



**STATEMENT**  
**OF**  
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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**BEFORE THE**  
**SUBCOMMITTEE ON HEALTH**  
**COMMITTEE ON ENERGY AND COMMERCE**  
**U.S. HOUSE OF REPRESENTATIVES**  
**“REFORMING THE DRUG COMPOUNDING REGULATORY FRAMEWORK”**

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## INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS). Thank you for the opportunity to be here today to discuss important issues related to pharmacy compounding.

We are at a critical point where we must work together to improve the safety of drugs produced by compounding pharmacies. As the compounding industry has grown and changed, we have seen too many injuries and deaths over many years caused by unsafe practices. Dr. Margaret Hamburg, Commissioner of Food and Drugs, testified in front of the Oversight and Investigations Subcommittee on November 14, 2012, and April 16, 2013, regarding the tragic fungal meningitis outbreak associated with compounded methylprednisolone acetate (MPA), a steroid injectable product distributed by the New England Compounding Center (NECC). I testified in front of this Subcommittee on May 23, 2013, and provided additional details on the framework FDA has developed that could serve as the basis for the development of a risk-based program to protect the public health.

As both Dr. Hamburg and I testified, NECC was not an isolated incident. Indeed, over the past 20 years, we have seen multiple situations where compounded products have caused deaths and serious injuries. Also, we both testified that it is a matter of when, not if, another contamination incident will occur with compounded products. And since the NECC outbreak, we have identified contaminated products at other pharmacies and widespread sterile production issues

that have led to recalls and shutdowns of compounding operations. In one recent incident, the presence of floating particles, later identified to be a fungus, was reported in five bags of magnesium sulfate intravenous solution, resulting in a nationwide recall of all sterile drugs (over 100 products) produced by Med Prep Consulting, Inc., a state-licensed facility in Tinton Falls, New Jersey. Med Prep manufactured and repackaged sterile drug products for hospitals and health care facilities, including products intended to be injected into the vascular system of patients. After learning of the contaminated product, FDA conducted a for-cause inspection of Med Prep and issued an FDA Form 483,<sup>1</sup> which noted serious deficiencies in Med Prep's sterile processing. Thereafter, the Department of Justice, on behalf of FDA, filed a complaint for permanent injunction against Med Prep Consulting, Inc. in the U.S. District Court for New Jersey. The parties have signed a Consent Decree of Permanent Injunction, which was entered by the Court on June 27, 2013. The consent decree enjoins Med Prep and its president and owner from manufacturing, holding, and distributing drug products until they comply with certain requirements of the Federal Food, Drug, and Cosmetic Act and all applicable regulations.

In another recent recall, all sterile drug products (approximately 60 products) from a second pharmacy were recalled as a result of reports that five patients were diagnosed with serious eye infections associated with the use of repackaged Avastin. The firm has stopped all sterile compounding.

And just since I last testified six weeks ago, FDA has received reports of adverse events, including skin and soft tissue abscesses associated with Main Street Family Pharmacy's (Main Street) preservative-free methylprednisolone acetate for injection. FDA began to investigate immediately after receiving these reports, and, to date, we are not aware of any cases of

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<sup>1</sup> An FDA Form 483 is issued when investigators observe any significant objectionable conditions. It does not constitute a final Agency determination of whether any condition is in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act) or any of our relevant regulations, but the observations often serve as evidence of a violation of the FD&C Act and its implementing regulations.

meningitis associated with Main Street's products. However, Main Street, a Newbern, Tennessee, pharmacy licensed by the state of Tennessee, shipped methylprednisolone acetate to 17 states and other sterile products to at least 34 states. On May 28, 2013, Main Street announced a voluntary nationwide recall of all sterile products compounded by the pharmacy. The compounded products that are subject to the recall are those products with a use-by date on or before November 20, 2013. FDA issued an FDA Form 483 to Main Street on June 11, 2013. The 483 listed observations, including the presence of spiders in the clean room, failure to use a sporicidal cleaning agent, failure to clean equipment to prevent contamination, poor personnel aseptic practices, failure to review batch specification failures, failure to perform endotoxin and sterility testing, failure to obtain data to support expiration dates, failure to perform routine calibration on equipment, failure to retain samples of injectable drugs, inadequate record keeping, and failure to separate expired products from in-date products. The investigation into this matter is ongoing.

