TESTIMONY

OF

SCOTT GOTTLIEB, M.D.

COMMISSIONER OF FOOD AND DRUGS

FOOD AND DRUG ADMINISTRATION

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SUBCOMMITTEE ON HEALTH

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"EXAMINING IMPLEMENTATION OF THE COMPOUNDING QUALITY ACT"

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Introduction

Mr. Chairman, Ranking Member, and Members of the Subcommittee, I am Dr. Scott Gottlieb, Commissioner of Food and Drugs 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 speak with you today about drug compounding.

Five years ago, Congress, FDA, state regulators, and practitioners across the country grappled with the largest healthcare-related outbreak in recent history. The 2012 fungal meningitis outbreak, resulting from a compounder that shipped contaminated compounded drugs throughout the country, led to more than 750 cases of illness and 60 deaths in 20 states. The tragic proportions of this case were largely attributable to the company's large-scale, multistate distribution of an injectable drug intended to be sterile that had been prepared under inappropriate conditions. This outbreak underscored the need for improvement in compounding practices, as well as the need for more robust oversight of compounders, close Federal and state collaboration, and a clear legal framework that would provide for lawful compounding to meet patients' medical needs, while also providing FDA with tools to address unlawful compounding practices that threaten the public health.

The meningitis outbreak also made very apparent that there was a need to better define and separate the legitimate practice of pharmacy compounding from a growing number of enterprises that were acting as large-scale drug manufacturers seeking to operate outside of FDA's routine oversight, often creating substantial risk in the process by operating without adhering to good manufacturing practices, and evading proper oversight by inappropriately operating under the guise of a pharmacy under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Congress addressed these challenges in November 2013, by passing bipartisan legislation, the Drug Quality and Security Act (DQSA). The new law amended section 503A of the FD&C Act to remove its unconstitutional provisions (related to restrictions on the advertising of and solicitation of prescriptions for compounded drugs), thereby enabling FDA to fully implement

and enforce the remaining provisions of section 503A. The law also created the new section 503B, establishing the new category of outsourcing facilities, which often engage in larger-scale, nationwide distribution with the potential to expose more patients to the risks associated with compounded drugs, compared to more traditional pharmacy compounders that are regulated under section 503A. The new legislation was aimed at preventing future tragedies like we saw in 2012 and in many cases before then.

FDA's compounding program is a priority for the Agency. During the last five years, we have made great strides in DQSA implementation through policy development, oversight, and stakeholder outreach. FDA has produced a body of policy documents on a scale that clearly indicates the importance of this issue for the Agency; we have convened advisory committee meetings to obtain advice on scientific, technical, and medical issues concerning drug compounding; we have engaged in robust inspection and enforcement; and we have closely collaborated with state regulators and interested stakeholders.

Going forward, we are committed to issuing a series of additional policy documents to continue to implement the law. As the framework matures, we will address additional challenges, such as:

- How do we reduce regulatory burden without sacrificing minimal public health protections so that pharmacies that want to engage in larger-scale compounding across state lines, or undertake compounding for "office stock," to supply healthcare sites can more easily transition to 503B outsourcing facilities?
- How can we take steps to enable pharmacies that register as 503B outsourcing facilities to create a more high-quality supply of compounded drugs?
- As we learn more about the opportunities and risks of this expanding industry, how do we more clearly define the boundary between products that should and should not be compounded?

FDA already has taken many steps to implement the new framework created by DQSA. Specifically, since enactment of DQSA, we have issued 24 draft and final guidances to provide clarity to compounders on compliance policies, four proposed and final regulations addressing products that can or cannot be compounded or used in compounding, and a draft memorandum

of understanding (MOU) with the states addressing certain distributions of compounded drugs. We will be updating that MOU soon, taking into consideration the feedback we received from stakeholders. Before developing revised draft or final guidances, we have similarly considered thousands of stakeholder comments on the prior drafts. In addition, we have held eight meetings of the Pharmacy Compounding Advisory Committee where we have sought the Committee's advice on 48 bulk drug substances nominated for use in compounding, six categories of drugs for the "Difficult to Compound" list, and 31 substances for the "Withdrawn or Removed" list. We have held numerous stakeholder listening sessions, engaging with over 75 different organizations annually to hear their feedback on our proposed policies and oversight efforts. We have held six intergovernmental meetings with pharmacy regulatory bodies from all 50 states to discuss continued Federal and state collaboration and other matters of mutual concern.

