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January 25, 2021

Re: Docket No. FDA-2020-P-2028

Dear Mr. Rosebush:

This letter responds to your citizen petition submitted on behalf of the Outsourcing Facilities Association (OFA) and received by the Food and Drug Administration (FDA or Agency) on September 30, 2020 (Petition). The Petition requests that FDA:

> [I]ssue a regulation defining the term 'clinical need' under section 503B(B)(a)(2)(A)(i) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 353b(a)(2)(A)(i) and in full accordance with the definition requested herein, establish the list of bulk drug substances for which there is a clinical need (503B Bulks List) within the next 180 days . . . .

(Petition at 1).

We have carefully considered the issues raised in your Petition and other available information. For the reasons stated below, the Petition is denied.

I. BACKGROUND

A. Section 503B of the FD&C 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 human drug products compounded by an outsourcing facility[1] to be exempt from the following three sections of the FD&C Act: section

[1] Under section 503B(b) of the FD&C Act, a compounder can elect to register with FDA as an outsourcing facility. Section 503B(d)(4) of the FD&C Act defines an *outsourcing facility* as a facility at one geographic location or address that is engaged in the compounding of sterile drugs; has elected to register as an outsourcing facility; and complies with all of the requirements of section 503B of the FD&C Act. An outsourcing facility is not required to be a licensed pharmacy, although compounding must be done by, or under the direct supervision of, a licensed

505 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications or abbreviated new drug applications); section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and section 582 (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[3] unless (a) the bulk drug substance appears on a list established by the Secretary identifying bulk drug substances for which there is a clinical need (the 503B Bulks List), or (b) the drug compounded from such bulk drug substances 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 requires that FDA create a list of bulk drug substances for which there is a clinical need, by "publishing a notice in the Federal Register proposing bulk drug substances to be included on the list, including the rationale for such proposal," "providing a period of not less than 60 calendar days for comment on the notice[,]" and "publishing a notice in the Federal Register designating bulk drug substances for inclusion on the list[.]"[5]

B. Compounding, Generally

Compounded drugs can serve an important role for patients for whom an FDA-approved drug product is not appropriate, such as patients who have an allergy and need a medication to be made without a certain dye or hospital in-patients who need infusions of a drug combined with a particular diluent not specified in the approved product labeling. However, they also pose a higher risk to patients than FDA-approved drugs. In 2012, contaminated injectable drug products that a state-licensed compounding pharmacy shipped to patients and health care practitioners across the country caused a fungal meningitis outbreak that resulted in more than 60 deaths and 750 cases of infection. This was the most serious of a long history of outbreaks and other serious adverse events, including overdoses, associated with contaminated, super-potent, or otherwise poor-quality compounded drugs.

In response to this outbreak, Congress enacted the Drug Quality and Security Act (DQSA), which, among other things, added section 503B to the FD&C Act and created the category of

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pharmacist. In addition, an outsourcing facility may or may not obtain prescriptions for identified individual patients.

[2] Section 503B(a) of the FD&C Act.

[3] For the purposes of section 503B of the FD&C Act, *bulk drug substance* is defined to mean "the same as an active pharmaceutical ingredient as defined in 21 CFR 207.1(b)" (21 CFR 207.3). *Active pharmaceutical ingredient* is defined as "any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body," but the term "does not include intermediates used in the synthesis of the substance" (section 503B(a)(2) of the FD&C Act and § 207.1). Inactive ingredients are not subject to section 503B(a)(2) of the FD&C Act and will not be included in the 503B Bulks List.

[4] Section 503B(a)(2)(A) of the FD&C Act.

[5] Id.

compounders known as *outsourcing facilities*.[6] Drug products compounded by outsourcing facilities in accordance with the conditions of section 503B of the FD&C Act are exempt from FDA drug approval requirements and the requirement that they be labeled with adequate directions for use.[7] Because compounded drug products are not FDA-approved, they have not undergone FDA premarket review for safety, effectiveness, and quality. Although outsourcing facilities must comply with current good manufacturing practice (CGMP) requirements and are inspected by FDA according to a risk-based schedule, their drug products lack a premarket inspection and finding of manufacturing quality that is part of the drug approval process. Because compounded drug products are subject to a lower regulatory standard than FDA-approved drugs, they should not be used by patients who could use an FDA-approved drug.

Outsourcing facilities may or may not obtain prescriptions for identified individual patients and can, therefore, distribute compounded drugs to healthcare practitioners for "office stock" to hold in their offices in advance of patient need.[8] Given that outsourcing facilities can engage in nonpatient specific compounding and distribution of compounded drugs, and given that section 503B of the FD&C Act does not place conditions on interstate distribution that are applicable to other compounded drugs, the conditions in section 503B of the FD&C Act, including the limitation on use of bulk drug substances, are critical to prevent outsourcing facilities from growing into conventional manufacturing operations making unapproved new drug products without complying with critical requirements, such as new drug approval.

C. Compounding Drugs From Bulk Drug Substances

An outsourcing facility may be able to prepare a compounded drug product by using an FDA-approved drug product as a starting material. For example, outsourcing facilities may dilute FDA-approved drug products to produce solutions in intravenous bags for infusion by hospitals. Similarly, when pediatric or elderly patients are unable to swallow an FDA-approved tablet, outsourcing facilities sometimes manipulate (e.g., crush) the tablet to produce a liquid.

On other occasions, it may be necessary to compound a drug product using a bulk drug substance for a patient who cannot use an FDA-approved drug product, or a drug product compounded from an FDA-approved drug product. This may be the case, for example, if certain inactive ingredients that are appropriate for the route of administration of the FDA-approved drug product are not appropriate for another route of administration. Similarly, an outsourcing facility might compound a drug product from a bulk drug substance if there is a well-known, serious allergy in some patients to an inactive ingredient in the approved drug product containing that bulk drug substance.

