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BEFORE THE U.S. HOUSE COMMITTEE ON ENERGY AND COMMERCE,
SUBCOMMITTEE ON HEALTH

EXAMINING THE IMPLEMENTATION OF THE COMPOUNDING QUALITY ACT

January 30, 2018

Full Committee Chairman Walden and Ranking Member Pallone, Health Subcommittee Chairman Burgess and Ranking Member Green, and Members of the Subcommittee, thank you for the opportunity to participate in today's hearing. My name is Jenn Adams, and I am the President of PharMEDium. On behalf of PharMEDium, I wish to express our longstanding and continued support for the Drug Quality and Security Act (DQSA). I look forward to today's hearing and the Committee's continued work to ensure the faithful implementation of this important law.

A subsidiary of AmerisourceBergen, PharMEDium is the leading provider of pharmacy-outsourced, ready-to-use compounded sterile preparations. With over 20 years of experience, PharMEDium operates four outsourcing facilities registered with the Food and Drug Administration (FDA) pursuant to section 503B of the Food, Drug, and Cosmetic Act (FDCA), as established by the DQSA. PharMEDium was the first entity to register with FDA following the law's passage in 2013.

PharMEDium's operation is exclusively "sterile-to-sterile" compounding, which means that all of our products are prepared using only FDA-approved (or otherwise legally marketed) drugs in finished dosage forms and other FDA-cleared components, such as containers and diluents. Much of what we prepare for hospital and health system clients involves – as the name "outsourcing facility" suggests – outsourcing the very same production that they would have to do on site in order to prepare sterile drugs for administration to patients. We provide our hospital customers with an array of pre-admixed preparations for pain management, surgeries, and labor and delivery. For example, expecting mothers in labor are typically administered epidural and other compounded preparations of drugs for which the FDA approved versions are not manufactured in ready to administer forms. PharMEDium serves thousands of hospitals across all fifty states, and our customers range from small community hospitals to the nation's largest and most prestigious health systems and academic medical centers.

As one of the first organizations to endorse the DQSA, we are fully committed to its successful implementation. We welcome policies to facilitate the success of the law through a vibrant and competitive marketplace for outsourced sterile drug preparations, and appreciate Congress' continued interest and oversight. However, a fundamental premise of the law that remains equally true today is that compounded drugs should only be used when FDA-approved drugs do not meet a patient's clinical needs.

NECC and the DQSA: Congressional Response to a Public Health Tragedy

As Members of this Committee are acutely aware, in 2012, the interstate distribution of contaminated steroid injections by the New England Compounding Center (NECC) is reported to have resulted in over 750 cases of fungal meningitis and claimed the lives of 64 Americans. NECC had been the subject of multiple complaints, including warnings from PharMEDium. Thanks to the Energy & Commerce Committee's thorough investigation and sustained leadership, working in collaboration with the Senate HELP Committee, Congress passed the Compounding Quality Act (CQA) as Title I of the DQSA. The DQSA received broad bipartisan and bicameral support. Working through a transparent legislative process that engaged the full array of stakeholders, the authorizing Committees developed legislation that garnered 63 endorsement letters from diverse organizations ranging from the National Community Pharmacists Association (NCPA), and American Society of Health-System Pharmacists (ASHP), the Pew Charitable Trusts, Biotechnology Industry Organization (BIO), and PharMEDium, among many others.

The DQSA confirmed FDA's authority to enforce parameters of traditional pharmacy compounding under section 503A of the FDCA, centered on the prescription requirement. Additionally, it created a new section of the FDCA, section 503B, to regulate "outsourcing facilities." In exchange for the ability to compound drugs in larger volumes, without receiving patient-specific prescriptions as are necessary under section 503A, outsourcing facilities must: register with the FDA; submit to routine FDA inspections; pay annual fees; report all production and serious adverse events to the FDA; label products as compounded drugs "for office use only;" and most importantly, operate in accordance with current good manufacturing practices (cGMPs).

cGMPs are vital for non-patient-specific compounding because these standards provide the highest degree of quality assurance and are designed for larger volume production, as opposed to prescription-by-prescription production. cGMPs are a series of guidelines and principles governing the preparation of drugs. In the context of section 503B, cGMPs are particularly focused on eliminating the potential for contamination of compounded medications and ensuring the uniformity of production, among other safety and quality issues. In our view, section 503A's prescription requirement is the lynchpin that makes the DQSA work. Specifically, it preserves the incentives for facilities to register as outsourcing facilities and provides a clear delineation for federal oversight. It utilizes a market-based approach that encourages entities wishing to engage in larger volume compounding to make the necessary investments in quality systems to submit to FDA oversight and routine inspections.

