February 11, 2019

BY ELECTRONIC FILING http://www.regulations.gov, Dkt. No. FDA-2014-D-0779

From: Pharma & Biopharma Outsourcing Association
10 Alta Vista Dr.
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To: Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Comments from Pharma & Biopharma Outsourcing Association (PBOA) on Docket No. FDA-2014-D-0779 for "*Current Good Manufacturing Practice--Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act; Draft Guidance for Industry*".

Dear Sir or Madam,

On behalf of the Pharma & Biopharma Outsourcing Association ("PBOA"), a trade association representing Contract Manufacturing Organizations and Contract Development & Manufacturing Organizations ("CDMOs"), I am pleased to offer feedback on the recent draft guidance, "Current Good Manufacturing Practice--Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act; Draft Guidance for Industry". Our Quality Technical Group and Serialization Working Group, composed of quality, operations, and serialization leads from more than 20 of our member companies, have discussed this draft guidance and commend FDA on their efforts to reduce risks to public health while executing the intent of the Compounding Quality Act (CQA) and section 503 to the FD&C Act. For the reasons outlined herein, PBOA firmly believes that all 503B facilities must be held to the same cGMP requirements as traditional pharmaceutical manufacturers.

We understand that section 503 of the FD&C Act was intended to implement controls around compounders following the meningitis outbreak of 2012 that resulted from products produced by New England Compounding Center, which sickened over 800 people and resulted in the deaths of 76. Compounded drugs fill an important need for patients who cannot be treated by an FDA-approved drug, as for a patient with an allergy to an inactive ingredient in an approved formulation or one who cannot take the drug in its approved dosage form (such as a tablet). Sections 503A and 503B have restrictions built in to reduce the risk to public health when there are commercially available and FDA-approved products; however, a provision allows compounders under 503A or 503B to fill an unmet clinical need or in times of shortage, opening the door to interpretation and manipulation. As stated in FDA Guidance Document "*Compounded Drug Products That are Essentially Copies of approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act*", compounding copies of these

products would unnecessarily expose patients to potentially dangerous drug products that have not been shown to be safe and effective. In addition, these restrictions are intended to preserve the integrity of the drug approval process.

Also according to FDA communications, an outsourcing facility is defined in section 503B(d)(4) of the FD&C Act [21 U.S.C. § 353b(d)(4)], as a facility at one geographic location or address that – (i) is engaged in the compounding of sterile drugs; (ii) has elected to register as an outsourcing facility; and (iii) complies with all of the requirements of this section. As per the regulations, outsourcing facilities must comply with other applicable provisions of the FD&C Act, including 501(a)(2)(B) [21 U.S.C. § 351(a)(2)(B)], regarding current good manufacturing practice (cGMP), and section 501(a)(2)(A) [21 U.S.C. § 351(a)(2)(A)], regarding insanitary conditions. cGMP requirements for the preparation of drug products are established in Title 21 of the Code of Federal Regulations (CFR) parts 210 and 211.

Furthermore, for a compounded drug product to qualify for the exemptions under section 503B, (i) the labeling of the drug must include certain information (section 503B(a)(10) of the FDCA [21 U.S.C. § 353b(a)(10)]); (ii) the drug is not essentially a copy of one or more approved drugs, unless the bulk drug substance appears on the 503B bulks list, established by the Secretary to identify drug substances for which there is a clinical need, or appears on the current drug shortage list under section 506E at the time of compounding, distribution, and dispensing; and (iii) the drug must be compounded in an outsourcing facility that is in compliance with the registration and reporting requirements in section 503B(b). Under the labeling requirements every drug product compounded must include the statement "*This is a compounded drug*"; a statement "*Not for Resale*"; a statement of quantity or volume; specific information to facilitate adverse event reporting; and a list of active and inactive ingredients. Under the registration and reporting requirements for Section 503B, an outsourcing facility must submit a report to FDA upon initially registering, once in June of each year, and once in December of each year, each of which must identify the drug products compounded by that facility during the previous 6-month period (section 503B(b)(2) of the FDCA [21 U.S.C. § 353(b)(2)]).

Based on our understanding of these regulations, if any product produced by an outsourcing facility fails to meet the specified labeling requirements or the firm fails to submit the required reporting, the facility no longer qualifies for the exemptions provided by section 503B, and the facility is considered equivalent to any other cGMP manufacturing facility under section 505, section 502(f)(1), and the section 582 (the DSCSA). We understand that since the DQSA was enacted, FDA has conducted more than 500 inspections of compounders, leading to more than 180 warning letters and over 150 product recalls. Compounded drugs are acknowledged by FDA to pose unique risks to public health because they are not approved and don't undergo a pre-market review for safety or quality. Amplifying these concerns, 503B facilities appear to be permitted to distribute products across state borders, unlike traditional compounding pharmacies under 503A; this can make gathering information on adverse events very difficult. Based on a review of recent 483s and warning letters issued to registered outsourcing facilities and communications from FDA, 503B facilities raise concerns due to insanitary conditions that represent a serious health risk.