While engaging in policy development and stakeholder outreach initiatives, we have maintained robust oversight. We have conducted close to 500 inspections of 503A and 503B facilities between the passage of DQSA and the end of fiscal year 2017. We have observed problematic conditions during the vast majority of these inspections and have overseen more than 150 recalls of compounded drugs and issued more than 180 warning letters. We also have worked in close coordination with our Federal and state partners, sending more than 70 referral letters to state regulatory authorities for follow up on certain inspectional findings and working with the Department of Justice on civil and criminal enforcement actions.

We will continue to engage in a robust level of oversight and enforcement activity in 2018, as we take new steps to make sure that we are fulfilling FDA's goal to assure the quality of human drugs, while also meeting the needs of patients for compounded products. We also will take measures that preserve lawful pharmacy compounding practices, while reducing regulatory burden without sacrificing critical public health protections for pharmacies that intend to engage in large-scale compounding and become 503B outsourcing facilities.

It is clear to me that our policy development, oversight, and collaboration initiatives have had a significant public health benefit. Since embarking on these efforts, we have, in many cases, observed improved compliance with the law. For example, since issuing our final guidance

concerning the prescription requirement under section 503A, we have observed that many pharmacies obtain valid prescriptions for individually identified patients. This is consistent with the statutory requirement for compounding under section 503A and many state laws and enforcement policies that now align with this provision of Federal law.

Collaboration with states has also improved our ability to address rapidly potential outbreaks and emerging quality problems before they cause widespread harm. Likewise, our inspection and enforcement efforts have, in many cases, prompted compounders to implement corrective actions to address egregious conditions and practices at their facilities before they result in patient injury.

These initiatives also have fulfilled another critical objective: preserving access to compounded drugs for patients who have a medical need for them. In enacting section 503A in 1997 and section 503B in 2013, Congress recognized the value of compounded drugs to patient care and intended to give FDA necessary authorities to address unlawful compounding that could cause serious harm, while preserving access to lawful compounding as an important tool in healthcare providers' toolbox for patient treatment. To that end, the policies that we have developed in guidance attempt to achieve that balance between patient access to lawful compounding and addressing unlawful compounding that could cause harm. When we received comments suggesting that policies proposed in draft guidance could have an adverse impact on access to lawfully marketed compounded drugs, we have taken a close look at the policies and, when appropriate, made revisions.

Our commitment to preserving needed access to compounded drugs is also evident from our oversight approach. We are encouraged by the recent increase in our letters closing out inspections of pharmacies that comply with the law, often after having received a warning letter, and our letters referring inspections to state boards of pharmacy regarding pharmacies that appear to meet certain conditions of section 503A and that have committed to correct readily addressable violations of Federal law. FDA is focusing its enforcement priorities on the subset of compounders that are most appropriately overseen primarily by FDA rather than the states.

This progress notwithstanding, challenges remain. Unfortunately, there remain compounders whose practices present significant risks to patients. The risks are greater when it comes to sterile

drugs. For example, during our initial inspections, we have seen vermin, such as cockroaches, in the area where employees prepare for sterile processing; employees processing sterile drugs with exposed skin that sheds particles and bacteria; contamination, including bacteria and mold, in the environment where sterile drugs are produced; and much more. In some cases, pharmacies that produce drugs under these conditions ship them to healthcare facilities and patients nationwide. While we have seen problematic conditions at both 503A and 503B facilities, the majority of the most concerning findings were associated with those regulated under section 503A.

These and similar violations have led to many cases of serious patient harm. Despite a heightened level of oversight activity, FDA has received a steady stream of reports of serious adverse events related to compounded drugs since 2012, mostly associated with pharmacies regulated under section 503A.

