American Pharmacists Association®
Improving medication use. Advancing patient care.
APhA

October 3, 2016

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

[Submitted electronically to www.regulations.gov]

Re: Insanitary Conditions at Compounding Facilities, Guidance for Industry (Docket ID: FDA-2016-D-2268-0001)

Dear Sir/Madam:

APhA is pleased to submit these comments on FDA's draft guidance entitled "Insanitary Conditions at Compounding Facilities, Guidance for Industry" (the "Guidance"). Founded in 1852 as the American Pharmaceutical Association, APhA represents more than 62,000 pharmacists, pharmaceutical scientists, student pharmacists, pharmacy technicians, and others interested in improving medication use and advancing patient care. APhA members provide care in all practice settings, including community pharmacies, hospitals, long-term care facilities, community health centers, managed care organizations, hospice settings, and the uniformed services.

As APhA has previously stated in other communications to FDA, we are pleased that the Agency responded to our members' feedback and issued a notice of a change to its procedure for inspections to determine if compounders are 503A facilities before applying cGMPs.[1] While APhA appreciates FDA continuing to offer additional clarity regarding acceptable compounding practices, we have concerns about the language of some of the provisions in the Guidance and caution that in some cases, FDA appears to go beyond congressional intent by imposing higher standards on compounding pharmacists and pharmacies than required by states.

In addition, APhA is concerned that some of the examples provided by FDA do not account for the differences in the practice of nuclear pharmacy and pharmacists working with radiopharmaceuticals. As FDA is aware, there continues to be ambiguity regarding the applicability of FDA's Drug Quality and Security Act (DQSA) regulatory activity[2] on the

[1] *See* FDA. Notice of Change in Process for Inspections of Certain Compounders. July 12, 2016. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM510684.pdf

[2] Section 704 of the Federal Food, Drug, and Cosmetic Act states that FDA has the authority to inspect all facilities where drugs are manufactured, prepared for sale or distribution, stored or inventoried. However, this authority is

practice of nuclear pharmacy because it is specifically exempted from 503A, and preexisting FDA guidance also exempts it from cGMPs.[3] Only adding to the confusion is the fact that most of the work of nuclear pharmacies or of pharmacists handling radiopharmaceuticals is not actually "compounding." While compounding pharmacies create what are essentially new drug products designed to meet patient needs, most nuclear pharmacies are preparing radiopharmaceuticals from kits that are already FDA-approved—activity that falls outside of the Food, Drug, and Cosmetic Act's (FD&C) definition of "compounding."[4] APhA has previously requested that FDA expeditiously issue regulatory documents to provide clarity to nuclear pharmacists and pharmacies when handling radiopharmaceuticals and also recommends additional modifications to the draft Guidance to reflect this unique practice setting.

I. Potential to Exceed Congressional Intent

It was clear Congress wanted to continue to allow traditional pharmacy compounding when it passed the DQSA because it left 503A virtually untouched. In accordance with 503A and DQSA, compounding that complies with 503A remains under the purview of states' Boards of Pharmacy. Consequently, APhA is confused by FDA's statement in the Guidance that its intent is to "assist State regulatory agencies in understanding some examples of what FDA considers insanitary conditions."[5] While the FD&C Act deems a drug adulterated if it is "prepared, packed, or held under insanitary conditions,"[6] pharmacies meeting the requirements of 503A are regulated and inspected under state authority not FDA. Accordingly, while the Guidance may be helpful to 503A compounders and the states, APhA reiterates that the authority over 503A pharmacies remains with the states.

A particular area in the Guidance where we are concerned by FDA's overreach is with its statement recommending "that compounding facilities that are not registered with FDA as outsourcing facilities also conduct routine environmental monitoring during operations." FDA even notes that this requirement is in "interim cGMP draft guidance."[7] APhA views this as an attempt by FDA to impose regulations and standards on pharmacies and other traditional compounders that are in conflict with the DQSA and congressional intent and a standard to which they may incorrectly hold 503A pharmacies.

II. Clarification Needed

There are various provisions in the Guidance that while APhA may not necessarily disagree with the intent, we believe the wording is unclear or confusing:

---

limited, and does not extend to a pharmacy's "records, files, papers, processes, or controls." *See* pages #2, 3, 4, 6, 7 of the Guidance for potential violations of the Section 704 records exemption.

[3] *See* FDA. Guidance for Industry. Nuclear Pharmacy Guideline. Criteria for Determining When to Register as a Drug Establishment. 1984. Available at: http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070293.pdf

[4] *See* 21 U.S.C. §353a(f). Available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm376733.htm

[5] *See* Lines 37-40.

[6] *See* 21 U.S. Code § 351 - Adulterated drugs and devices. Available at: https://www.law.cornell.edu/uscode/text/21/351

[7] *See* Lines 239-245. #7 footnote.

