Ayesha Ahmed
General Counsel
Nexus Pharmaceuticals, Inc.
400 Knightsbridge Parkway
Lincolnshire, Illinois 60069

August 21, 2023

Re: Docket No. FDA-2022-P-2998

Dear Ms. Ahmed:

This letter responds to the citizen petition (Petition) submitted to the Food and Drug Administration (FDA or we) by Nexus Pharmaceuticals, Inc. (Petitioner) on November 23, 2022, and the supplement to the Petition submitted on May 23, 2023 (Supplement). In the Petition, you request that FDA:

(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 Federal Food, Drug, and Cosmetic Act …

(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) ….[1]

We have carefully reviewed your Petition, your Supplement, and other information available to the FDA. For the reasons stated below, your Petition is granted as to your first request. With respect to your second request, that we rescind the guidance for industry *Interim Policy on Compounding Bulk Drug Substances Under 503B of the Federal Food, Drug, and Cosmetic Act* (January 2017) (2017 Interim Policy Guidance), FDA has not reached a decision on your Petition at this time. We will respond to the remaining request in your Petition once we have reached a decision.

I. BACKGROUND

A. Section 503B of the Federal Food, Drug, and Cosmetic Act

Section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353b) describes the conditions that must be satisfied for drug products compounded in an outsourcing

[1] Petition at 1.

facility to be exempt from section 505 of the FD&C Act (21 U.S.C. 355) (concerning the approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)), section 502(f)(1) of the FD&C Act (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use), and section 582 of the FD&C Act (21 U.S.C. 360eee–1) (concerning drug supply chain security requirements).[2]

One of the conditions that must be met for a drug product compounded by an outsourcing facility to qualify for the exemptions under section 503B of the FD&C Act is that the outsourcing facility may not compound a drug using a bulk drug substance unless: (1) the bulk drug substance appears on a list established by the Secretary of Health and Human Services identifying bulk drug substances for which there is a clinical need (the 503B Bulks List), or (2) the drug compounded from the bulk drug substance appears on the drug shortage list in effect under section 506E of the FD&C Act (21 U.S.C. 356e) at the time of compounding, distribution, and dispensing.[3]

Section 503B of the FD&C Act directs FDA to establish the 503B Bulks List by: (1) publishing a notice in the *Federal Register* proposing bulk drug substances to be included on the list, including the rationale for such proposal; (2) providing a period of not less than 60 calendar days for comment on the notice; and (3) publishing a notice in the *Federal Register* designating bulk drug substances for inclusion on the list.[4]

FDA is evaluating bulk drug substances nominated for inclusion on the 503B Bulks List. The guidance for industry *Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (March 2019) (Clinical Need Guidance) addresses FDA policies for developing the 503B Bulks List, including the FDA's interpretation of the phrase *bulk drug substances for which there is a clinical need*, as it is used in section 503B of the FD&C Act. The Clinical Need Guidance also addresses the factors and processes by which FDA intends to evaluate and list bulk drug substances. The 2017 Interim Policy Guidance describes FDA's policy regarding outsourcing facilities that compound human drug products using bulk drug substances while the 503B Bulks List is being developed.[5]

B. FDA's Evaluation of Ephedrine Sulfate for the 503B Bulks List

In the *Federal Register* of September 3, 2019, FDA issued a notice in which it evaluated nine nominated bulk drug substances, including ephedrine sulfate, under the section 503B statutory

---

[2] *See* section 503B(a) of the FD&C Act.
[3] *See* section 503B(a)(2)(A) of the FD&C Act.
[4] *See* section 503B(a)(2)(A)(i)(I) to (III) of the FD&C Act.
[5] As described in the 2017 Interim Policy Guidance, FDA has categorized nominated bulk drug substances that may be eligible for inclusion on the 503B Bulks List into Categories 1, 2, and 3. Category 1 includes bulk drug substances that may be eligible for inclusion on the 503B Bulks List, were nominated with sufficient supporting information for FDA to evaluate them, and have not been identified by FDA as appearing to present significant safety risks. Category 2 includes bulk drug substances that were nominated with sufficient supporting information to permit FDA to evaluate them and may be eligible for inclusion on the 503B Bulks List; however, FDA has identified significant safety risks relating to the use of these substances in compounding, pending further evaluation. Category 3 includes bulk drug substances that may be eligible for inclusion on the 503B Bulks List but were nominated with insufficient supporting information for FDA to evaluate them. FDA placed ephedrine sulfate in Category 1 during the pendency of FDA's evaluation of ephedrine sulfate for inclusion on the 503B Bulks List.