Table 2. Examples of Adverse Events Associated with Drugs Prepared by Compounding Facilities over the Past 5 Years.

Year	Facility Location	Adverse Events
2017	Texas	At least 43 patients had adverse events, including vision loss, after receiving compounded steroid-and-antibiotic eye injections.
2017	California	Two patients had hypersensitivity reactions, and one died, after receiving an intravenous medication prepared with a compounded curcumin product.
2016	Indiana	Three infants had serious adverse events after receiving compounded morphine sulfate that was nearly 2500% as potent as it should have been.
2016	South Dakota	Seven patients had thyrotoxicosis after receiving superpotent compounded oral liothyronine products. Three patients were hospitalized in an intensive care unit.
2015	Florida	The FDA received several reports of adverse events possibly associated with compounded vitamin D_3 capsules that were approximately 300% as potent as they should have been.
2015	Texas	A patient died after using a compounded topical anesthetic cream. A court heard evidence that the cause of death was ketamine and cyclobenzaprine toxicity.
2015	Alabama	In five patients who received betamethasone sodium phosphate and betamethasone acetate, redness, swelling, and pain developed at the injection site. Three of the patients were hospitalized and had cultures that were positive for *Staphylococcus aureus*.
2014	Florida	At least 37 patients had serious adverse events after receiving intravitreal injections of repackaged Avastin (bevacizumab) or Lucentis (ranibizumab).
2014	Several states	The FDA received several reports of adverse events associated with compounded products that should have contained L-citrulline but instead contained a different active ingredient. Subpotent L-citrulline in patients with certain urea-cycle defects can lead to high ammonia levels, which is serious and potentially life-threatening.
2014	Indiana	Several neonates experienced oversedation after receiving superpotent compounded midazolam.
2014	Texas	A patient had severe flushing, stinging, and dizziness after an infusion of compounded magnesium sulfate in normal saline. The patient's blood had increased levels of magnesium.
2013	Tennessee	Twenty-six patients reported adverse events, including skin abscesses, after receiving injections of compounded methylprednisolone acetate that was contaminated.
2013	Texas	Bacterial bloodstream infections developed in 15 patients, and 2 died, after receiving infusions of compounded calcium gluconate contaminated with bacteria.
2013	Georgia	Five patients had endophthalmitis after receiving ophthalmic injections of repackaged Avastin.
2013	Texas	Six patients had adverse events, including fever and flulike symptoms, after receiving injections of compounded methylcobalamin.
2012	Massachusetts	Some 753 patients had fungal meningitis and other infections after receiving steroid injections that were contaminated with fungus. At least 64 patients died.

Reprinted from "Toward Better-Quality Compounded Drugs- An Update from the FDA," by Woodcock, Janet, and Dohm, Julie, 2017, *New England Journal of Medicine, 377*, 2511.

Just to name a few recent examples: this past year at least 43 patients experienced vision impairment and vision loss after receiving eye injections of a compounded drug that was contaminated by a 503A pharmacy. The year prior, three infants experienced serious adverse events after receiving a compounded drug manufactured by an outsourcing facility at a strength that was 20-fold greater than the strength indicated on the drug's prepared label. In 2013, bacterial blood-stream infections developed in 15 patients, and two patients died, after receiving

contaminated infusions that FDA subsequently found had been compounded by a 503A pharmacy under inappropriate conditions. Because the vast majority of 503A pharmacies do not report adverse events to FDA, our records probably include only a small proportion of the adverse events that actually occur.

These problems emphasize the need to improve the quality of compounded drugs, and it is therefore critical that FDA continues to implement the authorities that Congress entrusted to the Agency to address compounders whose practices create serious patient risks, at the same time that FDA takes measures that preserve lawful pharmacy practices. Moving forward, we intend to expand and focus our DQSA implementation, oversight, and collaboration with state regulators and other stakeholders to continue to achieve the goals set out by DQSA.

