EXAMINING DRUG COMPOUNDING

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

ONE HUNDRED THIRTEENTH CONGRESS

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EXAMINING DRUG COMPOUNDING

THURSDAY, MAY 23, 2013

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

The subcommittee met, pursuant to call, at 9:58 a.m., in room 2322, Rayburn, Hon. Joseph R. Pitts (chairman of the subcommittee) presiding.

Present: Representatives Pitts, Burgess, Shimkus, Murphy, Gingrey, Lance, Guthrie, Griffith, Bilirakis, Ellmers, Barton, Pallone, Dingell, Engel, Capps, Matheson, Green, Butterfield, Barrow, Christensen, Castor, and Waxman (ex officio).

Staff Present: Clay Alspach, Chief Counsel, Health; Mike Bloomquist, General Counsel; Karen Christian, Chief Counsel, Oversight; Paul Edattel, Professional Staff Member, Health; Brad Grantz, Policy Coordinator, O&I; Sydne Harwick, Legislative Clerk; Nick Magallanes, Policy Coordinator, CMT; Carly McWilliams, Professional Staff Member, Health; Andrew Powaleny, Deputy Press Secretary; Krista Rosenthall, Counsel to Chairman Emeritus; Chris Sarley, Policy Coordinator, Environment & Economy; Heidi Stirrup, Health Policy Coordinator; John Stone, Counsel, Oversight; Brian Cohen, Minority Staff Director, Oversight & Investigations, Senior Policy Advisory; Alli Corr, Minority Policy Analyst; Eric Flamm, Minority FDA Detailee; Ruth Katz, Minority Chief Public Health Counsel; Elizabeth Letter, Minority Assistant Press Secretary; Karen Nelson, Minority Deputy Committee Staff Director for Health; Stephen Salsbury, Minority Special Assistant; Rachel Sher, Minority Senior Counsel; and Ryan Skukowski, Minority Staff Assistant.

OPENING STATEMENT OF HON. JOSEPH R. PITTS, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Mr. PITTS. The subcommittee will come to order. The Chair will recognize himself for an opening statement.

The purpose of today's hearing is to hear from FDA and healthcare experts regarding the history and importance of drug compounding to patients and the current regulation of compounding on the Federal and State levels. As we are all aware, in the summer and fall of 2012 a Massachusetts company, the New England Compounding Center, NECC, shipped over 17,000 vials of an injectable steroid solution from 3 contaminated lots to healthcare facilities across the country.

After receiving injections of NECC's contaminated steroid, over 50 people died from complications associated with fungal meningitis; further, almost 700 others were stricken with meningitis or other persistent fungal infections. The outbreak ranks as one of the worst public health crises associated with contaminated drugs in the history of the United States.

This committee began an investigation into the matter, and on October 9th a bipartisan committee letter was sent to FDA requesting details surrounding the outbreak and the prevention of future outbreaks. On October 17, the committee sent a letter to FDA asking for all documents related to the outbreak, including internal memoranda and communications with NECC. The Oversight and Investigations Subcommittee held a hearing on November 14, 2012, where Dr. Margaret Hamburg testified examining whether the meningitis outbreak could have been prevented. Two days later, on November 16th, the committee sent yet another letter to FDA stating that the agency had not provided any of the internal communications or memoranda in response to the October 17th letter.

It was not until March 21st, 2013, over 5 months after the original request, and after being threatened with the possibility of a subpoena, that FDA fully complied with the committee's document request. It should be noted that the Massachusetts Department of Public Health had fully complied with the committee's document request, turning over thousands of pages of documents related to its interactions with NECC before the November hearing took place.

On April 16, 2013, the O&I Subcommittee held another hearing entitled, "A Continuing Investigation Into the Fungal Meningitis Outbreak: Could It Have Been Prevented?" and released a 43-page report on its investigation into the NECC tragedy. The report stated that FDA had been aware of potential problems at NECC since 2002. During her testimony at the November hearing, Dr. Hamburg repeatedly expressed uncertainty about FDA's authority over compounding pharmacies, partially due to conflicting opinions on the matter issued by two different circuit courts of appeals in 2009.

This uncertainty, however, has not stopped FDA from engaging in multiple enforcement activities against compounding pharmacies engaged in practices similar to those of NECC since the outbreak took place. This year alone, FDA has announced recalls from compounding pharmacies in Augusta, Georgia, and Lake Mary, Florida, and St. Petersburg, Florida. In addition, the FDA in October of 2012 was prepared to issue new guidance related to compounding enforcement under its authority under Section 503.

Since the outbreak, however, the FDA has called for new authority that creates a new category of compounding manufacturers. From what I understand, there are concerns that creating this new category could undermine drug safety by lowering standards and also weaken intellectual property protection.

I would like to thank Dr. Woodcock for appearing before us today to explain her understanding of FDA's authority over compounding pharmacies and what actions the agency is taking to ensure that future outbreaks can be prevented. And I would also like to thank all of our other witnesses for sharing their expertise on compounding and its importance to patients.

Thank you. And I will yield the balance of my time to Congressman Barton.

[The prepared statement of Mr. Pitts follows:]

PREPARED STATEMENT OF HON. JOSEPH R. PITTS

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From what I understand, there are concerns that creating this new category could undermine drug safety by lowering standards and also weaken intellectual property protection.

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I would also thank our other witnesses for sharing their expertise on compounding and its importance to patients.

Thank you, and I yield the balance of my time to Rep. _____.

Mr. BARTON. Thank you, Mr. Chairman. I am glad to be here today. We are glad to have Dr. Woodcock. She is a longtime witness before the committee, and we have great respect for her. We look forward to hearing what you have to say.

I think it is pretty obvious to neutral observers that the facts do indicate that the FDA had authority that it refused or chose not to use in the situation that we are investigating. I am sure Dr. Woodcock will elaborate on that and may have a counter point of view.

Mr. Chairman, on the second panel I have a good friend and former constituent, Mr. Joe Harmison, who is in the audience. He is the past president of the Texas Pharmacy Association, the past president of the National Community Pharmacists Association. He is that rare breed, he still owns and operates his own pharmacy. The only thing I can find negative about him is that he graduated from the University of Oklahoma School of Pharmacy back in 1970. Other than that, he is a great guy and a good friend, and I am sure he will be very helpful in his testimony on the second panel.

I might also take personal privilege just to say that Mr. Shimkus, to my right, threw out a runner at third base today in our intersquad game, as we get ready to battle the Democrats who have beat us the last 4 years in the congressional baseball game. So Shimkus is getting in game for that. With that, I yield back.

[The prepared statement of Mr. Barton follows:]

PREPARED STATEMENT OF HON. JOE BARTON

Thank you, Chairman Pitts for holding this hearing. I applaud the Committee's oversight and investigative work on the recent meningitis outbreak. The facts indicate that the Food and Drug Administration did not use its full authority and act quickly against the company compounding and distributing the tainted medication. I look forward to hearing from our witnesses today in the Health Subcommittee to determine what if anything needs to be done legislatively to prevent further harm to innocent Americans.