FDA's significant progress toward enforcing the prescription requirement and implementing the fundamental rules of the road for the new outsourcing facility sector are critical to the success of the DQSA and to the ultimate goal of ensuring patients have access to a safe supply of medically necessary compounded medications. In just over four years, the agency has issued proposed and final regulations on numerous aspects of the DQSA, issued numerous final guidance documents, and is actively working to finalize a number of additional guidance documents currently in draft form.

FDA has also conducted hundreds of inspections of registered outsourcing facilities, identifying areas of needed improvement in every inspection conducted. Speaking for PharMEDium, we have undertaken major investments in personnel, systems, and process enhancements pursuant to achieving the highest possible quality for our compounded products. Yet there is more work to be done, both in terms of outsourcing facilities fully meeting FDA's expectations for our respective operations, as well as FDA taking steps to fully implement the law.

From PharMEDium's perspective, implementing final cGMP standards for outsourcing facilities is a critical and foundational step toward the successful implementation of the DQSA, so that we know exactly what requirements apply, and that states also have clarity and certainty as to governing standards for outsourcing facilities. We understand that the agency is working to finalize its 2014 draft guidance and proceed to rulemaking. In tailoring cGMPs to specific compounding operations, it is critical that final standards are oriented to the particular challenges presented by different types of compounding operations, their source (i.e., raw or starting) materials, sterile practices, and finished products. Although PharMEDium supports efforts to facilitate additional entities registering as outsourcing facilities, the very high bar on compliance with quality assurance must be maintained in any such initiative.

Moreover, it is imperative that FDA continue to work with states to ensure that the ongoing patchwork of inconsistent state requirements is replaced by consistent, national standards for outsourcing facilities, as the DQSA envisioned. Harmonization of compounding standards is particularly important to ensuring uniform, safe products. Unfortunately, several states have rigidly followed alternative quality regimes such as the model act, and refuse to recognize FDA's pronouncements regarding how to apply the regulatory GMPs (i.e., 21 C.F.R Parts 210 and 211) to outsourcing facilities, while others have promulgated their own alternative standards for outsourcing facilities. In addition, some states have not yet updated their statutes and regulations, and thereby are unable to appropriately license and regulate outsourcing facilities. In short, the lack of finalized cGMP regulations for outsourcing facilities has contributed to a patchwork of inconsistent requirements that in some cases conflict with FDA's expectations.

Vague policies and lax enforcement of bulk drug substances undermine the DQSA and threaten patient safety

While FDA has made commendable strides in implementing the DQSA, PharMEDium urges FDA to begin policing the DQSA's strict standards on compounding from bulk drug substances, which are typically the nonsterile raw materials that contain the active pharmaceutical ingredients (APIs) used to make drugs.

As the Committee knows, the DQSA prohibits compounding using bulk substances unless: (1) the drug is in shortage at the "time of compounding, distribution, and dispensing"; or (2) FDA determines that there is a "clinical need" that is not being met by approved products, and includes the substance on a list of such ingredients.[1] Unless one of these circumstances is present, outsourcing facilities are expected to compound using only FDA-approved drugs and cleared components. These restrictions were established based upon the fundamental reasons that

[1] FDCA § 503B(a)(2).

the use of bulk drug substances introduces additional safety risks, and their use in place of an approved drug undermines the integrity of the drug approval system.

In several guidance documents, FDA has failed to clarify these provisions, which has inadvertently exacerbated the misuse of bulk drug substances. First, in its *Interim Policy on Compounding Using Bulk Drug Substances*, finalized in June of 2016, FDA announced open-ended enforcement discretion toward a list of nearly 200 substances, including more than 100 of which are the active ingredients in one or more FDA-approved drugs. Therefore, these substances are being used in compounding even when there is no legitimate clinical need served by the bulk-compounded version that couldn't be served by the FDA-approved drug. Despite comments from PharMEDium and many others, FDA has declined to impose any restrictions on the use of these bulk substances.

As noted, PharMEDium has seen a dramatic marketplace shift toward purchasing bulk-compounded versions of several critical drugs since these policies were issued. This trend threatens to undermine the federal drug approval system and adds additional safety risks for patients. Of particular concern, many of these bulk-compounded drugs appear to be unlawful copies of FDA approved drugs. For example, rather than starting with an FDA-approved finished vial of a particular drug, an entity can prepare simple dilutions or reconstitutions from bulk APIs, enabling them to undercut the approved drugs and the drugs prepared by outsourcing facilities from approved drugs. In the above example of pain management epidurals, some compounders are substituting the FDA-approved finished drugs, such as a vial of fentanyl, with nonsterile API powders, despite the absence of a clinical rationale for doing so. Moreover, hospitals and other providers are not necessarily aware that they are receiving products compounded from bulk API rather than from approved drugs.