Policy Development

I am personally committed to continuing to implement DQSA consistent with our Congressional mandate to protect the public health. FDA also plans to take steps that preserve lawful pharmacy practices and expand the opportunities for pharmacies that want to engage in larger-scale compounding to efficiently become 503B facilities. I hope that recent policy developments, as well as new steps that we will take in 2018, demonstrate my commitment to engaging with the stakeholder community to develop policies aimed at both preserving access to drugs produced by compounding facilities for patients who have a medical need for them, while protecting those patients from poor quality drugs that cause serious harm.

In advance of today's hearing, FDA announced that we issued three critical final guidances: one on certain manipulations of biological products by pharmacies and outsourcing facilities, and the other two regarding compounding drugs that are essentially copies of commercially available or approved drugs under sections 503A and 503B, respectively. The final biologics guidance marks the culmination of several years of thoughtful deliberation about how to strike the right balance between addressing the high risks for contamination and other product quality problems presented by biological products that are manipulated outside of their approved labeling, and the need to also preserve access to such products when they meet appropriate quality standards. The

final guidance reflects stakeholder input on both the initial draft guidance and revised draft guidance on this topic.

The final guidances concerning compounded drugs that are essentially copies under sections 503A and 503B describe how FDA intends to implement the statutory restrictions on compounding drugs that are essentially copies of commercially available or approved drugs. Receiving a compounded drug when a commercially available or approved drug meets the patient's medical needs puts that patient at unnecessary and unacceptable risk from receiving a drug that has not been proven safe and effective and that may have been produced under substandard manufacturing conditions. DQSA reflects the recognition that this practice can also undermine the new drug and abbreviated new drug approval processes in the United States. Why would sponsors seek approval of applications for life-saving treatments if compounders could simply produce copies of those drugs? These guidance documents reflect the careful consideration of input from stakeholders in the form of comments on the draft guidances and during stakeholder listening sessions.

I expect that implementation of these three guidance documents, as well as other steps that FDA recently announced it will be taking in 2018, will further FDA's mission of reducing the risks that drugs produced by compounding facilities present to patients who have a medical need for them. At the same time, our policies will seek to expand opportunities for compounding pharmacies. Looking ahead, we intend to continue this momentum by issuing additional policy documents to implement the compounding provisions of the law in the coming months. While we have numerous policies in development, I'll discuss just three examples that I am prioritizing.

Many of the members of this subcommittee are familiar with the provision of section 503A of the FD&C Act directing FDA to develop a standard memorandum of understanding (MOU) with the states addressing the interstate distribution of "inordinate amounts" of compounded drugs and providing for appropriate state investigation of complaints associated with compounded drugs distributed outside the state in which they are compounded. The statute provides that pharmacies and physicians located in states that have not entered into such an MOU cannot

distribute more than five percent of their compounded drugs interstate and qualify for the exemptions under 503A. This provision of the statute is important for several reasons, including:

- Preventing compounders purportedly operating under the exemptions in section 503A from growing into conventional manufacturing operations, making unapproved drugs and operating a substantial portion of their business interstate without adhering to current good manufacturing practice (CGMP) requirements and other provisions intended to ensure the manufacture of quality drugs;
- Addressing the logistical, regulatory, and financial challenges faced by state regulators, such as difficulties states can face in investigating and responding to multi-state outbreaks associated with compounded drugs, when a substantial proportion of a compounder's drugs are distributed outside of a state's borders; and,
- Reducing the risk to patients that are being treated with drugs from a poor performing pharmacy located in another state with inadequate controls.

It is important that FDA's implementation of this provision of the statute address these objectives, while also maintaining our commitment to preserve access to compounded drugs for patients who have a medical need for them. After issuing a draft MOU in 2015, FDA received more than 3,000 comments and has since heard feedback that the proposed policies could lead to access concerns. We have taken this input seriously and will soon issue a revised draft MOU for comment that we believe will address the most significant concerns that have been raised.

Another important document that I would like to highlight is our guidance concerning CGMP requirements for outsourcing facilities. As previously noted, outsourcing facilities engage in larger-scale, nationwide distribution and are not subject to the conditions on interstate distribution or the requirement for compounding to be based on prescriptions for individually identified patients. As a consequence, outsourcing facilities have the potential to expose more patients to the risks associated with compounded drugs. Therefore, the statute importantly subjects outsourcing facilities to CGMP requirements.

