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EXAMINING IMPLEMENTATION OF THE COMPOUNDING QUALITY ACT

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

ONE HUNDRED FIFTEENTH CONGRESS

SECOND SESSION

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[1] The committee did not receive a response to Mr. Gottlieb's submitted questions for the record by the time of printing.

EXAMINING IMPLEMENTATION OF THE COMPOUNDING QUALITY ACT

TUESDAY, JANUARY 30, 2018

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 11:00 a.m., in room 2123 Rayburn House Office Building, Hon. Michael Burgess (chairman of the subcommittee) presiding.

Members present: Representatives Burgess, Guthrie, Barton, Upton, Shimkus, Latta, McMorris Rodgers, Lance, Griffith, Bilirakis, Long, Bucshon, Mullin, Hudson, Collins, Carter, Green, Schakowsky, Matsui, Sarbanes, Schrader, Eshoo, DeGette, and Pallone (ex officio).

Staff present: Adam Buckalew, Professional Staff Member, Health; Karen Christian, General Counsel; Kelly Collins, Staff Assistant; Zachary Dareshori, Staff Assistant; Paul Eddatel, Chief Counsel, Health; Margaret Tucker Fogarty, Staff Assistant; Adam Fromm, Director of Outreach and Coalitions; Ali Fulling, Legislative Clerk, Oversight & Investigations, Digital Commerce and Consumer Protection; Jay Gulshen, Legislative Clerk, Health; Ed Kim, Policy Coordinator, Health; Bijan Koohmaraie, Counsel, Digital Commerce and Consumer Protection; Katie McKeogh, Press Assistant; Mark Ratner, Policy Coordinator; Jennifer Sherman, Press Secretary; Danielle Steele, Counsel, Health; Tiffany Guarascio, Minority Deputy Staff Director and Chief Health Advisor; Samantha Satchell, Minority Policy Analyst; Kimberlee Trzeciak, Minority Senior Health Policy Advisor; and C.J. Young, Minority Press Secretary.

OPENING STATEMENT OF HON. MICHAEL C. BURGESS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. BURGESS [presiding]. I would like to call the subcommittee to order.

And I recognize myself for an opening statement.

Today's hearing marks the Health Subcommittee's first look at the Compounding Quality Act, which passed under Title I of the Drug Quality and Security Act nearly 5 years ago. Prior to then, the last time Congress examined the drug compounding issue was in 1997, when it passed the Food and Drug Administration Modernization Act, touching upon the Food and Drug Administration's authority to regulate compounded drugs and establishing Section 503A in the Federal Food, Drug, and Cosmetic Act.

A tragic outbreak of fungal meningitis in 2012, when the New England Compounding Center shipped over 17,000 contaminated vials of a compounded steroid medication throughout the country, resulted in one of the worst and most fatal drug safety incidents in the history of the United States, where more than 750 people developed fungal infections in 20 states and, subsequently, 60 people lost their lives. This outbreak prompted Congress to act, with the Energy and Commerce Committee taking the lead in the House, through a series of investigations and a series of hearings on the issue.

Today we will convene two panels of witnesses. And I do want to welcome back Dr. Gottlieb, Commissioner of the Food and Drug Administration. Thank you for coming back to our subcommittee this morning.

The agency has been very active over the last several months on drug compounding, most recently, releasing the 2018 Compounding Policy Priorities Plan. Your insights today, Dr. Gottlieb, are certainly appreciated.

Later in our second panel, we will hear directly from representatives of the pharmacies, physicians, patients, and manufacturers who will share their perspective on the implementation of Title I under the DQSA. We will also have a patient of the New England Compounding Center to share her personal story from the 2012 incidents and her experience since that time. All of the testimony from today's hearing are critical in our understanding of the compounding issue as the Food and Drug Administration works to strike the proper balance that would continue to advance patient safety while ensuring patients access to compounded medication.

Being a physician who has worked with compounding pharmacists during my time in practice, I know the important role and the value that these individuals serve in the delivery of patient care. Compounded drugs serve a unique need of patients that cannot utilize an FDA-approved product due to, for example, an allergy to one of the product's ingredients or the primary route of the product's administration. Many of us remember the swine flu epidemic of 5 years when compounding for the anti-flu medications in an elixir form was absolutely critical to protect children who had been recently infected.

Because of the process involved in creating a compounded medication, we all acknowledge the fact that proper oversight is necessary, whether by the Food and Drug Administration itself or a state's regulatory body, such as its board of pharmacy. Preventing poor compounding practices that can lead to contamination or erroneous product strength, quality, and purity is the goal we all aspire to, so that another New England Compounding Center does not happen. Thinking back to that fungal meningitis outbreak, I was not only heartbroken by the patients' lives lost or harmed, but I was also troubled by what seemed to be missed opportunities that could have prevented the tragedy.

Title I of the DQSA accomplished two things. First, the law further clarified the Food and Drug Administration's authority to regulate traditional pharmacy compounding practices under Section 503A, which had seen several court challenges. Second, it added Section 503B to the Federal Food, Drug, and Cosmetics Act, cre-

ating a new category of drug compounders known as outsourcing facilities. These outsourcing facilities engage in larger-scale, national distribution of sterile drugs in bulk quantities and have, thus, heightened statutory requirements, such as complying with good manufacturing processes and being subject to certain registration, reporting, and inspection requirements.

Over the last 4 years, the Food and Drug Administration has issued numerous draft and final guidance documents, proposed and final rules, and a draft memorandum of understanding to implement the Title I provisions. There has been discussion and debate over the manner that the agency has used to implement Title I.

In my home State of Texas, there already exists in statute the framework and manner in which a compounding pharmacy should conduct its practice. Other stakeholders have also expressed concern around office-use compounding and the prescription requirement. I hope these and other issues in the drug compounding space will be discussed today.

So, I am encouraged by the interest of all the stakeholders involved in this important debate, many of whom are represented today. I am certainly encouraged by the commitment of the Food and Drug Administration with Dr. Gottlieb's commitment to work with Congress in ensuring that patients have access to products that are tailored to their clinical needs while equipping agency officials with the requisite tools to protect public health.

Again, I want to welcome our witnesses and thank you for being here.

And I will recognize Mr. Green, 5 minutes, for an opening statement.

[The prepared statement of Mr. Burgess follows:]

PREPARED STATEMENT OF MICHAEL C. BURGESS

The Subcommittee will come to order.

The Chair will recognize himself for an opening statement.

Today's hearing marks the Health Subcommittee's first look at the Compounding Quality Act which passed under Title I of the Drug Quality and Security Act (DQSA) nearly 5 years ago. Before then, the last time Congress examined the drug compounding issue was in 1997 when it passed the Food and Drug Administration Modernization Act, touching upon the Food and Drug Administration's (FDA) authority to regulate compounded drugs and establishing section 503A in the Federal Food, Drug, and Cosmetics Act (FFDCA). However, the tragic outbreak of fungal meningitis in 2012, when the New England Compounding Center shipped over 17,000 contaminated vials of a compounded steroid medication throughout the country, resulted in one of the worst and most fatal drug safety incidents in U.S. history, where more than 750 people developed fungal infections in 20 states and over 60 people died subsequently. This outbreak prompted Congress to act, with the Energy and Commerce Committee taking the lead in the House through a series of investigations and hearings on the issue.

Today we will convene two panels of witnesses. First, I want to welcome Dr. Gottlieb, Commissioner of FDA, back to the Subcommittee this morning. The agency has been very active over the last several months on drug compounding, most recently releasing the 2018 Compounding Policy Priorities Plan. Your insights today are certainly appreciated.

Later, we will hear directly from representatives of pharmacies, physicians, patients, and manufacturers who will share their perspective of the implementation of Title I under DQSA thus far. We will also have a patient of the New England Compounding Center to share her personal story from the 2012 incident and her experience since that time. All of the testimonies from today's hearing are critical in our understanding of the compounding issue as FDA works to strike the proper

balance that would continue to advance patient safety while ensuring patients' access to compounded medicines.

Being a physician who has worked with compounding pharmacists during my practice, I know the important role and value these individuals serve in the healthcare delivery system. Compounded drugs serve a unique need of patients that cannot utilize an FDA-approved product due to, for example, an allergy to one of the product's ingredients or the primary route of the product's administration. Because of the process involved in creating a compounded medication, we all acknowledge the fact that proper oversight is necessary, whether by FDA or by a state's regulatory body, such as its board of pharmacy. Preventing poor compounding practices that can lead to contaminations or erroneous product strength, quality, and purity, is the goal we adhere to so that another New England Compounding Center does not happen again. Thinking back to that fungal meningitis outbreak, I was not only heartbroken by the patients' lives lost or harmed, but also troubled by what seemed as missed opportunities that could have prevented this tragedy.

Title I of DQSA accomplished two things. First, the law further clarified FDA's authority to regulate traditional pharmacy compounding practices under section 503A which saw several court challenges. Second, it added section 503B to FFDCA creating a new category of drug compounders know as outsourcing facilities. These outsourcing facilities engage in larger-scale, national distribution of sterile drugs in bulk quantities and thus have heightened statutory requirements, such as complying with current good manufacturing practices and being subject to certain registration, reporting, and inspection requirements.

Over the last 4 years, FDA has issued numerous draft and final guidance documents, proposed and final rules, and a draft memorandum of understanding (MOU) to implement the Title I provisions. There has been much discussion and debate over the manner the agency has implemented Title I of DQSA. In my home State of Texas, there already exist in statute the framework and manner in which a compounding pharmacy should conduct its practice. Other stakeholders have also expressed concerns around "office-use" compounding and the prescription requirement. I hope these and other issues in the drug compounding space will be discussed today. So, I am encouraged by the interest of all of the stakeholders involved in this important debate—many of whom are represented here today—and the commitment of FDA to work with Congress in ensuring patients have access to products that are tailored to their clinical needs while also equipping agency officials with the requisite tools to protect public health.

I again want to welcome our witnesses and thank you for being here. I look forward to your testimony.

OPENING STATEMENT OF HON. GENE GREEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. GREEN. Thank you, Mr. Chairman, for having this hearing.

In 2012, the interstate distribution of contaminated compounded drug products led to an outbreak of fungal meningitis in 20 states, which tragically resulted in 64 deaths and left 750 people with infections that were often severe and cause long-term damage. The New England Compounding Center, the NECC, the entity responsible for the compounding and shipping of the contaminated drugs, had been the subject of prior complaints and had been investigated by both the FDA and the Massachusetts State Board of Pharmacy. However, in part, because of uncertainty over the validity of Section 503A of the Food, Drug, and Cosmetics Act, it was not clear which copy, the FDA or the state, was on the beat, and the NECC continued to operate.

Unfortunately, while it was the most fatal incident to date, the NECC outbreak was not a one-off event. It certainly wasn't the first tragedy and hasn't proven to be the last. Just last year, we learned that at least 43 patients were left with diminished vision from a steroid antibiotic injection compounded by a Texas pharmacy. FDA studies have found quality problems with drugs compounded in other pharmacies, including sub- and super-potent

drugs and contamination. According to one report, from 1990 to 2005, FDA became aware of almost 240 serious illnesses and deaths associated with improperly compounding products, with the actual number likely to be greater since pharmacies are not required to report adverse events to the FDA. The Pew Charitable Trust published a report in 2014 that identified more than 25 reported compounding errors or potential errors linked to more than a thousand adverse events between 2001 and 2013.

Following that NECC outbreak, Congress finally took action with the Compounding Quality Act, CQA, and the Drug Quality and Security Act, DQSA, was signed into law in 2013. In a sideline, I want to thank my colleagues Congressman Griffith and Congresswoman DeGette because we worked together on a bipartisan basis to solve this problem. It solved to protect patients and provide industry with clarity for drawing a distinct line between the authority between state boards of pharmacy and the FDA. CQA made two key changes in reestablishing the FDA role regarding traditional compounding under Section 503A, creating a new category of drug compounders deemed outsourcing facilities under Section 503B.

The NECC outbreak and other adverse events underscored the need to establish a strong legal framework to provide for safe compounded medications that meet patients' needs while clarifying and strengthening oversight of such drugs to protect public health. There was an obvious need to address the growing number of enterprises that had cropped up during the time of legal uncertainty between the states and the FDA. Many of these enterprises had come to act like drug manufacturers operating outside FDA's standard oversight, often failing to meet current good manufacturing practices and skirting oversight by inappropriately operating under the guise of 503A pharmacy.

DQSA was not perfect, and like all compromises, not every problem was solved to everyone's satisfaction, and not everyone got exactly what they wanted. During bipartisan, bicameral negotiations, we tried to address as many discrepancies as we could and satisfy the needs of patients, providers, pharmacists, and manufacturers. What is ultimately important is that DQSA fixed the problems that led to the deadly fungal meningitis outbreak and required the FDA to succeed where in the past it had not.

Compounded medications fill an important role in our healthcare system, offer patients an option when an approved drug does not fit their needs. Patients' ability to timely access safe compound drugs is vital, and pursuit of this goal is something I believe we all share. I understand questions remain about the office stock, bulk lists, the memorandum of understanding, the interstate distribution, and copies of FDA-approved products, and other issues. More needs to be done to foster a robust 503B sector, support traditional pharmacists, ensure patient access to needed medications, and inform providers on how they can get the drugs they need when they need them, so they can successfully treat their patients.

As the FDA and stakeholders continue to work on the implementation of DQSA, and the agency, patients, providers, and industry continue to learn and adjust, I hope we can work together to refine the rules of the road, so patient access isn't unduly diminished and patient safety is upheld.

Thank you, Mr. Chairman. I yield back my time.
[The prepared statement of Mr. Green follows:]

PREPARED STATEMENT OF HON. GENE GREEN

Thank you Mr. Chairman.

In 2012, the interstate distribution of contaminated compounded drug products led to an outbreak of fungal meningitis in 20 states, which tragically resulted in 64 deaths and left more than 750 people with infections that were often severe and caused long term damage.

The New England Compounding Center (NECC), the entity responsible for compounding and shipping the contaminated drugs, had been the subject of prior complaints and had been investigated by both FDA and the Massachusetts state board of pharmacy.

However, in part because of uncertainty over the validity of Section 503A of the Federal Food Drug and Cosmetic Act, it was not clear which "cop"—the FDA or the state—was on the beat and the NECC continued to operate.

Unfortunately, while it was the most fatal incident to date, the NECC outbreak was not a one-off event.

It certainly wasn't the first tragedy and hasn't proven to be the last.

Just late last year, we learned that at least 43 patients were left with diminished vision from a steroid antibiotic injection compounded by a Texas pharmacy.

FDA studies have found quality problems with drugs compounded by other pharmacies, including sub- and super-potent drugs and contamination.

According to one report, from 1990 to 2005, FDA became aware of almost 240 serious illnesses and deaths associated with improperly compounded products, with the actual number likely being greater since pharmacies are not required to report adverse events to the FDA.

Pew Charitable Trusts published a report in 2014 that identified more than 25 reported compounding errors or potential errors linked to more than 1,000 adverse events between 2001 and 2013.

Following the NECC outbreak, Congress finally took action and the Compounding Quality Act (CQA) of the Drug Quality and Security Act (DQSA) was signed into law in 2013.

It sought to protect patients and provide industry with clarity by drawing a distinct line of authority between state boards of pharmacy and the FDA.

CQA made two key changes: re-establishing FDA's role regarding traditional compounding under section 503A and creating a new category of drug compounders deemed "outsourcing facilities" under section 503B.

The NECC outbreak and other adverse events underscored the need to establish a strong legal framework to provide for safe compounded medications that meet patients' needs while clarifying and strengthening oversight of such drugs to protect public health.

There was an obvious need to address the growing number of enterprises that had cropped up during the time of legal uncertainty between the states and FDA.

Many of these enterprises had come to act like drug manufacturers operating outside FDA's standard oversight, often failing to meet current good manufacturing practices and skirting oversight by inappropriately operating under the guise of a 503A pharmacy.

DQSA was not perfect, and like all compromises, not every problem was solved to everyone's satisfaction and not everyone got exactly what they wanted.

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What was ultimately important is that DQSA fix the problems that led to the deadly fungal meningitis outbreak and require the FDA to succeed where in the past, it had not.

Compounded medications fill an important role in our health care system and offer patients an option when an approved product does not fit their needs.

Patients' ability to timely access safe compounded drugs is vital, and pursuit of this goal is something I believe we all share.

I understand questions remain about office stock, bulks lists, the Memorandum of Understanding and interstate distribution, copies of FDA-approved products, and other issues.

More needs to be done to foster a robust 503B sector, support traditional pharmacists, ensure patient access to needed medications, and inform providers on how

they can get the drugs they need when they need them so they can successfully treat their patients.

As the FDA and stakeholders continue to work to implement DQSA, and the Agency, patients, providers and industry continue to learn and adjust, I hope we can work together to refine the rules of the road so patient access isn't unduly diminished and patient safety is upheld.

Thank you and I yield back.

Mr. BURGESS. The Chair thanks the gentleman. The gentleman yields back.

Pending the arrival of the full committee chairman, Mr. Walden, let me recognize the gentleman from New Jersey, 5 minutes for an opening statement.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. Thank you, Mr. Chairman.

I would like to submit to the record a joint statement from the Association for Accessible Medicine's Biotechnology Innovation Organization, the National Association of County and City Health Officials, Pew Charitable Trusts, Pharmaceutical Research and Manufacturers of America, PharMEDium, and Trust for America's Health. If I could ask unanimous consent to have a copy of it——

Mr. BURGESS. Without objection, so ordered.

Mr. PALLONE. Thank you.

[The information appears at the conclusion of the hearing.]

Mr. PALLONE. Mr. Chairman, thanks for holding today's hearing on the Compounding Quality Act, which passed with broad support from stakeholders and bipartisan, bicameral support in Congress in 2013. Passage of the Compounding Quality act was about patient safety. Congress came together in response to the horrible tragedy of actions by the New England Compounding Center, or NECC, that led to 64 people losing their lives. And despite a history of complaints and investigations by both the FDA and the Massachusetts State Board of Pharmacy, NECC was allowed to continue compounding products given to patients on a scale and in a manner that should never have been allowed. The new law was meant to clarify drug compounding laws. It was also supposed to make clear the lines and requirements for traditional pharmacies that want to compound and those pharmacies that compound on a larger scale.

I think we all agree and support maintaining patient access to compounded drug products. Undoubtedly, there are patients with unique medical needs for which a traditional prescription drug product is not appropriate, whether for pediatric patients, seniors, or those with allergies. However, we must all remember that compounded drug products are not without risk. Compounded drug products are not reviewed by FDA prior to coming to the market for safety and effectiveness. Traditional compounding pharmacies are also not required to report on the compounded drug products they produce or report adverse events.

While this law was intended to prevent another tragedy like the one at NECC, adverse events associated with compounded drug products are still occurring. Since passage of the law, there have been more than 140 recalls associated with compounded drugs. We have also seen reports of serious health events. For example, just

last summer, 43 patients suffered vision impairment after receiving compounded eye injections of a drug containing a combination of a steroid and an anti-infective agent. Also, last year three infants received a compounded morphine preparation that was 25 times the strength that was indicated on the label, resulting in at least one hospitalization. These are just two examples of why clearly identified standards and requirements must be maintained if we are going to protect patient health.

Recently, FDA released the agency's 2018 Compounding Policy Priorities Plan identifying next steps the agency will be pursuing in regards to implementing the Compounding Quality Act, including revisions to current guidance. As FDA moves forward, I would caution the agency to ensure that any revisions that it makes do not enable an environment that could allow for another NECC to occur. We must maintain appropriate patient safeguards and clear lines between what activities are permissible for traditional pharmacies and what activities are permissible for outsourcing facilities. Patient safety and the protection of public health must be at the forefront of any guidance revisions that the FDA considers, and the American people deserve confidence that the drug products they receive are safe and held to strong quality standards.

So, I want to thank Commissioner Gottlieb and all of our witnesses for being here today. I want to go beyond just today's hearing, Commissioner, and mention that you have been really great at trying to reach out to Members of Congress, much more so than most of the agency leaders. So, thank you for that. And I look forward to a robust discussion about the implementation of the Compounding Act.

I yield back, Mr. Chairman.

[The prepared statement of Mr. Pallone follows:]

PREPARED STATEMENT OF HON. FRANK PALLONE, JR.

Thank you, Mr. Chairman, for holding today's hearing on the Compounding Quality Act, which passed with broad support from stakeholders and bipartisan, bicameral support in Congress in 2013.

Passage of the Compounding Quality Act was about patient safety. Congress came together in response to the horrible tragedy of actions by the New England Compounding Center (NECC) that led to 64 people losing their lives. Despite a history of complaints and investigations by both the FDA and the Massachusetts State Board of Pharmacy, NECC was allowed to continue compounding products given to patients on a scale and in a manner that should have never been allowed. The new law was meant to clarify drug compounding laws. It was also supposed to make clear the lines and requirements for traditional pharmacies that want to compound and those pharmacies that compound on a larger scale.

I think we all agree and support maintaining patient access to compounded drug products. Undoubtedly there are patients with unique medical needs for which a traditional prescription drug product is not appropriate, whether for pediatric patients, seniors, or those with allergies. However, we must all remember that compounded drug products are not without risk. Compounded drug products are not reviewed by FDA prior to coming to the market for safety and effectiveness. Traditional compounding pharmacies are also not required to report on the compounded drug products they produce or report adverse events.

And while this law was intended to prevent another tragedy like the one at NECC, adverse events associated with compounded drug products are still occurring. Since passage of the law, there have been more than 140 recalls associated with compounded drugs. We've also seen reports of serious health events. For example, just last summer, 43 patients suffered vision impairment after receiving compounded eye injections of a drug containing a combination of a steroid and an anti-infective agent. Also last year, three infants received a compounded morphine prep-

aration that was 25 times the strength that was indicated on the label resulting in at least one hospitalization. These are just two examples of why clearly identified standards and requirements must be maintained if we are going to protect patient health.

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As FDA moves forward, I would caution the agency to ensure that any revisions that it makes does not enable an environment that could allow for another NECC to occur. We must maintain appropriate patient safeguards and clear lines between what activities are permissible for traditional pharmacies and what activities are permissible for outsourcing facilities. Patient safety and the protection of public health must be at the forefront of any guidance revisions FDA considers. The American people deserve confidence that the drug products they receive are safe and held to strong quality standards.

I want to thank Commissioner Gottlieb and all of our witnesses for being here today. I look forward to a robust discussion about the implementation of the Compounding Quality Act.

Thank you.

Mr. BURGESS. The Chair thanks the gentleman. The gentleman yields back.

The Chair now recognizes the gentleman from Michigan, Mr. Upton, 5 minutes for an opening statement.

Mr. UPTON. Well, thank you, Mr. Chairman, and I would ask unanimous consent to put Chairman Walden's full statement into the record.

Mr. BURGESS. Without objection, so ordered.

[The prepared statement of Mr. Walden follows:]

PREPARED STATEMENT OF HON. GREG WALDEN

It has been nearly 5 years since enactment of the Compounding Quality Act as a part of the Drug Quality and Security Act. The signing of that law was set in motion by an unprecedented public health tragedy caused by the egregious actions of a compounding pharmacy in Massachusetts. The New England Compounding Center distributed contaminated drugs across America to be injected into the spines and joints of unsuspecting patients. Over 750 individuals were infected with fungal meningitis, more than 60 lost their lives, and those who were spared continue to suffer the devastating impact to this day. In fact, one of the witnesses we will hear from, Nancy Dargan, has bravely shared the heart wrenching details of her near-death experience and the consequences she and her loved ones continue to bear. While this devastating event was historic in its magnitude, it was not the first time patients had been harmed by improperly compounded products and it wasn't the last.

Following the New England Compounding Center tragedy, this Committee worked to get to the bottom of what went wrong-clearly the system for oversight of compounding had failed to protect public health. The Subcommittee on Oversight and Investigations conducted a thorough examination, and published a report that served as the basis for the policies of the Compounding Quality Act.

While products approved by the FDA as being safe and effective should be relied on in the majority of circumstances, there is an appropriate role for compounded medical products in our health care system. Certain patients have unique medical needs and cannot be treated with available FDA-approved products. Furthermore, as we'll hear from our physician witnesses today, certain medical specialties require the availability of compounded medicines in their offices to provide timely and efficient treatment. In drafting the Compounding Quality Act, this Committee sought to strike the right balance.

Where medications are compounded in advance of a patient specific prescription to be stored for future use, it is vital that they be prepared under heightened standards for safety and that FDA play a larger role. While it is important to maintain patient access to medications that can be tailored to meet their unique needs, it is just as important that sufficient safeguards are in place to ensure these medications are safe, work as intended, and prepared under sanitary conditions. Pharmaceutical compounding has traditionally been regulated at a state level, but when compounding begins to look more like manufacturing we have learned that patients

are at the greatest risk. Over time, even before the 2012 meningitis outbreak, Congress has sought to increase the FDA's oversight where compounding goes beyond patient-specific activity. A prescription written for a patient is what clearly delineates between traditional compounding for an individual's needs, and manufacturing.

While outsourcing facilities are intended to meet healthcare providers' needs for office-stock compounded products, it is also critical that implementation of the law does not undermine our nation's drug approval framework. The regulatory system for both innovative therapies and generic drug products, reflects an intricate balance, keeping us on the cutting edge of medicine while making more affordable medications available to millions of Americans. It now falls on FDA to uphold the integrity of that system, by making sure that outsourcing facilities do not evade the requirements of the Hatch-Waxman Amendments, and do not undermine the protections in place that drive pharmaceutical research and development.

For FDA to achieve the goals of Congress, FDA must ensure that outsourcing facilities do not compound products that are essentially copies of approved drugs. That includes compounding that consists solely of preparing an approved product for administration as indicated in that product's labeling, or that involves no more than trivial modifications to approved therapies. FDA must also guarantee that bulk drug substances are not used in compounding by outsourcing facilities, until there has been a final determination that there exists a clear clinical need to do so.

I'd like to thank all of our witnesses for being here today, particularly Commissioner Gottlieb, to share your expertise on this important topic. The Energy and Commerce Committee is committed to making sure that patients have access to safe and effective medicines that meet their needs, and this Compounding Quality Act is an important aspect of that goal.

Mr. UPTON. And also, a letter from our colleague, Mr. Bishop, enter the letter into the record.

Mr. BURGESS. Without objection, so ordered.

[The information appears at the conclusion of the hearing.]

OPENING STATEMENT OF HON. FRED UPTON, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. UPTON. So, Mr. Chairman, the 2012 outbreak of the fungal meningitis resulting from contaminated steroid injections manufactured by the New England Compounding Center, NECC, was certainly a failure of epic proportions. Of the 753 people that were sickened by the outbreak, 264 called Michigan their home. Yes, we were the largest state hit. Nineteen of the 64 deaths caused by the tragedy were from Michigan, and three of them were constituents of mine.

I was chairman of the full Energy and Commerce Committee at the time that this happened, and we immediately launched a bipartisan investigation to find out what went wrong. I am not going to go through the full history of what happened then, but I will say that those at the NECC who were responsible were, in fact, brought to justice. And this committee crafted legislation to empower the FDA to ensure that the heinous acts of negligence like this one would never happen again. We wanted to fix the problem.

That legislation, the Drug Quality and Security Act, DQSA, is currently being implemented by the FDA, and it takes a number of measures to ensure safety, not the least of which are much-needed restrictions on the use of bulk compounded material as opposed to FDA-approved products when there is not a clinical need to do so.

I am pleased to see the new Commissioner here to update us on how DQSA implementation is going and what we in Congress can

do to help move the process along. We appreciate cooperation, and again, the cooperation of Members on both sides of the aisle.

And I will yield back the balance of my time.

[The prepared statement of Mr. Upton follows:]

PREPARED STATEMENT OF HON. FRED UPTON

The 2012 outbreak of Fungal Meningitis resulting from contaminated steroid injections manufactured by the New England Compounding Center (NECC) was a failure of epic proportions. Of the 753 people sickened by the outbreak, 264 call Michigan home. My home state was the hardest-hit. Nineteen out of the 64 deaths caused by this tragedy were from Michigan and three of them were constituents of mine.

I was serving as Chairman of the full Energy and Commerce Committee at the time this all happened and immediately launched an investigation to find out what went wrong. I won't go through the full history of what happened then, but I will say that those at NECC who were responsible were brought to justice and this committee crafted legislation to empower the FDA to ensure that heinous acts of negligence like this one never happen again.

That legislation, the Drug Quality and Security Act (DQSA), is currently being implemented by the FDA. It takes a number of measures to ensure safety, not the least of which are much-needed restrictions on the use of bulk-compounded material as opposed to FDA-approved products when there is not a clinical need to do so.

I am pleased to see Commissioner Gottleib here to update us on how DQSA implementation is going and what we in Congress can do to help move the process along.

Mr. BURGESS. The Chair thanks the gentleman. The gentleman yields back.

And we do want to thank all of our witnesses for taking time to be here today and taking time to testify before the subcommittee. Each witness will have the opportunity to give an opening statement, followed by questions from members. We will have two panels today.

The first panel, we will hear from Dr. Scott Gottlieb, the Commissioner of the United States Food and Drug Administration.

Dr. Gottlieb, once again, we appreciate your being here today, and you are recognized for 5 minutes for your opening statement, please.

STATEMENT OF SCOTT GOTTLIEB, COMMISSIONER, UNITED STATES FOOD AND DRUG ADMINISTRATION

Dr. GOTTLIEB. Thank you, Chairman Burgess, Ranking Member Green, members of the subcommittee. I appreciate the invitation to testify at today's hearing on implementation of Title I of the Drug Quality and Security Act.

We are all here together today because, more than 5 years ago, we grappled with the devastating consequences of the 2012 outbreak of fungal meningitis caused by the manufacturer that was compounding under the guise of a state-licensed pharmacy that shipped contaminated compounded drugs throughout the country. It led to more than 750 illnesses and 60 deaths in 20 states.

Because of this tragedy, Congress acted to ensure that something like this would never happen again. No one wants to see another such outbreak occur, and I am personally committed to ensuring that FDA does its part to help prevent future deaths from poor quality compounded drugs.

The 2012 outbreak as well as other issues we have seen through our compounding oversight underscore the need to improve compounding practices and more robust oversight of compounders,

supported by close federal and state collaboration. It also highlighted the need for a clear legal framework that would provide for compounding to meet patients' needs while also equipping the FDA with authorities to address unlawful practices that threaten the public health.

Unfortunately, since enactment of DQSA, there have been other tragedies and cases of serious and unnecessary patient harm which reinforce why our work is so critical. The FDA's compounding program is a priority for the FDA, given its profound public health implications, and we are committed to implementing the DQSA framework.

We have issued 24 draft guidances and final guidances, a final rule, and three proposed rules, and a draft MOU with the states. We have held eight meetings with the Pharmacy Compounding Advisory Committee to discuss 48 bulk drug substances nominated for use in compounding, as well as six categories of drug products nominated for the list of drugs that present demonstrable difficulties for compounding.

On the oversight and enforcement front, since enactment of the DQSA, the FDA has conducted nearly 500 inspections and we have issued more than 180 warning letters advising compounders of significant violations of federal law. We have overseen more than 150 recalls involving compounded drugs, and we have worked with DOJ on multiple civil and criminal enforcement actions and set up a joint task force with them.

But I know there is still a lot left to be done, and I know that there are some who say we haven't implemented certain aspects of DQSA with the speed you had hoped. We have had our own challenges addressing certain aspects of this complex framework, including our constant challenge to make sure we are striking the right balance between safety and access, and addressing the oftentimes very divergent views on these issues. I want you to know I am personally committed and involved in these efforts and committed to getting these things right, to making sure that we strike a careful balance and take measure of your concerns.

In implementing the DQSA over the years, FDA has aimed to develop policies that support the growth of the outsourcing facility sector. Compounding pharmacies and outsourcing facilities can help meet the legitimate patient needs when an FDA-approved drug is not available to meet such medical needs. We know that we must balance the critical role that compounding plays in helping patients and providers advance public health while ensuring that compounders do so in a manner that protects patients from poor quality compounded drugs and does not undermine the drug approval process.

And so, our actions to date, as well as the comprehensive 2018 Compounding Policy Priorities that we unveiled a few weeks ago, focus squarely on protecting patients from harm and establishing regulatory clarity, so our outsourcing facilities can meet important protections in Section 503B and our quality standards.

One of my key goals is to make it more feasible and lower cost for a large swath of pharmacies to transition to becoming outsourcing facilities, which are subject to greater FDA oversight. We are also working to help ensure patient access to compounded drugs

when they need them. For instance, we are taking steps to help providers identify outsourcing facilities that make, or would be willing to make, compounded drugs for office stock to treat patients who have medical need for them.

Let me be clear on one thing. I am committed to getting the things we have committed to done. All of the commitments made under the plan I released 2 weeks ago will be completed in 2018.

I would like to just close by briefly mentioning another critical public health matter. Today we took new action to address the epidemic of opioid addiction. We took steps to limit the dispensing of Loperamide, an OTC drug, that is increasingly being abused for its opioid-like qualities when it is taken at very high doses and dangerous doses. I hope you will take the time to look at the statement we issued, as we continue to work together to address this critical public health crisis. There is no magic bullet to solving this crisis. It is only going to be through continued and vigilant steps, like the one we took today, that I can hope we can start to reverse some devastating trends.

I look forward to answering your questions today and continuing to share more with you during the year ahead, as we build on our past efforts as part of our public health mission.

[The prepared statement of Dr. Gottlieb follows:]

TESTIMONY

OF

SCOTT GOTTLIEB, M.D.

COMMISSIONER OF FOOD AND DRUGS

FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON HEALTH

COMMITTEE ON ENERGY AND COMMERCE

U.S. HOUSE OF REPRESENTATIVES

"EXAMINING IMPLEMENTATION OF THE COMPOUNDING QUALITY ACT"

JANUARY 30, 2018

RELEASE ONLY UPON DELIVERY

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.

Mr. BURGESS. The Chair thanks the gentleman for his testimony, and we will move into the question portion of the hearing. I will begin with questioning and recognize myself for 5 minutes.

Commissioner, in the information you provided us, you had a list of adverse events associated with drugs prepared by compounding facilities in the past 5 years. Presumably, that is the lifetime of the DQSA. The one at the top of the list has been mentioned by a couple of people on the dais this morning, in Texas, some steroid antibiotic eye injections that caused problems with vision loss. Is there something more that could have been done in DQSA to prevent this or was the problem found more rapidly because of the tools that you were given in the DQSA? Help us sort of understand. Here is something that happened in my backyard. Is it something that we should have worked harder to prevent or was, in fact, the outbreak less than it would have been because you had tools to use?

Dr. GOTTLIEB. Well, thank you for the question, Congressman.

I think, as we start to exercise these new authorities, we are learning a lot. The scope of the kind of enforcement activities we take have also changed. In the early days of implementation and historically, a lot of the focus has been on issues of sterility with things like eye drops or things that are used intravenously or intramuscular injections.

I think what we are seeing more and more, and where we are starting to focus more of our inspectional activities, is on formulations that are compounded in ways where they might be super-potent. The challenge is that, when the pharmacies make potency errors, it is usually a logarithmic, log error, so thereby a factor of 10 or 20. So, you can get potencies that can cause significant harm.

I think this underscores the need to make sure that, when drugs are being compounded on a wide basis and distributed on a wide basis, it is done in facilities where we can apply GMP standards to them. And this is, in part, why I think Congress contemplated the whole creation of the 503B structure, where drugs that would be used on a wider scale would be compounded under that kind of supervision.

Mr. BURGESS. Let me ask you a question. Obviously, it was before your tenure when we had the hearings after the New England Compounding Center problems. But it was clear to some of us during the course of those investigations and the work that the committee did—and Chairman Upton was correct to reference it; this committee, the full committee, took the leadership on this issue. But there were places where the FDA clearly fell short of its responsibility to protect public health, despite what appeared retrospectively to be clear warnings that the New England Compounding Center was engaged in dangerous activities. So, are you confident that the FDA now has the clear authority it needs to ensure that we don't see a repeat of those things that happened in 2012?

Dr. GOTTLIEB. I testified at those hearings as a private citizen in 2013 here in Washington. I was working at a think tank at the time and weighed in at the time. I think I felt what Congress contemplated was a framework that gave the FDA the proper tools to provide oversight over this industry. But I think we need to keep in mind that we are now implementing a framework on an indus-

try that is vast, that grew up, that was allowed to grow up largely outside regulatory purview for a long period of time, and retrofitting a regulatory framework back onto an already existing industry is always a difficult task.

Do I believe the authorities and the tools that we are able to exercise are robust? I do. I think that it is going to take time to get them fully implemented and get the kinds of tools and practices we want applied over that industry. And it is superimposed on an environment where, admittedly—and people have good arguments on both sides of this debate—there has been some discussion around how FDA is using those authorities and whether they are using them in an appropriate fashion. I believe we are and I believe we need to continue to move forward.

Mr. BURGESS. Yes, I expect we may hear about that this morning in our second panel. I guess that is the concern. Or what I would like to ask is the efforts that you and the agency have taken to engage the physician community, patient community, other stakeholders, where they may have perhaps the feeling that things have tightened up too much.

Dr. GOTTLIEB. Well, this isn't going to work unless we are working closely with the providers and the state authorities. This law, Congress contemplated a framework that very much was envisioned where FDA would have close collaboration with medical societies and state authorities, and there was a lot of shared jurisdiction between the Federal and the state framework around both the 503A and the 503B facilities. States dually inspect a lot of the 503B facilities.

So, I think it is going to be very important for us to continue to work closely with the state communities and the provider groups. I believe we have. I think that there is more alignment there than perhaps is widely perceived, as obviously some 503A pharmacies that want to engage in certain practices where there is a line that we need to draw to make sure that we are providing the proper oversight, and I think we are going to hear about that tension today. I think that is a large place where we still have some area of disagreement.

Mr. BURGESS. Very well. I want to be respectful of everyone's time because we do have a long hearing today. I am going to recognize Mr. Green for 5 minutes for questions.

Mr. GREEN. Thank you, Mr. Chairman.

Thank you, Dr. Gottlieb, for being here this morning, but also the good work you are doing at the FDA.

I appreciate the continued emphasis the FDA has put on the issue of compounding drugs and hope to keep working with the agency on implementation in our shared goal of striking the right balance, so we can promote patient access without compromising patient safety. I am encouraged to see the FDA is actively working to implement the patient safety measures that are included in the DQSA.

In particular, I am pleased to see that FDA is taking steps to encourage registration of 503B outsourcing facilities. In your 2018 Compounding Policy Priorities Plan you suggested the FDA will be taking a more risk-based approach to the development and implementation of current good manufacturing practices, or CGMPs. I

understand FDA is working on revising the 2014 draft guidance to apply CGMP requirements in a way that is tailored to the nature of the specific operations conducted by an outsourcing facility and move away from one-size-fits-all. I appreciate the agency's goal of improving patient safety by making the regulatory framework more flexible by recognizing volume as a factor in its risk-based evaluation.

Can you elaborate more about the agency's thinking around what has been referred to as "503B-light"?

Dr. GOTTLIEB. Thanks for the question, Congressman.

What I am envisioning is a framework where—the GMP standards are not a fixed standard. It is a risk-based standard. We want to try to devise that framework in a way where we could titrate the level of the regulatory touch to what the facility is doing, the size of the facility, how many drugs they are developing, how they are shipping them, whether the drugs are oral drugs or they are parenteral drugs that are going to be injected, which would be sterile drugs and have higher risk.

The idea is that, by trying to adjust the level of the regulatory oversight to the level of risk, we could potentially allow more 503A facilities to make the conversion into being 503B facilities. That is why we are taking the time to revise that guidance.

There are things where we have some flexibility, like retention of samples, lot release, the stability studies that we require, where if it is a pharmacy doing something on a small scale, not shipping widely, compounding drugs that are relatively low-risk, we might be able to dial back some of that level of regulatory oversight versus someone who is engaging in larger-scale manufacturing. But, again, with the goal of seeing more 503A pharmacies become 503B pharmacies where they are able to engage in the kinds of things that some pharmacies want to do.

We want to bring down the cost of doing that. We have done some economic analysis around what it would cost. I think it is still a little bit too expensive to see some of the small 503A pharmacies opting into that. So, we are trying to take another crack at that.

Mr. GREEN. OK. Thank you.

And I do have concerns about the possibility of creating a two-tiered system. In the pursuit of flexibility, I am concerned of the impact this may have on 503B facilities that compound biologics, which are especially vulnerable to degradation.

How would you respond to these concerns? Can you tell me how you plan to ensure that CGMPs that apply to 503Bs will hold these facilities to the highest standards of sterility and stability?

Maybe I didn't understand that language.

[Laughter.]

Dr. GOTTLIEB. I understand your concerns. I share them. The first thing I am going to do is come up with a better name for it than "503B-light," before that takes hold.

But I will tell you that we are very mindful of that. So, for example, you reference biological products. They are particularly vulnerable to contamination and to bacterial growth. That would be something that would be higher-risk, where we would apply more oversight.

We are talking about trying to create a standard that is flexible, as is all our GMP oversight. It is a risk-based framework. If a pharmacy is engaging in small-scale manufacturing of relatively low-risk products, they wouldn't be subject to all of the same requirements that someone who is engaging in large-scale manufacturing of higher-risk sterile products would be. As they move through the continuum of risk, our level of oversight would increase. It needs to be a flexible standard. It is a flexible standard in every other realm of our regulation. It ought to be here. But you are absolutely right that there is a continuum of risk, and we need to be very mindful that we are matching our regulatory touch appropriately to that level of risk.

Mr. GREEN. Could you submit your economic analysis for the record, for the committee?

Dr. GOTTLIEB. I can provide it just off the cuff right here. When we looked at it—and again, this was very preliminary work and it is in draft form—but when we looked at it, we estimated that it would cost a large manufacturer about a million dollars to become a 503B facility, a large pharmacy, and a medium-sized pharmacy, about $600,000. We think that there are things we can do to further titrate the level of regulatory touch, that there are more buckets. Because, again, a 503A pharmacy that wants to engage in relatively low-risk compounding but still ship, but they are developing low-risk products on a small scale in small batches, there are ways, I think, to adjust the level of regulation to more appropriately match the level of risk that they are creating.

Mr. GREEN. Well, I understand you want to use resources where the problem is.

Dr. GOTTLIEB. Exactly.

Mr. GREEN. And I appreciate that.

Dr. GOTTLIEB. We want to be efficient.

Mr. GREEN. Thank you, Mr. Chairman. I know I am out of my time.

Mr. BURGESS. The Chair thanks the gentleman. The gentleman yields back.

The Chair recognizes the gentleman from Texas, the vice chairman of the committee, full committee, Mr. Barton, 5 minutes.

Mr. BARTON. Thank you, Mr. Chairman.

And, Commissioner, thank you for being here. I want to echo what Mr. Pallone said. You have been accessible, and we appreciate your personal availability to the members of the subcommittee.

I have been on this committee for 32 years. We have got an ongoing sense of friction or tension between the FDA and the compounding pharmacist. It is kind of a love-hate relationship.

A lot of my compounding pharmacists in Texas are fairly active in the national compounding associations. They have a feeling that the big, old bad federal FDA picks on them. How would you respond to that? Do you think your FDA picks on compounding pharmacists? Or do you think that they are being a little bit too sensitive?

Dr. GOTTLIEB. Well, I am not going to comment on their feelings and their motives. I am certainly sensitive to the concerns; I would say that, Congressman. This is an important reason why we want

to make sure we are working closely with the states. Because I think if we are working cooperatively with the states, and the states are able to assert their responsibilities and obligations under DQSA, but in concert with us, I think that the more that we can rely on local regulation, the more that local pharmacies are going to feel that they have a closer continuity to the nexus of the oversight, if you will.

Mr. BARTON. OK. Well, that leads to my next question. It is almost like you and I coordinated. I was going to ask this, you were going to answer that, then I would follow up.

What is the current relationship in terms of a working relationship or a cooperative relationship between the FDA and the state regulatory authorities that oversee compounding pharmacists? Do you think it has improved? When we had the problem back in 2010-2011 that led to the bill that you have talked about, Massachusetts and the Federal FDA didn't seem to get along at all. They didn't talk to each other, didn't share information. Today would you say that that relationship has improved, is good? How would you characterize it?

Dr. GOTTLIEB. Well, I will tell you the relationship is a lot better today and gets better with time. I think it is continuing to expand in terms of the scope of the collaboration and just through the contact we are having with state authorities. Those relationships are important to sound regulation being built. We invite states to join us on inspections. We hold monthly meetings with the National Association of Boards of Pharmacy. We provide training to state compliance officers. There are frequent telecons with state officials.

You don't have to take my word for it. You could look at the GAO report in 2016 that looked at this very question of what the perception was of the states of FDA's communication with the states, and 60 percent said very or somewhat satisfied. They were very or somewhat satisfied with the communication. Now a "D" usually doesn't sound good, but in this context I think it was. It was supportive of my contention that the relationships are much improved from where they were when I was at FDA the last time, prior to NECC. Twenty-three percent reported they were dissatisfied. We want to work on that. I think, hopefully, if I come back here a year from now and we are talking about this, we are going to be able to talk about an even more cooperative environment.

Mr. BARTON. With respect to the opioid crisis, are there some special task forces, special programs, extra effort being utilized right now between the FDA and the state regulatory authorities? And kind of as a secondary question, would you consider the opioid crisis more of a federal issue or a state issue, or is it about 50/50?

Dr. GOTTLIEB. Well, I think it is an everything issue. I have said before that I think that this is beyond the scope, certainly, of any one agency, but even the Federal Government, to try to tackle it. We are going to need to work closely with local officials to try to address this crisis. And we have been doing that. We have had a lot of conversations with local officials, state AGs, on different things that we could be doing in collaboration with the states around various aspects of this crisis.

I would say that the one thing that I am still very concerned about is the level of federal oversight in the IMFs, in the inter-

national mail facilities. I have spoken with some of the Members about this, and trying to get more resources into those facilities, particularly FDA resources. We play an important role in those facilities doing track and trace and analysis on some of the synthetic fentanyl coming in and doing investigations to trace them back to their source. And that is a big concern of mine.

Mr. BARTON. The last question, the Pharmacy Compounding Advisory Committee currently has no one on it who is a compounding pharmacist. Don't you think there should be at least one voting member who is an actual compounding pharmacist on that committee?

Dr. GOTTLIEB. We are going to be issuing a solicitation probably within days—the FR notice is with my office—to solicit a new member or members on that committee. So, there will be an opportunity to expand the composition of that committee. As you know, there are 12 members on that committee. One is appointed by the NABP, one by USP. It leaves 10 members. Of those, seven are licensed pharmacists. I think five are physicians in total. So, there is good clinical representation. To the extent that someone with a business perspective of being a pharmacist can add to the composition of that committee in a thoughtful way, that is something we would certainly think about.

There is one compounding pharmacist on the committee. He is the industry rep.

Mr. BARTON. But he doesn't get to vote.

Dr. GOTTLIEB. He doesn't get to vote, you are right. We will certainly take this into consideration. I have heard the concerns of Members on this. We will certainly take it into consideration as we think about the new solicitation.

Mr. BARTON. I would encourage that.

And I yield back.

Mr. BURGESS. The gentleman yields back. The Chair thanks the gentleman.

The Chair recognizes the gentlelady from California, Ms. Eshoo, for 5 minutes, please.

Ms. ESHOO. Thank you, Mr. Chairman, for holding this hearing.

And, Commissioner Gottlieb, it is good to see you, and thank you for your testimony and your work on this issue.

We spoke, I think it was last summer, about—at that point, there was a recent incident of patients being harmed by compounded products. Specifically, there were 50 patients, some of whom went blind after receiving a compounded antibiotic during cataract surgery last July.

I was talking to a doctor friend this last week. I said, "What's the most common surgery in the country?" And he said cataracts. So, that really broadens this out when you think of 50 patients, some of whom went blind during their cataract surgery. It wasn't too regular for them.

Obviously, we need to do everything we can to protect patient safety, so that these incidents stop happening, including, I think, following up on the warning letters.

There are two areas that I have always thought that are absolutely fundamental to what we do, both when I was in county gov-

ernment and here in the House of Representatives. That is public health and public safety. The two are combined in this issue.

So, what I want to ask you is, of the dozens of warning letters posted by FDA, how often have you pursued enforcement action? And what else can the agency do with its enforcement resources to ensure that compounded drugs are safe?

Dr. GOTTLIEB. I appreciate the question. It gets at something that we are trying to work, which is to improve our collaboration with DOJ to try to make sure that we can bring enforcement action when we see something particularly egregious, so we issue a warning letter and a firm is non-compliant. That was the genesis of the task force that we formed with DOJ. It is early days; I think it is yielding dividends in terms of our ability to work cooperatively. But this is something that we are looking at, pushing on, trying to do more of.

Ms. ESHOO. Have there been any enforcement actions?

Dr. GOTTLIEB. There has absolutely been enforcement actions, and there is activity that we have in progress. Obviously, we are always working on various activities. But I am hopeful that we will be able to continue to work effectively with DOJ in this regard.

Ms. ESHOO. In the two sections of the Compounding Quality Act—let me say something, because I listened to the conversation earlier about the FDA, what Congress did, what happened, and then, what Congress did. I think it is important for all of us to recall that the FDA had not been given authority by the Congress in this very area when the tragedy that took place out of Massachusetts, that spread out over the country, took place. So, I know there are a lot of questions to be raised, but the FDA did not have the authority. In my book, I think that the Congress didn't maybe on a proactive basis examine the issue and give the agency the authority.

At any rate, in the two sections of the Compounding Quality Act, it defines that drugs may only be compounded from bulk drug substances when FDA-approved drugs are in shortage. Now, recently, the agency announced enforcement discretion related to an interim list of substances that include more than a hundred approved drugs.

So, what specific steps are you going to take to ensure that there is a legitimate clinical need for the bulk drug substances currently being used by compounders and how are you going to enforce this?

Dr. GOTTLIEB. I think you are referring to the 503B bulk drugs list, right?

Ms. ESHOO. Right. Right.

Dr. GOTTLIEB. So, as you know, we received about a thousand nominations for different drugs to be on that list. We have selected 200 that we allowed onto that list under what we call Category I drugs. Now what we need to do is go through and reexamine all 200 to make sure they belong on that list. And we believe some of them are going to fall off and perhaps many will fall off. Some might be added, but probably many are going to fall off.

We are going to issue in March a guidance document that I outlined in the 2018 plan we put out that is going to define the parameters in which we are going to do those assessments. And then, we need to go through and assess each drug individually, which, as

you know, is a resource-intensive process. Each evaluation is between 20 and 80 pages long.

Probably the first complement of drugs that we will render a decision on will be this fall. It is probably going to be a small number. It may be five drugs. But we need to go through that entire list.

But it is important to put in perspective where that 200 came from. Those were drugs that were currently being compounded off of bulk substance at the time that this law was implemented. So, what we effectively did was freeze the market. What we said was we don't want to create more compounding, but we also don't want to start pulling things out of the marketplace and create access issues, especially with respect to the outsources, because we want to see this industry grow up, for one. And on the second hand, we have now new regulatory tools to assert good manufacturing practices. So, we can provide more oversight. So, the idea was to freeze the market while we, then, did those assessments, which is what we are doing now.

Ms. ESHOO. Thank you very much, Commissioner. I couldn't mean that more. You are in such an important role in the life of our country. So, thank you very much.

Thank you, Mr. Chairman.

Mr. BURGESS. The Chair now would like to recognize the gentleman from Kentucky, the vice chairman of the Health Subcommittee, Mr. Guthrie.

Mr. GUTHRIE. Thank you, and thank you, Mr. Chairman.

Thank you, Commissioner, for being here today.

I kind of want to follow up on what was just said. Five years ago there was a judge in Kentucky, a very prominent citizen, Eddie Lovelace of Albany, Kentucky, who went in for a routine procedure and was contaminated with medicine from the New England Compounding Center and died just shortly after what was going to be a routine procedure. Obviously, his family and the whole community is devastated, and Dr. Lovelace is just one person who was affected by this awful outbreak. And this was tragic and it is the reason I believe we must ensure compounded drugs are safe while striking a good balance of access to compounded drugs.

It is the theme of what you have said this morning, but I thought I would just give you a more open-ended look at it. Because in your testimony you mention the balance that is needed. And so, I just want to give you the floor to, how are you ensuring that Americans have access to lawfully-marketed compounded drugs while ensuring safety? You have addressed that just earlier, but I just give you the time.

Dr. GOTTLIEB. I think the way to ensure that, to be very direct, is to make sure this law gets implemented. I think that this was a good vision by Congress and it is a good framework that provides FDA with the tools that it needs to provide proper oversight. We need to now make sure it gets implemented.

I think where we are going to be able to continue to improve the posture of the industry, and the ability of this industry to provide the critical products that patients need and access to drugs, is going to be to try to see the 503B outsourcing sector become more viable. I think many of us, when this law was first implemented, envisioned that that sector would grow much more quickly than it

has. And I think if there are things that we can do through regulation, and I think that they are, to help that industry continue to expand, that is going to be important because, ultimately, that is going to provide more access to the kinds of sterile drugs that some people need on a wider scale and need to be distributed to institutions. The 503A facilities provide a critical function on a local level, giving patients differentiated products through the practice of pharmacy, so that they can get products that are individualized, tailored to their clinical needs.

Mr. GUTHRIE. Do you think 503A should report adverse outcomes to the FDA?

Dr. GOTTLIEB. As you know, the bulk of the adverse events that are reported by 503 facilities are typically either not reported or reported to the states. The states do share that information with us. They are not directly reported to FDA.

Would it help FDA target its inspections better if they had access to that information more readily? I would have to say it would. It would make it more efficient. A lot of our inspections of 503A facilities are for-cause inspections, are on the basis of information. But I think that this is also an area where, through our cooperation with the states, we are going to get access to that information where we need it. Because if we are working closely with the states, they are going to help guide us where we should be inspecting. Because, for example, a 503A facility might be engaging in activities that tip it over into being a 503B and subject to the federal scheme.

Mr. GUTHRIE. Thank you. Thank you for those answers.

And if I could change the subject just for about a minute or so left, I had an oncologist that contacted my office. Her daughter is an intern in the office. I know her pretty well. And she was stating concern on the shortage of saline, so to change it a little bit. She said it has been exasperated by the flu epidemic this year. We see these shortages in just basic medicines. And so, can you please provide the most recent FDA developments of the saline shortage?

Dr. GOTTLIEB. There are two different components to this, or, actually, three different components to this. There were these small bags that were in shortage prior to the hurricane that struck Puerto Rico, the 100-milliliter bags that are typically used to dilute drugs and, then, administer drugs to patients. That shortage was exacerbated by the hurricane because one of the primary manufacturers of those bags is located in Puerto Rico and was knocked out of production. That facility is now back in full production. In fact, all the facilities that we have concerns about in Puerto Rico are now back on grid power and most of them are at full production.

And we have brought in additional supply from additional facilities out of ex-U.S. manufacturing sites, to make up for that shortfall. So, there should be much more supply coming into the market.

There is also a shortage of the larger-volume bags. While we haven't declared a shortage, there are spot shortages of the 1-liter bags that are used for volume repletion, and those are also being strained by the flu, the flu outbreak. We have taken additional steps to bring in additional supply of the 1-liter bags as well.

There is also some tight supply of the empty 1-liter bags because a lot of compounding pharmacies and hospitals, when they can't get

access to filled bags, they buy empty bags and fill them themselves in a compounding-type facility.

We have taken additional steps. We are going to have more to say about this on Thursday. I was going to put it out today, but we were delayed in getting our information out. We are going to be putting out a statement on Thursday talking about the steps we are taking to get more of those empty bags onto the market. Some of those were manufactured in Puerto Rico.

I will just close by saying that the time it takes for a bag to go from the manufacturing line to your hand in the hospital as a clinician is about 6 weeks. I don't know this isn't a more efficient supply chain, but that is what I have been quoted. It takes weeks for it to make its way to the provider setting. And so, the additional supply that we have brought on—and it is substantial—is going to take some time to flow through the market.

Mr. GUTHRIE. Thank you for your attention to that. You all have been really good to work with.

Thank you.

Mr. BURGESS. The Chair thanks the gentleman. The gentleman yields back.

The Chair recognizes the gentlelady from Illinois, 5 minutes for questions, please.

Ms. SCHAKOWSKY. Thank you, Dr. Gottlieb. But I want to apologize that I missed much of your testimony. We have a number of hearings going on that I had to be at.

I also wanted to thank you for meeting with some of us about Essure, the contraceptive device that I know has harmed many women, from meeting with some of those women. So, I hope we can continue that conversation because I am very concerned about it.

Most people presume that the prescription that the doctor writes for them, and they fill it, is safe and effective. This is true because the FDA is considered the absolutely gold standard in drug review.

We have all talked about now the 64 people who tragically died because of this drug at the New England Compounding Center. So, obviously, that was an impetus for passing the Compounding Quality Act to improve safety.

And so, I wanted to just say that drugs that enter the bloodstream, the eye, the spine, are supposed to be sterile, but the FDA has received adverse events reports that these compounded products were contaminated, reminiscent of the problems at the NECC.

There have also been reports of sub-/super-potent drug products in 2016. Three babies received compounded morphine that was 20 times stronger than the label indicated. One of those infants had to be rushed by helicopter to a nearby children's hospital.

So, here's my first question: Commissioner Gottlieb, the FDA has been active in implementing the Drug Quality and Security Act. There have been over two dozen guidance documents issued, four rules, numerous public engagements focused on proper implementation of this law. While these are meaningful steps, what more can we do to reduce the number of adverse events associated with compounded drug products?

Dr. GOTTLIEB. I will just start out by echoing your concerns, Congresswoman. All drugs have risks. We know that. But I don't think anyone should be put at risk because a drug was improperly manu-

factured. At the very least, we should guarantee that a drug that purports to be manufactured in a certain way and purports to be sterile is actually a sterile product. That is the bedrock and the essence of what we are trying to achieve with respect to the authorities under this law.

I think that there are things that we can do going forward, including continued implementation. We have heard the concerns of Congress that certain aspects of how we have implemented this have been slower than Congress expected. I think we didn't fully appreciate the complexity of this law. But I think, as we continue to implement this framework, we are going to be able to exert even better and more efficient oversight. And that is going to increase the level of safety and assuredness that the public can have.

I think there is more that we can do on the enforcement side as well, getting back to the other question. That is going to be an area that we continue to look at, both in terms of what we are doing, how we target our inspections based on what we are learning, looking at issues like potency now because we see those coming up more, as well as what additional resources we can put against it.

This is a program—and I don't want to get too deep into the resource question; I will save it for an appropriations hearing, but——

Ms. SCHAKOWSKY. Feel free. Feel free.

[Laughter.]

Dr. GOTTLIEB. But this is a program where we do operate by in some cases begging, borrowing, and stealing from other aspects of the agency, other parts of the agency. For example, the team that I have, the policy team in the Drug Center that is working on the guidance development that you referenced and a lot of this policy development, is four people. They borrow resources from the review divisions, but, remember, those reviewers that they are tapping have PDUFA goals and BsUFA goals and GDUFA goals. They have user fee goals against their time that they have to prioritize their time in certain ways.

So, I think that there is certainly an opportunity to think about how we can grow this program in ways that could better address some of those safety issues.

Ms. SCHAKOWSKY. What more do you think the FDA could and should do to ensure safety at 503A compounding pharmacies?

Dr. GOTTLIEB. I think getting in place the MOU is going to be an important step. The MOU will provide for adverse event reporting back to FDA through the states. And so, I think that as we get that framework in place, I think that there is going to be a lot more we could do to better target our inspectional resources in areas of risk, in areas where the 503A facilities might be crossing into being a 503B facility that would be subject to GMP standards.

So, I am hopeful. We are making good progress on that. We are going to have it out this year. I am hopeful that, as we get that agreement in place with the states, that is going to increase our level of oversight.

Ms. SCHAKOWSKY. Well, we will be looking at that. Thank you very much.

I yield back.

Mr. BURGESS. The gentlelady yields back. The Chair thanks the gentlelady.

The Chair recognizes the gentleman from Michigan, 5 minutes for questions, please.

Mr. UPTON. Thank you, Mr. Chairman.

And, Dr. Gottlieb, it is good to see you here again. We appreciate your go-to attitude in trying to get things right. We understand that and we are with you every step. We appreciate your work on opioids, something that impacts every one of our districts.

And I have to say, as we worked on the Cures legislation out of this committee, the $500 million extra that we added to the FDA budget was almost a no-brainer. So, we appreciate the work of your crew, and we want to make sure that you have the resources to make sure that things, in fact, are safe and that you are not missing any steps.

I have got a couple of specific questions for you. Hopefully, I can get through all three.

It is critical that, until the clinical need list is issued, the FDA not permit bulk drug substances to be used in compounding, absent a final determination of clinical need, once all statutory criteria have been satisfied. Can you confirm that, once the FDA has identified its criteria for clinical need, that bulk drug substances, including those that the FDA has currently placed in Category I, would not be permitted to be used in compounding, absent such a determination?

Dr. GOTTLIEB. Well, we have put out the essential copies of this, which you know, the essential copies guidance. We are going to have the criteria for the development of the bulk drugs list for the 503B facilities, which is what I believe you are referring to, because we are further along on the bulk drugs lists for the 503B facilities, we will have that criteria out in March. And by the end of the year, we will have specified some bulk drugs that should either come on or off that list. There could be some that fall out pretty quickly from that list, based on safety considerations or a clear lack of clinical need. And so, we are going to do those assessments.

Then, we are going to also have to contemplate how we change our inspectional priorities to prioritize inspecting or taking action on the basis of 503B facilities compounding drugs that might not be on that list. Right now, under our risk-based framework, we need to change some protocols in terms of how we go about looking for some of those other questions, to your point.

Mr. UPTON. Is the President's budget going to include more money for inspections?

Dr. GOTTLIEB. Well, I don't want to get ahead of the President. So, I am not fully aware of what is going to end up in the budget. It is probably a question best put to OMB at this point.

Mr. UPTON. It was never Congress' intent that small tweaks to approve drugs, like minor changes in concentration or inactive ingredients, would satisfy the criteria for clinical need and open the door to compounding from bulk substances under the DQSA. Would you agree that a clinical need can only be found where there exists a genuine patient need unable to be addressed by approved drug products requiring a significant change from the approved drug?

Dr. GOTTLIEB. Well, again, Congressman, I don't want to get ahead of my career officials who right now are drafting guidance to define that very question. But the type of definition that you put forward would certainly seem to comport with a reasonable interpretation of what a final standard would be.

Keep in mind, also, that we articulated in the essential copies guidance, and we are going to re-articulate in the guidance that we put out in March, that if there is an FDA-approved product available that you can compound from, you have to compound from that product. So, if a 503B facility is compounding from bulk, but they can otherwise be compounding from an FDA-approved product, for example, diluting it down if they are providing a more dilute formulation to satisfy a certain clinical need, they have to start with that FDA-approved product. That is a principle that we have put forward. I think that is going to address some of the issues that have been raised with respect to what is on and not on the 503B bulks list at this time.

