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OFA

OUTSOURCING FACILITIES ASSOCIATION

January 8, 2024

Dockets Management Staff (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2015-D-3539 for Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act Guidance for Industry; DRAFT GUIDANCE

I. About the Outsourcing Facilities Association ("OFA")

The Outsourcing Facilities Association ("OFA") is the trade association representing FDA-registered outsourcing facilities ("503Bs") operating pursuant to Section 503B of the Federal Food, Drug, and Cosmetic Act ("FD&C Act"). OFA's members provide compounding and repackaging services to patients, healthcare providers, and healthcare facilities, and strive to ensure the specific needs of both providers and patients are met with safe and effective compounded and/or repackaged medications under the current Good Manufacturing Practices ("cGMP") standards and guidance of the FDA. OFA has been actively following U.S. Food and Drug Administration's (the "FDA") implementation of the Compounding Quality Act[1] ("CQA") and has brought together members of industry to advocate for a safe, reasonable and practical application of the CQA.

OFA respectfully submits this comment in response to FDA's Draft Guidance on the Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act ("Draft Guidance"). OFA encourages the use of FDA-approved product when available and appropriate. If finalized, the Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the FD&C Act Guidance for Industry will be a step back in time, moving the industry to pre-NECC standards. In addition, FDA's proposed action has the potential to drastically harm the 503B industry and its ability to help address the national crisis involving drug shortages, particularly pediatric and oncology drug shortages. A significant unintended consequence of the implementation of this guidance will be that several of our OFA members will open 503A facilities in order to avail themselves of the more favorable bulk ingredient rules of Section 503A as compared to the increasingly restrictive 503B limitations. This will mark a significant failure in moving compounding in the United States under the cGMP standards.

II. FDA's Draft Guidance will decrease access to quality compounded drugs

[1] Drug Quality and Security Act, Pub. L. No. 113-54, 127 Stat. 587 (codified at 21 U.S.C. § 353b)

OFA strongly disagrees with FDA's proposed policy: "FDA does not intend to categorize bulk drug substances that the public nominates for inclusion on the 503B bulks list on or after the date this guidance is finalized."

First, data, not drug manufacturer concerns,[2] should inform FDA's policy—the data shows that FDA has moved at a snail's pace in developing the "clinical need list," also referred to as the "503B Bulks List." In fact, OFA recently filed a lawsuit, and settled with the FDA, because of the speed that FDA was reviewing those previous nominations.[3]

In more than 10 years since the passage of the Drug Quality and Security Act[4] ("DQSA"), the FDA has only included 5 bulk drug substances on the "503B Bulks List" that is **less than one percent** of all categorized bulk drug substances reviewed, none of which are sterile drug products. Instead, FDA has focused its efforts in creating a "no clinical need list" despite no clear statutory authority to do so. Rather than following its Congressional directive to create the 503B Bulks List, FDA is instead proposing to not include substances on the list. This method is a waste of resources and creates burdens to patient access if a clinical need arises in the future. For example, if there is currently no clinical need—the FDA should remain silent and allow additional nominations. Currently, FDA has found "no clinical need" for 22 bulk drug substances.

As of January 8, 2024	Number of 503B Bulk Drug Substances	Percentage of Categorized Bulk Drug Substance Nominations
Category 1	321	31.3%
Category 2	10	1.0%
Category 3	669	65.1%
Included on the "clinical need list," also referred to as the "503B Bulks List"	5	0.5%

[2] Multiple drug manufacturers have requested that the FDA rescind the current Interim Policy on Compounding Bulk Drug Substances Under 503B of the FD&C Act (January 2017). These manufacturers would be the sole manufacturer of their respective drug products absent 503Bs meeting clinical needs. First, outsourcing facilities are meeting clinical needs of patients and providers with different dosing, dosage forms, and avoiding excipients and allergens. Additionally, if an FDA-approved drug product goes on the FDA Drug Shortage list, it is vital for outsourcing facilities to already have API available in order to respond to the shortage as quickly as possible. See Citizen Petition from Verrica Pharmaceuticals (October 11, 2023), Document ID FDA-2023-P-4510-0001; Citizen Petition from Nexus Pharmaceuticals (November 23, 2022), Document ID FDA-2022-P-2998-0001. OFA also notes that decreasing access to bulk drug substances is a shortsighted request among a small minority of drug manufacturers and will actually inhibit drug development through NDA and ANDA pathways, as FDA will be taking away a primary means for pharmaceutical companies to assess market usage and viability, as well as safety, of new and innovative preparations.