FDA recognizes that there are differences between outsourcing facilities and conventional drug manufacturers that warrant certain differences in how manufacturing standards are applied to compounding. Outsourcing facilities can fulfill providers' needs for non-patient specific compounded drugs for "office use" or "office stock," which can range in volume, and sometimes may be produced in relatively small batches. Accordingly, our policies for CGMP requirements for outsourcing facilities, such as stability testing and product release testing requirements, should be sufficiently flexible to facilitate compounding in small batches. We need to make sure that our policies encourage appropriate compounding by 503B facilities on a small scale and are not overly burdensome so that it would be more feasible for pharmacies to become 503B outsourcing facilities.

FDA issued a draft guidance on CGMP for outsourcing facilities in July 2014 that reflects FDA's intent to recognize the differences between outsourcing facilities and conventional drug manufacturers, and to apply CGMP requirements in a way that is tailored to the nature of the specific compounding operations conducted by outsourcing facilities, such as production in small batches.

FDA is working on revising that guidance to incorporate changes that reflect comments we received on the 2014 draft, as well as additional feedback from stakeholders concerning the need for a policy that is sufficiently flexible to account for the production of small batches of compounded drugs for office use. We intend for this guidance to create a risk-based policy recognizing that one element of risk is the volume of a product being compounded. By considering volume and associated patient exposure, we believe we are able to take closer measure of some of the risks associated with the compounded drugs being made by a 503B outsourcing facility.

A third example of a significant policy priority is implementation of the provisions of sections 503A and 503B concerning bulk drug substances that can be used in compounding, in addition to those types of bulk drug substances the statute explicitly allows to be used in compounding. Section 503A directs the Agency to develop a list of bulk drug substances that can be used in compounding through notice-and-comment rulemaking, and section 503B directs FDA to

develop the list by issuing a Federal Register notice. Approximately 65 substances were nominated for the 503A bulks list, and approximately 200 for the 503B bulks list, with adequate supporting information for FDA to evaluate them. Since enactment of DQSA, FDA has dedicated considerable Agency resources toward developing the framework for evaluating nominated bulk drug substances, conducting extensive scientific reviews, presenting recommendations to the Pharmacy Compounding Advisory Committee (the Committee), and considering input from the Committee and other stakeholders as it makes decisions regarding the disposition of the substances nominated for the section 503A bulk drug substances list. The Agency has evaluated and presented to the Committee nearly all of the bulk drug substances nominated for use in compounding under section 503A and has issued a proposed rule concerning the first ten. As we near completion of the initial phase of our evaluation of bulk drug substances nominated for use under section 503A, we are turning our attention to the substances nominated for use in compounding under section 503B. The subcommittee should expect to see considerable progress on the development of policies relating to the 503B bulks list, and continued progress on the 503A bulks list, in the coming months.

Oversight

Next, I would like to discuss our oversight efforts. As I noted earlier, we have conducted hundreds of inspections of 503A pharmacies and 503B outsourcing facilities, many of which have resulted in significant findings concerning risks to patients. Our inspections have resulted in recalls, temporary cessations of operations, warning letters, and civil or criminal enforcement actions. We believe that these regulatory efforts, instituted under the new framework Congress created, have prevented outbreaks and other cases of serious patient harm. We intend to continue these important efforts, and to continue to post all FDA inspectional findings and regulatory actions on our website so this important information is available to purchasers of compounded drugs and other interested parties.

However, based on the experience we have acquired over the last five years in implementing DQSA, we are further refining and focusing our approach to compounding oversight. Our goal is to leverage our limited resources to achieve the greatest public health impact. Going forward, we

are focusing our oversight efforts on outsourcing facilities under section 503B and pharmacies under section 503A that are large-scale, multi-state distributors.

Congress created the category of outsourcing facilities to serve as a source of higher-quality compounded drugs, particularly for office use, where providers may want to have a stock of drugs on hand in anticipation of procedures that they might perform in their offices. The outsourcing facility sector consists of about 75 entities and is growing. Most of the current registrants, who prior to registering as outsourcing facilities had been compounding drugs for years without routine federal oversight, and pursuant to production standards that did not meet CGMP requirements, are still adjusting to tighter production standards and routine, risk-based federal oversight mandated by DQSA.