Mr. UPTON. And when do you think that order will be made?

Dr. GOTTLIEB. That is a principle that I believe we put forward. I believe that is articulated in the copies guidance that we just put out, but it is going to be re-articulated in the March guidance that we put out. The question will then become, well, when are you going to take enforcement action solely on the basis of that issue? Because it is one thing for us to put out a guidance. If people don't follow our guidance, we have to take enforcement action. And that is where I mentioned that we are going to relook at protocols and how we prioritize our enforcement activity, on the basis of those kinds of considerations as well.

But, as you know, we have a risk-based framework. We prioritize our limited inspectional resources and enforcement resources in places where we believe there is direct patient risk. And we are still in a realm where we are dealing with a lot of direct patient risk before we just look at, for example, economic harm, although that certainly is within the criteria that we look at and will be within our protocols.

Mr. UPTON. Thank you. I yield back.

Mr. BURGESS. The Chair thanks the gentleman. The gentleman yields back.

The Chair recognizes the gentlelady from Colorado, Ms. DeGette, 5 minutes for questions, please.

Ms. DEGETTE. Thank you, Mr. Chairman.

As Mr. Green mentioned, he and Congressman Griffith and I worked really hard after that terrible tragedy of the New England Compounding Center to come up with our Compounding Quality Act, which was subsequently folded into the Drug Quality and Security Act. We are really proud of that bipartisan work. But, as we are seeing today, it takes constant tweaking and review to make sure that these pieces of legislation are working.

Commissioner Gottlieb, one of the things that I am hearing from a lot of stakeholders about is what to do about office use. A lot of providers are saying that people are having difficulty accessing types of medication because of the requirement that we have for prescription. Now what they say is that these medicines are not lu-

crative enough to use 503B outsourcing facilities, but that the patients need them. And so, there are shortages.

I want to be clear. I have got strong reservations about undermining or loosening the DQSA's prescription requirement in any way, given the consideration that any move in that direction could have an impact on patient safety. But I do want to make sure that patients with unique needs that cannot be met by FDA-approved medications can get the treatment that they need. It is really a balancing test.

And so, I wanted to ask you if you think there are ways that we can resolve these potential access problems without undermining the prescription requirement and exposing patients to unnecessary risk.

Dr. GOTTLIEB. I appreciate the question, Congresswoman. To your point, this is one of the tensions that we are grappling with, because we care very much about these access issues that you have highlighted and need to preserve the practice of medicine. And we need to preserve the ability of physicians to get access to these drugs to use in their offices.

We have seen an environment where we see more of the 503Bs doing small batches. About one-third of registered 503Bs do small batches. We are trying to take steps to better match clinicians with 503Bs that either are currently manufacturing drugs they might need, but also historically have manufactured drugs that would be needed, and are willing to run small batches. So, we are starting to post that information prospectively on our website.

I think, as we also try to look at how we can create a more flexible framework for how we apply GMP standards to the 503Bs and see more smaller pharmacies that might want to make a business in doing small batches become 503B facilities, where they are still subject to GMP standards, I think that is going to also help address this.

I made the comment earlier that the 503B sector has not grown as quickly as we had envisioned and had hoped at the time, including myself when I testified before this committee. But I think that it is still early days, and I still think we are going to see a robust industry take shape here.

Ms. DEGETTE. Do you think it would be helpful to work more on giving timely and transparent information for providers about which of these facilities are making these compounded medications?

Dr. GOTTLIEB. I absolutely do. We are doing that. We do it now prospectively. We are just starting to really do it, because we are starting to get those reports electronically. One of the things we are considering is, can we go back and do it retrospectively, because we have the histories on what the facilities used to produce. That could be helpful as well.

Ms. DEGETTE. It would help those facilities, too.

Dr. GOTTLIEB. It would help the facilities.

We are also going to be issuing either an FR notice to create a docket to solicit from provider groups input, in a more systematic way solicit input on where they are seeing access issues around certain products, so that we could, then, see what steps we could take to try to help provide more efficiency to 503Bs that might

want to make those products. Because, right now, a lot of what we know is anecdotal.

Ms. DEGETTE. Right. Right.

Dr. GOTTLIEB. We want to develop that information on a more systematic basis.

Ms. DEGETTE. In a systemic way.

Now one last thing about drug pricing. Some people say that compounded alternatives to expensive medicines could actually provide financial relief to patients. But I think there is a real risk, in that marketing unapproved bulk compounded drugs could be really risky to patients. I am concerned that some press reports are already saying this is going on. I just wondered, I don't think that, certainly, the policies that this committee has endorsed are meant to be using compounded drugs to lower prescription drug prices if it is at the expense of patient safety. I am wondering if you can comment very briefly on that.

Dr. GOTTLIEB. We believe that, if there is an FDA-approved option available, that is always the best option for the patient because it is going to provide the greatest assurance of safety and efficacy for the patient and to the provider. And I also believe, as you have seen me try to demonstrate through the actions we have been taking, that there are a lot of avenues we can go down to try to address the issues of cost and competition in the marketplace. And we will continue to do that.

Ms. DEGETTE. So, it is not one or the other really?

Dr. GOTTLIEB. It is not one or the other.

Ms. DEGETTE. I thank you.

Thank you, Mr. Chairman. I yield back.

Mr. BURGESS. The Chair thanks the gentlelady. The gentlelady yields back.

The Chair recognizes the gentleman from Illinois, Mr. Shimkus, 5 minutes for questions.

Mr. SHIMKUS. Thank you, Mr. Chairman.

And Scott, it is great to have you here. I appreciate the testimony.

This is a tough issue we have wrestled with for a long time. I think my colleague, Congresswoman DeGette, just actually kind of wove the story and the concerns that I have, and when we talk to some of our folks in different congressional districts.

So, the 503A and the 503B issue, for me, it always comes down to the small-town, rural compounder and the way these rules will be etched or the memorandum of understanding or the batch size and the mileage distance, especially when you have got a rural district—for me, it is 33 counties, five hours north and south drive, a three-hour east-to-west drive. It is a little different environment than a metropolitan area and a different area of the return on investment based upon what you are producing. You are not really going to manufacture for a large group, but in a small batch. And then, you might have across-state-line issues, especially in a rural area on the Illinois-Indiana border. I see my colleague, Mr. Griffith, nodding his head.

So, can you kind of weave for the small pharmacist compounder, who I haven't had personally any problems as far as I have represented that area—he is trying to address this being able to pro-

vide what is being requested of him. Sometimes it is even these issues with the—I am not a doctor—the eye drop issue for the optometrist who doesn't have the shots in the doctor's office, although it is something they need immediately, in essence. And there is not a prescription because the person hasn't come in yet to be able to get the prescription. And then, you have a delay of providing the medicine.

So, for that small compounder, what should he take home from my vague question?

[Laughter.]

And what assurances can you give him that we are trying to allow him to continue the work he has been doing?

And I know we have got our veterinarian here, too. These guys also use their compounding ability in veterinarian medicine. So, a veterinarian would ask the compounder in rural America. So, he needs to be there for not just humans, but also for the animal health that he also is able to provide for the veterinarian.

Dr. GOTTLIEB. I can go a lot of different ways with this question.

Mr. SHIMKUS. Well, I went a lot of ways with the questions.

[Laughter.]

Dr. GOTTLIEB. But I will go right to where I think you are going, which is the question of the prescription requirement and whether or not that small-town pharmacist who is providing drugs over a large geographic area still needs to have a prescription in hand in order to provide a drug back and the difficulty of doing it over a large geographic expanse I think is the essence of what you are asking.

The bottom line is that we believe that the line of demarcation for what constitutes the practice of pharmacy versus what constitutes drug manufacturing has to remain the prescription. The practice pharmacy, if you go and look at the bylaws of states and how they define a practice pharmacy, I did that before coming to the hearing. I spent my weekend looking at that. Embedded in the bylaws of state boards of pharmacies is the idea of the prescription and the named patient. That is the essence of what it means to be practicing pharmacy.

We also understand that Congress contemplated other thresholds and struggled with it, and arrived back at the prescription being the line of demarcation, both 20 years ago when 503 was originally drafted, as well as when it was recodified in DQSA. Because other kinds of schemes that were contemplated, volume-based schemes, for example, didn't provide the kind of delineation that you could apply a regulatory structure to. We can't regulate against "we'll know it when we see it." We need a clear line that we can force against and we can enforce against with our limited resources.

As far as veterinary medicine is concerned, as you know, we recently pulled the guidance that sought to define what our regulation was going to look like in that realm. And we pulled that for a variety of reasons, but, largely, because we don't think we got it right. I will say we will be reissuing that this year. But I will say that the issues around compounding in the veterinary space are different than issues around compounding in the human space. The practice of pharmacy in the veterinary space is a different kind of practice of medicine than it is in the human space. And so, our

framework will also look different. It will be reflective of the practice of veterinary medicine.

Mr. SHIMKUS. All right. Thank you.

Mr. BURGESS. The Chair thanks the gentleman. The gentleman yields back.

The Chair recognizes the gentleman from Oregon, Dr. Schrader, 5 minutes for questions, please.

Mr. SCHRADER. Well, thank you.

And I thank my colleague for asking some good questions about veterinary medicine. That is near and dear to our heart.

We use compounders a lot in our practice, I don't think inappropriately, but, as you alluded to, the size of the animal, the different metabolism of an animal, the lack of a particular drug that has worked historically that is affordable for my patients, that is a different beast to some degree. I appreciate the thoughtfulness that USDA under your guidance and FDA is actually approaching the whole veterinary guideline issue. So, I want to thank you for that.

While I have had a lot of experience in using compounders in smaller communities to make sure my patients get the best medication possible, I am new to the regulatory framework with all this. I don't profess to be knowledgeable. So, my questions might be a little arcane and pretty obvious.

But the whole 503B opens up a potential, as I think you have alluded to and some of the questions have alluded to, problem for circumventing a lot of the regulatory framework that our generic manufacturers, for instance, have to apply. What are the major differences—well, first, I will say I fully support the continued definition of pharmacy prescription. It has to have a prescription to be able to do that. I think that is for the safety of any patient, human or animal. That is critical, and I urge you to continue to use that as a very bright line.

But, having said that, then what do you see as the big demarcation between your 503B regulatory framework versus your generic regulatory framework? How do you see that as different, and what constitutes the guidelines there?

Dr. GOTTLIEB. Right. By generic, I think you mean 503A, traditional pharmacy compounding, 503B being the outsourcing facility. And the difference is the prescription, whether or not that the drug is being compounded on the basis of a named patient in response to a lawful prescription from a provider. That is the traditional practice of pharmacy. That is a 503A compounder.

A 503B compounder is engaging in manufacturing. They are manufacturing either in small batches or on a larger scale, not in response to individual prescriptions that they have received from a provider, but in anticipation of orders, and they are doing advanced shipping. They might be doing what we all office stock. They might be shipping to providers to allow those products to be stocked inside the offices.

That is traditional manufacturing. There is no way around it. Whether you do it with 10 units or you do it with 100 units, you are engaging in manufacturing, and those circumstances, instead of applying the traditional regulatory framework where they would be subject to regulations around the sanitary conditions, which is what you would apply to 503A pharmacy, in the context of the

503B setting you are applying GMP standards, some form of GMP, not GMP-light, but some form of GMP. I don't want to call it "GMP-light".

Mr. SCHRADER. So, similar to the generic manufacturing that would go on?

Dr. GOTTLIEB. Subject to good manufacturing practices, I mean, good manufacturing practices, as I said at the outset, are not a fixed standard. They are risk-based. And so, they look different depending on the manufacturer that you are evaluating. But it would be some form of GMP standards that you would be applying. You would be doing lot release, sterility testing, batch testing. You would be retaining samples. You would provide for the compounding in a sterile environment if you are compounding a sterile product. So, you would be applying the GMP standards, traditional GMP standards.

Mr. SCHRADER. Whatever level you are approaching that manufacturer?

Dr. GOTTLIEB. There are basic principles of regulation with respect to the good manufacturing practices. So, when we say "level," I think that there are things you can do to make it less expensive if you are doing it on a smaller scale. So, for example, you require a lot of small batches. If you are only going to be making a small batch, if you are only shipping a small amount, you would require that facility to retain a lot of samples. There are ways that you can apply the GMP standards in a fashion that comports with the level of the volume and the level risk you are creating. And that is what we are seeking to do in the more flexible framework that we are contemplating.

Mr. SCHRADER. So, I guess the last question: what do you see as the role with the state regulatory framework versus the federal regulatory framework. The interstate commerce piece would, obviously, be a federal purview. How do you juxtapose the state regulatory framework on these 503A and, more importantly, the 503B pharmacies?

Dr. GOTTLIEB. The MOU is going to define sort of the interplay between the state and the federal scheme and the level of activity that a 503A can engage in that might cross it into being subject to federal oversight because it is engaging in interstate commerce, interstate activity. And we have talked about various thresholds, about how much product can cross a state line before a compounder should or ought to be subject to at least our attention, to make a decision on whether or not it is subject to, should be subject to FDA oversight.

Here again, this is not going to be a fixed standard when we are contemplating this. It is not going to be, if you ship 31 products, you are subject to the federal scheme, but if you had only shipped 30, you would be fine. We are going to try to take a risk-based approach here as well, and it is going to be based on volume, percentage of products you are shipping across the state line, the kinds of products you are shipping across the state line, the manner in which you are doing it. And so, we are going to have a threshold in which we want notification by the states, but, then, we are still going to make an independent decision whether or not it should be subject to a federal inspection because of the activity.

And the essence is, if I could just close, the essence is that, if a pharmacy is subject to state regulation, but is shipping most of its product out of state, it can't be subject to state regulation anymore. Because if you are in New Jersey and you are subject to the New Jersey Board of Pharmacy and New Jersey inspectors, but most of your products are going to New York, the New York inspectors don't know. Then, they can't provide the oversight that they need to in a trace-back. So, it is important that the states be aware of what is going on within their states.

Mr. SCHRADER. Very good. Thank you.

And I yield back.

Mr. BURGESS. The Chair thanks the gentleman.

The Chair recognizes the gentleman from New Jersey, Mr. Lance, 5 minutes for questions.

Mr. LANCE. Thank you very much, Mr. Chairman.

And thank you for being here, Commissioner.

The district I serve provides innovative medicines for patients across the country. Protecting these patients is, of course, a top priority for all of us, and so is protecting the FDA's gold standard. As the Drug Quality and Security Act is implemented, we need to ensure that we provide the incentive for innovator and generic manufacturers to go through the FDA process. To do this, we need to make sure that commercially-available drug products cannot be copied. How is the agency protecting patients and the gold standard as you implement the Drug Quality and Security Act?

Dr. GOTTLIEB. Well, Congressman, thanks for the question. I would like to assert that we are protecting the interest of patients by implementing this statute and making sure that we continue to move through the regulatory steps to, for example, finalize the 503B bulks list, finalize the guidance on sanitary conditions, finalize the list on bulk substances that the 503A facilities can compound from, make sure we get the MOU in place, so we can provide proper oversight of 503B and 503A facilities, in concert with the states, and work closely with our state partners. And so, we are going to continue to work through that.

With respect to the first part of your question about just the sort of economic issues inherent in situations where a compounder might be copying a drug that is otherwise an FDA-approved product, we have asserted in the copies guidance certain activities that we would believe fall outside the scheme contemplated by DQDA. We are going to reassert those in the guidance that we issue in March with respect to the criteria for what should and shouldn't be on the bulk drugs list. Then, it is going to be a question of taking enforcement action where we see companies or compounders engaging in activity that falls outside that scheme that we both articulated in our guidance as well as Congress contemplated in the statute. That is what we are going to be focused on doing.

I will say, though, our enforcement activities will be, as they should be, guided by patient risk, first and foremost. But we will be baking into our protocols in terms of how we take enforcement action the kinds of considerations that you talked about, because that is what Congress has asked us to do.

Mr. LANCE. Thank you.

I was pleased to see that the agency's 2018 Compounding Policy Priorities Plan—and I am interested to hear more about the forthcoming flexible risk-based approach to current good manufacturing practices. Recognizing the agency's goal to increase the number of 503B outsourcing facilities, recognizing the compliance costs for larger 503B facilities and the investment necessary to satisfy the statute, is the agency concerned that the multi-tiered 503B regulatory approach may affect incentives for these facilities?

Dr. GOTTLIEB. Well, quite the opposite, we feel that we hope that by taking a tiered approach based on risk, we might provide the opportunity for more 503A pharmacies to step across the line into being 503B pharmacies and consider it worth the economic investment. Becoming a 503B pharmacy is not without some investment in cost for most 503A facilities. They don't have the kinds of facilities to be subject to GMP oversight. And so, it is going to require some investment. But we are hoping that we could provide a framework where more facilities can find it, have the ability to make the capital investments and raise the capital necessary to make those investments because they see a better opportunity on the other side of that in terms of trying to increase their volume and increase the kind of activity that they are engaged in. We think by having more 503A facilities converting to being 503B facilities, it is going to facilitate access and, also, give them the ability to grow.

A 503A facility that is trying to engage in some low level of manufacturing, even if they can do it under the radar of regulators, if they grow to a certain proportion, eventually, they are going to pop up. And so, they are basically capped under this legislation. If they step across that threshold and become a 503B, they have much more latitude to engage in broader manufacturing.

Mr. LANCE. Thank you, Commissioner.

And, Mr. Chairman, I yield back 27 seconds.

Mr. BURGESS. The Chair thanks the gentleman.

The Chair recognizes the other gentleman from New Jersey, the ranking member of the full committee, Mr. Pallone, 5 minutes for questions.

Mr. PALLONE. Thank you, Mr. Chairman.

I wanted to ask you about this issue of distribution versus dispensing. Section 503A of the law prohibits a pharmacist, pharmacy, or healthcare provider from distributing compounded drug products across state lines that exceed 5 percent of the total prescriptions distributed or dispensed unless the product is compounded in a state that has entered into a memorandum of understanding with FDA that addresses the distribution of inordinate amounts of compounded drug products and provides for investigation by the state into complaints associated with compounded drug products that are distributed interstate. And FDA released a draft MOU in February 2015 that proposed defining inordinate amounts for purposes of interstate distribution to no greater than 30 percent of all products distributed or dispensed.

So, in terms of this distribution versus dispensing, Commissioner, some have suggested that the MOU is only intended to apply to drugs that are distributed without a prescription. What is your view about the purpose of the MOU and the public health

purpose it serves? Are there some drugs, such as those dispensed directly to patients, which could be excluded consistent with that purpose?

Dr. GOTTLIEB. Well, in my weekend reading of pharmacy bylaws, the other observation that I had is that the bylaws make specific reference to the word "dispense" as part of their definition of what constitutes the practice of pharmacy. It is our view, and we feel strongly, that the practice of pharmacy always contemplates the dispensing of the drug. Now in certain circumstances the drug is going to be dispensed and, then, distributed across state lines, and that is where the MOU comes into play. The MOU contemplates drugs that are dispensed and shipped across state lines, and shipping is a form of distribution, as I think you all agree. But we think that dispensing is part and parcel of the activity of practicing pharmacy, and no compounded drug can be distributed without first being dispensed, because dispensing is the act of creating that patient-specific prescription.

And I will just say, and to address the elephant in the room, because this has been contemplated as one of the beliefs in terms of why DQSA might have contemplated something different with respect to office stock than FDA's current interpretation of how we perceive the law to have been written, I don't think that redefining the practice of pharmacy, which involves the activity of dispensing a product to a patient, is a good way to try to create a framework for office stock. I am open to the debate about office stock and the merits of it. I think we have been clear from the agency's standpoint the risks that we feel it creates if a 503A facility is getting engaged in it. But I would hate to see the practice of pharmacy redefined as a sort of backdoor into that. I think if we are going to have a discussion about the merits of 503A facilities engaging in some level of manufacturing and shipping, we ought to just do that directly.

Mr. PALLONE. All right. Then, let me get to my second question. Recently, you announced the agency's intention to modify the allowable percentage of compounded drug product distributed into a state to effectively eliminate the 30-percent threshold and, instead, implement certain reporting requirements that will be triggered at a 50-percent threshold. And this strikes me as a weakening of an important patient protection and in contrast to what you have noted in your testimony is the stated goal of this provision in the statute, which says, "Preventing compounders reportedly 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 requirements and other provisions intended to ensure the manufacture of quality drugs." So, would you explain how increasing the allowable threshold for interstate distribution to 50 percent is consistent with the goal of the statute of preventing compounders from making unapproved drugs and operating a substantial portion of their business interstate without adhering to the CGMPs?

Dr. GOTTLIEB. Well, I appreciate the question, Mr. Chairman. I don't see it as a weakening. I see it as a strengthening, because we are going from a hard threshold of 30 percent to a risk-based

threshold of 50 percent. It is not 50 percent—it is not 49 percent and you are all good, and 51 percent and you are now subject to a different scheme. There are going to be other tests that we apply to make assessments about what the appropriate scheme is for a particular facility.

It is the case, though, that there are facilities—for example, a border-state pharmacy that develops TPN, total parenteral nutrition; a home infusion company that provides patient-specific, named patient products on a prescription basis and might ship more widely that are engaging in the traditional practice of pharmacy; they are doing it on the basis of named patients in response to an individual prescription, but they might be shipping more of those products. They might be lower-risk, too, depending on what they are doing.

And so, the reality is that there are a lot of different kinds of pharmacies situated across the spectrum in terms of the activity that they are engaged in. And we don't think a sort of fixed standard where there is a fixed line based just on volume makes the most sense. We want a volume-based standard, but also a standard that allows us to make an assessment about what the kind of activity is. And it is another effort on our part to be risk-based. I think, ultimately, our enforcement is stronger when we are taking a risk-based approach.

Mr. PALLONE. All right. Thanks a lot.

Thank you, Mr. Chairman.

Mr. BURGESS. The Chair thanks the gentleman. The gentleman yields back.

The Chair recognizes the gentleman from Virginia, 5 minutes for questions, please.

Mr. GRIFFITH. Thank you very much, Mr. Chairman. I appreciate it greatly.

Let me get the record a little bit straight because I think it was confused a little bit earlier. While we had criminal conduct by NECC, we also had timid lawyers at the FDA. Ohio had warned the FDA there was a problem. Colorado had outright banned NECC from putting products into their state. And FDA was aware of it and didn't even bother to seek a warrant to go in and see what was going on. So, as we move forward, let's continue on that.

Also, I think in the next panel there will be some question about the intent, and you touched on that in your testimony with Mr. Shimkus a little bit earlier. But I want to go back to when the bill passed in September of 2013. At that time, now-Ranking Member Green said, in part, "While I believe the FDA dropped the ball with regards to the NECC, with this law they must succeed where in the past they failed." And I know you are working hard on that.

This bill still lacks clarity in many important areas: office use, how nuclear pharmacies are regulated, and repackaging of sterile products. I look forward to working with my colleagues to provide meaningful oversight of the FDA to make sure another NECC-type outbreak never happens again, and make sure they are using the type of enforcement discretion necessary to preserve patients' access to critical medicine.

In that same press release—because it was a bipartisan effort, as you heard earlier, Mr. Green, myself, and Ms. DeGette worked

hard on trying to get this portion of the DQSA right, and to the best of our ability, although we had some disagreements with our Senate colleagues. I said on that occasion that, "The Drug Quality and Security Act leaves a large portion of existing law intact. It also leaves many areas of practice where clarification may still be needed, particularly as it relates to office use, repackaging, and nuclear pharmacies. Along with my colleagues, I will continue working to oversee the FDA's interpretation and implementation of this law."

And I think that is what we are doing today. Some folks have characterized this, because I am leading the push for office use, as wanting to undo everything that DQSA stood for. Obviously, I wouldn't have drafted it and fought hard along with my colleagues to get it, if that was my intent.

But I do have questions. And one of those was raised by your testimony to Mr. Shimkus in answering his questions where you indicated that twice they had decided that you had to have a prescription in order to issue a drug, and that Congress had made that decision. But I am looking at 503A, little "a" to big "A", and it says, as one of the things, it says, "or is by a licensed pharmacist or a licensed physician in limited quantities before"—before—"the receipt of a valid prescription order for such individual patient."

Obviously, the law—and that was the old law, which was not changed and which we were assured that the practices weren't going to change at the times we were negotiating this by folks in the Senate saying they didn't want to do this because the FDA wasn't going to change anything. It clearly anticipates that in some cases you won't have a prescription until afterwards. We had debated making sure that a prescription was written within 7 days at the time that we were negotiating it. But this seemed acceptable at the time, and the reason that I put that into my statement—and others may have put it into their statement—and the statement on the floor was we were given the assurance that office use was going to remain pretty much the same, and for 503A pharmacies I think that is important.

So, how do you rectify that you think there needs to be a prescription with the actual wording of the law? There are also other references, future-looking references, in the next section.

Dr. GOTTLIEB. Yes, thank you, Congressman, for the question. I appreciate your longstanding dedication to this issue and your longstanding work on it. And you and I have had the time to talk about this on many occasions.

With respect to the nuclear pharmacies, I will just say we will be putting out a guidance that will specifically address radiopharmaceuticals.

But, in respect to your specific question about the language you quoted, I believe that that language and we believe that language was contemplating anticipatory compounding, basically, compounding on an expectation that you were going to receive a certain volume of prescriptions. Because we know, with the 503A pharmacies—and I know you are very familiar with the practice of pharmacy—sometimes when you mix up one batch, when you are mixing up a batch, you can't just mix up one drug. You mix up 10 at a time or 15 at a time. And you can do that if there is an expec-

tation that you know you get 30 prescriptions a month or 40 prescriptions a month. So, we allow for that.

What we have said in guidance is that you can mix up a level of volume in anticipation of what you your prescriptions might be over the course of a 30-day period to provide that kind of flexibility. That is what I believe the statutory language that you referenced was anticipating and that we have allowed for.

Mr. GRIFFITH. And I disagree, just based on the debate that we had when we were doing this a number of years ago in 2013, because we anticipated there would be continued office use. That is why we were looking at putting in the 7-day requirement. And as Ms. DeGette said, there has got to be a balance. As Mr. Shimkus said, we are worried about rural areas.

I do appreciate that you are concerned about the state lines because, having now been made famous by the GEICO commercial where the lizard jumps from Tennessee to Virginia and back and forth, and back and forth, that is my district. And so, you have got a pharmacy on either side of that state line. You just turn around and you cross the state line.

The other day I was traveling in my district and I went from Virginia to West Virginia, to Virginia, to West Virginia, back to Virginia, then ended up the day going from Virginia to Tennessee, back into Virginia, and back into Tennessee, and then, back home in Virginia, just to try to talk to my constituents and do what I needed to do.

So, I appreciate you paying attention to that as you look at the flexibility side, but I really believe that the existing law allows for some office use from the smaller folks. We were trying to get to the big guys and the larger guys because of the NECC problem, which was shipping into all the states, not just across the Tennessee line or the Virginia line.

I yield back.

Dr. GOTTLIEB. I understand and appreciate concerns, Congressman, the impact on small pharmacies.

Mr. GRIFFITH. And I yield back. Thank you, Mr. Chairman.

Mr. BURGESS. The Chair thanks the gentleman.

And the Chair recognizes the gentleman from a similar small state, Maryland, for 5 minutes.

Mr. SARBANES. Small, but powerful, and home to the FDA.

Welcome, Commissioner.

People have touched on kind of the partnership, regulatory partnership between your agency and what happens at the state level. I wanted to explore that a little bit more.

I was looking at your testimony on page 3, where you talked about the 500 inspections that have been conducted, 503A and B facilities, since the passage of the new law and the end of the last fiscal year; how you have observed problematic conditions during the vast majority of these inspections, overseeing more than 150 recalls of compounded drugs, issued more than 180 warning letters. You have also 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.

So, I am just curious how that is going. There must be some states that are better partners than others. Obviously, you have to

rely to a certain degree on those follow-up inspections. And maybe without naming specific states, you could give me an example of a state that is engaged in this partnership in a very productive and efficient way, and why that is the case, what you would point to as indicating kind of a high standard in terms of the partnership, and the follow-up, and all the rest of it. And then, maybe give me an example, again without naming the state, of a place where that is not going so well. And what does the agency do, either because it is required to in some element or just because you regard it as your responsibility to help states to get to where they can be the best possible partners in this effort at oversight?

Dr. GOTTLIEB. Congressman, thanks for the question. To your point, there is a fair degree of variability. I think it would be risky of me to try to characterize a good state and a not-so-good state, because it is not something I have actually asked the question of my folks, and I would want to contemplate it in concert with them. Because the field people, the field team that is engaged in these efforts are going to have the best perspective. We could certainly get you that perspective, but I wouldn't want to mischaracterize the state.

I will say, though, broadly, that what we are seeing directionally is that the states are starting to conform more to DQSA now. And so, there has been discussion, for example, of states' pharmacy bylaws that might allow for certain practices that DQSA we don't believe contemplates. We are starting to see more of the states conform their practices, their inspectional activity, as well as their laws, to be compliant with the DQSA, be consistent with the principles of the DQSA.

For the states that might be moving in a different direction or not moving as quickly in the direction that was envisioned by DQSA, I think what it creates for us is more of a resource burden. Those are the states that we might have to put more resources into to make sure that we are providing the same level of oversight that we would be to a state that is sharing information with us very cooperatively and reporting to us, so we can target our inspections better.

A lot of our inspections are for-cause inspections. A lot of them are based on information we derive from the states. If the states aren't reporting to us as efficiently, then we need to do more work to try to derive that information on our own. It is just a more resource-intensive process.

Mr. SARBANES. Is there an opportunity to provide, I don't know, technical assistance or other support to the states, as they are trying to come into compliance with this effort?

Dr. GOTTLIEB. We do that. As the scheme contemplates, we provide a lot of resources or technical assistance within the context of the resources we have available to do this in terms of training to state inspectors, training around inspectional issues that they might need to be aware of as they start to inspect, for example, 503B facilities and do their own GMP inspections. We do dual inspections with the states. We invite the states in on our inspections, so that they can both learn alongside of us as well as dually inspect some of these facilities and share information. So, there is a lot of stuff that we are trying to do in concert with the states.

As I sunk deeper into this and understanding how we were applying this framework when I re-arrived at FDA 10 months ago, there were a lot of aspects of this that looked very similar to FISMA, the framework envisioned in FISMA, where the regulatory scheme is very much dependent upon a close Federal/state partnership.

Mr. SARBANES. Thank you. I yield back.

Mr. BURGESS. The Chair thanks the gentleman. The gentleman yields back.

The Chair recognizes the gentleman from Georgia, 5 minutes for questions, please.

Mr. CARTER. Thank you, Mr. Chairman.

And thank you, Dr. Gottlieb, for being here. I want to commend you and thank you for your adherence to safety, and I think it is very important.

It has been mentioned more than once during this hearing that there has to be a balance between accessibility and safety. I think that is perhaps one of the areas that I struggle with. And you and I have had many conversations.

I want to ask you, first of all, about the rulemaking process, because that is of great interest to me, being a relatively new Member of Congress, only in my second term, my third—I guess I am starting my fourth year now. So, I am getting older, but I am still learning about the rulemaking process.

I noticed that, since the passage of DQSA, that you have used oversight guidance documents to really enforce this and to really enforce what you want the agency to see out there. Although we probably disagree, and we do disagree, you say it is with stakeholder input; I say it has not been with stakeholder input. And I am just wondering how you can justify that, particularly in light of the fact that just recently the Office of the Associate Attorney General issued a new policy to DOJ that guidance policies will not be converted into rulemaking. So, how are you justifying this, that you are going to use guidance policy for rulemaking here?

Dr. GOTTLIEB. Thank you, Congressman.

We have a long history of issuing non-binding guidance in many contexts. And our guidance practice—and this question has come up in other contexts well outside this context—our guidance practices, generally, have been used as a model for other agencies and for OIRA as well in terms of what we do, how we issue guidance, what we use guidance for under the Administrative Procedures Act.

So, I feel confident that, on the whole—and we can have a debate around any individual guidance—but I feel confident that, on the whole, we have adhered to good practices in terms of how we promulgated guidance in multiple——

Mr. CARTER. I don't mean to interrupt, but you even answered Representative Upton's question about the guidance, that you expected it and that you were using the guidance for enforcement. You are, essentially, saying that this guidance is going to be enforced.

Dr. GOTTLIEB. There is——

Mr. CARTER. Even though the DOJ has been told that, no, it cannot be converted into rulemaking. Quite honestly, I have not read

this from the Associate Attorney General. Perhaps they said this is going to apply to the DOJ, but not to the FDA. I don't suspect that was the case; maybe it is.

Dr. GOTTLIEB. Well, we could take enforcement action now. We don't need the guidance document in order to take the enforcement action. The guidance document is a way to provide public discussion around how we intend to take our enforcement action. So, we can both inform the public as well as learn from the public. The guidance document itself isn't the basis for the enforcement action, you are absolutely right. We have regulatory authority that has been given to us by Congress.

Mr. CARTER. Well, what about stakeholder input? Because that is something that is very concerning to me, that I don't feel like we have had stakeholder input. I know that you are coming out with a new MOU. My hope is that you are going to have more stakeholder input into that. The existing MOU, although I was not here at the time, I don't think there was sufficient stakeholder input into that.

One thing, in particular, about this is the difference between dispensing and distributing. As you know, the DEA has said that distributing is going to be overseen by the FDA, but the dispensing is going to be overseen by the state boards of pharmacies. Yet, you seem to want to oversee dispensing as well through the FDA.

Dr. GOTTLIEB. I am not familiar with the particular definition of dispensing and distributing, probably under the Controlled Substances Act, that you have derived from—I don't know, is it a regulation or a guidance document? So, I can't speak to how the DEA might have defined something in a certain context, again under the Controlled Substances Act, which is my presumption.

We believe that, under this law and under the practice of pharmacy, with products that we regulate, and outside of the context of controlled substances, the practice of pharmacy involves the dispensing of a product, just like the practice of pharmacy involves a patient——

Mr. CARTER. But why is it that the FDA thinks that they have to intercede the state boards of pharmacy? That has always been something that the state boards of pharmacies——

Dr. GOTTLIEB. We need to work with them.

Mr. CARTER. OK. I have got just a few seconds left. Now I want to ask you about something that has been brought up by Ms. DeGette, by Mr. Griffith, and that is office use. And that is something that I think you have absolutely got wrong here.

But I want to ask you just from a perspective of a Member of Congress. It is my understanding that not once, not twice, but three times, through appropriations language, that the FDA has been instructed to revisit this and to look at this. In fact, in 2016, it said, "The committee understands the intent of the DQSA was not to prohibit compounding pharmacies from operation under existing 503A exemptions. Therefore, the committee directs the FDA to issue a guidance document on how compounding pharmacists can continue to engage in office-use compounding."

Why do you ignore these? Why have you not ignored it once, not twice, but three times? I don't get it.

Dr. GOTTLIEB. Congressman, those appropriation riders I believe preceded my arrival at FDA. I would be happy to work with this committee, or anyone in Congress, to contemplate if they want to have a discussion around the statute and what we can do to continue to improve this on this legislation.

But we have to keep patients in mind and make sure patient safety drives the decision we make. And remember why we are here. We are here because pharmacies were engaging in manufacturing without any standards in place.

Mr. CARTER. Dr. Gottlieb, I could not agree with you more. I commend you on your dedication to safety. Again, we get back to the balance between access and safety. And that is just you and I live in different worlds. You are in a different world than what I previously was in my career in pharmacy, and I saw firsthand the access issue and how people struggled with it. That is just a difference that we have and that I hope that you will take into consideration in the future.

Thank you very much.

Dr. GOTTLIEB. Thank you, Congressman.

Mr. BURGESS. The gentleman yields back.

So, Dr. Gottlieb, once again, I think we have gotten everyone on the committee. I will just ask, Mr. Green, do you have a follow-up question before we leave?

Mr. GREEN. No. Oh, I guess we do, Mr. Chairman.

[Laughter.]

Mr. BURGESS. I could intuit that.

Mr. GREEN. OK. Commissioner, one of the most important ways FDA is conducting oversight and ensuring compliance with the DQSA has been through inspections. Since the enactment of the Drug Quality and Security Act, FDA has conducted nearly 500 inspections, issued more than 180 warning letters identifying significant violations of compounding pharmacies, issued more than 70 letters referring to inspectional findings to state regulatory bodies, and overseen more than 120 recalls of compounded products.

Commissioner Gottlieb, as I noted, FDA has conducted hundreds of inspections in compounding pharmacies and identified numerous violations. Will you describe briefly for us some of the violations and conditions FDA found when they were inspecting both 503A compounding pharmacies or 503B outsourcing facilities?

Dr. GOTTLIEB. I brought some slides with me, if the chairman would let me use them, of some of the things that we found. So, we can close on this, if that is OK. I don't know if we have them teed up.

Thank you, Mr. Chairman.

This is visible microbial contamination on a ceiling tile in a clean room.

If we go to the next slide, this is a HEPA filter located immediately above an ISO5 workbench that was observed to have a stained surface. The stain was due to a drug product which had exploded due to excessive pressure when forcing non-sterile product through a sterilizing filter, a device used to force the product sterilizing, in other words, a stainless steel caulking gun that was not sterilized.

Next slide. This is a sleeve used in the aseptic glovebox for aseptic manipulation. You can see it is damaged where it is circled.

Next slide. This is a toaster oven that was used to dry heat sterilize glassware. The oven wasn't capable, as we can probably presume, of reaching high enough temperature to be effective for that purpose.

Next slide. This is a ceiling above the doorway to a clean room with exposed insulation. This was supposed to be a clean room that would store products manufactured.

Next slide is a kitchen dishwasher that was actually being supplied with tap water and home detergent and used to clean equipment, equipment and the utensils that come in contact with products that were intended to be sterile.

And they jumped my bug. This was a bug.

But, we also saw things like coffee filters being used to filter particulate matters. We find things that are deeply concerning. And these are sterile, these are facilities that are manufacturing sterile products, or at least intended to be sterile products.

I appreciate the question.

Mr. GREEN. Thank you.

Mr. BURGESS. The Chair observes that debate on the floor has proceeded to the point where Mr. McGovern is making some fairly significant gestures, which usually means he is concluding and we will be voting shortly. So, I will advise the committee that we will recess upon the votes that are called on the floor.

But we thought Ms. McMorris Rodgers was coming back, and she is. So, I will recognize her.

Mrs. MCMORRIS RODGERS. Thank you, Mr. Chairman.

Mr. BURGESS. But, again, I observe that the vote on the floor is probably very close. Mr. McGovern is making smaller and smaller circles with his hands, and that usually means we are getting there.

[Laughter.]

Mrs. MCMORRIS RODGERS. OK. Very good. OK.

Well, Commissioner, thanks for being here.

I wanted to ask about the 503As and the 503Bs, and just what the intent is moving forward as far as preserving them separately, or what your thoughts are.

Dr. GOTTLIEB. Well, thank you, Congresswoman, for the question. On the 503A, are you talking about the bulks list or just the different facilities?

Mrs. MCMORRIS RODGERS. Well, I understand that you have issued some guidelines related to 503As, 503Bs, and I wanted just to understand better what you think the future is for the 503As.

Dr. GOTTLIEB. Well, the general question with respect to the 503As is we believe that the 503As, which is a traditional practice of pharmacy, should continue to flourish. We believe it provides an important product for patients, the practice of pharmacy being able to individualize products on the basis of a prescription for an individual patient.

On the 503Bs, we do hope, and we always envisioned, that there would be more facilities converting into being outsourcing facilities. We also believe that more 503A facilities would opt to become 503B facilities. Now, in full disclosure, we have not seen the industry

grow up the way we had hoped. We still believe it is early. And we intend to try to promulgate a set of policies that we believe that will, hopefully, provide a flexible regulatory framework based on risk that is going to allow more pharmacies to contemplate becoming 503B facilities. Because there is an argument to be made that, when a pharmacy can become a 503B facility and engage in larger-scale manufacturing, under GMP compliance standards, we are able to apply a level of oversight that ensures the sterility of the products that are being manufactured. That could, hopefully, provide for more patient access.

But, with respect to the 503A facilities that were contemplated in the statute, and always enshrined in statute, that is the traditional practice of pharmacy that we believe should be preserved and protected, and provides an important opportunity for patients to get products that are tailored to their unique clinical needs.

Mrs. MCMORRIS RODGERS. So, you anticipate that they will be preserved as you move forward, the 503A——

Dr. GOTTLIEB. Well, they are. They are being preserved. The question becomes the scope of the activity and whether or not 503A facilities can and should be engaging in larger-scale manufacturing, and manufacturing and distributing products. And we believe that DQSA contemplated a scheme where that kind of activity would move into the 503B facilities that would be subject to GMP standards, if you were engaging in manufacturing and wider-spread distribution.

That is what brought us here. It was the fact of pharmacies like NECC engaging in manufacturing under the guise of a pharmacy license, not subject to standards that ensure the sterility of those products, that created the risks that brought Congress to contemplate this new framework.

Mrs. MCMORRIS RODGERS. OK. Well, I look forward to talking further about this with you.

Dr. GOTTLIEB. Thank you.

Mr. GRIFFITH. Will the gentlelady yield?

Mrs. MCMORRIS RODGERS. Yes. Yes, I would be happy to yield.

Mr. GRIFFITH. And I would just ask, in relationship to 503A, because we were talking about it earlier, if that didn't contemplate office use, then why has FDA allowed it up until this point in time? Because that is existing law and was existing law before DQSA, and it was allowed.

Dr. GOTTLIEB. Yes, it is a good question, Congressman. And I was at FDA over part of the time that we struggled with the 503A statute. As you know, after the Western States case vacated certain aspects of that law, FDA was on shaky legal ground with respect to trying to contain and implement that statute——

Mr. GRIFFITH. We know.

Dr. GOTTLIEB [continuing]. With the division in it.

Mr. GRIFFITH. I know, and, yes, that was, again, timid lawyering, because that just dealt with advertising. It didn't have anything to do with anything else, and it was not ruled, the question of severability was not ruled on by the Supreme Court.

Dr. GOTTLIEB. Right. I think what the agency would have said at the time was that it had a difficult time bringing cases under that statute, and we also at the time faced a lot of pressure from

Congress on the implementation of 503A. I think DQSA was not only a clarification of the statute and removed the offending provision, but was a clear declaration from Congress that you wanted the agency to be vigilant with respect to these——

Mr. GRIFFITH. No question about being vigilant. Just we didn't anticipate eliminating something that had been in practice under the existing law that we left as the existing law.

But, that being said, also, you showed the pictures of things you found as problems in compounding pharmacies, but you also found problems, which is why you do your job, in large manufacturers as well from time to time. Isn't that correct?

Dr. GOTTLIEB. Absolutely right.

Mr. GRIFFITH. Thank you very much. I yield back.

Mr. BURGESS. The gentleman yields back.

The Chair recognizes the gentleman from Texas for a unanimous consent request.

Mr. GREEN. Mr. Chairman, I would also like to ask the Commissioner to submit those slides for the record.

Mr. BURGESS. Without objection, so ordered.

[The information appears at the conclusion of the hearing.]

Mr. BURGESS. I do have one follow-up question that I feel compelled to ask. Because we are going to hear from a patient in the next panel, and Mr. Guthrie referenced—I think it was Mr. Whitfield's constituent in several Congresses ago who came and talked to us about losing a spouse after the Exserohilum infection that they acquired.

Does the agency have an opinion on when it is the duty of a physician or a surgery center or a hospital to inform a patient that they are receiving a medication from a compounding pharmacy as opposed to one of the other pharmacies?

Dr. GOTTLIEB. I don't have a view on that, Congressman. I have seen survey data with respect to that, I think including data that was developed by Pew. So, I know you have a witness who can speak to that, the development of that data, on the next panel.

As you know, there are labeling requirements for the products that are produced by the 503B facilities that provide warning information and certain disclosures, but not necessarily that it was a compounded product.

Mr. BURGESS. It doesn't escape me that the witness we had several Congresses ago, and likely the one we are going to hear from today, may very well tell us that they never had any idea what a compounding pharmacy was; they never heard of it before. And now, their lives have been seriously affected by——

Dr. GOTTLIEB. Well, I would say that, here again, I think this gets to the question of the prescription as a line of demarcation. Because if the prescription is the line of demarcation, if you are going into a 503A facility and getting a compounded product, you know that. If you are going into a doctor's office and you are getting a product from that doctor's office, and that was produced by a compounding pharmacy, not subject to sterility standards, you don't know that. That is why it is important, we believe, to have a mechanism in place to make sure that, when those products are being provided in that sort of de-identified way, because you no longer have that relationship to the pharmacist and understand

where and how that product was manufactured, that there are standards applied for sterility to how that product was developed.

Mr. BURGESS. I also appreciate your comments that this is all about patient safety, and that is why we all want to get it right. We may not agree on everything on the dais here, one side or the other, but we do want to get it right. And we appreciate your efforts in trying to help us get that right.

That will conclude the testimony from the first panel.

Again, we are very close to a series of votes on the floor. So, I am going to ask that we actually not take a break between panels. We will let Dr. Gottlieb gather his papers up and leave, and just take a second to put the nameplates out. But we probably better proceed directly into the second panel.

I call the subcommittee back to order.

Once again, as we transition to our second panel of witnesses, I do want to thank all of our witnesses for being here and taking time to testify before the subcommittee. Each witness will have the opportunity to give an opening statement, followed by questions from members.

Again, I will advise that we will recess when votes are called on the floor.

But today we are going to hear from Dr. George Williams, President-Elect of the American Academy of Ophthalmology; Dr. Bruce Brod, the Chairman of the Congressional Policy Committee for the American Academy of Dermatologists; Shawn Hodges, Vice President, International Academy of Compounding Pharmacists; Jacob Olson, the President and CEO of Skywalk Pharmacy, on behalf of the National Community Pharmacists Association; Jenn Adams, Senior Vice President, Clinical Product Solutions, PharMEDium Services; Molly Ventrelli, Vice President, Regulatory Affairs, Fresenius Kabi; Elizabeth Jungman, Director of Public Health of the Pew Charitable Trusts, and Nancy Dargan, a former patient of the New England Compounding Center.

We appreciate all of you being here today.

Dr. Williams, you are now recognized for 5 minutes for a summary of your opening statement.

STATEMENTS OF GEORGE WILLIAMS, PRESIDENT-ELECT, AMERICAN ACADEMY OF OPHTHALMOLOGY; BRUCE BROD, CHAIRMAN, CONGRESSIONAL POLICY COMMITTEE, AMERICAN ACADEMY OF DERMATOLOGISTS; SHAWN HODGES, VICE PRESIDENT, INTERNATIONAL ACADEMY OF COMPOUNDING PHARMACISTS; JACOB OLSON, PRESIDENT AND CEO, SKYWALK PHARMACY, ON BEHALF OF THE NATIONAL COMMUNITY PHARMACISTS ASSOCIATION; JENN ADAMS, SENIOR VICE PRESIDENT, CLINICAL PRODUCT SOLUTIONS, PHARMEDIUM SERVICES; MOLLY VENTRELLI, VICE PRESIDENT, REGULATORY AFFAIRS, FRESENIUS KABI; ELIZABETH JUNGMAN, DIRECTOR OF PUBLIC HEALTH, THE PEW CHARITABLE TRUSTS; AND NANCY DARGAN, FORMER PATIENT OF THE NEW ENGLAND COMPOUNDING CENTER

STATEMENT OF GEORGE WILLIAMS

Dr. WILLIAMS. Chairman Burgess, Ranking Member Green, and members of——

Mr. BURGESS. And do be sure your microphone is on and pull it close.

Dr. WILLIAMS. Is it working?

Chairman Burgess, Ranking Member Green, and members of the committee, I am honored to be testifying to you on behalf of the American Academy of Ophthalmology on a topic critical to the practice of ophthalmology.

My name is George Williams. I am a practicing retina specialist from Michigan. I am also the Immediate Past Secretary of the American Academy of Ophthalmology; Secretary of Federal Affairs, and current President-Elect for the Academy.

As the world's largest association of eye physicians and surgeons, the Academy seeks to protect sight and empower lives by setting standards for ophthalmic education, advocating for our patients and the public.

Access to safe and effective compounded repackaged drugs is vitally important to the practice of ophthalmology. This is due in large part to the uniqueness of our specialty, as we utilize drugs in dosage forms that differ from other areas of medicine. Effective treatment often requires that drugs be compounded or repackaged in concentrations or doses that are tailored to a patient's specific needs and unusual route of administration to the eye. These drugs are used in the successful treatment of several ophthalmological treatments, including diseases that threaten sight such as age-related macular degeneration.

Ophthalmology's treatment of patients facing sight-threatening diseases such as AMD requires access to drugs known as vascular endothelial growth factor inhibitors, or VEGF inhibitors. These include the FDA-approved anti-VEGF treatments ranibizumab and aflibercept, as well as repackaged bevacizumab, or Avastin. The Academy has long advocated for access to all three treatments, as individual patients may respond differently and have better outcomes with one treatment versus another.

Since the passage of the DQSA, the Academy's advocacy efforts have included focus on protecting access to repackaged Avastin. The Academy is aware of adverse event clusters associated with

intravitreal injections of repackaged bevacizumab, including events in Georgia and Florida. Events like these, along with the passage of the DQSA, have led to the necessary changes at compounding pharmacies and improvements in the safety of this treatment.

Because of our efforts since 2013 to track outcomes of patients who receive anti-VEGF therapies, we have been able to gather data on effectiveness and safety of these treatments. The American Academy of Ophthalmology utilized our IRIS registry, which is the nation's largest comprehensive eye disease clinical registry, to track adverse events associated with the use of these products from January of 2013 to June of 2016. These data clearly showed no statistically significant difference in adverse events among different anti-VEGF agents, including repackaged Avastin.

Today repackaged Avastin remains a safe and effective treatment option for patients facing sight-threatening disease, and Academy efforts to protect access are ongoing. The new guidance from FDA, which represented a step in the right direction, was recently finalized by the agency. The Academy will continue to engage with the agency, Congress, and compounding facilities to ensure patient access to repackaged bevacizumab.

The Academy is also concerned about continued access to other non-biologic compounds or drugs for office use. The FDA has issued final guidance on office use that we believe threatens access to compounded drugs for such use, requiring patient-specific prescriptions before a compounded drug can be distributed by a traditional compounding pharmacy. We are concerned that policy outlined in the final guidance forces practitioners to rely solely on outsourcing facilities to meet all of their needs for office-use drugs.

I would like to share a few examples of how implementation of the DQSA is having some unintended consequences, is impacting access to compounded and repackaged drugs. This is why the Academy is supporting policy that ensures access to drugs for office space use, such H.R. 2871, the Preserving Patient Access to Compounded Medications Act, introduced by Congressman Morgan Griffith.

I would like to discuss a patient from my state of Michigan. She is a 31-year-old lady who wears soft contact lenses and developed an infection in her eye. She was eventually determined to have a serious infection known as acanthamoeba keratitis. The standard treatment for this is the use of a drug called polyhexylmethyl biguanide. Essentially, this is pool cleaner. This was prescribed, but, unfortunately, it was not available in the state of Michigan. As a result, the patient's ophthalmologist in Michigan was forced to contact doctors at the University of Illinois-Chicago and to obtain the drug from Chicago. However, Chicago was unable to provide the drug in Michigan, and the patient, suffering from severe eye pain, was forced to drive 225 miles from Michigan to Chicago in order to obtain this therapy. Fortunately, she responded well. But this is an example of the type of problems we have when patients cannot access immediately important therapies.

The Academy has other examples of this involving the use of autologous serum drops that are given topically and have been used for more than three decades. These drugs are critical to the management of severe dry eye. However, due to compounding regu-

lations, many compounding facilities have stopped producing these drops.

In closing, ophthalmology strongly believes that compounded drugs must be produced safely and be subject to critically important testing. We do believe that regulatory policy in this arena can become restrictive and, in turn, negatively impact physicians' ability to properly and effectively treatment patients. It is important that, as implementation efforts move forward, the FDA strives to find a more balanced approach. We believe that increased direct engagement with the physician community is a strong path forward, and we look forward to future opportunities with FDA, Congress, and other stakeholders on these important issues.

Thank you.

[The prepared statement of Dr. Williams follows:]

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Statement for the Record

George Williams, MD

American Academy of Ophthalmology

U.S. House of Representatives Energy and Commerce Committee

Subcommittee on Health

Hearing

"Examining Implementation of the Compounding Quality Act"

January 30, 2018

Chairman Burgess, Ranking Member Green, and members of the Committee, I am honored to be testifying before you on behalf of the American Academy of Ophthalmology on a topic critical to the practice of ophthalmology. My name is George Williams, MD, and I am a practicing retina specialist from Michigan. I am also the immediate past Secretary for Federal Affairs and current President-elect for the Academy. As the world's largest association of eye physicians and surgeons, the Academy seeks to protect sight and empower lives by setting the standards for ophthalmic education and advocating for our patients and the public.

Background:

Compounded drugs play a vital role in the treatment of patients across medical specialties, including ophthalmology, dermatology, allergy and immunology, otorhinolaryngology, and others. Ophthalmology is a unique specialty that uses drug dosage forms not commonly used in other areas of medicine. These dosage forms include ophthalmic topical solutions, suspensions, ointments, and treatments that are injected into the eye. In addition, many drugs that are critical to the treatment of ophthalmology patients must be compounded or repackaged for concentration or dosage size, as drug manufacturers do not always make products appropriate for use in the eye. The use of compounded drugs is essential to the treatment of several ophthalmological conditions, including age-related macular degeneration, neovascular glaucoma, infectious endophthalmitis, bacterial corneal ulcers, and other potentially blinding infections and diseases. Compounded pharmaceuticals are also used in surgical settings, as well as for diagnostic office procedures.

Because of the frequent need for these treatments, ophthalmologists rely heavily on access to drugs for "office use" which is the provision and administration of a drug to a patient in the physician's office or other treatment setting without a patient-specific prescription. Having access to drugs for "office use" enables ophthalmologists to have these treatments readily available should patients arrive at the office in need of emergent care due to conditions such as severe infections. A delay in treatment, even by a few hours, can result in permanent vision loss. In other cases, such as the treatment of age-related macular degeneration (AMD), ophthalmologists need to have drugs on hand because they do not know whether a patient will need treatment until an examination can be performed.

The Academy actively engaged with Congress as it sought to create a new oversight structure for compounding pharmacies following the debacle with the New England

Compounding Center. Since the passage of the Drug Quality and Security Act (DQSA), the Academy has been working with ophthalmic subspecialty organizations to ensure continued access to compounded and repackaged drug products for ophthalmology. The Academy and other physician organizations have also tried to engage with the Food and Drug Administration as it has worked to implement the DQSA to maintain access to the treatments that our physicians, and more importantly, their patients need. Despite years of effort, we continue to hear from our members about difficulties they have accessing important compounded drugs. Therefore, this issue remains a critical priority for the Academy and we appreciate the opportunity to share our perspective on DQSA implementation efforts.

Repackaged Biologics:

The Academy has been a vocal advocate for policy that ensures access to all three, current vascular endothelial growth factor (VEGF) inhibitor treatments used by ophthalmologists in the treatment of our patients. This includes the FDA-approved anti-VEGF treatments ranibizumab and aflibercept, as well as repackaged bevacizumab. Availability of these products is critical to patients facing sight-threatening eye disease. We know that individual patients respond differently and may have better outcomes with one treatment versus another.

Since 2005, repackaged bevacizumab (Avastin) has been an essential treatment option for various blinding eye conditions such AMD, diabetic retinopathy, central retinal vein occlusion, neovascular glaucoma, and others. Its use in terms of efficacy and safety is supported by rigorous federally-funded evidence-based clinical research. Ophthalmologists have administered millions of repackaged bevacizumab injections to patients. In fact, during

2014 alone, the Academy estimates over four million injections were administered to patients. The Academy is aware of adverse event clusters associated with intravitreal injections of repackaged bevacizumab, including 2013 events in Georgia and 2014 events in Florida. Events like these, along with the passage of DQSA, have led to necessary changes at compounding pharmacies and improvements in the safety of repackaged bevacizumab.

Since the passage of DQSA, the Academy has tracked endophthalmitis rates within 15 days of an injection among patients with AMD who received anti-VEGF treatments, including compounded bevacizumab. The American Academy of Ophthalmology utilized our IRIS® Registry (Intelligent Research in Sight), which is the nation's largest comprehensive eye disease clinical registry, to track adverse events associated with use of these products from January 2013 to June 2016. The data showed no statistically significant difference in adverse events among different anti-VEGF treatments, including repackaged bevacizumab.

While we understand that the FDA does not factor cost considerations into its policy decisions, the potential financial impact of drugs is often an important consideration for patients. The price differential between the two branded products and repackaged bevacizumab is substantial. Patients may be financially unable to afford the co-insurance and deductible payments associated with the branded products. While the average Medicare beneficiary pays $11 (co-payment) for one treatment with repackaged bevacizumab, the same beneficiary would pay approximately $400 (co-payment) per dose of the FDA-approved alternatives. Many of these patients require monthly treatments. Patients who find it difficult to afford the more expensive alternative may have to make the choice to forgo treatment and will eventually lose vision. Currently, some patients lacking financial resources find access to the FDA-approved products through patient assistance

programs set up by the manufacturers. It is unlikely that these programs could handle the increased demand for approved products created by loss of access to bevacizumab.

If ophthalmology were to lose access to repackaged bevacizumab when medically appropriate, it could cost the Medicare program up to $2 billion per year as physicians are forced to use more expensive treatments.

In February 2015, FDA released Draft Guidance for Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application. The Academy expressed grave concerns over the impact of the policies included in the draft guidance on the ophthalmic use of bevacizumab. In its original draft guidance, the FDA proposed a maximum five-day beyond use date (BUD) for repackaged biologics. Traditionally, compounding pharmacies conduct sterility testing on each lot of repackaged bevacizumab for a period of roughly 14 days prior to shipment. The proposed 5-day BUD would have meant the repackaged drug would have expired before it left the facility or it would have required facilities to forego critical sterility testing which our members would have found to be unacceptable. The proposed 5-day BUD would have effectively ended ophthalmology's use of repackaged bevacizumab.

Fortunately, FDA has listened to the concerns raised by the Academy and other ophthalmology subspecialties. In January 2017, the FDA released an updated draft guidance, which created a pathway to a longer BUD for repackaged biologics in accordance with additional sterility testing outlined by the agency. The new guidance represented a step in the right direction and was recently finalized by the agency. While optimistic about the updated policy, it is important that outsourcing facilities have clarity from FDA with respect

to required testing to extend a repackaged biologic's BUD. The Academy will continue to engage with the agency, Congress and compounding facilities to ensure patient and physician access to repackaged bevacizumab is protected.

Prescription Requirement for 503A

The Academy is concerned about continued access to other, non-biologic, compounded drugs for "office-use. The FDA has issued final guidance on office-use that threatens access to compounded drugs for such use by requiring a patient-specific prescription before a compounded drug can be distributed by a traditional compounding pharmacy. We are concerned that policy outlined in the final guidance forces practitioners to rely solely on outsourcing facilities to meet all their needs for office-use drugs.

While we understand that outsourcing facilities can meet much of ophthalmology's needs, we know that the financial costs involved with testing and Current Good Manufacturing Practices (cGMP) compliance is an impediment to the production of all the compounded drugs ophthalmology relies on. These concerns stem directly from conversations with several outsourcing facilities that have conveyed doubts about their ability to prepare certain compounds that aren't traditionally ordered in bulk. Regardless of how critical these drugs are for patients; their business model is not to compound drugs at a financial loss. Facilities have also explained that in instances where they are willing to prepare small batch drugs to meet a given need, physicians and patients alike will face steep costs that may render many drugs unaffordable. The loss of access to these products is exceedingly

problematic, especially if they are used to treat urgent or emergent conditions, as a treatment delay of even a few hours can result in a patient suffering permanent vision loss.

As an example of the unintended consequences of this policy, I would like to share a story from one of our members treating patients in my home state of Michigan.

The patient is a 31-year-old woman who resides in the state of Michigan. She is a soft lens wearer and having developed eye pain, she saw a local provider and given a diagnosis of Herpes simplex keratitis. Initial cultures were negative but over the next week she developed radial perineuritis of her cornea, a sign highly suggestive of Acanthamoeba keratitis. Cultures of her contact lens case grew Acanthamoeba and compounded polyhexamethyl biguanide (PHMB) was prescribed. Unfortunately, the local Michigan pharmacy was not then able to compound PHMB and another source, Leiter's pharmacy in San Jose, CA, could not ship it to Michigan. The Michigan ophthalmologists contacted the University of Illinois at Chicago (UIC) Eye and Ear Infirmary and their cornea fellow talked with their pharmacy, which is very experienced with PHMB compounding. They were willing to supply the drug, but only within Illinois, and only if the patient registered as a UIC patient. The patient, then having extreme light sensitivity and severe pain, was driven from Livonia, Michigan to Chicago, 225 miles each way, by her husband. Fortunately, she responded well to PHMB treatment and regained full vision over the course of three months.

Stories like these are why the Academy has been so vocal on this issue and why we support policy that ensures access to drugs for office-use, such as H.R. 2871, the Preserving Patient Access to Compounded Drugs Act, introduced by Congressman Morgan Griffith. While we adamantly believe that compounded drugs must be manufactured safely and be subject to

critically important testing, there is a point where policy becomes restrictive and in turn negatively impacts a physician's ability to properly and effectively treat our patients. It is also important that we point out that ramifications stemming from access issues are exacerbated in more rural parts of the country.

The Academy, as well as other physician groups, has highlighted availability concerns to FDA both through written comment and during the agency's 2017 listening session with physician stakeholders. In a step towards increasing awareness of drug availability, the FDA recently released a product list of compounded drug products currently being provided by outsourcing facilities. While the Academy appreciates the release and update of the product list, it did not alleviate our previously mentioned concerns as many compounded ophthalmic drugs remain absent from the list.

In addition, I would note that according to the FDA's list, some of the compounded drugs used by ophthalmology are only being made by a single facility. This raises questions regarding the ability of that facility to meet ophthalmology's needs nationwide. We are concerned that dependence on a single facility leaves physicians and patients vulnerable to supply interruptions should that facility's production encounter technical difficulties or is perhaps impacted by a natural disaster. There is also the potential for inflated costs to obtain the drug. Ophthalmology's recent experiences with ophthalmic drugs in the generic market, including rapid price increases and shortages, have made the Academy sensitive to these types of problems.

The Academy hopes to discuss ways to improve future updates of the product list with the agency, including ways to include more real-time information, detailing contact information for facilities, pricing, and other information that would improve awareness and timely acquisition of available products.