Review of the 11 warning letters issued to registered 503B facilities over the past two years revealed that poor understanding of the labeling or reporting requirements of section 503B have led to many observations. In particular, FDA's approval for the manufacture of drug products in their facility under section 505 and labeling not meeting the requirements of 502(f)(1), requiring the labeling bear adequate directions for use, often result in misbranded products. Introduction of misbranded products into interstate commerce results in further observations from this cascade of infractions that ultimately originate from not understanding the requirements imposed by 503B. In some cases, facilities were organized according to the requirements of section 503A, which are exempted from cGMP requirements under section 501(a)(2)(B), but were cited for cGMP violations during their inspections as 503B facilities. Warning letters also cited media program inadequacies, ineffective smoke studies, defective environmental monitoring programs, incomplete process validations, questionable Quality Control material testing, lack of stability studies and analytical development to justify release specifications and shelf-life, lack of Quality oversight, incomplete/inadequate investigations, and other serious deviations from cGMP requirements are common observations sited on 483s and warning letters to these firms. Of particular concern to PBOA members is the number of times that 503B facilities have been found using automated vial filling machines to produce commercial products, sometimes without having performed any media fills or process validations. Section 503B was never intended to allow outsourcing facilities to produce batch sizes that would justify an automated filler or distribute commercial products.

Of the 73 companies listed on the FDA website as having registered with FDA as outsourcing facilities, 64 have 483s posted from their most recent inspection, three have 483s that are not yet posted, four have not yet been inspected, and two did not receive 483s from their most recent inspection. Review of these 483s reveals an alarming 420 observations, 57 of which are repeated from previous inspections or warning letters (13.5%). Out of the 483s reviewed, 27 of these contained 503B violations for labeling or reporting (39 observations). The remaining observations can be categorized as related to aseptic systems deficiencies (34%), facilities deficiencies (9%), or quality systems-related deficiencies (55%). Some noteworthy observations for each category are summarized in the table below.

Representative Observations by Category		
Aseptic Systems	**Facilities**	**Quality Systems**
Inadequate cleaning and disinfecting procedures	HEPA filter specs and smoke studies don't support facility design and operation	Insufficient data to support shelf-life or Beyond Use Dating (BUD)
Calibrations not completed	Facility design insufficient or creates cross-contamination risks	Poorly developed or unvalidated analytical methods
Failure to clean after mold or spore forming organisms detected	Storage areas not temperature mapped	No microbiology methods or testing performed
Clothing inadequate for operations	Rusty or dirty equipment and/or rooms	Poor laboratory control over release and visual inspection

Representative Observations by Category		
Aseptic Systems	**Facilities**	**Quality Systems**
Incomplete, deficient, or absence of media fills to cover aseptic operations	Materials of construction (facility or equipment) not compatible with aseptic operations	Inadequate, non-existent, or not scientifically justified specifications.
Sterilizing process not validated		Responsibilities of the Quality unit poorly defined, undefined, or not followed
Containers & closures not sterilized or sterilization process not validated		SOPs not followed
Equipment sanitization insufficient		Dispensing or distributing batches prior to release, closing investigations, or deviations
Environmental monitoring inadequate or non-existent		Data integrity issues
		Inadequate labeling and documentation control

Two particularly egregious 483s cited 13 and 16 observations including distributing product with gowning sampling failures (triggering deviations eight and nine months after the incidents, some never being investigated) and environmental monitoring failures for non-viable particles. In many of these events, the Head of QA was cited as recording the failures and then failing to initiate a deviation. The Quality group was cited as not having appropriate responsibilities/authorities, employees were found to not follow written procedures, crucial equipment was not calibrated, and the facility resulted in observations for design being inadequate to prevent cross-contamination and furniture in disrepair inside the ISO 7 rated environment. One of these 483s contained seven repeat observations from prior inspections. This facility was found to have inadequate media fills, poor aseptic procedures, inadequate responsibility/authority of the quality unit, releasing product that didn't meet specification or wasn't tested for sterility, inadequate environmental and personnel monitoring, incomplete validations, broken or rusty equipment, inadequate gowning, not having a stability program to support shelf-life/BUDs, and ineffective labeling controls. This facility was cited for both labeling and reporting deficiencies associated with section 503B and in each case these observations were repeated from their prior inspection. Repeat observations are always a concern because they demonstrate either poor understanding of the origins of the original observations or worse, that the organization is unwilling to learn or improve. The repeated 503B infractions, in particular, appear easily remedied and therefore seem to demonstrate poor organizational culture of quality.