Section 503B of the FD&C Act limits the bulk drug substances that outsourcing facilities can use in compounding to those that are used to compound drugs in shortage or that appear on a list developed by FDA of bulk drug substances for which there is a clinical need.[9] Section 503B of

[6] See Pub. L. No. 113-54, §102(a), 127 Stat. 587, 587-588 (2013).
[7] Section 503B(a) of the FD&C Act.
[8] Section 503B(d)(4)(C) of the FD&C Act.
[9] Section 503B(a)(2)(A)(i), (ii) of the FD&C Act.

the FD&C Act subjects any bulk drug substance used by an outsourcing facility—irrespective of whether it is a component of an approved drug product—to these conditions.

Section 503B of the FD&C Act includes this limitation, among others, to help ensure that outsourcing facilities do not grow into conventional manufacturing operations making unapproved new drug products without complying with critical requirements, such as new drug approval. Outsourcing facilities, as opposed to other compounders, may compound and distribute drug products for office stock or office use without first receiving a prescription for an individually identified patient[10] and without conditions on interstate distribution that are applicable to other compounded drugs.[11] Because of these differences and others, section 503B of the FD&C Act places additional or different conditions on drugs compounded by outsourcing facilities, including limitations on the outsourcing facilities' use of bulk drug substances, which are more stringent than those placed on other compounders' use of bulk drug substances.[12] Section 503B of the FD&C Act requires FDA review of bulk drug substances before outsourcing facilities may use them in compounding outside of the context of a drug shortage. FDA review is not required for the large majority of the bulk drug substances that other pharmacy and physician compounders use, such as components of FDA-approved drug products and drugs that are the subject of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph. FDA's review provides an important safeguard to help ensure that outsourcing facilities do not use bulk drug substances to compound drug products when there is no clinical need to do so, which, in turn, reduces the potential for them to operate as conventional manufacturers of unapproved new drug products.

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[10] By contrast, section 503A of the FD&C Act, concerning compounding by licensed pharmacists in State-licensed pharmacies or Federal facilities, or by licensed physicians, requires that compounding under that section be based on the receipt of a valid prescription for an individually identified patient. This means that the pharmacist or physician compounding under section 503A of the FD&C Act must compound either: (1) after receiving a valid prescription for an identified, individual patient; or (2) before receiving a patient-specific prescription, in limited quantities, based on a history of receiving valid orders generated solely within the context of an established relationship with the patient or prescriber. See FDA's final guidance for industry *Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act* (December 2016). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fdaguidance-documents.

[11] Under section 503A of the FD&C Act, drug products must be compounded in a State (i) that has entered into a memorandum of understanding with the Secretary which addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such State; or (ii) that has not entered into the memorandum of understanding described in clause (i) and the licensed pharmacist, licensed pharmacy, or licensed physician distributes (or causes to be distributed) compounded drug products out of the State in which they are compounded in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician.

[12] Licensed pharmacies and physicians who compound drugs under the conditions of section 503A of the FD&C Act, including the requirement to compound drugs only pursuant to a prescription for an identified individual patient, may use many bulk drug substances by operation of the statute, without action by FDA. See section 503A(b)(1)(A)(i)(I)- (II) of the FD&C Act (providing that a drug product may be compounded consistent with the exemptions in section 503A of the FD&C Act if the licensed pharmacist or licensed physician compounds the drug product using bulk drug substances . . . that comply with the standards of an applicable USP or NF monograph, if a monograph exists, and the USP chapter on pharmacy compounding; or if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary).

In addition, allowing outsourcing facilities to compound a drug product from a bulk drug substance that is a component of an FDA-approved drug product because of, for instance, economic incentives, when the approved drug product, or a drug product compounded from the approved drug product, would be medically appropriate for the patient, would reduce the incentive for applicants to seek FDA approval of drug products. For example, use of bulk drug substances instead of an approved drug product to compound a different formulation, strength, route of administration, or dosage form, rather than simply diluting or otherwise manipulating the approved drug product, reduces the incentive for applicants to invest in and seek FDA approval of such drug products. Furthermore, applicants might not have an incentive to continue marketing their FDA-approved drug products if they face competition from similar drug products compounded from bulk drug substances that have not had to demonstrate safety and efficacy. Limiting outsourcing facilities' use of bulk drug substances to situations in which an approved drug product or a drug product compounded from the approved drug product would not meet an identified medical need helps retain important incentives for applicants to conduct the research and testing necessary to obtain FDA approval and continue to market the approved drug product.

When it is feasible to compound a drug product by starting with an approved drug product, there are also certain benefits of doing so over starting with a bulk drug substance. Approved drug products used in compounding have undergone premarket review for safety, effectiveness, and quality, and are manufactured by a facility that is subject to premarket assessment, including site inspection. After the premarket assessment, FDA conducts routine, risk-based inspections to verify that the manufacturer has systems in place to assure proper design, monitoring, and control of manufacturing processes and facilities. In addition, during pre-market review of FDA-approved drug products, the quality standards and controls with respect to ingredients, and the specific processes and facilities used to produce the bulk drug substance and drug products, are similarly assessed. This includes a review of evidence to evaluate the safety of the bulk drug substance and any inactive ingredients used in the product. For example, FDA evaluates whether the applicant's proposed specifications for purity, potency, and other attributes of the bulk drug substance are appropriate for its use in the drug product, and whether studies demonstrate the safety of the impurity levels and the stability of the bulk drug substance through the product's expiration date. In contrast, FDA does not conduct a premarket review of the quality standards, specifications, and controls for bulk drug substances used in compounding. In addition, FDA does not conduct a premarket assessment of the manufacturer of the bulk drug substance, including a premarket site inspection to verify manufacturing operations are under control, prior to bulk drug substances from that facility being used in a compounded drug product.