In particular, I would like to welcome a fellow Texan to the hearing, Mr. Joe Harmison, testifying today on behalf of the National Community Pharmacists Association. I have known Mr. Harmison for twenty years or so and the Committee could not have asked a more respected and experienced pharmacist to come to DC to share the community pharmacy perspective regarding issues relating to drug compounding. I hope he can explain the vital role community pharmacies play in compounding drugs for their patients and the difference between his operation and those of his association versus what was happening at the companies compounding the drugs that caused the recent outbreak.

With that Mr. Chairman, I welcome the witnesses, look forward to the hearing, and yield back.

Mr. PITTS. Chair thanks the gentleman.

Now recognize the ranking member of the subcommittee, Mr. Pallone, 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, Chairman Pitts. I am pleased that the Health Subcommittee is finally having a hearing to examine drug compounding. But, unfortunately, we are months behind. While we are having our first hearing today to gather information on this topic, our colleagues in the Senate have already worked together to

produce and mark up bipartisan legislation in the Health Committee. And so I think this delay is regrettable here.

Access to compounding drugs is crucial for patients who have unique medical needs. We know that the New England Compounding Center that distributed the contaminated compounded product last year, resulting in the meningitis outbreak that claimed over 50 lives and infected over 700 patients, was clearly a bad actor. However, NECC will not be the last bad actor. Similar tragedies will undoubtedly occur again unless we address the significant gaps that exist in the current regulation and oversight system of compounded products. If patients are to have confidence in the safety and quality of these drugs, we must ensure that compounders meet safety and quality standards.

While traditional compounders who mix medications to fill a prescription for a specific person are regulated at the State level, and drug manufacturers are regulated by the Federal Government, there are a growing number of companies that do not fall into either of these categories. Many companies are compounding drugs without prescriptions and shipping large quantities of the products across State lines; in essence, acting more like manufacturers than the traditional compounders. In the absence of clear lines of authority, these companies experience very little State or Federal oversight.

So as we begin to examine drug compounding, I urge my colleagues to use this as an opportunity to move forward to determine what changes are needed rather than looking back and casting blame. We must stop questioning whether the FDA needs new authority. In fact, the past few months of examination by our Oversight Committee and the Senate Health Committee it has become abundantly clear that conflicting court opinions and ambiguous language in the law show that the FDA does not have adequate authority to oversee compounders. And that is why I support efforts to help identify a new category of companies to be subject to Federal regulation and oversight and provide FDA the tools and resources it needs to properly regulate them.

So, Mr. Chairman, I hope today can be the start to this committee coming together in a bipartisan manner to address this issue and create greater clarity in the law so the tragedies like the one involving NECC do not happen again. The American people should know that the drugs that they receive are safe and effective.

So I thank all our witnesses. I know we have a second panel. I look forward to hearing about how Congress can best address the gaps in regulation and oversight that were unfortunately highlighted by the NECC meningitis outbreak and how all stakeholders can work together to protect the public health.

I don't know if anybody wants any of my 2 minutes on my side. You would, Mr. Dingell? I yield to Mr. Dingell.

Mr. DINGELL. I thank the gentleman for yielding. I thank you for having this hearing. I welcome our first panel member today. Good to see her back before the committee.

This committee has a great opportunity. We can quibble all we want about whether we have the authority, whether it is needed or not. Simple fact of the matter is people are dying, people are being made sick. And many people in this compounding industry,

if that is what you want to say it is, have been studying ways to get around food and drug regulation and to continue, for all intents and purposes, becoming manufacturers.

The question is, do we want to persist on that while we engage in a monstrous quibble, or do we want to get down and cut the corners that come from courts and judges trying to resolve a question that is probably well beyond their competency.

Having said these things, I would urge us to move forward on legislation, effective legislation. This committee has a remarkable history in this Congress, which is noteworthy for having done very little, to have in fact moved forward with a number of important pieces of legislation in a bipartisan fashion. I see no reason why we should not continue that kind of effort with all the blessings to the public that that obtains.

So I would urge us to move forward. Let's put these rascals in the compounding industry into a place where they have law to obey, where everyone understands what it is, and where we can make our people safe. My State of Michigan suffered huge losses to people in sickness and death stemming from wrongdoers who were deliberately skating around the law. And unsafe pharmaceuticals well beyond the reach of Food and Drug were in fact poisoning and killing our people.

This is a wonderful opportunity. I commend you for making it possible. I look forward to working with you. I commend my colleague Mr. Pallone for his wise counsel and leadership. And I look forward to working on this matter in an effective way where we do go forward together to solve a major problem for our people. Thank you.

Mr. PITTS. Chair thanks the gentleman.

Now recognize the vice chairman of the subcommittee, Dr. Burgess, 5 minutes for an opening statement.

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

Mr. BURGESS. Thank the chairman for the recognition. And I do support the efforts to examine the role that traditional compounding pharmacists play in the healthcare system. I know the value that they provide, having used them in my practice for a number of years.

But we are also going to hear this morning how this incident necessitates broad new authorities. Recently the Food and Drug Administration has inspected over 50 compounding facilities. You have to ask yourself, by what authority did these 50 inspections occur? If the FDA has the authority today, they had it 6 months ago. The fact is one of the following statements must be true: The agency is acting without authority and risking litigation or they have the authority and have always had the authority and have simply failed to use it.

Documents obtained by the Oversight and Investigations Subcommittee are deeply troubling, and I believe show FDA negligence. New England Compounding Center was making upwards of 30,000 vials of product without prescriptions and yet the Food and Drug Administration questioned whether they had authority under the Food, Drug, and Cosmetic Act over manufacturing?

The Food and Drug Administration was aware that this compounding facility was making poor products for years. They never followed up on warning letters. Frustrated FDA staff could not even warn the State of Massachusetts. Whistleblowers, doctors providing dozens of adverse event reports and law firms dealing with substandard conditions came forward and the FDA did nothing. They didn't even pick up the phone.

This is an example of circling the wagons after the crisis, and this member is having none of it. The bureaucracy held up the guidance for years. Testimony that is as provided through our Oversight and Investigations Subcommittee—the testimony that has been provided to both the Oversight and Investigations Subcommittee and this subcommittee today has been carefully crafted to avoid asking who failed America and who allowed NECC to introduce contaminated product in its supply line.

I cannot in good conscience entertain discussion of legislation when not one person has been fired, reprimanded, or held culpable at the Food and Drug Administration. In fact, legislating transfers the blood of those dead and harmed from the agency responsible to us, the subcommittee and to Congress.

Massachusetts fired people because they should have known, and yet the Food and Drug Administration, who did know, now wants new authority. To what end is new authority going to provide protection to the public if the Food and Drug Administration, by its own admission and track record, refuses to pick up and use the tools they had at their disposal. The Food and Drug Administration refused to go after those operating so far outside the bounds of legality in traditional compounding. Why in the world would we trust them to regulate a legitimate compounder?

Until the agency admits where it failed the American public, I for one am not going to be a party to letting them get away with this dereliction of responsibility. To do otherwise invites further incompetence from one of the most important agencies under our jurisdiction and sets a dangerous precedent for other agencies under our purview.

I would like to yield the balance of the time to the gentleman from Virginia, Mr. Griffith.

Mr. GRIFFITH. Thank you, Dr. Burgess.