Physician In-Office Compounding

The Academy is also concerned about FDA policy that may infringe upon physician in-office activities, including reconstitution of botulinum toxin with an anesthetic. These are low risk activities that have been performed in physician offices for years without increasing odds of adverse events. The FDA, as well as the United States Pharmacopeia, has expressed concern over such activities elevating risks to patients but these concerns are not supported by credible data. In fact, the Academy tracked 91,623 botulinum injections between 2013 and 2016 through its IRIS data registry with only 61 potential adverse events.

While we understand that compounding activities, specifically sterile compounding, should not be undertaken in a physician's office, minor office preparation activities that have been a safe and effective part of patient care should not be considered compounding activities by regulatory bodies. The Academy believes that any efforts to include these activities under the definition of compounding are misguided and will be detrimental to patient care.

Engagement with Physician Community

As DQSA implementation efforts move forward, we urge the FDA to make additional strides in engaging with the physician community and for the agency to be more proactive in finding avenues to incorporate physician perspectives. While the FDA has convened stakeholder "listening sessions," the limited time allocated to those sessions have not always allowed for substantive discussion of the issues of concern to the physician community. It has also been challenging for many stakeholders to engage the FDA in one-on-one discussions. The inability to communicate directly with agency leadership and DQSA implementation staff on these issues has been a major source of frustration for the stakeholder community.

Additionally, given our specialty's heavy reliance on compounded and repackaged drugs, the Academy has been disappointed that an ophthalmologist has not been selected to serve on the FDA's Pharmacy Compounding Advisory Committee (PCAC).

Closing Remarks

Despite serious concerns about implementation policy, we remain tremendously supportive of efforts by Congress and FDA to improve the safety of compounded drug products. As implementation efforts move forward, we would urge a greater emphasis on ensuring policy that promotes patient safety does not do so at the expense of patient access to these vital treatment options.

The Academy stands ready to work with any and all stakeholders on efforts to improve implementation of the law and ensure compounded drugs remain safe and effective treatment options for our patients. On behalf of the Academy and the ophthalmic community, I thank you for your time in allowing me to discuss this critically important issue. I look forward to your questions.

Mr. BURGESS. Thank you, Dr. Williams.

Dr. Brod, 5 minutes for an opening statement, please.

STATEMENT OF BRUCE BROD

Dr. BROD. Thank you, Chairman Burgess, Ranking Member Green, and members of the Health Subcommittee.

I am Dr. Bruce Brod. I am pleased to share with you my perspective as a dermatologist, a view that is shared by the American Academy of Dermatology Association.

Dermatologists rely heavily on compounded medications that are medically necessary and life-changing. We safely and effectively prepare and administer low-risk topical and intralesional compounded medications to a wide range of patients, including individuals presenting with special and emergent needs and persons suffering from rare diseases, including children.

Current policy adversely affects the practice of medicine in two significant ways, the first being with respect to maintaining a small supply of office-use compounded medications for administration to patients in our offices. Dermatologists have historically obtained compounded medications from 503A compounding pharmacies for immediate use in the office without the need for a patient-specific prescription. However, current policy now restricts this. While we understand the FDA intended 503B outsourcing facilities to be a meaningful resource for providing physicians with office-use stock, not all office-use compounded medications used by dermatologists are produced by 503Bs, including non-sterile topicals as well as sterile intralesional drugs used for injection in the skin.

The FDA's website reflects a partial list of drugs that registered outsourcing facilities have reported producing, starting December 2016, but ending May 2017. So, the list is retrospective and it is incomplete, and it doesn't indicate if these drugs will be produced in the future. Furthermore, we have no indication that 503Bs will provide flexibility in the various concentrations that we use in our offices.

The FDA lists only the facilities that are registered. Yet, it doesn't contain any contact information, real-time product availability information, or price listing. So, physician practices literally must go on a scavenger hunt for these needed compounds. In addition, dermatologists have reported that the outsourcing facilities have quoted prices that are cost-prohibitive.

If a compounded drug is not available from an outsourcing facility, a patient now requires, first, a trip to the physician office for evaluation and diagnosis, then a trip to the pharmacy to obtain the prescription, and then, thirdly, a followup visit back to the physician to finally have the treatment administered. Those two additional steps impose new burdens on the patient, delayed treatment, and create inefficiencies in our practices.

When compounded medications are handled outside of a provider's control, there are also major safety concerns regarding proper storage, handling, and application. When the dermatologist cannot be sure how it has been stored between patient pickup at the pharmacy and administration in the office, it calls into question the integrity of the medication.

An additional safety concern is the risk that patients may be tempted to self-administer the drugs prior to returning to the physician's office. Many of the powerful compounds in dermatology are used to destroy unwanted malignant and benign skin lesions. And so, if they are spilled on the skin by patients, they will cause scarring and disfigurement.

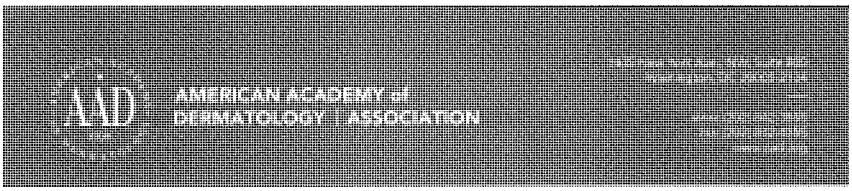
The second way current policy adversely affects the practice of medicine pertains to dermatologists' preparation of low-risk sterile and non-sterile medications in the office setting. Because of the FDA's broad definition of compounding, many simple in-office preparations are considered compounding. Buffering lidocaine, for example, is a widely-used local anesthetic in dermatologic procedures. Without our ability to buffer lidocaine with sterile sodium bicarbonate, patients, including children, will endure painful injections of lidocaine. Using the buffered lidocaine allows us to perform very extensive skin cancer surgeries in an outpatient office setting without the risks and costs of sedation.

Because the FDA considers reconstituting certain FDA-approved neurotoxins with sterile saline to be compounding, the FDA's proposed guidelines imply that physician offices are compounding facilities, subject to the same equipment and process requirements as high-volume compounders. Many of those requirements are simply unworkable for dermatology offices, both structurally and financially.

Accordingly, we are encouraged that the FDA mentions routine clinical practice and negligible patient risk in its 2018 Compounding Policy Priorities Plan, which states that providers would not be subject to the same compliance policy in certain cases. The manner in which we routinely buffer and dilute our injectable medications in dermatology is really part of our normal practice of medicine.

While we greatly appreciate the FDA and U.S. Pharmacopeia are working with medical specialties to explore an urgent-use exemption, we have real concerns that an exemption based on a restrictive timeframe will negatively affect patient access. The well-being of our patients is our primary concern and responsibility. On behalf of the American Academy of Dermatology Association, I want to thank you for holding this hearing, and I am happy to address any questions.

[The prepared statement of Dr. Brod follows:]



Statement for the Record

Bruce A. Brod, MD, FAAD

American Academy of Dermatology Association
Chair, Congressional Policy Committee

Hearing

Examining Implementation of the Compounding Quality Act

Subcommittee on Health

House Committee on Energy & Commerce

U.S. House of Representatives

January 30, 2018

Introduction

Thank you, Chairman Burgess, Ranking Member Green, and members of the Health Subcommittee for the opportunity to appear before the Committee at this hearing entitled "Examining Implementation of the Compounding Quality Act," and to speak about the importance of physician access to compounded medications to treat dermatology patients. My name is Bruce Brod. I am a board-certified dermatologist on staff at the Hospital of the University of Pennsylvania, and a clinical professor at the University's Perelman School of Medicine. I currently serve on the Board of Directors of the Pennsylvania Academy of Dermatology and Dermatologic Surgery, and as chair of the American Academy of Dermatology Association's Congressional Policy Committee. I was also in private practice for 22 years in Lancaster, Pennsylvania.

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My testimony will focus on ways the Drug Quality & Security Act (DQSA) has adversely affected the practice of medicine for dermatologists in two significant ways: first, (1) with respect to maintaining a small supply of office-use compounded medications for administration when patients present; and second, (2) when dermatologists prepare low-risk sterile and non-sterile medications in the office setting.

The Academy appreciates the Committee's efforts to maintain the safety of compounded medications in wake of the meningitis outbreak from contaminated sterile drugs compounded by the New England Compounding Center that tragically resulted in dozens of deaths and hundreds of injuries. As physicians, we take an oath to "first do no harm." The well-being of our patients is our primary concern and responsibility, and having a safe supply of medications with which to treat our patients is of utmost importance.

During the drafting process of the DQSA in 2013, the Academy engaged with staff from your Committee and the Senate HELP Committee so that a final legislative solution not only provided a safe drug supply, but also would not interfere with the practice of medicine. We appreciated the public statements of Chairman Burgess, Ranking Member Green, and others that noted the importance of maintaining patient access to office-use drugs and ensuring that compounding regulations should not interfere with the practice of medicine.

Dermatologists diagnose and treat more than 3,000 skin, hair and nail diseases, including many that are chronic and disabling. We rely heavily on compounded medications that are not only medically necessary, but life changing. For decades, dermatologists have safely and effectively prepared and administered low-risk topical and intralesional compounded medications to a wide range of patients, including individuals presenting with special and emergent needs, persons

suffering from rare diseases, and children. We have a long and consistent record of safely and effectively prescribing and administering compounded medications in a clinical setting. The administration of compounded medications is not only a common type of treatment, but it is an essential component of many dermatology practices. It is critical to a dermatologist's ability to provide proper and timely care for our patients, which can result in better outcomes and lower health care costs.

Office-use Compounded Medications

In accordance with state law, dermatologists have historically obtained compounded medications from section 503A compounding pharmacies prior to receipt of a patient-specific prescription for administration to patients within their own offices, a practice referred to as "office-use." Dermatologists rely on and value the relationship with 503A compounding pharmacies to help meet our patients' needs. However, the Food & Drug Administration's (FDA) December 2016 final guidance on the *Prescription Requirement under 503A of the Food, Drug and Cosmetic Act* restricts 503A compounding pharmacies from providing office-use compounded medications prior to receipt of a patient-specific prescription. This limits physicians' access to important compounded medications.

While we understand the FDA intended for the newly created 503B outsourcing facilities to be a meaningful resource for providing physicians' office-use stock, in practice, these outsourcing facilities have not been able to meet all the needs of physicians and our patients. Less than 75 outsourcing facilities are registered with the FDA. The FDA's website lists only the facilities that are registered, but with no contact information, no real-time product availability information, and no price list. Physician practices have the administrative burden of going on a scavenger hunt to seek this

information. In addition, dermatologists have reported that the outsourcing facilities have quoted prices that are cost prohibitive. We also have no indication that 503B outsourcing facilities will provide flexibility in the various concentrations that we use in our offices, flexibility that had been guaranteed by the 503A compounding pharmacies.

Dermatologists rely on compounding pharmacies to produce compounded medications to meet their patients' needs. These compounded medications include non-sterile topicals used to treat warts, molluscum contagiosum, disfiguring birthmarks, skin cancer, alopecia areata, hyperpigmentation, psoriasis, and cutaneous T-cell lymphoma, among others, as well as intralesional drugs which are injected directly to areas of skin affected by skin cancer and sexually transmitted diseases. Recently, the FDA made public a list of compounded medications that entities listed as FDA-registered outsourcing facilities reported producing between December 2016 and May 2017. The list is retrospective, and it does not indicate if these drugs will be produced in the future. Furthermore, as the FDA indicates, not all outsourcing facilities have submitted their product list, the list is not neither exhaustive nor even complete.

The unintended consequence of the restrictive interpretation of the DQSA is limited and/or delayed access to needed treatments, which could ultimately result in increased patient morbidity. It can also result in unnecessary increases in health care expenses for both patients and the health care system, or no care at all.

If a compounded drug is not available from an outsourcing facility, under the FDA's final guidance requiring a patient-specific prescription for access, what could previously have been treated in one office visit now requires: 1) a trip to the physician office for evaluation and diagnosis, 2) a trip to the pharmacy to obtain the prescription, and 3) a follow-up visit to the physician office to

finally have the treatment administered. These two additional steps are not only inefficient for the physician practice, but also impose new burdens on the patient and delays in patient care. The patient is now confronted with an additional co-pay for a specialist office visit, which may be difficult to schedule to begin with, as well as the possibility of further missed school for a child or work time for an adult.

These hurdles undermine timely treatment and continuity of care. They increase the risk of non-adherence as well as the risk that patients will not attend follow up visits. The patient's condition could persist without the necessary care and treatment, which is safe and effective and, in most cases, inexpensive.

When compounded medications are outside a provider's chain of control, there are safety concerns regarding the proper storage, handling, and application that need to be considered. Some compounded medications require certain temperature and storage restrictions. When a provider does not maintain control of the medication and cannot be sure how it has been stored between the time the patient picks it up at the pharmacy and then returns to the physician's office for administration, there is no guarantee regarding the integrity of the medication. For example, if stored at a high temperature, there are risks of inactivating the active ingredients of Betacaine-Lidocaine-Tetracaine (BLT), a topical anesthetic.

Many compounded medications should only be administered by a licensed health care professional in an office setting. As many of the compounded medications are used topically to destroy unwanted skin lesions, there are certain risks if accidentally applied to normal areas of skin. Patients may cause harm or permanent disfigurement should they administer these drugs themselves. As such, they should be administered by the dermatologist. For example, cantharidin

can burn healthy skin and squaric acid can cause severe allergic contact dermatitis if applied improperly. A topical bleaching cream of hydroquinone, retinoid and steroid used to treat melasma, which is a pigmenatary disorder common in women, and other pigment disorders can cause permanent blue-black pigmentation if not stored or handled properly, and should be applied only for a limited duration.

Another reason a health care provider should directly supervise the application of certain compounded medications is that systematic lidocaine toxicity can occur if a numbing cream is applied for too long or over a large surface area of the skin. Seizures, cardiac arrest, and death have occurred in otherwise healthy individuals who applied this numbing cream without proper supervision of a licensed medical professional prior to certain medical procedures.

In-Office Preparations

A second unintended consequence of the DQSA having an adverse impact on patient access occurs with in-office preparation of drugs. Because the FDA's definition of compounding -- "combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient" -- is broad, many in-office preparations are considered compounding and are being subject to scrutiny though they are very simple and low risk.

A widely used local anesthetic in surgical dermatologic procedures is lidocaine buffered in the clinical setting with epinephrine and/or sodium bicarbonate. Common practice is to add sodium bicarbonate to manufactured lidocaine with epinephrine to decrease the pain of delivery, especially for children and patients requiring extensive outpatient skin cancer surgery. This allows us to perform more extensive skin cancer surgeries in a more cost effective outpatient setting, also negating the need for higher volumes of anesthesia. We have buffered lidocaine syringes readily available, as

many are used each day when patients present and are in need of in-office surgical treatment and important diagnostic biopsies. Given the shortage of manufactured lidocaine with epinephrine, dermatology practices must resort to adding epinephrine to lidocaine and other local anesthetics themselves for pain control and vasoconstriction.

Simple in-office preparations are considered "compounding" as opposed to mixing when the medication is not prepared pursuant to the manufacturer's labeling (e.g., reconstituting certain FDA approved neurotoxins with sterile saline for the treatment of hyperhidrosis). As a result, low-risk, low-volume, in-office preparations are subject to the FDA's guidance on *Insanitary Conditions at Compounding Facilities*, which is currently in draft form. Under this draft guidance, the FDA proposed that physician offices be considered a "compounding facility" subject to the same equipment and process requirements as high-volume compounders. Many of these proposed requirements, which include International Organization for Standardization Class 5 (ISO 5) area (including laminar flow hood), and gowning apparel (e.g., sterile gowns, gloves, mask, foot covers), are simply unworkable for dermatology offices both structurally and financially.

The activities we are performing should be considered the normal practice of medicine. While the FDA and U.S. Pharmacopeia are working with medical specialties to explore an urgent use exemption, we have real concerns that patient access will be harmed by an exemption based on a restrictive timeframe or that remains overly burdensome. For example, peer reviewed journal articles show that buffered lidocaine and reconstituted botulinum toxins are safe for patient use for up to four weeks, assuming that current aseptic practice is followed.

We are appreciative that the FDA's 2018 Compounding Policy Priorities Plan mentions that the agency will publish revised draft guidance and address concerns we raised about these low-risk

practices. The FDA stated it plans to define the circumstances in which mixing drugs and applying them in a manner that is low risk would not be subject to the same requirements as its risk-based approach. We look forward to working with the FDA to ensure that requirements imposed on providers do not adversely impact patient access.

On behalf of the American Academy of Dermatology Association and its member dermatologists, I thank you for holding this hearing, and for your commitment to maintaining timely access to safe and effective compounded medications. The Academy looks forward to working with you as you address the unintended interference on the practice of medicine and patient access.

Mr. BURGESS. Thank you, Dr. Brod.

Mr. Hodges, you are recognized for 5 minutes, please.

STATEMENT OF SHAWN HODGES

Mr. HODGES. Yes, sir. Yes, sir. Good afternoon, committee members.

Mr. Chairman and members of the subcommittee, my name is Shawn Hodges, a pharmacist and owner of Innovation Compounding, a compounding-only pharmacy located in Kennesaw, Georgia, just outside of Atlanta. I also serve as the Vice President of the International Academy of Compounding Pharmacists, IACP, an organization that represents more than 4,000 pharmacists, technicians, students, and members of the compounding community who focus on the specialty of pharmacy compounding. I would like to express my gratitude and appreciate to the Health Subcommittee for taking the time to understand compounding pharmacy and patient access issues from a pharmacist's perspective with the implementation of DQSA.

In 2012, a pharmacy owner who lost sight of his moral compass and violated his oath as a practicing pharmacist violated both state and Federal laws and regulations related to quality and safety. As a result, more than 60 lives were lost and hundreds more fell ill, some to this day, nearly 5 1A½ years later. As compounders, our top priority is adhering to the highest-quality compounding standards to prevent something like this from happening again.

Since NECC, all regulatory bodies have made a concerted effort to improve the practice of pharmacy. In November of 2013, the DQSA was signed into law, somewhat clarifying the FDA's joint authority with the state boards of pharmacy, to monitor the quality of pharmacy compounding. State boards of pharmacy also updated pharmacy regulations and hired additional state inspectors to monitor and inspect compounding pharmacies. USP, the organization that sets the standards for governing compounding pharmacies, is revising its standards to continue to ensure best practices of pharmacy compounding, which can reduce the risk of harm to patients and compounding pharmacy employees.

As DQSA is well into its fourth year, I would also like to share with the committee what the professional compounding pharmacy has experienced and provide suggestions on how all pharmacies, state boards, and the FDA can actually strengthen DQSA while protecting access to lifesaving compounded preparations. As I rely the suggestions of IACP and other key pharmacy stakeholders, please note that our overall goal is to encourage an open, transparent dialog with all stakeholders, public and private. We strive to work closely with FDA in developing an appropriate balance between regulating quality and safety without eliminating patient access.

Pharmacies which are compliant and meet USP guidelines and state board of pharmacy rules fear that FDA overreach will impact patient care. This fear has been substantiated by actions of FDA investigators. My pharmacy team experienced this firsthand in an FDA inspection that lasted for 11 days over a period of 4 months.

It is important to acknowledge that the FDA investigations were fulfilling their assigned duties and expressed a keen interest in the

quality of our preparations. For that, I had the utmost respect for them. However, many requests about our pharmacy had little to do with the quality of our compounded preparations, but were, rather, in how we operated our pharmacy practice that is regulated by the boards of pharmacy. Luckily, our pharmacy team employed attorneys who are knowledgeable of both state and Federal pharmacy laws and regulations to advise FDA that they were inspecting outside the scope given to them under the law. Many of our fellow compounding pharmacists have had similar experiences.

I would also like to share IACP's concerns as it relates to the memorandum of understanding between FDA and the states, which could limit patient access for preparations that are only available across state lines. Last week we were encouraged by Commissioner Gottlieb's 2108 Compounding Policy Priorities Plan that states he would rescind the current draft MOU and prepare a new draft for public comment. However, we still remain concerned that the FDA proposes to define distributing and dispensing as one and the same. As noted in all other Federal and state regulations, these are two distinct activities. If this is not corrected, the impact on patient access to medications will be detrimental, particularly for patients near state borders who rely on compounded medications from neighboring states.

Another of our primary considerations for review is the role of office-use compounding. I regularly hear from prescribers who need compounded medications for office use that they cannot obtain from outsourcing facilities in small dosages necessary to expeditiously meet patients' needs. The fundamental concept of office use from 503A pharmacies offers solutions to prescribers who are faced with unique challenges, whether a dentist needs a fast-acting, liquid anti-anxiety drug on hand in case an autistic child may have a panic attack or a hospice nurse that suddenly needs a compounded nausea medication because she has terminally-ill patient who is not responding to a manufactured product. The purpose of office use is to support prescribers who otherwise do not have access to a GMP product.

In closing, we at IACP want to be clear that our goal isn't to interfere with FDA's inspections on quality, but to ensure that FDA investigators who inspect compounding pharmacies are aware of and spec within the boundaries of FDCA. They also must have a working knowledge of USP standards and relevant state regulations. Likewise, we don't seek to weaken the DQSA in a way that will allow pharmacies to operate as drug manufacturers. Our goal is to have an open and consistent dialog with Congress and the FDA to establish policies that more effectively balance patient safety with patient access, because patient access is a patient safety issue.

We thank you for the opportunity to appear here today and provide our input, and we do look forward to continuing to work with you on these common goals.

[The prepared statement of Mr. Hodges follows:]

January 24, 2018

The Honorable Dr. Michael Burgess
Chairman, Subcommittee on Health
Energy and Commerce Committee
U.S. House of Representatives
Washington, D.C. 20515

The Honorable Gene Green
Ranking Member, Subcommittee on Health
Energy and Commerce Committee
U.S. House of Representatives
Washington, DC 20515

RE: Testimony Submitted for Health Subcommittee Hearing on DQSA Implementation

Dear Chairman Burgess, Ranking Member Green and Members of the Health Subcommittee:

On behalf of the IACP Board and our members, we thank you for holding this subcommittee hearing on the important issues surrounding the Drug Quality and Security Act of 2013 (DQSA), and for the opportunity to submit our organization's input.

IACP is an association representing more than 4000 pharmacists, technicians, students, and members of the compounding community who focus on the specialty practice of pharmacy compounding. Compounding pharmacists work directly with prescribers including physicians, nurse practitioners and veterinarians to create customized medication solutions for patients and animals whose health care needs cannot be met by manufactured medications.

Every day, compounding pharmacists serve patients in a variety of areas including: autism, oncology, dermatology and pediatrics, in a variety of practice settings including hospice in-patient units, emergency rooms, surgical centers, physician clinics, and even Federal Facilities like the VA. Compounding pharmacists also have served patients such as pre-term infants who require parenteral nutrition (PN). PN provides intravenous lifesaving therapy for patients whose gastrointestinal (GI) tracts are not functioning or cannot be accessed, or where nutritional needs cannot be met with oral or enteral diets. These are just a few examples of how compounding pharmacists are working with physicians to provide life-saving medications for patients.

Again, we thank you for including IACP in this important hearing and for the opportunity to provide the subcommittee with our input. We look forward to working with you on compounding pharmacy policies that protect both patient safety and patient access to critical medications.

Sincerely,

Erik Tosh, D.Pharm, FIACP, FACA

IACP President

Executive Summary:

For over three years, IACP has worked with a coalition of over 30 prescriber and pharmacy organizations (the "DQSA Coalition") on issues related to the Food and Drug Administration's implementation and enforcement of the Drug Quality and Security Act of 2013. IACP and the other member organizations of the DQSA Coalition have worked to provide stakeholder input directly to the FDA and through Congress to improve patient safety and patient access to compounded medications. In certain areas, we believe the FDA is overstepping the regulatory authority given to the agency by Congress in the Federal Food, Drug and Cosmetic Act as amended by the DQSA and infringing upon the traditional role of state boards of pharmacy in the regulation of the practice of pharmacy. We strongly endorse bipartisan legislation, HR2871, the *Preserving Patient Access to Compounded Medications Act,* by Rep. Griffith (R-VA) and Rep. Cuellar (D-TX) as a needed clarification of the DQSA that will better delineate the practice of pharmacy from drug manufacturing.

While encouraged by some of the intended policy changes announced in the "2018 Compounding Policy Priorities Plan" released by the FDA, IACP is hopeful that this hearing will result in improved dialogue between the FDA and stakeholders, and that future FDA compounding policies will better reflect the input the Agency has received from prescribers and pharmacists. Our written testimony for this hearing of the Health Subcommittee is focused on the following policy areas:

- Office-use compounding pursuant to state pharmacy laws and regulations;
- The draft sample MOU between FDA and states on interstate distributions;
- Appropriate inspection standards for compounding pharmacies;
- Compounding with dietary supplements;
- Policymaking through Guidance for Industry instead of rulemaking;
- The Pharmacy Compounding Advisory Committee (PCAC).

Introduction:

IACP understands and supports the need to protect public health and safety through strong laws and regulations that provide appropriate oversight over both drug manufacturing and the practice of compounding pharmacy. It is also critical that those laws establish clear and definitive lines between compounding and manufacturing and whether state boards of pharmacy or the Food and Drug Administration (FDA) are the appropriate regulators over those distinct activities. Although it was a goal of Congress in passing the DQSA to better brighten this line and improve patient safety and access to compounded medications, in many ways the law has unfortunately had the unintended consequence of providing less clarity to pharmacists, state boards of pharmacy and medical providers, and in addition jeopardizing patient access to critical, often life-saving compounded medications.

Rather than working with stakeholders through the formal rulemaking process to implement the DQSA and establish compounding policies that balance public safety with patient access and adhere to the law's statutory language and congressional intent, the FDA has instead issued draft guidance for industry (GFI) documents that are often in conflict with the statute and congressional intent, and then finalized without any reflection of the stakeholder input received from providers and pharmacists. These GFI documents are treated by the FDA as though they have the weight of law or regulation, which they do not, and are used by the FDA to establish federal violations that lead to state licensed and compliant "503A" pharmacies being inspected under drug manufacturer standards rather than standards established by state pharmacy laws and regulations.

IACP was hopeful that a new Administration and new FDA Commissioner would lead to a reset of the agency's policies that stress the importance of compounding a high-quality preparation, rather than displacing the role of state boards of pharmacy in regulating the practice of compounding. Unfortunately, we have yet to see any significant movement away from the policies of the last Administration, nor have we seen a willingness to work with stakeholders towards improving the FDA's compounding policies to better reflect the practice of medicine and pharmacy in the real world, and the state laws and regulations that regulate those professions.

For over three years, IACP has been working with a coalition of more than 30 pharmacy and provider organizations (the "DQSA Coalition") on the issues our members and their patients are having with FDA's implementation and enforcement of the DQSA. The DQSA Coalition was pleased and encouraged when bipartisan legislation, HR2871, *The Preserving Patient Access to Compounded Medications Act,* was introduced by Rep. Morgan Griffith (R-VA) and Rep. Henry Cuellar (D-TX) in June of last year. This legislation, which now has 43 cosponsors, would address several of these issues and amend the DQSA in a way that would better clarify state and federal regulatory authority over compounding, and better balance patient safety and patient access to critical medications. HR2871 has been endorsed by 50 national and state pharmacy and medical provider organizations.

IACP strongly recommends that HR2871 be voted out of this committee and the full House and Senate this year and we look forward to working with you on that process. In the meantime, and for purposes of this subcommittee hearing, we appreciate the opportunity to provide our input on several specific policies the FDA has adopted in implementing and enforcing the DQSA that we and other organizations believe is contrary to the language of the law and its congressional intent, and that is unnecessarily jeopardizing patient access to critical medications.

Office-Use Compounding:

"Office-Use Compounding" refers to a pharmacist, pursuant to state pharmacy laws that authorize the practice, compounding a limited quantity of a medication that medical necessity requires be administered in an office or clinical setting by the prescribing physician and transferring the drug to the physician for administration to the patient. The majority of state pharmacy practice acts and related state regulations authorize some form of office-use compounding, usually as an exception to the prescription requirement under state law. IACP and multiple other organizations representing pharmacists and the providers who prescribe and treat their patients with compounded medications have provided the FDA with input as to the medical necessity of the administration of compounded medications by providers in office or clinical settings. The Congress has

weighed in on multiple occasions and in multiple ways (including statements in the congressional record, letters, and directives in appropriations bills that are enclosed in this submission) to remind the FDA that the DQSA was not intended to prohibit office-use compounding and does not preempt state laws that authorize office-use compounding. Indeed, appropriators have been very clear with the FDA in asserting congressional intent on the issue of office use. Relevant language in the House Reports accompanying the FY2016 and FY2017 Omnibus Appropriations Acts, as well as House Report language in the FY2018 FDA/Ag Appropriations Act is as follows:

Omnibus Appropriations Act: House Report 114-205, FY 2016:

> *The Committee is concerned that, since passage of the Drug Quality and Security Act (DQSA) of 2013, the FDA has interpreted provisions of Section 503A of the FDCA in a manner inconsistent with its legislative intent and with the agency's own previous positions. Specifically, the FDA has taken the position that under 503A, a pharmacist may not compound medications prior to receipt of a prescription and transfer the drugs to a requesting physician or other authorized agent of the prescriber for administration to his or her patients without a patient-specific prescription accompanying the medication. This practice, which is often referred to as `office-use' compounding, is authorized in the vast majority of states and was intended to be allowable under DQSA. The Committee is aware that in 2012, prior to passage of the DQSA, FDA was working on a draft compliance policy guide for 503A of the FDCA that provided guidance on how `office-use' compounding could be done consistent with the provisions of 503A. The Committee understands the intent of the DQSA was not to prohibit compounding pharmacists from operation under existing 503A exemptions; therefore, the Committee directs the FDA to issue a guidance document on how compounding pharmacists can continue to engage in `office-use' compounding before the receipt of a patient-specific prescription consistent with the provisions of 503A within 90 days after the enactment of this Act. (P.67)*

Omnibus Appropriations Act: House Report 114-531, FY 2017:

The Committee believes patient access to the right drug at the right time is of utmost importance. In instances where a commercially manufactured drug is not appropriate for a patient for a specific reason, a compounded drug may be the difference between life and death. Since passage of the Drug Quality and Security Act (DQSA) of 2013, the Committee has had concerns that the FDA interpreted provisions of Section 503A of the FDCA in a manner that might jeopardize the availability of compounded medications for "office use". The practice of "office use" occurs when a compounder will compound a batch of drugs in anticipation of receiving patient-specific prescriptions at a later time. It may also be the case of a doctor in his or her office maintaining compounded drugs on site because it is unsafe or impractical to issue a traditional prescription. This practice is authorized in the vast majority of states and was intended to be allowable under DQSA. The Committee is aware that on April 15, 2016, FDA released a new Draft Guidance on the issue of "office-use" compounding. The Committee directs the FDA to issue a Final Guidance that provides for "office-use" compounding of drugs, in appropriate circumstances as well as including drugs compounded in anticipation of a prescription for an identified individual patient. Such "anticipatory" compounded drugs must be based on the history of previous valid compound prescription orders, and on an established history between the prescriber and the patient and the compounder. (p 68-69)

House Committee Report to FY 2018 FDA/Ag Appropriations Bill:

The Committee continues to believe that patient access to the right drug at the right time is of utmost importance. In instances where a commercially manufactured drug is not appropriate for a patient for a specific reason, a compounded drug may be the difference between life and death. Since passage of the Drug Quality and Security Act (DQSA) of 2013, the Committee has had concerns that the FDA interpreted provisions of Section 503A of the FDCA in a manner that might jeopardize the availability of compounded medications for "office use". The practice of "office use" occurs when a compounder will compound a batch of drugs in anticipation of receiving patient-specific prescriptions

at a later time. It may also be the case of a doctor in his or her office maintaining compounded drugs on site because it is unsafe or impractical to issue a traditional prescription. This practice is authorized in the vast majority of states and was intended to be allowable under DQSA. The Committee directed the FDA to issue a Final Guidance that provides for "office-use" compounding of drugs, in appropriate circumstances as well as including drugs compounded in anticipation of a prescription for an identified individual patient. Such "anticipatory" compounded drugs is based on the history of previous valid compound prescription orders, and on an established history between prescriber, patient and compounder. Despite clear directives in previous reports accompanying FDA's appropriations bills for the agency to finalize guidance that authorizes office-use compounding, in December of 2016, the FDA finalized a Guidance for Industry (GFI) entitled "Prescription Requirement Under Section 503A of the FDCA," which expressly prohibits office-use compounding. The Committee directs the FDA to rescind this GFI and issue a proposed rule, subject to the notice and comment provisions in the Administrative Procedure Act. The proposed rule should be consistent with Congressional intent as stated in both Appropriations Reports and the DQSA, and that also allows for office-use compounding as authorized by state law. In the proposed rule, FDA should lay out the means by which office use is permissible while addressing such critical safety matters, such as maintaining controls on quantity and safety issues such as those related to office stock shelf life. Lastly, FDA's clarification on the line between traditional compounding and outsourced compounding will support state regulators, outsourcing facilities, and traditional compounders in their efforts to ensure that patients have access to safe compounded drugs while reducing the risks associated with sterile drugs produced in bulk. (page 67)

Yet, the FDA continues to ignore stakeholders and the Congress and substitute the agency's desired regulatory authority over compounding pharmacies for the authority actually given to the agency under the law. Stakeholders and the Congress have repeatedly reminded the FDA that in 2012, prior to passage of the DQSA,

the agency circulated a draft compliance policy guidance that would have allowed for office-use compounding under 503A of the FDCA, with some restrictions. The relevant statutory language of 503A was not changed by the DQSA, yet the agency now takes the position that the same statutory language prohibits office-use compounding by 503A pharmacies under all circumstances, even where expressly authorized by state law.

Similar to most, if not all, state and federal statutes governing the practice of pharmacy, the statutory language of Section 503A of the FDCA requires that drug products compounded by pharmacies must be *"for an identified individual patient based on the unsolicited receipt of a valid prescription order..."* However, this language does not speak to the timing of the prescription, and there are always statutory and regulatory exceptions to the prescription requirement based on the realities of medical practice and the needs of patients.

Indeed, Section 503A also clearly allows for "anticipatory" compounding *"in limited quantities before the receipt of a valid prescription order for such individual patient."* Additionally, Section 503A gives the FDA regulatory authority over the *"distribution of inordinate amounts of compounded drug products interstate..."* in the form of an FDA-developed MOU between states, or a default cap on interstate distributions equal to 5% of the *"total prescription orders dispensed or distributed by such pharmacy or physician."* Notwithstanding FDA's attempt to redefine the terms in Footnote 7 of the GFI on the Prescription Requirement Under FDCA 503A, it is clear from the plain language of the statute that Congress intended for the terms "distributed" and "dispensed" to be treated as the distinct activities they are in law and in medical/pharmacy practice, and that Congress recognized there are limited instances where it is appropriate and medically necessary for a pharmacist to "distribute" compounded medications to a physician or other prescriber prior to the receipt of a valid prescription order, including for administration to patients in an office or clinical setting.[4,5]

Given this context and the statute's plain language, together with the fact Congress did not in Section 503A of the FDCA expressly preempt state pharmacy laws and regulations that allow for limited quantity office-use compounding, we believe FDA has misinterpreted the law to prohibit office-use compounding. When inspecting 503A compounding pharmacies, FDA continues to use the fact that a pharmacy is doing office-use

compounding prior to receipt of a prescription, including where expressly authorized by state law, to remove the exemptions provided to pharmacies in the law and inspect them under current Good Manufacturing Practices (cGMPs) rather than under standards adopted by state pharmacy boards under state law. This is drastically reducing patient access to vital, and often life-saving, compounded medications.

FDA, Pew and others have asserted that leaving the issue of 503A office-use compounding to state laws and regulations will mean that pharmacies will be able to do unlimited compounding without safety and recordkeeping requirements. However, a look at the laws and regulations of the states that still allow office-use compounding, shows that the vast majority of them have quantity limitations, sterility requirements, and recordkeeping requirements that state lawmakers and boards of pharmacy have determined are appropriate to balance the interests of patient safety and patient access to critical compounded medications. Unfortunately, FDA has worked diligently to convince several states who previously allowed office-use compounding to repeal their laws and regulations in this space due to FDA's assertion that these laws and regulations are now in conflict with or preempted by the FDCA as amended by the DQSA. However, a majority of the states still authorize some form of office-use compounding by 503A traditional pharmacies, a clear recognition of the medical needs of patients in those states. Below are some examples of states that still allow some form of office-use compounding under restrictions and requirements determined to be appropriate in those states by state lawmakers and boards of pharmacy.

Texas:

Office-Use Compounding Authorized: Yes

Sterile: Yes

Non-Sterile: Yes

Statutory Reference: TX Occupations Code §562.152

Rule or Policy Reference: TAC §291.131

Prescription Requirement: No

Quantity Limitation: Yes

Comments: Texas statutes and Board regulations specifically authorize the compounding of a "reasonable quantity" of sterile and non-sterile drugs by pharmacies for office administration. The regulations further define reasonable quantity, require a written agreement between pharmacist and prescriber, and have strong recordkeeping and labeling requirements.

Washington:

Office-Use Compounding Authorized: Yes

Sterile: Yes

Non-Sterile: Yes

Statutory Reference: RCW 18.64.270

Rule or Policy Reference: WAC 246-878-020

Prescription Requirement: No

Quantity Limitation: Yes

Comments: The statute and the Board rules authorize distribution of limited quantities of compounded medications to licensed practitioners for office administration. Distribution of inordinate quantities is considered manufacturing.

Oregon:

Office-Use Compounding Authorized: Yes

Sterile: Yes

Non-Sterile: Yes

Statutory Reference: No

Rule or Policy Reference: OAR 855-045-0200

Prescription Requirement: No

Quantity Limitation: Yes

Comments: Oregon pharmacies may provide non-patient specific, non-controlled compounded drugs to OR practitioners under a Shared Service arrangement with the Oregon Board of Pharmacy.

Colorado:

Office-Use Compounding Authorized: Yes

Sterile: Yes

Non-Sterile: Yes

Statutory Reference: CO Code 12-42.5-118(6)(b)

Rule or Policy Reference: Colorado BOP Rule 21.00.20

Prescription Requirement: No

Quantity Limitation: Yes

Comments: Colorado resident pharmacies can compound and distribute to CO prescribers for office administration up to a 10% cap. Any compounding for out of state must be patient specific. An accredited compounding pharmacy can register as such with the board and then dispense and distribute compounded meds in unlimited quantities to CO prescribers and other pharmacies.

The FDA's assertion that the creation of 503B "outsourcing facilities" that are authorized to compound without receipt of a patient-specific prescription eliminates the need for 503A office-use compounding is inaccurate. 503B outsourcing facilities simply do not have the flexibility to meet these needs. These new entities must meet current good manufacturing practices (cGMP), which are designed for making large amounts of a limited variety of medications. To compound an order for a particular formula, extensive testing and validation must be done that can take a minimum of 90 to 120 days before the medication can be made available to either a healthcare provider or a medical professional. In addition, there must be a need for large quantities of the medication in order to make the business practice sustainable given the cost of standardizing of processes as required by cGMP. On the other hand, traditional compounding pharmacies, also known as 503A pharmacies, can provide necessary medication in a matter of days or even hours. In many cases, medications need to be prepared within hours to ensure a patient can transition from one site of care to another. Their flexibility allows them to quickly respond to the needs of patients and medical professionals for specialized medications that are not commercially available. For example, the majority of parenteral nutrition patients, especially those needing long-term therapy, need individualized formulations that are adjusted frequently. Customized parenteral nutrition compounds cannot be provided by 503B outsourcing facilities due to the lag time of dispensing created by the end-product testing requirements.

503B outsourcing facilities are restricted in the range of medications they can provide. They are able to compound medications that are on FDA's drug shortage list that is still under development, and can repackage finished product to customize dosage and delivery systems. However, when compounding from bulk ingredients (the most common form of compounding), they are limited by statute to a positive list developed by FDA. FDA has yet to develop the positive list and has been using enforcement discretion to allow 503B facilities to compound from bulk ingredients without the limitations of a list. But as soon as the agency develops the positive list, most bulk ingredients are likely to be excluded from what is allowed. Further, FDA is interpreting the statute authorizing outsourcing facilities as requiring an extensive documentation of clinical need before compounding of a medication is allowed. If FDA enforces this interpretation, a simple prescription

or medical order will no longer suffice and the required medication could not be obtained from a 503B outsourcing facility.

FDA claims that the demand for office use of compounded medications, which medical professionals depend on for emergency situations and other appropriate uses as allowed under most state laws, can be met by outsourcing facilities. With the prospects of a limited positive list, a requirement for documented clinical need, and a limited demand of many of these medications, outsourcing facilities simply will not and cannot meet the needs of patients and medical professionals. Furthermore, the greatest demand for office use is for non-sterile compounds (capsules, creams, tablets, powders, etc.). Establishing an outsourcing facility requires meeting extensive and costly sterile compounding regulations, and only a small number of outsourcing facilities are doing non-sterile compounding.

503B facilities will play an important role in our health care system, and are designed to meet the needs of hospitals and others in dealing with drug shortages. This should help alleviate some of the patient access problems in those settings; however, the requirements and cost of complying with cGMP prevents the compounding of small batches and limits the role they can play in meeting the needs of patients for compounded drugs in smaller office and clinical settings. This gap in patient access to compounded medications for office administration has been experienced by prescribers in a broad range of practice areas, but has had a particularly negative impact on the patients of dermatologists and ophthalmologists. Enclosed in our submission is a chart showing compounded medications needed by prescribers that they report they are unable to obtain from 503B facilities.

On Friday, January 19, FDA released a "2018 Compounding Policy Priorities Plan" that describes the agency's intention to issue a revised draft guidance document with a "new flexible, risk-based approach to requirements for outsourcing facilities." The policy is intended to make it easier for smaller pharmacies to register with the FDA as outsourcing facilities, and compound with or without patient specific prescriptions, including for office administration. While IACP will wait to see the actual language of the revised GFI and eventual proposed rule

before commenting in detail on this new policy proposal, we do have strong concerns about any proposal that could negatively impact patient access to compounded medications and are wary of FDA policies that would lead to the further federalization of the regulation of the practice of pharmacy, and weaken the traditional role of state boards of pharmacy as the appropriate regulatory authority over the profession.

We join the 65 Members of Congress who wrote to the FDA in May of 2017 asking that the final GFI on the 503A prescription requirement be rescinded, and that the agency work with stakeholders to develop a proposed rule that authorizes office-use compounding by 503A compounding pharmacies where authorized by state law in a way that protects both patient safety and patient access to the compounded medications they need.[1]

Definitions of the terms "Distribute" and "Dispense":

Section 503A of the Food, Drug and Cosmetic Act (FDCA) gives the FDA limited regulatory authority over the "distribution" of "inordinate quantities" of compounded medications across state lines in the form of a sample MOU between states to be established by the FDA in consultation with the National Association of State Boards of Pharmacy, or a default cap contained in the FDCA. The relevant section of the FDCA (21 U.S.C. §353a (b)(3)(B)) establishing the default cap on compounded medications shipped interstate, says that it applies to pharmacies in a state "(ii) that has not entered into the memorandum of understanding described in clause (i) and the licensed pharmacist, licensed pharmacy, or licensed physician distributes (or causes to be distributed) compounded drug products out of the State in which they are compounded in quantities that do not exceed 5 percent of the total prescription orders ***dispensed or distributed*** by such pharmacy or physician." (emphasis added). This section of the FDCA was not amended by the DQSA and was part of the 1997 Food and Drug Modernization Act that established Section 503A of the FDCA.

The draft MOU, in its Appendix, defines "distribution" to include the dispensing of compounding medications directly to a patient for the patient's use. In December of 2016, the FDA issued a Final Guidance for Industry (GFI) entitled "Prescription Requirement under 503A of the Federal Food, Drug and Cosmetic Act" that, in a footnote, also defines "distribution" to include dispensing a drug directly to a patient. The terms

"distribution/distributed" and "dispensing/dispensed" are clearly distinct and commonly understood terms in both medical practice as well as throughout federal and state law.[4]

The "dispensing" of medications, commonly understood to mean the transfer of a drug product to a patient or an agent of the patient for that patient's use, is the very essence of the practice of pharmacy, something appropriately regulated by state boards of pharmacy under laws established by state legislatures. The term "distribution" is commonly understood in medical practice and defined throughout federal and state law to mean the sale, transfer or storage of a drug product that does not include "dispensing" to a specific patient.

The very section of the FDCA (21 U.S.C. §353a(b)(3)(B)) giving the FDA regulatory authority over the "distribution of inordinate quantities of compounded medications" clearly distinguishes distribution and dispensing as the distinct activities they are by creating a default cap on interstate ***distributions*** that is based on a percentage (5%) of the total amount of prescriptions "***dispensed or distributed***" by the pharmacy or physician. (emphasis added). By redefining these key terms in the sample draft MOU and in a GFI, the FDA is asserting regulatory authority over the "dispensing" of compounded medications over state lines in a way that Congress never intended and that will jeopardize patient access to critical compounded medications. The FDCA was not intended to give FDA the authority to limit the patient specific "dispensing" of compounded medications, only the "distribution" of "inordinate quantities" of compounded medications shipped over state lines.

It is highly unusual and inappropriate for the FDA to, in a GFI and a sample MOU, attempt to redefine key statutory terms to meet their policy interpretation of the statute, especially those that are defined elsewhere in federal state laws and regulations and with clearly understood meanings in practice. FDA, in the Notice of Availability for the MOU acknowledges the fact that these terms are defined elsewhere in federal law. In the notice the FDA asserts that because Congress did not provide a definition of "distribution" in this section of the FDCA that does not specifically exclude "dispensing". Congress intended for FDA to ignore the multiple federal and state statutory and regulatory definitions of these terms, as well and the medical and pharmacy

communities' common understanding of those terms, and instead use the "ordinary meaning" of those terms, which they analogize to manufacturers of other goods distributing those goods to their customers.

Congress has, through multiple letters to the FDA and in report language in the last two FDA appropriations bills (FY16 and FY17) told FDA their re-defining of these terms in a sample MOU and in a GFI is an "overreach," and is "unprecedented" and inconsistent with congressional intent of the statute. A copy of the congressional letter referenced above and dated May 23, 2017, is enclosed as an attachment to this testimony and the relevant report language is quoted below, including language from the House Report accompanying the FY 2018 bill. However, FDA continues to move forward with implementing compounding policies in a way that is inconsistent with the statutory language of this section of the FDCA and the definitions of these terms throughout federal and state law and congressional intent, which will threaten patient access to critical compounded medications. The access problem will be especially felt by patients served by compounding pharmacies near state lines that would, under FDA's interpretation of the FDCA, be subject to an arbitrary cap on the compounded medications they can "dispense" to specific patients across state lines.

Examples of definitions of the key terms "distribution" and "dispensing" can be found throughout state and federal health care and pharmacy law. For FDA to redefine these key terms in the MOU and GFI would not only expand the agency's regulatory authority over patient specific dispensing of compounded medications in a way Congress never intended, it would conflict with the commonly understood medical and legal definitions of those terms throughout state and federal health eare statutes causing unnecessary confusion and legal uncertainty at both the state and federal levels. Below are some examples of how these key terms are currently defined in state and federal law:

Federal Law Definitions:

21 CFR 208.3

Specifically, in 21 CFR §208.3,

§208.3 Definitions.

For the purposes of this part, the following definitions shall apply:

(a) Authorized dispenser means an individual licensed, registered, or otherwise permitted by the jurisdiction in which the individual practices to provide drug products on prescription in the course of professional practice.

(b) Dispense to patients means the act of delivering a prescription drug product to a patient or an agent of the patient either:

(1) By a licensed practitioner or an agent of a licensed practitioner, either directly or indirectly, for self-administration by the patient, or the patient's agent, or outside the licensed practitioner's direct supervision; or

(2) By an authorized dispenser or an agent of an authorized dispenser under a lawful prescription of a licensed practitioner.

(c) Distribute means the act of delivering, other than by dispensing, a drug product to any person.

(d) Distributor means a person who distributes a drug product.

21 U.S.C. §802(10)-(11)

In addition, the Controlled Substances Act defines "dispense" and "distribute" to mean two different things, and expressly excludes "distribute" from the act of dispensing. Specifically, the CSA states that a pharmacy which is:

> *registered to dispense a controlled substance may distribute (without being registered to distribute) a quantity of such substance to...another practitioner for the purpose of general dispensing by the practitioner to patients" unless the pharmacy's "total number of dosage units of all controlled substances which will be distributed by him" does not "exceed 5 percent of this total number of dosage units of all controlled substances distributed and dispensed by him during that calendar year."*

21 U.S.C. 581

In section 581 of the FDCA, the term "distribute or distribution" is defined:

§581 Definitions.

In this subchapter:

...

(5) Distribute or distribution.--The term `distribute' or `distribution' means the sale, purchase, trade, delivery, handling, storage, or receipt of a product, and does not include the dispensing of a product pursuant to a prescription executed in accordance with section 503(b)(1) or the dispensing of a product approved under section 512(b).

State Law Definitions:

Indiana:

IC 25-26-13-2

Definitions

Sec. 2. As used in this chapter:

...

"Dispensing" means issuing one (1) or more doses of a drug in a suitable container with appropriate labeling for subsequent administration to or use by a patient.

IC 25-26-14-4.7

"Distribute" defined

Sec. 4.7. As used in this chapter, "distribute" means to sell, offer to sell, deliver, offer to deliver, broker, give away, or transfer a legend drug, whether by passage of title or physical movement, or both. The term does not include the following:

(1) Dispensing or administering a legend drug.

(2) Delivering or offering to deliver a legend drug by a common carrier in the usual course of business as a common carrier.

(3) The provision of a legend drug sample to a patient by a:

(A) practitioner;

(B) health care professional acting at the direction and under the supervision of a practitioner; or

(C) hospital's or other health care entity's pharmacy that received the drug sample in accordance with this chapter and other applicable law to administer or dispense and that is acting at the direction of a practitioner; licensed to prescribe the legend drug,

Wisconsin:

Statute 450.01

(7) "Dispense" means to deliver a prescribed drug or device to an ultimate user or research subject by or pursuant to the prescription order of a practitioner, including the compounding, packaging or labeling necessary to prepare the prescribed drug or device for delivery.

(8) "Distribute" means to deliver, other than by administering or dispensing.

The Congress has been clear that its intent on this issue is for these terms to be treated as the separate and distinct activities that they are and has expressed that intent in the reports accompanying the final versions of

the FDA's appropriations legislation for FY2016 and 2017, as well as the House Report for the 2018 bill. Below is the language in each of those House reports.

Omnibus Appropriations Act: House Report 114-205, FY 2016:

The Committee is very concerned with the draft MOU that the FDA has proposed under Section 503A of the FDCA. The proposed MOU would complicate patient and prescriber access to compounded medications, and may have a deleterious effect on small pharmacies. Under the draft MOU, the FDA attempts to describe ''distribution'' as occurring when ''a compounded human drug product has left the facility in which the drug was compounded.'' In the DQSA, Congress only allowed the FDA to regulate ''distribution.'' But the MOU appears to exceed the authority granted in the statue by redefining ''distribution'' in a manner that includes dispensing—something unprecedented. This overreach could generate exactly the kind of costly and confusing litigation that Congress intended to avoid when it amended and rein- stated Section 503A. The Committee expects that, when a final MOU is proposed as a model agreement for the states to consider, that distribution and dispensing are treated as the different and separate activities that they actually are.

Omnibus Appropriations Act: House Report 114-531, FY 2017:

The agreement remains concerned with the draft MOU that the FDA proposed under Section 503A of the FDCA. Section 503A distinguishes between "distribution" and "dispensing" for the purposes of the MOU. In the DQSA, Congress only allowed the FDA to regulate "distribution." The MOU appears to exceed the authority granted in the statute by redefining "distribution" in a manner that includes dispensing. Congress did not intend to include dispensing of compounded drugs over state lines within the scope of the MOU. The MOU should not address dispensing of compounded drugs to a patient over state lines if all other requirements of 503A are met.

House Committee Report to FY 2018 FDA/Ag Appropriations Bill:

> *The Committee is also very concerned with the draft MOU issued February 13, 2015, entitled "Draft Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drug Products Between the State of ( ) and the Food and Drug Administration" as it applied to Section 503A of the FDCA. The proposed MOU would complicate patient and prescriber access to compounded medications, and may have a deleterious effect on small pharmacies. Under the draft MOU, the FDA attempts to describe "distribution" as occurring when "a compounded human drug product has left the facility in which the drug was compounded." In the DQSA, Congress only allowed the FDA to regulate "distribution." But the MOU appears to exceed the authority granted in the statute by redefining "distribution" in a manner that includes dispensing—something unprecedented. This overreach could generate exactly the kind of costly and confusing litigation that Congress intended to avoid when it amended and reinstated Section 503A. The Committee expects that, when a final MOU is proposed as a model agreement for the states to consider, that distribution and dispensing are treated as the different and separate activities that they actually are. (pages 67-68)*

We were encouraged to read in FDA's "2018 Compounding Policy Priorities Plan" issued Friday, January 19th that the agency, in the coming months, intends to pull down the current draft sample MOU and issue a "significantly revised draft MOU" that is intended to "address many of the concerns (they) have heard" in the thousands of public comments on the current draft sample MOU. The plan states the FDA's intention to raise the current MOU's 30% cap on the distribution of inordinate quantities of compounded medications interstate to 50% and indicates the new cap will trigger enhanced reporting requirements and FDCA violations that would lead to pharmacies being regulated like drug manufacturers. The new draft sample MOU will also purportedly relax some of the requirements on the states that sign the MOU. While we are pleased that the FDA has acknowledged the serious deficiencies in the current MOU that we and other stakeholders have been pointing out since its release, IACP will wait to see the actual language of the new draft sample MOU before

commenting in detail. However, we do have strong concerns that as described in the plan, the new draft sample MOU would still apply to interstate patient specific dispensing in violation of the plain language and congressional intent behind the FDCA, and pharmacists in states that do not sign the MOU would still be subject to a true 5% cap on these prescriptions that could lead to pharmacies that go over that arbitrary cap being regulated by the FDA like drug manufacturers.[5]

We join other stakeholders and the Congress in asking that FDA rescind the GFI and issue a proposed rule and final MOU that treats the distribution and dispensing of compounded medications as the distinct activities they actually are in medical and pharmacy practice and under the plain language of the statute.

Inspection Standards for 503A Pharmacies:

IACP would also like to raise the issue of FDA inspecting 503A compounding pharmacies under cGMP standards rather than under USP or other applicable pharmacy inspection standards adopted by state law or regulation. Often, FDA will cite a pharmacy for not obtaining patient-specific prescriptions before compounded medications leave a pharmacy and assert that the pharmacy has therefore lost its exemptions from cGMP standards, even when inspecting pharmacies in states where office-use compounding is specifically authorized by state law and/or regulation. FDA also routinely attempts to deny compounding pharmacies the records exemptions provide in 21 USC 374 (a)(2)(A) without citing any statutory authority to do so.

IACP believes that when inspecting state-licensed 503A pharmacies, the agency should work with state boards of pharmacy and use inspectors trained in USP or other applicable state pharmacy inspection standards. We believe that the FDA should cease using the agency's misinterpretation and misapplication of the prescription requirement under 503A as a pretext to conduct pharmacy inspections under manufacturer standards. As the Congress has attempted to remind the agency on multiple occasions, compounding pharmacies are not drug manufacturers, and should not be inspected under cGMP standards absent a clear showing of violations of 503A of the FDCA. This congressional intent was clearly expressed to the agency in the following House report language from the 2017 Omnibus Appropriations Act.

Omnibus Appropriations Act: House Report 114-531, FY 2017:

> *The Committee understands that the FDA is interpreting provisions of Section 503A of the FDCA to inspect state-licensed compounding pharmacies under current Good Manufacturing Practices (cGMPs) instead of under the standards contained in the United States Pharmacopeial Convention (USP) for sterile and non-sterile pharmaceutical compounding or other applicable pharmacy inspection standards adopted by state law or regulation. The Committee reminds the FDA that compounding pharmacies are not drug manufacturers, but rather, are state licensed and regulated health care providers that are inspected by state boards of pharmacy pursuant to state laws and regulations that establish sterility and other standards for the pharmacies operating within their states. Compounding pharmacies are more appropriately inspected using USP standards or other pharmacy inspection standards adopted by state law or regulation in the state in which a pharmacy is licensed. (p. 69)*

Compounding with Dietary Supplements:

Section 503A of the FDCA authorizes drug compounding by pharmacists and physicians using components of FDA approved drugs, or that appear on a positive list to be established by the FDA. In a June 2016 guidance for industry document on their interim policy on bulk ingredients, and later in the Final GFI on the Prescription Requirement Under 503A issued in December of 2016, FDA formally took the position that only a ***drug substance monograph*** met this requirement, without citing any statutory authority or legislative intent to back up this interpretation. The FDA's interpretation would eliminate compounding using dietary supplements, including those with USP dietary supplement monographs. This interpretation is inconsistent with the common

meaning attached to the term "monograph" and will limit patient access to compounded preparations using ingredients with a dietary supplement monograph. This interpretation of the law by FDA will mean that patients will have to rely on over the counter dietary supplements rather that allowing the prescribing physician and compounding pharmacist to work together to determine appropriate dosage levels and other medical considerations when dietary supplements are part of the recommended course of treatment. Again, this was done not through formal rulemaking but through a GFI. FDA should rescind the GFI and issue a proposed rule, or alternatively, the statute should be amended to clarify that either a drug substance or a dietary supplement monograph meets the statutory requirement as an ingredient that may be compounded under Section 503A of the FDCA.

Pharmacy Compounding Advisory Committee (PCAC):

The PCAC was originally created in 1997 under the Food & Drug Administration Modernization Act of 1997 (FDAMA); however, due to judicial rulings that held portions of §503A invalid, PCAC was dissolved. The PCAC Charter was re-established in 2012, and referenced in the Drug Quality and Security Act (DQSA) in 2013. PCAC held its first meeting in 2014. The committee is comprised of 14 members - 12 voting and two non-voting - who provide advice on scientific, technical and medical issues concerning drug compounding under sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act. Members and the Chair are selected by the Commissioner or designee from among authorities knowledgeable in the fields of pharmaceutical compounding, pharmaceutical manufacturing, pharmacy, medicine, and related specialties. The statue requires that members will include representatives from the National Association of Boards of Pharmacy (NABP), the United States Pharmacopeia (USP), ***pharmacists with current experience and expertise in compounding***, physicians with background and knowledge in compounding, and patient and public health advocacy organizations.

IACP is concerned that although we and other organizations have nominated multiple pharmacists with compounding experience and expertise, none of them have been selected to serve as voting members of the PCAC. There is currently one non-voting member who is a practicing compounding pharmacist. The nominees

are often informed by the FDA that their financial interest in a compounding pharmacy creates a conflict of interest that precludes their service on the PCAC.

By contrast, The Pew Charitable Trusts (Pew), a huge charitable entity with a significant lobbying/advocacy component has an employee who serves as a voting member of PCAC, including making recommendations to FDA on ingredients and medications that can be used in human compounding. These decisions can have a significant effect on competition and the profitability of large pharmaceutical companies that see compounded medications as competition to their commercially available drugs. As a result, recommendations by PCAC can affect the products of drug companies that have billions of dollars at stake for their high priced and market protected medications. It is often these pharmaceutical companies or those associated with them make nominations of ingredients to the PCAC's "difficult to compound" list and oppose nominations to the positive list of bulk ingredients that can be used in pharmacy compounding under 503A of the FDCA.

In addition to the financial conflicts arising from Pew's joint activities with the pharmaceutical industry, Pew has advocated for restrictions on the access of compounded medications that would be difficult - if not impossible - for their employee to ignore. These restrictions benefit the very pharmaceutical companies whose interest Pew lobbies for in jointly signed documents and efforts, and creates a conflict of interest that should preclude their participation in the PCAC. IACP recommends that PEW be removed from the PCAC and replaced with a voting member with experience and expertise in pharmacy compounding.

Guidance For Industry vs. Rulemaking:

IACP and other organizations have expressed concern with the FDA's policy of using Guidance For Industry (GFI) documents to implement and enforce the DQSA, rather than going through notice and comment rulemaking pursuant to the *Administrative Procedures Act*. As has been noted throughout this testimony, IACP has serious concerns that many of the policies that FDA has finalized and is enforcing through GFI do not adhere to the statutory language of the FDCA as amended by the DQSA, nor to its clear congressional intent. IACP believes the FDA should rescind the GFI that have been developed pursuant to the DQSA to date, and

issue proposed rules to be published in the *Federal Register*, seek and incorporate stakeholder input, and then finalize those rules consistent with the underlying statute. Unlike GFI, which do not have the weight of law and are merely FDA's current interpretation of the law, final agency rules are subject to judicial review and must adhere strictly to the laws they are based on. Given the serious consequences on patient safety and access, as well as the economic and regulatory burden the FDA's policies are having, it is appropriate that their policies be developed through the rulemaking process.

Conclusion:

Again, we thank you for holding this important hearing, and for seeking ICAP's input on the many issues surrounding FDA's implementation and enforcement of the DQSA. We strongly support HR2871 as a much-needed clarification and strengthening of the DQSA, and again urge the Congress to pass the bill this year. We stand ready to work with you to establish laws and regulation that protect patient safety, including access to critical compounded medications.

Citations

[1](2017, May). Congressional Support Letter [Letter to Commissioner Gottlieb]. Washington, D.C.

[2]Representative Griffith (VA), Representative Burgess (TX), and Representative Green (TX). "Drug Quality and Security Act." Congressional Record p.H5963. Available from: Thomas.gov.

[3]Representative Griffith (VA)."Preserving Patient Access to Compounded Medications Act of 2017." Congressional Record p.H2871. Available from: Thomas.gov.

[4]United States. Department of Health and Human Services. Food and Drug Administration. Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act. Final Guidance. Washington, DC: n.p. December 2016. Print.

[5]United States. Department of Health and Human Services. Food and Drug Administration. Draft Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drug Products between the State of [insert State]and the U.S. Food and Drug Administration. Washington, DC: n.p. February 2015. Print.

Accompanying Materials (Attached)

See attached for state office-use laws and chart.

See attached for office-use drug chart.

Mr. BURGESS. Thank you, Mr. Hodges.

Mr. Olson, you are recognized for 5 minutes. And because a vote has been called, we will take your testimony, and then, we will have to recess until after the votes. So, you may proceed.

STATEMENT OF JACOB OLSON

Mr. OLSON. Thank you. Thank you, Chairman Burgess, Ranking Member Green, and members of the subcommittee. Thank you for conducting this hearing on compounding.

My name is Jake Olson, and I am the pharmacist and owner of Skywalk Pharmacy. We have four locations in the greater Milwaukee area, serving patients of Children's Hospital of Wisconsin and clinics. I am testifying on behalf of the National Community Pharmacists Association. NCPA represents America's community pharmacists, including the owners of more than 22,000 independent community pharmacies that dispense nearly half of the nation's prescriptions.