In sum, section 503B's limitation on the 503B Bulks List to substances for which there is a clinical need serves important public health functions. First, it helps to limit patient exposure to compounded drug products, which have not been demonstrated to be safe and effective, to those situations in which the compounded drug product is necessary for patient treatment. Second, it preserves the incentives for applicants to invest in the research and testing required to obtain FDA approval and continue to manufacture FDA-approved drug products, thereby helping to maintain a supply of high-quality, safe, and effective drugs.

D. Process for Developing the 503B Bulks List

In the *Federal Register* of December 4, 2013 (78 FR 72838), FDA requested nominations for

bulk drug substances for the Agency to consider for inclusion on the 503B Bulks List (2013 FRN) and information to support their inclusion on the list.[13] In response to that request, interested groups and individuals nominated a wide variety of substances. However, many of those nominations were not for substances used in compounding as active pharmaceutical ingredients, or did not include sufficient information to allow FDA to evaluate the nominated substance.[14] To improve the efficiency of the process for the development of the 503B Bulks List, FDA reopened the nomination process and provided more detailed information on what it needs to evaluate nominations for the list in the 2014 *Federal Register* document *Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503B of the Federal Food, Drug, and Cosmetic Act, Concerning Outsourcing Facilities; Revised Request for Nominations* (2014 FRN) (July 2, 2014, 79 FR 37750). The notice advised nominators that they must identify a bulk drug substance that met the statutory definition applying to the 503B Bulks List, and to identify the drug products they intended to compound and provide more than general or boilerplate statements regarding the need to compound from the bulk drug substance.[15] Among other things, the 2014 FRN requested information about: the characteristics of the nominated substance; the drug product that will be compounded using the bulk drug substance; the conditions the compounded drug is proposed to treat; the nominator's rationale for compounding with the substance instead of an FDA-approved drug product; and what patient need the compounded drug would meet.[16]

On October 27, 2015 (80 FR 65770), the Agency opened a new docket, FDA- 2015-N-3469, to provide an opportunity for interested persons to submit new nominations of bulk drug substances or to re-nominate substances with sufficient information (2015 FRN). The 2015 FRN requested the same information to support a bulk drug substance nomination as the 2014 FRN.[17] The 2015 FRN included a recommended format for nominations to help nominators organize the information they submit to support a nomination. This docket is currently open.

As FDA evaluates bulk drug substances, it intends to publish a notice for public comment in the *Federal Register* that describes its proposed position on each substance along with the rationale

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[13] See *Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503B of the Federal Food, Drug, and Cosmetic Act, Concerning Outsourcing Facilities; Request for Nominations* (2013 FRN at 72839), available at https://www.federalregister.gov/documents/2013/12/04/2013-28978/bulk-drug-substances-that-may-be-used-to-compound-drug-products-in-accordance-with-section-503b-of.

[14] Some comments nominated several hundred substances, and approximately 10 comments nominated thousands of substances, including en bloc nominations of substances listed in the USP or NF, the British Pharmacopeia, the European Pharmacopeia, the Japanese Pharmacopeia, the Food Chemicals Codex, the Homeopathic Pharmacopeia of the United States, and the USP Dietary Supplements Compendium. Several submissions referenced a spreadsheet entitled "OTC Active Ingredients," which nominated all the ingredients on the spreadsheet numbering over 1,700 entries. Many nominated substances are typically inactive ingredients (e.g., flavorings, dyes, diluents) or food. Further, the nominations did not include sufficient information for the Agency to evaluate the clinical need for drug products compounded using the bulk drug substance. For example, the nominators of the en bloc submissions provided no justification for listing any of the specific substances on the list. To the extent information about the clinical need for the use of a bulk drug substance in compounded drug products was provided at all in individual nominations, many of the comments to the docket included a statement about the need for the use of bulk drug substances in compounding generally rather than information about the specific clinical need for drug products compounded using a particular bulk drug substance.

[15] See the 2014 FRN at 37752-37753.

[16] Id.

[17] See the 2015 FRN, Section II.B, Clinical Need to Compound.

for that position. After considering any comments on FDA's proposals regarding whether to include nominated substances on the 503B Bulks List, FDA intends to consider whether input from the Pharmacy Compounding Advisory Committee (PCAC) on the nominations would be helpful to the Agency in making its determination, and if so, it may seek PCAC input. Depending on its review of the docket comments and other relevant information before the Agency, FDA may finalize its proposed determination without change, it may issue a new proposal, or it may finalize a modification to its proposal to reflect new evidence or analysis regarding clinical need. FDA will then publish in the *Federal Register* a list identifying the bulk drug substances for which it has determined there is a clinical need and FDA's rationale in making that final determination. FDA will also publish in the *Federal Register* a list of those substances it considered but found no clinical need to use in compounding and FDA's rationale in making this decision.

1. Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the FD&C Act

On March 4, 2019, FDA issued the final guidance for industry *Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (Clinical Need Guidance).[18] The guidance describes FDA's interpretation of the statutory phrase *bulk drug substance for which there is a clinical need* and the factors FDA intends to consider when determining whether to include a bulk drug substance on the 503B Bulks List.

Section 503B of the FD&C Act directs FDA to publish a list identifying "bulk drug substances for which there is a clinical need." In the Clinical Need Guidance, FDA interprets this statutory language consistent with the text of section 503B(a)(2)(A) of the FD&C Act and the purpose of the 503B Bulks List, to mean that the 503B Bulks List may 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

The statutory requirement to create a 503B Bulks List reflects a judgment by Congress that it is necessary for FDA to determine which bulk drug substances are eligible for use in compounding by outsourcing facilities under section 503B of the FD&C Act outside the context of a drug shortage. FDA's clinical need assessments are critical safeguards for drug products that qualify for the section 503B exemptions and that are not subject to requirements of premarket approval, labeling with adequate directions for use, and drug supply chain security. They are one of the checks in section 503B of the FD&C Act that helps ensure outsourcing facilities do not operate like conventional manufacturers of unapproved new drug products without complying with these requirements. As noted previously, outsourcing facilities can distribute drug products without first receiving prescriptions for individually identified patients and without conditions on interstate distribution applicable to other compounded drugs. As explained above in section I.C., FDA's clinical need assessments help limit patient exposure to compounded drug products that have not been demonstrated to be safe and effective to those situations in which the compounded

[18] Available on the FDA guidance web page, https://www.fda.gov/industry/fda-basics-industry/guidances.

drug product is necessary for patient treatment and serve an important role in preserving the integrity of the drug approval process. The Agency does not interpret supply issues, such as backorders, to be within the meaning of "clinical need" for compounding with a bulk drug substance. We note that section 503B of the FD&C Act already allows compounding from bulk drug substances if the drug product compounded from such bulk drug substance is on the FDA drug shortage list at the time of compounding, distribution, and dispensing.