Last fall's fungal meningitis outbreak was a true public health crisis for our Nation. In Virginia's Ninth Congressional District, which I represent, there were two deaths and 50 confirmed cases of fungal meningitis associated with the sterile compounded injections from NECC. Approximately 1,400 patients in southwest Virginia were notified they could have been exposed to fungal meningitis because they received tainted steroid injections.

I clearly believe that FDA had the authority they needed to prevent the fungal meningitis outbreak. NECC was a manufacturer. The committee's thorough investigation has demonstrated the agency failed in their oversight and did not pursue regulatory action against NECC and Ameridose, who were acting illegally as manufacturers, not as compounding pharmacies, in violation of the Food, Drug, and Cosmetic Act.

With well over 130 community pharmacists provided invaluable access to health care in rural and remote communities in the

mountains of southwest Virginia, I do not support giving FDA broad new authority over the practice of pharmacy, which is the jurisdiction of our States. The type of compounding that goes on in our local pharmacies involves making special medications subject to the needs of the individuals based on a patient-specific prescription from their physician.

The real problem is large-scale operations like NECC who are acting illegally as drug manufacturers by making large batches of drugs, some of which are just copies of FDA-approved drugs, and then selling and shipping them all over the country.

In her testimony, Dr. Woodcock acknowledges that FDA was in the final stages of publishing new guidance differentiating pharmacy compounding from drug manufacturing. Three years later, FDA finally had all of its ducks in a row and was ready to go forward, but they did not do so in their draft guidance document. I believe there are some areas that need clarification. So we have been doing our due diligence to understand this issue and develop legislation that will make it clear how we define what a compounding pharmacy is, which is and should be regulated by the States, and what a drug manufacturer is, which should be regulated by the FDA.

Yield back.

Mr. PITTS. The chair thanks the gentleman.

That concludes our opening statements. We have two panels today. Our first panel today we have Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research, U.S. Food and Drug Administration.

Thank you for coming, Dr. Woodcock. You will have 5 minutes to summarize your testimony. Your entire written testimony will be placed in the record. You are welcome and recognized for 5 minutes.

STATEMENT OF JANET WOODCOCK, M.D., DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION

Dr. WOODCOCK. Thank you, Mr. Chairman, Vice Chairman, Ranking Member, and members of the committee. Thank you for the opportunity to testify.

This has really been an appalling tragedy of a kind not seen really since the early 1900s, where American citizens were harmed by grossly contaminated drug. But this is just the worst of a long series of outbreaks over the past 2 decades that have involved compounding pharmacies, and these have included multiple deaths, blindness, hospitalizations, and other types of harm. So this was just the worst of a continuing series of outbreaks.

As the Commissioner testified, we should have been more aggressive in applying our existing authorities to this industry, despite the ambiguities in the statute and despite challenges by industry. We are being more aggressive now, and we are inspecting the pharmacies that we know about that present the highest risk. And we are seeing really serious systemic quality issues, particularly around sterility practices.

In light of recent events, though, even with the tragedy that has occurred, some of these firms challenge our authority when we try

to go in and inspect them, and they delay or deny full access to our records. We have twice had to get administrative warrants from the court and have U.S. marshals accompany our inspectors. And we have had to threaten warrants in other cases to get cooperation to inspect these compounding pharmacies. And because we are inspecting and moving aggressively doesn't mean we are going to prevail in court.

Make no mistake, if the approach to this isn't changed, and I think legislation is probably the best approach, we will see more of these tragedies. We are already, since the outbreak, we have seen several episodes involving human harm from compounded products.

Lack of clarity in our statutory authorities really isn't the only concern. The industry has evolved tremendously since the time of the corner pharmacist and traditional compounding in response to a prescription. And this is still going on, and FDA has always said we felt this was appropriate. But another industry has grown up that is basically performing outsourcing for hospitals and making large amounts of dosage forms, often starting with FDA-approved products. And this industry was really never contemplated in the kind of authorities that we have.

So we feel that we need legislation to preserve the benefits of traditional compounding, which is in response to a prescription, and which we are not proposing that we should have authority over, further authority over, while at the same time giving us the right tools to regulate high-risk practices and products. We feel we need legislation that requires compliance with Federal quality standards; requires Federal registration, because right now we don't know who they are, we don't know where they are, and we don't know what they are making; and requires reporting to FDA of adverse events so that we can act before the problems get out of hand. Right now there is no requirement to send us reports of death or other harm that might occur with these products.

And for all pharmacy compounding we feel basic protections should be in place, including the fact that FDA should have access to the records so that we can go in and see whether they are shipping large amounts of product, all right, and what they are doing; and also, should there be an outbreak, we are not delayed by having to go to a marshal and have access to the shipping records.

A prohibition on compounding the most complex and highest-risk products. Our drug manufacturers, as you know, have problems manufacturing certain products because they are very complex, and they put a tremendous amount of science and effort into that. We don't think they should be compounded. That is a small list, but we think that list should be maintained. And clear labeling of compounded drugs to allow prescribers and patients to make more informed choices.

We look forward to working with you to explore funding mechanisms to support this oversight, should it be put in place. Remember, I think it really is a matter of when this is going to occur the next time, not if. That is the state that we are observing of the industry when we are inspecting them. We are all on notice, we owe it to the public and the victims of this incident and the numerous

outbreaks over the years to provide better protection in the future. I look forward to answering your questions.

Mr. PITTS. Thank you, Dr. Woodcock.

[The prepared statement of Dr. Woodcock follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

STATEMENT

OF

JANET WOODCOCK, M.D.

DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH

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 DRUG COMPOUNDING"

May 23, 2013

RELEASE ONLY UPON DELIVERY

INTRODUCTION

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

We are at a critical point where we must work together to improve the safety of drugs produced by compounding pharmacies. As the compounding industry has grown and changed, we have seen too many injuries and deaths over many years caused by unsafe practices. Dr. Margaret Hamburg, Commissioner of Food and Drugs, testified in front of the Oversight and Investigations Subcommittee on April 16, 2013, regarding the emergence of a tragic fungal meningitis outbreak associated with compounded methylprednisolone acetate (MPA), a steroid injectable product distributed by the New England Compounding Center (NECC). To date, that outbreak has been associated with 55 deaths and over 740 people sickened in 20 States. Sadly, NECC was not an isolated incident. Indeed, over the past 20 years we have seen multiple situations where compounded products have caused deaths and serious injuries. For example:

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

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

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

Since the NECC outbreak, ten additional firms have conducted voluntary recalls overseen by FDA of sterile compounded or repackaged drug products as of May 16, 2013. In one recent

incident, the presence of floating particles, later identified to be a fungus, was reported in five bags of magnesium sulfate intravenous solution, resulting in a nationwide recall of all sterile drug products produced by the pharmacy (over 100 products). Fortunately, we have not received reports of patient injury from these products. In another recent recall, all sterile drug products (approximately 60 products) from a second pharmacy were recalled as a result of reports that five patients were diagnosed with serious eye infections associated with the use of repackaged Avastin. Moreover, we believe that presently, there are hundreds of other firms operating as compounding pharmacies, producing what should be sterile products and shipping across State lines in advance of or without a prescription. However, the current legal framework does not provide FDA with the tools needed to identify and appropriately regulate these pharmacies to prevent product contamination.

