October 30, 2017

Eric Hargan, J.D.
Acting Secretary for Health
U.S. Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Acting Secretary Hargan:

As diverse stakeholders committed to ensuring the safety and reliability of compounded medicines for patients, we urge the Department of Health and Human Services (HHS) to continue strong implementation and enforcement of the bipartisan Drug Quality and Security Act of 2013 (DQSA).

We applaud HHS's significant progress toward implementing the DQSA and creating a clear framework for compounded medicines. As the administration continues to develop the new oversight system, we urge you to ensure that compounded medications are made under appropriate quality standards by adhering to these key principles:

1. **The prescription is the line between outsourcing facilities and traditional compounders.** As Congress established, the key distinction between outsourcing facilities, which provide stock supplies of compounded drugs, and traditional compounders, who tailor products to individual patients, is the prescription. This is a point Commissioner Gottlieb has repeatedly made in his public statements. As detailed further below, the prescription requirement is critical to ensure product quality, create oversight accountability, and maintain incentives for outsourcing facilities to invest in quality systems.

2. **Ensure that flexibility for outsourcing facilities does not compromise patient safety.** In September, Commissioner Gottlieb announced that the Food and Drug Administration (FDA) will soon release new draft guidance for industry that will tailor the applicable quality standards in order to encourage more pharmacies to register with the agency as outsourcing facilities. Flexibility on the part of FDA that enables more outsourcing facilities to enter the market would be positive for patients and providers, as

long as the new entrants maintain the quality standards envisioned for outsourcing facilities and satisfy the conditions set forth by Congress in order to be exempted from certain FDA requirements. The outsourcing facility category was established to ensure that hospitals and clinics have a safe supply of sterile compounded drugs; new flexibility must maintain the assurance of sterility and compliance with the law.

3. **Ensure that traditional compounders produce drugs under sanitary conditions**. Pharmacy and physician compounders who dispense or distribute drugs pursuant to a prescription ("traditional compounders") are subject to quality standards established by the states, and to federal rules designed to ensure that drugs are not made under insanitary conditions. Because patients have been harmed by compounded drugs made in both pharmacy and physician office settings, it is important to ensure the safety of patients taking drugs wherever they are made.

Background: The Drug Quality and Security Act Controls Risk and Enhances Accountability

The DQSA was passed under the shadow of a tragedy. In 2012 and 2013, roughly 750 patients were sickened and more than 60 died in a multistate outbreak of fungal meningitis associated with contaminated spinal injections prepared by a single compounding pharmacy in Massachusetts. These drugs were produced in large batches and shipped across the country. Congress responded forcefully to the outbreak by reaffirming the original compounding statute – section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA) – that allows pharmacists and physicians to prepare individual, prescription-based patient-specific medicines without having to go through the drug approval process and demonstrate safety and effectiveness. This type of compounding is often referred to as traditional compounding.

At the same time, Congress recognized that some hospitals and healthcare providers may need supplies of medications not made by pharmaceutical manufacturers, or not made in the specific form, combination, or strength that patients may require. These products, which need to be on hand, are known as "office stock," and present unique safety concerns. Because they are often held for a period of time before use, contamination can proliferate. This risk is increased as these products are typically made in larger volume so if they do become contaminated, or are produced incorrectly, more patients are exposed to the risk. To mitigate the higher risk associated with producing stock supplies of compounded drugs, Congress created the outsourcing facility category, governed by section 503B of the FDCA. Congress required that these facilities adhere to current Good Manufacturing Practices (cGMP)—rigorous requirements enforced by FDA that describe a full set of quality standards for the manufacturing, processing, packing, and storage of pharmaceutical products.

The statute was explicitly written to ensure that sterile drugs produced without a prescription would be held to more robust quality standards than medicines compounded pursuant to individual prescriptions in order to reduce the risks to patient safety. Furthermore, by distinguishing the two categories of compounders, the DQSA enhances accountability by making it clear – both for the regulators and the regulated industry – whether any given compounder is primarily regulated by the federal or state government.

The Prescription Requirement is the Lynchpin of the Oversight System for Drug Compounding

The statutory provision governing traditional compounding, FDCA section 503A, requires a valid prescription, and in December 2016, FDA finalized its prescription requirement guidance for industry elucidating that requirement. FDA's document appropriately affirms the DQSA's requirement that traditional compounders dispense compounded products only upon receipt of a valid prescription.

Because outsourcing facilities can produce and distribute drugs without a prescription while traditional compounders cannot, FDA calls the prescription requirement a "critical mechanism" for distinguishing traditional compounders from drugmakers that must comply with higher manufacturing standards. The prescription requirement also operates as a bright line rule, resolving the lack of clarity about which activities were subject to state versus federal oversight; confusing legal authority was an important contributor to the fungal meningitis outbreak that led to the DQSA. Finally, the prescription requirement preserves the incentives for facilities to register as outsourcing facilities – the DQSA is a market-based statutory regime that, instead of requiring compounders to register as outsourcing facilities, creates the incentive for them to do so by permitting facilities that invest in quality systems and submit to FDA inspection to sell products without prescriptions. If traditional compounders are allowed to prepare drugs without patient-specific prescriptions, that could remove incentives for companies to invest in the equipment, training, and specialized personnel necessary to comply with federal quality standards, and pose grave risks to patient safety.

FDA should continue to maintain the prescription as the clear line between traditional compounding and outsourcing facilities, and ensure that facilities that are producing office stock drugs adhere to the cGMP standards appropriate for creating stock supplies.

