Statement of

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"Reforming the Drug Compounding Regulatory Framework"

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Mr. Chairman and members of the Subcommittee, I am Jeffrey Francer, and I serve as Assistant General Counsel of the Pharmaceutical Research and Manufacturers of America (PhRMA). Thank you for the opportunity to present our views on improving the drug compounding regulatory framework in order to enhance patient safety.

PhRMA is a voluntary, nonprofit association that represents the country's leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. In 2012, PhRMA members alone invested nearly $50 billion in discovering and developing new medicines.

PhRMA shares the Committee's goal of advancing public health by ensuring that the Food and Drug Administration's (FDA) statutory authority and safety standards for pharmacy compounding are adequate to protect patients against the risks demonstrated over the past year.

There is no higher priority for biopharmaceutical companies than patient safety. We commend the Committee's diligence in investigating the causes of the recent tragedies involving pharmacy compounding and potential solutions.

PhRMA believes that medicines manufactured by our member companies, as well as those compounded by non-traditional pharmacies and manufacturers, should be regulated by FDA using a consistent, risk-based approach. This approach best serves the public health, because products that present similar risks should be regulated similarly.

PhRMA Supports FDA Oversight of Non-traditionally Compounded Drugs to Patients

In light of the incidents surrounding the New England Compounding Center (NECC) last year, it is clearly appropriate for Congress to revisit FDA's authority and obligations with respect to the compounding of prescription drugs. The ultimate objective of this endeavor should be, first and foremost, to ensure the safety of patients.

After reviewing FDA's existing enforcement authority, including the authority FDA applied to inspect NECC prior to the tragedy, PhRMA believes that patient health could be better protected by (1) clarifying FDA's existing authority to regulate non-traditional compounding, to the extent there is any ambiguity, and (2) ensuring that FDA has sufficient resources to protect the public health, including by considering its current authority to levy user fees on manufacturers to bolster its inspection resources.

Consistent with the goal of clarifying FDA's authority to regulate non-traditional compounding and ensuring that the agency has the resources necessary to protect public health, PhRMA would support legislation that would:

1. Clarify that FDA retains authority to regulate as a new drug (including through the application requirement and adulteration and misbranding provisions) any drug that is compounded outside of traditional compounding (*i.e.,* non-individual compounding), and any person involved in the manufacture, distribution, or marketing of such drugs;
2. Provide express inspection and registration authority for non-traditional compounders as manufacturers, including, to the extent that such authority is not clear, the ability to inspect records to determine whether pharmacies are engaging in non-traditional compounding;

3. Provide specific user fee authority to ensure that FDA has adequate resources to regulate non-traditional compounders as manufacturers;
4. Ensure that non-traditional compounders may not compound copies of marketed drugs subject to a new drug application (NDA) or biologics license application (BLA), including slight variations of those marketed drugs that are not intended for specific individuals for whom the variation is clinically important, and thus subvert the generic or biosimilar approval process;
5. Prohibit the compounding of specific drugs or drug categories, whether by statute or by giving the agency the discretion to exclude them on safety or efficacy grounds (*e.g.*, complex dosage forms and biologics, drugs removed from the market for reasons of safety or efficacy, and products containing drug substances that FDA has determined may not be used in compounding);
6. Appropriately limit the channels of distribution for compounded drugs, including through a prohibition on wholesale distribution; and
7. Delete the section of the Federal Food, Drug, and Cosmetic Act (FDCA) at issue in *Thompson v. Western States Medical Center*, section 503A(c).[1]

Within this framework, FDA could and should take a risk-based approach to the regulation of non-traditional compounding and prioritize inspections and enforcement using the same risk-based approach the agency applies to pharmaceutical manufacturing.

[1] 535 U.S. 357 (2002).

Comprehensive and complex legislation that creates a new classification of compounder (so-called "compounding manufacturers") is, however, unnecessary. Such an approach could result in regulatory confusion (both federal and state) and the application of different regulatory standards (and patient protections) for similar types of manufacturing. PhRMA does not believe that the creation of a new class of non-traditional compounding subject to standards different than NDA- or BLA-approved drugs and biologics best serves the public health. In fact, such a "third class" would actually decrease FDA's current statutory standards for regulating non-traditional compounders.

PhRMA Supports FDA's Use of its Existing Authority to Regulate Compounded Drugs and Biologics

A. Background on the Regulation of Biopharmaceutical Manufacturers

As mentioned at the outset, patient safety is the highest priority for PhRMA and biopharmaceutical companies that research, develop, manufacture, and bring to market new medicines. Biopharmaceutical research companies develop and market prescription medicines in accordance with FDA's exacting regulatory standards and industry practices. Our companies typically invest over $1.2 billion and 10 to 15 years to bring each new medicine to market. This investment includes performing nonclinical tests and extensive clinical trials to demonstrate safety and effectiveness, submission of an NDA or BLA for review and approval by FDA, establishing systems to assure manufacturing quality, and maintaining pharmacovigilance systems and other measures

to identify and respond to safety issues that may arise after pharmaceutical products are made available for use by patients.

