NEXUS PHARMACEUTICALS

Connecting Molecules to Medicine

SUBMITTED VIA REGULATIONS.GOV

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

November 23, 2022

CITIZEN PETITION

Nexus Pharmaceuticals, Inc. ("Nexus") respectfully submits this Citizen Petition pursuant to 21 C.F.R. § 10.30. This Petition requests that the Commissioner of Food and Drugs take the actions set forth below with respect to the compounding of bulk drug substances, including ephedrine sulfate, by outsourcing facilities.

A. Actions Requested

Through this petition, and for the reasons explained in more detail below, petitioners respectfully request that the U.S. Food and Drug Administration ("FDA" or "Agency") take each of the following actions within 180 days of the date of this petition.

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 ("FDCA") ("503B Bulks List").

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) ("503B Interim Policy").

B. Statement of Grounds

I. Executive Summary

This Citizen Petition requests that FDA finalize its proposal to exclude ephedrine sulfate from the 503B Bulks List. In September 2019, FDA issued a *Federal Register* notice proposing not to include ephedrine sulfate on the 503B Bulks List ("September 2019 Notice"). According to that notice, FDA found no basis to conclude that there is a clinical need for outsourcing facilities to compound drug products using the bulk drug substance ephedrine sulfate. That finding was based on the fact that the ephedrine sulfate nominations do not explain why the FDA-approved single-dose, preservative-free 50 mg/mL solution (for dilution) is medically unsuitable for certain patients and the fact that the nominations do not take the position or provide support for the position that drug products containing ephedrine sulfate must be compounded from bulk drug substances rather than by diluting the then-available approved drug product. FDA

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

received three comments in support of its proposal and four comments in opposition. The comments opposing FDA's proposal largely concentrated on the need to dilute the FDA-approved ephedrine sulfate prior to administration. Those comments are not persuasive. FDA established long ago that the need to dilute or otherwise manipulate an FDA-approved drug product prior to administration is not a basis for clinical need. Moreover, in April 2020, FDA approved EMERPHED®, Nexus's ready-to-use formulation containing ephedrine sulfate, which supplies an additional basis for FDA to find that there is no clinical need.

This Citizen Petition also requests that FDA rescind the 503B Interim Policy. This interim policy is not in accordance with law because it creates a pathway for the marketing of an unapproved new drug that is not authorized by statute and directly undermines the statute. In section 503B of the FDCA, Congress created a narrow exemption from the drug approval process for compounded drug products if certain statutorily-mandated conditions are met. One of those conditions is that a bulk drug substance must appear on either the 503B Bulks List or must be used to compound a drug product that appears on FDA's drug shortage list. FDA is developing the 503B Bulks List very slowly: since the 2013 enactment of section 503B, it has issued final determinations for only 14 bulk drug substances. Meanwhile, the 503B Interim Policy purports to authorize outsourcing facilities to compound drug products from more than 300 bulk drug substances and the category is growing. These substances do not appear on the 503B Bulks List and the Interim Policy does not require the drug products compounded from them to appear on FDA's drug shortage list. Thus, contrary to the statute, the 503B Interim Policy authorizes drug products to be marketed without FDA approval.

FDA has also applied the 503B Interim Policy in an arbitrary and capricious manner by including bulk drug substances in 503B Category 1 of the Interim Policy that do not meet the criteria for inclusion in that category. According to the 503B Interim Policy, 503B Category 1 substances were nominated with sufficient supporting information for FDA to evaluate them. However, FDA has placed substances in 503B Category 1 that were not nominated with all of the information that FDA had announced would be necessary to support a nomination. For example, ephedrine sulfate appears in 503B Category 1 even though its nominations do not include the following necessary information: why the FDA-approved single-dose, preservative-free ephedrine sulfate solution is not suitable for a particular patient population or why the drug products must be compounded from bulk drug substances rather than with the approved drug product. Moreover, FDA is not reassessing the appropriateness of keeping bulk drug substances in 503B Category 1 in light of new information, including its own approvals of drugs containing those substances. Ephedrine sulfate, for example, remains on 503B Category 1 even though there is no nomination for the substance that even mentions the approval of EMERPHED®.

