NEXUS PHARMACEUTICALS

Connecting Molecules to Medicine

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Dynna Gorham Bigby
Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20825

Supplement to Citizen Petition
Docket No. FDA-2022-P-2998

Dear Ms. Gorham Bigby:

Nexus Pharmaceuticals ("Nexus") submits this supplement to the Citizen Petition assigned Docket No. FDA-2022-P-2998 to update the U.S. Food and Drug Administration ("FDA" or "Agency") on the impact of the approval of EMERPHED® (ephedrine sulfate injection) in a single-dose, prefilled syringe on the arguments made in the Citizen Petition. The referenced Citizen Petition requested that the Agency issue a Final Notice in the *Federal Register* excluding ephedrine sulfate from the list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the Federal Food, Drug, and Cosmetic Act ("503B Bulks List") and issue a Final Notice in the *Federal Register* rescinding the *Interim Policy on Compounding Bulk Drug Substances Under 503B of the Federal Food, Drug, and Cosmetic Act* ("503B Interim Policy"). The approval of a single-dose, prefilled syringe of EMERPHED® makes this requested relief all the more warranted for the reasons provided below.

I. Background

In April 2020, FDA approved Nexus's EMERPHED® as a ready-to-use vial with a strength of 50 mg/10 mL for the treatment of clinically important hypotension occurring in the setting of anesthesia. Since that approval, Nexus has made EMERPHED® ready-to-use vials commercially available.

In September 2019, FDA issued a notice in the *Federal Register* proposing to exclude nine bulk drug substances, including ephedrine sulfate, from the 503B Bulks List.[1] In line with FDA's guidance, *Evaluation of Bulk Drug Substances Nominated for Use in Compounding*

[1] 84 Fed. Reg. 46, 015, 46017 (Sept. 3, 2019).

400 Knightsbridge Parkway | Lincolnshire, Illinois 60069
Telephone: 847-996-3790 | Fax: 847-996-3799
www.nexuspharma.net

Under Section 503B of the Federal Food, Drug, and Cosmetic Act ("Clinical Need Guidance"), FDA assessed whether 1) there was a clinical need for an outsourcing facility to compound a drug product and 2) the drug product must be compounded using the bulk drug substance.[2] The Agency determined that there was no basis to conclude that: 1) an attribute of EMERPHED® makes it medically unsuitable to treat certain patients and 2) the ephedrine sulfate drug products must be compounded using a bulk drug substance.[3] The proposed notice received only four comments in opposition. All of the comments opposing the proposal referred to providers' desire to avoid diluting the FDA-approved formulation (i.e., ready-to-use vial) and the compounders' ability to provide a ready-to-use formulation.

On November 23, 2022, Nexus submitted a Citizen Petition arguing in part that the desire for a different ready-to-use formula by the comments does not demonstrate clinical need. The Citizen Petition explained that none of the comments identified a single population for which a ready-to-use vial was medically unsuitable. Instead, the commenters focused on the risk of medication errors, risk of contamination, preventing drug shortages, or reducing costs. The Citizen Petition responded that the risk of medication errors, contamination, and drug shortages are not valid reasons to find a clinical need to compound ephedrine sulfate, and as FDA has reiterated for several years, FDA does not consider costs when determining whether a product should be included on the 503B Bulks List.[4] The nominators did not provide any bases to answer the first or second steps of the clinical need inquiry affirmatively. Because the nominators offered no information to demonstrate clinical need to compound ephedrine sulfate, the Citizen Petition concluded that FDA should finalize their proposed notice to exclude ephedrine sulfate from the 503B Bulks List.

Additionally, the Citizen Petition argued that the 503B Interim Policy should be rescinded because it violates the Administrative Procedure Act (APA). First, the interim policy violates the law because it creates a pathway for the marketing of an unapproved new drug that is not authorized by the Federal Food, Drug, and Cosmetic Act ("FDCA"). When creating section 503B of the FDCA, Congress intended to make a narrow exemption from the drug approval process if the statutorily-mandated conditions are met. By creating a new interim list called Category 1, which purportedly authorizes outsourcing facilities to compound from over 300 bulk drug substances, including ephedrine sulfate, FDA has added a new basis for compounding that goes outside the bounds of the statute and is subject to abuse. Second, the Citizen Petition demonstrated that FDA's application of the interim policy was arbitrary, capricious, and an abuse of discretion. FDA has placed substances on Category 1 that were not nominated with the required information required and FDA does not reassess the appropriateness of keeping bulk

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[2] FDA, *Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act*, at 9 (Mar. 2019) ("Clinical Need Guidance").

[3] 84 Fed. Reg. 46, 015, 46017 (Sept. 3, 2019).

