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OFA
OUTSOURCING FACILITIES ASSOCIATION

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September 30, 2020

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Outsourcing Facilities Association Citizen Petition

To Whom It May Concern:

On behalf of the Outsourcing Facilities Association ("OFA"), we submit the attached citizen petition requesting that the Commissioner of the United States Food and Drug Administration 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) and establish the list of bulk drug substances for which there is a clinical need.

This petition is being submitted in accordance with 21 C.F.R. § 10.30.

Should you have any questions regarding this petition, please do not hesitate to contact the undersigned.

Sincerely,

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Lee H. Rosebush
Chairman, Outsourcing Facilities Association

CITIZEN PETITION

The undersigned submits this petition under section 503B of the Federal Food, Drug, and Cosmetic Act to request that the Commissioner of the United States Food and Drug Administration 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) and in full accordance with the definition requested herein, establish the list of bulk drug substances for which there is a clinical need within the next 180 days.

Outsourcing Facilities Association

September 30, 2020

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I. Actions Requested

The Outsourcing Facilities Association ("OFA") 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.

> Proposed definition of "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).
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> > *Clinical Need – 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.*

A clinical need exists where a statement from the practitioner specifies that a clinical need exists to compound from said bulk drug substance. This determination by the prescribing practitioner for his or her patients would be provided by the health care practitioner or a person able to make the representation for the health care practitioner when a bulk drug substance nomination is received by the FDA. If such a statement is provided, the bulk drug substance qualifies for inclusion on the list of bulk drug substances for which there is a clinical need under section 503B(a)(2)(A)(i) of the FD&C Act, 21 U.S.C. § 353b(a)(2)(A)(i). After passage of the Drug Quality and Security Act, statements from prescribers were routinely provided in nominations for bulk substances. FDA initially supported this and there was even discussion about how the statement could best be provided. At that time, there was no talk of conflating this with the "essentially a copy" provisions in the statute. In this case, FDA appeared to recognize the practice of medicine. Later, for reasons unknown, FDA abandoned this and replaced it with the present proscriptive and largely dysfunctional approach to regulating compounding with bulk substances.

II. Executive Summary

The Drug Quality and Security Act[1] ("DQSA") established a new category of drug compounders under Section 503B of the Federal Food, Drug, and Cosmetic Act known as outsourcing facilities. Outsourcing facilities must register with the FDA and among other requirements, are subject to the same current Good Manufacturing Practices (cGMPs) as drug manufacturers. Outsourcing facilities are not subject to new drug approval requirements of Section 505 of the FD&C Act.[2] Outsourcing facilities may compound from bulk drug substances if the bulk drug substance appears on a list established by the FDA of bulk drug substances that can be used in compounding under section 503B, or if the drug compounded from the bulk drug substance

[1] Drug Quality and Security Act, Pub. L. No. 113-54, 127 Stat. 587 (codified at 21 U.S.C. 353b).
[2] *See* FD&C Act § 503B(a).

appears on FDA's drug shortage list. Thus, the 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. The DQSA directs the FDA to create a "list identifying bulk drug substances for which there is a clinical need," which is sometimes referred to as the "503B Bulks List." The 503B Bulks list is simply a list of bulk drug substances that may be used by 503B outsourcing facilities to compound drug products from bulk drug substances. The 503B Bulks List is to be a list of bulk drug substances, not a list of finished products that may or may not be compounded using bulk drug substance—that product-specific protection is supplied by the "essentially a copy" provisions of the FD&C Act.[3] Further, the FDA does not regulate the practice of medicine. To develop the 503B Bulks List, there must be a working definition of clinical need which the statute does not provide. For the reasons stated in this Petition, the FDA should define "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):

> *Clinical Need – 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.*

Failure by FDA to define clinical need will be contrary to the intent of Section 503B and will subject the public to substantial public health risks from the inability to obtain legally prescribed drugs from FDA-registered outsourcing facilities, and will drastically impair their ability to provide compounded medications from bulk substances, which are used to address many areas including drug shortages and the COVID-19 pandemic.