In 2003, I had the unique opportunity to open Skywalk Pharmacy as an independently-owned community pharmacy which would serve as the outpatient pharmacy for the Children's Hospital of Wisconsin, the first of its kind in the United States. My pharmacies specialize in treating pediatric patients with routine ear infections to cystic fibrosis, cancer, and organ transplants. I compound only non-sterile preparations and I am compliant with USP 795 standards. I am licensed only in Wisconsin. I do not ship compounded medications across state lines, and compounding comprises 20 percent of my business.

Many of my pediatric patients have health conditions that require medications that have not undergone FDA approval. In many cases drug manufacturers do not produce a commercially-available product in the necessary dosage form or strength for these patients' needs. Physicians call on me to help under these circumstances when compounding is the only option for their patients.

I am here today as a healthcare provider and small business owner to present some of my experiences and those of my fellow independent pharmacists regarding the FDA's implementation of the Compounding Quality Act.

First, it is imperative the state boards of pharmacy retain oversight of pharmacy compounding. I am not eligible to register as an outsourcing facility, nor would it make sense for me to do so. The dispensing of custom-made medications should continue to be regulated by the boards of pharmacy, as all other medical license profession practices are.

Second, physician office-use compounding needs are not being met. We used to provide compounds for dentists to treat pediatric patients who would present with urgent issues. However, we stopped doing this in 2013 due to the uncertainty caused by DQSA and conflicting Wisconsin state law. Dentists still request this compounded medication to be on hand in the event that a patient needs this treatment. Because I am no longer providing dentists with this office-use compound, the dentist now has to close up the tooth, have the patient leave, come down to my pharmacy, pick up a prescription, and then return to the dentist. This cannot happen in the same day. So, the child will continue with an infected tooth

until the dentist can reschedule an appointment. Most of these patients are innercity children with Medicaid. Transportation is a huge issue, and sometimes it will take a week or longer to get them to come back. All the while, the child is suffering.

Third, not all office-use compounding needs can be met by outsourcing facilities. 503B outsourcing facilities provide an important function in meeting the needs of healthcare providers and patients. However, outsourcing facilities are not able to meet the entire office-use market, nor are they able to replace the role of the traditional compounding pharmacies.

Because of the requirements placed on outsourcing facilities and the costs of complying with CGMP, they are not able to compound in small batches; thus, limiting the role they can play in meeting the immediate patient needs for compounds. By prohibiting 503A pharmacies to compound for office use, the FDA is severely limiting access.

Fourth, FDA needs to end inspection reporting discrepancies between manufacturers and compounding pharmacies. I often hear from my fellow compounders who have been inspected by the FDA about the 483 reports that may be issued post-inspection and posted publicly, like they were today, on FDA's website. I don't understand why these same reports are not also publicly posted for FDA-registered facilities. While FDA publicizes Form 483s and photographs from compounding pharmacy inspections, there is evidence of several of the same observations from CGMP manufacturers with no corresponding publicity. This treatment suggests there is intent by the FDA to sway the public and undermine the confidence that parents have in my ability to take care of their child's medications.

Fifth, the FDA must make changes to the Pharmacy Compounding Advisory Committee and related activities. I am very concerned that not one of the voting members of the committee compounds for human use on a daily basis, considering the committee is making recommendations that can vastly impact the practice of compounding. The previous FDA PCAC had at least three pharmacists with current experience and expertise in compounding. The FDA should select, at minimum, one practicing human compounder on the committee as a voting member.

Lastly, it is very confusing for me, as a compounder, to understand what I can or cannot compound with today because of some of the conflicting information.

In summary, NCPA is committed to working with members of the Health Subcommittee, the FDA, and other stakeholders regarding these important matters for a balanced approach to ensuring patient access to safe and effective compounded medications. Thank you.

[The prepared statement of Mr. Olson follows:]

United States House of Representatives Energy and Commerce Committee

Subcommittee on Health

Hearing: "Examining Implementation of the Compounding Quality Act"

Written Testimony of:

Jacob Olson, Pharm.D., R.Ph.

President & CEO, Skywalk Pharmacy

On Behalf of the National Community Pharmacists Association (NCPA)

January 30, 2018

Chairman Burgess, Ranking Member Green and Members of the Subcommittee:

Thank you for conducting this hearing on compounding and providing me the opportunity to share my views and personal experiences. My name is Jake Olson and I am a pharmacist owner of four pharmacies located in the Children's Hospital of Wisconsin and their outlying specialty clinics in the greater Milwaukee area.

In 2003 I opened Skywalk Pharmacy as the first independently owned community pharmacy located in a children's hospital in the United States to serve the unique needs of pediatric patients. My pharmacies specialize in patients with cystic fibrosis, oncology, and organ transplants with a focus on specialty and compounded medications. On average, we fill 500 prescriptions amongst my 4 locations, only for children.

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Of those 500 prescriptions, we compound roughly 100 of those per day by primarily taking tablets and capsules approved for adults, and making them into a liquid to be dosed correctly for a child. I am a member of the National Community Pharmacists Association (NCPA) and serve on NCPA's Compounding Steering Committee.

NCPA represents America's community pharmacists, including the owners of more than 22,000 independent community pharmacies. Together they represent an $80 billion health care marketplace and employ more than 250,000 individuals on a full or part-time basis. I am here today as a healthcare provider and small business owner to present some of my experiences and those of my fellow independent pharmacists, focusing on quality compounded preparations and patient access.

In this statement, NCPA would like to present our thoughts on important issues surrounding implementation of the Compounding Quality Act. According to a NCPA member survey, over 88% of our members provide some form of compounding services. Also, over 95% of survey respondents stated they do not plan to register as a 503B outsourcing facility. Therefore, most of our members are held to the laws and regulations of section 503A of the Food, Drug, and Cosmetic Act.

Compounding is a backbone of pharmacy practice and for many decades independent community pharmacists have provided millions of adults, children, and animals with access to safe, effective and affordable medications through compounding services. When manufactured drugs aren't an option, independent community pharmacists provide traditional pharmacy compounding to prepare customized medications for patients.

Independent community pharmacies perform a wide variety of compounding services including hormone replacement medications, making suspensions out of tablets and capsules to allow for pediatric patients to receive correctly dosed medications, different dosage forms for patients suffering from intractable nausea and vomiting, and removing allergy causing excipients from commercially available products, to name a few. Compounding services can help bridge the gaps during times of prescription drug shortages, such as those occurring now with oral suspensions used for flu patients.

It is important to note that pharmacist compounding is an integral part of the pharmacy profession and that compounding occurs in many pharmacy settings, including hospitals. All compounding pharmacies should be held to the same standards so that patients have assurance that they are receiving the same quality regardless of whether the compounded medication is from a hospital or community pharmacy.

It is essential that patient access to vital compounded medications is preserved in the patient-physician-pharmacist triad. Providers must be able to choose the best medication for the patient's well-being.

Along with every American, NCPA member pharmacists were horrified by the tragic consequences of the fungal meningitis outbreak triggered by the reckless actions of NECC. We appreciate the thorough, bipartisan approach that this committee undertook to examine what changes, from both the regulatory enforcement and legislative fronts, were necessary to help prevent such an epidemic from recurring, while preserving patient access to essential, customized medications. NCPA subsequently endorsed the bipartisan law that emerged from those efforts, the Compounding Quality Act.

However, because of the FDA's implementation and enforcement of the Compounding Quality Act, providers lack much needed clarity and access to compounded medications has been negatively impacted.

For providers to gain clarity and for access to be ensured, NCPA strongly supports bipartisan legislation, H.R. 2871, *the Preserving Patient Access to Compounded Medications Act*, by Reps. Morgan Griffith (R-Va.) and Henry Cuellar (D-Tex.).

We greatly appreciate this opportunity to provide our input on these important issues.

1. **State Board of Pharmacy Oversight of Pharmacy Compounding is Critical**

NCPA has always and will continue to advocate that pharmacy compounding is best regulated by the state Boards of Pharmacy while manufacturing is overseen by the FDA. Pharmacy compounding of medications is an important part of medical care that allows for the dispensing of custom-made medications and should continue to be regulated by state Boards of Pharmacy, as all other medical licensed professional practices are. If the FDA has a concern about an appropriately-licensed pharmacy, then the FDA has the authority to ask the state Board of Pharmacy to work with them to address the issue. If it is found that an entity acting under the guise of a pharmacy has exceeded their state-regulated authority, then the state Boards of Pharmacy should suspend the license of the pharmacy until it complies with state laws and regulations governing compounding or meets FDA standards and registers with the FDA.

2. FDA Must Reverse Stance on Office-Use Compounding

Office-use compounding occurs when a pharmacist compounds a limited quantity of a medication that due to medical necessity must be administered in an office or clinical setting by the physician. By prohibiting all office-use compounding by 503A pharmacies, FDA disregards the plain language of Section 503A and the fact that Section 503A permits office-use, as well as disregards Congressional intent that states should continue to oversee traditional compounding practice, including office-use compounding.

The majority of pharmacy practice acts and state regulations authorize some form of office-use compounding. In addition, Congress has weighed in on multiple occasions and in multiple ways reminding FDA that office-use compounding should still be allowed in states that authorize its use. This includes several Statements for the Record that were given and floor speeches that were made during passage of the Drug Quality & Security Act. [1]

Appropriators have also been clear with FDA on the issue of office-use and its allowance in the House Reports accompanying the FY2016 and FY2017 Omnibus Appropriations Acts, as well as House Report language in the FY2018 FDA/Agriculture Appropriations Act.

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[1] Senator Coburn (OK). "Drug Quality and Security Act." *Congressional Record* 159: 162 (November 14, 2013) p. S8029.
Senator Boozman (AR). "Drug Quality and Security Act." *Congressional Record* 159: 164 (November 18, 2013) p. S8073.
Representative Griffith (VA). "Drug Quality and Security Act." *Congressional Record* 159: 131 (September 28, 2013) p. H5963.
Representative Green (TX). "Drug Quality and Security Act." *Congressional Record* 159: 131 (September 28, 2013) p. H5963.

Unfortunately, FDA continues to prohibit all office-use compounding by 503A pharmacies, ignoring the plain language of Section 503A, Congressional intent, current state laws or regulations, and even contradicting the FDA's own current draft guidance document "Hospital and Health System Compounding Under the Federal Food, Drug, and Cosmetic Act," as well as FDA's previous rationale regarding office-use compounding. This previous rationale includes the FDA circulating in 2012 a draft compliance policy guidance that would have allowed for office-use compounding under 503A, with some restrictions. The relevant statutory language of 503A was not changed by the DQSA, yet FDA is taking the position that the same language now prohibits office-use compounding, even where expressly authorized by state law.

Section 503A limits interstate "distribution" of compounded medications to quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed unless a state enters a MOU with the FDA addressing the distribution of compounds above the 5% threshold.[2] Based on the statute, this 5% rule is meant to limit what constitutes "distribution" under Section 503A, that is compounding for office-use. Other Federal laws support this construction. For example, the Controlled Substances Act (CSA) permits pharmacies to distribute for office-use without a distributor's license so long as their office-use distribution does not exceed 5%.[3]

[2] 21 U.S.C. §353a(3)(B)
[3] 21 U.S.C. §802(10)-(11)

The permission contained within the CSA is the same statutory approach set up by Section 503A permitting pharmacies to distribute up to 5% of their compounded medications interstate, e.g., compounds for office-use. Many State laws also adopt a similar 5% rule permitting office-use distribution.[4]

NCPA contends that Congressional intent is very clear in that compounding for office-use is permitted under Section 503A. We fully support the 65 Members of Congress who wrote the FDA in May of 2017 asking that the final office-use guidance be rescinded and that the FDA work with stakeholders to develop a proposed rule that authorizes office-use compounding by 503A pharmacies when authorized by state law.

3. Not All Office-Use Compounding Needs Can be Met by Outsourcing Facilities

NCPA is very concerned that FDA has taken the position that health care providers can easily obtain all needs for office-use compounds via Section 503B outsourcing facilities. 503B outsourcing facilities provide an important function in meeting the needs of healthcare providers and patients, however outsourcing facilities are not able to meet the entire office-use market nor are they able to replace the role of traditional compounding pharmacies practicing under Section 503A.

[4] Wisc. Stat. §450.01(23)(e); Wisc. Admin. Code Pharm. §13.02(11)(e); 12 Alaska Admin. Code §52.695(5)(A); Ariz. Stat. §32-1981(7)(d)

Because of the requirements placed on outsourcing facilities (limited to positive list, clinical need, cGMP validation procedures) and the cost of complying with cGMP, outsourcing facilities are not able to compound in small batches, thus limiting the role they can play in meeting immediate patient needs for compounds. As an example, outsourcing facilities have told us that when an ophthalmologist or urologist needs a sterile compound which is not a common formula for that facility they must refer the clinic to a 503A pharmacy.

NCPA has continually offered FDA input regarding compounded medications that are needed by providers in office settings.

The following is a non-exhaustive list of both non-sterile and sterile compounded office-use products that community healthcare providers rely on from our members. As discussed above, 503B outsourcing facilities are not able to provide many commonly needed office-use products, and by prohibiting 503A pharmacies to compound for office-use, FDA is severely limiting access to these products.

- Anesthetic gels/creams for dental, ENT and dermatology practices. In the past, practices could keep a jar/pump or tube of these available in the office for when patients needed them. The patient-specific requirement has created several issues. MDs may not know what the patient needs until they are seen. If they need to do a procedure, now the patient must schedule a second visit because they don't have the anesthetic available in the office. This creates waste. Many patients only need a small amount, but when a patient-specific prescription is generated it is typically for 30 to 60 grams. Depending on the procedure the MD may only use 5 grams for the patient.

- Erectile Dysfunction injections (Tri-mix, Quad-mix). The first dose of these medications is always given in the office to determine the best formulation and dosage. Now patients are forced to buy it before the physician has tried it and they must transport it (sometimes refrigerated) to the office for their first dose. If it doesn't work, they must buy another prescription. The importance of the physician-patient interaction, including counseling and education, at the time of the office visit necessitates the medication be on hand to ensure access to the right dosage of medication at the right time.

- Phenol and Cantharidin both used in podiatry and dermatology. These are items that like anesthetic gels are easily kept in office for when a patient presents and needs them. They use a very small amount on each patient. Having a patient-specific prescription for a whole bottle is wasteful and again causes delay in treatment.

- Ophthalmic injections and "emergency" eye drops. The physician does not know when a patient will present with a need for these items. Pharmacies often get frantic phone calls at the end of the day for these medications. Literally waiting until the next day could cause loss of vision. Many times, the MD is forced to admit the patient to the hospital if they cannot locate these items within a few hours.

- Iontophoresis solutions for use in physical therapy (Potassium Iodide, Dexamethasone).

- Pain creams for hand therapists in a Hand, Shoulder & Elbow Surgical group. Mostly Ketoprofen, Gabapentin, and Lidocaine.

- Children's dentistry (Hydroxyzine Pamoate Suspension for anxiety).
- Chemical peels for dermatologists.
- Anesthetics for numbing prior to laser resurfacing.
- Lidocaine/Oxymetazoline for nasal rinsing in office.
- Phenol for inner ear procedure.

4. FDA Must Clearly Differentiate Between "Distribute" and "Dispense" In the MOU

NCPA remains concerned that FDA continues to use the term "distribute" and "dispense" in an interchangeable manner, when in fact these terms are distinct and clearly defined in both Federal and State law. In Section 503A, Congress did use the words "distribute" and "dispense" as mutually exclusive categories, in the same sentence, and separated them by "or."[5] Congress used the two words in the same sentence to mean two different things, as they have repeatedly used these two terms to mean different things.[6] NCPA requests that FDA follow the intent of Congress and treat these two terms as separate and distinct activities.

[5] 21 U.S.C. §353a(3)(B)(ii)
[6] FDCA §581(5), 21 U.S.C. §802(10)-(11), and 21 CFR §208.3

By defining "distribution" to include dispensing in the MOU, FDA disregards the plain language of Section 503A and the fact that Section 503A permits office-use, as well as disregards Congressional intent that states should continue to oversee traditional compounding practice. In the availability notice of the draft MOU, FDA states "interstate distributions of compounded drug products would count toward the 30 percent limit whether or not the compounded drug products satisfied the prescription condition, or other conditions, in section 503A of the FD&C Act."[7] FDA also states, "under our draft standard MOU, a distribution occurs when a compounded drug leaves the facility where it was made, regardless of whether the drug is also deemed to be dispensed." [8]

NCPA disagrees with FDA's inclusion of "dispensing" in the definition of "distribution," as the plain language of Section 503A does not support this conclusion. Section 503A states that the MOU should address the "distribution of inordinate amounts of compounded drug products interstate and provide for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such State." [9] There is no allowance in the statute for FDA to address dispensing in the MOU.

NCPA also disagrees with FDA's reasoning behind including "dispensing" in the definition of "distribution." That is, Congress did use the words "distribute" and "dispense" as mutually exclusive categories, in the same sentence, and separated them by "or." [10]

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[7] 80 Fed. Reg. 8877
[8] *Id*
[9] 21 U.S.C. §353a(3)(B)(i)
[10] 21 U.S.C. §353a(3)(B)(ii)

Therefore, FDA's assertion that there is nothing "to suggest that Congress understood distributed and dispensed to be mutually exclusive categories rather than overlapping categories" is not persuasive. Congress used the two words in the same sentence to mean two different things, as they have repeatedly used these two terms to mean different things.[11]

FDA should follow the plain language of the statute when developing the final MOU as directed by Congress, and ensure that the MOU only addresses "the distribution of inordinate amounts of compounded drug products interstate."[12] FDA should not include the interstate dispensing of compounded drugs in the definition of distribution, and instead leave the practice of dispensing compounded drugs to oversight by the States, as Congress intended.

By not allowing 503A pharmacies to compound for office-use, the current MOU eliminates all non-sterile office-use compounding and severely limits access to sterile office-use compounding.

NCPA is very concerned that FDA is attempting to regulate traditional compounding pharmacies and the patient-specific compounds they dispense through the MOU process. FDA, with the proposed MOU, would have the authority to oversee traditional compounding pharmacy practice based solely on the location of a patient.

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[11] FDCA §581(5), 21 U.S.C. §802(10)-(11), and 21 CFR §208.3
[12] 21 U.S.C. §353a(3)(B)(i)

Many pharmacies specialize in specific treatment areas and because of their expertise, these pharmacies have relationships with doctors and patients in wide geographic areas, are registered in multiple states, and ship their medications. Under the draft MOU, most would involuntarily be deemed an outsourcing facility by FDA. In some cases, these pharmacies may not compound sterile products, and therefore would not be eligible to become an outsourcing facility.

Also, based on the current proposed threshold and how it's calculated, pharmacies that provide only compounds, and no general non-compounded prescription products, will always be at a great disadvantage when calculating what constitutes an "inordinate amount of compounded human drug products interstate". Some NCPA members are compounding-only pharmacies, and do not dispense any non-compounded prescriptions, and therefore would be at a mathematical disadvantage to their colleagues who have "hybrid" pharmacies, i.e. those that provide both traditional prescription services in addition to compounds.

Specifically, we are concerned that the arbitrary cap provides no protections for patients who live in different parts of the country throughout the year or those that may live in states with smaller populations. They and the physicians who treat them would potentially not be able to obtain the compounds they need simply because they do not live in the same state with the pharmacy that they need to provide their medication.

The lack of any protections for border pharmacies is also of great concern to NCPA. FDA does not consider location of the pharmacy in the proposed MOU.

Many NCPA members are in areas, both urban and rural, that border one or more states and by not providing exceptions for these circumstances, FDA is punishing these pharmacies that may ship medications to their patients over state lines. While we appreciate FDA trying to account for some of these situations by allowing for an exemption for patients who drive or walk across state lines to pick up their own medications, this scenario is oftentimes not an option, especially for frail, elderly patients.

5. **FDA Must End Inspection Reporting Discrepancies Between Manufacturers and Compounding Pharmacies**

When inspected by the FDA, our members pharmacies potentially receive an FDA Form 483. This form is issued after an inspection when the investigator(s) observed any conditions that in their judgement may constitute violations of the Food Drug and Cosmetic Act and related Acts. It is important to note that the compounding inspections that have been conducted to date by the FDA are focuscd on community-based compounding pharmacies. FDA has inspected only 1 physician compounder and no federal facilities, to our knowledge. We are also unsure how many compounding pharmacies residing in health systems have been conducted but believe this number to be very small or none.

NCPA feels strongly about the quality of compounded medications and after learning of several of our members experiences with FDA inspections and subsequent public posting of Form 483s we sought information on how the inspections were like those of FDA-registered manufacturers. The observations being documented at FDA-registered facilities are very similar to those that FDA publicly reports as unsafe in a compounding environment.

When a Form 483 is presented to a compounding pharmacy, it is also posted by the FDA to the FDA website. Conversely, when perusing the FDA website to search for any Form 483s given to FDA-registered manufacturers, all that can be found are inspection citations and inspectional observation summaries. We have been unable to find any Form 483 for a FDA-registered manufacturer facility posted to the FDA website.

The manufacturer inspection citations are on an excel spreadsheet and list a brief description of the general nature of the violation. The inspectional observation summaries summarize the number of 483s in various fields and you can expand a specific field to see the frequency of the violation. The manufacturers found on these spreadsheets are well-known.

The information posted to the website pertaining to inspections of compounding pharmacies are much more detailed and in depth than those posted for FDA-registered manufacturers. Many of the observations found in compounding pharmacies are the exact same ones found in FDA-registered manufacturing facilities. However, FDA presents the findings of inspections of compounding pharmacies in a much more intense manner than those of registered manufacturers.

While FDA publicizes Form 483s and photographs from compounding pharmacy inspections, we have evidence of several of the same observations from cGMP manufacturers, with no corresponding publicity. This treatment suggests there is intent by the FDA to sway the public to be afraid of compounding.

The observations from inspections of compounding pharmacies have been over generalized as applying to the entire profession. This has led some to believe most of compounding is done in substandard conditions, when this is not the case. These overgeneralizations are detrimental to pharmacies and patients.

Violations do occur in even the most advanced manufacturing processes. Unfortunately, the public is unable to see more details of violations found in FDA-registered facilities as manufacturer 483s are not public information. At the same time, 483s from compounding facilities are publicized.

6. FDA Must Make Key Changes to the Pharmacy Compounding Advisory Committee (PCAC) and Associated Activities

As the FDA and PCAC members continue to consider which drugs nominated will be considered for inclusion on the 503A "positive" list, among other responsibilities, NCPA is committed to working with the FDA and stakeholders on these critical issues. However, we have concerns with the creation, oversight and operation of the PCAC and associated processes.

Among these concerns are the following:

Inadequate member selection and renewal processes. NCPA remains concerned that none of our nominees to the PCAC were ever contacted. Unfortunately, there is currently not one voting member of the PCAC who compounds for human use daily.

NCPA finds this fact astounding considering the Committee is making recommendations that can vastly impact the practice of compounding. The previous FDA PCAC had at least three pharmacists with current experience and expertise in compounding, one of which specialized in sterile compounding. The FDA should select at a minimum one practicing human compounder on the Committee as a voting member.

Despite Congressional intent and prior FDA actions to include voting members with current expertise and experience in compounding on the PCAC, it is our understanding the Agency has cited potential conflicts of interest in having compounding pharmacists as voting members of the Committee. However, the appearance of impartiality of the Committee could be questioned by voting members whose organizations actively lobby Congress on the very issues they vote upon while serving on the PCAC. We also ask that the FDA provide greater transparency throughout the process of selecting members to serve on the PCAC and make certain that the compounding pharmacy and patient voice of those who depend on these compounded medications are represented.

FDA's insistence that any bulk drug substance not voted onto the positive list can easily be obtained via the investigational new drug (IND) process. This is a cumbersome, timely and expensive process, especially for community health care practitioners who have previously presented their real-life concerns with the IND process to the Committee.

Unequal time allotted for nominators to defend substances and respond to Committee questions. Throughout this entire process, each nominated substance is given a total of 10 minutes to be defended by nominating organizations, and oftentimes nominators will have to split this time up, all while the FDA has unlimited time to present their review and opinions related to the nominated substances. In addition, nominators have a limited time frame to organize their presentations (normally less than 3 weeks), where FDA has months to prepare. NCPA has concerns that FDA allows their own representatives and speakers to participate via conference calls for all PCAC meetings, but has refused our request that stakeholders be allowed to do the same.

FDA's indication that it does not consider USP monographs for dietary supplements to be "applicable" USP or NF monographs, therefore limiting compounding to only USP drug monographs when no basis exists for FDA to exclude USP or NF monographs for dietary supplements. This is of great trouble to NCPA as it defies logic that these substances can be easily obtained by the public at any Costco, Wal-Mart or CVS for example, but in the hands of health care practitioners are not to be trusted. The practice of compounding is built on the patient-physician-pharmacist triad, and there is no better way to oversee the use of these preparations than through this relationship.

A confusing nominating and review process that leaves many unanswered questions for health care practitioners and patients who rely on compounds. NCPA contends that it was premature for the FDA to have solicited nominations for the 503A list, as well as selected six products to consider at the first PCAC meeting, before developing and agreeing on criteria used to develop the list.

In addition, when nominating we were asked for all possible uses of the substances, not the most likely. We are also concerned that the FDA has separated substances in the 503A bulk drug substances interim policy based on nothing more than if the Agency considers that adequate information to evaluate the substance was included as part of the nomination process. Not being able to compound with these substances (included on FDA's 503A List 3) is causing impaired patient access. Not to mention that many of the substances included on List 3 are by FDA's own definition not active pharmaceutical ingredients that should even be under discussion.

Lastly, NCPA has concerns regarding FDA's recommendations for the Difficult to Compound List. It is important that the PCAC keep in mind that while dosage forms under consideration for the List may not be utilized in compounding practices today, there may come a time when technology advances to the point where pharmacies could be able to make these dosage forms. NCPA strongly urges the PCAC to approach the Difficult to Compound List in a very limited way to not stifle future innovation, technology and research.

The intent via Congress of this process was to increase appropriate access to bulk drug substances without a USP/NF monograph or from an FDA approved product. Unfortunately, quite the opposite is occurring.

Conclusion

In summary, NCPA is committed to working with Members of the Health Subcommittee, the FDA, and other stakeholders regarding these important matters. NCPA strongly supports H.R. 2871, *the Preserving Patient Access to Compounded Medications Act* as a much-needed clarification and strengthening of the Compounding Quality Act. We appreciate your consideration of our statement. Thank you.

Mr. BURGESS. Thank you, Mr. Olson.

And I apologize, we were only able to get through half the panel. We will get to the rest of you immediately after this series of votes. It will probably take us 30 minutes to complete that task.

So, the committee stands in recess until immediately after the votes.

[Recess.]

Mr. BURGESS. I think to be respectful of everyone's time, I am going to call the subcommittee back to order. We are expecting other members to show up almost immediately.

But as we recessed for votes, we were about to hear from Jenn Adams, the Senior Vice President, Clinical Products Solutions from PharMEDium Services. So, Ms. Adams, you are recognized for 5 minutes.

STATEMENT OF JENN ADAMS

Ms. ADAMS. Thank you. Chairman Burgess, Ranking Member Green, and members of the subcommittee, thank you for the opportunity to participate in today's hearing.

My name is Jenn Adams, and I am the President of PharMEDium Services. On behalf of PharMEDium, I want to thank you for holding this hearing on the implementation of the Compounding Quality Act, which Congress enacted as a part of the Drug Quality and Security Act of 2013.

PharMEDium, which is a subsidiary of AmerisourceBergen, operates four 503B registered outsourcing facilities. I want to briefly describe, as we begin, what PharMEDium does, as our business models tracks exactly what Congress codified in the Compounding Quality Act. Our four facilities prepare ready-to-administer compounded sterile drugs for hospitals, so that they don't have to prepare these medications at a patient's bedside under conditions that could introduce more risks of contamination.

Many sterile drugs, such as injectables, in their FDA-approved form are not manufactured in ready-to-use doses. Therefore, the drugs have to be prepared by diluting or admixing the FDA-approved drug with diluents or other components to achieve the appropriate dose for patient care. We prepare these sterile drugs into customized preparations, as ordered by our hospital customers. And this is the primary need that outsourcing facilities fulfill. And PharMEDium exclusively compounds using only FDA-approved sterile drugs obtained from registered drug manufacturers. This practice fills a very different role than that of traditional pharmacy compounding, which involves filling an individual patient prescription as required by law.

Based on our experience in serving the needs of hospitals and healthcare systems, outsourcing facilities anticipate the need for drug preparations. We compound those preparations on behalf of our customers, and then, our customers dispense the medications to their patients. The types of drug preparations that are compounded are, by definition, not available from manufacturers; therefore, requiring these more custom formulations to meet the clinical needs of patients.

Both of these distinct types of compounding, by outsourcing facilities and also by traditional pharmacies, we believe are critical

in ensuring that patients have access to safe compounded medications when needed.

PharMEDium was, and remains, an active supporter of DQSA because we felt strongly that more oversight of our industry was needed. The premise of the DQSA is that outsourcing facilities are subject to FDA oversight and more stringent quality requirements. And as our industry shifts more toward manufacturing quality standards, significant investment has been and is required in our facilities, personnel, and equipment to comply with these heightened standards. At PharMEDium our investment has, indeed, been quite significant, and the enhancements we have made have been challenging to implement, but we are confident that these improvements are in the best interest of patients and we are committed to continuing on this path in cooperation with the FDA.

Unfortunately, the successful implementation of Section 503B is under a separate threat; namely, from the misuse of bulk drug substances. I mentioned earlier that PharMEDium only compounds from FDA-approved drugs, as opposed to starting from bulk drug substances, which are sometimes referred to as bulk active pharmaceutical ingredients, or API powders.

There are, indeed, circumstances in which it is sometimes necessary to compound from bulk drug substances, such as when an individual patient requires a dose that cannot be achieved when using the FDA-approved manufactured drug as a starting point. But using bulk powders and outsourcing facilities should be the rare exception versus the rule, as it requires using a version of the drug that has not gone through the FDA approval and, therefore, has not benefitted from all of the safeguards that are inherent to FDA's drug approval process, which are designed to mitigate the risks of contamination.

As a result, under the law, bulk powders are only to be used when clinically necessary and not simply substituted for the FDA-approved version of the drug. Nevertheless, right now we are witnessing rampant compounding from bulk drug substances in the marketplace, usually lacking any clinical justification, even for sterile drugs. This is particularly concerning because using bulk drug substances is much less expensive for the compounder; therefore, undercutting demand for the actual approved drugs and creating a loophole for compounders to circumvent the drug approval process.

In light of these and other risks, we remain concerned about the rapid uptake of bulk drug substance powders in place of FDA-approved drugs. As we have learned from history, which demonstrated the tragic impact of poor compounding practice, FDA should make every effort to implement the DQSA in a manner that preserves patient access to important compounded medications and that eliminates opportunities to perform an end-run around clear restrictions of the law.

While we commend FDA's overall efforts to implement DQSA, the agency has not tamped down on this rapidly growing abuse of bulks. Its release of an overly broad interim list of permissible drug bulk substances and its final guidance on what amounts to impermissible copies of approved drugs fail to call out these practices and will not curb these abuses. We appreciate, however, that FDA

announced that it would be releasing a separate draft guidance in March clarifying that bulk drug substances may only be used for compounding when there is a clinical need to compound drugs using these substances. FDA conformed that this restriction protects patient health and the drug approval process, for example, by helping to ensure that outsourcing facilities do not compound using a bulk drug substance when an FDA-approved version can be used to meet patient medical needs.

While this acknowledgment is important, it is even more important that FDA follow this statement up with the promised guidance as soon as possible, revise the guidance on copies, communicate this message to providers who may not be aware of the undisclosed use of bulks, and to rigorously enforce these restrictions. In order to ensure that patients have a reliable and safe source of sterile compounded preparations, it is also important that FDA continue to move forward as quickly as possible in finalizing other 503B policies that will provide certainty and clarity to the outsourcing industry providers and patients. In particular, the lack of final GMP standards for outsourcing facilities has exacerbated ongoing confusion among state regulators, many of whom continue to impose expectations that differ from that of FDA's.

Key congressional proponents champion the DQSA as clarifying the role of the states in regulating traditional compounding, and outsourcing to be regulated at the federal level. That vision has not yet been fully realized.

Again, thank you for the opportunity to contribute to this important dialog. I appreciate it, and I look forward to your questions.

[The prepared statement of Ms. Adams follows:]

WRITTEN TESTIMONY OF JENN ADAMS,
PRESIDENT
PharMEDium

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

EXAMINING THE IMPLEMENTATION OF THE COMPOUNDING QUALITY ACT

January 30, 2018

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[1] FDCA § 503B(a)(2).

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

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

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

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

[2] *Id.* § 503B(a)(5).

[3] *Id.* § 503B(d)(2)(B).

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

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

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

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

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

* * *

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

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

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

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

With that, I look forward to answering your questions.

Thank you.

Mr. BURGESS. Thank you, Ms. Adams.

Ms. Ventrelli, you are recognized for 5 minutes, please.

STATEMENT OF MOLLY VENTRELLI

Ms. VENTRELLI. Thank you. Chairman Burgess, Ranking Member Green, and members of the subcommittee, thank you for the invitation to testify today.

My name is Molly Ventrelli, and I am Vice President of Regulatory Affairs for Fresenius Kabi USA. Fresenius Kabi is a global healthcare company specializing in lifesaving medicines and technologies for infusion, transfusion, and clinical nutrition. We manufacture most of these medicines in Illinois, New York, and North Carolina, and we employ more than 3,000 people in the U.S. Additionally, Fresenius Kabi operates 18 compounding centers around the world, and we are in the process of launching our first U.S.-based 503B compounding center in a suburb of Boston.

We commend FDA's implementation of the DQSA, and we believe that FDA must continue to enforce the strong protections of the DQSA against illegal or improper compounding activity. Patient safety requires strict FDA oversight on outsourcing facility compounding by pharmacies that do not comply with FDA regulations and do not meet the highest standards for quality and CGMP.

Drug compounding plays an important role in the delivery of health care by allowing a pharmacist, by a patient-specific prescription, to tailor a therapy for an individual's unique needs. But it is critical to ensure the safety of patients receiving these compounded medications. Congress recognized this in drafting the DQSA and established the two regulatory structures, both 503A and 503B. Pharmacies that operate under 503A are those that compound according to specific prescriptions unique to a patient under state board of pharmacy oversight. They do not compound large quantities in advance of a patient prescription.

However, Congress also recognized that some hospitals and healthcare providers may need supplies of medications not made by pharmaceutical manufacturers or not made in a specific dosage form, combination, or strength that is medically required for patients. These products, which need to be on hand, represent unique safety concerns, as they are typically made in larger volumes. So, if they become contaminated or are produced incorrectly, more patients are exposed to harm. Congress required that these 503B facilities adhere to CGMP, rigorous requirements enforced by the FDA, with a full set of quality standards for the manufacturing, processing, packing, release, testing, and storage of pharmaceutical products.

It is important to note that 503B outsourcing facility compounders may not make a drug that is essentially a copy of an approved medicine except under certain highly limited circumstances like drug shortages. One key reason Congress included this was to preserve incentives for traditional manufacturers to continue to pursue FDA approval through the current NDA and ANDA review process. This protects patient safety and should be upheld.

We support the FDA's efforts to ensure patient safety by timely inspecting 503B compounders and issuing compliance guidance.

Fresenius Kabi is currently addressing this now at our site in Massachusetts.

We also commend the FDA for its continued risk-based inspections of unregistered compounding pharmacies. FDA's enforcement of 503A is also important to ensure that facilities that are essentially acting as outsourcers by selling significant amounts of commercially unavailable compounded sterile drugs in the absence of patient prescriptions should register as 503B outsourcers. In the interest of public health, the safety and manufacturing standards of compounders should be held to rigorous standards to ensure patient safety.

Additionally, to uphold patient safety, Congress sought to ensure that FDA-approved drugs would be used as source material by compounders whenever possible. Under the DQSA, compounders should not use bulk active pharmaceutical ingredients as an alternative to compounding from an FDA-approved medicine unless doing so would produce a clinical difference for an identified patient. Fresenius Kabi believes that there could be instances where several 503B outsourcing compounders are doing exactly this in contravention of federal law. It is our strong recommendation that the committee support FDA's rigorous oversight of pharmaceutical compounding.

Thank you for holding today's hearing, and I welcome any questions you may have. Thank you.

[The prepared statement of Ms. Ventrelli follows:]

Your Generics and Biosimilars Industry

Testimony of Molly Ventrelli
Vice President, Regulatory Affairs
Fresenius Kabi USA, LLC

U.S. House of Representatives Energy and Commerce Committee
Subcommittee on Health Subcommittee
January 30, 2018

Introduction

Chairman Burgess, Ranking Member Green and members of the subcommittee, thank you for the invitation to testify today. My Name is Molly Ventrelli and I am Vice President of Regulatory Affairs for Fresenius Kabi USA. I am testifying today on behalf of Fresenius Kabi USA, a member of the Association for Accessible Medicines, or AAM, which represents companies that develop and market generic and biosimilar medicines. Fresenius Kabi is a leading provider of generic sterile injectable medicines in the U.S., and proud of the important role generic and biosimilar medicines play in helping patients and reducing costs in the U.S. health care system.

AAM is the nation's leading trade association for manufacturers and distributors of FDA-approved generic and biosimilar prescription medicines. AAM members employ more than 36,700 individuals at nearly 150 facilities and manufacture more than 61 billion doses in the United States every year. AAM's core mission is to improve the lives of patients by advancing timely access to affordable generic and biosimilar medicines. Generic medicines represent greater than 89 percent of all prescriptions dispensed in the U.S., but only 26 percent of expenditures on prescription drugs, saving patients and payers nearly $5 billion every week.

Fresenius Kabi Background and Experience

Fresenius Kabi is a global health care company – with more than 30,000 employees around the world - specializing in lifesaving medicines and technologies for infusion, transfusion and clinical nutrition. Our portfolio consists of more than 400 injectable drugs administered predominately in hospitals and other clinical settings. These include chemotherapeutics, analgesics and anesthetics used in surgery, and a wide range of anti-infective and critical care drugs. We manufacture these products in three

states – Illinois, New York and North Carolina – and we employ approximately 3,000 people in the U.S. in research and development, manufacturing, distribution and other related functions.

Additionally, Fresenius Kabi operates 18 compounding centers around the world, and we are in the process of launching our first U.S.-based, 503B compounding center in suburban Boston. It is from these various experiences that I share my perspective with you today.

We commend FDA's implementation of the Drug Quality and Security Act of 2013 (DQSA). As you know, this bipartisan legislation was passed by Congress in response to a fungal meningitis outbreak that sickened over 700 Americans and killed 64. This was caused by the compounding of sterile medications under insufficient quality standards and in violation of federal law. In order to avoid future tragedies like this, FDA must continue to enforce the strong protections of the DQSA against illegal compounding activity, including federal prohibitions on compounding without an individual prescription by pharmacies that do not comply with FDA regulations and do not meet quality standards designed to better protect and ensure patient safety.

Drug Compounding Background

Drug compounding plays an important role in health care. In particular, it allows a pharmacist, through a patient specific prescription, to tailor a therapy for an individual's unique needs – for instance, to add flavor to a child's medication or provide the medication in a liquid instead of solid form. But it is critical for us all to ensure the safety of patients who receive compounded medications, specifically, outsourcing facility compounded products as the 2012 outbreak demonstrated. Compounding should not be used for widespread manufacturing and distribution as a substitute to the FDA generic drug review process gold standard.

Congress recognized this when crafting the DQSA, and established two regulatory structures for the oversight of drug compounding: 503A and 503B. Pharmacies that operate under 503A are those that compound according to specific prescriptions unique to a patient ("one patient, one prescription") and under state board of pharmacy oversight. They do not compound large quantities of product in advance of a patient prescription.

However, Congress also recognized that some hospitals and healthcare providers may need supplies of medications not made by pharmaceutical manufacturers, or not made in a specific form, combination, or strength that is medically required for patients. These products, which need to be on

hand, often referred to as "office stock," present unique safety concerns due to the amount of time between compounding and administration of the drug to the patient. This risk is increased as these products are typically made in large volumes. Therefore, if they do become contaminated, or are produced incorrectly, more patients are exposed to the risk. To mitigate the higher risk associated with producing stock supplies of compounded drugs, Congress created the outsourcing facility category, governed by section 503B of the Food Drug and Cosmetic Act (FDCA). Congress required that these facilities adhere to current Good Manufacturing Practices (cGMP)—rigorous requirements enforced by FDA that describe a full-set of quality standards for the manufacturing, processing, packing, storage and testing of pharmaceutical products. Generic manufacturers are held to these robust standards to ensure the safety and efficacy of our products. To protect patients from another tragedy, outsourcing compounders must also be held to these rigorous standards as Congress intended.

Quality Standards

Compounded medications produced under conditions that guarantee potency and stability and are free of contamination can help patients in need and have a place in the U.S. healthcare system. Therefore, compounders registered under 503B of DQSA must comply with standards consistent with cGMPs that apply to regulated drug manufacturers. Recent history has proven the need for clear and strong regulation of standards for this space.

503B facilities, called "outsourcing facilities", allow for appropriate FDA regulation of mass production of compounded products. If these outsourcing facilities elect to register with FDA, and agree to meet critical regulatory and quality standards, they may provide hospitals and clinics with standing supplies of non-patient-specific compounded medicines that are regularly prescribed, when an FDA-approved product is not available. It is important to note that compounders registered under section 503B may not make a drug that is essentially a copy of an approved medicine except under certain highly limited circumstances. One of the primary reasons Congress was so clear in drafting 503B this way was to preserve incentives for traditional manufacturers to continue to pursue FDA approval through the current NDA and ANDA process. It is critical that this standard be upheld.

We support the FDA's efforts to ensure patient safety by inspecting compounders under the new 503B category in a timely fashion, and issuing guidance to make clear how 503B facilities should comply with federal law. We also commend the FDA for its continued risk-based inspections of compounding pharmacies not registered with the FDA that may not be in compliance with the provisions of 503A or 503B. One lesson learned from the fungal meningitis outbreak is that some licensed pharmacies operated outside the bounds of traditional, patient-specific compounding pharmacy practice. As

Congress has repeatedly noted, the FDA has the authority to address facilities that are illegally manufacturing drugs in violation of federal law. These facilities are not entitled to any of the exemptions that apply to compounding pharmacies; and are therefore subject to the requirements placed on manufacturers including adherence to cGMPs. FDA must be allowed to enforce federal law to prevent compounding activities that increase safety risks to patients.

FDA's enforcement of 503A is also important to ensure that facilities that are essentially acting as outsourcers, i.e., selling significant amounts of commercially unavailable compounded sterile drugs in absence of patient prescriptions, register as FDA 503B outsourcers. Congress' intent under DQSA was for this kind of larger-scale, non-patient specific compounding to be conducted not by traditional pharmacies but by 503B registered facilities that meet higher quality standards and submit to FDA oversight.

We also note that Congress did not alter the law prohibiting the repackaging or compounding of biologics without FDA oversight, and encourage FDA to include such activities in its enforcement priorities.

Additionally, a compounding pharmacy that seeks to compound a copy of a commercially available drug on the drug shortage list should be overseen by the FDA and should not only notify FDA, but also be inspected by the FDA prior to beginning the compounding of that product. In the interest of protecting public health, the safety and manufacturing standards of compounders producing commercially available products on the drug shortage list should not be lowered below the standards required of pharmaceutical manufacturers.

Protecting the FDA approval process

Another key to protecting patients is safeguarding the FDA approval process for new drugs. To uphold patient safety, Congress sought to ensure that FDA-approved drugs would be used whenever possible, including in the rare circumstances in which FDA-approved ingredients might be necessary in the use of compounded formulations. Under the DQSA, compounders should not use an active pharmaceutical ingredient (API) from any source, except those available through an FDA-approved source, unless doing so would produce a clinical difference for an identified patient. This is commonly referred to as patient-prescription specific compounding. In addition, the DQSA prohibits the compounding of drugs that are essentially a copy of an FDA-approved medicine, unless FDA has placed that drug on the drug shortage list. It is critical that these provisions be enforced to avoid a disincentive to invest in new drug approvals and in the production of approved versions of drugs. While compounded drugs are an

important option when approved drugs cannot meet a patient's clinical needs, products that have been evaluated and approved through FDA's approval process are the gold standard.

State Boards of Pharmacy quality standards applied to pharmacies are appropriate for patient-specific preparations, but not for outsourcing facility operations at a larger scale, where significantly more individuals are exposed. We must ensure that flexibility for outsourcing facilities does not compromise patient safety.

Drug Compounding is Not the Appropriate Response to Rising Drug Prices

Despite what some might argue, drug compounding – whether conducted under 503A or 503B – is not a solution to the issue of high drug prices. Congress has clearly recognized that the solution to high drug prices is greater competition from lower cost FDA-approved generic and biosimilar medicines. In the past year, Congress has taken important steps to encourage greater availability of generics – including in therapeutic areas without generic competition – through enactment of the Generic Drug User Fee Act. Moreover, FDA Commissioner Gottlieb continues to prioritize generic competition as part of the FDA Drug Competition Action Plan. And multiple legislative proposals are under consideration in Congress that would lead to greater competition through generic and biosimilar medicines. In contrast, seeking to use mass drug compounding as a solution for more drug competition ignores the tragic events of 2012-2013 and more recent warnings of the safety of compounded drugs – including some that FDA has called out even since the enactment of DQSA as having significant quality problems.

Conclusion

On behalf of Fresenius Kabi and member companies of AAM, I extend our gratitude to the subcommittee for holding today's hearing. I'd also like to thank the FDA and Commissioner Gottlieb for the steps the Agency has taken to-date to strengthen the oversight of compounding, and for clarifying today FDA's path forward. We recognize the role compounders play in delivering special care to patients, but as we know all too well, it should not be done at the expense of quality and patient safety.

Mr. BURGESS. Thank you, Ms. Ventrelli.

Ms. Jungman, you are recognized for 5 minutes, please.

STATEMENT OF ELIZABETH JUNGMAN

Ms. JUNGMAN. Good afternoon. I am Elizabeth Jungman, Director of Public Health Programs at the Pew Charitable Trusts. We are an independent, nonpartisan research and public policy organization with a longstanding focus on drug quality, including compounding. I want to thank you for holding this important hearing.

This committee has a long history of working to protect Americans from the risk of substandard compounded drugs. Five years ago, even before we knew the full scope of the fungal meningitis outbreak, your oversight team investigated how the crisis began, and you worked with the Senate and across party lines to pass the DQSA. This legislation is making a difference.

Today I will stress the importance of preserving it. Efforts to weaken the DQSA pose very real risks for patient safety. I will also share some new findings showing that DQSA is spurring better compounding oversight in the states.

I was privileged to be among the Senate committee staff that helped develop the DQSA. We knew then the provisions would be met with resistance, but each round of negotiations started with a new count of illnesses and deaths, and it was a powerful motivator to push past that controversy and get the job done.

The meningitis outbreak is, of course, not the only case of harm. As we have heard today, just last year 43 people in Texas had contaminated antibiotics injected into their eyes and several suffered vision loss. Also, last year 41 patients received contaminated injections in a New Jersey clinic. They developed joint infections caused by microorganisms that should only be found in human mouths.

Americans expect their government to play a major role in making food and drugs safe. Eighty-seven percent of Americans think that, according to a Pew Research Center survey.

FDA evaluates the safety and effectiveness for most drugs and sets manufacturing quality standards, but compounded drugs are not subject to those protections, and, thus, should only be used when commercial alternatives won't work. There is a big difference between drugs prepared for a single patient who will use it immediately and drugs prepared in bulk quantities for use at some undetermined future date.

Compounding for a single patient is a traditional part of pharmacy practice. The risks of dangerous contamination are relatively low and the impact for errors is contained. States oversee patient-specific compounding and mandate quality standards.

But, if compounded drugs are going to be kept onhand, so-called office stock, the risks are greater. They are often stored for some period of time, increasing the chance that contaminates like bacteria and fungus can grow. And since they are not tailored to specific patients, they products are frequently produced in bulk, multiplying the consequences of any error.

That is why Congress created outsourcing facilities. In exchange for meeting appropriate manufacturing standards, outsourcing facilities can compound drugs without prescriptions. Congress has

decided twice, first 20 years ago and again in 2013, that traditional compounding should require a patient-specific prescription. If compounders want to sell stock supplies, they must invest in the equipment, training, and specialized personnel necessary to mitigate the risk. That dividing line between stock supply and individual prescription creates accountability.

This committee's investigation demonstrated the importance of clear and enforceable lines, so that facilities and their regulators know who is responsible for oversight and what rules apply. The prescription requirement is very clear. Either a patient's name is on the product or it is not.

While FDA regulates outsourcing facilities, states are still the primary regulator of traditional pharmacies, and they play an important role in ensuring the safety of compounded drugs. In 2014, Pew convened an advisory committee of pharmacy regulators, state pharmacy regulators, and other compounding experts to identify best practices for states. Next month, Pew, together with the National Association of Boards of Pharmacy, will release a 50-state assessment.

I am happy to say that most states now conform to best practices in two key areas. First, states are widely adopting quality standards that have been established by the USP, the United States Pharmacopeia. And second, states are aligning with Federal law on the prescription requirement.

However, there is more work to be done. Ideally, states should inspect compounding pharmacies every year, but our study showed that we haven't met this mark. That is why state and Federal regulators must prioritize the most risky operations.

To wrap up, since the DQSA became law, states have made important changes, and other stakeholders like outsourcing facilities have made significant investments, too. To avoid undermining that progress, Congress and the FDA must continue to protect, implement, and enforce the DQSA.

Five years ago, this committee acted boldly to draw clear lines that protect patients from another tragedy. This hearing reminds us of why we need that law and what could happen if it is weakened.

I welcome any questions.

[The prepared statement of Ms. Jungman follows:]

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Testimony of Elizabeth Jungman, The Pew Charitable Trusts
before the Committee on Energy and Commerce
Subcommittee on Health
United States House of Representatives
January 30, 2018

Chairman Burgess, Ranking Member Green, and members of the Subcommittee:

Five years ago, the full extent of the fungal meningitis outbreak caused by contaminated compounded injections was still being revealed. As the case count and fatality count went up day by day, this Committee took action. The Energy and Commerce Committee oversight team investigated the root causes, and then Committee members worked with your counterparts in the Senate, and across party lines, to pass legislation that is already making a difference: the Drug Quality and Security Act (DQSA).

I am Elizabeth Jungman, director of public health programs at The Pew Charitable Trusts. Pew is an independent, nonpartisan research and public policy organization with a longstanding focus on drug quality issues, including pharmaceutical compounding.

Weakening the DQSA would threaten patient safety. I am here today to convey Pew's strong support for the continued, robust implementation and enforcement of the law. I will also share findings from a not-yet-published study showing that the DQSA has also helped spur state-level improvements in compounding oversight.

When this legislation was being developed, I worked for the Senate, and had the privilege of being a part of the negotiating team. As Members and other stakeholders who were here will recall, we knew that the changes in practice that experts told us were necessary to protect patients would not be universally popular. But each round of staff negotiations started with a new count of the illnesses and deaths discovered since we had last met, and that was a powerful motivator to persevere and create a bill that would protect patients. Years later, we cannot let ourselves forget the stories that created the imperative to act.

Patients get hurt when compounding goes wrong

While the meningitis outbreak is the most extensive known example of harm to patients from compounded drugs, there have been many other cases of serious illness, injury, and death associated with them. Appended to my testimony is information on more than 70 adverse events that have been publicly reported since 2001, although we think our list probably underestimates the scale of the problem.

For example, last year, 43 people in Texas were harmed after a compounded steroid antibiotic was injected into their eyes, including patients who suffered vision loss.[1] That is unacceptable; patients deserve access to compounded products that they can trust.

Patients should receive the highest-quality product that meets their clinical need

Poll data from the Pew Research Center indicates that the vast majority of Americans (87%) expect the government to play a "major role" in ensuring the safety of medicines and foods.[2] For most drugs, FDA fills that role by evaluating safety and effectiveness, and setting manufacturing quality standards. Compounded drugs are not subject to these protections.

An FDA-approved drug is the gold standard, and should be the first choice whenever possible. But some patients have medical needs that approved products cannot meet. For them, compounded drugs can be an important tool.

When a pharmacist tailors a drug for an individual patient who will use it immediately, the risks of any contaminants growing are limited, and the public health impact from any error is contained. States primarily oversee patient-specific compounding, which is called "traditional" compounding, and mandate quality standards appropriate to its risks.

But sometimes, clinical circumstances require that providers keep compounded drugs on-hand, known as "office stock." These products carry distinct risks for patients, because rather than being used immediately, they are often stored for a period of time before use, increasing the opportunity for any contaminants like bacteria and fungus to grow to dangerous levels. Also, they are frequently produced in bulk, multiplying the consequences of microbial contamination, adulteration, and under or over-potent products.

To mitigate these risks, Congress created a special category of compounder to supply office stock – outsourcing facilities, established under section 503B of the DQSA. FDA's quality standards for outsourcing facilities are similar to those for approved drugs, called current Good Manufacturing Practice standards (cGMP). In exchange for investing in meeting these standards, outsourcing facilities can compound drugs without prescriptions.

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[1] U.S. Food and Drug Administration, "Compounded Triamicinolone and Moxifloxacin Product for Intravitreal Injection by Guardian Pharmacy Services: Alert to Health Professionals - Serious Adverse Events Reported," accessed Nov. 14, 2017, https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucmS69123.htm.

[2] Pew Research Center, "Government Gets Lower Ratings for Handling Health Care, Environment, Disaster Response" (2017), file:///C:/Users/acohen2/Downloads/12-14-17-Government-release.pdf.

FDA has indicated that forthcoming regulations will apply these quality standards flexibly, to allow compounders of varying sizes to register as outsourcing facilities.[3] But while tailoring standards to risk is sensible, and having more entrants to the outsourcing facility market could be a good thing, any flexibility in the standards that apply to outsourcing facilities must preserve the role that Congress created these facilities to fill: reliable sources for safe supplies of compounded office stock.

The prescription requirement helps ensure that compounded drugs are produced under appropriate standards

To ensure that all drugs are compounded under suitable quality standards and with appropriate oversight, it is essential that the two categories of business engaged in this practice – traditional compounders and outsourcing facilities – be clearly delineated and defined. To that end, Congress has twice determined – first 20 years ago, and then in 2013 – that traditional compounding should require a patient-specific prescription. If compounders want to sell stock supplies, they must invest in the equipment, training and specialized personnel necessary to comply with cGMP.

Furthermore, a clear dividing line helps ensure that both regulated facilities and regulators know who is responsible for overseeing any given compounder, and what rules apply. Congress considered a variety of ways to distinguish traditional compounders from outsourcing facilities, but the downside to other proposals, like designating categories based on production volume, was that the difficulty in enforcing them would have undermined accountability. The prescription requirement, in contrast, is very clear – you have a patient name on the pill bottle, or you don't. Congress decided – twice – that the benefits of that clarity outweighed the downsides of prohibiting office stock by traditional compounders.

States are important partners

The vast majority of compounded drugs are produced by traditional compounders – pharmacists or physicians who dispense patient-specific drugs, and are primarily regulated by states – and so appropriate state oversight of compounding is an important component of a safe marketplace.

In 2014, as many state officials sought to determine which reforms would help them oversee drug compounding most effectively, Pew convened an advisory committee of state pharmacy

[3] Nate Raymond, "Exclusive: FDA Plans New Compounding Pharmacy Policy, Agency Head Says," *Reuters*, Sept. 15, 2017, https://www.reuters.com/article/us-usa-fda-pharmacies-exclusive/exclusive-fda-plans-new-compounding-pharmacy-policy-agency-head-says-idUSKCN1BQ2RV; U.S. Food and Drug Administration, "2018 Compounding Policy Priorities Plan," accessed Jan. 22, 2018, https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm592795.htm

regulators and other experts to identify best practices that were most achievable by states.[4] We then released an assessment of state policies, relative to those best practices, in 2016.[5] About two weeks from now, Pew, along with the National Association of Boards of Pharmacy, will release an update to that research,[6] but I can preview some findings today. They show that the majority of states now conform to best practices in two key areas.

First, among the best practices was a recommendation that states adopt widely-recognized quality standards established by the United States Pharmacopeial Convention (USP). The forthcoming report will show that the vast majority of state boards of pharmacy have adopted either those standards, or other strong quality standards, for the compounders they oversee.[7]

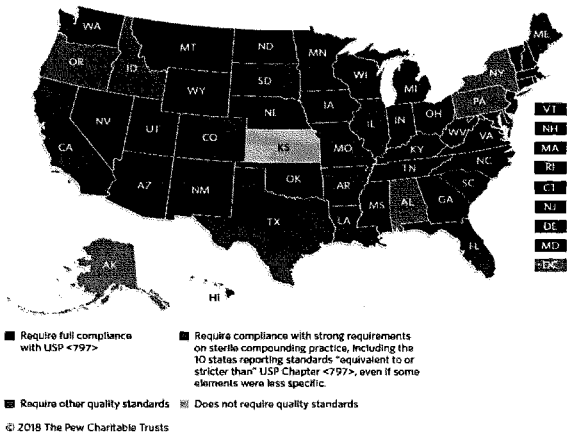

Fig. 1. State adoption of quality standards. Pew/NABP (forthcoming February 2018)

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[4] The Pew Charitable Trusts, "Best Practices for State Oversight of Drug Compounding" (2016), http://www.pewtrusts.org/~/media/assets/2016/02/best_practices_for-state_oversight_of_drug_compounding.pdf.

[5] The Pew Charitable Trusts, "National Assessment of State Oversight of Sterile Drug Compounding" (2016), http://www.pewtrusts.org/~/media/assets/2016/02/national_assessment_of_state_oversight_of_sterile_drug_compounding.pdf.

[6] The Pew Charitable Trusts and the National Association of Boards of Pharmacy, in press, "State Oversight of Drug Compounding" (2018). The report will be posted at the following URL on approximately Feb. 14, 2018: http://www.pewtrusts.org/statecompounding.

[7] Thirty-two state boards of pharmacy require traditional pharmacies that compound sterile drugs for humans to be in full compliance with the quality standards established by USP in its general Chapter <797> "Pharmaceutical Compounding—Sterile Preparations." An additional 11 states have strong requirements on sterile compounding practice – which 10 states characterized as "equivalent to or stricter than" USP Chapter <797>, even if some elements were less specific. An additional four states have pending policy changes that, if passed, would require full compliance with USP Chapter <797> or other strong state requirements.

Second, the best practices recommend that states align with federal law on the prescription requirement – and the forthcoming report will show that the vast majority of states now do. Thirty-nine states and the District of Columbia prohibit traditional pharmacies from compounding sterile office stock for humans – through their laws or regulations, state guidance, or by advising compounders to follow the federal law prohibiting the practice.

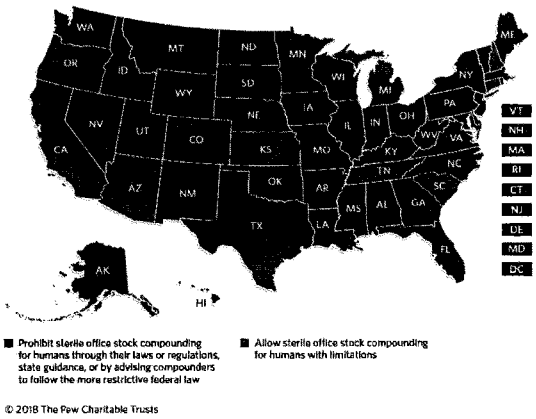

Fig. 2 State adoption of prescription requirement. Pew/NABP (forthcoming February 2018)

While many states fall short of the best practice standard of annual inspections, which would ensure compliance with these policies, states' adoption of key policies regarding quality standards and the prescription requirement are promising steps in ensuring that states are doing their part to ensure the safety of compounded drugs.

Congressional support for the federal compounding law will help ensure its effectiveness

The DQSA was passed under the shadow of an unfolding tragedy. Congress – this committee – acted boldly, in the face of pushback and controversy, to draw clear lines that help ensure drug quality. This hearing is an important reminder of why Congress passed federal compounding law, and what could happen if Congress doesn't protect it, and encourage its robust implementation. I am honored to have had the opportunity to be a part of it, and welcome any questions.

A data table from THE PEW CHARITABLE TRUSTS January 2018

U.S. Illnesses and Deaths Associated With Compounded or Repackaged Medications, 2001-17

Pew's drug safety project has identified 71 reported compounding errors or potential errors associated with 1,416 adverse events, including 114 deaths, from 2001 to 2017. However, a 2015 survey found that only 30 percent of states (13 of the 43 that responded) require sterile compounding pharmacies to report serious adverse events.[1] Of the states that require reporting, the type of information that is required to be reported may vary, further contributing to an incomplete picture of adverse events associated with compounded medications. Even in states with strong adverse event reporting requirements, illnesses and deaths caused by compounded drugs are not always linked to the compounding error.[2,3,4] Because many such events go unreported, this chart is an underestimation of the number of compounding errors since 2001. Contamination of sterile products was the most common error; others were the result of compounders' miscalculations and mistakes in filling prescriptions.

Drug compounding can be an interstate operation; compounders may prepare medicines in one state and ship them to another. States may encounter oversight challenges if an out-of-state compounder shipping into their jurisdiction is held to a different quality or regulatory standard than in-state compounders. As a result, for each row below, the state where the compounding error or potential error occurred and the state(s) where the adverse event(s) occurred are listed. Harmonized minimum quality standards for anyone who compounds drugs – in any setting – across states would help address challenges in regulating out-of-state compounders and ensure that all compounding meets strong baseline criteria for preparing safe drugs and protecting patients.