[3] *Outsourcing Facilities Association V. Becerra et al*.1:22CV01702. OFA reserves all rights to pursue remedies available for breach of the settlement agreement.

[4] Drug Quality and Security Act, Pub. L. No. 113-54, 127 Stat. 587 (codified at 21 U.S.C. § 353b)

Included on the "no clinical need list"	22	2.1%

If not for the categorization process, 503Bs could only compound drug products from 5 bulk drug substances unless the drug appeared on FDA's drug shortage list. Interestingly, absent the categorization process, outsourcing facilities could not even comply with the conditions of Section 503B that require a 503B Outsourcing Facility to produce one sterile human use compound. Currently, no qualified compounds appear on the 503B Bulks List. That is to say, the FDA has placed restrictions on the route of administration for each of the 5 bulk drug substances that appear on the 503B Bulks List: "for topical use only" or "for oral use only." The definition of "outsourcing facility" requires the facility to engage in the compounding of sterile drugs for human use. Section 503B(d)(4)(a). It is impossible to be an outsourcing facility if only compounding from the 5 bulk drug substances on the 503B Bulks List because there are no sterile drugs included on the flawed 503B Bulks List.

FDA's intention to no longer categorize 503B bulk drug substances would further erode the ability of outsourcing facilities to compound from bulk drug substances. Many 503B outsourcing facilities will de-register with the FDA and instead operate under Section 503A of FD&C Act because the conditions for compounding using bulk drug substances are more favorable and expansive. A state-licensed pharmacy may compound following the USP chapters on compounding using bulk drug substances that:

1. Comply with the standards of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, if a monograph exists, and the USP chapter on pharmacy compounding;

2. If such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or

3. If such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, appears on a list developed by the Secretary through regulations issued by the Secretary under subsection (c) of section 503A.

Thus, the existence of a USP monograph or being a component of an FDA-approved drug product permits a state-licensed pharmacy to compound from a bulk drug substance—503B outsourcing facilities are not afforded the same flexibilities and also must adhere to cGMP.

If finalized, FDA's policy will decrease the amount of FDA-registered outsourcing facilities and push compounding to Section 503A which according to the FDA, is a lower quality standard. In fact, many of our members are already contemplating this very possibility. And, by doing so, FDA will have encouraged these facilities to deregister, compound at a lower standard, and increased the likelihood of another potential NECC-like event from occurring. Accordingly, FDA's action increases patient risk. In pushing compounding to 503A pharmacies, it is important to note that a 503A pharmacy requires a prescription for a named patient for everything it dispenses, and it would be impossible for them to supply sterile compounded products in bulk to

clinics, hospitals and other entities that need to have the drugs on hand for patients yet to be named, without allowing for Anticipatory Compounding. This will create a divisive situation for owners as they grapple with whether to follow the needs of hospitals and patients in their States, or the FDA rules. Coupled with the current regulatory environment for 503A compounding pharmacies, facing potential restrictions dependent on FDA's finalization and implementation of the compounding MOU and state adoption, creates unnecessary risks to patient access. Alternatively, hospital pharmacies, compounding under Section 503A would need to fill the void and most hospital pharmacies are not equipped to compound large volumes necessary for patient needs from bulk drug substances. Hospital investment into compounding is a burden on the healthcare system and"[f]or some hospitals, implementing best practices guidelines such as United States Pharmacopeia (USP) <797> standards can be time-consuming and costly."[5] If finalized, this Draft Guidance will drastically decrease the amount of drug products compounded by outsourcing facilities, in turn decreasing the ability of hospitals to source quality compounded drug from outsourcing facilities which is concerning considering that "most hospitals that obtained non-patient specific compounded drugs from outside compounders got them from outsourcing facilities."[6] Also, in the process of pushing compounding to 503As, FDA is giving away its own authority since the states would now be in control of registration, inspections, and enforcement. And while FDA might wish for fewer outsourcing facilities, those remaining in the business would be insufficient to help ameliorate shortages in an environment where FDA has been somewhat lacking and the current generic and branded drug companies have abandoned supply of drug and forfeited their responsibilities to pay attention to hospital, health care provider, and patient need.

Further, the environment medications are compounded or prepared in affects potential microbial contamination. When compounding products, the quality standard between 503A pharmacies and 503B outsourcing facilities differs. For 503A pharmacies, United States Pharmacopeia (USP) outlines the minimum standards to be followed in the United States—USP chapter 795 (for nonsterile products), USP chapter 797 (for sterile products), and other associated chapters such as USP chapter 85 (endotoxin testing), USP chapter 71 (sterility testing), and USP chapter 800 (hazardous preparations). 503B outsourcing facilities follow the same quality standard as conventional drug manufacturers, cGMPs.