III. Statement of Grounds

A. For an outsourcing facility to compound using bulk drug substances, the bulk drug substance must appear on a list, established by the Secretary, of bulk drug substances for which there is a clinical need, or the drug compounded from such bulk drug substance appears on the drug shortage list.

1. The Secretary must establish a reliable and realistic list of bulk drug substances for which there is a clinical need.

The FDA requires that a drug must be "compounded in an outsourcing facility that does not compound using bulk drug substances . . . , unless the bulk drug substance appears on a list established by the Secretary identifying bulk drug substances for which there is a clinical need. . ."[4] or "the drug compounded from such bulk drug substance appears on the drug shortage list."[5]

[3] *See* section 503B(a)(5) of the Federal Food, Drug, and Cosmetic Act (codified at 21 U.S.C. 353b(a)(5)).
[4] FD&C Act § 503B(a)(2)(A)(i).
[5] FD&C Act § 503B(a)(2)(A)(ii).

The term "clinical need" appears in Section 503B but is not defined in the FD&C Act, in FDA regulation, or anywhere else in the United States Code. FDA's failure to define clinical need through regulation sent a district court judge to a dictionary to discern its possible meaning: [6]

> Turning to the dictionary for guidance, "clinical" means "relating to the observation and treatment of actual patients rather than theoretical or laboratory studies," OXFORD DICTIONARY,[7] and "need" means "circumstances in which something is necessary; necessity," OXFORD DICTIONARY.[8] Thus, Congress required FDA to determine whether a bulk drug substance is "necessary" for the "treatment of actual patients." That question, however, begs another one: "Necessary" relative to what? Whether something is "necessary" cannot be determined in a vacuum. The presence or absence of "need" must be measured against some point of reference. Is vasopressin "necessary" as a bulk drug substance in the sense that physicians "need" it to treat patients? The answer is "yes." Vasopressin has therapeutic value for patients and therefore it is "needed" for treatment. On the other hand, is vasopressin "necessary" as a component of a [compounded from] bulk drug product such that, without it, physicians would be unable to treat patients? The answer is "no." The FDA-approved drug Vasostrict can serve the same clinical purpose as Plaintiffs' product. Thus, whether there is a "clinical need" for a particular bulk drug substance depends on how one frames the question.[9]

In finding that physicians would be able to treat patients without bulk vasopressin, the court relied on a dictionary because FDA had not (and still has not) defined the term through regulation, drawing upon the FDA's expertise and mindful of the complexity of the issues and the relevant science. At the present time, the current Category 1[10] list under FDA's Interim Policy appears to be, in effect, the bulk substances list. But FDA could remove substances from that list at any moment, leaving the entire outsourcing facility industry and the supply of the drug itself in serious jeopardy. And, with FDA drawing upon its guidance regarding the "essentially a copy" provisions to shape the lists,[11] this danger is heightened, and more damage will accrue to patients who need these compounded products, including to treat Covid-19 and any other current and future drug shortages and pandemic situations. The existence of an FDA-approved drug that serves the same clinical purpose as a drug product compounded from bulk drug substance does not resolve the necessity of compounded products from bulk drug substance for treating actual patients. Asking whether physicians would be unable to treat patients without a drug product compounded from bulk drug substance either requires asking the FDA to 1) ask each physician treating these patients;

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[6] Athenex, et al. v. Alex M. Azar II, et al., Civ. No. 19-cv-00603 (APM) (D.D.C. 2019) at 11.
[7] https://en.oxforddictionaries.com/definition/clinical (last visited August 18, 2020).
[8] https://en.oxforddictionaries.com/definition/need (last visited August 18, 2020).
[9] Athenex at 11–12.
[10] U.S. Food & Drug Admin., INTERIM POLICY ON COMPOUNDING USING BULK DRUG SUBSTANCES UNDER SECTION 503B OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT GUIDANCE FOR INDUSTRY (Rev. 1, Jan. 2017) (Interim Policy). Under the Interim Policy, FDA does not intend to take action against an outsourcing facility for compounding a drug using a bulk drug substance that does not appear on the 503B Bulks List and that is not used to compound a drug that appears on the FDA drug shortage list if the bulk drug substance appears on 503B Category 1, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467374.pdf.
[11] Both the 503B Bulks List and the Category 1 list.