When FDA originally published its interim guidance on this topic in 2014 [Docket FDA-2014-D-0779], 19 comments were received and are available on the FDA's website. As of February 6, 2019, no new comments have been posted, although the recent government shutdown may

account for a lag in submissions being reviewed and posted. The feedback letters can be categorized as coming from small compounding pharmacies, larger multi-site clinics, industry associations, and industry organizations. None of the comments received originated from an exclusive contract development and manufacturing organization (CDMO).

Advanced Pharma expressed concern that "*…we are apprehensive about the ability of outsourcing facilities to continue to meet the demands of hospitals and other healthcare facilities if the proposed guidelines are too rigid and too closely resemble the expectations of drug product manufacturers*". The fact that Outsourcing (Compounding) Facilities are presenting themselves as the solution to drug shortages and permitted to distribute their products regionally across state borders is precisely why they should be held to the same standards as traditional drug product manufacturers. In its feedback letter Advanced Pharma suggests breaking 503B operations into two categories, those that conduct Sterile-to-Sterile ("S-S") compounding and those conducting Non-sterile-to-Sterile ("N-S"). S-S facilities effectively combine commercially available sterile products to generate a sterile compounded product that by virtue of the operation is small scale for a targeted patient pool. Facilities that conduct Non-sterile-to-Sterile operations would effectively be the ones representing the greatest risk to public health. However, in its feedback letter, Advanced Pharma suggests that S-S operations should not need to conduct endotoxin testing as per USP<797> and that reliance on the manufacturer's CoA should be sufficient for determining potency. This puts undue burden on the original manufacturer's CoA, as the product is not being used as it was intended at the time of release and the container-closure system is changed as part of these compounding operations. Furthermore, review of the 483s issued to these facilities indicates that the quality operations at many Outsourcing (Compounding) Facilities are not successful in generating products with the desired potency, thus PBOA feels that potency testing should absolutely remain a requirement for release of the compounded products.

In July of 2016 Advanced Pharma hosted an FDA inspection at its Houston, TX facility, which yielded five observations. These observations cited inadequate controls placed on cleaning and sanitization procedures (repeat observation) and unacceptable laboratory controls in that it failed to conduct endotoxin testing on any epidural products produced at this facility and did not conduct routine potency testing for any products produced. The facility was also found to have inadequate calibration of its environmental monitoring equipment and no written procedures outlining calibration requirements. Finally, this firm failed to meet the labeling requirements outlined by section 503B(a)(10)(A). Specific to Advanced Pharma's argument that testing for potency should not be a requirement at release, by failing to conduct potency testing on any products it produces, Advanced Pharma has never demonstrated any data to support that this testing is unnecessary.

In its 2014 submission, Baxter supported FDA's efforts and acknowledged the need for different standards for S-S and N-S operations. Baxter made a point that Beyond Use Dates (BUDs) or shelf-life dating be based upon scientific data rather than arbitrary standards. The company suggested that the use of manufacturer's labeling should be sufficient for assigning BUDs, however, this overlooks the fact that changing the formulation will likely have an impact on stability and could negate the manufacturer's assigned expiry dating. The inability to predict the

stability of a compounded drug product should necessitate the production of small batches for use as quickly as possible after release testing or that a stability study be conducted. This would allow compounding facilities to cater to small patient populations while minimizing the risk to public health.

In the letter submitted by Pentec Health, the company stresses that most 503B facilities will be predominantly or exclusively performing S-S compounding starting from FDA-approved products and will be producing products for a specific patient or small group of patients, which are considered low- or medium-risk compounding under USP<797>. For clarity, these are the exact same operations laid out as acceptable by FDA for 503A facilities. Pentec's letter argued that the interim draft guidance, as written, considers all compounding as equivalent to high-risk compounding under USP<797>, which was supported by the letter submitted by PEW Charitable Trusts. PEW commissioned a comparison study for cGMPs imposed on traditional manufacturers and USP<797>. In its letter PEW supports FDA's position in most aspects of the guidance, but requested more clarity around the need for endotoxin and sterility testing, particularly in high-risk compounding. Pentec requested that FDA increase its incorporation of the risk-based approach presented in USP<797> when drafting the final guidance to reflect "*this reality*". Adopting the PEW recommendation holds 503B facilities to a higher standard when conducting N-S compounding.