The Clinical Need Guidance also describes the two-part analysis that FDA intends to use in evaluating substances nominated for placement on the 503B Bulks List to determine whether there is a clinical need for outsourcing facilities to compound using the bulk drug substance. Under Parts 1 and 2 of its analysis, FDA intends to evaluate the nominated bulk drug substances in the context of information provided by the nominators about the drug products proposed to be compounded and the proposed uses of those drug products. The Agency may also consider additional information about the bulk drug substances that was not included in the nomination, such as information described in public comments submitted to the Agency, obtained during outreach to stakeholders such as medical organizations, or that is otherwise identified during the Agency's review, if the Agency concludes it may be relevant to its decision whether to place a bulk drug substance on the 503B Bulks List. The Agency may request additional information from nominators or persons who have submitted relevant docket comments to help inform its review. Nominators or members of the public who believe that different considerations would establish that there is a clinical need for a particular bulk drug substance were requested to present those to the Agency by submitting a comment any time to docket FDA-2015-N-3469.[19]

E. *Athenex v. Azar*

As FDA finalized its Clinical Need Guidance, the Agency also finalized its evaluation of two bulk drug substances, vasopressin and nicardipine hydrochloride, and issued a *Federal Register* notice documenting the Agency's determination that there is no clinical need for an outsourcing facility to compound using these bulk drug substances.[20] Specifically, FDA decided not to include either substance on the 503B Bulks List because each substance is a component of FDA-approved drug products, and FDA found no basis to conclude that an attribute of the relevant approved drug products makes them medically unsuitable to treat certain patients for a condition that FDA had identified for evaluation after reviewing nominations for those substances. Additionally, FDA found no basis to conclude that any of the drug products that the nominations proposed to compound using these substances must be compounded using a bulk drug substance rather than using an FDA-approved drug product.[21]

The Agency's decision was reviewed in *Athenex Inc. v. Azar*, 397 F. Supp. 3d 56 (D.D.C. 2019). The plaintiffs in *Athenex* argued that under the clinical need standard, FDA could only consider "whether there is a 'clinical need' for the bulk drug substance itself, without reference to the availability and suitability of an FDA-approved product," and without considering what drug

[19] Available at https://www.regulations.gov/document?D=FDA-2015-N-3469-0001.
[20] *List of Bulk Drug Substances for Which There Is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (84 FR 7383, March 4, 2019).
[21] Id.

products the bulk drug substance would be used to compound.[22] Plaintiffs argued, further, that under this standard the 503B Bulks List would "include every active ingredient contained in an FDA-approved drug plus active ingredients that are "not components of FDA-approved drugs . . . if their clinical need is shown some other way[.]"[23] The only substances FDA would exclude, as part of the minimal review urged by plaintiffs, would be "unproven, fringe ingredients."[24]

The *Athenex* court rejected plaintiffs' proposed interpretation, holding instead that "FDA's method of determining whether there is a 'clinical need' for a bulk drug substance gives effect to the unambiguously expressed intent of Congress" and that plaintiffs' interpretation was contrary to that intent.[25] The court explained that the clinical need standard requires FDA to perform a sorting function—to distinguish bulk drug substances for which there is a clinical need from those for which there is not—and this required applying its expertise to consider whether there was a need for the finished drug product that would be compounded from the bulk drug substance given the availability of the FDA-approved products containing the same bulk drug substance.[26] This determination was rooted in the text of section 503B(a)(2)(A) of the FD&C Act and the structure and purpose of that provision. The court noted that the definition offered by plaintiffs would have "authorize[d] large-scale compounding with a wide array of bulk drug products" but "[i]f Congress had intended to sanction such an expansive practice, the court would have expected it to say so more clearly."[27] The statute generally prohibits outsourcing facilities from compounding with bulk drug substances, and creates an exception only when FDA identifies bulk drug substances for which there is a "clinical need" or when a drug appears on FDA's drug shortage list, indicating that Congress did not mean for FDA to place bulk drug substances on the list "as a matter of course."[28] Instead, section 503B of the FD&C Act prescribes "procedural prerequisites" for developing the 503B Bulks List which "make[s] clear that Congress intended for FDA to apply its expertise in determining whether a bulk drug substance fills a 'clinical need.'"[29]

Congress required FDA to establish the list by publishing a notice in the *Federal Register* identifying each bulk drug substance it proposed to include on the 503B Bulks List, including the Agency's rationale, and provide at least 60 days for public comment before reaching a decision.

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[22] *Athenex*, 397 F. Supp. 3d at 62. Plaintiffs also argued FDA's application of its interpretation of "clinical need" to vasopressin was arbitrary and capricious. Id. at 74.
[23] Id. at 66.
[24] Id. at 67.
[25] Id. at 58.
[26] See, e.g., id. at 65 ("Only when 'clinical need' is assessed against the availability and suitability of an approved drug does the term perform the classifying function that Congress intended.").
[27] Id. at 67.
[28] Id. The court observed that the limited authorization in section 503B of the FD&C Act to compound using bulk drug substances under section 503B (i.e., compounding under the "clinical need" and the drug shortage provisions) is an "exception within an exception." Id. at 66-67. Section 503B of the FD&C Act confers exceptions to generally applicable public health protections (sections 502(f)(1), 505, and 582 of the FD&C Act) when a compounded drug meets all of the requirements in section 503B of the FD&C Act. Additionally, under section 503B(a)(2) of the FD&C Act, an outsourcing facility generally may not compound drugs using a bulk drug substance. It may do so only if the substance is included on a list of bulk drug substances for which FDA has determined there is a clinical need or it is used to compound an approved drug on FDA's drug shortage list.
[29] Id.

