (cyclophosphamide for injection); FDA-2009-P-0088 (doxercalciferol); FDA-2011-P-0339 (acetylcysteine injection).

[20] See Letter from Janet Woodcock, Director Center for Drug Evaluation and Research, to Steven Sklar and Peter Safir, Docket Nos. FDA-2011-P-0339 and FDA-2012-P-0507 (hereinafter "2012 Petition Response"); see also Cumberland, 981 F. Supp. 2d at 53 (holding that FDA's finding that the original Acetadote formulation was not withdrawn for safety or effectiveness was not arbitrary or capricious).

[21] See 2012 Petition Response. The 2012 Petition Response also explained that edetate disodium "is not a preservative, buffer, or antioxidant." Id. at 7.

original formulation of Acetadote. As such, it is unnecessary for FDA to designate a new RLD and RS.

III. CONCLUSION

FDA previously determined that the original formulation of Acetadote (acetylcysteine) Injection, 6 g/30 mL, containing edetate disodium was not withdrawn from sale for reasons of safety or efficacy. FDA can therefore accept submission of and approve ANDAs referencing this formulation, provided they meet all applicable requirements. The designation of another RLD and reference standard containing edetate disodium is not necessary. For the reasons described in this response, the Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

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