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Washington, DC 20004
www.pewtrusts.org

November 26, 2018

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Comments on Draft Guidance Document for Industry: Insanitary Conditions at Compounding Facilities (Docket ID: FDA-2016-D-2268)

Dear Sir or Madam:

Pew is pleased to offer comments on FDA's September 2018 draft guidance document relating to insanitary conditions for drug compounding under the Federal Food, Drug, and Cosmetic Act (FDCA). Pew is an independent, nonpartisan research and policy organization with a longstanding focus on drug quality and safety, including compounding.

In general, the draft guidance provides helpful direction to compounders and regulators. This updated draft includes additional and detailed examples of insanitary conditions that add important clarity to the guidance. However, we are concerned that FDA has expressed a policy of enforcement discretion with respect to physicians. The risks associated with compounding exist in all settings, and FDA has not articulated a public health rationale for effectively excusing physicians from the prohibition against producing drugs under insanitary conditions. The development of a comprehensive insanitary conditions guidance is critical to the safety of compounded drugs, and the agency undermines this objective by excluding physician compounding from its enforcement of the guidance.

Insanitary Conditions Standards Are an Important Protection for Patients

Drug compounding can be vital to patient health, but also presents potential risk. Compounding under insanitary conditions have been linked to outbreaks of severe and deadly infections. Under section 501(a)(2)(A) of the FDCA, insanitary conditions are those that could cause a drug to become contaminated with filth or rendered injurious to health. Examples of insanitary conditions provided in the guidance include, but are not limited to: the presence of vermin, mold, and standing water in the production or adjacent areas; use of non-pharmaceutical grade ingredients; construction occurring adjacent to production without measures to prevent contamination of the compounding area; and inadequate handling of hazardous or potent drugs (which can lead to cross-contamination).

In the most well-known example of injury from compounding, in 2012-2013, 778 people developed fungal meningitis and other infections – and 76 died – from being injected with contaminated preservative-free methylprednisolone acetate (MPA) that was compounded in a Massachusetts facility

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under insanitary conditions, including mold and bacteria in the clean rooms.[1] But this is hardly the only example of harm. Also in 2012-2013, 26 patients experienced adverse events, including skin abscesses, caused by MPA injections that a Tennessee compounder working under insanitary conditions distributed to facilities in 17 states.[2] In 2013, five people treated in Georgia and Indiana developed serious bacterial eye infections after receiving contaminated injectable bevacizumab that was repackaged in a Georgia facility under insanitary conditions.[3] The compounding facility lacked a system for monitoring environmental conditions and did not adequately validate its sterilization processes, among other deficiencies.[4] That same year, 15 patients in Texas developed bacterial bloodstream infections, and two patients died, after receiving infusions of contaminated injectable calcium gluconate compounded in a Texas facility under insanitary conditions.[5]

Under federal law, any drug is considered adulterated if it has been "prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health."[6] The compounding provisions of the FDCA exempt compounded drugs from some federal law provisions but there is no exemption allowing for compounding under insanitary conditions. Thus, while pharmacy and physician compounders regulated under 503A are primarily regulated by states, which set their own quality standards, and while outsourcing facilities are subject to federal cGMP requirements, insanitary conditions laws apply to drugs compounded in all of these settings.

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[1] U.S. Department of Justice, "14 Indicted in Connection with New England Compounding Center and Nationwide Fungal Meningitis Outbreak," accessed Nov. 7, 2018, https://www.justice.gov/opa/pr/14-indicted-connection-new-england-compounding-center-and-nationwide-fungal-meningitis.

[2] U.S. Food and Drug Administration, "FDA's Human Drug Compounding Progress Report: Three Years After Enactment of the Drug Quality and Security Act" (2017), https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm536549.pdf; Centers for Disease Control and Prevention, "Multistate Investigation of Suspected Infections Following Steroid Injections," accessed Nov. 26, 2018, http://www.cdc.gov/hai/outbreaks/TN-pharmacy/index.html.

