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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

Docket No. FDA-2016-D-2268

RE: Draft Guidance for Industry - Insanitary Conditions at Compounding Facilities

Dear Sir or Madam:

Thank you for the opportunity to submit our comments on the Food and Drug Administration's (FDA) Draft Guidance for Industry – Insanitary Conditions at Compounding Facilities. As FDA considers finalizing the proposed new guidance for pharmacy compounding, the International Academy of Compounding Pharmacists (IACP) appreciates the opportunity to share our perspectives and to work with FDA in the future on this very important issue.

IACP is an association representing more than 3,600 pharmacists, technicians, students, and members of the compounding community who focus on the specialty practice of pharmacy compounding. Compounding pharmacists work directly with prescribers including physicians, nurse practitioners and veterinarians to create customized medication solutions for patients and animals whose health care needs cannot be met by manufactured medications.

IACP understands and supports the need to protect public health. However, when providing guidance, it is essential that FDA adheres to the plain language of statutes and Congressional intent that preserve patient and prescriber access to vital compounded medications. Ensuring compounded medications are not prepared under insanitary conditions should be of the upmost importance, however, Guidance to the matter for state licensed pharmacies should ensure that proper adherence to State law and USP General Chapters <795> and <797> are not superseded.

The current draft guidance fails to follow Congressional intent, current State laws or regulations and USP General Chapters <795> and <797> as it pertains to pharmaceutical compounding. It also appears to attempt to exert current Good Manufacturing Practices (cGMP) on pharmacies which are clearly exempt from these requirements via Section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

IACP is concerned, both from the language contained in this guidance and from the agency's recent announcement on inspections, effective August 1, 2016, that the FDA will attempt to use findings regarding insanitary conditions as a mechanism to find a pharmacy not compliance with Section 503A and hold the pharmacy as an unregistered Outsourcing Facility or Manufacturer.

Since Section 503A provides an exemption from cGMP if the pharmacy is in compliance with the rest of the Section and since the Section does not outline non-compliance with Section 501(a)(2)(A) as a provision, a pharmacy operating with insanitary conditions present means solely that the products compounded by the pharmacy may have been adulterated. Therefore, a pharmacy should not be held to cGMP standards because of a violation of Section 501(a)(2)(A).

IACP recommends, along with other stakeholder groups, the FDA consider the prevailing community standards (either State regulations or USP) to be the base standard for inspections to ensure a pharmacy in compliance with Section 503A is not being inspected using cGMP standards.

1. **In providing examples of insanitary conditions, FDA outlines examples which go far beyond what is required by both State law and USP General Chapters <795> and <797>.**

To begin with, the provision of the examples is confusing as the FDA seems to insinuate these examples are wholly not allowed to occur at a pharmacy in compliance with Section 503A, while in the same document, provide much narrower recommendations for identifying insanitary conditions (Section B of the guidance) and corrective actions (Section C of the guidance).

Additionally, many of the examples go well beyond what is required by State law for licensure and compliance by a pharmacy. For example,

- Lines 117-119 describe the handling of beta-lactam, hazardous or highly potent drugs. Not only does the Guidance not define the terms "hazardous" or "highly potent drugs," the guidance reaches beyond the requirements outlined in USP <795> or <797>. Handling of beta-lactam drugs is a daily occurrence at almost all pharmacies, where staff will reconstitute these drugs for patient use. The guidance appears to require "adequate containment, segregation, and cleaning of work surfaces, utensils and personnel to prevent cross-contamination," none of which are required by USP <795> or <797>. Additionally, FDA does not define "adequate containment, segregation, and cleaning," which leads pharmacies to only guess as to what FDA would expect for compliance for this issue. This example appears to be a requirement from cGMPs and IACP respectfully requests this example be stricken from the guidance.
- Lines 120-121 fail to define "adequate controls to prevent contamination" or "adjacent area". This example appears to be a requirement from cGMPs and IACP respectfully requests this example be stricken from the guidance.

- Lines 127-130 do not fully describe how garbing should be done to prevent contaminations. IACP recommends referencing USP Chapter <797> for garbing procedures.
- Lines 131-132 fail to define a frequency in which gloves should be changed. IACP recommends referencing USP Chapter <797> for this procedure.
- Lines 146-149 do not define how quickly personnel should be allowed to move in the vicinity of open containers or needles, leaving pharmacies to only guess as to what FDA expects with this requirement. IACP recommends further definition or clarity for this example.
- Lines 178-180 appear to prohibit the use of an ISO 5 laminar flow hood located in an ISO 7 clean room, as non-aseptic activities are not allowed in this space. This example not only appears to be a requirement from cGMPs, but it flies in the face of the requirements of many State laws and USP <797>. IACP recommends this example be stricken from the guidance.
- Lines 184-194 are extremely problematic, both from the viewpoint of State laws and USP Chapter <797> but also from current pharmacy cleanroom design. For example,
    - Materials not being allowed to flow into the ISO 7 area from an unclassified area. The guidance does not consider instances where the anteroom may also be ISO 7, nor are provisions allowed for the use of compounding aseptic isolators.
    - Air vents between the classified and unclassified areas is prohibited, which makes positive pressure clean room design impossible. Without the use of air vents, how is the clean room to be designed to achieve positive pressure?
    - Required pressure differentials are not defined, leaving ambiguity on how the pharmacy is to comply with this issue.
    - IACP recommends this section be more clearly defined and directly point to requirements outlined in USP Chapter <797>.
- Lines 210-211 do not define "adequate" when describing the sterilizing filter and additionally require the use of a "pharmaceutical grade" filter, without defining such. While pharmaceutical grade filters exist in the marketplace, they are not available at the pharmacy level and do not meet the needs of pharmacies engaged in compounding. IACP recommends the guidance incorporate the requirements outlined in USP Chapter <797> regarding filtration.
- Lines 217-219 require the use of sterile cleaning pads or wipes, which are not required per USP Chapter <797>. IACP recommends using requirements from the Chapter regarding cleaning and disinfecting for this guidance.