In February 2018 Pentec hosted an FDA inspection at its Boothwyn, PA site, which yielded five observations. This site was found to have inadequate temperature, humidity, and pressure monitoring for its ISO 5 facility, which did not record or preserve the data. The monitoring of these environmental conditions was found to be incomplete and was not considered as part of batch release. In addition to this, viable air and surface samples were not collected as part of its equipment qualification and procedures on equipment cleaning and maintenance were found inadequate. Finally, Pentec was cited for not determining hold times and assigning time limits for its aseptic operations. The Pentec 483 was actually one of the better EIRs, but appears to justify the FDA's position that all compounding at a 503B facility should be considered high risk.

Pentec also argued that holding 503A facilities and 503B facilities to different cGMP standards is arbitrary and capricious and that doing so provides motivation for facilities registered as both 503A and 503B to operate under their 503A license when convenient for their operation. According to the FDA Guidance "*Facility Definition Under Section 503B of Federal Food, Drug, and Cosmetic Act, Guidance for Industry*", which adds clarification as to what qualifies as a facility under section 503B, it is explicitly stated on page 3, "*By registering as an outsourcing facility, an entity is electing to have its compounded drugs regulated under section 503B of the FD&C Act, not section 503A. **Drugs compounded at an outsourcing facility are not eligible for the exemptions provided in section 503A, even if the conditions in that section are met with respect to the particular drug***".

PharmMEDium submitted a letter requesting FDA avoid a "one size fits all" approach to regulating 503B compounding operations. In this letter the company draws attention to a government study of hospitals utilizing compounded sterile productions (CSPs) in 2012, which found that fewer than one percent of CSPs employed N-S compounding that started with non-

sterile starting materials. PharMEDium argues that it is unfair and burdensome to hold all 503B compounding operations to the cGMP standards that are required to ensure N-S operations do not create undue risk to public health. PBOA feels that creating a tiered system of regulatory control is unruly and would be impossible to manage. In its letter, PharMEDium requests that lines of distinction around the approach to sterility also be employed to distinguish S-S from N-S operations.

Four of PharMEDium's sites are registered with FDA as 503B Outsourcing Facilities, each have received 483s in their most recent inspections. In December 2017 the Memphis, TN facility issued a massive recall of 56 lots of 31 different products due to lack of sterility assurance immediately following its most recent FDA inspection. The 483 issued cited 13 observations including release and distribution of lots with failures of environmental monitoring that revealed spore-forming and non-spore-forming bacteria and fungus, as well as batches with sterility failures, endotoxin failures, and potency failures. Observations were also issued on facility design and maintenance, aseptic technique, SOPs, training and quality failures. The other three PharMEDium 503B facilities received 16 observations (nine repeated), 11 observations, and 13 observations (two repeated) across aseptic technique, facility design, and failures of quality, among others. The large number of sterility failures observed at these sites would stand against the company's argument that S-S operations should be held to a lower standard and present less risk than N-S operations.

While compounders serve a valuable role in providing patients individualized services and products, the use of compounding facilities to replace qualified manufacturing facilities for the production of finished products introduces unnecessary risks to patient health and safety. The original intent for creating 503B facilities was to help provide access to drugs and the ability to cater to individual patient needs, not to circumvent the normal path of commercial supply. As with nearly every rule and law, some will seek to exploit exemptions and efficiencies intended to help the public for their own personal gains.

We appreciate the work the FDA is doing to bring control to facilities seeking to operate as 503Bs and ensure public health. However the challenge appears daunting and significant time will be required to raise the standards of these facilities. During this process, it cannot be taken for granted that products prepared by 503B facilities are safe. While it is true that a small number of these facilities operate in compliance with cGMP guidelines, the vast majority have significant deficiencies with operational quality and aseptic techniques that raise serious safety concerns when taking their products.

Feedback from many compounding pharmacies from 2014 implores FDA to not create multiple classifications of cGMPs or inequivalent standards for 503A and 503B facilities that may engage in virtually identical operations. PBOA agrees that having multiple varieties of "cGMP standards" will create a tremendous burden on inspectors and organizations to interpret and apply these differing regulations and acknowledges the need to allow 503A and B facilities the ability to rapidly accommodate the needs of individual patients. However, shortcuts to the development process represent considerable risk to public safety. For example, any N-S compounding operation employing terminal sterilization or sterile filtration without studying the

impact on the product is not in the best interests of any patient. In traditional drug development, studies are necessary to show that formulations are stable and preserve effectiveness whenever terminal sterilization is employed. Further, all manufacturing materials, including sterilizing filters, are required to be tested to demonstrate they are compatible with formulations and that adsorption or degradation do not alter the potency of a product. These are very simple and routine studies conducted during normal drug development, but they are not required by any compounding organization, and this places risk upon the patient who takes compounded products.