With respect to timing, this Citizen Petition requests that FDA take each of these actions within 180 days. This timeline is reasonable. By placing this bulk drug substance

in 503B Category 1, FDA has permitted outsourcing facilities to compound from ephedrine sulfate since at least 2018. FDA continues to permit this compounding, despite determining in 2019 that there is no clinical need for outsourcing facilities to compound drug products using the bulk drug substance ephedrine sulfate and despite approving EMERPHED® in 2020 in a presentation that does not require dilution. The time has come to remove ephedrine sulfate from 503B Category 1 and finalize the determination to exclude ephedrine sulfate from the 503B Bulks List. In addition, the 503B Interim Policy should be rescinded within 180 days because the policy and its application violate the Administrative Procedure Act (APA).

Taking the requested actions will advance FDA's mission to protect public health by reducing patients' unnecessary exposure to compounded drugs that have not undergone FDA review for safety, efficacy, and manufacturing quality. With respect to ephedrine sulfate specifically, vulnerable patients being treated for clinically important hypotension in the setting of anesthesia should not be unnecessarily exposed to the risks of compounded drugs, including risks relating to dosing, stability, and sterility, when an approved drug product—EMERPHED®—can meet their medical needs. Acting on these requests also will promote the integrity and effectiveness of the drug approval process and encourage companies to invest in the research and testing required to obtain FDA approval for their drug products.

II. Nexus Requests that FDA Issue a *Federal Register* Notice to Finalize Its Proposal that Ephedrine Sulfate Not Be Included on the 503B Bulks List

A. Legal and Regulatory Background: Clinical Need Analysis

Under section 503B, an outsourcing facility may compound from a bulk drug substance only in two circumstances: (1) if the substance appears on the 503B Bulks List, or (2) if the bulk drug substance is used to compound a drug that appears on the drug shortage list in effect under section 506E of the FDCA at the time of compounding, distribution, and dispensing.[1] The FDCA requires FDA to develop the 503B Bulks List by issuing a notice in the *Federal Register* identifying bulk drug substances for inclusion on the list, providing a public comment period of at least 60 days, and then publishing another notice in the *Federal Register* designating bulk drug substances that will be included on the list.[2]

An FDA guidance, *Evaluation of Bulk Drug Substances Nominated for Use in*

[1] FDCA § 503B(a)(2)(A).

[2] Note that although the statute directs FDA to identify those substances that it will include on the list, the Agency also is engaging in this process to identify by *Federal Register* notice the bulk drug substances that the Agency will not include on the 503B Bulks List. See, e.g., 84 Fed. Reg. 7,383 (Mar. 4, 2019).

Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act, states that the Agency interprets the statutory language "bulk drug substances for which there is a clinical need" in section 503B(a)(2)(A) of the FDCA to mean that the 503B Bulks List can "include a bulk drug substance if: (1) there is 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."[3] This guidance describes the factors that FDA intends to consider when determining whether the clinical need standard has been met and sets forth a two-part test. The first part pertains to bulk drug substances that are components of FDA-approved drug products and asks: (a) whether there is a basis to conclude that an attribute of the approved drug that makes it medically unsuitable for certain patients and the compounded drug is intended to address that attribute ("part 1(a)" of the analysis), and (b) whether there is a basis to conclude that the drug product must be compounded from a bulk drug substance ("part 1(b))" of the analysis).[4]

The second part of the test applies to bulk drug substances that proceed through part 1 or that are not components of FDA-approved drug products. There, FDA balances considerations relating to the physical and chemical characteristics of the substance; any safety issues raised by the use of the substance in compounding; the available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any; and the current and historical use of the substance in compounded drug products.[5]

B. FDA's Proposal Not to Include Ephedrine Sulfate on 503B Bulks List

On September 3, 2019, FDA issued a notice in the *Federal Register* proposing not to include nine bulk drug substances, including ephedrine sulfate, on the 503B Bulks List.[6] FDA made this finding even before approving Nexus's ready-to-use EMERPHED®. The September 2019 Notice first states that the nominations for ephedrine sulfate 5 mg/mL and 10 mg/mL injections "do not identify an attribute of the FDA-approved drug products"—then single-dose, preservative-free 50 mg/mL solution for dilution—that "is medically unsuitable for certain patients."[7] The September 2019 Notice further concludes that the nominations provide "no basis to conclude that an attribute of the FDA-approved product makes it medically unsuitable to treat certain

[3] 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").

[4] *Id.* at 11-14.

[5] *Id.* at 11-12, 14-17.

