



November 26, 2018

The Honorable Scott Gottlieb, Commissioner
Division of Dockets Management (HFA-305)
Food and Drug Administration (FDA)
U.S. Department of Health and Human Services (HHS)
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-2268-0672)

Dear Commissioner Gottlieb:

APhA is pleased to submit these comments on FDA’s revised draft guidance for industry entitled “Insanitary Conditions at Compounding Facilities,” (hereinafter referred to as the “Guidance”). Founded in 1852 as the American Pharmaceutical Association, APhA represents 64,000 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.

We are pleased FDA responded to APhA members’ feedback and issued a notice of a change to its procedure for inspections to determine if compounders are section 503A facilities before applying cGMPs.¹ Similarly, we are pleased the Guidance incorporated a few of APhA's recommendations—providing an exemption for “foot covers” to touch the floor,² use of the term “segregated compounding area (SCA)”³, and clarification on “unidirectional airflow”.⁴ Furthermore, APhA appreciates FDA’s above clarifications and the release of the recent final guidance “Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies, Federal Facilities, and Certain Other Entities.”⁵ While APhA appreciates FDA

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 See, Line 166.

³ See, Lines 106, 108, 110. Footnote #6.

⁴ See, Line 190. Footnote #10 which states “FDA does not intend to object to the temporary blocking or disruption of first air in the ISO 5 area when necessary for the safe handling of radiopharmaceuticals, such as the placement of a shielding material for the radiopharmaceutical in the ISO 5 area.”

⁵ FDA. Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies, Federal Facilities, and Certain Other Entities. Final Guidance. September 2018. Available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM534811.pdf>

offering additional clarity regarding acceptable preparation and compounding practices, we continue to have concerns with some of the provisions in the Guidance.

APhA offers the following comments and recommendations on specific areas of the Guidance developed with input from our members, including feedback from our APhA Academy of Pharmacy Practice and Management (APhA-APPM) Compounding Pharmacy Special Interest Group (SIG), consisting of over 5,000 members, and Nuclear Pharmacy Practice SIG, consisting of over 2,200 members.

I. Potential to Exceed Congressional Intent

As previously mentioned by APhA to FDA, Congress was clear it wanted to continue to allow traditional pharmacy compounding when it passed the Drug, Quality and Security Act (DQSA) because it left compounding under section 503A exemptions virtually untouched. In accordance with the DQSA, compounding that complies with section 503A remains under the purview of state boards of pharmacy. While the Guidance may be helpful to section 503A compounders and the states, pharmacies compounding in compliance with section 503A are regulated and inspected under state authority, not FDA. Therefore, APhA does not believe 501(a)(2)(A) gives FDA the general authority to inspect pharmacies compounding pursuant to section 503A. APhA recommends FDA modify this language and clarify, as stated later on in the Guidance, that authority over pharmacies compounding under section 503A exemptions remains with the states.⁶

II. Recommendation to Expand Physician Compounding/ Repackaging Exemption to Licensed Pharmacists

As FDA knows, section 503A of the Food, Drug and Cosmetic Act provides an exemption for compounding “...by a licensed pharmacist or licensed physician in limited quantities before the receipt of a valid prescription order for such individual patient...”⁷ In the Guidance, FDA states it “...generally does not intend to take action under section 501(a)(2)(A) against a physician who is compounding or repackaging a drug product, or who is mixing, diluting, or repackaging a biological product, provided that such activities occur in the physician’s office where the products are administered or dispensed to his own patients.”⁸ Because 503A treats pharmacists and physicians similarly, APhA emphasizes that any exemption for physicians should be extended to pharmacists. Failure to do so would be inconsistent with current law and fails to recognize pharmacists’ compounding education and training, which is more than other health care professionals.

⁶ See, Lines 76-69. “However, compounding facilities that are not registered with FDA as outsourcing facilities are primarily overseen by the states and, as explained above, generally are not routinely inspected by FDA.”

⁷ See, 21 USC 353a `SEC. 503A. PHARMACY COMPOUNDING. (2)(A). Available at: <https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm376733.htm>

⁸ See, Footnote #3.

III. Clarification/ Modification Needed

There are various provisions in the Guidance, that while APhA may not necessarily disagree with the intent, we believe clarification/ modification is required:

1. Lines 104-112: In addition to referencing USP <797>, APhA recommends FDA reference USP <825> and revised USP <725>⁹, once finalized, and include relevant terminology such as “segregated radiopharmaceutical processing area” or “SRPA” in addition to the SCA.¹⁰
2. Lines 126-127, 129-130, 138: FDA references “...the production area or adjacent areas” in a number of the examples. APhA requests clarification on what constitutes adjacent. For example, is adjacent specifically the rooms and areas touching the walls of the production areas?
3. Lines 140-149: APhA requests clarification on or examples of what would constitute “inadequate dedication, segregation, and containment (e.g., a powder containment hood) of a suite, room, or piece of equipment based on risk?” Similarly, what would constitute “inadequate cleaning” and “inadequate control over the movement of personnel and materials?”
4. Lines 160-161: While the mandate of sterility for critical gown components is important, APhA notes “sterile masks” is not listed in the gowning and garbing requirements of USP <797>.¹¹ APhA recommends the Guidance should not go beyond current standards and requirements.
5. Line 163: APhA recommends FDA use appropriate terminology, including “donning” rather than “putting on”, to align with professional compounding practices.
6. Lines 178-180: APhA recommends modifying the Guidance to require gowns and foot covers to be changed only after each shift or if visibly torn or insanitary which is consistent with both USP <797> and USP <825>. APhA also recommends changing “cleanroom” to include “cleanroom suite” to align with USP <797>.¹²
7. Lines 192-197: APhA recommends modifying the statement “Exposing sterile drugs and materials to lower than ISO 5 quality air” to “Exposing sterile drugs and critical components (i.e., supplies that touch drug components) to lower than ISO 5 quality air.” APhA also recommends providing an exemption for syringes, sterile gloves and sterile