Contamination rates differ between preparation in the clinical environment and preparation in the pharmacy environment.[7] Compared to traditional hospital pharmacies, FDA-registered 503B outsourcing facilities prepare and compound sterile injectable medication under cGMP. Following cGMPs with FDA oversight provides the greatest assurance of patient safety.[8] Historically,

[5] Gianturco SL, Yoon S, Yuen MV, Mattingly AN. Outsourcing facilities and their place in the U.S. drug supply chain. *J Am Pharm Assoc (2021)*. 2021;61(1):e99-e102. doi:10.1016/j.japh.2020.07.021.

[6] U.S. Department of Health and Human Services, Office of Inspector General Most Hospitals Obtain Compounded Drugs From Outsourcing Facilities, Which Must Meet FDA Quality Standards (June 2019) ("Outsourcing facilities are major sources for hospitals' compounded drugs. Among hospitals that obtained NPS compounded drugs from outside compounders, 89 percent of hospitals obtained them only from compounders that were registered with FDA as 503B outsourcing facilities.")

[7] Larmené-Beld KHM, Frijlink HW, Taxis K. A systematic review and meta-analysis of microbial contamination of parenteral medication prepared in a clinical versus pharmacy environment. Eur J Clin Pharmacol. 2019 May;75(5):609-617.

[8] Gudeman J, Jozwiakowski M, Chollet J, Randell M. Potential risks of pharmacy compounding. Drugs R D. 2013;13(1):1–8.

compounding in hospital pharmacies is not performed under cGMPs and can result in patient harm.[9]

III. Pharmaceutical companies opposing FDA's bulk drug substance categorization process have abused the FDA-approval process

As aforementioned, multiple drug manufacturers have requested that the FDA rescind the current Interim Policy on Compounding Bulk Drug Substances Under 503B of the FD&C Act (January 2017). Yet, the current Interim Policy on Compounding Bulk Drug Substances Under 503B of the FD&C Act (January 2017) and associated categorization process have benefited these same manufacturers. Verrica Pharmaceuticals Inc. ("Verrica") is a perfect example of a manufacturer that has benefitted from outsourcing facilities. On July 21, 2023, Verrica's lead product, YCANTH™ topical solution 0.7% became the first FDA-approved cantharidin product.[10] Yet, 503B outsourcing facilities have been compounding cantharidin drug products from bulk drug substances since at least 2018 and likely longer.[11] Indeed, cantharidin appeared on the 503B Category 1 list as of January 13, 2017. There is documented evidence that 503B outsourcing facilities utilized cantharidin's Category 1 status and compounded cantharidin five years prior to Verrica receiving FDA approval.[12] Verrica had not even submitted its NDA in 2018.[13] Therefore, Verrica benefitted from seeing the patient and healthcare provider demand for cantharidin compounded by outsourcing facilities. The outsourcing facility market for compounded cantharidin essentially served as a test market for Verrica. After patient and healthcare provider demand for cantharidin compounded by outsourcing facilities had already existed, Verrica secured FDA-approval. Thus, Verrica directly benefitted from the current Interim Policy on Compounding Bulk Drug Substances Under 503B of the FD&C Act (January 2017) and categorization process. This example is exactly how the policy should work—503B outsourcing facilities compounding from bulk drug substances actually incentivizes firms to seek FDA approval. Adequately protecting the drug approval process is of paramount concern to the OFA. 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. 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, which the FDA should do, 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 is allocating too many of its own resources to a process that is really unnecessary and actually serves to undermine the intent of Congress in establishing outsourcing facilities.

OFA also notes that decreasing access to bulk drug substances is a shortsighted request among a

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[9] *Id.*
[10] Comment from Verrica Pharmaceuticals (January 8, 2024), Comment ID FDA-2015-D-3539-0022.
[11] *See* January to June 2018 outsourcing facility product report, available at https://web.archive.org/web/20190612181339/http://www.fda.gov/drugs/human-drug-compounding/information-outsourcing-facilities
[12] *Id.*
[13] *See* NDA Approval Letter for NDA 212905 stating that the FDA received Verrica's new drug application (NDA) dated and received September 13, 2019, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/212905Orig1s000ltr.pdf

small minority of drug manufacturers and will actually inhibit drug development through NDA and ANDA pathways, as FDA will be taking away a primary means for pharmaceutical companies to assess market usage and viability, as well as safety, of new and innovative preparations.

