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

December 7, 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 [Using] Bulk Drug Substances Under [Section] 503B of the Federal Food, Drug, and Cosmetic Act* (January 2017) . . . .[1]

On August 21, 2023, we issued a partial response to your Petition, granting your first request. This letter responds to your remaining request that we rescind the guidance for industry *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (January 2017) (2017 503B Interim Policy Guidance).[2]

FDA has carefully reviewed your Petition, your Supplement, and other information available to FDA. For the reasons stated below, your second request is denied. However, as detailed below, FDA has announced the issuance of a new draft guidance that, when finalized, will replace the 2017 503B Interim Policy Guidance. We welcome your comments on this new draft guidance.

I. BACKGROUND

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.
[2] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

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).[3]

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 the Department of Health and Human Services identifying bulk drug substances for which there is a clinical need (the 503B Bulks List) or (2) the drug product 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.[4]

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.[5]

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 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 503B 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.[6] On December 7, 2023, FDA announced in the *Federal Register* the issuance of a new draft guidance for industry *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (December 2023)

[3] *See* section 503B(a) of the FD&C Act.
[4] *See* section 503B(a)(2)(A) of the FD&C Act.
[5] *See* section 503B(a)(2)(A)(i)(I) to (III) of the FD&C Act.
[6] As described in the 2017 503B 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 bulk drug 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. *See* the 2017 503B Interim Policy Guidance at 5–6.

(2023 503B Interim Policy Draft Guidance or Draft Guidance).[7] The Draft Guidance, when finalized, will revise FDA's current interim policy with respect to categorization of certain substances nominated for inclusion on the 503B Bulks List, and it will replace the 2017 503B Interim Policy Guidance.

II. DISCUSSION

The Petition requests that FDA issue a final notice in the *Federal Register* rescinding the 2017 503B Interim Policy Guidance.[8] 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."[9] It goes on to state that the 2017 503B Interim Policy Guidance should be rescinded because it "authorizes outsourcing facilities to compound from over 300 bulk drug substances . . . [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."[10, 11]

As described above, a notice in the December 7, 2023 *Federal Register* announced the availability of the 2023 503B Interim Policy Draft Guidance. When finalized, the 2023 503B Interim Policy Draft Guidance will replace the 2017 503B Interim Policy Guidance and describe FDA's interim policy concerning the use of bulk drug substances in compounding by outsourcing facilities while FDA continues to develop the 503B Bulks List.

FDA believes that the balance of public health interests relating to categorization of newly nominated bulk drug substances has changed since the issuance of the 2017 503B Interim Policy Guidance.[12] Specifically, FDA believes that continuing such categorization no longer serves the 2017 503B Interim Policy Guidance's objective of preventing unnecessary disruption to patient treatment. Thus, the 2023 503B Interim Policy Draft Guidance, when finalized, would end the categorization of bulk drug substances into Categories 1, 2, or 3 for newly nominated bulk drug substances.

The *Federal Register* notice issued today invites public comment on the 2023 503B Interim

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[7] 88 FR 85293. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[8] Petition at 1, 7–12.

[9] *Id*. at 10; Supplement at 2–3.

[10] Petition at 10.

[11] The Petition also makes arguments about the treatment of ephedrine sulfate under the 2017 503B Interim Policy Guidance, including 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" (Petition at 11); *see* also Supplement at 3–4. As detailed in FDA's partial response to your Petition issued Aug 21, 2023, FDA will not address the Petitioner's arguments with respect to the treatment of ephedrine sulfate under the 2017 503B Interim Policy Guidance because FDA made its final determination not to include ephedrine sulfate on the 503B Bulks List. *See* 88 FR 56837 (*Federal Register* notice published Aug 21, 2023). As a result, ephedrine sulfate was removed from Category 1 and is no longer addressed by the 2017 503B Interim Policy Guidance.

[12] For more details about the revised interim policy, see the December 7, 2023 *Federal Register* notice and the 2023 503B Interim Policy Draft Guidance issued today (88 FR 85293).

Policy Draft Guidance. Because the process for public comment on the 2023 503B Interim Policy Draft Guidance will help shape the specific content of the final guidance, and because guidances may be revised over time in accordance with FDA's good guidance practices regulation (21 CFR 10.115), we decline to address here the arguments you make in support of your request regarding the 2017 503B Interim Policy Guidance.

Accordingly, we deny your request that we rescind the 2017 503B Interim Policy Guidance. We instead invite you and any other interested parties to review and submit comments to the docket on the 2023 503B Interim Policy Draft Guidance, in accordance with 21 CFR 10.115(h).[13] Doing so will permit FDA to efficiently finalize the Draft Guidance while taking into consideration all comments and information provided by the public, including any of your recommendations. You can submit electronic or written comments on the Draft Guidance at any time, but to ensure that FDA considers your comments before we begin work on the final version of the guidance, you should submit them by the date specified in the *Federal Register* notice of availability for the Draft Guidance.

III. CONCLUSION

For the reasons stated above, the Petition is denied as to your second request. This constitutes the final response to your Petition.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
Date: 2023.12.07 11:26:01 -05'00'

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

[13] *See* Docket No. FDA-2015-D-3539.