or 2) engage in the practice of medicine. The FDA does not regulate the practice of medicine, which the Commissioner of the FDA, Dr. Hahn, has publicly acknowledged.[12] Thus, a signed statement from a physician which attests to the clinical need for a bulk drug substance should satisfy the clinical need threshold. Otherwise, by not acknowledging the treating healthcare provider's intent, FDA has usurped this power and taken over the practice of medicine from the treating physician.

Further, the history of the 503B bulk drug substance nomination process shows a flawed and fragmented process which the FDA itself has recognized:

> FDA requested nominations for specific bulk drug substances for the Agency to consider for inclusion on the 503B Bulks List in the Federal Register of December 4, 2013 (78 FR 72838). FDA reopened the nomination process in the Federal Register of July 2, 2014 (79 FR 37747) and provided more detailed information on what FDA needs to evaluate nominations for the list. 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 renominate substances with sufficient information.[13]

In the original call for nominations in 2013, the FDA requested information regarding bulk drug substances and compounded products and even noted that the "FDA recognizes 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."[14]

After receiving thousands of bulk drug substances nominations, the FDA then moved the goalposts and redefined what information must be submitted for a bulk drug substance nomination to be considered complete.[15] A year later, the FDA opened a new public docket for 503B bulk drug substance nominations.[16] Next, in August 2018, the FDA proposed to not include bumetanide, nicardipine hydrochloride, and vasopressin.[17] Ultimately, the FDA decided to not include only nicardipine hydrochloride and vasopressin—the FDA did not make a final determination regarding bumetanide.[18] The non-inclusion of nicardipine hydrochloride and vasopressin but no

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[12] See FDA Commissioner Dr. Hahn's statement "We do not regulate the practice of medicine." See: https://www.fda.gov/news-events/fda-voices/bringing-cancer-doctors-perspective-fdas-response-covid-19-pandemic.

[13] List of Bulk Drug Substances for Which There is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act, 85 Fed. Reg. 46,126, 46,127 (July 31, 2020).

[14] 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, 78 Fed. Reg. 72,838, 72,839 n. 2 (Dec. 4, 2013).

[15] 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, 79 Fed. Reg. 37,750 (Jul. 2, 2014).

[16] Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503B of the Federal Food, Drug, and Cosmetic Act; Establishment of a Public Docket, 80 Fed. Reg. 65,770 (Oct. 27, 2015).

[17] List of Bulk Drug Substances for Which There is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act, 83 Fed. Reg. 43,877 (Aug. 28, 2018).

[18] List of Bulk Drug Substances for Which There Is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act, 84 Fed. Reg. 7,383 (Mar. 4, 2019).

determination of bumetanide for the 503B Bulks List is perplexing. Because the FDA has not provided a definition of clinical need, the FDA continues to shift the goalposts and keep outsourcing facilities guessing about when they should make the investment to provide practitioners with compounded drug products they seek for their patients. This continually shifting paradigm does not protect the public's health and has the unintended consequence of actually creating drug shortages (more fully discussed below).

Most recently, the FDA is proposing to include four additional bulk drug substances for the 503B Bulks Lists but only for topical dosage forms.[19] Surely, only allowing the compounding of certain dosage forms when compounding from bulk drug substance is not what Congress intended. If Congress did intend this limitation, Congress would have directed the FDA to make a list of finished drug products that outsourcing facilities may compound from bulk drug substance. Congress did not. Congress directed the FDA to make a list of bulk drug substances that outsourcing facilities may use in compounding. FDA continues to misinterpret its Congressional directive regarding the 503B Bulks List. Appropriately defining clinical need so that the public knows what standard is to be applied is the first step in correcting the missteps over the past seven years.