Nexus Pharmaceuticals, Inc. ("Nexus") is another glaring example of a pharmaceutical company that benefitted from using 503B outsourcing facilities as a test market prior to seeking FDA-approval.[14] Nexus received FDA approval of EMERPHED (ephedrine sulfate) injection, 50 mg/10 mL in April 2020. Nexus submitted an NDA on June 3, 2019.[15] Yet, 503B outsourcing facilities had been compounding ephedrine sulfate drug products from bulk drug substances since at least 2018 and likely longer. Indeed, ephedrine sulfate appeared on the 503B Category 1 list as of January 13, 2017. There is documented evidence that 503B outsourcing facilities utilized ephedrine sulfate's Category 1 status and compounded ephedrine sulfate at least two years prior to Nexus receiving FDA approval. Nexus had not even submitted its NDA in 2018 when outsourcing facilities were compounding from bulk ephedrine sulfate. Therefore, Nexus benefitted from seeing the patient and healthcare provider demand for ephedrine sulfate compounded by outsourcing facilities. The outsourcing facility market for compounded ephedrine sulfate essentially served as a test market for Nexus. Worse yet in the Nexus example is that Nexus did not perform any research to show that its ephedrine sulfate product is safe and effective. Instead, Nexus' NDA relied "on the Agency's previous findings of safety and efficacy of NDA 208289 (Akovaz) for the indication of treatment of clinically important hypotension occurring in the setting of anesthesia."[16] Nexus did not report any human research as part of its submission. Furthermore, FDA's current 2017 policy position did not stop or impact Nexus' own incentive to obtain an approval. However, similar to Verrica, once Nexus obtained FDA-approval, then Nexus began to petition to FDA to rescind the very policy it took advantage of. Nexus even complained to the FDA that it did not meet its business projections for EMERPHED sales in 2020 to which Nexus blamed on outsourcing facilities.[17] Again, in the case of Nexus, the evidence shows that 503B outsourcing facilities compounding from bulk drug substances, specifically Category 1, actually incentivizes firms to seek FDA approval.

OFA could continue to provide additional examples of such abuse, but we will stop after one more. Afterall, FDA has all of this information and critical thinking can connect the dots. Lastly, is the example of Mobius Therapeutics LLC ("Mobius"). First, Mobius's conduct does not rise to the level of egregiousness of Verrica and Nexus. Mobius submitted a drug application for mitomycin in 2010, well before the outsourcing facility industry existed. However, there still exists clinical needs for mitomycin drug products compounded from bulk mitomycin. Similar to Nexus, Mobius submitted "a 505(b)(2) application primarily based on literature. The studies

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[14] *See* Citizen Petition from Nexus Pharmaceuticals (November 23, 2022), Document ID FDA-2022-P-2998-0001.
[15] *See* NDA Approval Letter for NDA 213407 stating that the FDA received Nexus' new drug application (NDA) dated and received June 3, 2019, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/213407Orig1s000ltr.pdf
[16] Center for Drug Evaluation and Research Application Number: 213407Orig1s000, Summary Review, at 2 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213407Orig1s000SumR.pdf.
[17] *See* Citizen Petition from Nexus Pharmaceuticals Inc., Docket No. FDA-2021-P-0358, Fn 43 ("EMERPHED was projected to be Nexus's top selling product for 2020, but Nexus now forecasts that in view of outsourcing facilities' compounding of copies, Nexus may earn only approximately 20% of the ready-to-use ephedrine sulfate product market, as opposed to the nearly 100% that it could have tried to claim if it competed only with the FDA-approved high-concentrate product").

were conducted 10-15 years ago and demonstrate consistency in replication."[18] Mobius did not develop a novel drug substance. Yet, Mobius is urging the FDA to not allow any outsourcing facilities access to compound from bulk mitomycin.[19]

The interests of pharmaceutical manufacturers and the integrity of the drug approval process is appropriately and robustly protected through enforcement of the prohibition on compounding drug products that are essentially a copy of one or more approved drugs. The FDA should not bow to the whims of pharmaceutical manufacturers and rescind the 2017 policy when those same manufacturers took advantage of the policy and FDA-approval process. Decreasing access to bulk drug substances is a shortsighted request among a small minority of drug manufacturers and will actually inhibit drug development through NDA and ANDA pathways, as FDA will be taking away a primary means for pharmaceutical companies to assess market usage and viability, as well as safety, of new and innovative preparations.