The history of this issue shows that there is a need for appropriate and effective oversight of this evolving industry. It is clear that the industry and the health care system have evolved and outgrown the law, and FDA's ability to take action against compounding that exceeds the bounds of traditional pharmacy compounding and poses risks to patients has been hampered by limitations and ambiguities in the law, which have led to legal challenges to FDA's authority to inspect pharmacies and take appropriate enforcement actions.

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

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

Using a risk-based model, we identified 29 firms for priority inspections focused on their sterile processing practices. During these 29 inspections, in two instances, FDA identified secondary firms associated with the priority inspections, for a total of 31 firms. We have taken investigators who would normally be doing inspections of conventional drug manufacturers and assigned them to conduct inspections of those pharmacies whose history suggests a greater risk of potential quality issues with their compounded products. We have coordinated our inspections with State officials, who have accompanied our investigators in most cases. At the same time, we have also continued to conduct for-cause inspections, often at the request of our State counterparts who invited us to accompany them on the inspections. Since the fall, FDA has completed 26 for-cause inspections in addition to the 31 described above, as of May 16, 2013. When we identified problems during any of the inspections, at the close of the inspection, we issued an FDA Form 483[1] listing our inspection observations. We have issued an FDA-483 at the close of 47 of the 57 inspections we have conducted since last fall. We have seen some serious issues, including quality concerns that have led to product recalls. Observations have included: lack of appropriate air filtration systems, insufficient microbiological testing, and other practices that create risk of contamination.

Notably, even in light of recent events, and even though we are often working with the State inspectors, our investigators' efforts are being delayed because they are denied full access to records at some of the facilities they are inspecting. Just during the recent inspections, several

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

pharmacies delayed or refused FDA access to records, and FDA had to seek administrative warrants in two cases. And although we have been able to eventually conduct the inspections and collect the records that we have sought, our ability to take effective regulatory action to obtain lasting corrective action with regard to substandard sterility practices remains to be seen.

As we have noted in the past, our ability to take action against inappropriate compounding practices has been hampered by ambiguities regarding FDA's enforcement authority, legal challenges, and adverse court decisions, and we have learned that the law is not well-suited to effectively regulate this evolving industry. For example, hospitals have come to rely on compounding pharmacies that function as "outsourcers" producing sterile drugs previously made by hospital in-house pharmacies. If FDA brings charges against a pharmacy, alleging that it is manufacturing a "new drug" that cannot be marketed without an approved application, the pharmacy will have to either obtain individual patient-specific prescriptions for all of its products or stop distributing the products until it obtains approved new drug applications for them, something most outsourcers are unlikely to do. Several of the pharmacies FDA inspected are some of the largest outsourcers in the country. These pharmacies supply large numbers of sterile drugs produced in relatively large quantities to hospitals nationwide, and a shut-down at these firms is likely to cause disruptions in the supply of drugs to hospitals and other health care providers. FDA should have more tailored authorities appropriate for this type of compounding pharmacy.

In the Commissioner's appearances before the Committee on Energy and Commerce in November 2012 and April 2013, she presented a framework that could serve as a basis for the development of a risk-based program to better protect the public health, improve accountability, and provide more appropriate and stronger tools for overseeing this evolving industry. Since

November, we have met with over 50 stakeholder groups, including pharmacy, medical, hospital, payer, and consumer groups, and State regulators, to help further our understanding and inform our framework. Today, I will first provide background on FDA's current legal authority over compounded drugs, then review that framework, and suggest specific actions that Congress can take to help us better do our job and prevent future tragedies like this one.

FDA's Legal Authority over Compounded Drugs

FDA regards traditional pharmacy compounding as the combining or altering of ingredients by a licensed pharmacist, in response to a licensed practitioner's prescription for an individual patient, which produces a medication tailored to that patient's special medical needs. In its simplest form, traditional compounding may involve reformulating a drug, for example, by removing a dye or preservative in response to a patient allergy. It may also involve making an alternative dosage form such as a suspension or suppository for a child or elderly patient who has difficulty swallowing a tablet. FDA believes that pharmacists engaging in traditional compounding provide a valuable medical service that is an important component of our health care system. However, by the early 1990s, some pharmacies had begun producing drugs beyond what had historically been done within traditional compounding.

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

The compounding industry objected to this approach and several bills were introduced, some with significant support, to limit the Agency's oversight of compounding.[2] In November 1997, S. 830, the Food and Drug Administration Modernization Act of 1997 (FDAMA), was signed into law as Public Law 105-115.[3] FDAMA added Section 503A to the FD&C Act, to address FDA's authority over compounded drugs.[4] Section 503A exempts compounded drugs from three critical provisions of the FD&C Act: the premarket approval requirement for "new drugs"; the requirement that a drug be made in compliance with current good manufacturing practice (cGMP) standards; and the requirement that the drug bear adequate directions for use, provided certain conditions are met. These provisions were the subject of subsequent court challenges, which have produced conflicting case law and amplified the perceived limitations and ambiguity associated with FDA's enforcement authority over compounding pharmacies. In 2002, immediately after a Supreme Court ruling that invalidated the advertising provisions of Section 503A, FDA issued a revised compliance policy guide on compounding human drugs. Several additional legal challenges and court decisions then followed. More recently, FDA made significant progress toward issuing another CPG. In fact, FDA was on track to publish a revised draft CPG in the fall of 2012, but the fungal meningitis outbreak intervened and we are now reevaluating the draft. It is important to note, however, that a CPG is not binding on industry and updating the CPG would not alleviate all issues with Section 503A.

A look at FDA's attempts to address compounding over the last 20 years shows numerous approaches that were derailed by constant challenges to the law. As a result, presently, it is unclear where in the country Section 503A is in effect, and Section 503A itself includes several

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

[3] Public Law 105-115, FDAMA, 111 Stat. 2296 (Nov. 21, 1997), available at *http://www.gpo.gov/fdsys/pkg/PLAW-105publ115/pdf/PLAW-105publ115.pdf*

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

Apart from Section 503A, there are additional provisions in the statute that have impeded effective pharmacy compounding regulation. For example, if certain criteria are met, the FD&C Act exempts compounding pharmacies from registration and the obligation to permit access to records during an inspection. As a result, FDA has limited knowledge of pharmacy compounders and compounding practices and limited ability to oversee their activities.

Looking Ahead

The Administration is committed to working with Congress to address the threat to public health from limitations in authorities for effective oversight of certain compounding practices. To that end, FDA has developed a framework that could serve as the basis for the development of a risk-based program to protect the public health.

Risk-based Framework

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

Further, we believe there should be a distinction between two categories of compounding: traditional and non-traditional. Traditional compounding would include the combining, mixing,

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[4] Id.

or altering of ingredients to create a customized medication for an individual patient with an individualized medical need for the compounded product, in response to a valid patient-specific prescription or order from a licensed practitioner documenting such medical need. Traditional compounding, while posing some risk, plays an important role in the health care system, and should remain the subject of State regulation of the practice of pharmacy.