Further, the FDA did not provide any indication of how it would evaluate bulk drug substance nominations for "clinical need" until the FDA issued Draft Guidance on March 26, 2018.[20] The FDA finalized this guidance on March 4, 2019 without providing a definition of "clinical need" but outlining an impractical two-part evaluation process.[21] The expectation that nominations submitted in 2015 will contain the criteria to meet an undefined arbitrary standard for which the evaluation criteria was not announced until 2018 and finalized in 2019 is nonsensical. The FDA must have a clear, consistent, reliable and statutorily responsible process in place before evaluating bulk drug substances for inclusion on the 503B Bulks List. At a minimum, because the 503B Bulks List is a list of bulk drug substances for which there is a clinical need, the FDA must define clinical need. Without a definition of clinical need, the 503B Bulks List is useless. At best, the list remains stagnant, as it has since its inception. In the worst-case scenario for patients, the 503B Bulks List fluctuates from day-to-day, making it impossible for outsourcing facilities to develop products with bulk drug substances, fearing that the next day, the FDA could propose to exclude a substance already on the list. The FDA must stop moving the goalposts and instead define clinical need.

Moreover, by taking the approach that it has, *i.e.* without defining clinical need, the FDA is subjecting outsourcing facilities to Section 505 of the FD&C Act, but outsourcing facilities are statutorily exempted from Section 505.[22] Section 505 of the FD&C Act provides the process for new drug approvals which are specific to route of administration, dosage form, and strength.[23]

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[19] List of Bulk Drug Substances for Which There is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act, 85 Fed. Reg. 46,126 (July 31, 2020).

[20] Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act; Draft Guidance for Industry, 83 Fed. Reg. 12,952 (Mar. 26, 2018). Draft guidance available at https://beta.regulations.gov/document/FDA-2018-D-1067-0001.

[21] Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act; Guidance for Industry, 84 Fed. Reg. 7,390 (Mar. 4, 2019).

[22] FD&C Act § 503B(a).

[23] *See* FD&C Act § 505(j)(2)(A)(iii).

Clinical need must be defined because the FDA continues to confuse the standards for drugs compounded in an outsourcing facility with the standards that apply to FDA-approved drugs.

2. Outsourcing facilities may not compound drugs that are essentially a copy of one or more approved drugs.

Section 503B prohibits outsourcing facilities from compounding a drug product that is "essentially a copy of one or more approved drugs."[24] This prohibition works independently of the clinical need determination. Even when a bulk drug substance appears on the 503B Bulks List, outsourcing facilities are still prohibited from compounding a specific product that is essentially a copy of one or more approved drugs.[25] The FDA's approach to clinical need has conflated and confused these two separate issues, and that misstep has harmful consequences.

B. A broad definition of clinical need will allow outsourcing facilities to mitigate drug shortages.

Under the current framework, a clinical need exists for many bulk drug substances which is not being met by the FDA-approved products containing the bulk drug substance. Yet, the FDA has not placed any of these substances on the 503B Bulks List. Based on Section 503B of the FD&C Act, outsourcing facilities may compound a drug product from bulk drug substance if the FDA-approved product containing the bulk drug substance appears on the FDA Drug Shortage List or if the FDA places the substance on the 503B Bulks List, finding that there is a clinical need for such bulk drug substance.

The FD&C Act defines a drug shortage as "a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug."[26] Manufacturers must notify FDA at least six months prior to "a permanent discontinuance in the manufacture of the drug or an interruption of the manufacture of the drug that is likely to lead to a meaningful disruption in the supply of that drug in the United States."[27] Drugs are placed on the FDA Drug Shortage List based on manufacturer reports. However, manufacturers are disincentivized to report drug shortages because if the FDA-registered manufacturer reports a drug shortage and the FDA places the drug on the FDA Drug Shortage List, then 503B outsourcing facilities may compound from bulk drug substance essentially a copy of the FDA-approved drug product. Data is available which shows that actual patients are not having clinical needs met by FDA-approved products and the FDA-approved product is not on the FDA Drug Shortage List. Healthcare providers also report shortages which are not included on the FDA Drug Shortage List.[28] Other