IV. FDA's Draft Guidance will adversely affect the ability of 503B outsourcing facilities to mitigate drug shortages

Drug shortages are no longer event-driven anomalies – they have become a structural problem in our drug supply chain and market mechanisms. However, while government and the private sector are gaining more of a grasp of the causes, solutions remain terribly elusive, except for the success stories of 503B Outsourcing Facilities.

503B outsourcing facilities are an important solution to address shortages, and have demonstrated the ability to step in and do so many times, including under COVID-19. While there is no silver bullet, and OFA does not pretend our industry alone can solve this complex problem and all shortages, any comprehensive set of solutions must include a role for 503B outsourcing facilities. In fact, Outsourcing facilities are the only real immediately available, turnkey solution to a problem that currently has few demonstrable solutions. Outsourcing facilities, at their small to mid-size scale, are able to pivot to ramp up production much more quickly than a conventional manufacturer producing at a much larger scale. Many OFA members specialize in sterile injectable products for hospitals – which are most prone to shortages. Outsourcing facilities are required by law to register with FDA, undergo both regular scheduled and periodic risk-based inspections, and meet the same robust manufacturing safety and quality standards as traditional prescription drug manufacturers, FDA's cGMP. Importantly, 503B outsourcing facilities are located only in the United States and every dose from an outsourcing facility is made in the United States and on our soil.

It has been quite evident that FDA has not given outsourcing facilities a pass on meeting cGMP requirements and may even be tougher on outsourcing facilities than FDA registered drug manufacturers of FDA approved products. For example, FDA has recently released multiple 483s that discuss horrendous cGMP violations[20] involving FDA approved drug manufacturers.

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[18] Center for Drug Evaluation and Research Application Number: 022572Orig1s000, Summary Review at 13, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022572Orig1s000SumR.pdf

[19] Comment from Mobius Therapeutics, LLC (January 8, 2024), Comment ID FDA-2015-D-3539-0023.

[20] FDA 483 Issued to Kilitch Healthcare India Limited (October 20, 2023), available at https://www.fda.gov/media/174190/download; FDA 483 Issued to Intas Pharmaceuticals (December 2, 2022),

Yet, the Commissioner of the FDA recently released a statement calling many of them the "Pharmacy of the World."[21] And, ironically, in 2019 FDA told Congress[22] that Indian drugmakers had the lowest rate of acceptable inspection outcomes among some 90 countries even though foreign manufacturers receive notice that the FDA is coming. 503Bs are not afforded the same luxury which is how inspections should be conducted—by surprise. Moreover, Dr. Janet Woodcock testified in October 2019 to the House Energy and Commerce Committee, Health Subcommittee, that it is "true both for innovator drugs and generic drugs" that FDA has to make hard choices between enforcing quality at a plant and avoiding a drug shortage. However, FDA does not really take those same drug shortage considerations for the outsourcing facility industry.

FDA policymakers—whose authority is derived and is based on the protection of public health within the United States—tout the capabilities of foreign countries. Yet, FDA policymakers ignore patient safety concerns at foreign drug manufacturers while proposing policy that is directly responsible for a lack of domestically made drug products to supply American-made medicines. FDA continues to tear the domestic industry down with policy proposals like this Draft Guidance. This Draft Guidance cannot be the result of thinking through drug availability and shortages that currently plague our country. At a minimum, the United States must onshore the production of API and finished dosage forms identified in the Drug and Biologic Essential Medicines, Medical Countermeasures, and Critical Inputs for the List Described in Section 3(c) of the Executive Order 13944. Also, the United States must ensure adequate supply and increase gap redundancies by removing restrictions on 503B outsourcing facilities' ability to compound such medications—namely by placing these medications on the 503B Bulks List. Unfortunately, nobody can predict what will be required to respond to the next pandemic. Therefore, we must be prepared and increase 503B access to bulk drug substances.