[3] U.S. Food and Drug Administration, "Clinical Specialties Compounding Pharmacy 6/27/14," accessed Nov. 13, https://www.fda.gov/iceci/enforcementactions/warningletters/2014/ucm416208.htm; Laura S. Edison et al., "Endophthalmitis Outbreak Associated With Repackaged Bevacizumab," *Emerging Infectious Diseases* 21, no. 1 (2015): 171–73, http://dx.doi.org/10.3201/eid2101.141040.

[4] U.S. Food and Drug Administration, "483 Issued to Clinical Specialties Compounding," accessed Nov. 8, 2018, https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM348419.pdf.

[5] U.S. Food and Drug Administration, "FDA's Human Drug Compounding Progress Report;" U.S. Food and Drug Administration, "FDA Announces Nationwide Voluntary Recall of All Products for Sterile Use from Specialty Compounding," last accessed Nov. 26, 2018, https://wayback.archive-it.org/7993/20170112025131/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm364644.htm.

[6] 21 U.S.C. § 351(a)(2)(A).

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The insanitary condition standard maintains a federal floor for sanitary conditions, ensuring at least a minimal level of consistency across the country which states can (and should) exceed. Pew published a study in 2016 that found significant variation among states in their regulation and oversight policies for sterile compounding.[7] A 2018 update to that study showed that state officials have strengthened compounding oversight laws and rules since the 2016 assessment, though there remains room for improvement.[8] Given the disparity between states, it is in the best interest of public health that minimum quality standards of sanitary conditions exist for all places drugs are compounded. And, although states retain primary responsibility for inspecting and overseeing pharmacy and physician compounders, it is important that FDA tell compounders what it considers to be insanitary conditions so they can address any concerning conditions in their facilities, and that the agency use its authority to intervene when insanitary conditions put patients at risk.

FDA's updated draft guidance is an improvement over the past iteration. The additional detail included in the examples of insanitary conditions provides greater clarity that will offer important direction to compounders and regulators. Articulating that failing to conduct required environmental monitoring and media fill studies are examples of insanitary conditions also improve the document. Pew suggests that the agency periodically update its guidance to incorporate other concerning practices that the agency or state partners observe during inspections, which would serve as useful guidance for compounders seeking to improve their quality practices.

Exempting Physicians May Expose Patients to Adulterated Drugs

In a footnote in the draft guidance, FDA indicates that it does not intend to take action against physicians who compound or repackage a drug product, or mix, dilute, or repackage a biological product, provided that these activities occur in the physician's office where the products are administered or dispensed to the physician's patients. There is no public health rationale for effectively exempting physicians from the need to maintain sanitary conditions. The exemption leaves open the potential that a physician could establish relationships with patients for the sole purpose of providing them with compounded drugs, potentially leading to widespread exposure to drugs compounded under insanitary conditions.

Physician compounding is not intrinsically safer than pharmacy compounding. In fact, research looking at the influence of environmental cleanliness and risk manipulations on prepared syringes suggests that drugs prepared outside of controlled pharmacy environments, such as in a hospital ward, may be at

[7] The Pew Charitable Trusts, "National Assessment of State Oversight of Sterile Drug Compounding" (2016), https://www.pewtrusts.org/-/media/assets/2016/02/national_assessment_of_state_oversight_of_sterile_drug_compounding.pdf.
[8] The Pew Charitable Trusts, "State Oversight of Drug Compounding" (2018), https://www.pewtrusts.org/-/media/assets/2018/02/drug_safety_assesment_web.pdf.

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higher risk for contamination.[9] And, while drugs compounded in a physician's office may be used promptly—thus minimizing the time for contaminants to grow—this is not universally true.[10] The compounding environment is critical to the quality of the end-product,[11] and physicians' offices may be less likely to have the facility design and equipment to support sanitary practices.