In summary, many examples provided either refer to requirements outlined in cGMP, from which pharmacies in compliance with Section 503A are exempt from, or far outstrip requirements outlined in USP General Chapter <795> or <797>. IACP recommends utilizing

requirements from these Chapters and State laws in crafting examples of insanitary conditions for this guidance.

2. **With identifying insanitary conditions, FDA appears to require pharmacies to comply with cGMP while ignoring the exemption provided in Section 503A.**

While the guidance appears to allow compliance to USP Chapter <797> for routine environmental monitoring, FDA attempts to directly require pharmacies to comply with cGMP within footnote 7 ("FDA recommends that compounding facilities that are not registered as outsourcing facilities also conduct daily environmental monoitoring [*sic*] during operations.").

Additionally, we are concerned by the requirement of pressure differential measuring and how frequently this monitoring should occur and what the exact difference in the pressures should be. Again, IACP recommends to directly reference USP <797> to provide clarity.

3. **FDA's recommendations for corrective actions appear to far outstrip States' powers and go well beyond States' requirements currently in place for pharmacies.**

The corrective actions outlined, including issuance of recalls and the decision of stopping production, appears to remove the State Boards of Pharmacy authority over state licensed pharmacies and replaces it with FDA's recommendations. The list provided in the guidance is overly broad, ill-defined and extremely open for interpretations. For example:

- Appearance of insects in "immediately adjacent" areas to the ISO 5 area. Given an openly broad interpretation of this sentence, one would seem to think the appearance of a single fly in the waiting area of a pharmacy (which is adjacent to the ISO 5 area) would require the immediate cessation of production and initiation of a recall. IACP does not believe this is what the FDA is requiring, however, this requirement needs to be more clearly defined.
- Removing sterile products without "a robust and intact container closure system". This phrase is not defined in the guidance, leading pharmacies to only guess as to what the FDA would require for compliance with this provision. IACP recommends using requirements from USP Chapter <797> for further definition.
- Once again, the Guidance appears to require the use of "pharmaceutical grade" filters, which, as stated before, is problematic at the pharmacy level. IACP recommends the Guidance incorporate the requirements outlined in USP Chapter <797> regarding filtration.

Additionally, the FDA recommends, but does not require, a pharmacy to notify the local FDA District recall coordinator when the pharmacy decides to instate a recall and references FDA's current guidance, "Product Recalls, Including Removals and Corrections." Again, this is the agency's clear attempt to put itself between the pharmacy and the Board of Pharmacy which holds the license for the pharmacy. Decisions regarding whom to notify regarding a recall should rest solely with the applicate Board of Pharmacy, should a recall occur, as the Board is

responsible for the direct rules and regulations affecting the practice of pharmacy. It is up to the respective Boards of Pharmacy to decide if notification and/or action by the FDA is warranted.

4. **The guidance appears to require the pharmacy to surrender the records exemption provided in Section 704(a)(2) of the FD&C Act.**

While the guidance does not require the production of records created by the pharmacy attempting to comply with Section B of this guidance (e.g. testing reports of particulate, personnel and surface sampling, certification records of the ISO 5 area, pressure differential measurements, media fill testing results, etc.), one can certainly envision FDA requiring a pharmacy to produce those records to demonstrate compliance with section B of the guidance. This places the pharmacy in an impossible situation – either produce the records and theoretically waive the records exemption provided in Section 704(a)(2) or not produce the records and face further scrutiny from the FDA.

A balance must be struck between the agency's inspection authority, the State Boards' authority over licensees and the exemptions provided by Federal law to pharmacies "in conformance with any applicable local laws regulating the practice of pharmacy…" If the FDA is conducting a "routine" inspection in which the FDA has no knowledge the pharmacy has violated any State law, rule or regulation, the records exemption remains intact. A pharmacy should not be forced to volunteer the records exemption in an attempt to show compliance with a non-binding and not legally enforceable document. IACP urges the FDA to continue working with State Boards of Pharmacy to develop a framework to identify insanitary conditions, primarily using USP General Chapters <795> and <797> for requirements, and preserving the pharmacy's right to the records exemption provided by Federal law.

Lastly, we did note reference to footnote 3 on the first page of the document, however, the footnote does not appear in the document.

Thank you for the opportunity to submit our comments and IACP looks forward to working with the FDA in the future on this very important issue.

Sincerely,

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Executive Vice President
International Academy of Compounding Pharmacists