standard and proposed not to include them on the 503B Bulks List.[6] Ephedrine sulfate was nominated for inclusion on the 503B Bulks List to compound drug products that treat acute bronchospasm, drug-induced hypotension due to anesthesia, and nasal congestion.[7] The proposed route of administration was intravenous, the proposed dosage form was a preservative-free solution, and the proposed strengths were 5 milligrams (mg)/milliliter (mL) and 10 mg/mL.[8]

The September 2019 *Federal Register* notice stated that ephedrine sulfate is a component of FDA-approved drug products.[9] At the time of the September 2019 *Federal Register* notice, FDA-approved ephedrine sulfate was available as a single-dose preservative-free 50 mg/mL solution for dilution and intravenous administration.[10] In the September 2019 *Federal Register* notice, FDA found that the nominations for including ephedrine sulfate on the 503B Bulks List did not explain why the FDA-approved single-dose, preservative-free 50 mg/mL solution (for dilution) is medically unsuitable for certain patients.[11] FDA's review of the nominations revealed that there was (1) no basis to conclude that an attribute of the FDA-approved drug product makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation, and (2) no basis to conclude that the ephedrine sulfate drug products proposed in the nominations must be compounded using a bulk drug substance rather than the approved drug product. Therefore, FDA proposed not to include ephedrine sulfate on the 503B Bulks List.

Today, FDA issued a notice in the *Federal Register*, announcing its final decision not to include ephedrine sulfate on the 503B Bulks List.[12] As detailed in the notice, before reaching this determination, FDA thoroughly considered the comments submitted in response to the September 2019 notice. FDA has determined that there is no basis to conclude that the FDA-approved drug products that contain ephedrine sulfate are medically unsuitable for the uses proposed in the nominations. In addition, no further information was supplied during the comment period that supports the need for compounding ephedrine sulfate drug products from bulk drug substances. Accordingly, FDA found that there is no clinical need for outsourcing facilities to use bulk ephedrine sulfate in compounding. Thus, the August 21, 2023 *Federal Register* notice reflects FDA's final determination not to include ephedrine sulfate on the 503B Bulks List.[13] The 503B Bulks List available on FDA's website has been updated to reflect this determination.[14] Additionally, because ephedrine sulfate has been evaluated by FDA and is not being added to the 503B Bulks List, it has been removed from Category 1 and is no longer addressed by the 2017 Interim Policy Guidance.

---

[6] 84 FR 46014.
[7] *Id.* at 46017.
[8] *Id.* at 46017–18.
[9] *Id.* at 46018.
[10] *Id.* Today, ephedrine sulfate is available in the form of several FDA-approved drug products, including Emerphed (ephedrine sulfate), NDA 213407, held by the Petitioner, Nexus Pharmaceuticals, Inc. Emerphed was approved by FDA after the September 2019 *Federal Register* notice as a preservative-free, 25 mg/5mL (5 mg/mL) single-dose, premixed, labeled syringe (not for dilution) (approved February 28, 2023) and a preservative-free, 50 mg/10mL (5 mg/mL) single-dose, premixed vial (approved April 17, 2020).
[11] 84 FR 46018.
[12] 88 FR 56837
[13] *Id.*
[14] 503B Bulks List, available at https://www.fda.gov/media/120692/download.

II. DISCUSSION

A. Evaluation of Ephedrine Sulfate for the 503B Bulks List

The Petition first requests that FDA "[i]ssue 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 [FD&C Act]."[15] The Petition states that "[n]one of the public comments" filed in response to the September 2019 notice to not include ephedrine sulfate on the 503B Bulks List "supplies a reason to alter FDA's finding that there is no basis to conclude that the ephedrine sulfate injections approved at the time were medically unsuitable to treat patients, or that the ephedrine sulfate proposed to be compounded needed to be compounded from bulk drug substances."[16] The Petition also states that FDA's approval of Emerphed — Nexus's prediluted, ready-to-use formulation containing ephedrine sulfate that was approved by FDA after publication of the September 2019 notice — rebuts comments that only outsourcing facilities can produce diluted formulations, thereby "suppl[ying] an additional basis for FDA to find that there is no clinical need."[17]

As detailed in the *Federal Register* notice issued today, August 21, 2023, and as discussed above, having considered the comments to the docket and other available information, FDA has found that there is no clinical need for outsourcing facilities to use bulk ephedrine sulfate in compounding. Therefore, FDA has made its final determination not to include ephedrine sulfate on the 503B Bulks List. The 503B Bulks List available on FDA's website has been updated to reflect this determination. Ephedrine sulfate has also been removed from Category 1 and is no longer addressed by the 2017 Interim Policy Guidance.