This procedure was found to be inconsistent with the definition plaintiffs had offered, which would require the Agency to include all approved drugs and monograph drugs on the list in a fairly rote manner.[30] The court also observed that if Congress "wanted all active ingredients found in FDA-approved products to automatically appear on the 'clinical need' list, it passed up a straightforward way to express that intent."[31] Congress could have simply exempted those substances from the general prohibition on compounding with a bulk drug substance, as it did for compounding under section 503A of the FD&C Act. Instead, it required an affirmative FDA review and a process of notice and comment to build the 503B Bulks List.

Finally, the court determined that FDA's review under the clinical need provision did not amount to interference with the practice of medicine but rather "regulates the type of drug that reaches the marketplace," a decision that "rests well within FDA's regulatory authority under the FDCA[.]".[32] In sum, the court explained, "FDA's interpretation of 'clinical need' is the only interpretation compatible with the rest of the law."[33]

II. DISCUSSION

The Petition requests that:

> . . . the Food and Drug Administration (FDA) issue a regulation defining the term 'clinical need' under section 503B(a)(2)(A)(i) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 353b(a)(2)(A)(i) (*hereinafter* 'FD&C Act') and in full accordance with the definition requested herein, establish the list of bulk drug substances for which there is a clinical need (503B Bulks List) within the next 180 days.

(Petition 4).

Specifically, the Petition requests that FDA define "clinical need" for purposes of section 503B(a)(2)(A)(i) of the FD&C Act to mean: "[a] healthcare practitioner's intent or determination to prescribe or administer a compounded drug product containing said bulk drug substance in the healthcare setting for his or her patients" (Petition at 4).

The Petition's requests are denied for the reasons set forth below.

A. The Petition's Proposed Definition is Contrary to Law and Would Undermine the Law's Public Health Purpose

As set forth in FDA's Clinical Need Guidance, and as recognized by the *Athenex* court, the clinical need standard in section 503B of the FD&C Act requires FDA to perform a sorting

[30] Id.
[31] Id. at 68-69.
[32] Id. at 72.
[33] Id. (internal quotation marks omitted). See also id. at 73. "For the sake of completeness," the court added that if the statute were to remain ambiguous after employing the traditional tools of statutory construction, it would also have ruled in favor of FDA because the Agency's interpretation was based on a permissible construction of the statute and offered a reasoned explanation for why it chose that interpretation. Id. at 73.

function so that bulk drug substances are included on the 503B Bulks List only if FDA determines there is a clinical need for outsourcing facilities to use such bulk drug substances in drug compounding. In light of the statute's text, structure, and purpose, this review requires FDA to consider the drug products that outsourcing facilities propose to compound with the bulk drug substance, and the need for such compounded products in light of the FDA-approved drugs that are available. The Agency's review provides critical public-health protections and helps ensure that outsourcing facilities do not operate as conventional manufacturers. It protects patients by helping to ensure they are not unnecessarily exposed to compounded drugs that have not been subject to premarket review for safety or efficacy when an FDA-approved drug is available. It also protects the integrity of the drug approval process.

The definition of clinical need proposed by the Petition, like the definition offered by the plaintiffs in *Athenex*, would impermissibly narrow, and apparently even eliminate, this critical task that Congress charged the Agency to perform.

The Petition explains that under its proposed definition, "a signed statement from a physician which attests to the clinical need for a bulk drug substance should satisfy the clinical need threshold" (Petition at 7; see also Petition at 4). The Petition's proposed definition would render the process Congress prescribed for establishing the 503B Bulks List without purpose. Section 503B(a)(2)(A) of the FD&C Act directs FDA to establish a public list of bulk drug substances for which there is a clinical need and to establish this list through a public process: the Agency must publish a notice in the *Federal Register* identifying each bulk drug substance it proposes to include in the list, including the rationale for each proposal and to provide a period of at least 60 days for public comment. If Congress had intended to authorize use of bulk drug substances for compounding as suggested by the Petitioner there would be no apparent purpose for establishing the 503B Bulks List through this public process.[34] The process reflects a Congressional charge to the Agency to apply its expertise, with public input, which the Petition's definition would undo.[35]

The Petition states that although FDA "does not regulate the practice of medicine," its clinical need review has "usurped this power and taken over the practice of medicine from the treating physician" (Petition at 7). However, the Agency's review under the clinical need standard only regulates the ability of certain compounded drug products to reach the market and is well within its traditional authorities.[36] The Agency is fulfilling its statutory mandate of regulating the

[34] If Congress had intended to authorize compounding from bulk drug substances when any prescriber had an "intent or determination to prescribe or administer" a drug compounded using a bulk drug substance, it passed up much clearer and more straightforward ways of doing so. For example, Congress could have omitted the FD&C Act's section 503B(a)(2)(A)'s general prohibition on compounding with bulk drug substances and the 503B Bulks List so that prescribers could submit a prescription or order directly to outsourcing facilities that reflected their "intent or determination" to use a drug compounded from a bulk drug substance.

[35] We note that the definition of "clinical need" proposed by the Petition does not contemplate that FDA will apply its expertise even to screen out substances from the 503B Bulks List that are "fringe" or "unproven," and in this respect the Petition goes even farther than the plaintiffs in *Athenex*.