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

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

In addition, FDA believes that with noted exceptions, certain products are not appropriate for compounding under any circumstances. These products would include: 1) what are essentially copies of FDA-approved drugs, absent a shortage justification based on the drug appearing on

FDA's shortage list; and 2) complex dosage forms such as extended release products; transdermal patches; liposomal products; most biologics; and other products as designated by FDA. Producing complex dosage forms would require an approved application and compliance with cGMP standards, along with other requirements applicable to manufactured drug products.

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

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

CONCLUSION

Given our experiences over the past 20 years and the recent fungal meningitis outbreak, we must do everything we can to clarify and strengthen FDA's authority in this area.

I am happy to answer any questions you may have.

Mr. PITTS. I will begin the questioning and recognize myself for 5 minutes for that purpose.

Dr. Woodcock, since the outbreak, the FDA has executed dozens of inspections and at least 11 companies were ordered to stop producing some or all drugs. Have any of the companies you inspected challenged the FDA authority? If so, how many?

Dr. WOODCOCK. Certainly, as I said, we have had several challenge our authority to even go in the firm and look at their records. Others have challenged and then yielded when we got the lawyers talking to one another. Now, as far as whether there will be court challenges, that is something I really can't speak to. But that certainly has been the history in the past.

Mr. PITTS. Can you provide a list to the committee of the companies who you have inspected and who have challenged your authority?

Dr. WOODCOCK. We will be happy to do so.

Mr. PITTS. According to the Senate HELP report, I quote, "As a result of increased oversight from both State and Federal regulators, at least 48 compounding companies have been found to be producing and selling drugs that are contaminated or were created in unsafe conditions or otherwise violate State licensing requirements. Ten companies have issued nationwide recalls of drugs compounded at their facilities. In at least four cases, the recall was issued in response to documentation of actual contamination. Further, 11 compounding pharmacies have been ordered to cease and desist operations, including two of those that had issued nationwide recalls."

Now, as you said, some of these companies challenged the FDA's authority. Can you explain how State and Federal regulators executed this increased oversight?

Dr. WOODCOCK. Well, we identified firms that we knew about basically from adverse event reports, from reports in the paper, from advertisements they had on a Web page and so forth, and we did a risk-based approach to inspecting what we felt were the highest-risk firms, based on what we knew. We don't know the whole universe of firms that are out there.

We also continue to do for-cause inspections. For example, if we get a report from a health department about a cluster of cases of an outbreak of one sort or another, we will immediately go into that pharmacy and inspect them. In all of those for-cause cases, we have gone in with the State authority. So we have gone in together, all right. And in most of the other inspections that we did that we planned, the 31 inspections, we have gone in with the State authorities as well.

Mr. PITTS. What were the biggest challenges that you faced during that period?

Dr. WOODCOCK. Well, the challenges mainly were getting access in some cases to be allowed to inspect, all right, particularly some of their records. But the real thing that we have found is that the aseptic processing practices, which means how you try to make a drug to ensure that it is sterile, are not anywhere near the quality that is necessary to mass produce sterile drugs. There is a tremendous deficit of quality in their practices that almost assure that these drugs will at some point be contaminated.

Mr. PITTS. What are some of the lessons the agency has learned during the period of this outbreak?

Dr. WOODCOCK. Well, I think we have learned that there are pervasive practices that are unsafe that are going on across the portion of this industry that we have investigated. Primarily, we are targeting those sterile manufacturers because that is the highest risk when you are actually injecting drugs into the body. So that is one thing we have learned, is the pervasive nature of unsafe practices across the section of industry that we have inspected.

Mr. PITTS. In your testimony you reference nine separate incidents where compounded products caused deaths and serious injuries. Explain briefly the actions the FDA took following each of these incidents.

Dr. WOODCOCK. Well, over the years, our actions have been primarily reactive. OK. So when we have learned of an outbreak, as I said, we have gone in. Often we go in with the State. The State, because they hold the pharmacy license, they are able to shut down the firm right away. Like that is how those 11 firms you referred to were shut down. OK.

We have to call for and we often do talk to the firm and say we are going to go to the press if you don't do a recall, because we don't have the authority—they don't hold a license with us, so we can't just shut them down. We would have to then go court if they still refused to shut down their operations.

Mr. PITTS. My time has expired. Chair recognize the ranking member 5 minutes for questions.

Mr. PALLONE. Thank you. Dr. Woodcock, your testimony mentions the various court challenges that the compounding industry has brought over the years regarding FDA's authority over compounding pharmacies. But I would like to learn more about that litigation and the impact it has had on FDA's ability to oversee the industry.

Those cases center around Section 503A of the act, which was enacted as part of the 1997 FDA Modernization Act. And that law attempted to delineate when compounded drugs were new drugs and therefore subject to FDA regulation. Section 503A also restricted compounding pharmacies' right to advertise.

So I am going to put a map of the U.S. up on the monitors here. It is up there. This map was not prepared by me or my staff, it was actually prepared by the International Association of Compounding Pharmacies, the main compounding industry lobbying group. On this map, the red States and blue States do not represent States that voted Democrat or Republican. They represent the different rules under which compounding pharmacies operate.

So let's look at the red States. Those represent the Ninth Circuit Court, whose jurisdiction includes the Western States. And as IACP notes on this chart, in 2001, the Ninth Circuit Court ruled that the advertising component of Section 503A was unconstitutional and that the rest of 503A was void because it was inextricably tied to the advertising component, or that it was not severable, as we say. Is that correct?

Dr. WOODCOCK. Yes.

Mr. PALLONE. OK. Then in 2002, the Supreme Court agreed with the Ninth Circuit that the advertising ban was not constitutional, but the Court did not address the question of whether that ban could be severed from the rest of Section 503A. The result of that decision then was that the advertising ban was unconstitutional throughout the country, and the entirety of Section 503A remained invalid in those red States on the map. The Supreme Court decision also meant that whether the remaining parts of Section 503A was effective in the rest of the country was an open question. Is that your understanding?

Dr. WOODCOCK. That is my understanding.

Mr. PALLONE. So let's look now at the blue States on the map, Texas, Louisiana, and Mississippi. Those States represent the Fifth Circuit. 2008, the Fifth Circuit Court of Appeals held that the unconstitutionality advertising restrictions did not affect the standing of the rest of Section 503A. So that means that in Texas, Louisiana, and Mississippi, Section 503A is in effect. Am I correct on that?

Dr. WOODCOCK. That is my understanding.

Mr. PALLONE. And am I correct that the gray States on the map then represent the rest of the country, where we just don't know how courts would rule on whether Section 503A, apart from the advertising restriction, is or is not in effect?

Can you tell us what the impact of this 503A patchwork has been on FDA's ability to oversee the compounding industry? Have compounding pharmacies been able to take advantage of this confusion over the law to block FDA's ability to aggressively enforce the court authority it does have over compounders?

Dr. WOODCOCK. Yes, I think that definitely contributed to the inability of FDA to have an effective regulatory program. All right. We have different circuits with different meanings of the statute that was passed by Congress in 1997. In some areas, the statute is thrown out; in other areas, it is partially operational; in other areas, we don't know if we went to court what type of decision we would get.

Mr. PALLONE. So this seems to me to be all that we as Members of Congress need to see to understand the dire need for clarifying the FDA's authorities here. What I don't understand is I am hearing from the GOP here on the committee that they don't seem to want to give the FDA additional authority even though the Senate passed a bill on a bipartisan basis that does. And yet I don't see any alternative.