[6] 84 Fed. Reg. 46,014, 46,015, 46,017 (Sept. 3, 2019).

[7] *Id.* at 46,018.

patients for a condition that FDA has identified for evaluation."[8] The September 2019 Notice goes on to state that "[t]he nominations do not take the position or provide support for the position that drug products containing ephedrine sulfate must be compounded from bulk drug substances rather than by diluting the approved drug product" and that "FDA finds 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."[9]

FDA received seven comments on its proposal with respect to ephedrine sulfate. Three submitted comments in support,[10] and four submitted comments in opposition. Below is a summary of the comments in opposition.

Comments opposing FDA's proposal:

- **Nephron 503B Outsourcing Facility**: Referring to the pre-Nexus approved product, the comment asserts that the FDA-approved drug product is "clinically unsuitable" because it "is only available in a formulation which must be diluted before administration," which increases the risk of medication errors. Further, the commenter asserts that placing ephedrine sulfate on the 503B Bulks List would help to prevent drug shortages.[11]

- **Reed Smith**: Again referring to the pre-Nexus approved product, the comment argues that FDA-approved ephedrine sulfate is medically unsuitable because it is not in ready-to-use form, and the need to dilute it prior to administration increases the risk of contamination and medication errors. The comment further argues that DEA quotas limit the amount of approved drug product that outsourcing facilities can obtain. According to the comment, the drug product proposed to be compounded must be made from bulk drug substances because this involves fewer manipulations than compounding from the approved drug, which decreases the risk of contamination. The comment states that prohibiting the compounding of ephedrine sulfate from bulk drug substances will lead to

[8] *Id.*

[9] *Id.*

[10] The three comments came from Fresenius Kabi (the company "concurs with the FDA's analysis and conclusions regarding purported clinical need, or lack thereof"), Public Citizen (the organization "strong[ly] endorse[s] the agency's proposal to exclude. . . ephedrine sulfate . . . from the 503B Bulks List"), and PharMEDium Services (arguing that there is no clinical need to compound ephedrine sulfate). *See* Fresenius Kabi Compounding LLC, Comment to Docket No. FDA-2018-N-3240, at 2 (Nov. 4, 2019); Public Citizen Health Research Group, Comment to Docket No. FDA-2018-N-3240, at 2 (Nov. 4, 2019); PharMEDium Services, LLC, Comment to Docket No. FDA-2018-N-3240, at 7 (Nov. 4, 2019).

[11] Nephron 503B Outsourcing Facility, Comment to Docket No. FDA-2018-N-3240, at 1 (Nov. 4, 2019).

drug shortages.[12]

- **Outsourcing Facilities Association**: Referring to the pre-Nexus approved product, the comment states that FDA-approved ephedrine sulfate drug products are medically unsuitable because they require dilution prior to use, whereas outsourcing facilities produce ready-to-administer product. The comment further states that DEA quotas limit the amount of approved drug product that outsourcing facilities can obtain. According to the comment, it is necessary to compound the ephedrine sulfate from bulk drug substances because the fewer manipulations involved would reduce manpower, time, and the risk of contamination.[13]

- **Health system pharmacist**: The comment submits that the pharmacist's health system "switched to the API Ephedrine syringes because it is half the price of the sterile to sterile ones and it keeps our cost down."[14]

There has been little movement for ephedrine sulfate since the September 2019 Notice. No other comments have been posted about ephedrine sulfate in the docket. On January 27, 2022, FDA released a final *Federal Register* notice excluding one bulk drug substance from the 503B Bulks List and including, for topical use only, four bulk drug substances on the 503B Bulks List.[15] Within that notice, the Agency stated that it was not making a final determination on ephedrine sulfate and other nominated substances from the September 2019 Notice, but that the substances "remain under consideration."[16]

C. Nexus's Request to FDA to Finalize the Proposal to Exclude Ephedrine Sulfate from the 503B Bulks List

Over three years have passed since FDA issued its notice proposing not to include ephedrine sulfate on the 503B Bulks List. None of the public comments from 2019 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.

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[12] Reed Smith, Comment, to Docket No. FDA-2018-N-3240, at 7-10 (Nov. 5, 2019).

[13] Outsourcing Facilities Association, Comment to Docket No. FDA-2018-N-3240, at 2-7 (Nov. 4, 2019).