[36] See, e.g., *United States v. Evers*, 643 F.2d 1043, 1048 (5th Cir. 1981) ("[W]hile the [FDCA] was not intended to regulate the practice of medicine, it was obviously intended to control the availability of drugs for prescribing by physicians."); *United States v. Regenerative Scis., LLC*, 741 F.3d 1314, 1319–20 (D.C. Cir. 2014); (citing Evers and

outsourcing facilities' production and distribution of compounded drugs, not telling physicians what drugs to prescribe.[37] Additionally, even if a bulk drug substance is unavailable for compounding under section 503B of the FD&C Act, a prescriber who wishes to prescribe a compounded drug product to meet the individualized needs of a specific patient may do so under the provisions set forth in section 503A of the FD&C Act.[38]

The Petition claims that the Agency's consideration of factors that help to preserve the integrity of the drug approval process when evaluating nominations for the 503B Bulks List is "unnecessarily duplicative" of the essentially a copy provision of section 503B of the FD&C Act[39] (Petition at 11-12), and that:

> [e]ven if the FDA placed on the 503B Bulks List every bulk drug substance that appeared in an FDA-approved drug product found in the Orange Book, the integrity of the drug approval process would be adequately protected via the prohibition on compounding drug products that are essentially a copy of one or more approved drugs . . .

(Petition at 11).

However, as the *Athenex* court explained, the Agency's review of clinical need under section 503B(a)(2) of the FD&C Act complements and does not duplicate the individual practitioner's determination of a clinical difference under the essentially a copy provision. There are multiple, overlapping provisions within section 503B of the FD&C Act that reflect Congress's intent that compounded drugs be used primarily to fill gaps left by FDA-approved drugs, and these provisions reinforce one another.[40] The clinical need and the essentially a copy provisions are distinct, but in conjunction with each other and the other statutory limitations placed on compounding, they help to further important public health goals.[41] Section 503B(a)(2) of the FD&C Act restricts outsourcing facilities' use of bulk drug substances to compound drugs, while section 503B(a)(5) of the FD&C Act prohibits outsourcing facilities from compounding a drug that is "essentially a copy of one or more approved drugs," which may involve a prescriber determination about the clinical difference that a compounded drug could make "for an individual patient."[42] These statutory limits help to reduce the potential for outsourcing facilities

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noting that the FDCA "regulate[s] the distribution of drugs by licensed physicians"); *Gonzales v. Raich*, 545 U.S. 1, 28 (2005) ("the dispensing of new drugs, even when doctors approve their use must await federal approval.").

[37] *Athenex*, 397 F. Supp. 3d at 67 (finding that the procedural prerequisites set forth in section 503B of the FD&C Act for establishing the 503B Bulks List "make clear that Congress intended for FDA to apply its expertise in determining whether a bulk drug substance fills a 'clinical need'").

[38] Section 503A(b)(1) of the FD&C Act. The catalog of bulk drug substances that may be used to compound drug products under section 503A, provided the other conditions of section 503A are met, includes bulk drug substances that are the subject of an applicable U.S. Pharmacopoeia or National Formulary monograph, are a component of an FDA-approved drug product, or are on a list of additional substances compiled by FDA (see 21 CFR 216.23).

[39] Under section 503B(a)(5) of the FD&C Act, a compounded drug may not be essentially a copy of one or more approved drugs. Section 503B(d)(2) of the FD&C Act defines the term "essentially a copy of an approved drug" for purposes of section 503B of the FD&C Act.

[40] *Athenex*, 397 F. Supp. 3d at 70-72.

[41] The two statutory provisions are not "unnecessarily duplicative." For example, even if a bulk drug substance is on the 503B Bulks List, outsourcing facilities would still be prohibited from using that bulk drug substance to compound drug products that are essentially copies of approved drug products.

[42] Section 503B(d)(2) of the FD&C Act (defining "essentially a copy").

to operate as conventional manufacturers of unapproved new drug products, to limit patient exposure to compounded drug products, which have not been demonstrated to be safe and effective, and to preserve the incentives for conventional manufacturers of drugs to invest in the research and testing required to obtain FDA approval and to continue to manufacture FDA-approved drug products.

We also note that FDA's clinical need review protects patients and the premarket approval process by restricting the marketing of unapproved drug products compounded from bulk drug substances that may not be subject to the essentially a copy provision. For example, the essentially a copy provision under section 503B(d)(2)(B) applies to a compounded drug product if one of its components is a bulk drug substance that is a component of an FDA-approved drug or certain unapproved nonprescription drugs.[43] In contrast, the general prohibition on compounding from bulk drug substances in section 503B(a)(2) of the FD&C Act applies more broadly to compounding with *any* bulk drug substance, so that an exception is required before an outsourcing facility may use the substance to compound under section 503B of the FD&C Act (i.e., the substance must be included on the 503B Bulks List or used to compound a drug on FDA's drug shortage list). This means that the clinical need provision limits the use of bulk drug substances, including, potentially fringe or unproven substances, to compound drugs that would not be regulated by the essentially a copy provision under section 503B(d)(2)(B).

The Petition further states that "[a]dopting this definition [of clinical need] would effectively solve the regional drug shortage phenomenon" and any "healthcare-provider-reported" shortages (Petition at 10). As an illustration of the purported need to adopt the Petition's definition of "clinical need," the Petition states that "[o]ne example of a bulk drug substance for which … a clinical need exists is cyclopentolate hydrochloride ophthalmic solution because there are shortages at the healthcare-provider level . . ." (Petition at 10). As of the date of this letter, cyclopentolate ophthalmic solution is included on FDA's drug shortage list, and thus, outsourcing facilities may compound cyclopentolate hydrochloride ophthalmic solution from a bulk drug substance because it appears on FDA's drug shortage list.[44] The Petition's example of cyclopentolate hydrochloride ophthalmic solution illustrates that section 503B(a)(2)(A)(ii) is functioning as intended. Congress addressed supply issues when it provided that bulk drug substances may be used to compound a drug on FDA's drug shortage list at the time the compounded drug is compounded, distributed, and dispensed. We do not find a basis in the statutory language of section 503B of the FD&C Act to permit the listing of bulk drug substances for use in compounding based on potential, future additions to FDA's drug shortage list, or to respond to local, regional or quickly changing supply conditions (let alone a shortage reported by

[43] Section 503B(d)(2)(B) of the FD&C Act. See also guidance for industry *Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (January 2018).