In 1997, for better or worse, Congress spelled FDA's authorities over compounding pharmacies. I think that law is out of date and should be updated. But putting that aside, courts have invalidated that statute, our statute, in a major swathe of the country. I think it is irresponsible for us to stand by and expect FDA to cobble together a piecemeal approach to regulating the practice of compounding pharmacy, a practice that, as evidenced by the NECC, bears great risk for patients all over the country.

I don't quite understand why my colleagues on the other side, at least here in the House, not in the Senate, don't want to step in and clarify the rules of the road. I think we have to do that, otherwise we are going to continue to have these problems with

compounding pharmacies. And I hate to say anything positive about the Senate, but they are moving in that direction and we need to do the same.

Thank you.

Mr. PITTS. We are presently voting on the floor. We have two votes. We will recess until the second vote is over and then reconvene. We will have another series of vote around noon. So if you can stay, Dr. Woodcock, we will recess at this time for floor votes and be back as soon as the members finish their second vote.

[Recess.]

Mr. PITTS. Time of our recess having expired, we will reconvene and continue our Q&A session. Chair recognize the vice chair of the subcommittee, Dr. Burgess, 5 minutes for questions.

Mr. BURGESS. I thank the chairman.

And thank you, Dr. Woodcock, again for being here.

So between 2002 and 2012, according to our investigation on Oversight and Investigations Subcommittee, the New England Compounding Center was the subject of at least 52 adverse event reports. Numerous offenses documented throughout the investigation that was undertaken by both FDA and State regulators.

So, you know, the big question is, why not do something? Why not take action? And to tell you the truth, it was a little hard to read through some of the emails that we finally got. Your folks were literally pulling their hair out about we can't just send another warning letter, we have already sent one to which it took us 2 years to respond and we will have to do something. And it was like they got right up to the point of having to do something and then no one wanted to do it. Is that an unfair assessment.

Dr. WOODCOCK. Well, I am unable to comment specifically on NECC because of the ongoing criminal investigation. However, generally, I would say we should have been more aggressive overall in this industry. There was a pattern for many firms that we were looking at of adverse events. And, as I said, there were a series of outbreaks. Every year, practically, we would have an outbreak due to contaminated compounded product, and we should have been more aggressive in going after this industry.

Mr. BURGESS. Well, again, I just don't understand some of your folks. They just had to be losing their minds over this stuff. Samia Nasr, a name kept coming up in the emails that were provided to us. Does she still work at the agency?

Dr. WOODCOCK. Yes.

Mr. BURGESS. I know you can't comment on employment. But, I mean, I think she did the right thing to bring all these things to people's attention, but it must have driven her crazy that the people just above her wouldn't do something.

Dr. WOODCOCK. As I said, overall, we should have been more aggressive as this industry continued to be responsible for outbreaks. We investigated outbreaks, we investigated reports, and we did respond reactively to problems. But we did not proactively do everything we could.

Mr. BURGESS. And as a consequence you had 50 deaths and 500 people who are living with long-term disability as a consequence of the Exserohilum in the betamethasone.

Dr. WOODCOCK. Well, we have more people who have died than that. We have people blinded. We have people with disabilities as a result of these outbreaks over the last 12 years. And I would say, frankly, if you want my opinion, that we could have done more——

Mr. BURGESS. I do.

Dr. WOODCOCK [continuing]. The States should have done more, and Congress could have intervened when these statutes were struck down.

Mr. BURGESS. You know, and the ranking member had a nice map up there. He made a nice little comment about red and blue States. But, honestly, the 503A limitation doesn't affect Massachusetts at all. I mean, we are talking about Texas and California, Fifth Circuit, Ninth Circuit, but Massachusetts is outside that. So what prevented you in Massachusetts?

Dr. WOODCOCK. As I said, I can't specifically discuss this particular case because of the ongoing investigation.

Mr. BURGESS. OK.

Let me ask you this: How difficult is it to get an injunction from a judge? You go a judge and say, we have got a problem here. How difficult is it to get an injunction?

Dr. WOODCOCK. We, as I understand it, I am not one of the agency lawyers, I am a physician, as you know, but we make a recommendation to the Justice Department, who then proceeds to do the legal activities. And just because we initiate legal action doesn't necessarily mean we will prevail in court.

Mr. BURGESS. How many times have you not prevailed?

Dr. WOODCOCK. I don't know. We can get back to you.

Mr. BURGESS. Would you get us that information?

Dr. WOODCOCK. Absolutely.

Mr. BURGESS. Out of all of the challenges that you have submitted to companies, how many have actually stood up to you and said, we don't want to do it?

Dr. WOODCOCK. I think there are—we do bring our cases that have the best facts, all right, as we sort through the cases we put forth those that have the best facts that we would be most likely to win.

Mr. BURGESS. Well, again, it is just so frustrating to think that the guidance that supposedly was going to come out, that was going to solve this problem, just really seemed to be enmeshed in the bureaucracy for 3 years. Is that a fair time length?

Dr. WOODCOCK. I think that is fair. However, that was trying to make the best of a bad situation. We do not have the tools that fit this industry, right?

Mr. BURGESS. You know what? I disagree. Because do you not have power under the Food, Drug, and Cosmetic Act to regulate manufacturers?

Dr. WOODCOCK. Yes.

Mr. BURGESS. You define manufacturers. Someone is making 30,000 vials of stuff a month, is that a manufacturer?

Dr. WOODCOCK. Well, say, if I am Janet the pharmacist, all right, and I have a pharmacy that is licensed in a State, right, and I am compounding drugs, right, and then I decide, well, I want to broaden my activities, and my State allows the anticipatory compounding and my State allows office stock, right, so I can com-

pound those in advance of or without a prescription and send them. And there is no——

Mr. BURGESS. 30,000 vials a month?

Dr. WOODCOCK. There is no—what is the number? That is the thing we have been struggling with for 12 years. Is it 10 vials? Is it 1,000 vials?

Mr. BURGESS. Well, let me ask you this question.

Dr. WOODCOCK. There is no volume limit in the statute. Excuse me for interrupting you.

Mr. BURGESS. Well, Massachusetts Board of Pharmacy fired people. Is the Food and Drug Administration going to let anyone go?

Dr. WOODCOCK. No.

Mr. BURGESS. No?

Dr. WOODCOCK. No.

Mr. BURGESS. I yield back, Mr. Chairman.

Mr. PITTS. Chair thanks the gentleman.

Now recognize the gentlelady from Florida, Ms. Castor, 5 minutes for questions.

Ms. CASTOR. Thank you very much.

I wanted to get just to that point. Where do we draw the line? Because I think as legislation is developed, and your testimony is that you do not want and it is not appropriate to capture the community pharmacists who are compounding——

Dr. WOODCOCK. That is correct.

Ms. CASTOR [continuing]. And that is not the source of problems. So where do you recommend the dividing line should be? What is the criteria in law? Has the Senate addressed this in their bill? Where do they carve out so that the community pharmacists that are compounding are protected and others that have exceeded that and are really the large-scale manufacturers, how do we develop that criteria?