These are just some of the cases we've seen since the fungal meningitis outbreak. To date, since September 26, 2012, FDA is aware of 17 firms that have conducted recalls—12 firms have conducted recalls overseen by FDA<sup>2</sup> and five firms have conducted recalls overseen by the state in which the firms are located. In addition, since September 26, 2012, we are aware of 19 firms that ceased sterile operations, in some cases voluntarily, and in other cases due to partial or full shutdowns imposed by state licensing authorities. FDA has issued two Warning Letters to date. However, we believe that presently, there are many other firms operating as compounding pharmacies, producing what should be sterile products and shipping them across state lines in

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<sup>2</sup> While in most instances firms eventually agree to voluntarily recall drugs that FDA believes pose a risk, FDA lacks the authority to compel such recalls, and critical time can be lost in negotiations between FDA and a firm, leaving the public exposed to potentially serious health risks. The Agency has mandatory recall authority for medical devices, infant formula, and many other foods, but not for drugs.

advance of or without a prescription. These pharmacies are licensed by the states and generally are not registered with FDA. We may not even become aware of a firm's existence until it has already produced drugs that have caused patients harm.

Notably, even in light of recent events, and even though we are often working with the state inspectors, our investigators' efforts are being delayed because they are denied full access to records at some of the facilities they are inspecting. Just during the recent inspections, several pharmacies delayed or initially refused FDA access to records, and FDA had to seek administrative warrants in two cases. And although we have been able to eventually conduct the inspections and collect the records that we have sought, our ability to take effective regulatory action to obtain lasting corrective action with regard to substandard sterility practices remains to be seen.

The history of pharmacy compounding shows that there is a need for appropriate and effective oversight of this evolving industry. The industry and the health care system have evolved and outgrown the law, and FDA's ability to take action against compounding that exceeds the bounds of traditional pharmacy compounding and poses risks to patients must evolve as well.

Limitations and ambiguities in the law have led to legal challenges to FDA's authority to inspect pharmacies and take appropriate enforcement actions.

#### FDA's Recent Efforts

Using a risk-based model, we identified 29 firms for priority inspections focused on their sterile processing practices. During these 29 inspections, in two instances, FDA identified secondary firms associated with the priority inspections, for a total of 31 firms. We have taken investigators who would normally be doing inspections of conventional drug manufacturers and assigned them to conduct inspections of those pharmacies whose history suggests a greater risk

of potential quality issues with their compounded products. We have coordinated our inspections with state officials, who have accompanied our investigators in most cases. At the same time, we have also continued to conduct for-cause inspections, often at the request of our state counterparts who invited us to accompany them on the inspections. Since the fall, FDA has completed 31 for-cause inspections in addition to the 31 described above, as of June 30, 2013.

When we identified problems during any of these inspections, at the close of the inspection, we issued an FDA Form 483 listing our inspection observations. We have issued an FDA-483 at the close of 52 of the 62 inspections we have conducted since last fall. As described above, we have seen serious issues, including practices that create a risk of contamination and other quality concerns. While firms have voluntarily recalled products in some of these cases, recalls are a temporary fix designed to get product off the market immediately. We need to do everything we can to clarify and strengthen FDA's authority in this area.

As we have noted in the past, our ability to take action against inappropriate compounding practices has been hampered by ambiguities regarding FDA's enforcement authority, legal challenges, and adverse court decisions interpreting that authority. For example, hospitals have come to rely on compounding pharmacies that function as "outsourcers" producing sterile drugs previously made by hospital in-house pharmacies. If FDA were to bring charges against a pharmacy, alleging that it is manufacturing a "new drug" that cannot be marketed without an approved application, the pharmacy would have to either obtain individual patient-specific prescriptions for all of its products or stop distributing the products until it obtains for them approved New Drug Applications (NDA),<sup>3</sup> something most outsourcers are unlikely to do.

Specifically, a new drug application must include proof that the drug is safe and effective and be

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<sup>3</sup> Compounded drugs generally could not satisfy the requirements of an abbreviated NDA, which include evidence that the drug is the same as the reference listed drug in dosage form, strength, route of administration, quality, performance characteristics, and intended use.

accompanied by an application fee set by the reauthorization of the Prescription Drug User Fee Act (PDUFA) last year. FDA drug approvals are manufacturer-specific, product-specific, and include requirements relating to the product. Many outsourcers compound hundreds of products, each of which would require a separate application.