[4] Clinical Need Guidance at 9.

drug substances in 503B Category 1 in light of new information, including FDA's own approvals of drugs containing those substances.

Pursuant to FDA's regulations, FDA must furnish a response to a citizen petition within 180 days of receipt of the petition.[5] The due date for a response to the citizen petition was May 22, 2023, yet Nexus has not received a response.

II. EMERPHED®'s approval as a prefilled syringe further shows there is no clinical need to compound ephedrine sulfate

On March 1st, 2023, FDA approved EMERPHED® in 25 mg/5 mL and 50 mg/10 mL single-dose, prefilled syringes for the treatment of clinically important hypotension occurring in the setting of anesthesia.[6] As some prescribers expressed a preference for a prefilled syringe, Nexus developed a new product and sought this approval to introduce the next generation of safe and effective, ready-to-administer ephedrine sulfate products.[7]

Nexus's ability to meet this prescriber preference eliminates suggested reasons for compounding ephedrine sulfate. As noted above, the comments to the *Federal Register* Notice proposing to exclude ephedrine sulfate from the 503B Bulks List focused on the risk of medication errors, risk of contamination, preventing drug shortages, or reducing costs. EMERPHED® prefilled syringes now satisfy commenters' preferences for a presentation that has the potential to lower the risk of medication errors and risk of contamination. Additionally, EMERPHED® prefilled syringes are not in shortage, and FDA continues not to consider costs when determining whether a product should be included on the 503B Bulks List. Thus, EMERPHED®'s approval as a prefilled syringe further demonstrates that there is no clinical need to compound drug products with ephedrine sulfate.

III. EMERPHED®'s approval as a prefilled syringe further illustrates why ephedrine sulfate should not be subject to FDA's 503B Interim Policy

FDA's ongoing enforcement discretion over compounding ephedrine sulfate, especially in the face of the approval of EMERPHED® prefilled syringes, underscores why the 503B Interim Policy should be rescinded. The Agency in practice is not updating the 503B Interim Policy to account for new information that should change a drug's categorization on the list. For example, the Agency itself found *almost four years ago* that there is no clinical need to compound ephedrine sulfate and nothing in the comments could have changed that finding. Consistent with that finding, the Agency should have stopped applying its enforcement

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[5] 21 C.F.R. § 10.30(e)(2).

[6] *See* Nexus Pharmaceuticals, *Nexus Pharmaceuticals, Inc. Receives FDA Approval for EMERPHED® (ephedrine sulfate injection) Pre-Filled Syringe* (Mar. 1, 2023), https://www.nexuspharma.net/news-articles/nexus-pharmaceuticals-inc-receives-fda-approval-for-emerphed-r-ephedrine-sulfate-injection-pre-filled-syringe.

[7] *Id.*

discretion policy to compounded ephedrine sulfate. The approval of EMERPHED®'s prefilled syringe presentation, which addresses the only remaining arguments posed by outsourcing facilities to continue compounding ephedrine sulfate, makes the continued discretion even more arbitrary and capricious. FDA should discontinue application of the 503B Interim Policy to ephedrine sulfate and rescind the 503B Interim Policy.

IV. Conclusion

With the approval of EMERPHED® in ready-to-use, prefilled syringes, providers can avoid dilution, while ensuring they provide patients a safe and effective, FDA-approved product. Thus, FDA has even more reason to exclude ephedrine sulfate from the 503B Bulks List. As described in the Citizen Petition, there is no clinical need to compound ephedrine sulfate and, with the approval of EMERPHED® in prefilled syringes, Nexus has addressed the different presentation preferences by physicians and pharmacists. Moreover, the Interim 503B Bulks Policy should be rescinded because it is not in accordance with law, and its application to ephedrine sulfate, despite new information indicating that the bulk drug substance does not belong in Category 1, is arbitrary, capricious, and an abuse of discretion.

Because over 180 days have passed since Nexus submitted the original Citizen Petition, Nexus respectfully asks that FDA respond immediately to the Citizen Petition again and grant the requested relief repeated below:

1. Issue a Final Notice in the *Federal Register* excluding ephedrine sulfate from the list of bulk drug substances that outsourcing facilities can use in compounding under section 503B of the FDCA.

2. Issue a Final Notice in the *Federal Register* rescinding the *Interim Policy on Compounding Bulk Drug Substances Under 503B of the Federal Food, Drug, and Cosmetic Act* (January 2017).

Sincerely,

Ayesha Ahmed
General Counsel
Nexus Pharmaceuticals

400 Knightsbridge Parkway | Lincolnshire, Illinois 60069
Telephone: 847-996-3790 | Fax: 847-996-3799
www.nexuspharma.net