[44] See the FDA Drug Shortages web page, available at https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Cyclopentolate%20Ophthalmic%20Solution&st=c. The Agency continually monitors the drug supply and updates the drug shortage list regularly, based on information from sponsors, prescribers, patients, and other sources. See the FDA Drug Shortages Frequently Asked Questions web page, available at https://www.accessdata.fda.gov/scripts/drugshortages/dsp_faq.cfm#updates.

an individual prescriber) when a drug is not on FDA's drug shortage list.[45]

The Petition also objects to FDA's evaluation of bulk drug substances for inclusion on the 503B Bulks List based on the drug products they would be used to compound, i.e., considering their dosage form, indication or dosage strength (Petition at 5, 8, 12). The Petition states that "FDA is to establish a list of bulk drug substances that may be used in compounding, not a list of finished dosage forms and strengths that may be compounded from bulk drug substances" (Petition at 5). However, as the *Athenex* court noted, only when FDA's review considers "the actual way in which the active pharmaceutical ingredient supplies a therapeutic benefit—by its administration as a finished drug product—does the inquiry produce the kind of categorization that Congress surely envisioned."[46] In addition to the points made elsewhere in this response, we note that the 503B Bulks List relates solely to compounding finished drug products starting from bulk drug substances. This clarifies that the "clinical need" FDA is to determine involves the necessity of treating a patient with a compounded finished drug product using that bulk drug substance; the bulk drug substance is not required in general or for direct administration, but rather to compound a finished drug product. The "clinical need" assessment can only be made in the context of the *drug products* that will be compounded using that bulk drug substance.

Finally, we disagree with the Petition's suggestion that "FDA is subjecting outsourcing facilities to section 505 of the FD&C Act" or recreating the drug approval process (Petition at 8, 12). As noted, FDA's evaluation of the clinical need for outsourcing facilities to use the nominated bulk drug substances in compounding involves consideration of the finished drug products they will be used to compound. However, the clinical need review FDA conducts is, necessarily, far less rigorous, and less comprehensive than the Agency's review of drug products as part of the new drug approval process. The drug approval process is conducted based on extensive data submitted in new drug and abbreviated new drug applications, which are not available for the nominated substances. Additionally, the Agency's review during the drug approval process includes premarket evaluation of the specific drug product (i.e., the finished dosage form containing the active ingredient and any inactive ingredients); its proposed labeling; the applicant's chemistry, manufacturing, and controls information; and a premarket assessment of the establishments where approved drug products will be manufactured.[47] Evaluating a bulk

[45] The Petition states that manufacturers are disincentivized to report interruptions or discontinuations in drug manufacture to FDA because if their drug is added to the drug shortage list, outsourcing facilities would be authorized to use bulk drug substances to compound the listed drug under section 503B(a)(2)(A)(ii) of the FD&C Act (Petition at 9). We note that the FD&C Act addresses this concern by requiring manufacturers to notify FDA of the discontinuance or interruption of prescription drugs to treat serious or life-threatening conditions (see section 506C of the FD&C Act; see also 21 CFR 314.81(b)(3)(iii)), and of withdrawals from the market (see section 506I of the FD&C Act). Further, the Agency does not rely solely on manufacturers to provide FDA with information about drug shortages. The Agency also receives information from stakeholders, including health care professionals, professional groups, public health organizations (including the American Society of Health-System Pharmacists) and patients. See the FDA Drug Shortages Frequently Asked Questions web page, available at https://www.accessdata.fda.gov/scripts/drugshortages/dsp_faq.cfm#updates.

[46] *Athenex*, 397 F. Supp. 3d at 65.

[47] See 21 CFR 314.50.

drug substance in the context of the final compounded drug product is quite different than FDA's drug approval process.[48, 49]

B. FDA Has Interpreted Clinical Need Through a Robust and Transparent Process

The Petition states that "the FDA must define clinical need" by regulation (Petition at 8, see also Petition at 4). It states that this is a "minimum" requirement to have a "clear, consistent, reliable and statutorily responsible process in place" for the 503B Bulks List and would allow "the public [to] know what standard is to be applied . . ." (Petition at 8). We do not agree. The statute sets forth a legal standard that the Agency must apply and prescribes a process to follow to add bulk drug substances to the 503B Bulks List. Congress did not direct the Agency to issue regulations to implement the list.[50]

Instead of issuing regulations, FDA has proceeded in a manner that is consistent with sections 503B(a)(2)(A) and 701(h) of the FD&C Act and with FDA's good guidance practices regulations at 21 CFR 10.115, by developing guidance that provides: (1) FDA's current thinking about the interpretation of the clinical need standard and how it intends to evaluate bulk drug substances under that standard; (2) FDA's policies for reviewing nominations; and (3) an interim compliance policy for section 503B(a)(2)(A)(i) of the FD&C Act pending review on the merits.[51] These documents were developed as level 1 guidance, which means that each was initially published in draft form and the public was afforded an opportunity to comment before the guidance was finalized.