Year	Reported cases	Reported deaths	Adverse event(s)	Compounding error	Product	State where compounding error occurred	State(s) where adverse event(s) occurred	Notes
2017	43[5]		Vision impairment, poor night vision, loss of color perception, ocular discomfort, nausea, loss of balance, etc.	Not reported	Injectable steroid antibiotic combination for administration in the eye	TX	TX	
2017	2[6]	1	One case of cardiac arrest; both experienced immediate hypersensitivity reactions	Product contained ungraded PEG 40 castor oil	Injectable curcumin emulsion infusion	CA	Not reported	
2017	1[7]		Paralysis (partial: face)	Not reported	Compounded injectable	TX	TX	

2017	41[8]		Septic arthritis	Bacterial contamination	Intra-articular injectable	NJ	NJ	Investigation revealed inappropriate use and handling of pharmacy bulk packaged products.
2017	1[9]		Hemorrhagic occlusive retinal vasculitis	Not reported	Intraocular injectable of triamcinolone, moxifloxacin, and vancomycin (TMV)	NJ	Not reported	
2017	2[10]		Tissue erosion at injection site	High pH; no glutamine detected in samples	Compounded injectable of glutamine, arginine, and carnitine (GAC)	FL	Not reported	
2016	17	2[11]	Fungal bloodstream infections	Contamination[12]	Injectable saline, heparin, vancomycin, and ceftazidime	NY	NY	IV flush solutions were not compounded under quality standards set by the United States Pharmacopeial Convention and were used past appropriate beyond-use dating. The two deaths occurred within 12 weeks of the fungal infection, but it is unclear whether the deaths were a result of the infections.
2016[13]	1		Overdose	Dose of manganese chloride 1,000 times stronger than usual dose[14]	Injectable manganese chloride	Not reported	Not reported	High manganese dose of 800 mg, compared with usual dose of 0.15-0.8 mg/day. Patient showed no resulting symptoms, but manganese overdose can result in side effects on the nerves and brain.
2016	3		Unspecified serious adverse events	Dose of morphine sulfate stronger than labeled concentration[15]	Injectable morphine sulfate	IN	IL, IN[16]	
2016	6[17]		Septic arthritis	Contamination	Viscosupplementation knee injectable	Not reported	SC	
2016	1[18]		Abscesses and osteomyelitis	Contamination	Unknown injectable	Not reported	NM	Investigation revealed unsafe injection and compounding practices.
2016	7[19]		Thyrotoxicosis	Super-potent compounded drug	Compounded oral liothyronine	SD	Not reported	
2015	7[20]		Hepatitis C	Contamination	Unknown injectable	CA	CA	Investigation into the clinic revealed infection control breaches and ongoing issues with infection control practices.
2015	Several[21]		Unspecified	Adulterated and misbranded drug product (contained different API)	L-citrulline	NY	Not reported	Some samples of the product were found to contain a different amino acid (N-Acetyl-Leucine) than what the label claimed, and others did not contain any L-Citrulline.
2015	5[22]		Redness, swelling, and pain at injection site	Contamination	Compounded betamethasone phosphate and betamethasone acetate	AL	Not reported	
2015	"Several"[23]		Unspecified	High dose of vitamin D_3[24]	Oral multivitamin capsule	FL	Nationwide[25]	High vitamin D_3 can cause significant short- and long-term effects.
2014-15	"Several"[26]		Unspecified	Contamination[27]	Sterile products	AL	Nationwide[28]	Administration of contaminated sterile

								products may result in serious and potentially life-threatening infections or death.
2014	Unknown		Oversedation	Dose of midazolam labeled with incorrect concentration[29]	Injectable midazolam	IN	Not reported	Compounded midazolam, a sedating agent, did not match the concentration on the product label. Oversedation can result in a range of effects from increased sleepiness to severe difficulty breathing.
2014	1	1[30]	Toxicity	Not reported	Compounded topical anesthetic cream (ketamine)	TX	TX	
2014	37[31]		Not reported	Contamination	Intravitreal injections of bevacizumab or ranibizumab	FL	Not reported	Bevacizumab and ranibizumab were repackaged in a manner that exposed sterile, preservative free vials to an uncontrolled environment.
2014	1[32]		Severe flushing, stinging, and dizziness	Dose of magnesium sulfate 200 times stronger than labeled concentration[33]	Compounded magnesium sulfate	TX	Not reported	
2013	1		Bacterial bloodstream infection	Contamination[34]	Injectable mineral product	TX	CA	Voluntary recall of injectable mineral product that contained bacteria with the potential for serious infection. A patient admitted to the hospital with an infection of the same bacteria.
2013	15	2[35]	Bacterial bloodstream infection	Contamination[36, 37,38]	Injectable calcium gluconate	TX	TX	The Centers for Disease Control and Prevention (CDC) has not conclusively linked the deaths to the contaminated drug.
2013	6		Fever, flu-like symptoms, soreness at injection site	Unknown[39,40]	Injectable methylprednisolone	TX	Not reported	A compounded injection was recalled due to complaints of fever, flu-like symptoms, and soreness at the injection site. Subsequent Food and Drug Administration inspection found that sterility and quality of the manufacturing process could not be assured.
2013	5		Serious bacterial eye infections	Contamination[41, 42,43]	Injectable bevacizumab for administration in the eye	GA	GA, IN	
2013[44]	8		Fungal eye infections	Contamination[45]	Injectable bevacizumab-triamcinolone for administration in the eye	Not reported	NY	Fungal infection of the eye caused significant visual impairment that persisted for at least three months from the incident.
2013[46]	1		Kidney failure and acute injury of the liver and pancreas	Unknown[47]	Injectable combination product for administration under the skin	Not reported	Not reported	Product is marketed for dissolving fat. The patient developed difficulties with digestion and metabolism as well as kidney failure, which required dialysis.
2012-	12		Bacterial bloodstream	Contamination	Parenteral infusion	Not reported	IL	Facility inspection revealed deficiencies

13[48]			infection					in the parenteral medication preparation and handling.
2012-13	26		Bacterial and fungal infections in skin and soft tissue	Contamination[49]	Injectable preservative-free methylprednisolone acetate	TN	AR, FL, IL, NC	Skin and soft tissue infections resulted after intramuscular injection of preservative-free product. Subsequent voluntary recall of sterile products was issued.
2012-13	778[50]	76	Fungal meningitis and other infections	Contamination[51,52]	Injectable preservative-free methylprednisolone acetate	MA	FL, GA, ID, IL, IN, MD, MI, MN, NC, NH, NJ, NY, OH, PA, RI, SC, TN, TX, VA, WV	Additional products (betamethasone, cardioplegia, and triamcinolone solutions) produced at the facility were also found to be contaminated, but adverse events linked to these products have not been reported.[53]
2012	47		Fungal eye infection; vision loss in majority of cases	Contamination[54]	Injectable brilliant blue-G (BBG) retinal dye and triamcinolone for administration in the eye	FL	CA, CO, IL, IN, LA, NC, NV, NY, TX	
2012	7		Bacterial bloodstream infection	Contamination[55]	Injectable fentanyl	NC	NC	
2012[56]	1		Overdose	Dose of flecainide four times stronger than ordered[57]	Oral flecainide liquid	Not reported	Not reported	Flecainide toxicity can cause abnormal heart rate and rhythms that can be severe and life-threatening, as well as increased liver enzymes, which can be an indicator of liver injury.
2012[58]	10	1	Bacterial bloodstream infection	Contamination	Contrast dye, anesthetic and steroid injections-single-dose vials	Not reported	AZ, DE	The outpatient pain clinic failed to follow Standard Precautions by using single-dose vials as multi-dose vials.[59]
2011-12[60]	15		Bacterial bloodstream infection	Contamination	Sterile products	Not reported	WV	Adverse events resulted from the use of bulk saline bag for IV flushes in a physician office practice.
2011[61]	1		Toxicity	Dose of 4-aminopyridine 10 times stronger than labeled concentration[62]	Oral 4-aminopyridine pills	Not reported	Not reported	Patient experienced stomach pain, anxiety, extreme sweating, and slow heart rate prior to developing life-threatening seizures. Following a complicated hospital stay, the patient sustained permanent short-term memory loss.
2011[63]	9		Bacterial eye infection, and one case of meningitis and encephalitis; four cases of loss of eyesight	Contamination[64]	Injectable bevacizumab for administration in the eye	Not reported	TN	
2011	12		Bacterial eye infection; three patients had eye removals	Contamination[65]	Injectable bevacizumab for administration in the eye	FL	FL	
2011	5		Blindness	Unintended presence of another medication[66]	Injectable bevacizumab for administration in the eye	CA	CA	Trace amounts of bortezamib, a cancer drug that is not intended for injection into the eye, were detected on a sample

								syringe.
2011	19	9	Bacterial bloodstream infection	Contamination[67]	Parenteral nutrition solution	Not reported	AL	
2010	1	1	Fatal overdose	Dose of sodium 60 times stronger than ordered[68]	Injectable sodium chloride	IL	IL	Acute sodium overload can cause symptoms ranging from fluid retention to seizures and coma, affecting multiple organs including lungs and kidneys. The patient was exposed to a potent sodium-containing fluid that was entered incorrectly during the preparation of the medication, resulting in death.
2010	1		Unspecified side effects	Dose of liothyronine 10 times stronger than ordered[69]	Oral liothyronine (T3)	AZ	Not reported	Liothyronine overdose can result in shakiness, increased heart rate, and palpitations.
2009	1	1	Fatality	Unknown[70]	Injectable hydromorphone	TN	Not reported	
2009	1	1	Fatal overdose	Dose of levothyroxine 18 times stronger than ordered[71]	Oral levothyroxine pills	NC	Not reported	
2009	9		Eye infection; at least one case of vision loss	Unknown[72]	Injectable preservative-free hyaluronidase for administration in the eye	FL	Not reported	Patients developed orbital cellulitis, a type of infection that results in inflammation of the eye.
2008[73]	1		Acute withdrawal	Dose of baclofen 7 percent of ordered dosage[74]	Injectable baclofen for administration in the spine	Not reported	Not reported	The product included a fraction of the intended dose of baclofen. Patient experienced frequent and severe spasms.
2008	1	1	Fatal overdose	Dose of sodium chloride 10 times stronger than ordered[75]	Injectable sodium chloride	NC	Not reported	Acute sodium overload can cause symptoms ranging from fluid retention to seizures and coma, and affect multiple organs including lungs and kidneys.
2008[76]	1		Persistent inflammatory reaction	Unknown[77]	Mesotherapy injections	Not reported	CO	Seven months after receiving mesotherapy injections, patient developed a persistent immune-mediated inflammatory reaction.
2007[78]	1	1	Fatal acute respiratory distress syndrome	Colistimethate sodium left in solution longer than recommended[79]	Colistimethate sodium inhaled solution	Not reported	Not reported	The prodrug of colistin is better tolerated than the active drug to which it converts. More than half of the prodrug is converted within two days in solution at a certain temperature. This premixed product was in solution for five weeks before further dilution for administration.
2007	3	3	Fatal overdose	Dose of colchicine eight times stronger than labeled concentration[80]	Injectable colchicine	TX	OR, WA	IV doses that exceed the standard single-use therapeutic dose of 2-4 mg per episode of gout have resulted in life-threatening toxicity. In this case, the doses were eightfold these limits.
2007	8	1	Bacterial bloodstream	Contamination[81]	Injectable fentanyl	Not reported	CA, MD	

			infection					
2006	1		Decreased consciousness, low blood pressure, and lack of oxygen	Mislabeled product leading to administration of different drug than ordered[82]	Epidural morphine sulfate (fentanyl/bupivacaine was ordered)	MS	AZ	Both fentanyl and morphine are in the same class of sedative analgesics. The symptoms of decreased consciousness, hypoxia, and hypotension are consistent with higher than intended opioid exposure.
2006	At least 70		Redness, swelling, bruising, rash, fever, and cellulitis	Betamethasone made with incorrect amount of preservative[83,84]	Injectable betamethasone	AL	Not reported	The product was voluntarily recalled, and a subsequent reformulation continued to include an incorrect amount of preservative. An FDA investigation discovered at least 70 complaints associated with the drug.
2006	1	1	Fatal overdose	Dose of chemotherapy infusion diluted with toxic amount of sodium chloride[85]	Chemotherapy infusion	OH	OH	Acute sodium overload can cause symptoms ranging from fluid retention to seizures and coma, and affect multiple organs including lungs and kidneys.
2006	1	1	Fatal overdose	Dose of zinc 1,000 times stronger than ordered[86]	Neonatal parenteral nutrition solution	NV	NV	The dose was incorrectly entered for pharmacy preparation as milligrams instead of micrograms, resulting in a thousandfold overdose.
2005	3	1	Fatal overdose, cardiac arrest	Dose of lidocaine and tetracaine higher than usual[87,88]	Topical combination anesthetic creams (lidocaine and tetracaine)	NC	NC	
2005	19	1	Bacterial bloodstream infection	Contamination[89,90]	Injectable magnesium sulfate	TX	CA, MA, NC, NJ, NY, SD	
2004-06	80		Bacterial bloodstream infection	Contamination[91]	Injectable heparinized saline	TX	MI, MO, NY, SD, TX, WY	
2004-05	6		Bacterial eye infection; all cases had partial or complete loss of vision; two patients had eye removals	Contamination[92]	Trypan blue eye drops	Not reported	Not reported	
2004-05	11	3	Systemic inflammatory response syndrome	Contamination[93,94]	Cardioplegia solution for administration during heart surgery	MD	VA	
2004	2		Bacterial bloodstream infection	Contamination[95]	Injectable heparin-vancomycin	FL	CT	
2003	2		Overdose	Dose of liothyronine stronger than ordered[96]	Oral liothyronine (T3) pills	AZ	Not reported	Unused pills of both patients were analyzed, and the concentration of the active ingredient was found to be 800 and 900 times higher than intended. High T3 levels can result in shakiness, increased heart rate and palpitations.
2002-04	1	1	Fatal overdose	Dose of lidocaine and tetracaine higher than usual[97,98]	Topical combination anesthetic cream (lidocaine and tetracaine)	UT	AZ	

2002[99]	1		Toxicity	Dose of clonidine 10 times higher than ordered[100]	Oral clonidine capsules	Not reported	Not reported	Patient showed early signs of central nervous system depression (somnolence and drowsiness) and miosis (constricted or small pupils).
2002[101]	1		Toxicity	Dose of clonidine 87 times higher than ordered[102]	Oral clonidine liquid	Not reported	Not reported	Patient showed signs of central nervous system depression, consistent with severe clonidine toxicity. Miosis (constricted or small pupils) was also noted.
2002	2		Meningitis	Contamination[103]	Injectable methylprednisolone for administration in the spine	MI	MI	
2002	7	2	Fungal meningitis and sacroiliitis	Contamination[104,105,106]	Injectable methylprednisolone acetate for administration in the spine	SC	NC	
2001	2		Bacterial bloodstream infection	Contamination[107]	Injectable preservative-free heparinized saline	Not reported	Not reported	
2001[108]	1		Overdose	Dose of clonidine 1,000 times stronger than ordered[109]	Oral clonidine liquid	Not reported	Not reported	During preparation of liquid clonidine from solid pills, milligrams were substituted for micrograms, resulting in a thousandfold overdose. Patient's initial presentation included hyperventilation, an unusual feature of clonidine toxicity. Severe clonidine toxicity can result in low blood pressure, central nervous system depression (lethargy, mental status changes), and cardiopulmonary instability (heart and breathing problems).
2001	13	3	Five cases of meningitis; five cases of epidural abscess; one patient had an infected hip joint; two unspecified	Contamination[110,111]	Injectable betamethasone for administration in spine or joint	CA	CA	
2001	4		Bacterial bloodstream infection	Contamination[112]	Injectable ranitidine	Not reported	Not reported	
Total	1,416	114						

This chart includes U.S. illnesses and deaths associated with compounded or repackaged medications from 2001 to the present. Adverse events were drawn from FDA and CDC resources as well as journal and news articles.

In the total, "several" reported cases were counted as two adverse events, and an "unknown" number of reported cases were counted as zero adverse events.

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Mr. BURGESS. Thank you, Ms. Jungman.

Ms. Dargan, you are recognized for 5 minutes, please.

STATEMENT OF NANCY DARGAN

Ms. DARGAN. Thank you. Good afternoon, and thank you for the opportunity to be here today.

My name is Nancy Dargan and I live in Brighton, Michigan. I am going to tell you how a contaminated compounded medication permanently harmed my health, putting a premature end to my career and ruining my family's finances and plans for our future.

To begin my story, I have to travel back to early 2012. I was experiencing pain from arthritis in my back and hip, and my primary physician referred me to a pain clinic for periodic injections of a steroid called methylprednisolone, which is a compounded product.

The shots gave me some relief and I continued my busy career, my life as a grant writer, a business consultant. And everything changed that August. I had driven from my home in Michigan to West Virginia to meet with a new client and help them set up a nonprofit organization. During my stay I began to feel sick, but I didn't think very much of it at first. But the symptoms steadily worsened and I realized I had to cut my trip short.

As I drove home, an excruciating burning sensation developed in my right hip spreading down to my knee. The pain became so unbearable that I had to use my left foot for gas and brakes. I arrived in Michigan completely unable to bear weight on my leg, and my husband took me immediately to the hospital to figure out what was going on.

The doctors ordered x-rays, a spinal tap, a biopsy, and several other tests and expressed that my condition was something they had not seen before. They worked to treat my pain, but, initially, had no clear diagnosis. So, they sent me home.

It was there that I got a call from the pain clinic that had administered my steroid injections. They said I potentially received contaminated drugs and should go to the emergency room immediately.

By this time, the hospital staff were realizing that my case was not an isolated incident. Other patients were showing up at the hospital with infections and pains similar to mine, and like several of them, I was ultimately diagnosed with a fungal infection.

I underwent surgery and spent 2 weeks in the hospital. I was placed on a maximum dose of a drug called Voriconazole, a very powerful antifungal medicine with severe side effects that seemed nearly as bad as death itself. I took it four times a day for 14 months, even waking in the middle of the night for doses.

After I was discharged, my husband Mike became my caretaker, at great personal expense to him, both mentally and physically. His job was one of the worst a care partner can experience, dealing with the unknown effects of a major medical event. I can't tell you how many times Mike would come into the room and I would be carrying on a conversation with my daughter, who had died in 1979. That was the result of hallucinations caused by the antifungal medication. I would call out for our pet, and I would get frustrated because he wouldn't respond, and we had had him put down the year before due to cancer.

Through all this nightmare, Mike made sure that I made it to every doctor's appointment, even often three or four per week, on top of other tests, including blood draws every Friday. If something needed to be done, including our household chores, he did it. If something needed to be done around the house, he never left my side unless I was napping and he could get errands run. He was not only my caregiver, but my constant advocate.

Of course, all of this has had a devastating impact on our lives and plans for the future. Financially, we have lost everything to this event. The hospital and doctor bills were astronomical. I lost my ability to maintain self-employment and, regrettably, had to close my business and refer my clients to others.

We had partial ownership in a cabin left to my husband and his sister by his father, but had to sell our interest in this treasured family property which we enjoyed so much and which had such wonderful memories for my husband. I saw the grief in Mike's eyes every time we had to sell something he loved. The financial toll has threatened our retirement and our independence as we grow older together.

Today, 5 years after this tragedy began, I still have recurring symptoms and numerous side effects. I walk with a limp and cannot get an orthopedic surgeon to consider replacing my right hip because there are still fungal pockets on my bones. My pain levels are always elevated. My disease and treatment have made me vulnerable to opportunistic infections that have attacked my kidneys and my sinuses, and I still continue to suffer from short-term memory loss, and it is getting worse every year.

Before this happened to me, I had never heard of drug compounding, and I never would have imagined coming to Washington to speak about it. But I feel obligated to do so. Sadly, there are many others who have endured as much suffering and more. I weep for the 60-plus families who lost their loved ones to this deadly and preventable outbreak and for the hundreds of patients who live every day with the lasting consequences of illnesses caused by contaminated compounded drugs. Many of these people are friends and neighbors who live in our community, and I am here to speak up for them, too. I don't want another soul to experience what we have.

As a result of contaminated drugs and a failure to oversee them, I am now a person who will spend the rest of my days dealing with a complex illness. It wasn't easy for Mike and I to get here today. We hope that by sharing our story we can help prevent this from happening to someone else or anyone else.

Thank you for allowing me to take some of your time, and I welcome any questions you might have.

[The prepared statement of Ms. Dargan follows:]

Testimony of Nancy Dargan
before the Committee on Energy and Commerce
Subcommittee on Health
United States House of Representatives
January 30, 2018

Good morning, and thank you for allowing me to be here today to provide testimony regarding the Drug Quality Safety Act (DQSA). My name is Nancy Dargan, and I live in Brighton, Michigan. I am going to tell you about how a contaminated compounded medication permanently harmed my health, putting a premature end to my career and ruining my family's finances and plans for the future.

To begin my story, I have to travel back to early 2012. I was experiencing pain from arthritis in my back and my hip, and my primary physician referred me to a pain clinic, for periodic injections of a steroid called Methylprednisolone. The shots gave me some relief, and I continued my busy life as a grant writer and business consultant, until everything changed that August.

I had driven from my home in Michigan to West Virginia to meet with a new client and help them set up a nonprofit organization. During my stay, I began to feel sick, though I didn't think much of it at first. But the symptoms steadily worsened, and I realized I had to cut my trip short. As I drove home, an excruciating burning sensation developed in my right hip and spread down to my knee. The pain became so unbearable that I had to use my left foot for the gas and brake pedals. I arrived in Michigan, completely unable to bear weight on my leg, and my husband Mike took me to the hospital, to try to figure what was going on.

The doctors ordered x-rays, a spinal tap, a biopsy, and other tests, and expressed that my condition was something they had not seen before. They worked to treat my pain but initially had no clear diagnosis and sent me home. It was there that I got a call from the pain clinic that had administered my steroid injections. They said I'd potentially received contaminated drugs and should go to the emergency room immediately. By this time, the

hospital staff were realizing that my case was not an isolated one. Other patients were showing up at the hospital with infections and pain similar to mine, and like several of them, I was ultimately diagnosed with a fungal infection.

I underwent surgery and spent two weeks in the hospital. I was placed on the maximum dose of Voriconazole – a powerful antifungal medicine with side effects that seemed nearly as bad as death itself. I took it 4 times a day for 14 months, even waking in the middle of the night to receive a dose.

After I was discharged, my husband, Mike, became my caretaker at great personal expense to him, both mentally and physically. His job was one of the worst a care partner can experience – dealing with the unknown effects of a major medical event. I can't tell you how many times Mike would come into a room and I would be carrying on a conversation with my daughter who died in 1979 – the result of hallucinations caused by the antifungal medication. I would call out for our pet, Deuce, and would get frustrated when he wouldn't respond. We had put him down the year before due to cancer.

Throughout this nightmare, Mike made sure I made it to every doctor's appointment—often 3 or 4 per week—on top of other tests including blood draws every Friday. If something needed to be done, including all of our household chores, he did it. For 14 months, he never left my side unless I was napping and he could get errands run. He was not only my caregiver but my constant advocate.

Of course, all of this has had a devastating impact on our lives and plans for the future. Financially, we lost everything to this event. The hospital and doctor bills were astronomical. I lost my ability to maintain self-employment and regrettably had to close my business and refer my clients to others. We had partial ownership in a cabin left to my husband and his sister by his father, but had to sell our interest in this treasured family property, which we enjoyed so much and which held wonderful memories for my husband. I saw the grief in Mike's eyes every

time we had to sell something he loved. The financial toll has threatened our retirement and our independence as we grow older together.

Today, 5 years after this tragedy began, I still have recurring symptoms and numerous side effects. I walk with a limp and cannot get an orthopedic surgeon to consider replacing my right hip because there are still fungal pockets on my bones. My pain levels are always elevated. My disease and treatment have made me vulnerable to opportunistic infections that have attacked my kidneys and sinuses. I continue to suffer from short term memory loss, and it is getting worse year after year.

Before this happened to me, I had never heard of drug compounding, and I never would have imagined coming to Washington to speak about it. But I feel obligated to do so because sadly, there are many others who have endured as much suffering or more. I weep for the 79 families who lost their loved ones to this deadly and preventable outbreak, and for the hundreds of patients who live every day with the lasting consequences of illnesses caused by contaminated compounded drugs. Many of these people are friends and neighbors who live in our community, and I am here to speak up for them, too.

I don't want another soul to experience what we have. As a result of contaminated drugs, and a failure to oversee them, I am now a person who will spend the rest of my days dealing with a complex illness. It was not easy for Mike and I to get here today. We hope that by sharing our story, we can help prevent this from happening to anyone else.

Thank you for allowing me to take some of your time today to allow me ta share my story.

Mr. BURGESS. Thank you, Ms. Dargan. We appreciate your testimony, and appreciate all of you for spending so much time with us today.

I am going to yield to Mr. Griffith 5 minutes for questions, since he was the Representative who was instrumental in moving this legislation along several years ago. So, Morgan, you are recognized for 5 minutes.

Mr. GRIFFITH. Thank you, Mr. Chairman. I appreciate it very much, and appreciate all of you being here.

I think sometimes we are talking at cross-purposes because I don't think any of us want to see somebody like NECC coming back, because they were operating in a couple of dozen states, if I remember correctly, in my state and your state, Ms. Dargan——

Ms. DARGAN. California.

Mr. GRIFFITH [continuing]. And California. They have been kicked out of Colorado. They were national manufacturers who were lying about what they were doing. They weren't your traditional small pharmacy that was doing even small batches.

And so, what we have to do, as Ms. DeGette says, we have to try to find that balance, because we have situations that, in all fairness, I wasn't aware that one of the solutions to resolve the problem was that we were going to have folks going and picking up drugs. I forget who it was. I think a couple folks were talking about the dentist. Mr. Olson? And I think somebody, maybe Dr. Brod mentioned it, too, that they are having the patients have to go to pick up the drug from the pharmacist because of the new interpretation on 503A. I think we all think 503B and the new stuff is good stuff. It is a question of that balance.

And so, if you could, first, Mr. Olson, and then, Dr. Brod, just tell me quickly about you and your testimony, but what other situations besides the dentist who has to send somebody in and, then, a child has to go through or an adult has to go through pain for a day or two, until the dentist can get them back in?

Mr. OLSON. Thank you for the question, Congressman.

The dentist is the most critical one to my office. We have other dental products that we had provided in the past. But I think the other situation that we have is we are having to teach parents to do this themselves at home, instead of me providing it now. So, it is not necessarily an office-use situation, but because I am not able to compound it—for example, insulin dilutions, we are having to teach parents to dilute their own insulin at home. We are having to teach patients to draw up their own medications at home because we are not allowed to perform that in our pharmacy. And we are just unsure, if we do that, whether we will be violating anything.

Mr. GRIFFITH. Dr. Brod, you had some other examples?

Dr. BROD. Yes, several instances. So, we use cantharidin quite a bit. It is not commercially available. So, we are relying upon getting it from a compounding pharmacy. It is used to treat predominantly children and, also, genital warts, too.

So, you can envision a situation where a child comes in. They are a little scared to begin with. We recommend cantharidin. It is painless. Other treatments that we have, such as freezing or burning,

to get rid of warts and molluscum, common skin infections, are very painful and intimidating.

The parent took off of work. The child is out of school. We say, "You need a patient-specific prescription." The 503Bs, these are small batches, so we are having trouble getting them at any reasonable cost. So, the parent, then, has to go to the pharmacy, schedule another appointment back into the office.

The other problem, too, is we treat a lot of genital warts which carry oncogenic viruses. Patients with that don't want to come in in the first place. A lot of the other treatment alternatives, especially in patients with skin of color, can cause dyspigmentation and scarring. Things like cantharidin or podophyllin are really good options. And diminishing access creating inefficiencies I think is actually a public health issue.

Mr. GRIFFITH. Do you find that some people, when they find out they have got to go to the pharmacist and, then, make another appointment, that they just don't do the treatment at all?

Dr. BROD. Yes. Sometimes they don't do the treatment at all; they don't come for follow-up visits, yes.

Mr. GRIFFITH. Does anybody disagree that we all think that the 503B program as it was originally intended for those medium to larger folks is a good thing? Anybody disagree with that?

[No response.]

So, we have got to find that balance. Dr. Williams, do you have examples of where that balance is askew right now?

Dr. WILLIAMS. I do, I believe. One of the most devastating conditions that can occur in your eye is an acute bacterial infection. This can either be on the surface of the eye, as I discussed with that patient with a corneal problem, or in the——

Mr. GRIFFITH. I am running out of time. So, if I could get you to cut to the chase?

Dr. WILLIAMS. The answer to your question is, yes, we need office-based access to specific antibiotics that are not available through the 503B mechanism.

Mr. GRIFFITH. And you don't need a big batch? You just need a couple of small batches, isn't that correct, from time to time?

Dr. WILLIAMS. I just need enough to have on the shelf, so when that one patient a week comes in, I can take care of him.

Mr. GRIFFITH. And I worry about my rural areas and my folks who have a problem, suddenly an emergency late at night or on the weekend, and there is no compounding pharmacy readily available in that small, rural community. Is that a concern for your doctors as well?

Dr. WILLIAMS. Absolutely. That is one of the most common scenarios that we hear.

Mr. GRIFFITH. That is what I am hearing, too.

I appreciate all your testimony. I think everybody had some valid points. I figure we have got to figure out a way. Our job is to help work with the FDA and find that proper balance.

And with that, Mr. Chairman, I yield back.

Mr. BURGESS. Thank you, Mr. Griffith.

I am going to proceed with my 5 minutes for questions. Mr. Green, I will come to him next. I was going to give him time to collect his thoughts since he just rushed in here.

Dr. Williams, several references have been made to an ophthalmic preparation that was injected after cataract surgery. Now a patient comes in for cataract surgery in an outpatient facility. They are coming in with the expectation that they are either going to need drops or injection after the surgery, is that correct?

Dr. WILLIAMS. That is correct.

Mr. BURGESS. So, in that instance, could they not come in with the prescription already in hand or having picked it up themselves at a pharmacy? What would prevent that from being the way this would be administered?

Dr. WILLIAMS. So, for an elective procedure such as cataract surgery, that would be a possibility. The drug that the specific episode, it is still not exactly clear what happened. It does not appear to be a contamination in the sense of a microbial or infectious cause. It seems to be that there was a toxicity involved when the two drugs were mixed. And so, it is still not entirely clear exactly what happened. But, even if those patients had had a prescription and brought that in, it probably would not have changed the outcome in this particular case.

Mr. BURGESS. Correct. The compounds would have been the same and the doses and the route of administration would have been the same, and the outcome you would predict would be the same. So, I think that is a point well-taken. Just having a prescription does not necessarily protect you in all instances from an untoward event.

In the case of the methylprednisolone acetate—and I do remember that so vividly from our hearings a couple of years ago—so, here you have got a compound that has to be preservative-free because it is going into the epidural space and you don't want to damage a nerve with a preservative. And, of course, being a steroid, it reduces the body's ability to fight infection. So, it is like everything culminated in these cases to really create literally one of the worst things that I can recall having ever seen.

In addition to all the sympathy I have for everyone else, the sympathy for the emergency room doctors—I know we had a patient here in the previous hearing, and it was so difficult for the attending physicians in the emergency room to really get a grasp of what was going on, similar to other events that have happened in this country. When there was anthrax in the post office here in suburban Washington, the same thing, the emergency room doctors, seeing those patients out of context, it made it very, very difficult for them.

Ms. Adams, you referenced the bulk active pharmaceutical ingredients. Can you give us an idea of which bulk pharmaceutical ingredients you are talking about?

Ms. ADAMS. Yes, I can. Thank you.

So, when we look at the list, as an example, of the 200 permissible substances in Category I for bulk compounding right now, as we cross-reference that list, we feel that almost half of them have an FDA-approved vial that could be used rather than bulk substances. So, it is a long list that we think needs much revision.

Mr. BURGESS. OK.

Ms. ADAMS. And I think important to note, revising the list is something that for sure needs to happen. But, in addition to that—

that is not a holistic approach—we also think that, really, to address the issue beyond just that list of 200 substances, essentially copy needs to be revised to differentiate between compounding that starts from FDA-approved vials and compounding that starts from bulk substances.

Mr. BURGESS. And are you assisting the agency in revising that list?

Ms. ADAMS. We are. We have got a good dialog going with the agency. We have got an opinion, which we have documented for them, and we are happy to continue to serve as a resource in that regard.

Mr. BURGESS. Very well.

Mr. Olson, again, thank you for being here for the people that you represent. Let me just ask you, on the FDA's draft memorandum of understanding, they decided to rescind the original draft and they are going through significant revisions. States are going to be required at some point, though, to sign onto this memorandum of understanding, is that correct?

Mr. OLSON. Yes, Congressman, that is my understanding.

Mr. BURGESS. And what will be the consequences if a state decided we are not going to sign onto that memorandum of understanding? How would that leave you?

Mr. OLSON. It would leave us very conflicted as to what we are supposed to do. Because if we abide by our state laws, that is what we should be abiding by. But in my situation I am only licensed in Wisconsin, so I wouldn't have to worry about the situation specifically. But I would think it would put pharmacies in bordering towns or bordering areas in a precarious position to figure out, well, wait, if the state I am in signed it, but the state I am shipping into didn't, then where does that leave me, or vice versa. Even though, to be fair, most of the time if you are shipping into another state, you have to be licensed in that other state as well. So, there is a state license that you would have in both states. It would just be the conflicting memorandum of understanding about whether you can ship and how much you can ship into that state.

Mr. BURGESS. Thank you.

And, Dr. Brod, just as an observation, years ago I remember discovering that a little bit of bicarbonate in a vial of lidocaine could make a tremendous difference as to what your patients thought about you. And I didn't realize I was compounding when I was doing that. I just thought I was being a nice guy. But in your testimony you reference that as an episode of compounding, is that correct?

Dr. BROD. A tremendous difference. And in speaking with colleagues who haven't been able to buffer in the office, they say that the patients note a distinctive difference. We are very reliant on it. We perform extensive surgeries, but we do it in the outpatient setting, Mohs surgery with reconstruction. Having the bicarb to buffer the lidocaine, so that injections in multiple areas of the face are tolerable, it really allows us to do surgery outpatient instead of going into a surgical facility with sedation and those types of things. So, it is a world of difference and our patients really appreciate it very much.

Mr. BURGESS. Before I yield to Mr. Green, let me just echo the comments of Mr. Griffith again. We appreciate so much you all being here. We recognize that there are some issues that we are going to have to work through, and we appreciate your help in getting there.

Mr. Green, you are recognized for 5 minutes, please.

Mr. GREEN. Thank you, Mr. Chairman.

I apologize to the panel about being late, but I had a medical that I couldn't do. I couldn't have any of my great staff deal with that.

But I want to thank you for being here. And you know that Congressman Griffith and Congressman DeGette and the chairman, we want to fix it because we want to make sure the system works. And that is what we did after the tragedies in Massachusetts with 65 people dying. But we appreciate you all being here and giving your stands on it, so we can actually work through and see what the solutions will be.

Ms. Jungman, I know the Pew Charitable Trust has done a lot of research on compounded drugs and was actively engaged in this issue before the DQSA was signed into law and since. I think it would be helpful to take a step back and get an understanding of why this law was necessary and how we can support its implementation in a manner that strikes the right balance between access and safety.

Ms. JUNGMAN. I would be delighted to answer that question, and thank you.

So, as you know, the history of compounding has a long and complicated legal history, right? It has been a part of traditional pharmacy practice for as long as pharmacy has existed. But over time businesses grew up; they were compounding at a larger scale. And Congress first tried to tackle that in the nineties, met some legal challenges that Dr. Gottlieb referred to. And NECC I think really brought to the forefront of everyone's mind the scale of the patient risk that was there.

We have done a lot of work trying to capture the adverse events that have happened in all sorts of facilities from compounding pharmacies, but there is really not a comprehensive way to know what the risks, what the scale of the impact is.

And so, what the DQSA does is draw really clear lines that are designed to ensure that patients have access to the highest quality product that meets their clinical need. So, if you can use an FDA-approved product, that is great. If you can't use an FDA-approved product, then you want a product that is made under appropriate quality standards. And so, there is a balance there that is about both ensuring that the quality standards are appropriate, but that the lines are really clear, so that everyone knows which side of the line they have to be on.

Mr. GREEN. I was a state legislator in Texas and we worked with our pharmacy board and trusted them. I know, typically, we have these national legislative groups that have standard pieces of legislation from state to state. So, we do have some kind of commonality between Texas and Louisiana, or whatever. But is there anything like that, so we wouldn't have such 50 different? Is there any agen-

cy that does that, and say, "This is the standard way you pharmacy boards deal with it."?

Ms. JUNGMAN. The National Association of Boards of Pharmacy does have a model law that does talk about some of these issues. There is, of course, still state variation. But the research that we will publish in about 2 weeks, not quite in time for this hearing, will show that states are really beginning to align with, really kind of come into compliance with each other and in line with DQSA.

Mr. GREEN. What is the history of responsibility between the state boards of pharmacy and the FDA? And how did DQSA change that defining line?

Ms. JUNGMAN. At the time that the NECC outbreak happened there was a lot of confusion. And I think we saw that in the hearings that happened at that time, where there was a lack of clarity about who was supposed to be taking charge of these institutions. And so, the DQSA really stressed accountability and clear lines for that reason. So, it was, of course, about improving the safety of the products, but it was also about making sure that everyone knew who was, to use the phrase that kept being used at the time, "on the flagpole". Which regulatory agency was in charge of any type of activity?

And so, the Congress at the time—and you gentlemen know this better than anyone—considered a lot of different ways of drawing those lines. Could you do it based on volume? Could you do it based on geographic reach? But, ultimately, the prescription requirement was the line that was clear and enforceable, and that was considered to be really important for ensuring that the right quality standards were applied.

Mr. GREEN. When we had the hearings earlier on the tragedy in Massachusetts, I remember we had FDA and the Massachusetts Pharmaceutical Board, and they looked at each other. Here we were sitting up here and saying, somebody has got to be minding the store, and that is what we are looking for.

States are critical partners in the effort to ensure patient access to safe compounded drugs. And I understand Pew will soon release a report with our National Association of Boards of Pharmacy which assesses best practices that are more achievable by the states. Hopefully, we can have that coordination. Again, we just want somebody to make sure, whether it is the state level or across border lines, the FDA, somebody needs to be minding the store to make sure we don't have an incident like we did in Massachusetts, well, literally countrywide, but it originated there.

Thank you.

Ms. JUNGMAN. Thank you.

Mr. GUTHRIE [presiding]. Thank you.

And I will now recognize myself for 5 minutes for questions.

Dr. Williams, your testimony has been about the critical need for office use of compounded drugs. How do we ensure office use is allowed while protecting patient safety?

Dr. WILLIAMS. Well, I think that is the critical issue we have been discussing all day. We do not think that the patient-specific prescription contributes to safety in any way. It would allow us to track the use of drugs perhaps. But, for the incidents where timely treatment is critical—and as I mentioned earlier, infections of the

eye, even a delay of an hour or two will have adverse effects. So, we need to be able to have these drugs available in office. We can just pull them off the shelf. And it is just absolutely critical.

I alluded earlier to the pool cleaner for this type of infection. And it sounds crazy that we would use a pool cleaner for an infection in the eye, but I can assure you, if you had that infection, you would want immediate access to that treatment.

Mr. GUTHRIE. Thank you very much.

Ms. Adams, some compounded drugs for ophthalmology are being done only be a single facility. Do you why this is and was this the case before DQSA?

Ms. ADAMS. Thank you.

I don't have specific knowledge of where ophthalmology drugs are compounded and in what scale. PharMEDium is strictly sterile-to-sterile compounding in our 503B facilities. And as we stand right now, we do not serve the ophthalmology patient population. So, I don't have specific knowledge of that.

Mr. GUTHRIE. Would you know anything about that, Dr. Williams? Is it done by a single facility and why is that the case? Was it the case before DQSA?

Dr. WILLIAMS. So, before the DQSA, it was done by a single facility, so-called traditional or 503As. There are many ophthalmic drugs that are available through 503Bs, and we encourage our members to use those. It is these relatively rare conditions, but, yet, very potentially catastrophic, where we need immediate access. And simply writing a prescription and, then, having the patient have to go get it, if, in fact, they can get it—these are drugs that are not typically manufactured or compounded at a high rate. So, for a rural population, it could be literally hundreds of miles, as I stated in my statement.

Mr. GUTHRIE. Yes, absolutely. Thank you very much.

I am going to yield the time, my remaining time, to Mr. Griffith of Virginia.

Mr. GRIFFITH. Mr. Hodges, I am going to ask you a question. It is getting down a little deeper in the weeds, and we still want to reach a balance. But the committee has heard, much to their chagrin, all about my family's allergy issues. And some pharmacies specialize in serving patients with specific needs, such as a drug without a particular dye or ingredient for those patients who do have allergies to those particulars. And they do it because they specialize. They do it in multiple states.

If the shipment of a patient-specific compounded prescription is limited by the memorandum of understanding, will patients be able to get all of these medications from local pharmacies?

Mr. HODGES. Thank you, sir.

Simply put, no, they will not. Not all pharmacies make all products for every type of patient population. So, for instance, we engage in allergy immunotherapy. There are only a handful of pharmacies in the country that offer that. And so, it is particularly a concern for us that we cannot meet these patients' needs because we are not able to provide it, in fear of the MOU, if it is implemented.

And so, what we want to do is work closely with the FDA. We have some ideas about what we can do to ensure the quality and

access. We have ideas. But we are looking for a sit-down with the Commissioner. We have requested this year and years prior we have sent letters, and we are not getting a response. And so, what we would like to do is ask that the Commissioner have a sit-down with us. We have some ideas on what we can do.

But, to answer your question, it would be a problem if the MOU went into effect, especially for patients that live across state borders.

Mr. GRIFFITH. All right. I appreciate that.

I will tell you that Commissioner Gottlieb, of all the folks that we have dealt with at that level, is probably the most responsive that the committee has found. And so, we will work towards that. But he is very responsive, tries to listen, tries to pay attention. And so, it is a good working relationship. Hopefully, together we can find a balance to the issues that have been raised by today's hearing.

I appreciate all of you very much.

And I yield back, Mr. Chairman.

Mr. GUTHRIE. Thank you. The gentleman yields back, and I yield back my time.

Seeing that there are no further members wishing to ask questions, I would like to thank all of our witnesses for being here today.

I would like to submit the statements from the following for the record: American Society of Health-System Pharmacists; American College of Mohs Surgery; Avella; Outsourcing Facilities Association; American Society of Cataract and Refractive Surgery; National Association of Chain Drug Stores; American Pharmacists Association; a joint statement from the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma and Immunology.

[The information appears at the conclusion of the hearing.:]

Mr. GUTHRIE. Pursuant to committee rules, I remind members they have 10 days to submit additional questions for the record, and I ask that the witnesses submit their response within 10 business days upon receipt of the questions.

Without objection, the subcommittee is adjourned.

[Whereupon, at 2:43 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

Joint Statement for the Record

Hearing of the Energy and Commerce Committee,
Subcommittee on Health
on
Examining Implementation of the Compounding Quality Act

January 30, 2018

The undersigned stakeholders from the public health, manufacturing, and outsourcing facility communities, appreciate this opportunity to submit a statement for the record outlining our recommendations on the full implementation and enforcement of the Drug Quality and Security Act (DQSA).

We applaud the Energy and Commerce Committee's (Committee) bipartisan efforts to defend the DQSA and ensure its proper implementation[1], including by holding this hearing. We also commend the Committee's continued work with the Food and Drug Administration (FDA or Agency) as part of those efforts. We too look forward to continuing to work with the agency as it implements the DQSA, including the recently released Compounding Policy Plan and guidances.[2]

As the Committee members know, millions of Americans rely on prescription medicines on a daily basis, and they expect and trust that those drug products will be safe and effective. Some of those Americans rely on receiving compounded medicines, whether it is because they are allergic to a dye in the original drug, because they are unable to swallow pills and need a liquid form, or for any other of the number of reasons that an FDA-approved drug might not meet a patient's medical need. Due to the leadership of this Committee, Congress enacted the DQSA in 2013, in response to a public health crisis associated with compounded drugs, where approximately 76 people died and 778 individuals in 20 states were stricken with meningitis or other infections.[3] The DQSA was intended to ensure that compounded drugs meet appropriate standards to ensure drug quality, and to protect patients. It is imperative that all members of the health care

[1] Such as the House vote against the Carter Amendment, which failed by recorded vote: 141-279.
[2] FDA, "2018 Compounding Policy Priorities Plan" (January 2018); FDA, "Compounded Drugs That Are Essentially Copies of Approved Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act" (January 2018).; "Compounded Drugs That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act" (January 2018).; and "Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application" (January 2018).
[3] Tennessean. "Meningitis Outbreak Trial: Potentially Deadly Bacteria Found in NECC Drugs" (October 2017). https://www.tennessean.com/story/news/2017/10/12/meningitis-trial-new-england-compounding-center/759459001/

system work together to ensure that patients are protected, and that compounded drugs are made under appropriate quality standards. As Congress provides oversight over the implementation of the law, we recommend that the oversight follow these principles:

Ensure compounding is performed under appropriate standards wherever it occurs[4]

The foundation of the DQSA is a risk-based approach, ensuring that compounding takes place under quality standards appropriate to the level of risk of the drugs being produced. Current federal law, as amended by DQSA, will help prevent another tragedy – but only if compounding is performed in a way that is consistent with the law, and if FDA prioritizes the law's implementation and enforcement.

Regulators should ensure that physicians can acquire compounded drugs produced under the appropriate standards, unless physicians are able to produce drugs under those standards themselves. Similarly, if current Good Manufacturing Practices (cGMPs) are tailored to the needs of smaller-scale producers, any such revision must preserve outsourcing facilities as a reliably safe supply of sterile office stock product.

Ensure that patients who have a clinical need for a compounded drug have access to the highest-quality product

Compounded drugs benefit patients who have a medical need for a particular drug formulation that is not commercially available. It is important that these drugs are produced in full compliance with applicable standards and under conditions that guarantee potency, stability and freedom from contamination.

Encourage the implementation of an effective, robust "Section 503B" program

The DQSA established the outsourcing facility category to ensure hospitals, other health care facilities, physicians, and patients have access to a safe supply of high-quality, sterile drugs. This category provides for the compounding of drugs under rigorous standards different than those that apply to traditional compounders, including adherence to cGMPs. 503B outsourcing facilities can compound without patient-specific prescriptions, strongly differentiating 503B facilities from traditional compounders. This distinction is integral to the DQSA because it incentivizes compounding facilities to register with FDA and ultimately make the investments necessary to bring their facilities into compliance with the standards under Section 503B. DQSA also clearly restricts the use of bulk ingredients for 503B compounding except when truly clinically necessary. This restriction must be enforced by FDA.

Preserve the traditional role of pharmacy practice consistent with the DQSA prescription requirement

A key distinction between Section 503A and Section 503B in the DQSA is the prescription requirement. While Section 503B allows for outsourcing facilities following cGMP standards to provide stock supplies of medications, Section 503A dictates that traditional compounders must obtain individual patient prescriptions to compound and dispense or distribute medications. Although limited quantities can be produced in advance of the receipt of a prescription in the case that a history for such prescriptions exists, a prescription

[4] Such as the enforcement of the MOU provision of Section 503A(b)(3)(B)(i), which establishes an agreement between a State and the FDA regulating the distribution of inordinate amounts of compounded drug products. The MOU provision ensures that there are adequate protections and regulations in place, which makes states responsible for investigating complaints about compounded drugs made in the state and distributed outside of the state. This ensures that compounders shipping compounded drugs interstate are held to robust quality and safety standards. In their recently released "2018 Compounding Policy Priorities Plan", FDA stated that they intend to release a revised version of the current MOU, with language that would increase the amount considered to be "inordinate" from 30 to 50 percent of total drugs distributed interstate, as well as putting a mechanism in place that would require reporting obligations on compounders that distribute more than 50 percent across state lines.

must be received prior to distribution. The foundational aspect of a prescription requirement ensures the traditional practice of pharmacy is maintained, including the accountability of a patient care triad between a patient, a prescriber, and a pharmacist.

Protect the FDA approval process (innovator and generic pathways) by ensuring that commercially available drug products cannot be copied

Another key to protecting patients is safeguarding the FDA approval process for new drugs. Unlike compounded drugs, FDA approved drugs are supported by substantial evidence demonstrating safety and efficacy. To uphold patient safety, Congress sought to ensure that FDA-approved drugs would be used whenever possible, including in the preparation of compounded formulations. Compounders should not use an active pharmaceutical ingredient (API) from a bulk substance that is available through an FDA-approved medication unless doing so would produce a clinical difference for an identified patient. In addition, federal law prohibits the compounding of drugs that are essentially a copy of an FDA-approved medicine, unless FDA has placed that drug on the drug shortage list. It is critical that these provisions be fully implemented and enforced to avoid a disincentive for a drug maker to invest in new drug approvals and in the production of approved versions of drugs. While compounded drugs are an important option when approved drugs cannot meet a patient's clinical needs, only products that have been evaluated and proved through FDA's approval process meet the gold standard for safety and efficacy.

In conclusion, the undersigned organizations[5] believe that enabling FDA to further implement and enforce the DQSA will create a clearer framework for compounded medicines and protect the patients who rely on them. We again thank the Committee's leadership and would like to offer our help in ensuring this bipartisan law is successfully implemented so that the nation's patients are protected.

Association for Accessible Medicines

Biotechnology Innovation Organization

National Association of County & City Health Officials

Pew Charitable Trusts

Pharmaceutical Research and Manufacturers of America

PharMEDium

Trust for America's Health

[5] Some of these organizations have joined together to form the Compounding Quality Coalition.

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COMMITTEE ON
WAYS AND MEANS

SUBCOMMITTEE ON
HUMAN RESOURCES

SUBCOMMITTEE ON OVERSIGHT

January 30, 2018

The Honorable Michael Burgess
Chairman, Subcommittee on Health
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Burgess:

Thank you for your leadership and for holding today's hearing entitled "Examining Implementation of the Compounding Quality Act."

As you are well-aware, in 2012, the New England Compounding Center in Massachusetts manufactured and distributed contaminated steroids to clinics and hospitals across the country. It was a horrible tragedy. Hundreds of people developed fungal meningitis after receiving these tainted injections. Sadly, dozens died as a result and most others are still dealing with the terrible illness today.

The epicenter of the outbreak was Michigan's 8th District, which is the community I represent. More than 200 people became sick and 15 people died after receiving this tainted NECC injection from a clinic in our district. My staff and I have talked with and remained in close

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contact with many of the victims – including Mrs. Dargan, who is before the subcommittee today - as far as updates on compensation and legislation goes. Because of the reckless disregard for the health and safety of the recipients of these drugs, the Department of Justice secured convictions against 14 individuals, and 25 counts of 2nd Degree Murder against the two main defendants for deaths occurring in 7 states.

Although this outbreak happened five years ago, the consequences are still very real today. Whether it's someone who lost a loved one, or a victim now living with chronic pain and sickness, or a family member caring for an ill victim, this is a national tragedy – and these people need to be heard.

Not only have the day-to-day lives of these victims been irretrievably altered, they've also been financially ruined. Co-pays on some of the drugs and treatments for the fungal meningitis they contracted can cost up to $5,000/month.

That's where Congress can play a significant role. Since I arrived in the House in 2015, I've been working with 18 of my colleagues – many of whom serve on your subcommittee - to help secure a separate victims compensation fund through the Department of Justice. We are pleased to report $40 million was authorized through this fund and allocated to the Massachusetts Attorney General's office last year, which is now responsible for handling the disbursement process. As a result, many victims have received some much-needed additional financial help from this fund, and may be eligible to receive additional compensation beyond what has already

been paid. Additional information so can be found on my website, mikebishop.house.gov by searching the term "meningitis".

These funds can be helpful, but the work is not done. These are innocent Americans whose lives have been destroyed by criminals who will never meet them… will never hear the pain in their voices… will never see the irreversible damage they have caused. But I see it. And the colleagues of mine who have victims in their districts see it, too.

I was a former prosecutor in my local community, so I know victims of crime need an advocate to stand up for them. Nothing will reverse the damage that has been done, but at the very least, we must ensure justice for these people, and we must hold those responsible accountable for their actions.

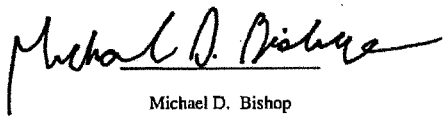
Above all, no one should have to worry if the medically "approved" injection they are about to receive is contaminated. People should not have to live in fear, or worry, or become ill, because a compounder didn't do their job properly.

That's why we cannot loosen our oversight over the industry responsible for mixing important – and potentially dangerous –drugs. The Drug Quality and Security Act was passed in the aftermath of the NECC fungal meningitis outbreak, and it serves as an important reminder for us all today. We must ensure these industry regulations are maintained: **this is about saving lives.**

I will continue to do my part to preserve this legislation and support the victims of the NECC fungal meningitis outbreak. It is the job of Congress to fight for those who need a voice in the legislative process, and I stand ready to help all of you however I can

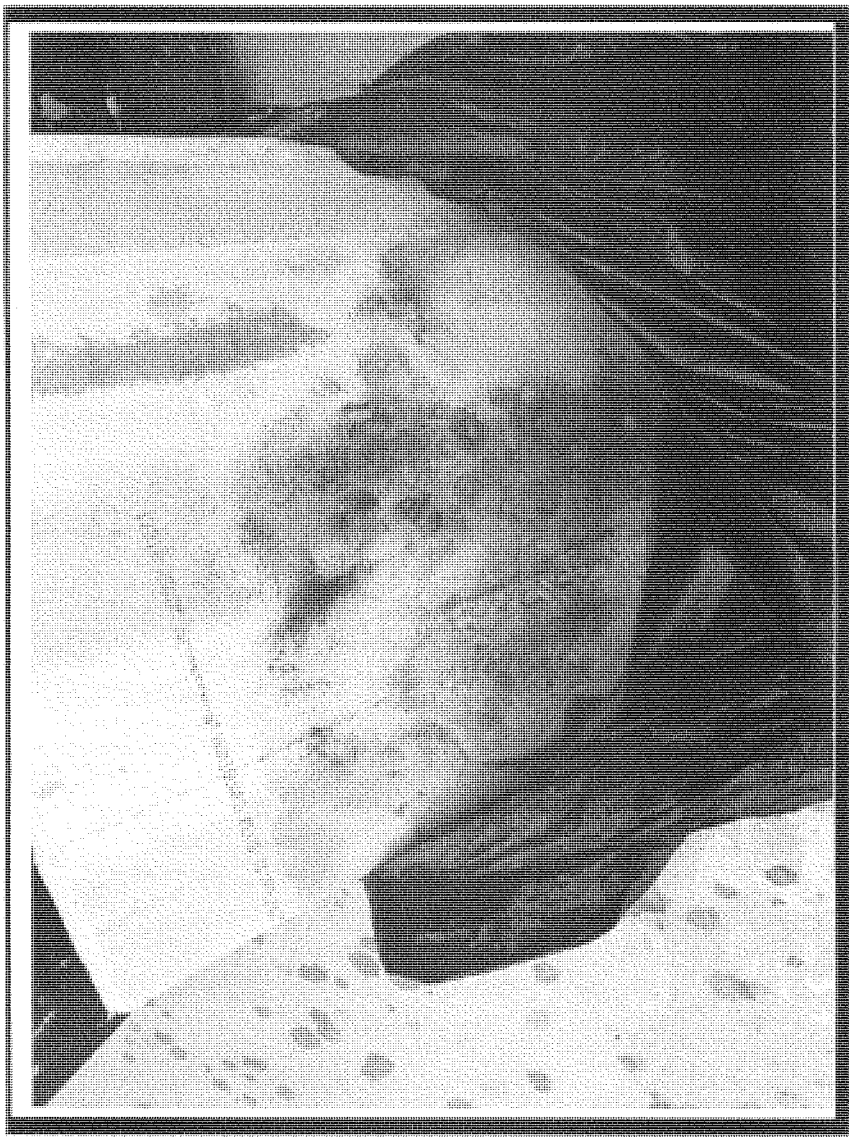
Thank you again for your steadfast leadership. I stand ready to work with you.