Dr. WOODCOCK. Well, the Senate is attempting to set forth a framework, and we feel they are going in the right direction. But those clear lines between who is a drug manufacturer, who is a traditional compounder, and who is the new category of compounding manufacturing, we still feel are not clear enough. So that we could have people masquerading—and some of the other witnesses I think are going to talk about this, by my reading of their testimony, OK—that we could have people masquerading as traditional compounders or as compounding manufacturers who really were competing with the generic drug industry or the innovator drug industry and actually should have sent us applications and paid a user fee and gone through the established process that we have had in the United States since 1962. And so that is really the issue, is how do you draw those boundaries.

Ms. CASTOR. And what are your recommendations then?

Dr. WOODCOCK. Well, what we had proposed is that we pick off the highest risk category, which is those sterile products that are shipped interstate. All right. So they are shipped around the country. That is probably the highest risk, because the longer you store the sterile product the more likely, if they are contaminated, that there will growths that can grow up. And obviously sterile products are a high risk. And interstate is one sort of marker for volume.

And this industry that has grown up, the outsourcing industry is valuable to hospitals. We have heard from the hospitals. They feel they can't do without these folk. And they generally take FDA-approved products and they mix them or they put into convenience dosage forms. If you have gone to a clinic in an office building and you have had a procedure, you may have received products from one of these firms that put you to sleep or whatever. And they package them, say, in syringes and so forth and send them to these various clinics and also to hospitals.

We feel that type of industry, they produce in pretty high volume that is the highest risk. And they should have full aseptic processing controls, just like the regular drug industry does. So we agree with carving them out and having certain requirements for them, but not submitting a new drug application, having to pay a user fee, and going through that entire process.

Ms. CASTOR. So highest risk, crossing State lines.

Dr. WOODCOCK. State lines.

Ms. CASTOR. Sterile products.

Dr. WOODCOCK. Right.

Ms. CASTOR. You recommend. And then to clarify your last part regarding—what if it is a compounding that is going to hospitals within a State.

Dr. WOODCOCK. Well, what we propose is that would be regulated by the States. The States could decide whether they have capacity to do that. I think you may hear from some of the other witnesses that in fact that type of compounding, especially at volume, because it is the mass production that really increases the risk, both the risk of contamination and the consequences of contamination once it occurs, because it goes to so many people, right, and the risk is there for intrastate, but the States we feel could decide whether they would regulate those type of activities or not permit them, right.

And then the traditional compounding is really where a doctor—and I have done this too, all right—a doctor writes a prescription to a pharmacy and asks them to, for an individual patient who has a specific need, to make a dosage form that isn't available commercially because they have a very specific medical need for that. We feel that should be preserved, but a box should be put around it and there shouldn't be competition with established generic products. Because there is always more risk than for a regular product for any of these compounded products.

Ms. CASTOR. Thank you very much.

Mr. PITTS. Chair thanks the gentlelady.

Now recognize the chair emeritus of the full committee, Mr. Barton, for 5 minutes for questions.

Mr. BARTON. Thank you, Chairman Pitts.

I have very troubled, Dr. Woodcock, by your opening statement. I do give you credit for integrity and honesty and forthrightness. But you ended up saying that it is not if this is going to happen again, it is when it is going to happen. That is pretty strong. You are talking about people dying.

And I have attended, not in their entirety, but I have attended every hearing that we have done on this issue with NECC. And it is not that Republicans are not willing to regulate, it is not that

we are not concerned. It is that we do think there is a true State-Federal partnership, and we do think that State regulatory authority is as good as Federal if it is within the State. And we don't see a reason to preempt the States unless the States either can't do it or won't do it.

And what struck me in the answers to Dr. Burgess' questions was at some point in the process anybody at the FDA could have picked up the phone and called the State regulatory authority and apparently never did.

Now, I don't understand that. If you really believe that what you said is true, that it is not if it is going to happen again, it is when it is going to happen again, if you have a list of compounders that you think are problematic or in danger of actually endangering human life, if you really think the FDA doesn't have the authority to shut those people down or make them clean up their act, you have an obligation, or somebody that is designated by you, to call the State regulatory authority to inform them of the problem and to take whatever steps are necessary to make sure that the State does.

Now, why haven't you done that? Or why haven't people at your agency done that? That is what I don't understand.

Dr. WOODCOCK. We have done that more recently. And we have, as I said, we have worked hand in glove with the State authorities. We have done joint inspections with them. They have taken the steps to close down many of these pharmacies after the inspection. And we are sending them our findings, we send them letters. We post our 483s, which are our findings of the inspection, so they that are available to the public. And we work very closely with the State authorities.

However, there are 23,000 compounding pharmacies in the United States, according to the industry. They don't have to tell us who they are and they don't have to report to us if they have problems. So we are——

Mr. BARTON. Well, but they can't operate if they don't tell you or don't tell the State. You are not telling me there are 23,000 compounding pharmacists that are operating out in the ether and that are not subject or not licensed by somebody.

Dr. WOODCOCK. They are licensed by States. They are licensed pharmacies. And I read a report by some of the members who looked at what amount of control and tracking the States have over the different pharmacies, and many States do not have a lot of understanding of what activities those pharmacies are engaged in, particularly whether they are shipping to other States and so forth. Different patterns in different States, but not all States really have close control over what those pharmacies are doing as far as compounding.

Mr. BARTON. Well, the witness that is in my district, Mr. Harmison, I have been in his pharmacy. I mean, he is the true small independent businessman. He has got a compounding room, I think one or two rooms, and has two or three pharmacists, including himself.

Now, I have also been in other compounding pharmacist situations in Texas where they have 10 or 15. And it is much more of a mass production-type situation. So there is a difference. But the

FDA, in conjunction with the States, should be able to determine who has jurisdiction and what needs to be done.

I don't think Mr. Pitts or Mr. Upton or any of the Republicans are unwilling to sit down and help clarify, to use your term, what needs to be done. If there truly is a gap and it truly is best to regulate at the Federal level, I would say that the Republicans are open to it. But if it is simply a question of communication between the Federal Government and the State regulatory authority, I would encourage you to facilitate that communication, because I don't want "if" to become "when."

Dr. WOODCOCK. Right. Well, we had a 50–State meeting. We have been in close contact with the Association of National Boards of Pharmacy. So we are talking to them twice a week. We are talking to all the State boards in the States where we go in and have these inspections. And, as I said, we do the inspections with them.

We have heard from many States that they would prefer Federal regulation of these larger-scale facilities. But the real question here is and has always been the question is where to draw the line. All right. So you have the traditional pharmacist, they are compounding in response to a prescription. I, as a physician, I have written prescriptions for compounded products that were very valuable to my patients. That is one. All right. And you mentioned, OK, then there is somebody, if they have five rooms——

Mr. BARTON. My time has expired, and the chairman has been very gracious. We can work on helping define and helping to clarify. I think there is a bipartisan trust on this committee and this subcommittee that can do that, if you and the stakeholders will begin to communicate with each other. I think this is a solvable problem. But it is not necessarily the answer it is going to be more Federal regulation. It may be, but it is not automatic that it will be.

With that, Mr. Chairman, thanks your time, and I yield back.

Mr. PITTS. Chair thanks the gentleman.

And now recognize the ranking member emeritus of the full committee, Mr. Dingell, 5 minutes for questions.