1. Gowning apparel - While FDA understands booties (either separate or part of gowns) are part of the gowning apparel, the Agency may have overlooked that they are part of the uniform that touches the floor.[8]

2. Quick movement - While we understand the difficulty in defining "quick movement," APhA asks that the final guidance account for different pharmacy practice settings.[9] For example, when working with radiopharmaceuticals, personnel seek to prepare products quickly to minimize personnel's exposure.[10]

3. Sporicidal agent - "Infrequent" is a very subjective term so we ask FDA to supply some additional language to better guide personnel as to what does or does not constitute "infrequent" use of sporicidal agent under the cleaning and disinfecting requirements.[11]

4. Segregated compounding area (SCA) - FDA should replace the undefined term segregated production area (SPA) with SCA,[12] as there are multiple, clear references to SCAs in both USP <797>[13] and <800>.[14]

III. Allowances for Nuclear Pharmacies and Radiopharmaceuticals

As mentioned above, APhA asserts that in most cases nuclear pharmacists' and pharmacies' activities with radiopharmaceuticals is preparation and not compounding. Consequently, APhA continues to ask for additional guidance to provide clarity on the applicability of FDA compounding regulations and guidances on the preparation of radiopharmaceuticals.

---

[8] *See* Lines 127-130. *"Putting on gowning apparel improperly, in a way that may cause the gowning apparel to become contaminated. This includes, for example, gowning in non-classified areas, gowning apparel touching the floor, or putting on sterile gloves improperly (e.g., touching the outside of a glove with bare hands)."*

[9] This is particularly important for nuclear pharmacy in order to achieve personnel ALARA under federal law to reduce the amount of time as one of the key components of radiation safety. ALARA is defined "as low as is reasonably achievable" [which] means making every reasonable effort to maintain exposures to radiation as far below the dose limits in this part as is practical consistent with the purpose for which the licensed activity is undertaken, taking into account the state of technology, the economics of improvements in relation to state of technology, the economics of improvements in relation to benefits to the public health and safety, and other societal and socioeconomic considerations, and in relation to utilization of nuclear energy and licensed materials in the public interest." *See* U.S. Nuclear Regulatory Commission. 10 CFR 20.1003. December 2, 2015. Available at: http://www.nrc.gov/reading-rm/doc-collections/cfr/part020/part020-1003.html

[10] *See* Lines 148-149. *"Quick movement of personnel disrupts the airflow and increases the risk of bringing lesser quality air into the ISO 5 area."*

[11] *See* Lines 220-221. *"No, improper, or infrequent, use of a sporicidal agent in the facility's cleanrooms and ISO 5 area."*

[12] See Lines 181-183. *"ISO 5 area open to non-classified rooms (segregated production area). Lower quality air from the surrounding room entering the ISO 5 area increases the risk of introducing microbial contamination into drug products being manipulated."*

[13] *See* USP. General Chapter <797> Pharmaceutical Compounding—Sterile Preparations. Pgs. 9, 33, 71, 109. September 25, 2015. Available at: http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/usp-gc-797-proposed-revisions-sep-2015.pdf. Also, *See* Pg. 8 Low-Risk Level CSPs with 12-Hour or Less BUD - which defines specific controls for situations involving a SCA involving sufficient air pressure differentials with air flow. One such condition is the compounding performed in a hospital radiopharmacy. Limited numbers of distribution channels exist to obtain radiopharmaceuticals. It is recognized that there is a special population that is outside the daily distribution range of a commercial nuclear pharmacy and that radiopharmaceuticals are not reasonably available.

[14] *See* USP. General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings. Pgs. 16-18. Available at: http://www.usp.org/sites/default/files/usp_pdf/EN/m7808_pre-post.pdf

Furthermore, while APhA and its members working with radiopharmaceuticals are committed to the highest quality standards to ensure patient safety, we believe the unique nature of nuclear pharmacy and radiopharmaceuticals (e.g., due to the instability of these products, nearly all are given a beyond use date of less than 24 hours) warrants policies that allow for this critical practice area without affecting patient safety. APhA would like to highlight provisions/language in the Guidance that will be problematic to this important area of practice:

1. *"Conducting aseptic manipulations or placing equipment/supplies in an area that blocks the movement of first pass air around an open container, whether before or after it is filled with sterile product. If unidirectional air over the critical surface is blocked, the area is no longer protected. If it is blocked by personnel conducting aseptic manipulations, contamination on personnel, particularly on exposed skin, could be introduced to the critical area."*[15] While this language aligns with USP <797>, APhA would like FDA to provide additional allowances for the preparations of radiopharmaceuticals. Nuclear pharmacists operate behind lead shielding, either through a hood or biological safety cabinet (nuclear pharmacy isolator), and cannot directly view placing the radioactive material into the syringe or vial the dose is in. Thus, nuclear pharmacists have to draw vertically, blocking the unidirectional air in a laminar flow hood when handling radiopharmaceuticals. In addition, the septum is typically recessed from the lead vial shielding, also obstructing it from first pass air. Due to the lack of a direct sight line, which prevents exposure, nuclear pharmacists cannot draw horizontally. Accordingly, APhA strongly urges FDA to allow in the Guidance an accommodation for blocking of unidirectional air when necessary in safely handling radiopharmaceuticals in a vertical hood and when patient safety is not affected.