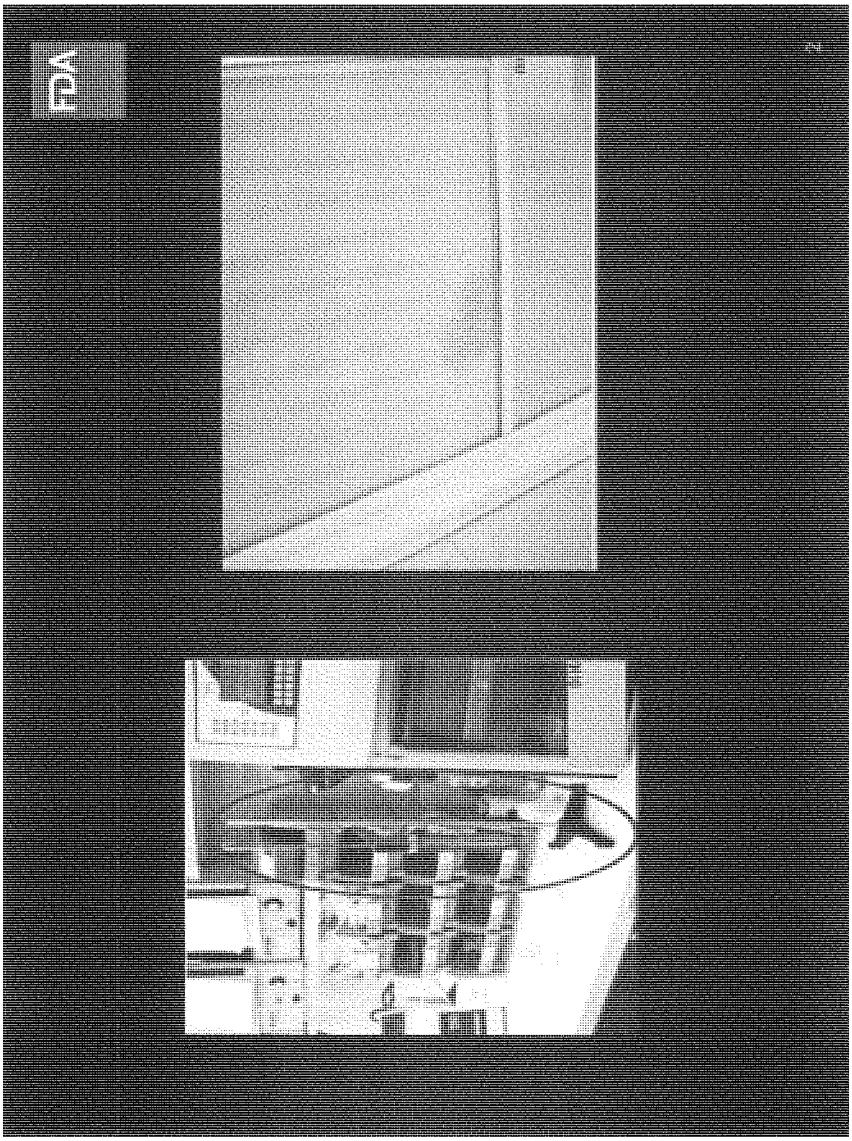
Sincerely,

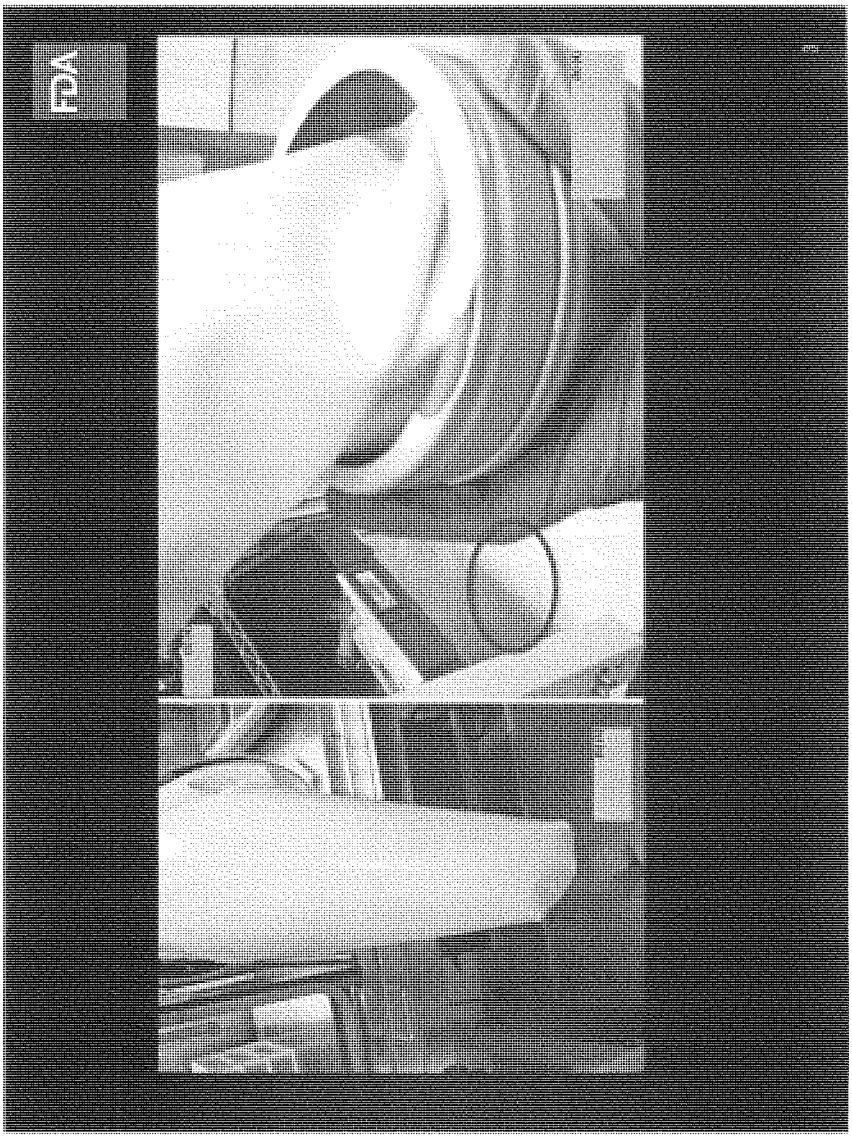


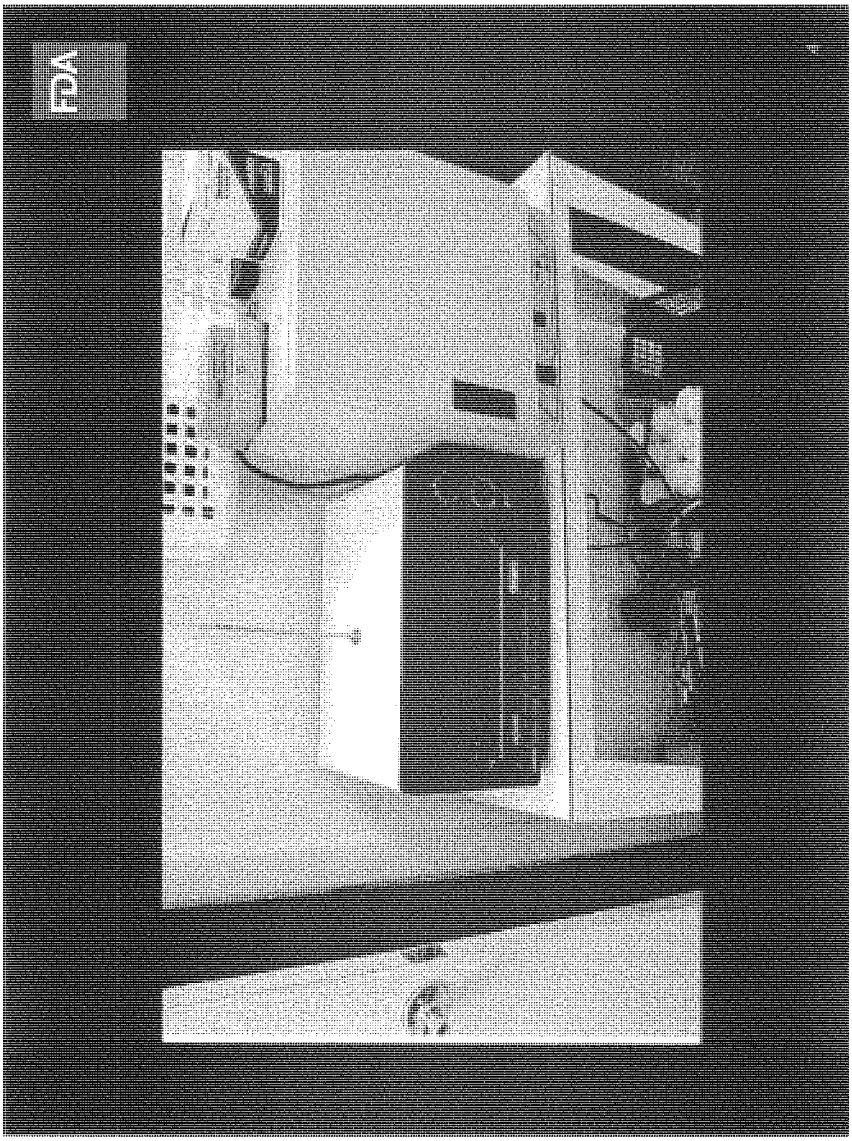
Michael D. Bishop

Member of Congress





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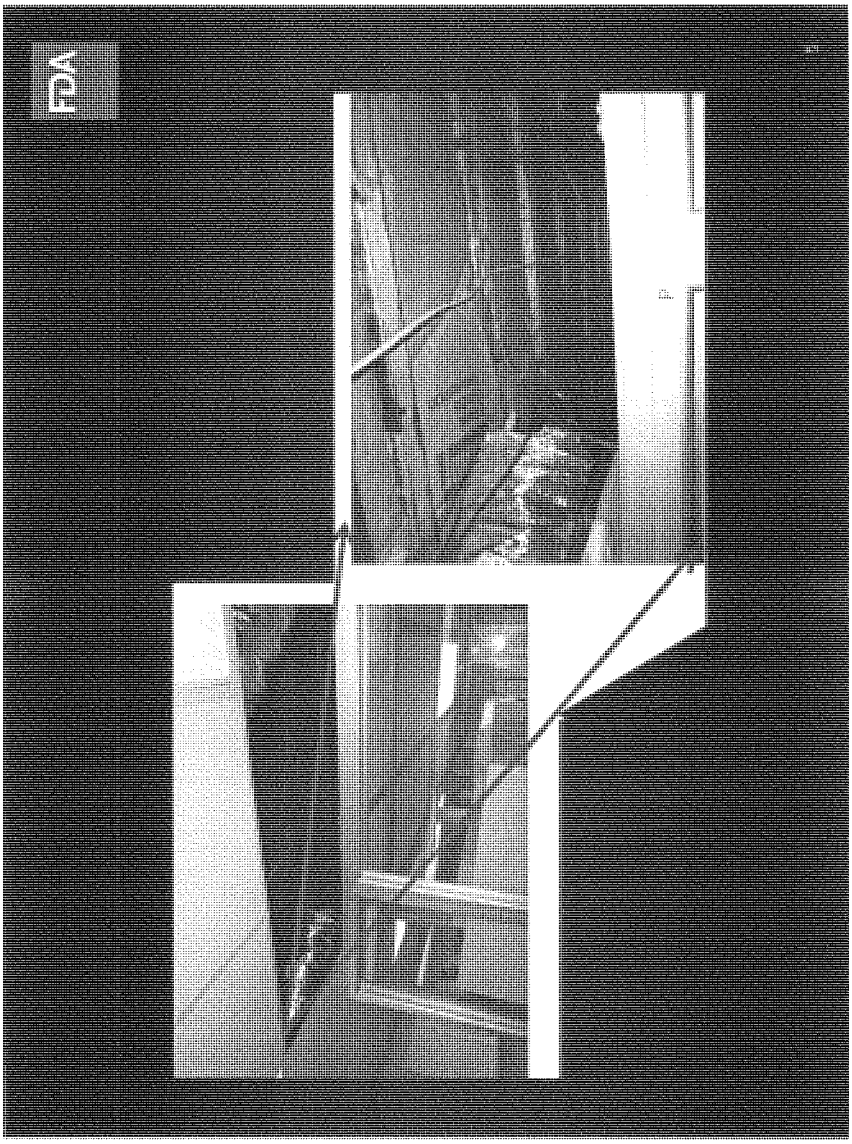

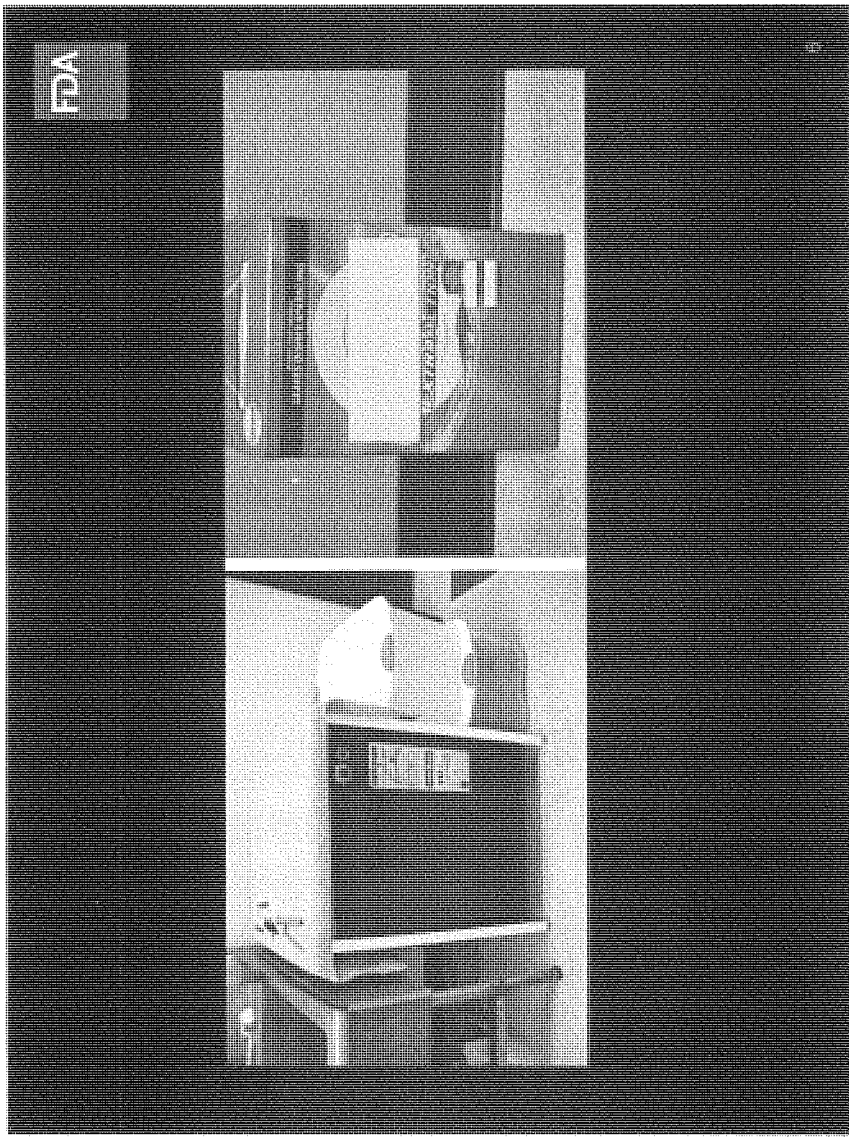
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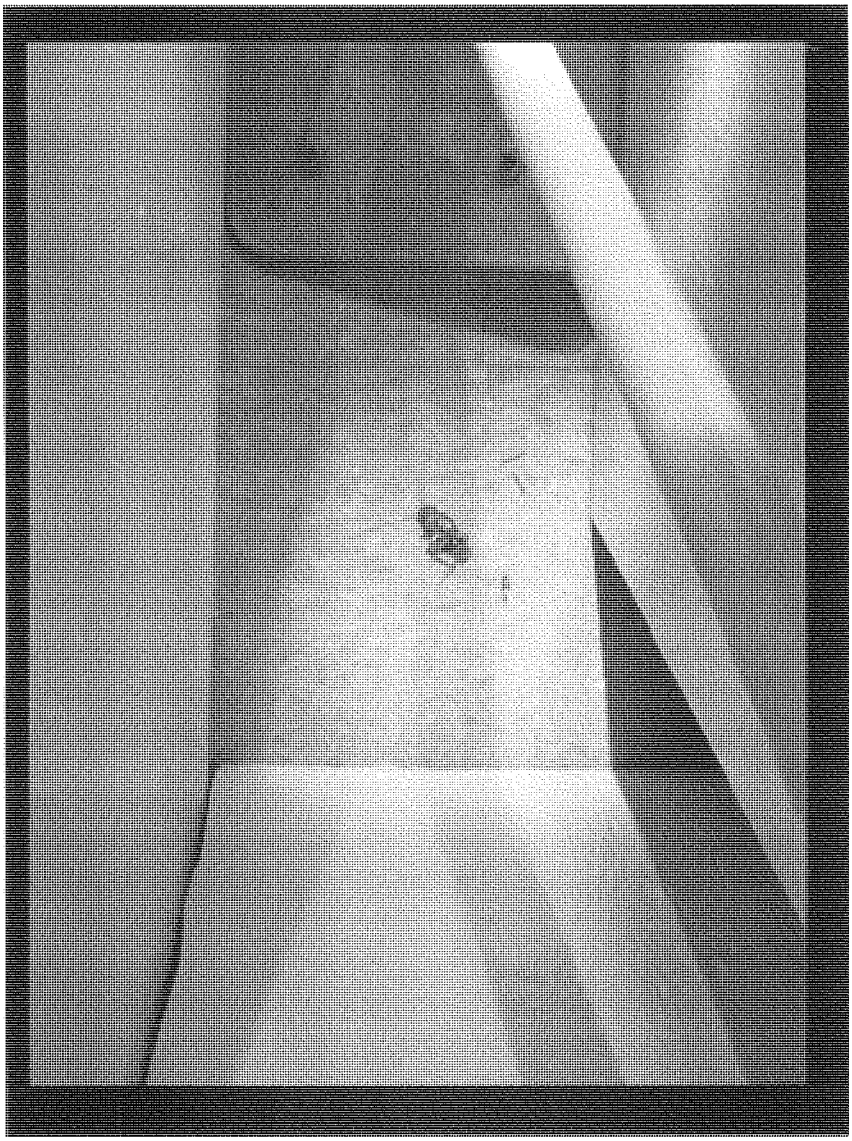

Committee on Energy and Commerce
Subcommittee on Health

Hearing on: "Examining Implementation of the Compounding Quality Act"

January 30, 2018

Statement for the Record
Submitted by ASHP

American Society of Health-System Pharmacists
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ASHP Statement for the Record
January 30, 2018

ASHP (American Society of Health-System Pharmacists) is pleased to offer the following statement for the record on pharmaceutical compounding. ASHP represents pharmacists who serve as patient care providers in acute and ambulatory settings. The organization's 45,000 members include pharmacists, student pharmacists, and pharmacy technicians. For more than 75 years, ASHP has been at the forefront of efforts to improve medication use and enhance patient safety.

In the fall of 2012, the New England Compounding Center (NECC) was behaving more like a manufacturer than a state-licensed pharmacy. That year, as a result of NECC's lack of sterile practices, more than 700 people in 20 states were diagnosed with fungal meningitis and other infections after receiving contaminated medication. Sixty-four patients in 9 states died, making it the deadliest meningitis outbreak in U.S. history.

To help prevent tragedies like the NECC meningitis outbreak, ASHP supports a compounding framework that not only balances safety with patient and clinician access to essential compounded medications, but that also recognizes the different distribution models in hospital and health-system pharmacies. ASHP advocated passage of the Drug Quality and Security Act (DQSA), and we remain committed to ensuring that it is implemented in a manner that protects its goals.

ASHP believes that the current legislative language of the DQSA is sufficient for the FDA to implement an appropriate regulatory structure and that *no additional compounding legislation is needed at this time*. The use of a prescription for an identified individual patient is a key differentiator between pharmacy compounding and manufacturing. We remain concerned that loosening certain requirements of the DQSA would result in an environment not unlike the one that caused the meningitis outbreak to occur.

To meet the needs of patients, hospitals prepare a vast array of compounded sterile preparations every day, the majority of which are prepared in-house by pharmacy departments. The compounded

medications that hospitalized patients need range from simple intravenous admixtures to complex customized medications that are not available off-the-shelf, such as multi-ingredient cardioplegia solutions for heart surgery, precisely measured combinations of epidural pain medication, and adult medications prepared in concentrations that can be safely administered to babies and children. Hospitals prepare or purchase compounded medications based on specific patient needs and individual medication orders or in anticipation of needs for patients under their direct care. It is important to note that in hospitals, no medication — compounded or otherwise prepared — is administered to the patient unless there is a patient-specific medication order.

ASHP believes that the FDA is an important partner in ensuring that pharmacists and the patients they serve can access safe and high-quality compounded medications. We have been working with the agency to ensure that guidances account for hospitals' and health systems' unique care delivery models, which differ significantly from traditional community pharmacy models in a number of ways, including the following:

- Patient responsibility: Hospitals and health systems are accountable for patient care outcomes. Thus, for the purposes of both quality and outcomes tracking, it is beneficial for hospitals and health systems to maintain full control over all elements of patient care, including pharmacy access. In-house compounding of medications facilitates tracking of adverse events as well as oversight of care quality. Further, it allows hospitals and health systems to arrange pharmacy operations to provide patients and clinicians with compounded medications when they are needed, without significant wait times.

- Safety and Quality Regulations: While all 503A compounding falls under the purview of the state Boards of Pharmacy, compounding in hospitals cannot be disassociated from, and is itself

subject to, other quality and safety standards applicable to hospitals and health systems. These include Centers for Medicare & Medicaid Services (CMS) regulations for reimbursement, Joint Commission (TJC) standards, U.S. Pharmacopeia (USP) chapters <797> and <800>, quality metrics (e.g., for accountable care organizations, patient-centered medical homes, etc.), and state and local department of health regulations. Hospitals and health systems are strongly incentivized to ensure that all facets of a patient's treatment, including medications, are as safe and effective as possible. Strong 503A compounding programs are essential to this effort.

- Limited Compounding: Hospital pharmacists seek to avoid compounding medications when an FDA-approved, commercially available therapeutic alternative is available. Compounding consumes resources and time, and it introduces additional risk into the medication-use process. Further, hospitals and health systems are not incentivized to compound on a large scale. Drugs are often bundled and, therefore, are not reimbursed separately, reducing or eliminating any financial incentive associated with compounding. Thus, in the hospital and health-system context, compounding volume has some built-in limitations that are not applicable in other settings.

These differences underlie FDA's creation of tailored compounding guidances for hospitals and health systems. Such targeted oversight decreases the chances of creating unintended access limitations for hospital and health-system patients, while still allowing FDA and clinicians to protect patient health and safety. Thus far, ASHP has supported FDA's efforts to craft tailored compounding regulation for hospitals and health systems. In particular, we look forward to the forthcoming hospital/health system-specific guidances related to repackaging, mixing, and diluting biologics, and 503B documentation requirements. Regarding published guidance, FDA has promulgated a draft hospital and health-system guidance regarding hospital compounding generally. Although we believe this guidance is a reasonable starting

point, we have asked the agency to revisit and revise certain facets before finalizing it. Specifically, although ASHP agrees that non-patient-specific compounding must be subject to reasonable limitations, we oppose using an arbitrary 1-mile radius in which distribution (not dispensing) of non-patient-specific medications is allowed. Imposing a geographic distance requirement could push compounding out of the pharmacy and back to the bedside, with negative consequences for patients. In order to comply with FDA's proposed hospital and health system guidance, hospitals and health systems would need to reconfigure existing care delivery models — many which have been heavily vetted by various accrediting bodies and regulators, and all of which are designed to maximize patient health and safety. To avoid disruption of functional delivery systems, ASHP supports retaining the requirement that hospitals and health systems distribute compounded medications only to healthcare facilities under common control for use within the four walls of those facilities. We believe removing and replacing the geographic distribution limitation proposed by FDA with a time-based standard is more appropriate and in the best interests of patients.

In place of an arbitrary limitation, ASHP urged the FDA to consider allowing hospitals and health systems to use the USP Chapters <797> and <800> beyond-use date (BUD) time frames for handling of non-hazardous and hazardous sterile compounding. USP Chapter <797> delineates the procedures and requirements for compounding sterile preparations. It focuses on ensuring that compounding pharmacies provide the conditions and institute practices to prevent harm to patients from microbial, chemical, or physical contamination; excessive bacterial endotoxins; variations in product strength; or poor-quality ingredients. Further, in order to meet USP Chapter <797> standards, all personnel involved in sterile compounding must undergo specific training and testing. Similarly, USP Chapter <800> describes the standards for the handling and administration of hazardous drugs with patient safety, worker safety, and environmental protection taken into consideration.

We anticipate that FDA will release a revised version of this guidance with an opportunity to comment.

503B Outsourcing Facilities

FDA suggested that, should the geographic limit create difficulties, 503B outsourcing facilities (hereinafter, "503Bs" or "outsourcing facilities") can fulfill hospital and health-system needs. ASHP considers 503Bs essential to a strong compounding framework, but we remain concerned that, at present, 503Bs do not have the capacity to meet all system needs. Specifically, the wait times and longer turnaround times that some of our members have encountered when purchasing from 503Bs suggests that they are already straining to meet demand. Outsourcing facilities typically make large batches of compounded drugs and are not equipped to provide tailor-made products to hospitals and health systems. While many of our members rely on 503Bs, they also recognize that these outsourcers are limited in what they can produce. As a result, hospitals and health systems compound products to meet their own unique patient needs and do so in quantities significantly below a 503B's volume.

CONCLUSION

ASHP thanks the subcommittee for the opportunity to submit this statement. As noted earlier, ASHP believes that the DQSA established a sufficient regulatory framework for the FDA to implement the law and that no further legislation is needed at this time. ASHP remains committed to working with Congress and industry stakeholders to ensure that patients have affordable access to lifesaving and life-sustaining medications.

Committee on Energy and Commerce
Subcommittee on Health
"Examining Implementation of the Compounding Quality Act"

Statement of the American College of Mohs Surgery

2123 Rayburn House Office Building Washington, D.C. 20515
January 30, 2018

Thank you for organizing this hearing to examine the U.S. Food and Drug Administration's (FDA) implementation of Title I of the Drug Quality and Security Act (DQSA), which was enacted nearly five years ago in the wake of the fungal meningitis outbreak caused by the New England Compounding Center (NECC).

The American College of Mohs Surgery (ACMS) represents more than 1,400 Mohs micrographic surgeons who have successfully completed extensive fellowship-training in Mohs micrographic surgery following their dermatology residency training. Mohs micrographic surgery is the most effective and efficient treatment for advanced or difficult to treat skin cancers. In line with its mission, ACMS sets and promotes the highest standards of patient care relating to Mohs micrographic surgery.

Skin cancer is the most common form of cancer in the United States and a growing epidemic. [1, 2] There are more new cases of skin cancer diagnosed each year than the combined incidence of cancers of the breast, prostate, lung and colon.[3] One in five Americans will develop skin cancer in the course of their lifetime.[4]

We appreciate that the subcommittee will hear testimony from physician compounders, including a dermatologist. The ability to prepare local anesthetics in our offices is critical to the continued provision of integrated, coordinated, high quality and cost-effective skin cancer care.

Preparation of Local Anesthetics by Mohs Surgeons is Safe, Effective, and Poses No Documented Risk to Patient Safety

Mohs surgeons prepare local anesthetics in their offices within 24 hours of Mohs micrographic surgery. Specifically, Mohs surgeons prepare buffered or diluted lidocaine to ease pain and discomfort during Mohs micrographic surgery by adding commercially purchased sodium bicarbonate solution to commercially purchased 1% lidocaine hydrochloride with epinephrine. This simple step significantly decreases the painful/burning sensation at the time of injection and speeds up the onset of anesthesia.[5] The enhanced tolerability of the local anesthetic achieved

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[1] https://www.cdc.gov/cancer/skin/statistics/index.htm
[2] https://www.cdc.gov/cancer/skin/call_to_action/index.htm
[3] Stern RS. Prevalence of a history of skin cancer in 2007: results of an incidence-based model. *Arch Dermatol.* 2010;146(3):279-282.
[4] https://www.skincancer.org/skin-cancer-information/skin-cancer-facts
[5] McKay W, Morris R, Mushlin P. Sodium bicarbonate attenuates pain on skin infiltration with lidocaine, with or without epinephrine. Anesth Analg. 1987;66(6):572–574. doi: 10.1213/00000539-198706000-00015.

allows the procedure to be performed without the need for systemic anesthetics, thereby greatly reducing cost and risk of complications.

To achieve the proper anesthetic mixture or concentration, Mohs surgeons prepare buffered or diluted lidocaine using the aseptic technique -- a practice that has been proven safe and effective for decades.[6, 7, 8] Mohs surgeons only prepare buffered or diluted lidocaine for use in their offices for their own patients – not distribution or resale. This process is required, as buffered and diluted lidocaine with epinephrine, while remaining safe, begins to lose its vasoconstrictive efficacy after 7 days.[9] Thus, it would be difficult to receive the compounded drug through a large distributor, such as an outsourcing facility.

The Scientific Advisory Committee of ACMS, composed of leading Mohs surgeons who practice at highly regarded institutions across the country, with many who serve on the National Comprehensive Cancer Network Guideline panel for Non-melanoma Skin Cancer, agree that use of the aseptic technique for preparing buffered or diluted lidocaine in the office is safe, appropriate, and consistent with the current literature.[10]

We emphasize that the practice of medicine includes preparing local anesthetics. State boards of medicine are responsible for regulating the practice of medicine. However, from the viewpoint of the FDA, Mohs surgeons would generally be preparing buffered or diluted lidocaine in accordance with section 503A of the Federal Food, Drug and Cosmetic Act (FD&C Act) and with patient specific prescriptions.

Impact of FDA Guidance on Physician Office Compounding

In August 2016, FDA released draft guidance -- "*Insanitary Conditions at Compounding Facilities*" -- that sets forth new standards for physician offices that compound under section 503A. For example, physician offices would be required to have engineering control devices capable of maintaining an ISO Class 5 environment or be deemed "insanitary." The FDA and Centers for Disease Control and Prevention (CDC) have yet to produce any scientific evidence to suggest there has been a problem to warrant this level of precaution with respect to physician office preparation of compounded medications.

Because Mohs surgery is overwhelmingly performed in the office setting, Mohs surgeons would need to equip their offices as if they were compounding pharmacies to comply with the guidance, if finalized as currently drafted. The expense and impracticality would prohibit most Mohs surgery practices from making such a conversion, despite the current safety record of the use of

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[6] Kimyai-Asadi, A., Goldberg, L., Peterson, R., Silapint, S., and Jih, M. The incidence of major complications from Mohs micrographic surgery performed in office-based and hospital-based settings. J Am Acad Dermatol 2005;53:628-34.

[7] Melman, D., & Siegel, D. (1999). Prefilled Syringes: Safe and Effective. *Dermatologic Surgery,* 492-493. Retrieved May 29, 2017, from http://www.ncbi.nlm.nih.gov/pubmed/10469100

[8] Larson PO, Ragi G, Swandby M, Darcey B, Polzin G, Carey P. *Stability of buffered lidocaine and epinephrine used for local anesthesia*, J Dermatol Surg Oncol. 1991 May;17(5):411-4.

[9] Pascuet E, Donnelly RF, Garceau D, Vaillancourt R. Buffered Lidocaine Hydrochloride Solution With and Without Epinephrine: Stability in Polypropylene Syringes. *The Canadian Journal of Hospitol Pharmacy*. 2009;62(5):375-380.

[10] Letter to USP from Christopher Bichakjian, MD, Chair, ACMS Scientific Advisory Committee dated January 27, 2016

buffered lidocaine among Mohs surgeons. This means patient access to Mohs micrographic surgery would be severely hindered. Instead, patients would be directed to hospital outpatient departments (HOPD) for skin cancer care and treatment, significantly increasing costs to patients and insurers, including the Medicare program, unnecessarily. We note that some health plans have attempted to limit Mohs micrographic surgery to the office setting because costs in the HOPD are high, which means some patients may not have access to the procedure at all.

While we remain deeply concerned with this draft guidance, FDA recently announced its 2018 Compounding Policy Priorities Plan[11] that the agency will take a step back from the previous position and re-examine these issues. Specifically, FDA stated:

> *"This guidance will address concerns raised by some providers who compound small quantities of drugs in their offices for patient use, and as part of their routine clinical practice. This came up in the setting of certain dermatological procedures, for example. The FDA plans to better define the circumstances under which we believe drugs are being mixed and applied in a manner that creates negligible patient risk, and therefore wouldn't be subject to the same compliance policy under the agency's risk-based approach to implementing these requirements."*

We believe the FDA can help prevent future problems, such as those associated with the New England Compounding Center (NECC), without imposing a one-size-fits-all approach. We have urged FDA to either exclude physician offices from the definition of "compounding facilities" in any finalized guidance or provide a meaningful exemption that does not impede Mohs surgeons' ability to safely prepare buffered or diluted lidocaine, which is the standard of care and within the scope of Mohs surgical practice. Any exemption would ideally be consistent with the current literature, which demonstrates that prepared buffered lidocaine is safe and effective for patient use for periods not less than two weeks. ACMS is unable to accept an "immediate use" exemption of less than 24 hours given the safe anesthetic preparation practices and long-standing safety record in Mohs micrographic surgery, coupled with the need for patient access.

ACMS is cautiously optimistic that FDA's forthcoming revised draft guidance will maintain patient access to important, medically necessary medicines prepared in the physician-office setting.

The Role of USP in Physician Office Compounding and Recent Engagement

According to its website, the US Pharmacopeia (USP) is a scientific nonprofit organization that sets public standards for identity, strength, quality and purity of medicines. USP standards are recognized in various provisions of the federal Food, Drug and Cosmetic Act (FDCA), and in laws, regulations and policies promulgated by states. These standards are enforced by the U.S. Food and Drug Administration (FDA), states and other oversight organizations (such as The Joint Commission). Under the DQSA, Congress clarified FDA's authority over drug compounding and reaffirmed USP's role under Section 503A. FDA subsequently released guidance specifically referencing USP's *General Chapter <797> Pharmaceutical Compounding – Sterile Preparations*, including enforcement approaches.

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[11] https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm592795.htm

In September 2015, USP proposed revisions to General Chapter <797>. According to USP, based on the nature and significance of the public comments received, the chapter will be revised and is anticipated to be published in the Pharmacopeial Forum 44(5) Sept./Oct. 2018 for a second round of public comment. General Chapter <797> is expected to become official on December 1, 2019.

Recently, USP initiated a process whereby "expert consultants" selected from the physician community have been invited to provide advice and guidance as USP's Compounding Expert Committee (CEC) continues to revise and refine Chapter <797>, addressing key issues and definitions. ACMS' nominee, Allison Vidimos, RPh, MD, has been appointed as an expert consultant.

Request for Congressional Oversight to Ensure Patient Access to Medically Necessary Medicines

The unfortunate events associated with tainted intrathecal steroids and the resultant fungal meningitis outbreak in 2012 that prompted significant scrutiny over drug compounding in the United States, including passage of the Drug Quality and Security Act of 2013, is completely unrelated to how Mohs surgeons utilize local anesthetic mixed in their offices. And, while significant progress has been made with the FDA and USP, Congressional oversight is essential to ensure patients have continued access to physician-compounded medicines.

We look forward to working with the Members of this Subcommittee and the Congress, serving as subject matter experts on physician-office compounding, to safeguard the safety and health of our patients.

Statement for the Record of Avella
Energy and Commerce Health Subcommittee Hearing
"Examining Implementation of the Compounding Quality Act"
January 30, 2018

Avella of Deer Valley, Inc. and affiliated entities including Advanced Pharma Inc., D/B/A Avella of Houston (collectively, "Avella") are pleased to submit written testimony to the "Examining Implementation of the Compounding Quality Act" hearing before the Energy and Commerce Health Subcommittee. Avella has been, and continues to be, a strong supporter of the Compounding Quality Act ("the Act"). However, as a currently registered 503B, and as an entity that also dispenses compounded prescriptions under 503A, Avella would like to raise some concerns with the current implementation and enforcement landscape in the compounding world.

Avella currently serves the needs of thousands of patients and providers by providing both dispended and office use, through its 503B facility, compounded medications throughout the United States. Founded in 1996 as a single pharmacy located in Phoenix, Arizona, Avella has since expanded to include two national distribution facilities and community-based pharmacies in eight states while serving patient and/or provider needs in all 50 states. In February 2014, Avella's Deer Valley location was an early registrant with FDA as an Outsourcing Facility in accordance with Section 503B the Food, Drug and Cosmetic Act ("FFDCA"). Today, Avella is a national specialty and compounding pharmacy with unique expertise in ophthalmology treatments, and was the first ophthalmology pharmacy in the nation to earn the Pharmacy Compounding Accreditation Board's Seal of Accreditation. Because of the unique nature of ophthalmology and our hospital clients, a large portion of the medications Avella provides are customized to meet specific patients' unique medical needs.

As this Subcommittee is well aware, patient safety and product quality are a top priority for the industry. Avella, and others, are working tirelessly to lead the industry in such standards to help ensure that a health crisis, like that of the New England Compounding Center ("NECC"), which resulted in 64 deaths and hundreds of injuries due to contaminated sterile injectables, never happens again. For this reason, Avella expresses a number of concerns related to FDA's current implementation and enforcement pathways that could have an impact on patient safety.

I. Varying cGMP Standards Will Impact Product Quality and Put Patients at Risk

FDA's recently published a 2018 Compounding Priorities Plan ("2018 Plan") outlines a risk-based approach for the applicability of current Good Manufacturing Practice ("cGMP") standards for 503B facilities. Specifically, in the 2018 Plan, FDA stated that it wanted to encourage traditional compounders operating under Section 503A of the FFDCA to register as outsourcing facilities by applying varying degrees of cGMP standards to a facility based on the size and scope of the outsourcing facility's operations. Thus, "smaller compounders that compound limited volumes of drugs, and presumably present lower risks, may decide to register as outsourcing facilities."

Avella disagrees with this approach and advocates that instead, one, consistent cGMP standard should apply to all outsourcing facilities no matter the size of the entity or the volume of products

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that the entity compounds. Application of varying cGMP standards will only create confusion within the industry, stress the FDA's already limited resources, and significantly raise potential risk to patients. Most importantly, a lesser cGMP standard for small facilities has the potential to impact the quality of drug produced by those entities, and could result in patient harm. For example, if smaller entities are exempt from certain product testing requirements, a sub-standard product may be produced and administered to a patient in the same manner that caused NECC. In turn, an outsourcing facility subject to the higher cGMP standards would have the testing processes in place to identify such an issue. In reviewing this issue, Avella asks that Congress take the time to ask themselves a simple question: if the medication was being injected into your family member, would you want to have the assurance that the preparation was appropriately tested or to take a chance because the facility is a smaller one and not required to have a rigorous testing program?

For this reason, Avella believes that varying cGMP standards will only serve to create more risk in the marketplace and could result in another NECC-like tragedy.

II. A Risk-based Approach to FDA Oversight Could Prevent Future Patient Harm

Section 503B of the FFDCA mandates a risk-based inspection frequency, including consideration of certain risk factors such as compliance history, compounding risk level, and previous inspection history. Avella advocates that this portion of the statute be fully implemented as inspections are a key way to identify non-compliance and risky operations. If the most high-risk outsourcing facilities are identified, and inspected on a more frequent basis, there is a better likelihood that high-risk behavior will be corrected and patient harm may be prevented.

III. Memorandum of Understanding

In its 2018 Plan, FDA indicated that it planned to loosen the MOU standards to make it more feasible for states to sign the MOU, including altering the draft definition of "inordinate amount" from 30 percent or more of all drug dispensed to greater than 50 percent during the calendar month. In addition, distributing inordinate amounts would no longer trigger state action, but would instead trigger certain reporting requirements. Although the 30 percent and 50 percent thresholds appear to be arbitrarily determined, Avella advocates for clarification as to how such a calculation will be made on patient scripts (as opposed to office use). Further, FDA has expressed its goal to encourage more compounders to register as outsourcing facilities, so those entities that believe they will distribute inordinate amounts have an opportunity to does so as FDA-registered outsourcing facilities and should be held to the proper cGMP standards established and regulated by FDA.

Lee H. Rosebush
Chairman | OFA

Statement for the Record of the Outsourcing Facilities Association
Energy and Commerce Health Subcommittee Hearing
"Examining Implementation of the Compounding Quality Act"
January 30, 2018

The Outsourcing Facility Association (OFA) appreciates the opportunity to provide written testimony for the Energy and Commerce Health Subcommittee hearing titled "Examining Implementation of the Compounding Quality Act." OFA's members are strong supporters of the Compounding Quality Act. With that said, OFA members have concerns related to the Food and Drug Administration's recently released 2018 Compounding Policy Priorities Plan, as well as with current FDA guidance documents related to Outsourcing Facilities and compounding.

About OFA and 503B Outsourcing Facilities

OFA is the trade association representing FDA-registered 503B Outsourcing Facilities whose goal is to provide patients and healthcare providers with high quality and safe compounded medications. OFA members continuously work with patients, healthcare providers, and hospitals on a daily basis to ensure the specific needs and access, of both providers and patients, for compounded medications are satisfied.

FDA oversight of Outsourcing Facilities was authorized by Congress in the wake of the 2012 New England Compounding Center (NECC) scandal, in which 64 people died and hundreds more were harmed by NECC's fungal-contaminated sterile-injectable drugs. Patient advocacy groups, healthcare providers, and the pharmaceutical industry worked with Congress for a year to enact legislation that balanced the safety risks posed by batch compounding with the clear need for these products.

Outsourcing Facilities exist in the space between small pharmacies that compound drug products for individuals (subject to section 503A of the FD&C Act) and large pharmaceutical manufacturers. There are currently more than 70 FDA-Registered Outsourcing Facilities, located in 24 states, and the number is rapidly growing. These businesses must be registered with FDA as Outsourcing Facilities and must comply with all of the requirements of section 503B of the FD&C Act.

OFA's Specific Concerns

OFA supports the FDA's overall implementation and enforcement of the Compounding Quality Act as written and intended by the Congress. However, OFA has four areas of specific concern: 1) the impact FDA's risk-based current good manufacturing practices (cGMP) standards will have on product quality and safety; 2) patient access to 503B compounded medications; 3) FDA's consideration of cost; and 4) the use of bulk drug substance for compounding. These topics are discussed in greater detail below.

FDA's risk-based cGMP Standards will adversely impact product quality and safety

FDA announced in its 2018 Compounding Policy Priorities Plan that a risk-based approach will be utilized for the applicability of compounding standards, which will essentially allow FDA to permit a new, more flexible cGMP standard for smaller compounders. This policy will result in detrimental effects to current 503B Outsourcing Facilities and would allow a lesser standard of cGMP that would have a negative effect on the quality standards for compounded medications.

Specifically, the 2018 Plan notes that FDA plans to draft proposed regulations on cGMP requirements for Outsourcing Facilities. While OFA applauds FDA for moving forward with regulations, FDA's proposal, in the interim, is to revise the current 503B Outsourcing Facility cGMP draft guidance to describe a new flexible, risk-based approach to cGMP requirements for Outsourcing Facilities based on the size and scope of an Outsourcing Facility's operations. For the FDA to allow a "less rigid" cGMP standard simply because a compounding facility is smaller or produces limited volumes unnecessarily exposes patients to higher-risk compounded medications that could lead to patient injury or illness, the exact area that Congress and FDA sought to prevent after the NECC scandal. For example, "less rigid" cGMP standards might allow an entity to compound without requiring certain testing or meeting other standards, which would put patients at unknown risk for harm, as those drugs may not have undergone testing to ensure they are sterile, potent, and/or stable or be made in proper conditions. This is exactly why and how NECC occurred.

In addition, FDA has stated many times, both in administrative actions such as 483s and Warning Letters and in various public statements and testimony, that the current cGMP Standards are necessary to ensure patient access to quality compounded medications. By allowing a lesser cGMP standard, FDA would be reversing this position that Congress established in the DQSA to address NECC just a few years ago. Accordingly, OFA believes that one consistent cGMP standard should be utilized for 503B Outsourcing Facilities regardless of the volume of drug products compounded by the facility in order to ensure consistent quality of compounded drugs for patients and ultimately assuring patient access.

Patient Access to Compounded Medications

OFA and its members are committed to patient care and ensuring access to compounded drugs. In striving to meet this goal, OFA members work closely with prescribing practitioners and patients to compound drugs that serve the needs of patients and providers. At this time, OFA is not aware of issues limiting access to compounded drugs that are typically produced by Outsourcing Facilities. OFA is committed to an open dialog with FDA and patient advocacy groups about any known patient access issues with specific compounded medications that could otherwise be safely compounded.

FDA's Consideration of Cost

In its 2018 Plan, and recently released draft guidance documents, FDA stated that cost will not be taken into consideration in FDA's determinations relating to whether a compounded drug is an essential copy of an approved drug product. FDA has communicated various reasons for this, including that it seeks to preserve the new drug application and abbreviated new drug application process. Yet, FDA proposes to utilize cost as a consideration as to whether 503B Outsourcing Facilities are meeting patient access concerns. For example, FDA states that cost is one reason why FDA wants to offer flexible cGMP standards to pharmacies that are compounding in limited batches, to encourage them to register as 503B Outsourcing Facilities. Therefore, the question must be asked, why is cost being eliminated as a consideration when 503B Outsourcing Facilities are compared to drug manufacturers, but used as a consideration when comparing 503B Outsourcing Facilities and compounding pharmacies?

Bulk Drug List - Clinical Need Requirement

According to the Compounding Quality Act, 503B Outsourcing Facilities cannot compound with a bulk drug substance unless: 1) the bulk drug substance appears on a list developed by the FDA for which a determination of a clinical need has been made; or, 2) the drug compounded from the bulk drug substance is on the drug shortage list. According to FDA's 2018 Priorities Plan, FDA is still in the process of developing a Clinical Need list applicable to 503B Outsourcing Facilities. OFA, in reviewing the criteria that would possibly permit the FDA to make a determination of a clinical need, believes that the criteria utilized by FDA should actually define a clinical need. In the new drug approval process, FDA already reviews whether there is a clinical need for a drug substance. Specifically, during the new drug approval process FDA reviews the efficacy of a drug substance. Accordingly, FDA would not approve a drug if there was no "clinical need" for the drug. Therefore, OFA advocates that all drug substances used to make products listed in the FDA's Orange Book should be eligible for nomination on the clinical need list, as the FDA has already determined that there is a clinical need for those products. FDA has already determined that these products are both safe and efficacious for a patient to use for a specific disease. Accordingly, every component of a product that is listed in the Orange Book has a clinical need and, therefore, should be included on the clinical need and bulk drug substance list. To the legitimate concern of FDA to protect the new drug application process, the essential copy protection still exists. But the use of a bulk substance to compound, and the essential copy protection, should not be conflated. These are separate areas that must be reviewed accordingly.

Written Statement for the Record
Energy and Commerce Subcommittee on Health
"Examining Implementation of the Compounding Quality Act"

American Society of Cataract and Refractive Surgery
4000 Legato Road, Suite 700
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Tuesday, January 30, 2018

Chairman Burgess, Ranking Member Green, and members of the Subcommittee, the American Society of Cataract and Refractive Surgery (ASCRS) would like to thank the Energy and Commerce Subcommittee on Health for the opportunity to provide written testimony for the January 30, 2018, hearing titled "Examining Implementation of the Compounding Quality Act." ASCRS is a medical specialty society representing nearly 9,000 ophthalmologists in the United States and abroad who share a particular interest in cataract and refractive surgical care. ASCRS members annually perform the vast majority of cataract procedures in the United States.

We are very concerned that the Food & Drug Administration (FDA) is implementing Title I of the Drug Quality and Security Act (DQSA), the Compounding Quality Act, in a way that severely impacts patient access to compounded medications and creates an unnecessary burden on physician practices to secure compounded drugs. The practice of ophthalmology relies heavily on compounded drugs, and it is vital that physicians have an immediate supply of compounded drugs available in their offices to treat patients who present with emergent conditions. However, through the use of guidance documents—mostly in draft form, the FDA is restricting physicians' access to medications, which ultimately denies patients timely and effective treatment options.

The FDA's implementation of the DQSA and use of draft guidance documents has created an environment of uncertainty for stakeholders. While draft guidance documents are not legally binding, many stakeholders feel pressured to comply because it represents the agency's current thinking for policy enforcement. As a result, many compounding facilities are abiding by the polices set forth in draft guidance documents, especially compounding regulations. This has significantly impacted physician and patient access to compounded drugs.

When the DSQA was enacted, its sponsors indicated that it was not their intention to restrict the use of compounded drugs for office-use. However, since the implementation of the DQSA, physicians may only access compounded drugs from a 503A traditional compounder for office-use if they have a patient-specific prescription. For patients who present with an emergent condition and require immediate treatment, this is not an effective pathway to quickly secure compounded medications. As an alternative, physicians may procure compounded drugs from a 503B outsourcing facility without a patient-specific prescription; however, many 503B

outsourcing facilities are not producing drugs in the required quantities needed for ophthalmic care. Therefore, physicians' practices are experiencing difficulties in securing necessary drugs for patient treatment.

ASCRS remains committed to ensure patients and physicians have timely access to safe and effective compounded medications, and therefore, we strongly support and urge Congress to pass H.R. 2871, the Preserving Patient Access to Compounded Medications Act, bipartisan legislation sponsored by Reps. Morgan Griffith (R-VA) and Henry Cuellar (D-TX). This bill will amend the Federal Food, Drug, and Cosmetic Act and allow physicians to obtain compounded drugs from 503A traditional compounding pharmacies without a patient-specific prescription to treat patients that present emergent conditions.

Our chief recommendations to the Subcommittee include:

- **Limit the use of guidance documents, often still in draft form, because of the uncertainty of whether the described policies will be enforced; and**

- **Enact H.R. 2871, the Preserving Patient Access to Compounded Medications Act, bipartisan legislation sponsored by Reps. Morgan Griffith (R-VA) and Henry Cuellar (D-TX), to secure compounded medications for office-use compounding and safeguard patient access to treatment by allowing compounding in small quantities for office-use without a patient-specific prescription.**

Additionally, the FDA's 2015 draft guidance related to repackaged biologics would have made it very difficult for ophthalmic practices to access repackaged biologics. In this guidance, the FDA recommended a Beyond-Use Date (BUD) that would have severely impacted the ability of patients and physicians to access and use Avastin, a commonly used sight-saving drug in ophthalmology. ASCRS and the ophthalmic community advocated heavily against this proposal. Fortunately, the FDA took our concerns into account and amended the draft guidance to allow for extended BUD if in accordance with additional sterility testing.

Limit Use of Guidance Documents

As indicated above, ASCRS is concerned that FDA's routine use of guidance documents, often remaining in draft form for several years, creates significant confusion among physicians, pharmacies, and other stakeholders and an environment in which they feel forced to comply even though the documents are not finalized. The FDA's implementation of the DQSA showcases a larger pattern of regulatory overreach by the FDA that has involved the use of guidance documents, often still in draft form, that are not finalized. These guidance documents, while neither nonbinding or technically enforceable, create an environment of ambiguity, as new requirements are often cited in these documents without the benefit of notice or comment from the public. As a result, physicians and other stakeholders feel forced to comply due to the weight the agency and courts give these guidance documents.

Furthermore, these guidance documents create significant financial and administrative burdens on physicians and other stakeholders. The Administrative Procedure Act's (APA) rulemaking

process does not apply to "interpretative rules, general statements of policy, or rules of agency organization, procedure, or practice." Therefore, guidance documents do not consider estimates of costs, economic burdens, and administrative burdens before expecting stakeholders to comply. We believe that policy decisions by the FDA should be conducted through the formal APA rulemaking process, should be consistent with the intent of Congress when the law was passed, and should not create additional burdens. **We urge the Committee to review FDA's use of guidance documents to ensure the agency is following congressional intent related to the DSQA, and incorporating appropriate public input from all stakeholders.**

Patient-Specific Prescription Requirement for Office-Use Compounding

ASCRS is concerned with the final guidance on "Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act," as it will create further access issues to compounded drugs for office-use by requiring a patient-specific prescription for any drug compounded by a 503A traditional compounder. Before the enactment of the DQSA, it was very common for ophthalmic practices to routinely stock small quantities of compounded drugs to treat patients who present with emergent conditions in the office setting. However, this guidance prohibits physicians from keeping small quantities of compounded drugs for office-use, even to treat patients with emergent conditions that may cause blindness. **Physicians may access compounded drugs from 503B outsourcing facilities, but many of these facilities do not produce the drugs in the limited quantities or in ophthalmic solutions required by ophthalmologists.**

Timely Access to Compounded Drugs Needed for Emergent Cases
To reiterate, it is vital for patient care that ophthalmologists have immediate access to small quantities of compounded drugs for office-use to provide treatment to patients presenting emergent conditions. If an ophthalmologist does not have access to needed compounded drugs, this could have lasting negative consequences on a patient, such as extreme ocular damage or even complete blindness. For instance, if a patient presents a bacterial endophthalmitis—an infection where bacteria has reached the inside of the eye—and is not treated within 24 hours with the injection of compounded antibiotics, he or she will almost certainly experience the loss of an eye.

We appreciate that the FDA acknowledged the medical necessity of patients' access to compounded drugs in their physician's office in the final guidance, "Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act," while even highlighting an example from our specialty:

> "If a patient presents at an ophthalmologist's office with a fungal eye infection, timely administration of a compounded antifungal medication may be critical to preventing vision loss. In such a case, the ophthalmologist may need to inject the patient with a compounded drug product immediately, rather than writing a prescription and waiting for the drug product to be compounded and shipped to the prescriber."

However, in the footnote of this example, the FDA states, "such compounding would be subject to all of the conditions of section 503A or 503B . . . ." This is particularly alarming, as the

agency has recognized the importance of the availability of compounded medications for office-use, yet releases final guidance on prescription requirement under section 503A that does not ensure patients' timely access to medications. For example, the FDA acknowledged in this final guidance that "writing a prescription and waiting for the drug product to be compounded and shipped to the prescriber," also known as a patient-specific prescription, is not effective for patients experiencing a critical ophthalmic condition. Physicians have the alternative to obtain compounded medications from a 503B outsourcing facility. However, physicians experience many barriers in accessing necessary compounded medications to treat patients from a 503B outsourcing facility. In addition, many outsourcing facilities do not produce compounded drugs in the quantity needed by ophthalmology practices or in ophthalmic solutions, such as eye drops. This is not only an avoidable delay, but an additional burden on the practice to secure drugs to treat patients with emergent conditions.

Barriers to Access from 503B Outsourcing Facilities
This lack of access to compounded drugs from 503B outsourcing facilities, since the enactment of the DQSA, is evident in the dozens of reports from our members describing access issues to certain drugs for office-use from outsourcing facilities. It is clear from the final guidance and the proposed 503B pathway, that the agency has ignored comments from outsourcing facilities, specifically smaller facilities expressing their inability or lack of willingness to compound in the small quantities needed by many ophthalmologists to have on hand for emergent cases. Since drugs for emergent conditions are not used in ophthalmic practices on a regular basis, physicians generally order smaller quantities, which make it less cost-effective for the outsourcing facilities to produce. As a result, many outsourcing facilities do not produce in the requested quantities as indicated in recent FDA reports, thus limiting physician and patient access to these drugs.

503B Outsourcing Facilities Compounding Production Report
Not only are ophthalmologists reporting a lack of access to drugs from 503B facilities, FDA's own reports demonstrate it. Last year, the FDA finalized guidance, "Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act Solution," which requires 503B outsourcing facilities to submit reporting data on drug production. While ASCRS appreciates the FDA's steps toward transparency in drug availability, we remain very concerned that the most recent report finds that a number of ophthalmic drugs are missing from the list of available drugs or are not being produced in the small quantities needed by an ophthalmologist.* Additionally, the report indicates that some ophthalmic compounded drugs are being produced by only one facility. The dependence on one facility to produce compounded drugs needed in ophthalmology is particularly alarming, as it leaves the patient and physician community without access to the drug if there is any disruption in production.

To demonstrate the limited supply of compounded drugs from 503B facilities, please see Appendix A of this written statement, which includes a list of more than 100 ophthalmic drugs produced by a 503A traditional compounder before the enactment of the DSQA. Today, that same pharmacy has been converted to a 503B outsourcing facility and now produces just a handful of ophthalmic drugs.

* Upon request, ASCRS will provide a list of ophthalmic compounded drugs not being produced by 503B outsourcing facilitates.

Therefore, we strongly urge Congress to ensure that the FDA prioritize the needs of patients with emergent conditions by preserving physician access to compounded drugs for office-use from 503A compounding pharmacies. It is not effective for patients experiencing a critical ophthalmic condition to have to wait for a physician to write a prescription and for the drug product to be compounded and shipped to the prescriber to be treated. We urge Congress to prioritize the needs of patients and enact the Preserving Patient Access to Compounded Medications Act that would allow physicians' access to compounded drugs without patient-specific prescriptions for office-use from 503A traditional compounding pharmacies.

Repackaged Biologics:

ASCRS supports the provisions made in the final guidance, "Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application," which would allow 503B outsourcing facilities to extend the BUD of repackaged biologics, such as Avastin, if additional sterility testing is undertaken. ASCRS applauds the FDA's recognition of the importance of repackaged products to ophthalmology, and thanks the agency for creating provisions within this draft guidance that allow for the extension of BUDs for repackaged biologics beyond 24 hours with additional testing. The previously released draft guidance, in February 2015, proposed strict BUDs that would have severely impacted the ability of patients and physicians to access and use repackaged pharmaceuticals from outsourcing facilities and treat patients before drugs' expired BUDs. This was especially true for biological products repackaged for office use, such as Avastin. Avastin is a commonly used sight-saving drug that ophthalmologists use to treat age-related macular degeneration. The time involved in sterility testing of Avastin is 14 days, as it must be plated and left to incubate in an incubator. In addition, it takes the outsourcing facility two days to package, label, and review the drug to ensure it is clear with no particles. We applaud the FDA for recognizing the time constraints and for revising the guidance to ensure that patients have timely access to treatments.

Conclusion

We encourage Congress to intervene with the FDA's implementation of DQSA to ensure patients and physicians have continued access to compounded medications. Currently, ophthalmologists cannot access an immediate supply of some compounded drugs to treat patients who present with emergent conditions. We urge Congress to pass the Preserving Patient Access to Compounded Medications Act, which will secure compounded medications for office-use compounding and patient access to treatments.

We thank the Committee for the opportunity to bring these matters to your attention. We would be pleased to provide further input or clarification of our comments, as needed. Please contact Nancey McCann, director of government relations, at 703-591-2220 or nmccann@ascrs.org if you have any questions or would like to arrange a meeting.

APENDIX A: List of ophthalmic drugs/ injections being compounded before and after the enactment of the DQSA from same facility.

Ophthalmic drugs/ injections being compounded in a 503B outsourcing facility available in 2018:

Intravitreal Antibiotic Injections
Cefuroxime 10 mg/mL in 0.9% Sodium Chloride (Preservative-free) $34.50/1 mL in a 2 mL Vial
Moxifloxacin 1 mg/mL in Sterile Balanced Salt Solution (BSS) $34.50/1 mL Vial

Ophthalmic Injections
Lidocaine HCl 1%/Phenylephrine HCl 1.5% in sterile water for injection (Bisulfite-Free) $23.00/1 mL Vial

Ophthalmic Solutions
Atropine Sulfate 1% in 0.9% Sodium Chloride (Preservative-Free) $40.00/4 mL in an 11 mL Dropper Bottle
Edetate Disodium 3% in sterile water for Injection $161.00/10 mL in a 15 mL Dropper Bottle
Mitomycin 0.02% (0.2 mg/mL) in sterile water for injection $69.00/1 mL in a 2 mL Vial

Topical Dilation Agents
Cyclopentolate HCl / Tropicamide / Phenylephrine HCl
1 mL Bottle Cyclo HCl 1% / Trop 1% / Phenyl HCl 2.5% in sterile water for injection $30.00/Preserved 1 mL Dropper Bottle
5 mL Bottle Cyclo HCl 1% / Trop 1% / Phenyl HCl 2.5% in sterile water for injection $45.00/Preserved 5 mL Dropper Bottle
10 mL Bottle Cyclo HCl 1% / Trop 1% / Phenyl HCl 2.5% in sterile water for injection $74.50 Preserved 10 mL Dropper Bottle
Tropicamide 1%/Phenylephrine HCl 2.5% in sterile water for injection $74.55 each 10 mL in a 15 mL Dropper Bottle

Sterile Repackage
Avastin (bevacizumab) 2.5 mg/0.1 mL (25 mg/mL) (repackaged, Injection)

Ophthalmic drugs/ injections being compounded in a 503A pharmacy available before the enactment of the DQSA:

Anti Allergy Solutions
Cromolyn 4% Preserved or Preservative Free Ophthalmic Solution $73.05/10ml
Naphazoline HCL Preservative Free Ophthalmic Solution $65.65/10ml
Naphazoline/Pheniramine Preservative Free Ophthalmic Solution $65.65/10ml
Pheniramine 0.3% PF Ophthalmic Solution $65.65/10ml
Zinc Sulfate 0.25% Preservative Free Ophthalmic Solution $50.85/10ml

Anti-Infectives

Antibiotics
Amikacin Ophthalmic Solution 10-50mg/ml $97.20/10ml
Azithromycin 2mg/ml PF Ophthalmic Solution $102.60/10ml
Azithromycin 1% PF Ophthalmic Solution $102.60/10ml

Bacitracin 400u/gm/Dexamethasone 0.05% Oph Ointment $63.20/4gm
Bacitracin Ophthalmic Solution 5,000 or 10,000 u/ml $53.30/10ml
Cefazolin Ophthalmic Suspension $77.95/10ml
Ceftazidime Ophthalmic Solution $82.90/10ml
Chloramphenicol 0.5% Preservative Free Ophthalmic Solution $82.90/10ml
Chloramphenicol 1.0% Ophthalmic Ointment $77.95/4gm
Chlorhexidine Ophthalmic Solution $63.20/10ml
Clindamycin Preservative Free Ophthalmic Suspension varies
Clindamycin 1% Ophthalmic Ointment varies
Ciprofloxacin 0.3% Preservative Free Ophthalmic Solution $65.65/10ml
Clarithromycin 1% Ophthalmic Suspension $90.30/10ml Doxycycline 0.025%
or 0.1% Oph Solution $53.30/10ml
Fortified Cefazolin Ophthalmic Suspension $77.95/10ml
Fortified Gentamicin Ophthalmic Solution (also available Preservative Free) $64.40/7ml
Fortified Tobramycin Ophthalmic Solution (also available Preservative Free) $64.40/7ml
Fumidil B (bicyclohexylammonium fumagillin) $103.10/10ml
Gentamicin Preservative Free 3mg/ml Oph Solution $53.30/5ml
Imipenium/Cil 5mg/ml Pf Oph Solution $102.60/10ml
Kanamycin Ophthalmic Solution 40mg/ml $44.15/10ml
Levofloxacin 5-25mg/ml Ophthalmic Solution $53.30/10ml
Metronidazole 0.5% Preserved or Preservative Free Ophthalmic Solution $66.15/10ml
Metronidazole 0.75% Ophthalmic ointment $68.10/4gm
Neomycin 15mg/ml Ophthalmic Suspension $41.00/10ml
Paromycin 15mg/ml Ophthalmic Solution $102.60/10ml
Penicillin G Potassium Ophthalmic Solution $83.40/10ml
Piperacillin 10mg/ml Pf Oph Solution $117.40/10ml
PHMB 0.01% or 0.02% $92.75/15ml
Polymixin/Trimethoprim Preservative Free Ophthalmic Solution $102.60/10ml
Sodium Sulfacetamide 10%-30% Preservative Free Ophthalmic Solution $82.90/10ml
Sulfamethoxazole/Trimethoprim Ophthalmic Solution $65.65/10ml
Vancomycin 20mg/ml, 25mg/ml or 50mg/ml Ophthalmic Solution $77.95/10ml
Vancomycin 14mg/ml preservered (60 day exp date) $35/10ml
Tobramycin 0.3%/Dexamethasone 0.1% Oph Solution $65.65/5ml
Tobramycin 0.3% Preservative Free Oph Sol $77.95/10ml
Tetracycline 1% Preservative Free Oph Ointment $82.90/4gm

Anti-virals
Acyclovir 3% Ophthalmic Ointment $92.75/4gm
Cidofovir Ophthalmic Solution (Release is required) $225.85/3ml
Idoxuridine 1% or 0.1% Ophthalmic Solution $75.40/8ml
Idoxuridine 0.5% Ophthalmic Ointment $73.05/4gm
Trifluridine 1% Preservative Free Ophthalmic Solution $108.15/8ml
Trifluridine 0.5% Compounded Ophthalmic ointment $73.60/4gm
Vidarabine 3% Ophthalmic Ointment $92.35/4gm

Anti-fungals
Amphotericin 0.1-0.5% Ophthalmic Solution $77.35/10m

Clotrimazole 1% Ophthalmic Suspension $77.95/10ml
Fluconazole 2mg/ml Ophthalmic Solution $90.30/10ml
Flucytosine 10mg/ml Ophthalmic Solution $65.65/10ml
Itraconazole 1% Ophthalmic Suspension $78.95/10ml
Ketoconazole 5% Oph Suspension in Peanut oil $77.95/10ml
Micafungin 0.1% Oph Solution $144.25/5ml
Miconazole Nitrate 1% Ophthalmic Suspension $90.30/10ml
Natacyn Ophthalmic Suspension $231.52/15ml
Voriconazole 1% Cmpd Ophthalmic Solution $157.50/10ml

Cytotoxic Agents

Fluorouracil Ophthalmic Solution 1% $53.30/10ml
Thiotepa 1:2000/ 1:1000 Oph Solution $77.95/5ml
Mitomycin Injection or Ophthalmic Solution (all strengths) $45.52/1ml

Diagnostic Agents
Cocaine Ophthalmic Solution 4% & 10% Varies
Fluorescein Oph Solution 0.2% - 2% Preserved or Preservative Free $41.00/15ml
Glycerin 99.5% PF or Preserved Ophthalmic Suspension $32.06/10ml
Gonioscopic Gel (various strengths) $32.06/10ml
Hydroxyamphetamine 1% Preserved or PF 5ml $53.30/5ml
Lissamine Green 1% Preservative Free or Preserved Ophthalmic Solution $32.06/10ml
Rose Bengal Solution 1% Pres. Free or Preserved Ophthalmic Solution $41.00/10ml
Saccharin Sodium 10mg/ml $41.00/10ml
Sodium Saccharin 2% Ophthalmic Solution $41.00/10ml

Dry Eye Compounds
Albumin 5% Ophthalmic Solution $53.30/10ml
Aquasol A Ophthalmic Suspension $83.45/15ml
Calcium Carbonate 10% Ophthalmic Ointment $41.00/30gm
Castor Oil 2% Ophthalmic Suspension $32.06/10ml
Cyclosporine 0.2% Ophthalmic Ointment $62.65/4gm
Cyclosporine 0.05% in Cyclodextran Solution $83.35/10ml
Cyclosporine 0.05% /Dexamethasone 0.01 % in Cyclodextran Solution $90.30/10ml
Cyclosporine 0.05-2% Ophthalmic Suspension in Gum Cellulose varies
Dehydroepiandrosterone (DHEA) Ophthalmic Suspension 0.5% or 1% $90.30/10ml
Dextran Ophthalmic Suspension $32.06/10ml
Estradiol 0.01-0.03% Ophthalmic Suspension $93.75/10ml
GumCellulose Preservative Free Ophthalmic Solution 0.3% to 2.5% $16.00/15ml
Hyaluronic Acid PF Ophthalmic Suspension 0.5% $144.55 /10ml
Methylcellulose Preservative Free Ophthalmic Solution $16.00/15ml
Poly-Vinyl Alcohol/ Povidone Ophthalmic Solution $32.06/10ml
Rapeseed Oil 2% (Alpha Omega Drop) Suspension $32.06/10ml
Retinoic Acid (all trans) 0.01% Ophthalmic ointment $78.35/4gm
Retinoic Acid (all trans) 0.01% or 0.005% Ophthalmic Suspension $78.35/10ml
Serum Ophthalmic Drops varies

Sodium Carboxy Methylcellulose Ophthalmic Gel $16.00/15ml
Tacrolimus 0.02% Cmpd Ophthalmic Suspension $32.06/5 ml
Tacrolimus 0.02% Cmpd Ophthalmic Ointment $67.00/4 gm
Trehalose 3.78% Ophthalmic Solution $73.05/10ml
Vaseline Preservative Free Ophthalmic Ointment $78.55/4gm
Vitamin A 0.01% Oph Suspension (All Trans Retinoic Acid) $77.95/10ml
Vitamin A 0.01% Ophthalmic Ointment (All Trans Retinoic Acid) $78.35/4gm

Glaucoma
Acetazolamide 1% Preservative Free Ophthalmic Suspension $102.60/10ml
Apraclonidine Preservative Free ** Ophthalmic Solution $77.95/5ml
Betaxolol 0.125% Preservative Free** Ophthalmic Solution $53.30/5ml
Bimatoprost 0.015% PF** Ophthalmic Solution $107.55/3ml
Brimonidine 0.1% or 0.075% Preservative Free** Ophthalmic Solution $102.60/10ml
Brinzolamide 0.5% PF** Ophthalmic Solution $45.95/5ml
Carbachol 1.5%, 2.25% & 3% Preservative Free Ophthalmic Solution $90.30/10ml
Clonidine Preserved or Preservative Free Ophthalmic Solution $65.65/10ml
Dipivefrin 0.1% Pres'd or Pf Oph Solution $55/5ml, $75.00/10ml Dorzolamide 1% PF** Ophthalmic Drops $102.60/10ml
Dorzolamide 1%/Timolol 0.25% PF ** Ophthalmic Solution $97.2010ml
Epinephrine Bitartrate Preservative Free Ophthalmic Solution $74.35/10ml
Epinephrine Borate Preservative Free Ophthalmic Solution $97.20/10ml
Epinephrine HCL 1% Preserved Ophthalmic Solution $77.95/10ml
Latanoprost 0.0025% Preservative Free** Ophthalmic Solution $90.07/3ml
Levobutanol 0.25% PF** Ophthalmic Solution $53.30/5ml
Phospholine Iodide (all strengths) varies
Pilocarpine Preservative Free Ophthalmic Solutions 0.1% to 6% $65.65/10ml
Pilo 1%/Epi 1% Cmpd Ophthalmic Solution $41.00/5ml
Travoprost Z 0.002% Cmpd PF** Ophthalmic Suspension $83.35/3ml
Preservative Free Steroids
Dexamethasone Na Phos Injection 4-24mg/ml PF varies
Dexamethasone Sodium Phosphate Preservative Free Solutions $58.00/10ml
Dexamethasone 0.05% Ophthalmic Ointment $82.90/4gm
Dexamethasone 0.05% Lanolin Free Ophthalmic Ointment $82.90/4gm
Fluorometholone 0.1% PF Ophthalmic Suspension $55.00/5ml
Loteprednol 0.25% PF** Opthalmic Solution $74.35/ml
Methylprednisolone Na Succinate Preservative Free Ophthalmic Solution $77.95/10m
Prednisolone Acetate Preservative Free Ophthalmic Suspension $92.75/10ml
Prednisolone Sod Phos Preservative Free Ophthalmic Solution $82.90/10ml
Rimexolone 0.5% Cmpd PF ** Ophthalmic Solution $102.60/10ml
Triamcinolone 80mg/ml Preservative Free Compound Injection $20.00/1ml

Misc. Agents

Acetyl Cysteine 5-20% Ophthalmic Solution pf $77.95-97.70/10ml
Aminocaproic Acid 30% Ophthalmic Suspension $85.85/10m
Ascorbic Acid 10% Ophthalmic Suspension $87.85/10ml

Bevacizumab (Avastin) Cmpd Inj (various doses available) varies
Bevacizumab (Avastin) Topical Drops varies
Benoxinate 0.4% PF or Preserved Oph Solution $32.06/5ml
Boric Acid Ophthalmic Ointment $82.90/4gm
Brilliant Green 2% Ophthalmic Stain $32.06/10ml
Brilliant Blue G 0.25mg/1ml $10.00/1ml
Cysteamine 0.55% Cmpd Ophthalmic Solution $83.90/10ml
Diclofenac Sodium 0.1% Preservative Free Ophthalmic Solution $77.95/10ml
EDTA Preserved 0.4% to 3% varies
Ethanol (all concentrations) Ophthalmic Drops or Injectable $53.30/10ml
Indomethacin 0.5 or 1% Ophthalmic Suspension $92.75/15ml
Glutathione 6% Ophthalmic Solution $59.50/15ml
Glycerin 50% oral solution $55.60/220ml
Glycerin 50% Ophthalmic Solution $30.53/10ml
Guanethidine Preservative Free Ophthalmic Solution 2%, 5% or 7.5% varies
Heparin PF Ophthalmic Solution $32.06/10ml
Hyaluronidase Injection 150u/ml $15.00/1ml, $31.25/5 ml, $46.25 /10ml
Ibopamine 2% Ophthalmic Solution $65.00/5ml,$85.00/10ml
Interferon Alfa 2B Ophthalmic Solution (1-3mu/ml) $235.73/3-10ml (depends on strength)
Isosorbide 45% Cmpd Oral Solution $128.75/110ml
Medroxyprogesterone Acetate 0.5% or 1% Ophthalmic Suspension $40.91/10ml
PABA 10% Cmpd Ophthalmic Ointment $60.03/4gm
Phentolamine 0.083% Ophthalmic Solution $41.00/5ml
Physostigmine Salicylate 0.03%, 0.125% 0.25% or 0.5% Oph Solution $77.95/10ml
Physostigmine Salicylate Ophthalmic Ointment $87.85/4gm
Povidone-Iodine Ophthalmic Solution $53.30/10ml
Silver Nitrate Ophthalmic 0.5% or 1% Solution $53.30/10ml
Silver Protein 10% Ophthalmic Solution $44.15/10ml
Sodium Chloride 5% Ophthalmic Solution PF $53.30/10ml
Sodium Chloride 5% Preservative Free Ophthalmic Ointment $63.20/4gm
Sodium Citrate 10% Ophthalmic Solution $69.10/10ml
Tetrahydrolazine 0.05% PF Ophthalmic Solution $53.30/10ml
Vision Blue 0.06% Singles $52.00/each
Vitamin A 1%/ Vit C 1% /Glutathione 1%/DMSO 5% Ophthalmic Sol $98.70/10ml

Topical Anesthetics, Reversal Agents and Combo Dilating Agents

Atropine Sulfate Ophthalmic Solution 0.125% to 1% PF $50.90/10ml
Benoxinate 0.4% PF or Preserved Oph Solution $32.06/5ml
Cyclopentolate 0.5% to 1% P.F. $77.95/10ml
Cyclopentolate/Phenylephrine/Bupivicaine Combo Ophthalmic Solution varies
Cyclopentolate/Phenylephrine/Diclofenac Combo Ophthalmic Solution varies
Cyclopentolate/Phenylephrine Combo varies
Cyclopentolate/Proparacaine Combo varies
Dapiprazole 0.5% Topical Drops (compare to Rev-Eyes-Lyopholized) $40.00/6ml kit
Homatropine Preservative Free Ophthalmic Solution 5% $43.45/10ml
Lidocaine Ophthalmic Solution 0.5-0.4% $53.30/10ml

Phenylephrine Preservative Free Ophthalmic Solution 2.5% or 10% $53.30/10ml
Proparacaine Preserved or PF (0.03%, 0.05%, 0.1%, 0.25%) Ophthalmic Solution $43.35/10ml
Proparacaine 0.05% PH Adjusted Preserved Ophthalmic Solution $32.06/10ml
Proparacaine/Tropicamide/Cyclopentolate/Phenylephrine Combo Oph Sol varies
Scopolamine 0.25% Preservative Free Ophthalmic Solution $65.65/10ml
Tetracaine 0.5% PF Cmpd Ophthalmic Solution $32.06/5ml
Tetracaine 0.5% Ophthalmic Ointment $82.90/4gm
Tetracaine HCL 0.05% Preserved and Stabilized Oph Solution (Comfort Drops) $7.50/3 or 5ml
Tropicamide Preservative Free Ophthalmic Solution $53.30/10ml
Tropicamide 0.5%/Cyclopentolate 0.5%/PHN 2.5% Combo Spray $48.30/10ml
Tropicamide 1%/ Cyclopentolate 1% Ophthalmic Solution $53.30/10ml
Tropicamide 1%/ Phenylephrine 2.5% Preserved Ophthalmic Solution $53.30/10ml
Tropicamide 1%/ Phenylephrine 5% Preserved Ophthalmic Solution $53.30/10ml
Tropicamide 0.25%/ Phenylephrine 5% Preserved Ophthalmic Solution $53.30/10ml
Topicamide 1%/Cyclopentolate1%/Phenylephrine 2.5% Preserved Ophthalmic $54.80/10ml

Statement

of

The National Association of Chain Drug Stores

for the

United States House of Representatives

Committee on Energy and Commerce
Subcommittee on Health

Hearing on:

"Examining Implementation of
the Compounding Quality Act"

January 30, 2017
11:00 a.m.

