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STATEMENT

OF

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FOOD AND DRUG ADMINISTRATION

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BEFORE THE

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U.S. HOUSE OF REPRESENTATIVES

"EXAMINING DRUG COMPOUNDING"

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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 April 16, 2013, regarding the emergence of a tragic fungal meningitis outbreak associated with compounded methylprednisolone acetate (MPA), a steroid injectable product distributed by the New England Compounding Center (NECC). To date, that outbreak has been associated with 55 deaths and over 740 people sickened in 20 States. Sadly, 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. For example:

- In 1997, two patients were hospitalized with serious infections after administration of contaminated riboflavin injection prepared by a Colorado pharmacy.
- In 2001, 13 patients in California were hospitalized and 22 received medical care following injections from contaminated vials of a steroid solution. Three patients died as a result.

- In 2002, five patients in North Carolina suffered from fungal meningitis resulting from contaminated methylprednisolone acetate made by a South Carolina pharmacy. One person died.
- In 2005, contaminated cardioplegia solution, made by a firm located in Maryland, resulted in five cases of severe system inflammatory infections; three of these patients died.
- In 2007, three people died from multiple organ failure after a Texas compounder sold superpotent colchicine that was as much as 640 percent the labeled strength.
- In 2010, FDA investigated a cluster of *Streptococcus endophthalmitis* bacterial eye infections in patients who received injections of Avastin repackaged by a pharmacy in Tennessee.
- In 2011, there were 19 cases of *Serratia marcescens* bacterial infections, including nine deaths, associated with contaminated total parenteral nutrition products.
- In 2012, 43 patients developed fungal eye infections from contaminated sterile ophthalmic drug products. At least 29 of these patients suffered vision loss.
- Recently, in 2013, FDA investigated reports of five cases of eye infections in patients who received Avastin repackaged by a pharmacy in Georgia. The Avastin was contaminated with bacteria.

These incidents are emblematic of long-standing issues associated with the practice of compounding and the public health concerns that can result from unsafe practices in compounding pharmacies.

Since the NECC outbreak, ten additional firms have conducted voluntary recalls overseen by FDA of sterile compounded or repackaged drug products as of May 16, 2013. 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 drug products produced by the pharmacy (over 100 products). Fortunately, we have not received reports of patient injury from these products. 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. Moreover, we believe that presently, there are hundreds of other firms operating as compounding pharmacies, producing what should be sterile products and shipping across State lines in advance of or without a prescription. However, the current legal framework does not provide FDA with the tools needed to identify and appropriately regulate these pharmacies to prevent product contamination.

The history of this issue shows that there is a need for appropriate and effective oversight of this evolving industry. It is clear that 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 has been hampered by limitations and ambiguities in the law, which have led to legal challenges to FDA's authority to inspect pharmacies and take appropriate enforcement actions.

The fungal meningitis outbreak has caused the Agency to review our past practices with regard to our oversight of compounding pharmacies, and has led to some preliminary conclusions. In my view, even in the face of litigation and continuous challenges by industry to our authorities, we can nonetheless be more aggressive in pursuing enforcement actions against compounding pharmacies within our current authority. I can assure you that we are being more aggressive now. We have established an Agency-wide steering committee to oversee and

coordinate our efforts, and we have taken several important steps to identify and inspect high-risk pharmacies that are known to have engaged in production of sterile drug products.

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 26 for-cause inspections in addition to the 31 described above, as of May 16, 2013. When we identified problems during any of the inspections, at the close of the inspection, we issued an FDA Form 483[1] listing our inspection observations. We have issued an FDA-483 at the close of 47 of the 57 inspections we have conducted since last fall. We have seen some serious issues, including quality concerns that have led to product recalls. Observations have included: lack of appropriate air filtration systems, insufficient microbiological testing, and other practices that create risk of contamination.

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

[1] A form FDA-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.

pharmacies delayed or 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.

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, and we have learned that the law is not well-suited to effectively regulate this evolving industry. 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 brings charges against a pharmacy, alleging that it is manufacturing a "new drug" that cannot be marketed without an approved application, the pharmacy will have to either obtain individual patient-specific prescriptions for all of its products or stop distributing the products until it obtains approved new drug applications for them, something most outsourcers are unlikely to do. Several of the pharmacies FDA inspected are some of the largest outsourcers in the country. These pharmacies supply large numbers of sterile drugs produced in relatively large quantities to hospitals nationwide, and a shut-down at these firms is likely to cause disruptions in the supply of drugs to hospitals and other health care providers. FDA should have more tailored authorities appropriate for this type of compounding pharmacy.

In the Commissioner's appearances before the Committee on Energy and Commerce in November 2012 and April 2013, she 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. Today, I will first 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's Legal Authority over Compounded Drugs

FDA regards traditional pharmacy compounding as the combining or altering of ingredients by a licensed pharmacist, in response to a licensed practitioner's prescription for an individual patient, which produces a medication tailored to that patient's special medical needs. In its simplest form, traditional compounding may involve reformulating a drug, for example, by removing a dye or preservative in response to a patient allergy. It may also involve making an alternative dosage form such as a suspension or suppository for a child or elderly patient who has difficulty swallowing a tablet. 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.[2] In November 1997, S. 830, the Food and Drug Administration Modernization Act of 1997 (FDAMA), was signed into law as Public Law 105-115.[3] FDAMA added Section 503A to the FD&C Act, to address FDA's authority over compounded drugs.[4] 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 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 compliance policy guide 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 reevaluating 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

[2] 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

[3] 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*

provisions that have impeded FDA's ability to effectively regulate pharmacy compounding practices including those relating to prescription orders, medical need, and copying FDA-approved products.

Apart from Section 503A, there are additional provisions in the statute that have impeded effective pharmacy compounding regulation. For example, if certain criteria are met, the FD&C Act exempts 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,

[4] Id.

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 the 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.