[24] *See* FD&C Act § 503B(a)(5).
[25] We recognize the Athenex court stated that Section 503B's redundancies reflect the broader purpose of creating a clear market advantage for approved drugs, and that compounded drug products are used essentially to fill the gaps left by FDA-approved drug products, however we also note that outsourcing facilities have always been on notice that they cannot compound products that are essentially copies of one or more approved drugs.
[26] FD&C Act § 506C(h)(2): The statutory definition of "drug shortage" is not limited to medically necessary drugs.
[27] FD&C Act § 506C(a).
[28] American Society of Health-System Pharmacists (ASHP), Drug Shortages Statistics, https://www.ashp.org/Drug-Shortages/Shortage-Resources/Drug-Shortages-Statistics. New shortages are identified during the year and differ from active shortages. For 2019, the number of active shortages at the end of each quarter was 276, 282, 265 and 264, respectively

lists, such as that maintained by the American Society of Health-system Pharmacists, are more grounded in reality and reflect actual need for a drug and not a manufacturer-generated need.

To protect the public health by ensuring that patients have access to drugs for which there is a clinical need, the OFA requests that the FDA define clinical need as requested *supra* in Section I:

> *Clinical Need – 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.*

While not intended to substitute for a healthcare provider's attestation of a clinical need for his or her patient, which we contend alone meets the statutory test for a drug shortage, under this definition of clinical need, a healthcare practitioner's attestation that the bulk drug substance is required due to a healthcare-provider-reported shortage is one situation that would satisfy the clinical need threshold for inclusion on the 503B Bulk Drug Substance List. Adopting this definition would effectively solve the regional drug shortage phenomenon. Outsourcing facilities would then be able to mitigate shortages—both reported by manufacturers and reported by physicians and other health care providers, including directors of pharmacy, who are typically on the front line of procurement efforts. It is important to note that shortages may be regional and not necessarily always national in scope and FDA should take this into account when determining a shortage.

One example of a bulk drug substance for which such a clinical need exists is cyclopentolate hydrochloride ophthalmic solution because there are drug shortages at the healthcare-provider level, notwithstanding other reasons illustrating a clinical need to compound from the bulk drug substance. Healthcare providers reported the unavailability of cyclopentolate hydrochloride ophthalmic solution, and the drug product was placed on the ASHP drug shortage list on July 9, 2020.[29] Wholesalers are on allocation, and cyclopentolate hydrochloride ophthalmic solution is not available for purchase by 503B outsourcing facilities.[30] Cyclopentolate hydrochloride ophthalmic solution is not available for purchase by many healthcare providers who informed the FDA that "we are in need of this product for our hospital and clinics"[31] and urged the FDA to "add cyclopentolate to the Bulks List as soon as possible to avoid further disruption with patient care."[32]

By statute, an outsourcing facility may compound from bulk drug substances when the "bulk drug substance appears on a list established by the Secretary identifying bulk drug substances for which there is a clinical need . . .,"[33] or "the drug compounded from such bulk drug substance appears on the drug shortage list."[34] Illustrating the clinical need for many bulk drug substances and using cyclopentolate as a proxy, cyclopentolate does not appear on the FDA Drug

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[29] ASHP Drug Shortage List, https://www.ashp.org/Drug-Shortages/Current-Shortages/Drug-Shortages-List?page=CurrentShortages (last visited September 24, 2020).
[30] Letter from Robynn Pruett (September 14, 2020).
[31] Letter from Lara Nichols, PharmD, MPH, BCPS (August 5, 2020).
[32] Letter from Nena Falcon, RN (August 6, 2020).
[33] FD&C Act § 503B(a)(2)(A)(i).
[34] FD&C Act § 503B(a)(2)(A)(ii).

Shortage list, hence outsourcing facilities can only compound using bulk drug substance if cyclopentolate appears on the 503B Bulks List of substances for which there is a clinical need. Adopting OFA's proposed definition of clinical need would maintain the statutory intent of Congress with Section 503B while protecting the integrity of the drug approval process because sponsors would be incentivized to appropriately report drug shortages or maintain adequate supply chains so that patients do not experience a disruption in healthcare.