[14] Georgeta Titean, Comment to Docket No. FDA-2018-N-3240 (Oct. 8, 2019).

[15] 87 Fed. Reg. 4,240 (Jan. 27, 2022).

[16] *Id.*

The comments opposing FDA's proposal largely concentrated on the need to dilute the FDA-approved ephedrine sulfate prior to administration, whereas outsourcing facilities produce ready-to-administer formulations. As FDA has now long-established, the need to dilute or otherwise manipulate an FDA-approved drug product prior to administration is not a basis for clinical need under section 503B(a)(2)(A) of the FDCA.[17] Further, even if the need to dilute the FDA-approved drug product were relevant, EMERPHED®, which FDA approved after issuing the September 2019 Notice, is pre-diluted, and therefore ready-to-use.

FDA has also established that supply issues cited in the comments, including the prevention of backorders or shortages, are not relevant to the clinical need analysis. Section 503B provides a separate mechanism for outsourcing facilities to compound drugs from bulk drug substances, irrespective of whether they are on the 503B Bulks List, if they are used to compound a drug that appears on FDA's drug shortage list.[18] Since ephedrine sulfate was placed on 503B Category 1 in 2018, no ephedrine sulfate product has been included on FDA's drug shortage list.

Lastly, "FDA does not interpret considerations of cost to be within the meaning of clinical need."[19]

III. Nexus Requests that FDA Issue a *Federal Register* Notice Rescinding the Interim 503B Bulks List Because it Violates the APA

A. Legal and Regulatory Background: FDA's Interim Policy

In October 2015, FDA issued a draft guidance, which the Agency finalized in June 2016 and amended in January 2017, describing the Agency's policy regarding the use of bulk drug substances during the interim period while the Agency is developing the 503B Bulks List (Interim Policy Guidance).[20] FDA explained that it issued this guidance "[t]o

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[17] *See* 84 Fed. Reg. at 7,388 (explaining that "improved efficiency for prescribers or healthcare providers, or to address the possibility that the approved drug might be mishandled by a medical professional . . . is not clinical need to compound a drug product using a bulk drug substance").

[18] *See* FDCA § 503B(a)(2)(A)(ii); Clinical Need Guidance, *supra* note 11, at 9.

[19] *Id.* (quotation marks omitted).

[20] FDA, Guidance for Industry, *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (Rev. 1, Jan. 2017) (Interim Policy Guidance). *See also* FDA, *Draft Guidance for Industry, Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (Oct. 2015); FDA, *Guidance for Industry, Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (June 2016).

avoid unnecessary disruption to patient treatment while FDA considers the substances that were nominated with sufficient support to permit FDA to evaluate them."[21]

The Interim Policy Guidance describes the conditions under which FDA does not intend to take action against an outsourcing facility for compounding using a bulk drug substance that is not eligible for use in compounding under section 503B (i.e., that is not used to compound a drug that appears on FDA's drug shortage list at the time of compounding, distribution, and dispensing, and is not on the 503B Bulks List). Among the conditions that must be met for a bulk drug substance to qualify for this policy is that the bulk drug substance appear in "Category 1" as described in the guidance.[22]

Category 1 identifies bulk drug substances that may be eligible for the Interim Policy because they were nominated for inclusion on the 503B Bulks List with sufficient supporting information for FDA to evaluate them and do not appear to present significant safety risks.[23] Category 2 identifies bulk drug substances that FDA intends to evaluate the 503B Bulks List, but are not eligible for the Interim Policy because they present significant safety risks.[24] Finally, Category 3 identifies bulk drug substances that FDA does not intend to consider for the 503B Bulks List and are not eligible for the Interim Policy because they were not nominated for inclusion on the 503B Bulks List with adequate supporting information for FDA to evaluate them.[25] If a bulk drug substance is not eligible for the Interim Policy because it either was not nominated or appears in Category 3, stakeholders can submit a new nomination for the bulk drug substance. According to the Interim Policy Guidance, FDA intends to update its categorization of bulk drug substances monthly.[26]

FDA's 2015 Federal Register notice requesting nominations for bulk drug substances for inclusion in the 503B Bulks List identified specific "information about clinical need [that] is necessary to provide adequate support for nominations to the 503B bulks list," or, in other words, that is necessary for placement in Category 1.[27] The required information includes:

- a statement describing the medical condition(s) that the drug product to be compounded with the nominated bulk drug substances is intended to treat (i.e., what patient need is met by the drug product compounded with the bulk drug substance);

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[21] *Id.* at 7.