Outsourcers can provide valuable services if they compound drugs under certain conditions, including adhering to applicable Federal quality standards. For example, many hospitals rely on outsourcers to produce specialized dilutions of FDA-approved products to be used in anesthesia during surgery. However, outsourcers are unlikely to submit an NDA for each of the many specialized products hospitals request. While the health care system has grown to rely on obtaining these products from outsourcers, if they are produced under substandard sterile conditions, the risks to patients can outweigh any perceived benefits. These outsourcers are not traditional pharmacy compounders as they are compounding products without patient-specific prescriptions that are administered to sometimes thousands of patients nationwide. FDA's authorities should be appropriately tailored to effectively oversee these compounding activities.

#### FDA's Legal Authority over Compounded Drugs

In the Commissioner's appearances before the Committee on Energy and Commerce in November 2012 and April 2013, and my appearance in May 2013, we presented a framework that could serve as a basis for the development of a risk-based program to better protect the public health, improve accountability, and provide more appropriate and stronger tools for overseeing this evolving industry. Since November, we have met with over 50 stakeholder groups, including pharmacy, medical, hospital, payer, and consumer groups, and state regulators, to help further our understanding and inform our framework. I will now provide background on FDA's current legal authority over compounded drugs, then review that framework, and suggest

specific actions that Congress can take to help us better do our job and prevent future tragedies like this one.

FDA believes that pharmacists engaging in traditional compounding provide a valuable medical service that is an important component of our health care system. However, by the early 1990s, some pharmacies had begun producing drugs beyond what had historically been done within traditional compounding.

After receiving reports of adverse events associated with compounded medications, FDA became concerned about the lack of a policy statement on what constituted appropriate pharmacy compounding. In March 1992, the Agency issued a Compliance Policy Guide (CPG), section 7132.16 (later renumbered as 460.200) to delineate FDA's enforcement policy on pharmacy compounding. It described certain factors that the Agency would consider in its regulatory approach to pharmacies that were producing drugs.

The compounding industry objected to this approach and several bills were introduced, some with significant support, to limit the Agency's oversight of compounding.<sup>4</sup> In November 1997, S. 830, the Food and Drug Administration Modernization Act of 1997 (FDAMA), was signed into law as Public Law 105-115.<sup>5</sup> FDAMA added Section 503A to the FD&C Act, to address FDA's authority over compounded drugs.<sup>6</sup> Section 503A exempts compounded drugs from three critical provisions of the FD&C Act: the premarket approval requirement for "new drugs"; the requirement that a drug be made in compliance with current Good Manufacturing

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<sup>4</sup> H.R. 5256, Pharmacy Compounding Preservation Act of 1994, introduced Oct. 7, 1994, 1 co-sponsor; H.R. 598, Pharmacy Compounding Preservation Act of 1994, introduced Jan. 20, 1995, 141 co-sponsors; H.R. 3199, Drug and Biological Products Reform Act of 1996, introduced March 29, 1996, 205 co-sponsors; H.R. 1060, Pharmacy Compounding Act, introduced March 13, 1997, 152 co-sponsors; H.R. 1411, Drug and Biological Products Modernization Act of 1997, introduced April 23, 1997, 16 co-sponsors

<sup>5</sup> Public Law 105-115, FDAMA, 111 Stat. 2296 (Nov. 21, 1997), available at <http://www.gpo.gov/fdsys/pkg/PLAW-105publ115/pdf/PLAW-105publ115.pdf>

<sup>6</sup> Id.



Practice (cGMP) standards; and the requirement that the drug bear adequate directions for use, provided certain conditions are met. These provisions were the subject of subsequent court challenges, which have produced conflicting case law and amplified the perceived limitations and ambiguity associated with FDA's enforcement authority over compounding pharmacies. In 2002, immediately after a Supreme Court ruling that invalidated the advertising provisions of Section 503A, FDA issued a revised CPG on compounding human drugs. Several additional legal challenges and court decisions then followed. More recently, FDA made significant progress toward issuing another CPG. In fact, FDA was on track to publish a revised draft CPG in the fall of 2012, but the fungal meningitis outbreak intervened and we are now re-evaluating the draft. It is important to note, however, that a CPG is not binding on industry, and updating the CPG would not alleviate all issues with Section 503A.