Separately, the DQSA prohibits compounding what is "essentially a copy of one or more approved drugs."[2] FDA has issued guidance describing section 503B's prohibition on copying approved drugs, but has misinterpreted the definition of "essentially a copy" in a way that fails to provide an appropriate check on compounding from low-cost bulk API when it is clinically unnecessary to do so. The statutory definition states that a compounded "drug, a component of which is a bulk drug substance that is a component of an approved drug" is an unlawful copy "unless there is a change that produces for an individual patient a clinical difference, as determined by the prescribing practitioner[.]"[3] In implementing the requirement for documentation of a clinical difference, however, FDA has misstated the condition that the drug be compounded from bulk substances. The final guidance states that the prescriber determination requirement "applies to a compounded drug whether it was compounded from bulk drug substances or from drugs in finished form."[4] This creates the misperception that the clinical determination needed to justify combining FDA-approved fentanyl with FDA-approved ropivacaine in a pain management epidural might also satisfy the documentation requirement for starting with API powder for either drug (in place of using the FDA-approved versions). By

[2] *Id*. § 503B(a)(5).

[3] *Id*. § 503B(d)(2)(B).

[4] FDA, Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the FD&C Act, at 9 (Jan. 2018).

misapplying the definition, the policy creates a disincentive to compound from drugs in finished form and thereby encourages the exact type of unnecessary copying Congress set out to prevent.

The combined effect of these two ambiguous policies is to incentivize the rampant and widespread misuse of bulk drug substances, which are far riskier than compounding sterile drugs using FDA-approved drugs. Nonsterile APIs introduce risks into the compounding process that simply cannot be justified when a sterile finished drug can be used to meet patients' clinical needs. For example, because current policies do not specify that outsourcing facilities must use a particular grade of API and testing is often limited to identity/potency, the resulting impurity profile is unknown and, therefore, uncharacterized. Further, terminal sterilization introduces additional complexities (e.g., endotoxins and pyrogens) that would not be expected in aseptic processing of already sterile finished drugs and components.

FDA has announced its intention to issue new guidance in March clarifying that bulk drug substances may be used for compounding, "only when there is clinical need to compound drugs using these substances." FDA confirmed that this restriction "protects patient health and the drug approval process, for example, by helping to ensure that outsourcing facilities do not compound using a bulk drug substance when an FDA-approved drug can be used to meet patient medical needs."[5] Statements to describe the limitations on compounding using bulk drug substances when there is not a legitimate clinical need are welcomed and long overdue.
To protect the public health and preserve incentives to seek new drug approvals, however, FDA must also begin to enforce the DQSA's strict limitations on bulk substances.

PharMEDium is concerned that future draft guidance could be an inadequate response to the rampant and ever-increasing misuse of bulk drug substances. We urge FDA to take the following actions: (1) implement changes to the Interim Policy to place guardrails around the use of substances that correspond to an FDA-approved drug on the enforcement discretion ("Category 1") list; (2) revise the Essentially a Copy final guidance to accurately describe section 503B's prohibition on copying approved drugs based on a faithful reading of the law's definition of copies, which further limit how bulk substances may be used; and (3) issue the announced forthcoming guidance describing restrictions on the use of bulk dug substances with FDA-approved drugs are available as soon as possible.

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In summation, PharMEDium feels strongly that by preserving the regulatory clarity and certainty that the DQSA sought to create, FDA can best ensure patient safety. It is imperative that FDA faithfully enforce section 503B's restrictions on bulk drug substances to preserve the boundary between compounding and conventional drug making, and not allow compounders to become pseudo-manufacturers of drugs that circumvent the premarket approval process. This interpretation of the DQSA and corresponding enforcement is critical to protect patients. It is also essential to preserve the prescription requirement of section 503A as the clear line of demarcation between traditional pharmacies and federally regulated outsourcing facilities.

[5] FDA, 2018 Compounding Policy Priorities Plan, (Jan. 2018).

Without this line of demarcation, the framework of the DQSA would not be sustainable. Although FDA has myriad other policies to tackle as part of its oversight of drug compounding, we believe that fidelity to these basic principles will go a long way to ensuring the success of the DQSA.

Again, thank you for the opportunity to contribute to this important dialogue. Stakeholder engagement is vital to ongoing implementation efforts we welcome the opportunity to continue offering assistance in ensuring the success of this bipartisan public health endeavor.

With that, I look forward to answering your questions.

Thank you.