Flexibility for Outsourcing Facilities Must Not Compromise Patient Safety

FDA is robustly implementing and enforcing section 503B of the FDCA, including developing draft and final guidance for industry, and conducting inspections of outsourcing facilities. Seventy-one outsourcing facilities are currently registered with FDA. These facilities are permitted to produce unlimited quantities of stock supplies of compounded drugs for hospitals and other healthcare providers, including for physicians to use in their offices. Despite this, there have been reports of concerns about access to compounded medications for office use.

Flexibility on the part of FDA that enables more outsourcing facilities to enter the market could help resolve access issues and would be good for patients and providers, as long as the new entrants could maintain the quality standards envisioned for outsourcing facilities. Increased access to stock supplies of high-quality compounded medications would also help ensure that physicians and other healthcare providers do not attempt to prepare medications in their offices under less robust quality conditions.

As FDA develops guidance tailoring cGMP standards to smaller outsourcing facilities, it will be important to distinguish the quality standards that apply to traditional compounding from cGMP requirements. Most states require traditional compounders to comply with U.S. Pharmacopeial Convention (USP) standards on compounding. USP Chapter <797> is a widely recognized set of sterile compounding quality standards that,

while appropriate for traditional compounding, is not equivalent to the protections of cGMP. For example, key cGMP requirements, such as testing non-sterile ingredients for contamination prior to using them in sterile drugs and requiring personnel to be completely covered in sterile gowning, are not part of USP <797> requirements.[1] Outsourcing facilities can produce unlimited quantities of compounded drugs and ship them nationwide, thus, it is critical for outsourcing facilities to adhere to compounding quality standards that match the level of risk of these activities in order to fulfill the promise of this new category of compounder: to provide hospitals and physicians with a reliably safe and sterile supply of compounded drugs.

We recognize that adopting cGMP has cost implications (as it does for traditional manufacturers), and support flexibility to lower costs if sterility can nevertheless be maintained. While FDA should be as flexible as scientifically appropriate, failing to adhere to appropriate quality standards costs people their lives. From 2001 to 2017, more than 50 reported compounding and repackaging errors or potential errors were associated with 1,227 adverse events, including 99 deaths.[2] Contamination of sterile products was the most common error. FDA must develop standards that enhance access without compromising patient safety.

All Traditional Compounders Must Protect Patient Safety

While drug compounding commonly occurs at pharmacies, it may also take place in a doctor's office. Some research suggests that the frequency of contamination of parenteral drug preparations (a category of drugs including those administered through higher-risk routes of administration, such as intravenously or through injection) is higher in clinical environments than in controlled pharmacy environments.[3] Serious adverse events occurring as a result of physician office compounding include one recent example from 2016, when 17 people developed fungal bloodstream infections after they received contaminated compounded intravenous medications that were prepared at an outpatient oncology clinic in New York. In general, physicians' offices that compound should be held to the same standards as other compounding facilities, including FDA's requirements for ensuring compounding occurs under sanitary conditions.

In some instances, drugs must be compounded in a doctor's office that for medical reasons must be administered immediately after preparation. In circumstances where the drug is used immediately a contaminant, if present, would not have time to proliferate to harmful levels, and thus quality standards that take these reduced risks into account may be appropriate. However, practitioners compounding in doctors' offices must still have appropriate training and be held to a standard of care that includes good hand hygiene and aseptic technique. Furthermore, any special allowances for immediate use compounding must not permit or encourage this practice outside of what is medically necessary.

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[1] The Pew Charitable Trusts, "Pharmaceutical Compounding: Quality standards for different scales" (2015), http://www.pewtrusts.org/en/multimedia/data-visualizations/2014/pharmaceutical-compounding-quality-standards-for-different-scales.

[2] The Pew Charitable Trusts, "U.S. Illnesses and Deaths Associated With Compounded Medications or Repackaged Medications" (2017), http://www.pewtrusts.org/en/multimedia/data-visualizations/2017/us-illnesses-and-deaths-associated-with-compounded-medications-or-repackaged-medications.

[3] Peter Austin, K.S. Hand, and Marinos Elia, "Systematic Review and Meta-analysis of the Risk of Microbial Contamination of Parenteral Doses Prepared Under Aseptic Techniques in Clinical and Pharmaceutical Environments: An Update," *Journal of Hospital Infection* 91, no. 4 (2015): 306–18, doi:10.1016/j.jhin.2015.04.007.

State pharmacy regulators manage the oversight of compounding within pharmacies, but they typically do not have jurisdiction over medical practices, which are regulated by state medical boards. Thus, state pharmacy inspections, which help ensure compliance with state quality standards, are not conducted in physician office settings. It is thus particularly important that federal insanitary conditions standards for traditional compounders apply to both pharmacy and physician compounders, and that the federal government not adopt any policy that would encourage shifting compounding from pharmacy to physician environments. Instead, for those circumstances where FDA-approved options are not clinically appropriate, federal policy should focus on ensuring that physicians have access to safe supplies of compounded drugs produced under cGMP in outsourcing facilities.

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We applaud HHS's significant progress toward enforcing the prescription requirement and implementing the new outsourcing facility sector, and urge the agency to continue strong implementation and enforcement of the DQSA. Doing so will create a clear framework for compounded medicines, and safeguard patients who rely on them. We look forward to continuing to stay engaged with you on this important issue. Please do not hesitate to contact Sarah Despres at (202) 540-6601 if we can be of any assistance.

Sincerely,

American Public Health Association (APHA)
Association for Accessible Medicines (AAM)
Biotechnology Innovation Organization (BIO)
Pharmaceutical Research and Manufacturers of America (PhRMA)
The Pew Charitable Trusts

Cc: Scott Gottlieb, M.D., Commissioner of Food and Drugs, Food and Drug Administration
Brenda Fitzgerald, M.D., Director, Centers for Disease Control and Prevention
Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, Food and Drug Administration