We note that outsourcing facilities utilize diverse supply chains and must source bulk drug substance in order to compound from bulk drug substances and provide a gap supply during a drug shortage. There are multiple examples of 503Bs who have done this for life-saving drugs that are in shortage. But, in order for 503Bs to make these drug shortage products, bulk drug substance wholesalers must look to the 503B bulks list and the Category 1 list when deciding which bulk drug substances to offer. If a drug shortage occurs and the bulk drug substance is not already on Category 1 or the 503B Bulks List, a wholesaler must perform a business analysis as to whether to qualify a manufacturer and offer the bulk drug substance for distribution in the United States. If the shortage is not predicted to last long, a wholesaler will not expend resources to qualify a supplier. Additionally, even if the shortage is projected to last long enough for the bulk drug substance wholesaler to offer the bulk drug substance to the US market, locating and identifying

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available at https://www.fda.gov/media/164602/download; FDA Warning Letter Issued to Global Pharma Healthcare Private Limited (October 20, 2023), available at https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/global-pharma-healthcare-private-limited-657325-10202023

[21] Robert M. Califf, M.D., Commissioner of Food and Drugs , India's Unique Opportunity and Important Responsibility as the Pharmacy to the World, available at https://www.fda.gov/news-events/fda-voices/indias-unique-opportunity-and-important-responsibility-pharmacy-world

[22] Testimony of Janet Woodcock, Securing the U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program (December 10, 2019), available at https://www.fda.gov/news-events/congressional-testimony/securing-us-drug-supply-chain-oversight-fdas-foreign-inspection-program-12102019

API manufacturers, qualifying those manufacturers, importing API following qualification, and additional necessary testing of the first lots of API from a new supplier, can take many months. This months-long process diminishes the ability of outsourcing facilities to promptly and efficiently provide gap supply during a shortage. Patients cannot wait months for access to drugs in shortage. FDA, through this Draft Guidance, is effectively diminishing the supply chain and actually exacerbating drug shortages.

V. FDA's Draft Guidance will incentive compounders to not register with the FDA and instead compound under Section 503A

As previously mentioned, 503A compounders have greater flexibility when compounding from bulk drug substances. 503B outsourcing facilities may only compound from bulk drug substances in two instances:

1. The bulk drug substance must appear on a list developed by FDA of bulk drug substances that can be used in compounding under section 503B (or the interim category 1 list); or

2. The drug compounded from the bulk drug substance must appear on FDA's drug shortage list at the time of compounding, distribution, and dispensing.

503A compounding pharmacies have greater flexibility when compounding from bulk drug substances. A state-licensed pharmacy may compound from bulk drug substances that:

1. Comply with the standards of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, if a monograph exists, and the USP chapter on pharmacy compounding;

2. If such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or

3. If such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, appears on a list developed by the Secretary through regulations issued by the Secretary under subsection (c) of section 503A (or the interim category 1 list)

Thus, there remains the ability to compound under Section 503A for drugs that are subject to USP monographs and components of FDA-approved drugs and not pursuant to cGMP. And FDA is creating an incentive to compound under Section 503A rather than register with the FDA as an outsourcing facility if the Draft Guidance is finalized. We are aware of several 503Bs that have bought or continued to operate 503As as a contingency to this kind of policy being enacted.

VI. Other Matters

OFA urges the FDA to reconsider its policy on 503B bulk drug substances, especially in light of this Draft Guidance. As a reminder, 503Bs cannot compound an essential copy of an FDA-approved product, unless that product is on the FDA drug shortage list. However, without recognizing a 503Bs ability to compound substances that 503As have access to, FDA would

encourage more compounding at a lower standard in the 503A facility because a 503B will not be able to supply that product. Accordingly, FDA ***should encourage compounding at the higher 503B cGMP standard*** and recognize that 503Bs should be able to compound with the same bulk substances as a 503A (*e.g*. component of an FDA-approved product, USP monograph, or 503A Category 1 list) and supply those products to a 503A to ensure that they are compounded and dispensed to patients at the higher standard. Placing all bulk drug substances that are components of FDA-approved products or that have a USP monograph onto the 503B Bulks List and updating the list regularly with every new FDA drug approval and issuance of a USP monograph should be FDA's policy position. This should be the type of framework that FDA seeks to achieve through its policies. A framework that effectively neuters outsourcing facilities, such as the framework set forth in the Draft Guidance, ultimately creates additional risk to the very patients that FDA is legally bound to protect.

VII. Conclusion

FDA seeks to create a black hole where drugs can be disqualified on the strength of sometimes questionable data and left to languish in this state for an indeterminate period when in reality they might qualify and would help to alleviate shortages. FDA must not finalize the Draft Guidance as written. If finalized, the FDA will decrease access to quality compounded drugs, decrease the ability of outsourcing facilities to mitigate drug shortages, and increase the incentive to circumvent FDA-registration and instead compound under Section 503A.

Respectfully submitted,

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Lee H. Rosebush, Chairman OFA

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