[22] *Id.* at 8.

[23] *Id.* at 5.

[24] *Id.* at 5.

[25] *Id.* at 6.

[26] *Id.* at 9.

[27] 80 Fed. Reg. 65,770, 65,772 (Oct. 27, 2015).

- a list of FDA-approved drug products, if any, that address the same medical condition;
- if there are FDA-approved drug products that address the same medical condition, an explanation of why a compounded drug product is necessary (i.e., why the approved drug product is not suitable for a particular patient population);
- if the approved drug product is not suitable for a particular patient population, an estimate of the size of the population that would need a compounded drug product (e.g., for a drug product compounded from bulk because of patient allergies or other intolerances to excipients in FDA-approved drug products, FDA expects the supporting information to include a good faith estimate of the patient population with the specific medical condition that suffers from the allergy or intolerance, with citations to the literature regarding the incidence of the condition or a statement that a search was conducted and no references were found);
- a bibliography of safety and efficacy data for the drug compounded using the nominated substance, if available, including any relevant peer-reviewed medical literature; and
- if there is an FDA-approved drug product that includes the bulk drug substance nominated, an explanation of why the drug product proposed to be compounded must be compounded from bulk rather than with the FDA-approved drug product.[28]

503B Category 1 is a large and permissive category of bulk drug substances. The vast majority of bulk drug substances in 503B Category 1 are components of FDA-approved drugs. As of October 2022, 503B Category 1 includes over 300 bulk drug substances, and the category is growing. In October 2022 alone, FDA added 36 bulk drug substances to 503B Category 1.[29] Furthermore, within the next year, FDA has agreed to categorize its backlog of "nominated but not yet categorized substances" with an expectation of categorizing 25% of those substances every twelve weeks.[30] FDA also has agreed to review for possible recategorization all substances that were in Category 3 of the 503B Bulks List that have been nominated with additional supporting information.[31] Thereafter, FDA will aim to categorize nominated and renominated substances on the first business day of each month.[32]

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[28] *Id.*

[29] FDA, *Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (Oct. 5, 2022), https://public4.pagefreezer.com/browse/FDA/06-10-2022T10:52/https://www.fda.gov/media/94164/download.

[30] Settlement Agreement, *Outsourcing Facilities Association v. Becerra*, No. 1:22-cv-01702-CJN, ¶ 1 (D.D.C. 2022).

[31] *Id.* ¶ 2.

[32] *Id.* ¶ 3.

Ephedrine sulfate was nominated for the 503B Bulks List in May 2018, and FDA placed ephedrine sulfate into 503B Category 1 in July 2018. EMERPHED® was approved in April 2020. No nomination for ephedrine sulfate includes EMERPHED® in the list of FDA-approved drug products containing ephedrine sulfate or provides an explanation of why a compounded drug product is necessary (i.e., why EMERPHED® is not suitable for a particular patient population).

B. FDA's 503B Interim Policy and Its Application Violate the Administrative Procedure Act

1. Agency Action Not in Accordance with Law

The 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. In section 503B of the FDCA, Congress created a narrow exemption from the drug approval process for compounded drug products if certain statutorily-mandated conditions are met. One of those conditions is that a bulk drug substance must appear on either the 503B Bulks List or FDA's drug shortage list. Despite Congress enacting section 503B over nine years ago, FDA has made little progress on the section 503B Bulks List, with only four included substances and 10 excluded substances. Meanwhile, the Interim Policy authorizes outsourcing facilities to compound from over 300 bulk drug substances, including ephedrine sulfate. These substances 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. Yet, contrary to the statute, the Interim Policy authorizes the marketing of drug products compounded from these substances without any FDA approval of a marketing application.

2. Arbitrary and Capricious Agency Action

In the 503B Interim Policy Guidance, FDA explains that the Agency will consider a nomination for the 503B Bulks List only if it includes sufficient supporting information for the Agency to evaluate it.[33] According to FDA's request for nominations, the necessary information includes the following: a description of the medical condition the proposed compounded drug product is intended to treat; a list of approved drugs that treat the same condition, an explanation of why, if an FDA-approved drug product is available, a compounded drug is necessary and why the compounded drug must be compounded from a bulk drug substance rather than from the approved drug; and an estimate of the number of persons who would need the compounded drug.[34]

[33] Interim Policy Guidance, *supra* note 24, at 3.