C. The integrity of the drug approval process will be protected and strengthened through defining "clinical need" and enforcing the "essentially a copy" prohibition.

Adequately protecting the drug approval process is of paramount concern to the OFA. The OFA recognizes that compounded drugs are not FDA-approved and are therefore not evaluated for safety and effectiveness under FDA drug approval standards. The OFA advocates for using an FDA-approved drug product for the patient when medically appropriate. But, not placing bulk drug substances on the 503B Bulks List because the integrity of the drug approval process must be protected is unnecessarily duplicative. By statute, outsourcing facilities are exempt from Section 505 of the FD&C Act.[35]

Section 503B prohibits outsourcing facilities from compounding "essentially a copy of one or more approved drugs."[36] Section 503B(d)(2) defines essentially a copy of an approved drug as —

- A drug that is identical or nearly identical to an approved drug, or a marketed drug not subject to section 503(b) and not subject to approval in an application submitted under section 505, unless, in the case of an approved drug, the drug appears on the drug shortage list in effect under section 506E at the time of compounding, distribution, and dispensing;[37] or

- A drug, a component of which is a bulk drug substance that is a component of an approved drug or a marketed drug that is not subject to section 503(b) and is not subject to approval in an application submitted under section 505, unless there is a change that produces for an individual patient a clinical difference, as determined by the prescribing practitioner, between the compounded drug and the comparable approved drug.[38]

Even 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,[39] 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. In fact, FDA may be allocating too many of its own resources to a process that is really

[35] *See* FD&C Act § 503B(a).
[36] *See* FD&C Act § 503B(a)(5).
[37] FD&C Act § 503B(d)(2)(A).
[38] FD&C Act § 503B(d)(2)(B).
[39] U.S. FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (commonly known as the "Orange Book").

unnecessary and actually serves to undermine the intent of Congress in establishing outsourcing facilities.

D. FDA must define clinical need so as not to interfere with the practice of medicine. The DQSA does not limit compounded drugs to the FDA-approved indication.

In the DQSA, Congress provided for the use of bulk substances, for which there is a clinical need, by outsourcing facilities:

> (2) BULK DRUG SUBSTANCES.—The drug is compounded in an outsourcing facility that does not compound using bulk drug substances (as defined in section 207.3(a)(4) of title 21, Code of Federal Regulations (or any successor regulation)), unless— ''(A)(i) the bulk drug substance appears on a list established by the Secretary identifying bulk drug substances for which there is a clinical need, by— ''(I) publishing a notice in the Federal Register proposing bulk drug substances to be included on the list, including the rationale for such proposal; ''(II) providing a period of not less than 60 calendar days for comment on the notice; and ''(III) publishing a notice in the Federal Register designating bulk drug substances for inclusion on the list. . . .[40]

In the section of the statute noted above, Congress did not explicitly define clinical need, but it did provide for a process to determine clinical need. It is important to note that Congress did not say that the FDA must recreate the IND/NDA drug approval process to propose bulk substances for compounding by outsourcing facilities. Outsourcing facilities are not supplying bulk substances for inclusion in the manufacturing process for FDA approved drugs. Indeed, there are no provisions in the Act that would lead one to a reasonable belief that this was Congress' intent. Rather Congress expressed its intent, in the DQSA, and that was to outline a process for inclusion on a bulk substances list based on whether there was a clinical need for that bulk substance, not for a myriad of finished drug products. Clinical need has been decided by physicians (and other prescribers) who use their knowledge and professional judgment to make informed decisions in the treatment of their patients, *i.e.* the practice of medicine. The FDA is now inserting its judgment in place of the prescribing physician's, without knowing anything about the patient or patients for whom this compounded product is being used. Consider off-label prescribing of FDA-approved drugs. Manufacturers are not able to promote their drugs for off-label use as that would be a direct violation of the FD&C Act. However, it is well accepted that physicians may lawfully prescribe for off-label use and pharmacists may lawfully dispense those prescriptions; for the FDA to suggest otherwise would be interference with the practice of medicine. This can often lead to new uses for drugs, and manufacturers often then take this new off-label use through the IND process for FDA approval. Over the years, both the FDA and the courts[41] have recognized the "practice of medicine exception", dating from the legislative history of the 1938 FD&C Act where it was the intent of Congress that the FD&C Act was not intended to interfere with the practice of