When compounding in physician's offices occurs under insanitary conditions, that activity may not be detected until patients get hurt. Although state pharmacy regulators oversee compounding within pharmacies, they typically do not have jurisdiction over medical practices, which are regulated by state medical boards,[12] and FDA has noted that state medical boards do not exercise much oversight over physician compounding.[13] This lack of oversight means that states have minimal insight into physicians' compounding practices and are unlikely to identify at-risk practices unless patients sustain injuries that can be traced back to drugs compounded by a physician.

We appreciate that FDA has not entirely relinquished authority to enforce adulteration provisions with respect to physicians, and we recognize the practical challenge the agency would face in attempting to enforce insanitary condition standards with respect to physician compounding. However, explicitly exempting physicians from oversight gives countenance to business models where physicians could conduct compounding operations outside of the reach of meaningful oversight. Signaling that the agency will turn a blind eye to physician compounding under certain circumstances may embolden doctors and investors who see compounding outside of the bounds of enforced quality standards as a business opportunity to undercut pharmacy compounders, putting patients at risk. It is one thing to use agency resources to address areas perceived to pose the greatest risk, such as larger compounding operations than would be found in a physician's office when the compounding is for the physician's own patients, but another to explicitly forego enforcement in a guidance and thereby sanction the growth of practices that put patients at risk.

We recommend that FDA remove the footnote describing its enforcement policy for physician compounding. At minimum, the guidance should explicitly articulate that the physician exemption

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[9] Cyril Stucki et al., "Microbial Contamination of Syringes During Preparation: The Direct Influence of Environmental Cleanliness and Risk Manipulations on End-Product Quality," *American Journal of Health-System Pharmacy* 66, no. 22 (2009): 2032-36, http://dx.doi.org/10.2146/ajhp070681.

[10] A limited exemption for physicians' offices that are in full compliance with USP <797> standards for immediate-use drugs (which are administered within the hour as defined by USP) is appropriate. Under this standard, the immediate-use exemption cannot apply to hazardous drugs, and practitioners compounding in doctors' offices must still have training and be held to a standard of care that includes good hand hygiene and aseptic technique.

[11] Stucki et al., "Microbial Contamination of Syringes During Preparation."

[12] The Pew Charitable Trusts, "Best Practices for State Oversight of Drug Compounding" (2016), https://www.pewtrusts.org/-/media/assets/2016/02/best_practices_for-state_oversight_of_drug_compounding.pdf.

[13] U.S. Government Accountability Office, "Drug Compounding: FDA Has Taken Steps to Implement Compounding Law, But Some States and Stakeholders Reported Challenges" (2016), https://www.gao.gov/assets/690/681096.pdf.

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applies only to compounded drugs administered or dispensed to patients in the physician's office, and only for patients that have an established, preexisting relationship with that physician. As written, the footnote could be interpreted to allow physicians to compound in the office and dispense – for example by mail – to patients with whom the physician has no other relationship. Coupled with the limited oversight of physician compounding contemplated in the draft Memorandum of Understanding between FDA and the states, this exemption would potentially allow physicians to produce and ship unlimited quantities of products interstate without the state or federal government inspecting for or enforcing even the minimum insanitary conditions standards, let alone more meaningful product quality standards. If FDA intends to exempt physicians from the baseline conditions that otherwise apply to any compounder, at minimum that exemption should not apply when physicians compound for patients not in their direct care, or when they distribute compounded drugs.

The development of a comprehensive insanitary conditions guidance is critical to the safety of compounded drugs. Overall, with the exception of its treatment of physician compounding, Pew is supportive of FDA's draft guidance. Pew encourages FDA to finalize the guidance promptly and take enforcement action against compounders who expose patients to products made under insanitary conditions.

We thank you again for the opportunity to provide comments.

Sincerely,

Elizabeth Jungman, J.D., M.P.H.
Director, Public Health Programs