During this critical transition period, FDA is focusing our inspectional resources on helping outsourcing facilities comply with CGMP requirements. We are also engaging in pre-operational inspections and meetings to provide advice outside of the context of a formal inspection or regulatory action, as well as more frequent post-inspection correspondence and regulatory meetings. We see the growth of the outsourcing facility sector as a critical feature to enable patients and providers to access higher-quality compounded drugs. These endeavors should make it more efficient for outsourcing facilities to meet the requirements of DQSA, which, in turn should encourage pharmacies to register and re-register as outsourcing facilities. We believe this prioritization will yield greater voluntary compliance with CGMP requirements and other provisions of the FD&C Act.

With respect to section 503A pharmacies, we are working with the states to obtain the necessary data to identify large-scale, multi-state distributors, to help focus our inspection and enforcement resources on the subset of pharmacy compounders that engage in compounding activities that merit FDA oversight. This risk-based prioritization is intended to: assist FDA in identifying compounders that may be distributing non-patient specific compounded drugs and should consider registering as outsourcing facilities; focus FDA oversight on facilities that, should quality problems occur, have the potential to affect the largest number of patients and create the greatest risk; and target FDA oversight in a manner that is helpful to the states, especially those

who are not able to conduct oversight of non-resident pharmacies. We are undertaking these efforts in close collaboration with our state partners.

State and Stakeholder Collaboration

And that brings me to my final topic: state and stakeholder collaboration. These efforts are critical to successful policy development and inspection and enforcement. Our state partners are critical to the success of the DQSA framework that Congress created. We carefully consider all feedback we receive from states and stakeholders, including in the context of comments on draft guidances and proposed regulations, stakeholder listening sessions, state and FDA intergovernmental working meetings, and many other forums for discussion. FDA has been extremely responsive to the feedback the Agency has received from its state partners and I am personally committed to making sure that we build on this collaboration.

For example, we heard stakeholder concerns that we included on lists of inspectional observations issued to pharmacies, findings related to CGMP requirements from which the pharmacies might have been exempt. In response to those concerns, in 2016 FDA issued a notice announcing that the Agency would no longer include CGMP observations for pharmacies that meet the conditions of section 503A. We also recently heard that stakeholders had questions about the process and policies associated with becoming an outsourcing facility. To address these concerns, FDA recently issued an information guide for entities considering registering as outsourcing facilities, expanding on the resources available to them.

In addition, in the past, stakeholders have commented that they would like additional opportunities to meet with FDA to share their concerns, outside of the larger annual listening sessions. Just after enactment of DQSA, due to the large number of such requests, FDA was unable to accommodate them. However, now we are in a different place. The Agency has begun to grant stakeholder meetings, and we will continue to do so going forward, as resources permit.

We are also committed to continuing our close communication with our state partners, holding annual intergovernmental face-to-face meetings with representatives of the fifty states, inviting

states to accompany FDA on inspections and to participate in recall discussions with non-compliant firms, and answering questions about oversight and policy matters. We also routinely share inspection and enforcement information with state partners, including non-public information with those who have entered into information-sharing agreements that allow FDA to share such non-public information in accordance with Federal law. We will continue these efforts going forward, especially as we implement the MOU discussed earlier.

Conclusion

As my testimony describes, implementing the compounding provisions of the law in a manner that fulfills Congress' intent is often a balancing act. We must preserve access to compounded drugs for patients whose medical needs cannot be met by approved drugs while also taking steps to conduct appropriate oversight of compounding, particularly compounding on a larger scale and not in response to named patients and individual prescriptions. As we announced earlier this month, we are committing to taking a robust series of policy steps to continue to properly implement DQSA consistent with our public health mission mandated by Congress. We look forward to continuing to engage Congress and work with stakeholders, as we make sure that our efforts strike the right balance between patient safety and access.

I look forward to answering your questions.