[40] FD&C Act § 503B(a)(2).
[41] *See* Chaney v. Heckler, 718 F.2d 1174 (D.C. Cir. 1984), rev'd, 470 U.S. 821 (1985).

medicine.[42] Initially, the definition of drug was more expansive than the version that ultimately appeared in the statute. That definition included:

> [t]he term "drug", for the purposes of this act and not to regulate the "legalized" practice of [medicine] the healing art, includes…[43]

When Congress eventually passed the 1938 FD&C Act, that language was omitted, presumably to avoid confusion.[44] However the intent of Congress was clear as evidenced by this quote from senator Royal Copeland who introduced the bill.

> [t]he bill is not intended as a medical practices act and will not interfere with the practice of the healing art by chiropractors **and others** (emphasis added) in the States where they are licensed by law to engage in such practice…
>
> A common misunderstanding as to the effects and purposes of the bill, at least if the daily mail of the President and of the members of Congress is any indication, is that it will interfere with the practice of the various schools of healing, such as chiropractic, osteopathy, hydrotherapy and the like. There is no ground whatever for this belief. It is just too bad that well-meaning persons make these protests and thereby actually interfere with their own best interests.
>
> In no way will it interfere with the usual methods or the use of apparatus or devices employed in their regular practice by licensed healers of any school. No practitioner of the healing art can reasonably complain about the provisions of S. 2800.[45]

The FDA itself has relied on the fact that the FD&C Act does not regulate physicians in their practice. Finding for the Plaintiff death row inmates, in *Chaney v. Heckler*, 718 F.2d 1174 (D.C. Cir. 1983), the Court of Appeals for the DC Circuit noted:

> On appeal, FDA does not focus its energies on the argument that the unapproved use of drugs for lethal injection is outside the general jurisdictional provisions of the Act. Instead, FDA argues that state-sanctioned use of lethal injections comes within a commonly recognized exception to the Act's broad and protective coverage: the "practice-of-medicine" exemption. FDCA's legislative history expresses a specific intent to prohibit FDA from regulating physicians' practice of medicine. [46] According to the Commissioner, FDCA does not regulate physicians

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[42] *See* U. S. Government Printing Office. Legislative History of the Federal Food, Drug & Cosmetic Act and Its Amendments (1934) (the definition of the term drug included "for purposes of this Act and not regulate the practice of medicine…"). S. 2800, 73d Cong., 2d Sess.,§ 2(b)(1934).

[43] *Id.*

[44] *See* Charles Wesley Dunn. Federal Food, Drug, and Cosmetic Act: A Statement of Its Legislative Record 93 (1938).

[45] *Id.*

[46]The first bill to pass either house of Congress that was substantially similar to the present Act included within its definition of "drug" the qualification that it did not apply to "the regulation of the legalized practice of the healing art." S. 5, 74th Cong., 1st Sess. § 201(b), 79 Cong. Rec. 8351 (1935). In explaining this provision the committee reports emphasized that the bill was "not intended as a medical practices act and [would] not interfere with the practice of the healing art by chiropractors and others in the States where they are licensed by law to engage in such practice."

> in their practice because physicians are licensed by the states. Letter from the Commissioner at 3, JA 88. Since state prisons are also licensed by the states, the Commissioner thought that FDA did not have jurisdiction to regulate the use of drugs in capital punishment systems. *Id.* at 2–3, JA 87–88.
>
> The problem with the Commissioner's analogy is his starting point: that the practice of medicine is exempt because physicians are licensed by the states. There is scant legislative history on the subject, [47] but the few sentences that can be found are more fairly read as reflecting Congress' recognition that the states *do* regulate the practice of medicine and that a physician *cannot* be eligible for the practice-of-medicine exemption if he has not been so licensed. The practice-of-medicine exemption itself, however, cannot be attributed to the states' licensing of their physicians.
>
> The better explanation for the practice-of-medicine exemption is that Congress did not want to interfere with physicians' treatment of their patients. New uses for drugs are often discovered after FDA approves the package inserts that explain a drug's approved uses. Congress would have created havoc in the practice of medicine had it required physicians to follow the expensive and time-consuming procedure of obtaining FDA approval before putting drugs to new uses.[48] Thus Congress exempted the practice of medicine from the Act so as not to limit a physician's ability to treat his patients.[49]