PBOA understands 503B facilities must rapidly respond to patient needs, which requires flexibility compared to traditional manufacturing facilities. In such cases, however, there should be the ability to connect a patient receiving these products to the manufacturing activities. Any departure from the cGMP requirements placed upon traditional manufacturers represents a risk to the patient. For example, on lines 133-134 of the draft guidance and in Appendix A, FDA indicates that batches of drug product can be released without sterility testing results provided that such testing is completed, and the results are added to the batch documentation when they become available. This testing requires 14 to 21 days to complete, which impedes a compounding lab's ability to meet the patient's needs. However, the results of sterility testing are not going to help the patient receiving a non-sterile product after the fact. Additional relaxing of cGMP requirements within the draft guidance, where FDA "*generally does not intend to take regulatory action against an outsourcing facility,*" include:

- Line 509 – the identification or testing of each lot of containers and closures; and
- Line 612 – microbial and endotoxin testing of water used in aseptic compounding; and
- Line 635 – regarding testing to confirm the supplier's CoA
- Line 674 – regarding identification or testing of each lot of a product used as a source material; and
- Line 939 – regarding the release testing requirements; and
- Line 948 – regarding sterility testing of each lot of product; and
- Line 1012 – regarding stability testing; and
- Lines 1086-1090 – regarding limited stability testing is conducted to support a BUD; and
- Lines 1099-1106 – regarding the use of default BUDs and limited stability testing; and
- Line 1123 & 1140 – regarding the requirement to have data to support the stated in-use time for products requiring "manipulation" prior to administration; and
- Line 1205 – regarding the reserve sample requirements.

While PBOA acknowledges the need to enable Compounding Facilities to fulfill the mission they were created for, we feel that FDA should include additional requirements on products and facilities of Outsourcing (Compounding) Facilities to mitigate risks to patient safety. The requirements placed on the relaxed provisions outlined above only require compliance with cGMP requirements that are already in place for traditional manufacturing facilities and do not create additional controls to compensate for an inability to confirm quality by testing. Facility designs and equipment should employ additional engineering controls to ensure patient safety in lieu of the testing for quality assurance. Quality systems, employee training, and facility maintenance should all be held to a higher standard since the products produced will be used with limited quality control results. Administration of compounded products should bear

additional safety measures, for example, requiring the use of a compatible in-line filters for products that are administered without having sterility data as part of the release testing. PBOA believes that these and other measures will help protect patients who must use products from an Outsourcing (Compounding) Facility. Furthermore, we believe that the six-month production volume cut-offs allowed for relaxing cGMP requirements (5,000 units for non-sterile products and 1,000 units for sterile products regarding stability testing [Tables 2 & 3] and 10,000 units with regard to reserve samples [Line 1207]) are too high. The ability of an Outsourcing (Compounding) Facility to produce this volume of a product without 100% compliance with cGMP requirements seems contrary to the intent when the designations were created. Facilities that are producing this level of products are not "responding to an urgent patient need"; they are producing to inventory and should bear the full burden of compliance with cGMP requirements.

Compounding facilities should not be permitted to produce large quantities of any finished product for commerce nor be permitted to ship products across state lines for distribution, each of which creates challenges for management and monitoring authorities. Furthermore, despite being permitted exemption from the requirements of serialization under DSCSA, compounding facilities should always be required to track the patients who were intended to receive their products so that complete traceability is afforded to regulatory officials conducting investigations into adverse events such as those reported in the 483 issued to Amex Pharmacy, which received complaints of two patients experiencing blurry vision after being injected with Avastin injection repackaged by that firm. Following investigation, it was "unclear which lot was administered to the two patients". PBOA feels strongly that restricting compounding facilities from wide distribution or large-scale production of products will be the best way to allow for rapid response to patient's needs while minimizing wide-spread risk to public health.

PBOA appreciates the opportunity to review and provide comments pertaining to the draft guidance. We look forward to working with FDA on its continued efforts to provide operational standards and guidance to compounding facilities operating under section 503 of the FD&C Act.

Thank you for considering our views.

Respectfully,

Chris Verbicky, Ph.D., M.B.A.
Director, Scientific and Regulatory Affairs
PBOA

PBOA Member Companies

3M Drug Delivery Systems
Ajinomoto Bio•Pharma Services
Alcami
Avid Bioservices
Avista Pharma Solutions
Afton Scientific
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