In addition to complying with the requirement to obtain FDA approval before a new drug may be sold in the United States, biopharmaceutical research companies comply with the "gold standard" of quality manufacturing: FDA's current Good Manufacturing Practice (cGMP) regulations.[2] These regulations apply to all new prescription drugs approved for sale in the United States, wherever they are made, and extend to all components of a finished drug product, including active pharmaceutical ingredients, wherever they are sourced. FDA's cGMP requirements are based on the fundamental quality assurance principle that quality, safety, and effectiveness "cannot be inspected or tested into a finished product," but instead must be designed and built into a product.[3]

It is well established that inspections alone cannot be relied upon to ensure product quality and integrity, and that quality systems are vital to ensuring each product meets established specifications and requirements.[4] The quality systems approach to manufacturing drug products is embodied in the cGMP regulations and embraced by biopharmaceutical companies throughout the manufacturing process.

As the Subcommittee discussed during its last hearing on this topic, the FDCA requires that manufacturers provide proof of their ability to maintain a quality system, including the ability to manufacture under cGMP conditions, as part of the new drug

[2] Under current law, a drug is adulterated if the methods used in, or the facilities or controls used for, manufacturing a drug product do not conform to cGMP. 21 U.S.C. § 351(a)(2)(B). FDA regulations and guidance provide additional clarification regarding the expectations of cGMP in drug product manufacturing.

[3] 61 Fed. Reg. 20104, 20105 (May 3, 1996).

[4] *See generally* 21 C.F.R. Parts 210 and 211.

application. FDA also requires a pre-approval facility inspection for pharmaceutical manufacturers. In order to ensure patient safety, the agency should apply these same standards to non-traditional compounders that perform manufacturing steps and whom are regarded manufacturers under the FDA.

B. FDA Has the Authority to Regulate Non-traditionally Compounded Drugs and Biologics

PhRMA fully supports thorough FDA oversight of all compounded drugs and biologics manufactured outside of the exception for traditional pharmacy compounding under section 503A of the FDCA. The manufacturing of medicines, whether by manufacturers or pharmacies, should be regulated in a consistent, risk-based manner. The touchstone of such an approach is ensuring both safety and efficacy for patients.

Large-scale, commercial manufacturing of prescription medicines (including non-traditional compounding) should be governed by the same high standards as biopharmaceutical manufacturing—whether the producer is designated as a "pharmacy" or as a "manufacturer." At an absolute minimum, entities that engage in large-scale commercial production of pharmaceutical compounding should be subject—and in our view are currently subject—to the same cGMP requirements for quality manufacturing as are pharmaceutical manufacturers, with clear provision for inspections and enforcement actions by FDA. Moreover, large-scale compounding without a valid NDA or BLA would render the products unapproved new drugs in violation of section 505 of the FDCA.

It is our understanding that section 503A of the FDCA, as passed in 1997, was intended to accomplish these objectives. In other words, Congress intended for large-scale, commercial production of medicines to be regulated by FDA applying cGMP

standards. PhRMA supports this goal. Despite some uncertainty as to the enforceability of 503A due to a disagreement between two federal courts of appeal concerning the severability of the advertising restrictions in section 503A(c) that were invalidated by the Supreme Court in *Western States*,[5] PhRMA believes FDA has ample authority to regulate large-scale compounders under the other provisions of 503A and the general provisions of the FDCA.

FDA itself has taken this position in a Compliance Policy Guide (CPG) that it issued following the *Western States* decision. The CPG assumed that section 503A was invalid but nevertheless asserted the agency's authority to regulate large-scale, commercial compounding operations.[6] At that time, the agency stated, "[w]hen the scope and nature of a pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the Act, FDA has determined that it should seriously consider enforcement action."[7] FDA's compliance guidance also contains other criteria to help determine whether purported compounders should be subject to FDA's cGMP manufacturing requirements. These criteria include:

- Compounding of drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions.
- Compounding finished drugs from bulk active ingredients that are not components of FDA approved drugs without an FDA sanctioned investigational

[5] 535 U.S. 357 (2002).

[6] FDA, Compliance Policy Guide Section 460.200 (May 29, 2002).

[7] *Id*.

new drug application (IND) in accordance with 21 U.S.C. § 355(i) and 21 C.F.R. 312.

- Receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance has been made in an FDA-registered facility.
- Using commercial scale manufacturing or testing equipment for compounding drug products.
- Compounding drugs for third parties who resell to individual patients or offering compounded drug products at wholesale to other state licensed persons or commercial entities for resale.
- Compounding drug products that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products. In certain circumstances, it may be appropriate for a pharmacist to compound a small quantity of a drug that is only slightly different than an FDA-approved drug that is commercially available. In these circumstances, FDA will consider whether there is documentation of the medical need for the particular variation of the compound for the particular patient.

As the Committee's investigation has revealed, FDA had actually exercised some of its available enforcement authority in connection with the NECC compounding situation. For example, FDA carried out inspections of compounding pharmacies, worked with state authorities to suspend operations in noncompliant facilities, and arranged for recalls of potentially violative products.

To the extent that it may help clarify FDA's regulatory authority, PhRMA supports the amendment of section 503A to delete the promotional provisions in 503A(c) as well as to confirm the agency's authority to regulate compounded drugs under the remaining provisions of section 503A. PhRMA also would support legislation that expressly provides FDA with inspection and registration authority for non-traditional compounders as manufacturers of new drugs and provides for user fees to ensure that FDA has adequate resources to regulate such compounders.

The Creation of a New Regulatory Class—the "Compounding Manufacturer"—Unnecessarily Complicates the Existing Regulatory Scheme and Threatens Patient Safety

Consistent with FDA's compliance guidance, PhRMA believes that, with the exception of drugs and biologics compounded by state-licensed pharmacists (or state-licensed physicians) upon receipt of a prescription for an identified individual patient or in limited quantities based on a history of prescription orders, compounded drugs and biologics are unapproved new drugs or unlicensed biologics subject to FDA regulation under the FDCA and Public Health Service Act (PHSA). These drugs and biologics therefore require regulatory approval through an NDA, abbreviated NDA, or BLA. Drug products distributed in interstate commerce without an NDA would also be misbranded in violation of the FDCA.

The public health is best served when FDA regulates medical treatments consistent with the risks they present. Medicines that present similar risks should be regulated similarly. Accordingly, PhRMA believes large-scale compounding entities that are engaged in the manufacturing of compounded drugs and biologics (which would

include “compounding manufacturers,” as defined in the Senate bill) should be regulated in the same manner as traditional biopharmaceutical manufacturers.

PhRMA is, however, deeply concerned that the creation of a new “compounding manufacturer” classification will upset FDA’s longstanding regulatory distinction between the activities of federally regulated manufacturers, on the one hand, and the activities of state-regulated pharmacists, on the other hand. Exempting “compounding manufacturers” from the requirement to obtain an approved NDA or BLA raises patient safety concerns; indeed the application requirement is critical for proving to FDA that the manufacturer is able to create large batches of drug products safety and consistently. In addition, the complexities and myriad exceptions associated with the Senate bill's proposed “compounding manufacturer” category may result in further confusion and an inconsistent regulatory scheme.

Establishing a new third class of compounder would create an overly complex and confusing manner that could be difficult to implement. For example, it is unclear how a large-scale sterile product compounder would be treated differently if it stopped compounding sterile products but continued manufacturing large batches of non-sterile medicines. Significant FDA and state resources may be required to resolve open questions about the scheme. These resources would better protect the public health if used for inspections and enforcement under FDA’s existing authority over non-individual compounders.

Accordingly, PhRMA supports clarification of FDA's existing authority to apply a risk-based approach to the oversight of non-traditional compounding and not a new patchwork that would create a new sub-class of non-individual compounders.

Finally, PhRMA is concerned about risks to patient safety that could result from proposals to allow pharmacy compounding of "copies" of marketed pharmaceuticals in the event of a drug shortage. This potential exception could expose patients to unsafe drugs, because the compounder need not establish that the compounded version has a safety and efficacy profile equivalent to the FDA-approved product.

Commercial drug shortages may result from factors such as a manufacturer's determination that particular ingredients fail to meet the manufacturer's quality standards, or due to the implementation of new manufacturing processes designed to produce more finished products that meet FDA-approved release specifications. Compounding manufacturers may be using the same ingredients or methods a biopharmaceutical manufacturer (or FDA) deemed insufficient. Moreover, sponsors' efforts to coordinate closely with FDA's drug shortages group to address a shortage could be confounded by this alternative supply.

Conclusion

PhRMA thanks the Committee for the opportunity to provide testimony regarding how to clarify FDA's authority to regulate non-traditional compounding. Biopharmaceutical companies are committed to patient safety. The same safety standards that govern biopharmaceutical manufacturing should also protect patients who are treated with medicines manufactured by large-scale compounders. PhRMA would support legislation clarifying the agency's ability to regulate non-traditional compounders, however we believe that an entirely new regulatory scheme is unnecessary to correct the enforcement issues surrounding the tragic NECC incident.