2. *"Performing aseptic manipulations outside of an International Organization for Standardization Class 5 (ISO 5) area."*[16] FDA should modify this statement as it is in direct opposition to USP <797> which allows Mo-99/Tc-99m generators (and thereby their elution) to be maintained in an ISO Class 8 area.[17] In addition, USP <797> allows for immediate use provisions so as not to disrupt patient care. This is a clear example where FDA should clarify that the term "aseptic practices" under insanitary conditions applies only to compounding and does not apply to preparation of FDA-approved agents.

3. *"Use of non-sterilized or non-depyrogenated final containers/closures. Use of such container/closures could contaminate the drug product after it has been sterilized."*[18] FDA does not specify whether lead vial and syringe transportation shields are considered to be "final containers/closures." Therefore, APhA urges FDA to clarify that "final container/closures," refer to the syringe or vial that the radiopharmaceutical dose is dispensed in, and not the leaded containers (pigs) used in nuclear pharmacy.

[15] *See* Lines 150-155.
[16] *See* Lines 137-138.
[17] *See* USP. General Chapter <797> Pharmaceutical Compounding—Sterile Preparations. Pg. 134. September 25, 2015. Available at: http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/usp-gc-797-proposed-revisions-sep-2015.pdf
[18] *See* Lines 205-206.

4. "*Engaging in aseptic processing wearing non-sterile gloves. This could contaminate the critical area.*"[19] While USP <797> and <800> mandate the use of sterile gloves, current <797> language also states that "the use of technologies, techniques, materials, and procedures other than those described in this chapter is not prohibited so long as they have been proven to be equivalent or superior with statistical significance to those described herein."[20] Research has shown no statistical difference between using sterile gloves and non-sterile gloves wiped repeatedly with sterile alcohol.[21] This practice is important when working with radiopharmaceuticals so as to minimize time and exposure with products. Accordingly, FDA should modify the Guidance to reference the permissible use of non-sterile gloves wiped with sterile alcohol, particularly when working with radiopharmaceuticals.

5. *"Exposing unprotected sterile product, including stock solutions, to lower than ISO 5 quality air (e.g., removing it from the ISO 5 area without a robust and intact container closure system).*[22] FDA should modify the Guidance to allow "a robust and intact container closure system," to include a vial with septum, and a crimp or syringe.

6. *"A facility designed and/or operated in a way that permits poor flow of personnel or materials, or allows the influx of poor quality air into a higher classified area. Examples include…air return located next to the high efficiency particulate arrestance (HEPA) filter rather than near the floor."*[23] FDA should provide flexibility for air returns, in line with USP <797>,[24] as this could be a problem in a SCA or cleanroom that was not designed with low air returns.

APhA appreciates FDA's efforts to provide additional guidance for individuals and entities with regard to compounding and looks forward to forthcoming guidance providing regulatory clarity to pharmacists and pharmacies handling and preparing radiopharmaceuticals. We are happy to be a resource for FDA, especially with regard to the practice of nuclear pharmacy. Thank you again for the opportunity to provide comments on this important issue. If you have any questions or require additional information, please contact Michael Baxter, Director of Regulatory Affairs, at mbaxter@aphanet.org or by phone at (202) 429-7538.

[19] *See* Lines 133-134.
[20] *See* USP. General Chapter <797> Pharmaceutical Compounding—Sterile Preparations. Pg. 2. September 25, 2015. Available at: http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/usp-gc-797-proposed-revisions-sep-2015.pdf
[21] Trissel, Lawrence. Et. al. Effect of two work practice changes on the microbial contamination rates of pharmacy-compounded sterile preparations. Am J Health-Syst Pharm—Vol 64 Apr 15, 2007. Available at: http://www.cspinsourcing.org/files/ajhp-trissel-2007.pdf
[22] *See* Lines 139-141.
[23] *See* Lines 184-186, 188-189.
[24] USP recommends but does not mandate air returns on the floor. *See* USP. General Chapter <797> Pharmaceutical Compounding—Sterile Preparations. Pgs. 70, 99. September 25, 2015. Available at: http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/usp-gc-797-proposed-revisions-sep-2015.pdf

Sincerely,

Thomas E. Menighan, BSPharm, MBA, ScD (Hon), FAPhA
Executive Vice President and CEO

cc: Stacie S. Maass, RPh, JD, Senior Vice President, Pharmacy Practice and Government Affairs