A look at FDA's attempts to address compounding over the last 20 years shows numerous approaches that were derailed by constant challenges to the law. As a result, presently, it is unclear where in the country Section 503A is in effect, and Section 503A itself includes several provisions that have impeded FDA's ability to effectively regulate pharmacy compounding practices. Apart from Section 503A, there are additional provisions in the statute that have impeded effective pharmacy compounding regulation. For example, the FD&C Act exempts certain compounding pharmacies from registration and the obligation to permit access to records during an inspection. As a result, FDA has limited knowledge of pharmacy compounders and compounding practices and limited ability to oversee their activities.

### Looking Ahead

The Administration is committed to working with Congress to address the threat to public health from limitations in authorities for effective oversight of certain compounding practices. To that

end, FDA has developed a framework that could serve as the basis for the development of a risk-based program to protect the public health.

### Risk-based Framework

Recognizing the history of compounding practice, FDA supports the long-standing policy that all compounding should be performed in a licensed pharmacy by a licensed pharmacist (or a licensed physician), and that there must be a medical need for the compounded drug.

Further, we believe there should be a distinction between two categories of compounding: traditional and non-traditional. Traditional compounding would include the combining, mixing, or altering of ingredients to create a customized medication for an individual patient with an individualized medical need for the compounded product, in response to a valid patient-specific prescription or order from a licensed practitioner documenting such medical need. Traditional compounding, while posing some risk, plays an important role in the health care system and should remain the subject of state regulation of the practice of pharmacy.

Non-traditional compounding would include certain types of compounding for which there is a medical need, but that pose higher risks. FDA proposes working with Congress to define non-traditional compounding based on factors that make the product higher risk such as any sterile compounding in advance of or without receiving a prescription, where the drug is distributed out of the state in which it was produced. Non-traditional compounding would be subject to Federal standards adequate to ensure that the compounding could be performed without putting patients at undue risk, and FDA would inspect against and enforce these Federal standards. Such a definition focuses on the highest risk activities and offers a uniform degree of protection across all 50 states, for highest-risk compounding activities.

Non-traditional compounding should, because of the higher risk presented, be subject to a greater degree of oversight. Sterile products produced in advance of or without a prescription and shipped interstate should be subject to the highest level of controls, established by FDA and appropriate to the activity, similar to cGMP standards applicable to conventional drug manufacturers.

In addition, FDA believes that with noted exceptions, certain products are not appropriate for compounding under any circumstances. These products would include: 1) what are essentially copies of FDA-approved drugs, absent a shortage justification based on the drug appearing on FDA's shortage list; and 2) complex dosage forms such as extended-release products; transdermal patches; liposomal products; most biologics; and other products as designated by FDA. Producing complex dosage forms would require an approved application and compliance with cGMP standards, along with other requirements applicable to manufactured drug products.

FDA believes that there are other authorities that would be important to support this new regulatory paradigm. For example, FDA should have clear ability to collect and test samples of compounded drugs and to examine and collect records in a compounding pharmacy, just as the Agency does when inspecting other manufacturers. FDA should also have clear ability to examine records, such as records of prescriptions received, products shipped, volume of operations, and operational records, such as batch records, product quality test results, and stability testing results. Such inspections are necessary to determine when a pharmacy exceeds the bounds of traditional compounding, to respond to public health threats, and to enforce Federal standards.

FDA also believes that an accurate inventory of pharmacies engaged in non-traditional compounding would facilitate appropriate oversight and coordination with state regulators. In addition, FDA looks forward to working with Congress on potential improvements that may include label statements and adverse event reporting that have proven useful in other areas. A user-fee-funded regulatory program may be appropriate to support the inspections and other oversight activities outlined in this framework. We look forward to working with Congress to explore the appropriate funding mechanisms to support this work, which could include registration or other fees, as Congress has authorized and FDA has successfully implemented in other settings.

## **CONCLUSION**

Given our experiences over the past 20 years and the recent fungal meningitis outbreak, we must do everything we can to clarify and strengthen FDA's authority in this area. I am happy to answer any questions you may have.

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