Most recently, FDA Commissioner Hahn reiterated the fact that the FDA does not regulate the practice of medicine in his remarks on FDA's response to COVID-19, "We [the FDA] do not regulate the practice of medicine, that's a State issue."[50]

FDA now attempts, under cover of the DQSA, to reverse longstanding Congressional intent and court decisions on the practice of medicine exemption. Nowhere in the DQSA did Congress even hint that the FDA could or should now interfere with the practice of medicine. In fact, Congress reinforced the practice of medicine exemption when it provided for the clinical need exemption for bulk substances.[51] Yet, the FDA attempts to practice medicine under its current Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B by determining

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S. Rep. No. 361, 74th Cong., 1st Sess. 3 (1935); S. Rep. No. 646, 74th Cong., 1st Sess. 1 (1935). While the definition of "drug" as ultimately enacted did not include this proviso, *see 21 U.S.C. § 321(g) (1976)*, the legislative history makes clear that Congress did not want to limit a physician's ability to treat his patients.

[47] *See* S. Rep. No. 361, *supra* note 46, at 3, 5; S. Rep. No. 646, *supra* note 46, at 1, 2.

[48] The "new drug" provisions of FDCA require the filing of a new drug application, including full reports of investigations with respect to the drug's safety and effectiveness; a full list of the articles used as components of the drug; a full statement of the composition of the drug; a full description of the methods used in, and the facilities and controls used for, the manufacturing, processing, and packing of such drugs; samples of the drugs and the articles used as components; and specimens of the labeling proposed to be used. *21 U.S.C. § 355(b)*. An applicant may have to wait up to six months for action and participate in hearings. *Id. § 355(c)* & *(c)(2)*. Hence, these "new drug" provisions simply do not fit the reality of the clinical situation.

[49] *Chaney v. Heckler*, 718 F.2d 1174, 1179–1180 (D.C. Cir. 1983)

[50] U.S. Food & Drug Admin., *The Critical Role of Health Care Professionals During the COVID-19 Pandemic,* YOUTUBE (Aug. 11, 2020), at 49:00, https://youtu.be/50i9AMKc8to.

[51] *See* FD&C Act § 503B(a)(2)(A

on a case-by-case basis "whether there is an attribute of the FDA-approved drug product that makes it medically unsuitable for some patients."[52] The FDA must steer clear of regulating the practice of medicine. The FDA must stop case-by-case determinations for the 503B Bulks List so that medical doctors may practice medicine free from FDA's unauthorized intrusion. The FDA is certainly free to approach Congress to amend the FDCA and remove the practice of medicine exemption. But the seemingly endless flow of guidance documents and Federal Register notices is no substitute for Congressional intent.

IV. Conclusion

Based on the legal and policy grounds stated *supra*, the OFA requests that the FDA define, at a minimum, clinical need as requested in the Petition.

V. Environmental Impact

The petitioner requests a categorical exclusion from the requirement of preparing an environmental assessment. As provided in 21 C.F.R. § 25.31, neither an environmental assessment nor an environmental impact statement is required. To the best of the petitioner's knowledge, no extraordinary circumstances exist that may significantly affect the human environment as discussed under 21 C.F.R. § 25.21.

VI. Economic Impact

As provided in 21 C.F.R. §10.30(b), the petitioner agrees to submit economic impact information only if requested by the Commissioner of Food and Drugs following review of the Petition.

VII. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

[52] Guidance for Industry *supra* note 20 at 13.

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Respectfully submitted,

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