[34] 79 Fed. Reg. 37,751, 37,751-52 (July 2, 2014).

It 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. First, none of the nominations included a bibliography of safety and efficacy data for the drug compounded using the nominated substance. Instead, both nominations stated that because ephedrine sulfate is an "ingredient" of an FDA-approved product, the safety and efficacy data is "on file" with FDA for the commercial product and the data should be identical to what an outsourcing facility would produce if the facility utilized cGMP-validated processes and USP-defined finished product specifications.[35] Next, both nominations relied on overly broad and vague statements to describe a clinical need to compound ephedrine sulfate. One nominator focused on a "prescriber's preference" for varying concentrations of ephedrine sulfate, rather than identifying a patient population for whom the FDA-approved drug is unsuitable.[36] Similarly, rather than focusing on patients for whom the FDA-approved drug is unsuitable, the other nominator argued that there was a clinical need to compound ephedrine sulfate when "commercial product is on backorder or when a different strength or dosage form is ordered by a practitioner."[37] None of the nominators articulated a reason why the FDA-approved drug was medically unsuitable for anyone or estimated the size of the hypothetical population for whom the drug was medically unsuitable.

Neither nominator offered a valid reason for why ephedrine sulfate must be compounded from a bulk drug substance rather than be diluted from the approved product. One nominator provided no argument at all on this issue, while the other justified the request to compound by focusing on the purported benefits of compounding from bulk substances in general.[38] In the September 2019 Notice, the Agency rightfully determined that these nominations did not provide enough information to determine that there was a clinical need to compound ephedrine sulfate or a reason to compound ephedrine sulfate from a bulk drug substance.

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[35] Specialty Sterile Pharmaceutical Society, Nomination to Docket No. FDA-2013-N-1524, Document No. FDA-2013-N-1524-2292 (May 17, 2018); Rebecca Mitchell, Nomination to Docket No. FDA-2013-N-1524, Document No. FDA-2013-N-1524-2298 (May 18, 2018).

[36] Specialty Sterile Pharmaceutical Society, Nomination to Docket No. FDA-2013-N-1524, Document No. FDA-2013-N-1524-2292 (May 17, 2018).

[37] Rebecca Mitchell, Nomination to Docket No. FDA-2013-N-1524, Document No. FDA-2013-N-1524-2298 (May 18, 2018).

[38] Specialty Sterile Pharmaceutical Society, Nomination to Docket No. FDA-2013-N-1524, Document No. FDA-2013-N-1524-2292 (May 17, 2018); Rebecca Mitchell, Nomination to Docket No. FDA-2013-N-1524, Document No. FDA-2013-N-1524-2298 (May 18, 2018).

Additionally, following EMERPHED®'s approval in 2020, FDA should have required that the outdated nominations be updated to address the newly approved drug. FDA's 2015 Federal Register notice requires nominations to include a list of FDA-approved drug products and an explanation of why a compounded drug product is necessary (i.e., why the approved drug product is not suitable for a particular patient population).[39] Ephedrine 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.

FDA's failure to adhere to its own guidelines for the information needed to receive the benefit of the Interim Policy and the Agency's failure to reassess the categorization of the bulk drug substance ephedrine sulfate after EMERPHED® was approved are arbitrary, capricious, and an abuse of discretion and, therefore, in violation of the APA.[40] Because the Interim Policy and its application are unlawful, Nexus requests that FDA issue a final notice rescinding the policy.

C. Environmental Impact

Petitioners claim a categorical exclusion under 21 C.F.R. § 25.30(h).

D. Economic Impact

Information on the economic impact of this petition will be provided on request.

E. Certification

Pursuant to 21 C.F.R. § 10.30(b), the undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petitioner relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

[39] 2015 Federal Register notice, *supra* note 27, at 65,772.

[40] By categorizing and maintaining substances in Category 1 despite a lack of supporting information for the Agency to evaluate them, the FDA is engaging in a process that is arbitrary and capricious because "the agency has . . . entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise." *Motor Vehicles Mfrs. Ass'n of the United States v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).

NEXUS
PHARMACEUTICALS

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Respectfully submitted,
Ayesha Ahmed
Ayesha Ahmed
General Counsel
Nexus Pharmaceutical

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