2123 Rayburn House Office Building

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The National Association of Chain Drug Stores (NACDS) thanks Chairman Burgess, Ranking Member Green, and Members of the Energy and Commerce Committee Subcommittee on Health for the opportunity to submit a statement for the hearing on "Examining Implementation of the Compounding Quality Act."

NACDS and the chain pharmacy industry are committed to partnering with Congress, the Food and Drug Administration (FDA), state boards of pharmacy, and others in the pharmacy community on policies that support the delivery of high quality, affordable healthcare services that meet the diverse healthcare needs of patients across the country. NACDS represents traditional drug stores, supermarkets and mass merchants with pharmacies. Chains operate over 40,000 pharmacies, and NACDS' nearly 100 chain member companies include regional chains, with a minimum of four stores, and national companies. Chains employ nearly 3 million individuals, including 152,000 pharmacists. They fill over 3 billion prescriptions yearly, and help patients use medicines correctly and safely, while offering innovative services that improve patient health and healthcare affordability. NACDS members also include more than 900 supplier partners and over 70 international members representing 20 countries. Please visit www.NACDS.org.

As the face of neighborhood health care, chain pharmacies and pharmacists work on a daily basis to provide the best possible care to patients and to meet their medication needs. Where some patients require medicines that are not otherwise available as commercially-manufactured preparations, chain pharmacists perform prescription drug compounding to ensure that patients have access to medications necessary to treat their

medical conditions. These types of pharmacist compounding services have been offered by pharmacies since the early days of the pharmacy profession. Over the years, these services have remained a valuable and important component of our nation's healthcare system.

When Congress enacted the Drug Quality and Security Act ("DQSA), lawmakers recognized the importance of allowing pharmacists in retail community pharmacies to continue to provide traditional compounding services and maintained pharmacists' ability to do so under Section 503A of the Food, Drug, and Cosmetic Act. The chain pharmacy community supports the implementation of the DQSA in a manner that is consistent with the intent of Congress to maintain access to compounding services historically provided by retail community pharmacies.

Among its various actions to implement the DQSA, FDA published a draft memorandum of understanding (MOU) in 2015 outlining the responsibilities of FDA and individual state boards of pharmacy with respect to investigation and response to complaints related to interstate distribution of compounded drugs, and interstate distribution of inordinate amounts of compounded drugs. Like other pharmacy stakeholders, the chain pharmacy community is concerned that certain provisions in the draft MOU – if finalized and implemented – could impede retail community pharmacists' and pharmacies' ability to provide traditional compounding services that are permitted under Section 503A of the Food, Drug & Cosmetic Act.

Notably, Section 503A of the Food, Drug & Cosmetic Act clearly distinguishes the act of dispensing as separate from the act of distribution.[1] However, the language of the draft MOU defines the term "distribute" to include the act of "dispensing." In doing so, the draft MOU fails to maintain the important distinction between compounded products that are distributed versus compounded products that are dispensed.

Before finalizing the MOU, it is imperative that FDA remedy the inconsistency between the language of law and the MOU. Given that Section 503A establishes that the scope of the MOU is to "address the *distribution* [emphasis added] of inordinate amounts of compounded drug products," the language of the MOU should address distribution only.[2] Otherwise, the MOU may impede retail community pharmacies' ability to dispense compounded medications to their patients pursuant to a prescription.

Additionally, we are concerned that the draft MOU imposes an arbitrary cap on what constitutes an "inordinate amount" of compounded product distributed interstate. Imposing this arbitrary limitation is problematic for a number of reasons. It fails to take into consideration regional and geographic issues, individual pharmacy volume, and other factors that may necessitate higher rates of interstate distribution in certain circumstances. Furthermore, it is concerning that the cap on interstate distribution would be calculated using both compounded drug products that are distributed and *dispensed* [emphasis added] in and out of state. As we discussed above, the law establishes that the scope of

[1] 21 U.S.C. §353a(3)(B)(ii)
[2] 21 U.S.C. §353a(3)(B)(i)

the MOU is limited to distribution only. Including compounded drug products that are dispensed would be inconsistent with the language of the law.

Overall, the limitations established in the draft MOU regarding what constitutes an "inordinate amount" of compounded product may impede patient access to compounded products by restricting the supply of compounded products that may be distributed out of state. We believe that defaulting to any arbitrary cap is contrary to the overall goal of the MOU, which is to facilitate communication among the states and FDA on how to best trigger investigation of a compounding pharmacy where appropriate. For these reasons, the language establishing these specific limits should be eliminated from the MOU entirely.

We note that the 2018 Compounding Policy Priorities Plan published by FDA earlier this month acknowledges that because of the many stakeholder concerns with the draft MOU, FDA plans to substantially revise the MOU to address many of the concerns raised. We are hopeful that the concerns we highlighted in our comments above will be among the issues that FDA addresses before finalizing the MOU, as these are central to maintaining patient access to the important pharmacist compounding services provided in retail community pharmacies across the nation.

NACDS thanks the Committee for your consideration of our comments. We look forward to working with policymakers and stakeholders on these important issues.

U.S. HOUSE ENERGY AND COMMERCE
HEALTH SUBCOMMITTEE
"Examining Implementation of the Compounding Quality Act."
Tuesday January 30, 2018
11:00AM
Statement for the Record
The American Pharmacists Association

The American Pharmacists Association (APhA) appreciates the opportunity to submit the following Statement for the Record for today's U.S. House Energy and Commerce Health Subcommittee hearing "Examining Implementation of the Compounding Quality Act."

APhA, founded in 1852 as the American Pharmaceutical Association, represents more than 64,000 pharmacists, pharmaceutical scientists, student pharmacists, pharmacy technicians, and others interested in improving medication use and advancing patient care. APhA members provide care in all practice settings, including community pharmacies, hospitals, long-term care facilities, community health centers, physician offices, ambulatory clinics, managed care organizations, hospice settings, and the uniformed services.

APhA would like to thank Subcommittee Chair Burgess and Ranking Member Green for holding a hearing to gather Agency and stakeholder input on drug compounding as part of the Committee's ongoing oversight of the FDA's mission to ensure drug quality and security as the provision of safe, effective medications, including compounded medications, which is of paramount importance to APhA members and a goal shared by everyone here today. APhA would also like to note that legislation[1] providing appropriations to the federal agencies was recently signed into law. This legislation included report language clarifying congressional intent with regard to the Drug Quality and Security Act (DQSA), which aligns with APhA and other pharmacy organizations' interpretation and our comments. The language specifically:

- Calls on FDA to draft a Memorandum of Understanding (MOU) that addresses the "distribution" of compounded products over state lines;
- Calls on FDA to draft final guidance to allow pharmacists to compound for "office use" "in anticipation of receiving patient-specific prescriptions at a later time;" and
- Reminds FDA that pharmacies that compound under 503A are under the purview of state boards of pharmacy and are not to be held to current Good Manufacturing Practices (CGMPs).

MOU

APhA supports FDA finalizing an MOU which aligns with the congressional intent of the DQSA. The plain language of the Food, Drug and Cosmetic (FD&C) Act directs FDA to develop

[1] *See*, H. Rept. 114-531 - AGRICULTURE, RURAL DEVELOPMENT, FOOD AND DRUG ADMINISTRATION, AND RELATED AGENCIES APPROPRIATIONS BILL, 2017. Available at: https://www.congress.gov/congressional-report/114th-congress/house-report/531/1?q=%7B%22search%22%3A%5B%22H.+Rept.+114-531%22%5D%7D&r=1

an MOU that addresses "the distribution of inordinate amounts of compounded drug products interstate."[2] While DQSA does not explicitly define "distribution," the statutory text differentiates between "distribution" and "dispensing" in a number of places—a clear indication that Congress ascribed different meanings to the two terms.[3] Historically, the terms "dispense" and "distribute" refer to two different activities. In both FD&C[4] and the Controlled Substances Act,[5] Congress and FDA expressly recognized the different usage of "dispense" and "distribute," defining "dispensing" as something that is intrinsically clinical in nature, while defining "distribution" as the act of shipping or delivering a medication outside of the patient-provider relationship. To treat "distribution" and "dispensing" as interchangeable only in the context of DQSA not only creates confusion, it also implies that FDA is entering into the regulation of clinical decision-making related to prescribing—an area meant to be governed by states. Thus, in keeping with congressional intent, we believe that a final MOU should only address "distribution" of compounded medications across state lines and should have no effect on dispensing of prescriptions for identified patients by pharmacies compounding under section 503A. Congress noted that for the MOU, "inordinate" amounts or quantities refers to "amounts typically associated with ordinary commercial drug manufacturing."[6] It would be helpful for the Committee to clarify congressional intent with the FDA during today's hearing.

Office Use

APhA reiterates its concern with FDA's position in its recent final guidance prohibiting pharmacies from compounding for office use, despite existing federal law which states that a licensed pharmacist can compound "in limited quantities before the receipt of a valid prescription order for such individual patient" and a long history of the Agency allowing the practice.[7] While the FDA has indicated that office use compounded products should be fulfilled by outsourcing facilities, due to the cost and/ or time to comply with CGMP, 503B facilities cannot meet all the product demands of patients and providers. This is why many 503B facilities have defined formulary lists.[8] CGMP requirements include: procurement of bulk drug product(s) which meets CGMP; authoring procedures to compound the medication which meet CGMP; proper testing (validation, release testing, stability testing) and other requirements.[9] APhA members' conversations with 503B facilities have confirmed the inability of these facilities to supply many small batch medications commonly associated with office use (e.g., numbing creams/sprays, etc.). In addition, because of the time required to meet CGMPs, including, but not limited to the testing requirements, 503Bs are unable to immediately meet the needs of providers and patients unless facilities are currently compounding the product(s). Therefore, APhA

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[2] *See* 21 U.S.C. § 353a(3)(B). Available at: https://www.law.cornell.edu/uscode/text/21/353a

[3] *See e.g., id.* at (3)(B)(ii) (differentiating the "dispensed" and "distributed" through the use of the disjunctive "or", indicating that the terms are not interchangeable).

[4] Drug Supply Chain Security Act, §581(5) (2013) (defining distribute as "the sale, purchase, trade, delivery, handling, storage, or receipt of a product", but stating that it "does not include the dispensing of a product pursuant to a prescription executed in accordance with section 503(b)(1) or the dispensing of a product approved under section 512(b)").

[5] *See* 21 U.S.C. §802(10)-(11). Available at: http://www.deadiversion.usdoj.gov/21cfr/21usc/802.htm ; *See also* 21 C.F.R. §208.3 defining "distribute" as "the act of delivering, other than by dispensing, a drug product to any person", thereby expressly excluding dispensing from the act of distribution). Available at: https://www.law.cornell.edu/cfr/text/21/208.3

[6] *See,* S. Rept. 105-43 - FOOD AND DRUG ADMINISTRATION MODERNIZATION AND ACCOUNTABILITY ACT OF 1997. Available at: https://www.congress.gov/congressional-report/105th-congress/senate-report/43/1

[7] *See,* 21 USC 353a. SEC. 503A. PHARMACY COMPOUNDING. Available at: https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm376733.htm

[8] *See* SCA Pharmaceuticals. Product Catalog. 2016; Cantrell Drug Company. Product Catalog. 2016; and Leiter's Compounding Product Catalog, 2016.

[9] *See* FDA. Guidance for Industry Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act. July 2014. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm403496.pdf

strongly urges Congress to ensure that FDA follows its previous long-standing policy, as well as existing statute and the intent of Congress, and continue to allow pharmacies compounding under section 503A to compound "limited quantities" without a patient-specific prescription and defer to states for statutory or regulatory authority over pharmacies' office use compounding.

Anticipatory Compounding

Section 503A(a)(2) of the FD&C Act, allows a licensed pharmacist or licensed physician to compound "limited quantities"[10] before the receipt of a valid prescription order when there is a relationship between the prescriber and pharmacist or physician receiving the prescription, or the patient and pharmacist or physician receiving the prescription. In final guidance, FDA defined "limited quantity" as "a 30-day supply of a particular compounded drug" if that supply "is based on the number of valid prescriptions that the compounder has received for an identified individual patient in a 30-day period over the past year" (i.e., referred to as "anticipatory compounding"). While APhA appreciates FDA acknowledging "larger batch sizes can increase efficiency and reduce the likelihood of human error,"[11] because FDA is now attempting to define "limited quantity," we believe it is minimizing the value and benefit of anticipatory compounding.

Inspections

Finally, APhA was initially pleased with FDA's recent July 2016 "Notice" that starting August 1, 2016, FDA inspectors would make a "preliminary assessment" of whether pharmacies are in compliance with 503A before applying 503B standards in "Form FDA-483" investigations and would not include observations in its Form-483 based "solely" on CGMP under section 503B.[12] However, APhA has received multiple Form FDA-483s dated post-July 2016 regarding inspections of pharmacies compounding under section 503A, which indicate that FDA inspectors continue to inspect pharmacies, not outsourcing facilities under 503B, and cite CGMP noncompliance. APhA continues to have serious concerns that the pharmacies being cited are not 503B and are incorrectly being cited by FDA for CGMP. Accordingly, we are pleased that the 2017 appropriations legislation signed into law also requires FDA to recognize that federal oversight of pharmacies compounding under section 503A was not the intent of Congress, and that compounding pharmacies are not drug manufacturers—rather, they are "state licensed and regulated health care providers that are inspected by state boards of pharmacy pursuant to state laws and regulations that establish sterility and other standards for the pharmacies operating within their states."[13] We strongly urge the Committee to clarify to FDA the congressional intent of this language during today's hearing.

In addition, we have heard from nuclear pharmacies, which are exempt from the DQSA for the preparation of radiopharmaceuticals,[14] that FDA is inspecting these facilities based on these draft

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[10] *See* 21 U.S. Code § 353a - Pharmacy compounding. Available at: https://www.law.cornell.edu/uscode/text/21/353a

[11] In addition, compounding larger supplies of products often encourages quality control testing because costs can be spread out among a larger number of products.

[12] *See* FDA. Notice of Change in Process for Inspections of Certain Compounders. July 12, 2016. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM510684.pdf

[13] *See*, H. Rept. 114-531 - AGRICULTURE, RURAL DEVELOPMENT, FOOD AND DRUG ADMINISTRATION, AND RELATED AGENCIES APPROPRIATIONS BILL, 2017. Available at: https://www.congress.gov/congressional-report/114th-congress/house-report/531/1?q=%7B%22search%22%3A%5B%22H.+Rept.+114-531%22%5D%7D&r=1

[14] *See* 21 U.S.C. §353a(e). "``(e) Application.--This section shall not apply to-- ``(1) compounded positron emission tomography drugs as defined in section 201(ii); or ``(2) radiopharmaceuticals." Available at: https://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/pdf/USCODE-2010-title21-chap9-subchapV-partA-sec353a.pdf

guidances, not statutes, and then issuing Form FDA-483s for observations that are not applicable. While compounding creates what are essentially new drug products designed to meet patient needs, most nuclear pharmacies are preparing radiopharmaceuticals from kits that are FDA-approved—activity that falls outside of the FD&C's definition of compounding. We would appreciate the Committee inquiring why FDA is inspecting nuclear pharmacies as compounders when Congress specifically exempted them from the DQSA.

APhA would like to close by thanking the Committee for continuing to work with APhA and other pharmacy stakeholders to construct a framework in accordance with current statutory authority and congressional intent that ensures patients have access to safe and effective compounded medications. APhA looks forward to being part of future discussions on this topic. We hope to be a resource for Congress and FDA and are happy to be of assistance in any way possible.

Thank you again for the opportunity to provide comments on this important issue.

American Academy of Allergy, Asthma, & Immunology
American College of Allergy, Asthma, and Immunology
American Academy of Otolaryngic Allergy

Joint Statement for the Record
Before the House Energy and Commerce Health Subcommittee
Hearing Entitled
"Examining Implementation of the Compounding Quality Act"

Tuesday, January 30, 2018

Chairman Burgess, Ranking Member Green, and members of the Subcommittee, on behalf of the American Academy of Allergy, Asthma, & Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI), and the American Academy of Otolaryngic Allergy (AAOA), thank you for the opportunity to share our views on the implementation of the Compounding Quality Act. We hope you will consider our comments regarding efforts to establish heightened safeguards for compounded medications. The AAAAI and the ACAAI are the premier specialty societies representing more than 6,000 allergist-immunologists and related professionals worldwide dedicated to advancing allergy and immunology health care. The AAOA is the premiere otolaryngology (ENT) society focused on diseases of the respiratory tract, including allergy, and represents over 2000 members impacting over 8000 otolaryngologists.

Our written statement will discuss the recent proposed changes by the U.S. Pharmacopeia (USP) and the Food and Drug Administration (FDA) that would transform allergen immunotherapy (AIT) – a currently proven safe and effective disease modifying therapy – into a higher risk and less accessible treatment option.

Allergen Extracts and Allergen Immunotherapy
Allergen extracts are prepared based on the allergist's written order specifying the content, concentration, and dosing schedule. When a patient begins immunotherapy, he or she begins with highly diluted doses and the concentration gradually increases over time. Injections are typically between 0.5 and 1.0 mL and are administered subcutaneously. Usually, by the end of a year, a patient is on a maintenance dose and receives injections once or twice every month. For some patients, such as those with life-threatening stinging insect allergies, this course of treatment can create a change in the body's immune response that is potentially life-saving.

The mixing of allergen immunotherapy treatment sets begins with FDA approved allergenic extracts. Most, but not all, commercial allergenic extracts are 50% glycerinated. The allergenic extracts or "concentrates" are combined in a sterile vial using sterile syringes. Serial 5-fold or 10-fold dilutions are then made from the vial of concentrate using sterile saline (either normal saline or HSA saline) typically containing 0.4% phenol. Aseptic technique based on current USP Ch. <797> guidelines or the standards set forth in specialty-developed Practice Parameters is followed, and vials are labeled and stored in refrigerated conditions accordingly. Beyond-use dates (BUDs) are assigned based on the most recent expiration date of any of the component antigens. The inclusion of preservatives deters many infectious

concerns while allowing treatment to proceed safely by use of consistent extract over many months while the immune response to the allergens present increases.

A typical multi-dose vial of maintenance extract contains 10 doses designed to last over a 10-12 month period. Dilutions, which are given at the onset of treatment, are also prepared in 10 dose vials but storage time is less because the injections are given more frequently (e.g., weekly to bi-weekly).

Allergen extracts are uniquely situated compounded products. Allergen extracts require close monitoring at the time of the injection, and patients are closely monitored in the physician's office for reactions for at least 30 minutes post-injection. Additionally, patients receiving immunotherapy come to the physician's office at least monthly for injections. Before each new injection, patients are queried regarding any issues with the previous injection including any lesser reactions. The injection site is also physically examined. Any problems are reported to the physician. Based on the patient history and well-being, modifications are implemented to protect patients. For example, dose reductions or a postponed administration might be adopted if a patient has suffered an asthma flare. It is important that the allergist be able to make these changes on a timely basis so that the course of treatment is appropriate for the patient's current condition and not delayed. Anaphylactic reactions are always a possibility throughout immunotherapy treatment, and are the primary risk to allergen immunotherapy patients. The ability to compound and consistently monitor the use of allergen extract is fundamental to minimizing this risk.

Allergen immunotherapy has been safely compounded and administered in allergists' offices for over 100 years. This precision medicine technology is life altering and at times lifesaving. And unlike many other compounded treatments, AIT is administered subcutaneously and not parenterally or intrathecally, essentially eliminating any risk of systemic infection. Indeed, there is no documented evidence of an infectious risk from compounding allergen extracts in the office setting.

Current Standards
Current U.S. Pharmacopeia (USP) <797> standards, which are recognized by the FDA in regulation and guidance as required by statute, distinguish the unique nature of allergen extracts from other compounded drugs and provide specific requirements for their use. However, allergen extracts as compounded sterile preparations (CSPs) are not subject to the personnel, environmental, and storage requirements.

FDA Guidance
In February 2015, the Food and Drug Administration (FDA) issued draft guidance titled "Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application Guidance for Industry." Those FDA draft guidelines suggest in-office allergen extract compounding should follow the USP <797> instructions specific to allergen extracts and specified policies which provided special exceptions recognizing the unique nature of AIT. We previously submitted comments generally in support of the FDA draft guidance, and we are pleased that the final guidance released in January 2018 retains the special exemptions for allergen extracts.

Given that Congress has statutorily required the FDA defer to the USP for some key regulatory questions, we urge you to maintain oversight not only over the FDA process but also the USP process. As you may be aware, USP is in the process of crafting a significant revision to the <797> chapter that, if approved as proposed, could significantly alter the process of AIT compounding and administration that could significantly decrease access to this treatment.

In the fall of 2015, USP published a proposed revision of Chapter 797 that significantly altered the standards for sterile compounding, moving from a risk assessment-based series of requirements to one that treated all sterile compounding as equally and inherently dangerous, regardless of the contents or administration site of the compounded material. The proposed changes to the USP for allergen compounding are not based on published scientific data in which any infectious clinical problem(s) with allergen extract compounding has occurred. However, these proposed changes have the potential to significantly decrease the safety of AIT and place patients at increased risk for adverse outcomes.

Under the proposed revisions, allergen extracts would no longer have specific requirements for their use but would instead be treated similar to all other CSPs. The proposal would require that all sterile compounding, including allergen extract compounding, be performed in an ISO Class 5 environment. This contradicts current USP <797> guidelines and current FDA guidelines, without providing any evidence that such an approach is necessary to avoid infectious risk from mixing and administration of AIT. Therefore, we reject that the current standards (as previously agreed to by the USP and FDA) are insufficient to safely provide these services in the physician's office.

The USP proposal would also require discarding of all preparations after either 28 or 42-days regardless of manufacturer beyond use dates (BUDs). This change would require more frequent mixing of allergen extracts, significantly increasing the risk of an adverse event due to an allergic reaction because of extract lot variability with respect to content and potency, which can cause allergic reactions. In addition to safety concerns, shorter BUD requirements would impact the efficacy of therapy. This potential lack of efficacy relates to immunotherapy induction of tolerance developed when maintenance dosing is achieved, and the linkage to the timing of injections that are typically given monthly once the maintenance dose is reached. If the allergen preparation for maintenance therapy must be remade every month, it would prevent the patient from reaching the maintenance dose (and desensitization) because the schedule would have to be restarted with each newly prepared allergen extract material.

The proposed changes to USP <797> are not indicated by the medical literature, which supports the conclusion that allergen extract preparation following current <797> guidelines is safe and does not place patients at risk for infectious complications related to AIT. The over-reaching and dangerous USP proposal was met with almost 8,000 comments. The volume, intensity and extraordinary level of concern expressed in those comments reflects significant consideration from health care providers and patients, as well as an expectation that evidence supportive of this overreaching, "one-size-fits-all" approach should be provided before such draconian measures should be considered.

Recently, USP invited a private practicing allergist, Andrew Murphy, MD, FAAAI, to serve as an expert consultant, providing important input as the USP Compounding Expert Committee (CEC) completes work on its second draft of USP <797> for public comment (expected September 4, 2018). However, there is no opportunity for ongoing feedback from the national specialty organizations while this work is underway.

FDA Position

In August 2016, the FDA issued draft guidance on insanitary conditions at compounding facilities. The draft guidance duplicates USP's inappropriate proposal that would require an ISO class 5 environment (among other things) or otherwise declare mixed products insanitary. This is a broad over-reach, given that these environmental standards have not previously been applied to the much-broadened category of "compounding facility" cited in the FDA's proposal.

Additionally, we are concerned that through this draft guidance, FDA is fundamentally attempting to undermine the processes in place at the USP regarding the Chapter 797 proposed revision.

Recently, the FDA announced as part of its 2018 Compounding Policies Priority Plan[1] that the Agency plans to revisit some of these key issues in light of concerns raised by providers. Specifically, the document states (with respect to the insanitary conditions guidance): "This guidance will address concerns raised by some providers who compound small quantities of drugs in their offices for patient use, and as part of their routine clinical practice. This came up in the setting of certain dermatological procedures, for example. The FDA plans to better define the circumstances under which we believe drugs are being mixed and applied in a manner that creates negligible patient risk, and therefore wouldn't be subject to the same compliance policy under the agency's risk-based approach to implementing these requirements."

Therefore, we look forward to receiving more information from the FDA. Previously, we requested that the FDA withdraw this draft guidance, but we appreciate the FDA taking an initial step of recognizing the valid concerns we have presented. We urge Congress to continue to maintain oversight of the regulatory process to ensure that patient access is not unnecessarily hampered.

Impact of Proposed Changes

If the USP and FDA proposals are finalized, as initially drafted, patient access to AIT will be drastically reduced, if not eliminated, because allergists will no longer be able to prepare AIT vials for their patients in their offices. Moving allergen extract preparation to large compounding laboratories or pharmacies is not a viable alternative due to safety considerations. Patients experiencing allergic reactions to their immunotherapy injections require the allergist to change the content or dilution of the vials before they can receive the next injection. Failure to do so could result in a life-threatening systemic allergic reaction. These adjustments need to be done while the patient is in the office if the patient's treatment schedule is to continue without significant interruption or delay. Compounding pharmacies, located off-site from the allergist's office, would not be able to make these adjustments in a timely fashion.

Again, anaphylaxis is the major risk in an AIT treatment. This risk is carefully managed under current requirements by having the extract mixed onsite by physicians and staff with a personal knowledge and experience with each and every patient. Outsourcing extract preparation removes this important safeguard and severely limits a physician's ability to respond to any adverse allergic reactions to AIT or other considerations impacting treatment. The proposed revisions would require patients to start new extract vials every month, most likely changing source material in the extract, and thus significantly increasing risk for adverse and potentially fatal allergic reactions. These changes therefore decrease the safety and increase the risk to the patient, forcing physicians and patients to decide if the newly increased risk is actually worthwhile, all based on a hypothetical but undocumented risk of infection.

Conclusion

To date, neither the FDA nor the USP has provided any scientific data, case reports or anecdotal evidence that AIT compounding, following current USP guidelines and in accordance with section 503A of the FD&C Act, has resulted in an infection.

Members of Congress have previously weighed-in on this issue, urging the Secretary of the Department of Health and Human Services (HHS) to carefully weigh proposed regulations and the impact that they

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1 https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm592795.htm

have on patient care. The FDA has recognized the important and vital role of allergen immunotherapy in managing patients with allergic diseases. In addition, proposed changes in USP <797> decrease the safety of allergen immunotherapy and increase documented risk of anaphylactic reactions, in an effort to prevent what is no more than a hypothetical risk. Proposed changes are overreaching, not based on any data suggesting a risk of infectious complication from allergen extract compounding, and ignore the scientific data that supports the safety of allergen extract compounding. Failure to keep the current USP <797> guidelines for allergen extract compounding will significantly increase the risk/benefit ratio of AIT and needlessly place patients in danger of medical complications and potential death.

We urge Members of this Subcommittee and the Congress to actively oversee FDA's efforts to revise its compounding guidance documents. Forthcoming revisions should recognize that AIT compounding is a safe and unique compounding procedure that can continue following current <797> guidelines.

Thank you again for taking into consideration our written comments. I encourage you to contact Sheila Heitzig, JD, MNM, CAE, AAAAI Director of Practice and Policy, at (414) 272-6071 or sheitzig@aaaai.org, Jim Sublett, MD, ACAAI Executive Director of Advocacy and Governmental Affairs, at jsublett@familyallergy.com, or Jami Lucas, AAOA Executive Director and CEO, at lucas@aaoaf.org if you have any questions. The American Academy of Allergy, Asthma, & Immunology, the American College of Allergy, Asthma and Immunology, and the American Academy of Otolaryngic Allergy look forward to working with the Subcommittee to address issues of importance to our patients and ways in which we can promote public health.

GREG WALDEN, OREGON
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

ONE HUNDRED FIFTEENTH CONGRESS

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February 16, 2018

The Honorable Scott Gottlieb
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Gottlieb:

Thank you for appearing before the Subcommittee on Health on January 30, 2018, to testify at the hearing entitled "Examining Implementation of the Compounding Quality Act."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on March 3, 2018. Your responses should be mailed to Zack Dareshori, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, DC 20515 and e-mailed in Word format to zack.dareshori@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Michael C. Burgess, M.D.
Chairman
Subcommittee on Health

cc: The Honorable Gene Green, Ranking Member, Subcommittee on Health

Attachment

Attachment — Additional Questions for the Record

The Honorable John Shimkus

IV compounding automation has potential for improving safety, consistency, and compliance with best practices in many types of compounding pharmacies and settings. Although the FDA has embraced safety through automation in other contexts, the FDA has been silent on the issue of automation in compounding pharmacies and on how it will regulate, inspect, and audit compounding pharmacies that adopt IV compounding automation. Given the potential of technology to better address safety concerns and potentially drive down healthcare costs, as it does it other healthcare applications, what policy or regulatory considerations might facilitate adoption or further exploration of automated compounding technology?

The Honorable Morgan H. Griffith

1. Regarding essential copies, are you requiring physicians to document clinical need on every prescription, is this right?

    a. How does this requirement work with state laws that govern what constitutes a valid prescription?

2. At the hearing you stated that redefining the practice of pharmacy is not the best way to address office-use compounding. Can you please elaborate on what you meant by redefining the practice of pharmacy?

3. With the flu epidemic hitting the country particularly hard, I've heard reports that pharmacists are experiencing shortages of generic Tamiflu suspension. I've been told Medicaid only reimburses for the generic, which means pharmacists are faced with the choice of either giving their patients the brand medication at a loss to their business or compounding the generic formula. However, when pharmacists recently contacted FDA to ask if they would be in compliance should they choose to compound the generic they were told past guidance allowing for this was no longer current. I'm sure you can appreciate the urgency in getting an answer to this question and how confusing this can be to pharmacies especially in light of your agency's recently released "essential copies" guidance. Do you have an update for us today as to whether or not pharmacists can compound Tamiflu suspension?

4. Given the financial investment required for small town, lower volume 503A compounding pharmacies to become 503B outsourcing facilities, what steps is the agency taking to ensure that the prescription requirement won't be harmful to patients in rural communities needing immediate treatment with a compounded drug?

5. The agency put out its final guidance on repackaged biologics recently, which outlines additional testing required to extend the beyond-use date for drugs such as bevacizumab (Avastin). Have you worked with the outsourcing facilities directly to make sure they are able to meet these testing requirements to establish longer beyond-use dates?

6. The physician community and other stakeholder groups have expressed a desire for more direct discussion with the agency about implementation efforts and their concerns. Do you believe a greater emphasis on stakeholder input could be beneficial as implementation moves forward? What additional steps will the agency consider taking to better engage with the physician community and other stakeholders about compounding issues?

7. The FDA's 2018 Compounding Policy Priorities plan mentions "circumstances under which we believe drugs are being mixed and applied in a manner that creates negligible patient risk, and therefore wouldn't be subject to the same compliance policy." Physicians, like dermatologists, must perform simple and low-risk dilutions and mixing of manufactured drugs in the clinical setting, such as buffered lidocaine and reconstituted botulinum toxin, which falls under the FDA's broad definition of "compounding."

    a. Can you share any details about insanitary conditions equipment that the FDA is considering that will affect the physician community, specifically equipment or process requirements?

8. By statute, compounding from bulk ingredients at a 503B outsourcing facility is limited to a positive list developed by FDA. To date, this positive list has not been developed and the agency is using enforcement discretion to allow compounding from many bulk ingredients. The assumption is that FDA will eventually develop a positive list as mandated by the statute that it will enforce. If a compounding pharmacy does not have an assurance that the bulk ingredients it uses to compound will be on this eventual positive list, why would they invest the necessary capital and risk their business to convert to a 503B outsourcing facility when so much uncertainty exists?

9. FDA has indicated it will withdraw its draft MOU and issue a new one that will not have a hard cap on interstate distribution. The agency, however, is also insisting that it will include patient specific dispensing in the definition of distribution despite statutory language and precedent that does not support this definition. Regardless of how flexible FDA is with its proposed cap on interstate distribution, isn't it correct that if a state refuses to sign an MOU the default be a 5 percent limit on out-of-state distribution? And as long as FDA insists on defining distribution as including patient specific dispensing, won't patient access to medications from the pharmacy of their choice be disrupted if some states refuse to sign the MOU?

10. Please describe the process by which the FDA's Pharmacy Compounding Advisory Committee will consider substances nominated for the Difficult to Compound List. Will

every nominated substance be considered? What is the timeframe for doing so? Will FDA continue to provide approximately three weeks notice to private sector participants ahead of the PCAC meetings, or will additional time be provided so that they can more thoroughly prepare their presentations to the Committee?

11. Many of the policies surrounding the DQSA have been developed by the FDA under Guidance for Industry (GFI) documents rather than through the rulemaking process. It would seem that these policies affecting patient safety and access to critical medications warrant the stakeholder input, legal status and judicial review afforded to rules rather than GFIs which are not legally binding and merely represent the "current thinking of the FDA" on a given policy matter. Why has FDA has chosen this path for these important policies?

    a. Do you believe some of these policies would be more appropriately developed under the rulemaking process?

12. On Thursday, January 25th, the Associate Attorney General issued a memorandum that prohibits the Department of Justice from using civil enforcement authority to "convert agency guidance documents into binding rules." I am under the belief that you are required to follow this directive from the Department of Justice. Can you provide me with court opinions, rulings, and/or memorandums which indicate that you are not?

13. Most pharmacies don't compound sterile medications – only about 15% of pharmacies do. The statute states that you must compound sterile medications to be a 503B. The vast majority of pharmacies will therefore never register as a 503B with FDA. How will the new proposal referenced in your 2018 Compounding Priorities Plan improve access to nonsterile office use medications?

14. I appreciate recent explanations provided by FDA for their thought process on dietary supplement monographs for 503A pharmacies. Section 503A of the FDCA does not distinguish between groups of USP and NF monographs, but FDA policy has sought to restrict access to those monographs that reside in the Dietary Supplement section of USP. Does the FDA intend to change this guidance and if not, how does the guidance comply with the plain language of the statute?

15. FDA's current interpretation that a monograph is limited to *drug* monographs, and not dietary supplement monographs is concerning for many reasons. The statute does not distinguish between groups of USP and NF monographs. The effect of the policy is that FDA is requiring patients to purchase and take the supplement separately, rather than trust the medical judgement of the doctor and pharmacist as to dosage, interactions and other factors? Does this not have the effect of having the FDA insertig itself into the doctor – patient relationship?

16. The Pharmacy Compounding Advisory Committee is appointed by the FDA and considers substances that have been nominated for inclusion on the positive and negative

lists of bulk ingredients used in human compounding. Can you comment on why, to date, there has not been a voting member of the PCAC that is a compounding pharmacist with contemporary human compounding experience? Will you work to see that the FDA appoints a compounding pharmacist with human compounding experience to the PCAC?

17. FDA informs consumers about their inspections of all compounding pharmacies by posting Form 483 inspection findings and any subsequent warning letters on the agency website. Is this the same level of transparency in place for manufacturing facilities? If not, will FDA commit to equal transparency for all inspections?

18. Automation technology has recently entered the compounding space. Given the potential of technology to better address safety concerns and potentially drive down health care costs, is FDA considering implementing regulations that facilitate the adoption of this automated technology? Does FDA have the authority to do so or would they need additional authority from Congress?

19. What data do you have that, four years after DQSA was enacted, patients who receive compounded medications are safer than before? Do you believe innovation, particularly automation, in the way medications are compounded would help reduce human errors that can lead to contaminated drug products?

20. FDA Final Guidance on Mixing, Diluting and Repackaging of Biologics issued last month allows for preparation of allergen extracts that meet criteria for "prescription sets" including that they are prepared in accordance with USP standards. Yet pending FDA draft guidance on insanitary conditions would impose additional standards for allergen extracts that go far beyond what is required by USP. This seems inconsistent. Will FDA's Insanitary Conditions final guidance acknowledge the unique nature of allergen extract preparation for prescription sets consistent with its Final Guidance on Biologics?

21. Dr. Gottlieb, we appreciate your leadership and the previous leadership to establish the FDA's Office of Laboratory Science and Safety to serve as the single point of accountability for all laboratory science, and safety functions across the FDA. However, this office still lacks direct funding and permanent staffing.The External Laboratory Safety Working group recommended that this office should be directly funded to carry out its critical mission, and the CDC has followed this recommendation. There is really a need for oversight of all lab science research activities at FDA. In the area of drug compounding, FDA labs conduct microbiology testing in compounded drugs to detect bacterial and fungal contamination. In addition, you announced last Friday that the FDA closed a nicotine addiction study at an FDA lab after the death of four squirrel monkeys. When will the FDA Office of Laboratory Science and Safety be funded independently and staffed appropriately to provide critical oversight of the FDA laboratories?

22. How can we help you to ensure that this office is appropriately resourced and staffed in a timely manner to carry out its critical work?

23. It is my understanding that mixing and compounding are distinct acts. According to the ACAAI, when an allergist prepares an allergen extract, they mix several commercially manufactured, FDA approved antigens in a sterile vial using sterile syringes, following FDA standards specific to the mixing of allergen extracts. These patient-specific vials are then labeled and stored in refrigerated conditions. This produces a combination of different – naturally occurring – pollens or allergens into a single mixture. Compounding is functionally different in that it involves the combining of different drugs into a single new drug for an individual patient or into large lots for many patients. Unlike the mixing of naturally occurring allergens, when you combine different drugs, a biochemical effect often occurs that can bind these drugs together into a new, compounded drug.

    Based on these distinctions, I believe the preparation of allergenic extracts, which are biologics, constitutes mixing and not compounding, as defined by the FDA. Can the FDA confirm that preparation of allergen extracts is not compounding but rather mixing?

The Honorable Gus M. Bilirakis

1. DQSA was allows for compounded drugs from bulk drug substances when FDA-approved drugs are not commercially available or FDA has determined there is a clinical need for the substance. What precautions is the agency taking to ensure there is a legitimate clinical need for the bulk drug substances currently being used by compounders, and how is FDA enforcing this important provision of DQSA in the marketplace?

2. As I recall, Outsourcing Facilities can bulk compound drugs that are on an FDA list of approved bulk drugs, or are on a list of drugs that are in shortage, or have been discontinued commercially. How often or rapidly, does FDA plan to update this list so that patients never have an access problem obtaining medication they need?

3. Has FDA thought about ensuring a competitive marketplace in the outsourcing facility market? What happens if only one Outsourcing Facility is bulk compounding a specific medication? Could we have a situation like we have in the pharmaceutical market when there is no generic or a sole-source generic, and this leads to pricing spikes due to a lack of competition?

The Honorable Richard Hudson

1. As you know, for a drug to be lawfully compounded under Section 503B of the DQSA, the drug must not be "essentially a copy of one or more approved drugs," which means that the drug may not be identical or nearly identical to a drug that has been approved by FDA. Congress never intended for minor modifications of an approved drug—such as to a drug's dosage strength or inactive ingredients—to allow for the compounding of that drug. Instead, Congress intended to protect the public health, and to preserve the integrity of the FDA approval process, by permitting the compounding of a drug only in

connection with a particular patient medical need that cannot be met by an FDA-approved drug. Can you confirm that FDA agrees with this interpretation of the "essentially a copy" provision of the DQSA and that this interpretation is consistent with the Agency's thinking laid out in its January 2018 503B guidance?

2. Likewise, under Section 503B, there must be either a drug shortage or a demonstrated "clinical need" for compounding with bulk substances. A showing of "clinical need" requires a legitimate patient need that could not otherwise be met by compounding with the FDA-approved drug. The simple "convenience" of compounded product, such as a "pre-diluted" and packaged version of an approved drug, does not satisfy this requirement. Can you confirm that the Agency agrees with this interpretation of "clinical need," and confirm that this interpretation will be reflected in the Agency's forthcoming guidance in March 2018?

3. During the hearing, you said that, in its forthcoming March 2018 guidance, the Agency will reiterate that the DQSA does not permit the bulk compounding of drug substances when FDA-approved drugs can be used. You provided the example that when a compounder is diluting or otherwise changing the concentration of an FDA-approved drug, they have to begin with the approved drug and could not compound from bulk substances. Can you confirm that the Agency's forthcoming March 2018 guidance will explicitly address this statutory requirement and example? Additionally, can you provide insight into how FDA will proactively apply its risk-based enforcement approach against compounders who violate this requirement?

The Honorable Earl L. "Buddy" Carter

1. Regarding essential copies, are you requiring physicians to document clinical need on every prescription?

2. How does this requirement work with state laws that govern what constitutes a valid prescription?

3. At the hearing you stated that redefining the practice of pharmacy is not the best way to address office-use compounding. Can you please elaborate on what you meant by redefining the practice of pharmacy?

4. Most compounding pharmacies compound only non-sterile medications, and perhaps as high as 80 to 90 percent of these pharmacies do not engage in sterile compounding. FDA has consistently presented the 503B option as the easy way to address both the office use issue and limitations that would be imposed by an MOU that includes dispensing in the definition of distribution. Doesn't this argument fail since the vast majority of compounding pharmacies simply would not be eligible to convert to a 503B outsourcing facility since they do not engage in sterile compounding?

5. By statute, compounding from bulk ingredients at a 503B outsourcing facility is limited to a positive list developed by FDA. To date, this positive list has not been developed and the agency is using enforcement discretion to allow compounding from many bulk ingredients. The assumption is that FDA will eventually develop a positive list as mandated by the statute that it will enforce. If a compounding pharmacy does not have an assurance that the bulk ingredients it uses to compound will be on this eventual positive list, why would they invest the necessary capital and risk their business to convert to a 503B outsourcing facility when so much uncertainty exists.

6. FDA has indicated it will withdraw its draft MOU and issue a new one that will not have a hard cap on interstate distribution. The agency, however, is also insisting that it will include patient specific dispensing in the definition of distribution despite statutory language and precedent that does not support this definition. Regardless of how flexible FDA is with its proposed cap on interstate distribution, isn't it correct that if a state refuses to sign an MOU the default be a 5 percent limit on out-of-state distribution? And as long as FDA insists on defining distribution as including patient specific dispensing, won't patient access to medications from the pharmacy of their choice be disrupted if some states refuse to sign the MOU?

7. The two members of the Pharmacy Compounding Advisory Committee (PCAC) who represent compounding pharmacy and the pharmaceutical industry cannot vote, apparently because of potential conflict of interest issues. Yet, at least one voting member of the committee is from an organization that cosigns letters and actively lobbies with pharmaceutical interests that could potentially benefit financial from the recommendations of PCAC. Can you tell the committee what the conflict of interest rules are that govern voting status of PCAC members, and whether direct advocacy with drug companies that have a direct financial interest in PCAC decisions is a conflict of interest?

8. Please describe the process by which the FDA's Pharmacy Compounding Advisory Committee will consider substances nominated for the Difficult to Compound List. Will every nominated substance be considered? What is the timeframe for doing so? Will FDA continue to provide approximately three weeks notice to private sector participants ahead of the PCAC meetings, or will additional time be provided so that they can more thoroughly prepare their presentations to the Committee?

9. Many of the policies surrounding the DQSA have been developed by the FDA under Guidance for Industry (GFI) documents rather than through the rulemaking process. It would seem that these policies affecting patient safety and access to critical medications warrant the stakeholder input, legal status and judicial review afforded to rules rather than GFIs which are not legally binding and merely represent the "current thinking of the FDA" on a given policy matter.

10. Can you tell us why FDA has chosen this path for these important policies and whether you believe some of them would be more appropriately developed under the rulemaking process?

11. On Thursday, January 25th, the Associate Attorney General issued a memorandum that prohibits the Department of Justice from using civil enforcement authority to "convert agency guidance documents into binding rules." You are required to follow this directive from the Department of Justice, correct?

12. To my knowledge, FDA has not recently contacted compounding pharmacy stakeholder groups, specifically the stakeholders who have been most active in the PCAC process to discuss the Agency's new ideas on incentivizing "a larger swath of pharmacies" to register as 503B outsourcing facilities, or recently issued final Guidance documents. Dr. Gottlieb, will you commit to meeting with stakeholders to discuss these important issues?

13. Most pharmacies don't compound sterile medications – only about 15% of pharmacies do. The statute states that you must compound sterile medications to be a 503B. The vast majority of pharmacies will therefore never register as a 503B with FDA. How will the new proposal referenced in your 2018 Compounding Priorities Plan improve access to nonsterile office use medications?

14. Many provider groups are expressing patient need for access to office-use medications from 503A pharmacies. 503Bs cannot provide immediate access to medications and/or will not provide the limited quantities needed by some prescribers. Congress has provided clarification for FDA through multiple sets of appropriations report language and other written communications. Why does FDA continue to put up roadblocks to prescribers obtaining the medications they need from 503A pharmacies to treat patients in their office, while at the same time maintaining a limited exemption for hospitals? When does FDA intend to make a change in policy allowing needed office use medications to come from 503A pharmacies consistent with the intent of the law?

15. I appreciate recent explanations provided by FDA for their thought process on dietary supplement monographs for 503A pharmacies. Section 503A of the FDCA does not distinguish between groups of USP and NF monographs, but FDA policy has sought to restrict access to those monographs that reside in the Dietary Supplement section of USP. When will FDA correct this guidance to comply with the plain language of the statute?

16. FDA's current interpretation that a monograph is limited to drug monographs, and not dietary supplement monographs is concerning for many reasons. The statute does not distinguish between groups of USP and NF monographs. The effect of the policy is that FDA is requiring patients to purchase and take the supplement separately, rather than trust the medical judgement of the doctor and pharmacist as to dosage, interactions and other factors? Isn't this FDA inserting itself into the doctor – patient relationship?

17. There has been an organized process in terms of how FDA would proceed related to compounding from bulk substances, and no similar framework has been put forward by the agency related to the difficult to compound list. This lack of direction has caused uncertainty and confusion in the profession, and for those who depend on compounded medications to live healthier, better lives. Does FDA intend to lay out a similar framework for the difficult to compound list, and if so, when will additional information be available from the agency?

18. The Pharmacy Compounding Advisory Committee is appointed by the FDA and considers substances that have been nominated for inclusion on the positive and negative lists of bulk ingredients used in human compounding. Can you comment on why, to date, there has not been a voting member of the PCAC that is a compounding pharmacist with contemporary human compounding experience? To provide a more informed perspective for FDA and the PCAC, can you commit that the FDA will appoint a compounding pharmacist with human compounding experience to the PCAC?

19. FDA informs consumers about their inspections of all compounding pharmacies by posting Form 483 inspection findings and any subsequent warning letters on the agency website. Is this level of transparency in place for manufacturing facilities? Specifically, does FDA post each and every Form 483 and warning letter for manufacturers of commercially available drug products? Will FDA commit to equal transparency for all inspections?

The Honorable Frank Pallone, Jr.

Memorandum of Understanding

At the hearing we discussed further FDA's draft Memorandum of Understanding and the agency's recently announced plans to revise this MOU. One of the announced changes would be the elimination of the 30 percent threshold and instead implementing certain requirements that would be triggered at a 50 percent threshold. When asked about this, you noted that "There are going to be other tests that we apply to make assessments about what the appropriate scheme is for a particular facility."

1. Will you elaborate further on what other tests or assessments, in addition to volume, that FDA will be applying towards oversight of compounded drug products across state lines?

2. The draft MOU released in February 2015 would require that states that entered into the MOU to investigate complaints related to the compounded drug products compounded in the state and then distributed outside of the state, including complaints about adverse events. States would also be required to take action to determine the root cause of the problem, to notify FDA within 72 hours of complaints, and to maintain records related to complaints and investigations. It appears under the revisions to the MOU that have been announced, that exceeding the proposed 50 percent threshold would only trigger certain

reporting requirements for the state instead of a hard limit for state action. Under the proposed revised MOU, how do you intend to protect against the kind of race to the bottom in state regulatory oversight that helped lead to the NECC tragedy?

Economic Analysis

3. At the hearing you noted that FDA has undertaken an economic analysis regarding the costs for different entities to comply with current good manufacturing practices (cGMPs) for compounded drugs. You noted that you thought it is "still a little bit too expensive to see some of the small 503A pharmacies" opting into compliance with cGMPs as outsourcing facilities are required to do. Will you please provide FDA's economic analysis regarding compliance with these requirements for the record?

Resources

At the hearing that implementation activities of the Compounding Quality Act, such as inspections and examining potency issues, are dependent on what additional resources the agency can put towards it, and unlike other product areas that rely on user fees, the compounding program operates by "begging, borrowing, and stealing from other aspects of the agency, other parts of the agency."

4. What resources have been dedicated to implementation of the Compounding Quality Act since enactment?

5. What resources will be available under the President's proposed budget for fiscal year 2019 for implementing of the Compounding Quality Act, and in particular for additional inspections of compounding pharmacies and outsourcing facilities?

Access to Office Use Stock

One area of continued concern for many stakeholders is access to office use stock. FDA has generally taken the position that 503A pharmacies may not compound for office-use, and that this role is better is better filled by outsourcing facilities under 503B as they are subject to increased oversight and quality standards that may help to reduce the risk of quality problems such as contamination. Health care providers in particular have raised issue with this perspective as they are concerned that this prohibition on office stock may impact their ability to prepare and administer low-risk compound products in office, or to prepare compounded products in the case of an emergency such as a severe infection.

6. My understanding is that Section 503A of the Federal Food, Drug, and Cosmetic Act does allow for compounding in anticipation of a prescription in limited quantities if certain conditions are met. When is anticipatory compounding permitted under 503A?

One of the common complaints we have heard from 503A pharmacies is that registered 503B outsourcing facilities are unable to meet the needs of physicians and patients, and further it is difficult to identify outsourcing facilities that can meet their needs. On the second panel we heard

from Dr. Brod, chair of the American Academy of Dermatology Association, that "FDA's website lists only the facilities that are registered, but with no contact information no real-time product availability information, and no price list." He argues this results in physicians undertaking a scavenger hunt to identify 503B outsourcing facilities that can fit their needs.

7. What assistance has FDA provided to help 503A pharmacies access office use stock of necessary products? Further, what are your thoughts on requiring FDA to maintain additional information on 503B outsourcing facilities, such as contact information, product availability, and price lists?

8. One of the requirements of outsourcing facilities under section 503B is the submission of product lists to the FDA semiannually. FDA has noted that not all outsourcing facilities have been complying with this requirement, resulting in the posting of incomplete product lists. What steps, if any, is FDA taking to ensure compliance with this requirement?

Inspections

9. FDA's inspection authority is a critical tool to ensuring that pharmacies are compounding in accordance with the law, and to continue to be afforded the exemptions provided under the law. Since enactment of the Drug Quality and Security Act, FDA has conducted nearly 500 inspections, issued more than 180 warning letters identifying significant violations at compounding pharmacies, issued more than 70 letters referring inspectional findings to state regulatory bodies, and overseen more than 150 recalls of compounded drug products.

10. There has been much debate over whether or not FDA is the appropriate entity to be inspecting compounding pharmacies. Will you clarify for the Committee where FDA derives its authority to inspect compounding pharmacies?

11. Some stakeholders have argued that inspections of compounding pharmacies should be to USP standards or other pharmacy inspection standards adopted by the states rather than to good manufacturing practices. Will you explain why a compounding pharmacy may be inspected to cGMPs rather than USP standards?

12. Further, will you also discuss what outreach and education efforts FDA has undertaken to ensure that 503A compounding pharmacies understand the inspection process?

Patient Access

Critics of DQSA have argued that FDA's definition of compounding – the combining, mixing, or altering ingredients of a drug to make a medication tailored to the needs of an individual patient – is overly broad and has resulted in patient access issues to low-risk compounded drug products. For example, we heard from one of the witnesses on the second panel how some simple in-office preparations are now considered "compounding as opposed to mixing" when the medication is not prepared pursuant to the manufacturer's labeling subjecting them to the guidelines outlined in FDA's guidance on insanitary conditions.

13. Can you respond to this concern? What would be the potential risk of not requiring health care providers to meet the same standards as compounding facilities?

Patient Safety

While passage of the Compounding Quality Act was a strong step forward to addressing the safety issues associated with NECC and other largely unregulated compounding pharmacies that were compounding in bulk, safety issues associated with compounding pharmacies still persist. FDA has received adverse event reports of patient harm including contamination in drugs that need to be sterile because they are entering the bloodstream, the eye, or the spine. There have also been reports of drug products that are superpotent, for instance in the example in 2016 of three infants received a compounded morphine sulfate preparation at a strength that was greater than 20 times than that indicated on the label. One infant had to be taken by helicopter to a nearby children's hospital.

14. It seems that there is an incomplete picture of the whole problem – there are likely more events or deaths than we know of, attributable to compounded drugs given that the vast majority of 503A pharmacies do not report on adverse events. How does the FDA plan to work with states, which also have a large regulatory role, to increase reporting and reduce safety events that harm patients from these pharmacies?

The Honorable Anna G. Eshoo

1. Is FDA considering policies or regulations that facilitate the adoption of automation technology in the compounding space?

2. If yes, what is the timeline for this guidance or regulation?

GREG WALDEN, OREGON
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

ONE HUNDRED FIFTEENTH CONGRESS

Congress of the United States
House of Representatives

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February 16, 2018

Dr. George Williams
Chair of the Board of Directors
American Academy of Ophthalmology
20 F Street, N.W.; Suite 400
Washington, DC 20001

Dear Dr. Williams:

Thank you for appearing before the Subcommittee on Health on January 30, 2018, to testify at the hearing entitled "Examining Implementation of the Compounding Quality Act."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on March 3, 2018. Your responses should be mailed to Zack Dareshori, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, DC 20515 and e-mailed in Word format to zack.dareshori@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Michael C. Burgess, M.D.
Chairman
Subcommittee on Health

cc: The Honorable Gene Green, Ranking Member, Subcommittee on Health

Attachment

Answer to questions from Representative Eshoo.

1. To my knowledge, there is no formal, enforceable requirement by the FDA to disclose to patients that a compounded product is being used. The American Academy of Ophthalmology (AAO) recommends that ophthalmologists inform their patients about the risks, benefits and alternatives of all available treatment options and discuss the implications of compounded products.
2. As noted above, the AAO recommends that patients be informed of the risks of all treatments including compounded drugs
3. In my personal practice, I follow the above recommendations to fully inform patients about the risks, benefits and alternatives to treatment with compounded drugs. This process involves both verbal and written disclosure using an informed consent following the recommendations of the Ophthalmic Mutual Insurance Company. I have attached these recommendations.

See OMIC attachment

OMIC OPHTHALMIC MUTUAL INSURANCE COMPANY
(A Risk Retention Group)

Intravitreal Anti-VEGF Treatment for Adults Patients: Risk Management Recommendations

OMIC is grateful to the ophthalmologists on our Board for their expertise. This specific document reflects the input of the following Board and staff members: Anne M. Menke, RN, PhD; George Williams, MD, Trexler M. Topping, MD; Pauline Merrill, MD, Denise Chamblee, MD, Paul Weber, JD, Hans Bruhn, MHS, and Michelle Pineda, MBA.

PURPOSE OF RISK MANAGEMENT RECOMMENDATIONS

OMIC regularly analyzes its claims experience to determine loss prevention measures that our insured ophthalmologists can take to reduce the likelihood of professional liability lawsuits. OMIC policyholders are not required to implement these risk management recommendations. Rather, physicians should use their professional judgment in determining the applicability of a given recommendation to their particular patients and practice situation. These loss prevention documents may refer to clinical care guidelines such as the American Academy of Ophthalmology's Preferred Practice Patterns, peer-reviewed articles, or to federal or state laws and regulations. However, our risk management recommendations do not constitute the standard of care nor do they provide legal advice. If legal advice is desired or needed, an attorney should be consulted. Information contained here is not intended to be a modification of the terms and conditions of the OMIC professional and limited office premises liability insurance policy. Please refer to the OMIC policy for these terms and conditions.

Version 6/30/15

Vascular endothelial growth factor, or VEGF, is a protein that stimulates the growth of new blood vessels. Ophthalmologists administer intravitreal anti-VEFG agents for a variety of indications. Sometimes the indication has been approved by the Food and Drug Administration (FDA), other times it is off-label, or the medication itself may never have been approved for any eye indication. This risk management document presents suggestions to increase patient safety and decrease the likelihood of lawsuits related to these drugs. It also provides information about our revised sample consent documents for anti-VEGF agents.