⁹ See, USP General Chapter <795> Pharmaceutical Compounding – Nonsterile Preparations. March 30, 2018. Available at: <http://www.usp.org/compounding/general-chapter-795>.

¹⁰ See, USP General Chapter <825> Radiopharmaceuticals – Preparation, Compounding, Dispensing, and Repackaging. July 27, 2018. Available at: <http://www.usp.org/sites/default/files/usp/document/our-work/chemical-medicines/proposed-gc-825.pdf>

¹¹ See, USP General Chapter <797> Pharmaceutical Compounding – Sterile Preparations. July 27, 2018. Available at: <http://www.usp.org/compounding/general-chapter-797>

¹² Ibid.

wipes. These are sterile materials which will be exposed to lower than ISO 5 quality air when they are pulled out of the hood, a common practice in compounding. Additionally, APhA requests clarification as to whether the use of the terms "materials" and "supplies" in the Guidance has any significance or if the terms are interchangeable.

8. Lines 197-198: APhA recommends changing "disinfect" to "sanitize." Applying disinfectant to a vial of lyophilized sterilized drug component could potentially contaminate the drug product with the disinfectant.
9. Lines 209-210: Footnote #10 outlines an exemption for radiopharmaceuticals due to shielding and ALARA requirements.¹³ APhA recommends FDA also apply Footnote #10 to Lines 209-210 and clarify the critical area is the direct compounding area, not the entire ISO 5 hood.
10. Lines 237-239: APhA recommends placing an asterisk (*) next to this statement to be consistent with all the other bullet points in this section.
11. Lines 249-251: APhA recommends modifying the statement from "No or infrequent measurement of pressure differentials during operations to demonstrate proper airflow (i.e., airflow from areas of higher quality air to adjacent areas with lower quality air)*" to "No or infrequent measurement of pressure differentials between rooms designated as containing classified air during operations to demonstrate proper airflow (i.e., airflow from rooms of higher quality air to adjacent rooms with lower quality air)*." As written, inspectors could interpret a pressure differential requirement of hoods, which is not possible.
12. Lines 272-273: APhA recommends modifying "The presence of equipment unnecessary for aseptic operations, particularly particle generating equipment, in the ISO 5 area" to "The presence of equipment not described in SOPs for aseptic operations, assaying, and dispensing, particularly particle-generating equipment, in the ISO 5 area." The current statement is subjective and concerning for labeling, assaying, and compounding/dispensing logistics. APhA recommends that individual facilities be allowed to designate which equipment is necessary through its standard operating procedures (SOPs).
13. Lines 275-276: APhA recommends modifying this statement from "Equipment within or in close enough proximity to the ISO 5 area that could compromise the air in the ISO 5 area" to "Equipment within or in close enough proximity to the ISO 5 area unless validated with dynamic smoke studies or other appropriate testing to ensure the ISO 5 area is not compromised." As written, the current statement would not allow compounding in a hot cell. With radiopharmaceuticals, dynamic smoke studies and environmental monitoring validate use of equipment in close proximity.

¹³ See, 10 CFR 20.1003. Available at: https://www.nrc.gov/reading-rm/doc_collections/cfr/part020/part020-1003.html

14. Lines 326-327: This statement should use similar wording to USP <797> to determine which infections are concerning. Per USP <797>, (Lines 297-303) “Individuals that may have a higher risk of contaminating the CSP and the environment (e.g., personnel with rashes, sunburn, recent tattoos or oozing sores, conjunctivitis, or active respiratory infection) must report these conditions to their supervisor. The designated person is ultimately responsible for evaluating whether these individuals should be excluded from working in compounding areas before their conditions are resolved because of the risk of contaminating the CSP and the environment.”¹⁴
15. Lines 367-370: As stated previously, sterile wipes and sterile gloves are used routinely outside ISO 5 air for cleaning. Therefore, APhA recommends exempting both from this requirement.
16. Lines 377-378: Similar to Lines 249-251 (above), APhA recommends modifying this statement to clarify the pressure requirements pertain to rooms and not hoods.
17. Lines 390-393: APhA recommends this statement align with standards in the revised USP <797>¹⁵ (Lines 1798-1801) which states “The sterile compounding facility must document the implementation of the recall procedures. The recall must be reported to appropriate regulatory bodies as required by applicable jurisdictional laws and regulations (e.g., state board of pharmacy, state health department).”

Thank you again for the opportunity to provide comments on this important issue and we are happy to serve as a resource for FDA. 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.

Sincerely,



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Executive Vice President and CEO

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

¹⁴ See, USP General Chapter <797> Pharmaceutical Compounding – Sterile Preparations. July 27, 2018. Available at: <http://www.usp.org/compounding/general-chapter-797>

¹⁵ Ibid.