Thus, we grant your Petition to the extent you request that we issue a final notice in the *Federal Register* excluding ephedrine sulfate from the 503B Bulks List.

B. Rescind the 2017 Interim Policy Guidance

Second, the Petition requests that FDA "[i]ssue 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)."[18] The Petition argues that "[t]he 503B Interim Policy is contrary to law because it creates a pathway for the marketing of an unapproved new drug that is not authorized by statute and, indeed, directly undermines the statute."[19] It goes on to state

---

[15] Petition at 1, 4–7.

[16] Petition at 6. The Petition identifies seven public docket comments regarding FDA's September 2019 notice to exclude ephedrine sulfate from the 503B Bulks List. The Petition identifies three comments that were submitted in support of the FDA's proposal: Fresenius Kabi Compounding LLC, Comment to Docket No. FDA-2018-N-3240, at 2 (Nov. 4, 2019); Public Citizen's Health Research Group, Comment to Docket No. FDA-2018-N-3240, at 2 (Nov. 4, 2019); and PharMEDium Services, LLC, Comment to Docket No. FDA-2018-N-3240, at 7 (Nov. 4, 2019). The Petition also identifies four comments submitted in opposition of the FDA's proposal: Nephron 503B Outsourcing Facility, Comment to Docket No. FDA-2018-N-3240, at 1 (Nov. 4, 2019); Reed Smith, Comment to Docket No. FDA-2018-N-3240, at 7-10 (Nov. 4, 2019); Outsourcing Facilities Association, Comment to Docket No. FDA-2018-N-3240, at 2–7 (Nov. 4, 2019); and Georgeta Titean, Comment to Docket No. FDA-2018-N-3240 (Oct. 3, 2019).

[17] Petition at 2, 7; Supplement at 3.

[18] Petition. at 1, 7–12.

[19] *Id*. at 10.

that the 2017 Interim Policy Guidance should be rescinded because it "authorizes outsourcing facilities to compound from over 300 bulk drug substances, including ephedrine sulfate[, . . . that] do not appear on the 503B Bulks List and their use is not limited to compounding a drug product that appears on FDA's drug shortage list."[20] The Petition also states that "[i]t was arbitrary, capricious, and an abuse of discretion for FDA to include ephedrine sulfate in 503B Category 1 of the Interim Policy because the nominations of this bulk drug substance did not contain all of the information that FDA had announced would be necessary to support a nomination."[21] The Petition further states that "[e]phedrine sulfate should not remain in 503B Category 1 when no nomination for the substance even references EMERPHED®, much less explains why this FDA-approved drug does not further satisfy the clinical need for ephedrine sulfate."[22]

As discussed above and detailed in the *Federal Register* notice issued today, August 21, 2023, FDA has found that there is no clinical need for outsourcing facilities to use bulk ephedrine sulfate in compounding. FDA has therefore made its final determination not to include ephedrine sulfate on the 503B Bulks List. The 503B Bulks List available on FDA's website has been updated to reflect this determination. Ephedrine sulfate has also been removed from Category 1 and is no longer addressed by the 2017 Interim Policy Guidance. Therefore, we will not address further the Petition's arguments with respect to the treatment of ephedrine sulfate under the 2017 Interim Policy.

At this time, FDA has not reached a decision on your Petition to the extent you request that we rescind the 2017 Interim Policy Guidance. We will respond to this request separately once we have reached a decision.

III. CONCLUSION

For the reasons stated above, the Petition is granted in part as to your first request. We will respond to the remaining request in your Petition once we have reached a decision.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
Date: 2023.08.21 13:29:48 -04'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

[20] *Id.*
[21] *Id.* at 11.
[22] *Id.* at 12; Supplement at 3–4.