A. Approved indications for anti-VEGF drugs

The Food and Drug Administration (FDA) has approved a few drugs for the treatment of ophthalmic VEGF-mediated diseases. For ease of reading, the first reference to a drug will give its trade and generic name; thereafter, only the trade name will be given. Three other drugs that are not anti-VEGF agents are approved for some of the same indications.

- Age-related macular degeneration (AMD):
  - Macugen™ (pegaptanib), Lucentis™ (ranibizumab), and Eylea™ (aflibercept) are all anti-VEGF agents approved to treat AMD. Visudyne™ (verteporfin) is also approved to treat AMD.
- Diabetic macular edema (DME):
  - Lucentis and Eylea are approved to treat DME. Ozurdex™ (dexamethasone) and Iluvien® (fluocinolone acetonide) are also approved to treat DME.
- Diabetic retinopathy (DR):
  - Lucentis and Eylea are approved to treat DR in patients with diabetic macular edema.
- Retinal vein occlusion (RVO):
  - Lucentis and Eylea are approved to treat macular edema following retinal vein occlusion (RVO); Ozurdex is also approved for this.

Explaining to patients how these drugs work
The indications on the labels for these drugs state the conditions they are designed to treat. We have learned from field testing our revised forms that patients may have a difficult time understanding the names of these diseases, or get confused about which one they have. To make our consent forms easier to understand, we incorporated "plain language" principles. The goal is simple, short explanations. Here is how we describe the indications in our new sample forms:

- Eye surgeons treat some types of eye problems with a medication called [name of drug]. [Name of drug] can help prevent vision loss due to 2 types of eye problems:
  1) the growth of harmful blood vessels in your eyes
  2) swelling in the back of the eye (macular edema).

OMIC-insured ophthalmologists are not required to use our consent forms, and are encouraged to adapt them as needed. Sample forms can be found at www.omic.com/avastin/, www.omic.com/lucentis/, and www.omic.com/eylea/.

B. Off-label use of drugs
Off-label use of an approved medication is a common and legal part of the practice of medicine. OMIC believes that the treating ophthalmologist is in the best position to determine what a particular patient needs, and leaves this decision up to the physician's judgment.

- Ophthalmologists use the FDA-approved medications just discussed to treat other eye conditions. All such use is off-label.
- Eye surgeons use Avastin™ (bevacizumab), which has not been approved for intravitreal use or for eye conditions. All ophthalmic use of Avastin is off-label.
- Use of any anti-VEGF drug in the pediatric population is off-label.

OMIC recommends that you obtain consent for off-label use of anti-VEGF drugs. The OMIC website has sample consent forms for these medications, as well as risk management recommendations and a sample consent form for the use of anti-VEGF drugs to treat ROP. The Avastin consent form already addresses this off-label use. Here is sample language that can be added if Lucentis or Eylea are used off-label:

- The Food and Drug Administration (FDA) approved [name of drug] for treating some eye diseases. These diseases may cause the growth of harmful blood vessels in your eye and swelling (macular edema). Eye surgeons also use [name of drug] to treat other diseases that cause similar problems. This is called off-label use.

C. Preparation of Avastin
The medication comes in preservative-free vials intended for intravenous use at a much higher concentration on a single cancer patient. Avastin needs to be repackaged for intravitreal use. This repackaging must be done in compliance with the Drug Quality and Security Act (DQSA), which was passed on November 27, 2013. Under this law, repackaging must be done either by a compounding pharmacy or a federally-registered outsourcing facility.

Compounding pharmacies (CFs) operate under Section 503A of the law and are governed by their state board of pharmacy. They must be in compliance with USP (United States Pharmacopeia) Chapter 797, which regulates the compounding, transportation, and storage of compounded sterile products (CSP). CFs require a patient-specific prescription.

Section 503B of the DQSA created outsourcing facilities (OFs), which must register with the FDA, which governs them. OFs must comply with current good manufacturing practices as well as USP 797. OFs do not require a patient-specific prescription, so ophthalmologists may order in bulk from them.

"Credential" the compounding pharmacy or outsourcing facility:
- Ask the compounding pharmacy for:
    - Evidence of licensure in the state in which it is dispensing
    - Assurance that it maintains strict compliance with USP chapter 797 mandates
- Verify with the outsourcing facility that:
    - It has registered with the FDA
    - It maintains strict compliance with current good manufacturing practices

The pharmacy or outsourcing facility should provide prepare the medication for ophthalmic use, confirm the dose and sterility, identify a syringe suitable for this protein, provide storage and "beyond-use-date" instructions, and the lot number of the vial. The FDA is still determining the "beyond-use-date" requirements for repackaged Avastin.

D. Preventing endophthalmitis
The prescribing information for the anti-VEGF agents contain statements about actions ophthalmologists should take to prevent and manage known complications. These statements tend to reflect protocols in place during clinical trials for these drugs. Aspects of the protocols may not be necessary in clinical practice outside of the research setting. And guidelines published since the drug was approved make different recommendations, especially in relation to infection prophylaxis. Physicians should use their clinical judgment to determine what recommendations to follow.

FDA-approved labels for both Lucentis and Eylea state that the "intravitreal injection should be administered under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape, and a sterile eye speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide should be given prior to the injection." An expert panel reviewed published studies of intravitreal injection technique and monitoring and released guidelines in 2014.[1] The panel reached different conclusions about gloves, drapes, speculum, and antibiotics than the recommendations included in the label for Lucentis and Eylea.

Lack of evidence to support some labeling instructions

- The experts concluded that "there is insufficient evidence to support the routine use of pre-, peri-, or postoperative antibiotics to reduce the rate of endophthalmitis."[1]
- Sterile or non-sterile gloves may be used even though they have not been shown to reduce the risk of endophthalmitis.
- There is no evidence to support the routine use of a drape.

Recommendations to reduce the risk of endophthalmitis

The experts did make recommendations. Here are some key guidelines. Please see the article for full details.

- External infections
  - Postpone injection until active external infections, including blepharitis, have been treated and cleared, unless the benefits of injection clearly outweigh the risk of endophthalmitis.
- Povidone-iodine
  - Ensure that povidone-iodine (5-10%) is the last agent applied to the intended injection site before injection.
    - If a gel anesthetic is used, apply povidone-iodine both before and after application of the gel.
  - Povidone-iodine may also be applied to the eyelids, including the eyelid margins and eyelashes.
    - Avoid eyelid scrubbing or expressing material from the meibomian glands.
  - Prevent contact of the eyelashes and eyelid margins with both the injection site and the injection needle after final application of povidone-iodine and especially during the actual injection.
    - Use either a speculum or other technique, such as manual lid retraction.
- Aerosolized droplets
  - Reduce the spread of aerosolized droplets during the injection preparation and procedure.
  - Use a surgical mask or minimize speaking by the physician, assistants, and patients.
- Bilateral injections on the same day

[1] Avery RL et al. Intravitreal Injection Technique and Monitoring. Updated Guidelines of an Expert Panel. *Retina*. 2014: 34, number 12, S1-S18.

- Exercise caution when performing bilateral injections on the same day.
- Consider the injection for each eye as a separate procedure.
- Use separate site preparation, individual syringes, needles, etc.
- Use a different medication batch if using a compounded medication such as Avastin.

- Patient education and monitoring
  - Monitor patients for symptoms suggestive of endophthalmitis.
  - Instruct patients to contact you immediately if the eye becomes red, sensitive to light, painful, or develops a change in vision. Consider giving these instructions in writing.

E. Informed consent and documentation
Intravitreal injections carry many of the same risks as other intraocular procedures (i.e., infection, IOP changes, etc). There are a few risks specific to these drugs that raise questions for ophthalmologists.

Arterial thromboembolic events (ATEs)
Anti-VEGF agents have been safely administered to hundreds of thousands of patients. Clinical trials of Lucentis, Avastin, and Eylea have shown a low incidence of ATEs, defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death, including deaths of unknown cause. The relationship between administration of anti-VEGF agents and these events is unclear, as patients receiving these drugs have co-morbidities associated with ATEs.

Nonetheless, the labels for Lucentis and Eylea indicate that anti-VEGF drugs have a potential risk of ATEs. ATEs are also included in the warnings on the label for intravenous Avastin. The Lucentis label indicates that the risk for ATEs may be higher in patients with diabetes. Further research is needed to confirm this. We recommend warning all patients with diabetes who receive anti-VEGF drugs of this possible increased risk. OMIC recommends that you discuss the risk of ATEs with patients. We have addressed this risk in our sample consent forms for these drugs.

In addition to ATEs, the prescribing information for intravenous Avastin contains warnings about gastrointestinal perforations/wound healing complications, hemorrhage, hypertension, proteinuria, and congestive heart failure. These complications have not been related to intravitreal use, so OMIC has removed any discussion of them from our sample Avastin consent form.

Potential harm to the fetus
The FDA changed the safety labeling for intravenous Avastin, adding a section on embryo-fetal toxicity in June, 2015. The warning states that "Avastin may cause fetal harm based on the drug's mechanism of action and findings from animal studies."[2] Pregnant rabbits were given Avastin IV 10 mg/kg or more every three days, and congenital abnormalities were noted. It went on to say that "animal models link angiogenesis and VEGF...to critical aspects of female reproduction, embryo-fetal

[2] http://www.fda.gov/safety/medwatch/safetyinformation/ucm287610.htm

development, and postnatal development." The FDA instructs physicians to "advise females of reproductive potential to use effective contraception during treatment with and for 6 months after the last dose of Avastin."

The FDA does not know if intravenous Avastin causes harm to the human fetus. The FDA warning did not address intravitreal Avastin, as this use is off-label. The risk for intravitreal use is even less clear, however, as the intravitreal dose of Avastin is a fraction of this, and is only administered monthly. If the effect on the fetus is inherent to anti-VEGF agents, then Lucentis and Eylea may pose a similar risk. In any event, the warning would only apply to the small number of women who are pre-menopausal.

The warning was only issued for Avastin. Nonetheless, to reduce the potential liability for ophthalmologists using anti-VEGF drugs, we feel it is prudent to discuss the FDA warning with pre-menopausal women.

- Explain that the warning was issued for IV use, not for use in the eye.
- Explain that the FDA does not know if IV Avastin causes harm to the human fetus.
- Explain that the FDA does not know if intravitreal anti-VEGF drugs pose a risk for the human fetus.
- Advise the woman to talk to her regular doctor about whether to use birth control while she is getting Avastin, Eylea, or Lucentis, and for six months after the last dose.
- Ask the woman to sign a document discussing this possible risk, which is available at www.omic.com/avastin risk to fetus/, www.omic.com/lucentis risk to fetus/, and www.omic.com/eylea risk to fetus/.

Treatment of both eyes on the same day

- Document your decision-making process in the medical record.
- Inform the patient of the possibility of vision-threatening complications in both eyes.
- Explain the measures you will take to reduce the risk of infection (i.e., you will use a new syringe, needle, etc.).
- Ensure that the patient has a ride home before administering the injections.

Consent for ongoing treatment

In general, informed consent is considered valid until 1) the patient revokes the consent or 2) the patient's medical or ocular condition change so as to materially affect the nature of the procedure or the risk/benefit ratio. This means that unless either of these situations materialize, you need only obtain the patient's informed consent once as long as you document that the consent is for ongoing treatment, and the consent form states the same.

- Obtain consent for each eye.
- Obtain and document informed consent again if the patient's medical or ocular condition changes to the point that the risk/benefit ratio is affected.
- Review the risks and benefits on a regular basis, such as yearly.

Documentation

- Document the decision-making process that led to choosing the particular drug as

the treatment for the patient. Note results of earlier attempts at treatment and the results of diagnostic tests.

- Evaluate and document the continued need, effectiveness, and safety of the medication prior to each injection.
- Note the dose, lot number of the vial, any reactions to the injection and how they were handled, and the discharge and follow-up instructions.

RISK MANAGEMENT ASSISTANCE
OMIC policyholders may obtain confidential risk management help by contacting OMIC's Risk Management Hotline at 800.562-6642, option 4, or by emailing us at riskmanagement@omic.com.

GREG WALDEN, OREGON
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

ONE HUNDRED FIFTEENTH CONGRESS

Congress of the United States
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Minority (202) 225–3641

February 16, 2018

Dr. Bruce Brod
Chair, Congressional Policy Committee
American Academy of Dermatology
1445 New York Avenue, N.W.; Suite 800
Washington, DC 20005

Dear Dr. Brod:

Thank you for appearing before the Subcommittee on Health on January 30, 2018, to testify at the hearing entitled "Examining Implementation of the Compounding Quality Act."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on March 3, 2018. Your responses should be mailed to Zack Dareshori, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, DC 20515 and e-mailed in Word format to zack.dareshori@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Michael C. Burgess, M.D.
Chairman
Subcommittee on Health

cc: The Honorable Gene Green, Ranking Member, Subcommittee on Health

Attachment

AMERICAN ACADEMY of
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February 23, 2018

The Honorable Michael Burgess, MD (R-TX)
Chairman
House Energy & Commerce
Subcommittee on Health
2125 Rayburn HOB
Washington, D.C. 20515

The Honorable Gene Green (D-TX)
Ranking Member
House Energy & Commerce
Subcommittee on Health
2125 Rayburn HOB
Washington, D.C. 20515

Dear Chairman Burgess and Ranking Member Green:

Thank you for forwarding Congresswoman Anna Eshoo's questions from the "Examining Implementation of the Compounding Quality Act" hearing. I sincerely appreciated the opportunity to testify before your subcommittee, and share the experiences dermatologists and their patients have been facing since implementation of the Drug Quality & Security Act. I am happy to answer any questions you and Subcommittee members may have.

Dermatologists diagnose and treat more than 3,000 skin diseases, including skin cancer, eczema, infections, psoriasis, immunologic diseases, and many genetic disorders. Dermatologists rely heavily on compounded pharmaceutical products and especially topical compounded pharmaceutical products obtained via traditional compounding pharmacies to treat many of these skin diseases. As physicians dedicated to the safety and wellbeing of our patients, the Academy believes that a regulatory structure with appropriate safeguards is paramount to ensuring both the safety and continued access to compounded products from traditional compounders and pharmaceutical manufacturers.

The use of these types of compounded medications is an integral part of most dermatology practices and is extremely vital in providing the best patient care. A dermatology patient should have access to treatment with a compounded product in a timely manner. Over the years, dermatologists have been able to safely deliver treatments to meet individual patient needs, including patients with orphan diseases that do not have an FDA approved drug for treatment. Prescribing and/or directly administering compounded products allows us as dermatologists to tailor treatments to the unique needs of our patients, resulting in better outcomes.

1. Are you currently required, either by the American Academy of Dermatology or the FDA, to disclose to dermatology patients that they are receiving a compounded product?

There is no requirement by the FDA or the AAD to disclose to dermatology patients that they are receiving a compounded medication. Likewise, there is no requirement to distinguish between generic, branded, and specialty drugs.

Suzanne Olbricht, MD, FAAD
President

George J. Hruza, MD, MBA, FAAD
President-Elect

Theodore Rosen, MD, FAAD
Vice President

Jane M. Grant-Kels, MD, FAAD
Vice President-Elect

Barbara M. Mathes, MD, FAAD
Secretary-Treasurer

Marta J. Van Beek, MD, MPH, FAAD
Assistant Secretary-Treasurer

Elaine Weiss
Executive Director and CEO

2. Should dermatology patients be made aware of the risks associated with using compounded products?

There are risks associated with all pharmaceutical medications whether they be compounded, generic, branded, or specialty if not manufactured, stored, administered, or used properly. When prescribing a drug that has significant, incremental, or more risk than the patient may expect, the dermatologist will counsel the patient on expectations with the treatment and mitigating risk. In addition, the dermatologist takes into consideration the patient's ability to comprehend and adhere to the treatment plan prior to determining what drug to prescribe.

As I indicated in my testimony, some compounded drugs can produce adverse reactions if they are not applied as intended; therefore, a health care provider in the clinical office setting should administer them. If the compounded medication is one that may be appropriately administered outside the clinical setting, the dermatologist will also instruct the patient to speak to the pharmacist upon pickup at the pharmacy.

3. In your personal dermatology practice, do you disclose to patients when you are using a compounded product?

As noted above, I counsel my patients on the risks and alternatives involved in the entire spectrum of treatment options, including compounded, generic, specialty, and compounded medications.

Thank you for again for the opportunity to answer these questions. Should you have any additional questions or concerns, please feel free to contact Christine O'Connor, Associate Director, Congressional Policy at coconnor@aad.org or (202) 609-6330.

Sincerely,

Bruce A. Brod, M.D.
Immediate-Past Chair, Congressional Policy Committee
American Academy of Dermatology Association

GREG WALDEN, OREGON
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
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February 16, 2018

Ms. Jenn Adams
President
PharMEDium Services
150 North Field Drive; Suite 350
Lake Forest, IL 60054

Dear Ms. Adams:

Thank you for appearing before the Subcommittee on Health on January 30, 2018, to testify at the hearing entitled "Examining Implementation of the Compounding Quality Act."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on March 3, 2018. Your responses should be mailed to Zack Dareshori, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, DC 20515 and e-mailed in Word format to zack.dareshori@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Michael C. Burgess, M.D.
Chairman
Subcommittee on Health

cc: The Honorable Gene Green, Ranking Member, Subcommittee on Health

Attachment

PharMEDium
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February 26, 2018

The Honorable Michael C. Burgess, M.D.
Chairman, Subcommittee on Health
Committee on Energy and Commerce
U.S. House of Representatives
2125 Rayburn House Office Building
Washington, D.C. 20515-6115

Dear Chairman Burgess,

Thank you for inviting me to appear before your Subcommittee on January 30, 2018. I appreciated the opportunity to testify on the important matter of the Drug Quality and Security Act (DQSA), as well as the opportunity to respond to additional questions for the hearing record from you and the distinguished Ranking Member of the full Committee, Representative Frank Pallone, Jr.

Please find enclosed my responses to your questions. Should you have any questions, please do not hesitate to reach out at any time.

Sincerely,

Jenn Adams
President, PharMEDium Services

Enclosure.

Cc: Greg Walden, Chairman, Committee on Energy and Commerce
Cc: Frank Pallone, Jr., Ranking Member, Committee on Energy and Commerce
Cc: The Honorable Gene Green, Ranking Member, Subcommittee on Health

Responses to Questions from Chairman Burgess

Q1: FDA recently announced plans to issue future draft guidance to "ensure that outsourcing facilities do not compound using a bulk drug substance when an FDA-approved drug can be used to meet patient medical needs." Does this seem like an appropriate response to the concerns that have been raised about your competitors copying FDA-approved drugs by using bulk substances? What additional steps do you believe are needed to clarify the law and ensure industry's compliance?

A: Yes. PharMEDium remains hopeful that FDA's forthcoming guidance regarding restrictions on the use of bulk drug substances will make clear that outsourcing facilities *must* compound using FDA-approved drugs unless one of the narrow statutory exceptions to start from bulk active pharmaceutical ingredients (APIs) applies. The DQSA is clear that unless a drug is in shortage, compounders must use FDA-approved drugs unless there is a valid clinical need that is unmet by use of the approved version of the drug. As Commissioner Gottlieb testified before your Subcommittee, the DQSA requires that, "if there was an FDA-approved product available that you can compound from, you have to compound from that product."

PharMEDium remains disappointed that FDA's final guidance defining what is "essentially a copy" of an FDA-approved drug failed to clearly differentiate between drugs compounded from FDA-approved finished drugs and from bulk API, as required by the statute. Although we urge the agency to clarify this guidance, we believe that FDA can help resolve any confusion regarding the prerequisites to use bulk API in the forthcoming, separate guidance. Additionally, the agency will need to clearly communicate its policy to compounders, customers, regulators and the public, and most importantly, must strictly enforce the rules against compounders who circumvent these restrictions.

Q2. Given your testimony that FDA's interim policy on bulks allows compounders to use approximately 100 bulk drug substances that are the active ingredient of an FDA approved drug, do you support Commissioner Gottlieb's stated intention to re-evaluate and remove those bulk substances from the list? Or how do you recommend FDA resolve concerns over the inclusion of FDA-approved products on the bulks list?

A: Yes. As noted, of the nearly 200 substances on the Category 1 list of bulk drug substances for which FDA has announced it plans not to take enforcement action for the time being, more than 100 of them are the main active ingredient of an FDA-approved drug. Based on publicly available information, it appears that many of these substances were nominated without identifying the comparable FDA-approved drug or specifying a clinical need not served by that approved drug that would justify the need to use the bulk substance. Commissioner Gottlieb explained that the list is not necessarily based on the legitimacy of the need as much as a desire to "freeze" the number of bulks used in compounding. He stated that the agency plans to remove substances from the Category 1 list. Given the additional dimensions of risk that nonsterile bulk substances introduce into the compounding process, PharMEDium supports FDA's efforts to remove substances from the list that were nominated without adequate evidence of a distinct clinical need. However, it is also important to emphasize that the presence of a substance on the Category 1 list does not justify its use in any particular situation; rather, the use of a bulk substance must still be supported by establishing a clinical difference compared with the

approved drug. In particular, if an outsourcing facility compounds from a bulk drug substance on the Category 1 list that is the active ingredient of an FDA-approved drug, they should be required to obtain documentation of a prescriber's determination that the bulk-compounded drug produces a clinical difference for an individual patient. Thus, FDA's efforts to revise the Category 1 list should further specify the additional restrictions on using these substances.

Q3. Does PharMEDium support the FDA's plans to create what some are calling a "503B Lite" option for facilities to register with FDA but be held to more lenient standards that will lower their cost of compliance? Although the details have not yet been announced, do you have any concerns with what has been articulated about this forthcoming policy or are there circumstances under which you think this approach would not be appropriate?

A: PharMEDium supports efforts to broaden participation in the 503B category to ensure it is competitive and robust enough to meet legitimate demand for non-patient specific compounding of sterile drugs. As Commissioner Gottlieb explained at the hearing, "the [good manufacturing practices] GMP standard is not a fixed standard; it's a risk-based standard." We recognize that cGMPs must be appropriately tailored to meet the specific risks that various products, processes, and operations present. However, the size and scale of an operation are not significant factors in the relative risk level of the sterile products that a compounder prepares, and therefore should not be a deciding factor in determining which aspects of cGMP to apply. As the Commissioner explained, the applicable controls should be based on the risks that products present, such as biologics, rather than the size of the operation alone. Ultimately, the goal of the DQSA to have robust quality standards for all 503B products to ensure patient safety must not be undermined by efforts, however well-intentioned, to make the outsourcing facility category more accessible.

Q4. The Subcommittee heard testimony that many physician offices and other health care settings have unmet need for "office use" compounded products that cannot be served by 503B outsourcing facilities? Are these the types of products that PharMEDium makes and do you believe that other outsourcing facilities would have difficulties in meeting these needs?

A: PharMEDium is sympathetic to all concerns of patients lacking access to needed treatments, as all patients should have access to safe compounded drugs when FDA-approved drugs cannot meet their individual clinical needs. PharMEDium does not have a finite catalog of products that we make. Instead, we prepare products based on the specific formulations that customers order.

Other witnesses described the need for highly standardized preparations that are "widely used" across many physician practices, such as buffered lidocaine. Thus, it may be feasible for these needs to be met by currently registered outsourcing facilities, and prepared under section 503B cGMP standards. Outsourcing facilities are not currently making everything that physician offices need, and thus there should be more collaboration between providers, suppliers and regulators to provide accurate information, identify gaps, and address opportunities to meet this gap. It would be ill-advised to try to resolve a current shortfall in the supply of compounded drugs by creating a workaround to section 503B that eliminates the incentive to register with FDA. As the Subcommittee's hearing memo explained, the prescription requirement of section 503A is that incentive. From PharMEDium's perspective, allowing non-patient specific compounding to be performed by entities that are not registered with FDA and do not follow cGMPs poses an unjustified risk to patient safety.

Responses to Questions from Ranking Member Pallone

In your written testimony you noted that compounded drugs should only be used when FDA-approved drugs do not meet a patient's clinical needs. I agree that this was a fundamental premise of the law, and I believe it is one that should be held in the forefront of our minds as we work on successful implementation, and as the agency considers its enforcement of the law. One of the requirements of outsourcing facilities under section 503B is the responsibility to comply with current good manufacturing practices. These quality requirements are critical to ensuring the sterility and safety of compounded drug products.

Q1. Will you describe further the cGMP requirements that outsourcing facilities are held to and how they help to ensure the safety of compounded drug products?

A: As you know, outsourcing facilities are not exempt from section 501(a)(2)(B) of the FDCA, meaning that unlike traditional pharmacy compounders, we are required to comply with current good manufacturing practices (cGMPs). This means that like traditional drug manufacturers, outsourcing facilities must prepare compounded drugs under robust but flexible requirements designed to assure the quality of the finished sterile drug products. Producing sterile drugs products, particularly through aseptic processing, requires the awareness of, control over and monitoring of many process variables, each of which could cause an error that could ultimately lead to distribution of contaminated or otherwise substandard product. According to cGMPs, outsourcing facilities must understand the importance of a robust monitoring program that provides a high degree of assurance as to the level of microbial control of the sterile drug processing environment and compounding personnel, maintain facilities and equipment specifically tailored for use in the processing of sterile drugs, employ broad cleaning, sanitization and disinfection procedures – validating their efficacy, enforce strict aseptic processing controls at all times during sterile manipulations, as well as fully test all batches of drug products with scientifically sound laboratory testing and control methods. These controls are just a few of the important measures required under cGMPs to mitigate the myriad of variables that can impact the quality, integrity or sterility of a compounded sterile preparation.

Q2. Recently FDA announced that the agency will be issuing revised guidance on cGMPs that will propose flexibilities based on the size and scope of an outsourcing facility's operations. My understanding is the intent of this proposal is to encourage additional pharmacies that are currently operating under section 503A to register as outsourcing facilities under section 503B. Will you discuss your perspective on additional flexibility related to cGMPs and whether this is an approach that you would support as an outsourcing facility?

A: In general, PharMEDium supports efforts to broaden participation in the 503B category to ensure it is equipped to meet demands for legitimate non-patient specific compounding of sterile drugs. But access must not come at the expense of patient safety, and thus FDA must ensure that appropriate manufacturing standards govern outsourcing, especially the preparation of high-risk products such as sterile drugs.

Based on our experience operating under cGMP conditions, we believe that regulatory flexibility exists for FDA to appropriately oversee outsourcing. cGMPs are designed to be tailored to meet the specific risks that various products, processes, and operations present. Importantly, the size or

scale of an operation has little to do with the inherent risk of the activities performed during the manufacturing process, and therefore does not factor into the existing cGMP framework. cGMP exemptions could compromise product integrity, and should not be made for small batch size or limited distribution, and certainly not for high-risk products such as injectable drugs made from nonsterile API powders.

Q3. What important guardrails do you think the agency should consider in revising this guidance to ensure we are maintaining high standards for safety and quality of products compounded by outsourcing facilities?

A: We understand that FDA is preparing new guidance and ultimately new regulations, to help outsourcing facilities better understand how the obligations under 21 CFR Parts 210 and 211 apply to this industry, as those regulations originally contemplated large-scale, conventional drug manufacturing of few, large, uniform batches. As Commissioner Gottlieb emphasized during his appearance before the Subcommittee, the cGMP framework is inherently flexible and designed to empower manufacturers to design processes to proactively account for the risks they identify. Appropriate guardrails should include heightened obligations for high-risk drug products, such as manipulated biologics, and robust qualification of high-risk components, such as nonsterile bulk API. Bulk API introduces considerable risk into the compounding process, which cannot always be fully accounted for under anything short of the full regulatory cGMPs, and thus is considered the riskiest form of compounding by USP and other experts. Accordingly, specific guardrails should be in place to ensure that only suitable sterile grades of bulk API are utilized, that incoming bulk materials are appropriately characterized, tested and that their manufacturers are qualified according to a define supplier quality management program, and additional investigations on requisite bulk substance manufacturing controls is undertaken.

Appropriate accommodations could be made for lower-risk components, such as FDA-approved or FDA-cleared starting materials that have themselves been manufactured under cGMP conditions, as well as for lower-risk products, such as nonsterile topical agents. Accommodations should not be made for high-risk products simply because they will be prepared in relatively small batches or distributed to a limited geographic area. These characteristics do not mitigate the risk of contamination, impurity, degradation, or other quality assurance aspects that cGMPs are designed to control.

One of the common complaints we have heard from 503A pharmacies is that registered 503B outsourcing facilities are unable to meet the needs of physicians and patients, and further it is difficult to identify outsourcing facilities that can meet their needs. On the second panel we heard from Dr. Brod, chair of the American Academy of Dermatology Association, that "FDA's website lists only the facilities that are registered, but with no contact information no real-time product availability information, and no price list." He argues this results in physicians undertaking a scavenger hunt to identify 503B outsourcing facilities that can fit their needs.

Q4. Does PharMEDium work with 503A pharmacies to provide products for purposes of "office use stock"? If so, will you discuss further the process by which a 503A pharmacy could request products for these needs? If no, what considerations does PharMEDium take into account when making a decision of whether or not to supply products for purposes of "office use stock"?

A: All of the products PharMEDium prepares are for "office stock" in that they are provided for use in hospitals and other health care settings by providers who are anticipating their need for ready-to-administer compounded sterile preparations (CSPs). PharMEDium receives orders from health care provider entities for CSPs and fills those orders to the customers' specifications. We do not receive prescriptions or other information about the patient. Most of our customers are hospital or health system pharmacies that operate pursuant to section 503A for their own compounding activities. Section 503B prohibits outsourcing facilities from engaging in wholesaling activities, meaning that we only supply CSPs to the end users that will dispense/administer them to the patient. We are not permitted to sell to independent pharmacies that in turn transfer the product to an end user. PharMEDium believes this obligation to sell directly to the end user is an important feature of section 503B which prevents outsourcing facilities from operating like conventional drug manufacturers and which also preserves the integrity of the supply chain of outsourced products.

We agree with other witnesses that FDA could provide additional information on its website to disseminate more useful information about outsourcing facilities, including their contact information and a link to their website. Displaying or otherwise disseminating this type of information is consistent with the statute, and would help to mitigate the "scavenger hunt" that was described.

Q5. One of the requirements of outsourcing facilities under section 503B is the submission of product lists to the FDA semiannually. FDA has noted that not all outsourcing facilities have been complying with this requirement, resulting in the posting of incomplete product lists. What steps, if any, is FDA taking to ensure compliance with this requirement?

A: PharMEDium recognizes that product reporting is a central obligation of section 503B, and we therefore support efforts to ensure all registrants come into alignment with statutory obligations. However, we cannot speak to what steps FDA is taking to address underreporting of compounded products by other outsourcing facilities. Efforts by FDA to ensure more accurate and complete reporting could assist in making sure the patient and provider communities are aware of the full range of products available through outsourcing facilities, as well as their processes and source materials.

GREG WALDEN, OREGON
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

ONE HUNDRED FIFTEENTH CONGRESS

Congress of the United States

House of Representatives

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February 16, 2018

Ms. Molly Ventrelli
Vice President, Regulatory Affairs
Fresenius Kabi
3 Corporate Drive
Lake Zurich, IL 60047

Dear Ms. Ventrelli:

Thank you for appearing before the Subcommittee on Health on January 30, 2018, to testify at the hearing entitled "Examining Implementation of the Compounding Quality Act."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on March 3, 2018. Your responses should be mailed to Zack Dareshori, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, DC 20515 and e-mailed in Word format to zack.dareshori@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Michael C. Burgess, M.D.
Chairman
Subcommittee on Health

cc: The Honorable Gene Green, Ranking Member, Subcommittee on Health

Attachment

2. Will you describe how the quality standards that compounding pharmacies are required to comply with under sections 503A and 503B differ from those of regulated drug manufacturers?

Manufacturers of FDA-approved drugs must comply with requirements known as current good manufacturing practices (CGMP). These standards are described in FDA's regulations at 21 CFR Parts 210 and 211. The regulations contain stringent requirements for personnel qualifications, facility design, production and process controls, environmental monitoring, laboratory controls, including required sterility and stability testing, and quality assurance and quality control, among other requirements.

Manufacturers must register with FDA and list the drugs that they produce or intend to produce, and FDA regularly inspects manufacturing facilities to determine whether they are in compliance with CGMP requirements. Before an Abbreviated New Drug Application (ANDA) is approved, FDA will look at the inspection history of the manufacturing facilities listed in the ANDA to determine whether they have been inspected and found to be in compliance with CGMP requirements, and will conduct pre-approval inspections when necessary.

In contrast to manufacturers of FDA-approved drugs, pharmacies that compound drugs in accordance with the conditions in section 503A are exempt from CGMP requirements. They do not register with FDA. As a result, FDA does not have an inventory of pharmacies compounding under section 503A, and FDA will not normally inspect such pharmacies unless an inspection is triggered by a request from a state, or FDA becomes aware of an adverse event or product quality problem that is traceable to the pharmacy. Additionally, the FDA may inspect these facilities when it is determined to be compounding large quantities without patient prescriptions. Because these compounding pharmacies are primarily regulated by the states, individual states determine what standards the pharmacies will be held to, how often they will be inspected by the state, and what action will be taken if the pharmacies are in non-compliance with the state requirements. The standards applicable to pharmacies operating under section 503A are much less rigorous than the CGMP requirements applicable to conventional manufacturers. In fact, these standards, set by United States Pharmacopeia, are not required by all states to meet full compliance standards.

Pharmacies that register with FDA as outsourcing facilities and compound drugs in accordance with the conditions of section 503B are required to follow CGMP requirements, but FDA has indicated that it intends to develop specific CGMP regulations applicable to outsourcing facilities that will be more suitable for compounding than those applicable to conventional manufacturers. It is particularly important to note that 503B facilities are not inspected by the FDA prior to launching a new product. In June 2014, FDA issued a draft guidance, *Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM403496.pdf). The draft guidance describes FDA's expectations regarding outsourcing facilities' compliance with the CGMP requirements in 21 CFR parts 210 and 211 during the interim period while FDA is developing the regulations. The guidance states:

> This interim guidance reflects FDA's intent to recognize the differences between compounding outsourcing facilities and conventional drug manufacturers, and to tailor CGMP requirements to the nature of the specific compounding operations conducted by outsourcing facilities while maintaining the minimum standards necessary to protect patients from the risks of contaminated or otherwise substandard compounded drug products. (Draft Guidance at 2).

In its recently issued 2018 Compounding Policy Priorities Plan (https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm592795.htm), FDA indicated it is revising the draft guidance "to describe a new flexible, risk-based approach to CGMP requirements for outsourcing facilities." FDA has indicated that its goal is "for more compounders to register as outsourcing facilities with the understanding that they can still meet the FDA's core requirements for drug quality, based on the size and scope of their compounding operations." How FDA will do so remains to be seen, and it will be important to ensure that FDA does not relax the CGMP requirements applicable to outsourcing facilities in a way that creates additional risk to patients who take a compounded product instead of an FDA-approved drug or create disincentives to the submission of NDAs or ANDAs by conventional drug manufacturers who must follow the stringent standards in Parts 210 and 211.

3. You noted in your testimony that outsourcing facilities, a category of compounding pharmacies created under DQSA to address the large-scale compounding needs of hospitals or health systems are required to comply with good manufacturing practices. What implications would there be for manufacturers if the cGMPs that 503B pharmacies are held to are weakened to allow for typically traditional pharmacies to enter into bulk compounding space?

If the CGMPs that 503B pharmacies are held to are weakened to allow pharmacies that currently compound under the conditions of 503A to register as outsourcing facilities and compound drugs without prescriptions for hospitals or health systems, patients could be put at significant risk of receiving substandard drugs. Submission of NDAs and ANDAs and compliance with CGMP requirements are costly, but the approval process and CGMP requirements significantly reduce the risk to patients of receiving poor quality products. If FDA establishes weak CGMP requirements for outsourcing facilities, hospitals and health systems may turn to those lower cost unapproved compounded products even when an approved product will fulfill the patient's needs, placing patients at risk, putting conventional drug manufacturers that hold NDAs and ANDAs at a competitive disadvantage, and reducing the incentives for companies to seek approval of NDAs and ANDAs. Drawing a regulatory line between these two facilities will be challenging at best. A consistent standard needs to be found so as to not reduce regulatory oversight to a level of individual interpretation.

4. One key difference between the requirements an outsourcing facility is held to and traditional drug manufacturers is that the compounded drug products compounded by an outsourcing facility are not subject to any premarket approval. How can FDA ensure that the traditional drug approval process is not undermined by the expansion of the outsourcing facility market?

In addition to continuing to require outsourcing facilities to comply with stringent CGMP requirements such as those applicable to conventional manufacturers, FDA must enforce the provisions of section 503B that limit the bulk drug substances that can be used by outsourcing facilities to compound, prohibit outsourcing facilities from copying commercially available drug products that are not on FDA's drug shortage list, and strictly enforce the limitations on compounding drugs on the drug shortage list, a practice that is permissible only while the drug remains on the drug shortage list. These provisions were included in the law to prevent outsourcing facilities from undermining the traditional drug approval process.

Section 503B(a)(2) states that outsourcing facilities can only compound using bulk drug substances that appear on a list established by FDA identifying bulk drug substances for which there is a clinical need. If a compounded medication can be made from an approved drug, then it should not be compounded from a bulk drug substance. If there is no clinical need for a product compounded from a bulk drug substance, then FDA should ensure that outsourcing facilities do not compound with that substance, and if a bulk drug substance is on the list and allowed to be used to compound, FDA should ensure that only patients with the clinical need for the compounded product are prescribed that product in place of the FDA-approved drug.

Section 503B(a)(5) states that outsourcing facilities cannot compound drugs that are essentially copies of one or more approved drugs. FDA recently issued a final guidance that describes how it intends to apply this prohibition to outsourcing facilities (*Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act*, https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM510153.pdf). It is critical that FDA make it a priority to take enforcement action against outsourcing facilities that violate the statutory prohibition against copying approved products. FDA must prevent outsourcing facilities from making small changes, such as different container systems or simple labeled dilutions, to approved products that are not clinically meaningful and then marketing them as appropriate substitutes for approved drugs. FDA must exercise similar oversight over pharmacies seeking to operate under section 503A and copying FDA-approved drugs, despite the differences between the statutory prohibitions against copying in sections 503A and 503B.

The definition of "essentially a copy of an approved drug" in section 503B(d)(2) specifies that a drug that is on the FDA's drug shortage list at the time of compounding, distribution, and dispensing is not considered to be "essentially a copy of an approved drug". To prevent outsourcing facilities from continuing to compound drugs long after they have been removed from the drug shortage list, FDA should strictly enforce the language of the statute.

Without strict oversight of compounding under both 503A and 503B, FDA's approval process for NDAs and ANDAs that is considered to be the gold standard domestically and globally could be undermined, placing patients at risk. Additionally, any bulk substance compounding should only be performed in CGMP conditions due to the high risk. Particularly when the final product is sterile injectable. Patients may be given unapproved compounded drugs that are not made under the rigorous CGMP standards applicable to manufacturers of approved drugs when there is no clinical need for them to get a compounded product. Lowering the bar so that compounding outsourcing facilities can make drugs on a large scale and distribute them without prescriptions and without complying with strict quality standards would place manufacturers of approved drugs at a competitive disadvantage. It would create disincentives for companies to submit NDAs and ANDAs, invest in state of the art manufacturing facilities and manufacture drugs in compliance with CGMP requirements. Congress enacted protections in section 503B to prevent this from happening, and FDA must enforce those provisions to ensure that Congress's intent is fulfilled.

5. You noted in your testimony that Fresenius Kabi will be launching a 503B compounding center. What consideration did you take into account when considering entering the 503B space?

Currently most Fresenius Kabi products in the U.S. serve hospital customers and we will continue to do the same with our compounding business. We replied to a request for proposal from a large health care delivery system in Massachusetts for outsourced compounding services and will be begin producing for this customer in Q2 of this year. Our longer-term plan is to look at similar provider networks to offer this service.

GREG WALDEN, OREGON
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

ONE HUNDRED FIFTEENTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON ENERGY AND COMMERCE
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February 16, 2018

Ms. Elizabeth Jungman
Director, Public Health
The Pew Charitable Trusts
901 E Street, N.W.
Washington, DC 20004

Dear Ms. Jungman:

Thank you for appearing before the Subcommittee on Health on January 30, 2018, to testify at the hearing entitled "Examining Implementation of the Compounding Quality Act."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on March 3, 2018. Your responses should be mailed to Zack Dareshori, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, DC 20515 and e-mailed in Word format to zack.dareshori@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Michael C. Burgess, M.D.
Chairman
Subcommittee on Health

cc: The Honorable Gene Green, Ranking Member, Subcommittee on Health

Attachment

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Philadelphia, PA 19103-7077

901 E Street NW 202.552.2000 Phone
Washington, DC 20004
www.pewtrusts.org

The Honorable Greg Walden, Chairman
Committee on Energy & Commerce
U.S. House of Representatives
Washington, DC 20515

The Honorable Frank Pallone, Ranking Member
Committee on Energy & Commerce
U.S. House of Representatives
Washington, DC 20515

The Honorable Michael Burgess, Chairman
Subcommittee on Health
Committee on Energy & Commerce
U.S. House of Representatives
Washington, DC 20515

The Honorable Gene Green, Ranking Member
Subcommittee on Health
Committee on Energy & Commerce
U.S. House of Representatives
Washington, DC 20515

Dear Chairman Walden, Ranking Member Pallone, Chairman Burgess, and Ranking Member Green,

Thank you for the opportunity to testify before the Subcommittee on Health on January 30, 2018 at the hearing entitled "Examining Implementation of the Compounding Quality Act." My responses to the questions for the record are below. If Pew can be of additional service to the Subcommittee, please contact Sarah Despres at sdespres@pewtrusts.org or 202-540-6601.

The Honorable Michael C. Burgess, M.D.

In testimony before this committee, allegations were raised regarding potential financial conflicts of interest and Pew's role as a voting member on the FDA's Pharmacy Compounding Advisory Committee. Would you please respond to these allegations?

In written testimony before the subcommittee January 30, 2018 the witness representing the International Association of Compounding Pharmacists alleged financial conflicts arising from Pew's joint activities with the pharmaceutical industry in connection with my service as a member of the Pharmacy Compounding Advisory Committee. I appreciate the opportunity to state unequivocally for the record that neither The Pew Charitable Trusts nor I personally have financial conflicts of interest in my work on the committee. The FDA process for choosing advisory committee members lays out guidelines for preventing conflicts of interest, and my appointment was vetted by FDA in accordance with those guidelines.

Pew is an independent, nonprofit organization dedicated to serving the public. We have a longstanding focus on drug safety. Over the last five years we have advocated for federal and state policies to ensure that patients who receive compounded drugs are protected from the risks associated with these medications. The benefits these safeguards provide to Americans' health are the only driver of our work on this issue.

The Drug Quality and Security Act mandates the range of expertise required to serve on the committee, and includes a representative from a public health advocacy organization. I was invited

to serve on the committee in that role when it was formed in 2014, and have served in that capacity since, with the exception of a one-year period during which another Pew employee served as the public health advocacy organization representative.

The Honorable Frank Pallone, Jr.

DQSA established the Pharmacy Compounding Advisory Committee to advise on scientific, technical and medical issues related to implementation of sections 503A and 503B of the Drug Quality Security Act and to make recommendations to the Commissioner. The Committee is required to include representatives from the National Association of Boards of Pharmacy, the United States Pharmacopeia, pharmacists with current experience and expertise in compounding, physicians with background and knowledge in compounding, and patient and public health advocacy organizations.

1. **As a member of the Pharmacy Compounding Advisory Committee can you describe briefly the matters that have come before the Committee for review?**

In accordance with its charter (see Appendix A), the Pharmacy Compounding Advisory Committee (PCAC) "provide[s] advice on scientific, technical, and medical issues concerning drug compounding under sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act, and, as required, any other product for which the Food and Drug Administration has regulatory responsibility, and make[s] appropriate recommendations to the Commissioner of Food and Drugs." This role is described in sections 503A(c)(1) and 503B(c)(2) of the FDCA. Thus far, the committee has made recommendations to FDA regarding: (1) bulk substances that should and should not be made available for compounding under Section 503A; (2) products that should be included on FDA's list of drugs that have been withdrawn or removed for safety or effectiveness reasons; and (3) products that are demonstrably difficult to compound.

2. **There has been criticism that the current Pharmacy Compounding Advisory Committee does not have a voting member that is a practicing compounding pharmacist. What is the Committee's current make-up and how are members selected for participation on the Advisory Committee?**

The PCAC charter (Appendix A) describes the process for selecting members as follows:

> "The Committee shall consist of a core of 12 voting members including the Chair. Members and the Chair are selected by the Commissioner or designee from among authorities knowledgeable in the fields of pharmaceutical compounding, pharmaceutical manufacturing, pharmacy, medicine, and related specialties. These members will include representatives from the National Association of Boards of Pharmacy (NABP), the United States Pharmacopeia (USP), pharmacists with current experience and expertise in compounding, physicians with background and knowledge in compounding, and patient and public health advocacy organizations."

The specific expertise required of the committee, including the public health advocacy role in which I serve, is mandated by statute in 503A(c)(1) and 503B(c)(2). In addition to voting members, the charter provides that "the Committee may include one or more non-voting members who are identified with industry interests."

According to the committee roster (attached as Appendix B), the current voting members have expertise in a range of areas including pharmacology, pharmaceutical formulation and processing, pharmacy compounding, consumer advocacy, clinical pharmacy, dermatology, anesthesiology,

pharmaceutical science, public health advocacy (Pew), and hospital and health system pharmacy. There are two nonvoting members: one from a pharmaceutical company, and one from a compounding pharmacy.

3. **It is my understanding that some members are not voting members of the committee. Can you describe why some members are voting and others non-voting? Further, can you discuss how FDA ensures that the membership of this Committee remains free of any financial, legal, or other conflicts?**

PCAC's charter describes non-voting members as those "who are identified with industry interests." Voting members are subject to a conflict-of-interest screening process prior to each meeting.

At the beginning of each PCAC meeting, an FDA representative reads a statement regarding the status of the committee's compliance with federal conflict of interest laws and regulations, including those found at 18 U.S.C., Section 208. In that statement, FDA represents that it has determined that the members of the committee (including any temporary members attending that particular meeting) are in compliance with the federal ethics and conflict of interest laws. FDA notes at the beginning of each meeting that members and temporary voting members of the committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for the purposes of 18 U.S.C., Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/cooperative research and development agreements; teaching/speaking/writing; patents and royalties; and primary employment.

In my experience, upon appointment to the committee, members must complete a general conflicts disclosure form (OGE Form 450). This is the form that executive branch employees who are less senior than public filers use to report their financial interests as well as other interests outside the Government. The purpose of this report, according to the instructions on the form, is to assist employees (PCAC members are "Special Government Employees") and their agencies in avoiding conflicts between duties and private financial interests or affiliations.

In addition, prior to each committee meeting, members are required to disclose financial, legal, and ideological conflicts (FDA Form 3410) directly relevant to the substance being discussed at the upcoming meeting. On occasion, committee members are excluded from particular votes because of these conflicts rules.

Section 503A of the law prohibits a pharmacist, pharmacy, or health care provider from distributing compounded drug products across state lines that exceed five percent of the total prescriptions distributed or dispensed, unless the product is compounded in a state that has entered into a memorandum of understanding with FDA that addresses the distribution of inordinate amounts of compounded drug products and provides for investigation by the state into complaints associated with compounded drug products that are distributed interstate. FDA released a draft MOU in February 2015 that proposed defining "inordinate amounts" for purposes of interstate distribution to be no greater than 30 percent of all products distributed or dispensed. More recently, FDA has indicated they will be revising this threshold to increase it to 50 percent.

4. **Under this construct, a pharmacy is severely limited in its ability to ship compounded drugs out of state unless the state in which the pharmacy operates has signed a MOU with FDA. If there is an MOU in place, then the pharmacy may be able to ship more compounded drug out of state. Can you explain why the law contemplates restricting interstate shipment of compounded drugs and how that restriction could impact patient safety?**

The MOU provision in section 503A addresses the circumstance when a compounder ships patient-specific drugs across state lines. When that happens, patients affected by the compounding activity are not in the state overseeing it. As an illustration of the potential consequences of failing to properly oversee interstate shipment of compounded drugs, during the fungal meningitis outbreak of 2012, products from one dangerous facility harmed patients in 20 states. No victims lived in Massachusetts, where the compounder was located.

As contemplated by the statute, the MOU gives pharmacies in states that agree to investigate and respond to complaints from patients outside of its borders more flexibility to sell products across state lines. As such, the MOU helps to ensure adequate oversight for patients who receive a patient-specific compounded drug made in another state.

FDA has indicated that it will issue a new draft MOU in 2018 that will not restrict distribution of high volumes of patient-specific drugs, but instead will identify facilities shipping significant quantities of drug interstate to federal authorities. The new MOU will require states to identify pharmacies that ship most of their product interstate and flag those pharmacies for FDA. This would then allow FDA to prioritize its oversight of 503A facilities – e.g. inspections to ensure compliance with federal guidelines on preventing insanitary conditions – on those pharmacies that do the most interstate shipment (where, arguably, the federal interest is strongest). The effectiveness of the provision, if finalized, will depend on states knowing when compounders dispense products over state lines, and regulators having sufficient authority to take action when that activity presents public health concerns.

5. **Some have suggested that the MOU is only intended to apply to drugs that are distributed without a prescription. Given the public health purpose of the MOU, are there some drugs, such as those dispensed directly to patients, which could be excluded consistent with that purpose? What impact could exclusions related to the distribution of compounded drug products across state lines could have on patient safety?**

It would be difficult to reconcile this position with the language of section 503A. The MOU applies to compounding under 503A, and all compounding under 503A assumes a prescription. As such, it would not make sense for the MOU provision to exempt the only drugs to which it applies: prescription-specific compounded drugs.

Limiting the MOU to drugs provided to healthcare providers would mean that a facility regulated as a traditional compounder could operate at manufacturer scale and dispense an unlimited amount of product interstate, without FDA oversight, as long as it had prescriptions. Any error or substandard practice would potentially affect many people nationwide; a pharmacy that prepares thousands of patient-specific drugs a week has the potential to affect many thousands of patients if their facility controls are insufficient to prevent contamination. And there really are facilities that sell very large volumes of patient-specific drugs. For example, patients who cannot eat and digest normally require intravenous administration of liquid nutrition that is tailored to their individual dietary needs; those infusions are often prepared by specialized compounders who may be located across the country from the patient.

The MOU provision addresses the risk of state-regulated traditional compounders engaging in manufacturer-scale drug production and distribution across state lines, and helps to ensure that this practice only occurs in states that have agreed to appropriately oversee this activity, e.g., by responding to complaints from patients in states to which the products are distributed.

In August 2016, FDA released guidance intended to help compounding pharmacies address insanitary conditions at their facility. This guidance document outlines examples of what the agency considers to be insanitary conditions and conditions that inspectors have observed, as well as procedures that compounding pharmacies can put in plan to ensure their facilities are sanitary and what actions should be taken if there are insanitary conditions.

6. **We heard at the hearing from providers that having to meet FDA's insanitary conditions guidance will make it more difficult for them to provide patients with certain compounded medications. I understand that Pew has concerns with exempting certain groups from those standards. What is the potential risk of not requiring doctors to meet the same standards as pharmacies?**

The safety of compounded preparations depends on the conditions under which they are made. Anyone who compounds drugs – in any setting – should be subject to appropriate quality standards and meaningful oversight.

Quality standards, such as those promulgated by the United States Pharmacopeia (USP), recognize that the level of risk posed by a drug is partly determined by when and how it is administered. Even if a medication has become contaminated, if it is administered immediately, as often occurs in physician offices, there is a lower risk of patient harm than if it sits on the shelf for a while, which gives those contaminants a chance to multiply to dangerous levels. As such, the USP's standards already strike a balance, to ensure patient access to drugs that have been made in a way that mitigates their risks.

If physicians do not have the equipment or specialized training to adhere to USP's quality standards, however, patients are put at risk. Patients should not have to sacrifice quality for access. Public health is not served by improving access to drugs that are not made under sanitary conditions, for which safety cannot be assured. Patients should have access to safe compounded drugs.

Your written testimony includes an appendix outlining illnesses and deaths associated with compounded or repackaged medications. From 2001 to 2017, Pew identified over 1400 adverse events, including 114 deaths, that were the result of an identified 71 reported compounding errors or potential errors.

7. **Will you describe briefly some of these adverse events Pew identified and the circumstances that lead to these adverse events?**

In 2017, at least 43 people in Texas had contaminated antibiotics injected into their eyes; several suffered vision loss. Also in 2017, 41 patients received contaminated injections at a New Jersey clinic. They developed joint infections caused by microorganisms that should only be found in our mouths. Precautions like aseptic technique and appropriate gowning are designed to prevent these types of errors. These cases illustrate the importance of adhering to robust quality standards when compounding drugs.

8. **In your review, did you see similar or different quality and safety issues between 503A compounding pharmacies and 503B outsourcing facilities?**

We have not formally compared quality and safety issues between 503A compounding pharmacies and 503B outsourcing facilities, so it is not really possible for me to speak to any similarities or differences between the categories, but we are aware of adverse events linked to drugs from both types of facilities.

9. Pew's review of the adverse events associated with compounded or repackaged medications highlighted that because adverse events associated with compounding are underreported, your review could constitute an underestimation of the number of compounding errors since 2001. What more could Congress or FDA do to improve adverse event reporting by compounding pharmacies to ensure that such information is more consistently shared with the federal government?

Outsourcing facilities are required to report all serious, unexpected adverse experiences to FDA. FDA has issued guidance to facilitate compliance with this requirement.

For traditional compounders, which are primarily subject to state oversight, states set adverse event reporting requirements. Pew published research in 2016 showing that only 30 percent of states (13 of the 43 that responded) require sterile compounding pharmacies to report serious adverse events. For these primarily state-regulated facilities, FDA may be better positioned than states to identify problems with particular drugs; if the same adverse events occur with the use of a product, regardless of where it is made, the federal agency might be first to become aware of the problem. States would need to keep track of adverse events linked to specific facilities to identify problematic compounders, but FDA may be able to offer technical assistance with those efforts as well.

10. The states also play a critical role in ensuring the safety of compounding pharmacies. What keeps states from falling short of annual inspections, a best practice your advisory committee identified? How can FDA better assist states as they continue to align with federal law?

The frequency of inspections for traditional pharmacies located in a given state is not typically dictated by that state's laws or regulations, but is instead often based on resources. Pew's new report demonstrates that states may be inspecting traditional pharmacies that do sterile compounding less frequently now than in 2015. Then, 26 states and the District of Columbia conducted routine inspections at least annually for in-state pharmacies that perform sterile compounding; today, just 22 states and the District do so. Interviews with state officials underscore the need for more financial resources and inspection capacity.

Appendix A
Pharmacy Compounding Advisory Committee Charter

Authority
The Pharmacy Compounding Advisory Committee is authorized by section 503A and section 503B of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 353a (c) (1) and 21 U.S.C. 353b (c)(2)), as amended by sections 102 and 106 of the Drug Quality and Security Act (Pub. L.113-54. The committee also is authorized by 15 U.S.C. 1451 et seq.;21 U.S.C. 321, 341, 342, 343, 343-1, 344, 345, 346, 348, 349, 350, 350a, 351, 352, 353(f), 355, 360b, 360c-j, 371, 375, 376, 378, 379e, 381, 393, 394, 881(b); 42 U.S.C. 217a, 241, 242, 242a, 262, 264; 21 CFR Part 14, 330.10(a); Pub. L. 92-463 (5 U.S.C. App.), and the Federal Advisory Committee Act, which sets forth standards for the formation and use of advisory committees.

Objectives and Scope of Activities
The Pharmacy Compounding Advisory Committee advises the Commissioner or designee in discharging responsibilities as they relate to compounding drugs for human use and, as required, any other product for which the Food and Drug Administration has regulatory responsibility.

Description of Duties
The Committee shall provide advice on scientific, technical, and medical issues concerning drug compounding under sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act, and, as required, any other product for which the Food and Drug Administration has regulatory responsibility, and make appropriate recommendations to the Commissioner of Food and Drugs.

Agency or Official to Whom the Committee Reports
The Committee provides advice to the Commissioner of Food and Drugs.

Support
Management and support services shall be provided by the Center for Drug Evaluation and Research.

Estimated Annual Operating Costs and Staff Years
The estimated annual cost for operating the Committee, including compensation and travel expenses for members but excluding staff support, is $125,603. The estimated person years of staff support required is 1.10, at an estimated annual cost of $86,898.

Designated Federal Officer
FDA will select a full-time or permanent part-time Federal employee to serve as the Designated Federal Officer (DFO) to attend each Committee meeting and ensure that all procedures are within applicable statutory, regulatory, and HHS General Administration Manual directives. The DFO will approve and prepare all meeting agendas, call all of the Committee and subcommittee meetings, adjourn any meeting when the DFO determines adjournment to be in the public interest and chair meetings when directed to do so by the official to whom the Committee reports. The DFO shall be present at all meetings of the full committee and subcommittees.

Estimated Number and Frequency of Meetings
Meetings shall be held approximately 4 times a year. Meetings shall be open to the public except as determined otherwise by the Commissioner or designee in accordance with the Government in the Sunshine Act (5 U.S.C. 552b(c)) and the Federal Advisory Committee Act. Notice of all meetings shall be given to the public.

Duration
Continuing

Termination
Unless renewed by appropriate action, the charter for the Pharmacy Compounding Advisory Committee will expire two years from the date it is filed.

Membership and Designation
The Committee shall consist of a core of 12 voting members including the Chair. Members and the Chair are selected by the Commissioner or designee from among authorities knowledgeable in the fields of pharmaceutical compounding, pharmaceutical manufacturing, pharmacy, medicine, and related specialties. These members will include representatives from the National Association of Boards of Pharmacy (NABP), the United States Pharmacopeia (USP), pharmacists with current experience and expertise in compounding, physicians with background and knowledge in compounding, and patient and public health advocacy organizations. Members will be invited to serve for overlapping terms of up to four years. Almost all non-Federal members of this committee serve as Special Government Employees. The core of voting members may include one or more technically qualified members, selected by the Commissioner or designee, who are identified with consumer interests and are recommended by either a consortium of consumer-oriented organizations or other interested persons. In addition to the voting members, the Committee may include one or more non-voting members who are identified with industry interests.

The Commissioner or designee shall have the authority to select members of other scientific and technical FDA advisory committees (normally not to exceed 10 members) to serve temporarily as voting members and to designate consultants to serve temporarily as voting members when: (1) expertise is required that is not available among current voting standing members of the Committee (when additional voting members are added to the Committee to provide needed expertise, a quorum will be based on the combined total of regular and added members), or (2) to comprise a quorum when, because of unforeseen circumstances, a quorum is or will be lacking. Because of the size of the Committee and the variety in the types of issues that it will consider, FDA may, in connection with a particular committee meeting, specify a quorum that is less than a majority of the current voting members. The Agency's regulations (21 CFR §14.22(d)) authorize a committee charter to specify quorum requirements.

If functioning as a medical device panel, a non-voting representative of consumer interests and a non-voting representative of industry interests will be included in addition to the voting members.

Subcommittee
Temporary subcommittees consisting of two or more Committee members may be established by the Commissioner or designee as needed to address specific issues within their respective areas of expertise.

Subcommittees make preliminary recommendations regarding specific issues for subsequent action by the full Committee. The Department Committee Management Officer shall be notified upon establishment of each subcommittee, and shall be provided information on its name, membership, function, and estimated frequency of meetings.

Recordkeeping
Meetings of the Committee and its subcommittees will be conducted according to the Federal Advisory Committee Act, other applicable laws and Departmental policies. Committee and subcommittee records will be handled in accordance with General Records Schedule 6.2, Federal Advisory Committee Records or other approved agency records disposition schedule. These records will be available for public inspection and copying, subject to the Freedom of Information Act, 5 U.S.C. 552.

Filing Date
April 25, 2016

Approved
March 30, 2016

Jill Hartzler Warner, J.D.
Associate Commissioner for Special Medical Programs

Charter is available at:
https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/ucm381305.htm

Appendix B
Pharmacy Compounding Advisory Committee Roster

Chairperson
Jurgen Venitz, MD, PhD
Expertise: Pharmacology
Term: 11/13/2014 – 9/30/2018
Professor and Vice Chairman
Virginia Commonwealth University
School of Pharmacy
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Designated Federal Officer (DFO)
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Robin H. Bogner, Ph.D.
Expertise: Pharmaceutical Formulation and Processing, Pharmacy Compounding
Term: 1/31/2017 – 9/30/2020
Professor
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Department of Pharmaceutical Sciences
69 North Eagleville Road, PBB 438
Storrs, Connecticut, 06269

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Roster is available at:
https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/ucm381301.htm

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ONE HUNDRED FIFTEENTH CONGRESS

Congress of the United States
House of Representatives

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February 16, 2018

Ms. Nancy Dargan
6543 Barrie Circle
Brighton, MI 48114

Dear Ms. Dargan:

Thank you for appearing before the Subcommittee on Health on January 30, 2018, to testify at the hearing entitled "Examining Implementation of the Compounding Quality Act."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on March 3, 2018. Your responses should be mailed to Zack Dareshori, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, DC 20515 and e-mailed in Word format to zack.dareshori@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Michael C. Burgess, M.D.
Chairman
Subcommittee on Health

cc: The Honorable Gene Green, Ranking Member, Subcommittee on Health

Attachment

1. From your perspective, are there portions of the Drug Quality Safety Act that you think should be strengthened, or better enforced, to prevent something like this happening again?

I would like to thank Congress for passing the Drug Quality and Security Act. As I understand it, this law is designed to prevent something like what happened to me – or worse – from happening again to someone else.

I worry that if that law is not fully implemented in the way Congress intended, patients will pay the price the way I have. Patients have to be assured that the drugs that they are taking, or drugs that are being injected into them, are safe. That was what Congress intended to do when it passed the DQSA. Congress and FDA need to take whatever steps are necessary to make sure that people who are compounding drugs have the training and equipment to do it safely.

2. What steps can the FDA or Congress take to improve patient awareness and safety when it comes to compounded drugs?

Patients shouldn't have to be aware of compounded drug safety issues. Most patients do not have the expertise needed to evaluate compounding safety. I am a well-educated and knowledgeable person who was totally blindsided by what happened to me. And it is also important to remember that in plenty of cases, patients do not have a choice about whether to take a compounded drug because there are many instances in which the compounded drug is the only drug available.

Patients should be able to assume their drugs are safe. FDA and states can make sure that compounders use safe procedures, and Congress can continue to pay attention – as they did by holding this hearing – to be sure that FDA is implementing the law.

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