In addition, as the Agency evaluates bulk drug substances for inclusion on the list, it has gone beyond the requirements in section 503B of the FD&C Act to help ensure transparency and afford opportunity for public input. Section 503B(a)(2)(A)(i) of the FD&C Act requires the Agency to publish a notice in the *Federal Register* proposing bulk drug substances for inclusion on the list, including its rationale, and to provide at least 60 days for public comment. The Agency has followed the statutory procedure in proposing to add four bulk drug substances to the 503B Bulks List. However, the Agency has used this same process when it has evaluated a

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[48] See 85 FR 46126 (July 31, 2020). In July 2020, FDA issued a *Federal Register* notice that evaluated 23 drug substances for inclusion on the 503B Bulks List. Following its evaluation, FDA proposed to include 4 substances on the 503B Bulks List and proposed not to include 19 substances on the 503B Bulks List. The analysis applied in this proposal is consistent with the analysis described in the Clinical Need Guidance and relies on substantially less information than the "substantial evidence of safety and effectiveness" required for FDA to approve a drug product under section 505 of the FD&C Act.

[49] In this letter, FDA has identified reasons supporting its denial and provided supporting considerations and analysis. We do not undertake to recapitulate all of the analysis supporting the court's opinion in *Athenex* or the Agency's briefing, but we considered them in developing this denial and incorporate them by reference here.

[50] Section 503B(a)(2)(A)(i) of the FD&C Act (prescribing the Federal Register procedure outlined above in this response for establishing the 503B Bulks List). *Compare* section 503A(b)(1)(A)(i)(III) (requiring FDA to issue regulations to list bulk drug substances for use in compounding under section 503A).

[51] See the Clinical Need Guidance; see also 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). FDA was not required to issue these guidance documents to implement the 503B Bulks List but took these steps to ensure transparency and afford opportunity for public input.

nominated bulk drug substance and proposed not to add it to the list, even though there is no statutory requirement to do so. In sum, the public knows what standard applies and how the Agency is applying it.[52]

The Petition also states that the Agency's current position has changed over time, and that such change is unfair to nominators. We do not agree and note that these statements omit important context. For example, the Petition states that "[i]n the original call for nominations in 2013, the FDA requested information regarding bulk drug substances and compounded products . . . " but then, "[a]fter receiving thousands of bulk drug substances nominations, the FDA moved the goalposts and redefined what information must be submitted for a bulk drug substance nomination to be considered complete" (Petition at 7). However, as explained above, many of the nominations FDA received in response to the 2013 FRN were not for substances used in compounding as active pharmaceutical ingredients or did not include sufficient information to allow FDA to evaluate the nominated substance.[53] In short, FDA did not receive much of the information it had requested. FDA issued its 2014 FRN to improve the efficiency of the process for the development of the 503B Bulks List by providing more detailed information on what it needs to evaluate nominations.

The Petition also faults the Agency for evaluating nominations submitted in 2015, before FDA issued its Clinical Need Guidance (Petition at 8). The Petition omits that the 2014 FRN requested information consistent with the Agency's current interpretation of the "clinical need" standard and approach to evaluating bulk drug substances. Nominators were requested to submit, among other things, information about: the characteristics of the nominated substance; the drug product that will be compounded using the bulk drug substance; the conditions the compounded drug is proposed to treat; the nominator's rationale for compounding with the substance instead of an FDA-approved drug product; and what patient need the compounded drug would meet.[54, 55] Since FDA issued the 2014 FRN, it has developed additional guidance

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[52] The Petition notes that the *Athenex* court consulted dictionary definitions to help ascertain the meaning of the statutory term "clinical need" and suggests that this reflects a flaw in FDA's decision not to issue regulations defining the term (Petition at 6). However, in this part of its opinion the court was reviewing FDA's actions to ensure they were authorized by the statute, and it therefore used a dictionary as one of the customary tools of statutory interpretation. The court ultimately concluded that the Agency's interpretation was the only interpretation consistent with the statute. If the Agency issues regulations to define the term "clinical need," its interpretation would have to derive from and be authorized by the statute.

[53] See Section I.D., describing the submissions FDA received.

[54] See the 2014 FRN at 37752-37753. Additionally, the notice explained that "clinical need" under the statute was "a clinical need for a specific drug product to be compounded with the nominated bulk drug substance," and therefore "it is necessary to identify the compounded drug product for which there is a clinical need and to demonstrate that the nominated bulk drug substance is required to compound that drug product." Id. at 37751-37752. The 2014 FRN also clarified that "[g]eneral or boilerplate statements regarding the need to compound from the bulk drug substance or the benefits of compounding generally" would not be sufficient. Id. at 37753.

[55] The Petition suggests that FDA's initial positions were significantly closer to the Petition's views, but this is not the case. For example, the Petition states that "[a]fter passage of the Drug Quality and Security Act, statements from prescribers were routinely provided in nominations for bulk drug substances," and that "FDA initially supported this and there was even discussion about how the statement could best be provided" (Petition at 4). However, the 2013 FRN requested a range of information, not simply "statements from prescribers," and FDA has consistently recognized that prescriber statements and patterns of current and historic use can help inform FDA's decision-making under the clinical need standard. See, e.g., the 2014 FRN, *List of Bulk Drug Substances for Which*

and policy through the public processes described above. These documents are not evidence of "moving the goalposts" or a "fragmented" process, but rather provide additional information about the Agency's thinking as it gains experience implementing the statute. The Agency has kept a docket open so that nominators and other interested persons may submit additional information to support or oppose a nomination, and FDA considers these submissions during its evaluation process. In addition, after FDA publishes its proposal to include or not to include a nominated substance on the 503B Bulks List, the nominator (or other interested persons) has another opportunity to support the nomination.

III. CONCLUSION

For the foregoing reasons, your Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13001212270, cn=Douglas C. Throckmorton -S
Date: 2021.01.24 19:14:09 -05'00'

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

There is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act, 85 FR 46126 (July 31, 2020). Similarly, the Petition notes that the 2013 FRN included a statement that "the available safety and efficacy data supporting consideration of a bulk drug substance for inclusion on the list may not be of the same type, amount, or quality as is required to support an NDA." FDA's current Clinical Need Guidance makes the same observation, see Clinical Need Guidance at 10, 14, 15.