Mr. DINGELL. You are most courteous. Thank you, Mr. Chairman. I ask unanimous consent to insert 2 letters which I wrote to FDA in the record——

Mr. PITTS. Without objection, so ordered.

Mr. DINGELL [continuing]. As well as responses from FDA. And I thank you, Mr. Chairman.

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

Mr. DINGELL. Now, these questions will be mostly yes or no. Does FDA have the authority to require all compounding pharmacies to register with the agency?

Dr. WOODCOCK. No.

Mr. DINGELL. Yes or no?

Dr. WOODCOCK. No.

Mr. DINGELL. Please submit for the record the new authority that you need.

Next question: Does FDA have the authority to require all compounding pharmacies to report adverse events?

Dr. WOODCOCK. No.

Mr. DINGELL. What authority is needed? Submit for the record, please.

Does FDA have the authority to require all compounding pharmacies to follow good manufacturing practices? Yes or no?

Dr. WOODCOCK. No.

Mr. DINGELL. What authority is needed? Submit it for the record.

Question four: Does FDA believe nontraditional compounders should be subject to appropriate good manufacturing practices the way manufacturers are? Yes or no?

Dr. WOODCOCK. Yes, as appropriate.

Mr. DINGELL. What is the authority which is needed? Submit for the record.

Does FDA believe risk-based inspection schedules are appropriate for nontraditional compounders? Yes or no?

Dr. WOODCOCK. Yes.

Mr. DINGELL. What authorities do you need to achieve that end? Submit for the record.

Does FDA have full authority to see all records when inspecting a compounding pharmacy? Yes or no?

Dr. WOODCOCK. I think that is being contested, as you know.

Mr. DINGELL. Yes, you have that problem between the different circuits.

Dr. WOODCOCK. Yes.

Mr. DINGELL. Plus submit to us what authority is needed.

Does FDA need additional authorities in these areas to ensure that outbreaks of the kind we have seen does not happen again? Yes or no?

Dr. WOODCOCK. Yes.

Mr. DINGELL. Yesterday, my colleagues in the Senate advanced bipartisan legislation giving FDA more authority over compounding pharmacies. It is my hope we in the House will do the same thing. I have long believed that we must provide agencies like FDA with clear authorities and necessary responses to properly help and to carry forward their mission. U.S. FDA has a fee system for the approval of pharmaceuticals and medical devices, amongst others. Please inform us whether you need that kind of authority, for purposes of the record.

Now, if we gave FDA the authority in this area, and I believe we should, I believe we also should have a strong user fee program. Would you submit for the record some information justifying such thing if you believe that is appropriate, Doctor.

Dr. WOODCOCK. Yes.

Mr. DINGELL. Now, would the user fee contained in the Senate bill provide the FDA with the necessary resources to carry out these new authorities? Yes or no?

Dr. WOODCOCK. Partially, 50 percent.

Mr. DINGELL. OK. Now, I have got just a little bit of time left. I am reminded of the situation we have here. We have got people being killed because we have unclear authorities. We have a responsibility to see to it that we clarify that as a part of our oversight responsibilities.

There is a great joke that they tell about a fellow who got a letter from an undertaker saying that his mother, or his mother-in-law, had just had a stroke and passed on. And he asked for instruc-

tions. He said should we cremate, should we bury, or should we embalm. And the guy thought for only a second and he sent back a telegram saying, do all three, take no chances.

Now, I think here we have got a problem where people are being killed by a dichotomy in the industry. And, Doctor, I want you to tell me, you have roughly three classes of compounders. Right? You have got essentially the manufacturing compounders who ship all over the country, huge volumes. Right?

Dr. WOODCOCK. Correct.

Mr. DINGELL. You don't have very clear authority over them, do you?

Dr. WOODCOCK. No.

Mr. DINGELL. And the States don't have the resources to do it, do they?

Dr. WOODCOCK. That has been documented.

Mr. DINGELL. OK. Now, having said that, you also have the ordinary pharmacies. We are not particularly after them. And they are supposed to be regulated by the States. They are licensed by the States. And they are identified by State regulations to the States. Right?

Dr. WOODCOCK. Yes. We believe the traditional practice of pharmacy compounding should be preserved and regulated by the States.

Mr. DINGELL. OK. Now, then we have the additional situation where you have the hospitals. And they have either in-house or they have people who contract with them to compound them to meet the specific needs of patients in the hospitals. Right?

Dr. WOODCOCK. Correct.

Mr. DINGELL. What authorities do you need there?

Dr. WOODCOCK. Well, we believe that the hospitals could operate under the regular rules of pharmacy. These are hospital pharmacies that are licensed by the State and also regulated by other authorities. We believe that outsourced contractors should be regulated under the compounding manufacturing.

Mr. DINGELL. So here now you have a muddled situation where the courts are getting in and assisting us to confuse an already obfuscated situation, and we need to do something to clarify it. And since the great events in Michigan, where a bunch of my constituents and others were killed, we have seen that the compounders have continued their same merry practices of disregarding the law and proceeding to send noxious compounds around that are compounded in unsafe atmospheres and climates. Is that right?

Dr. WOODCOCK. We have seen since the outbreak——

Mr. DINGELL. Yes or no?

Dr. WOODCOCK. Yes. Yes.

Mr. DINGELL. Mr. Chairman, I have used 44 seconds too many. Thank you.

Mr. PITTS. Chair thanks the gentleman.

Now recognize the gentleman from Virginia, Mr. Griffith, 5 minutes for questions. Mr. Griffith, you are recognized for 5 minutes.

Mr. GRIFFITH. Thank you, Mr. Chairman.

Thank you, Dr. Woodcock.

I am looking at your draft, not for implementation report on pharmacy compounding that was done in August of this year, and

I want to clarify this court issue. Disagree with me and tell me yes or no, I will ask you at the end of each part of this. But it appears that in April of 2002, based on this report, and I believe it to be correct, that the U.S. Supreme Court affirmed the Ninth Court's decision related to advertising and solicitation, but did not take up the severability as to whether or not the rest of the act would be in place after that date. Is that correct?

Dr. WOODCOCK. My understanding, yes.

Mr. GRIFFITH. And is it also correct that the Fifth Circuit found it was severable, and that decision came out in 2008?

Dr. WOODCOCK. Correct.

Mr. GRIFFITH. The FDA took no action—am I correct the FDA took no action to clarify the law between 2002 and 2008 when the Fifth Circuit came out with their opinion, isn't that correct? Yes or no.

Dr. WOODCOCK. Yes.

Mr. GRIFFITH. And it would also be correct that from 2008 until the incident with the fungal meningitis, the FDA never came to Congress and said we need clarification, isn't that true? Yes or no.

Dr. WOODCOCK. Yes.

Mr. GRIFFITH. And isn't it true that you were working on these draft guidelines because you believe there was a way to figure out around the court decision issue and regulate to the best of your ability with the Ninth Circuit being a little more difficult but that is why you worked on these guidelines for over 3 years; isn't that correct?

Dr. WOODCOCK. As I said, we were trying to make the best of a bad situation.

Mr. GRIFFITH. Wouldn't the right thing to have done to have come for clarification on the severability and just reenact the old law and take the advertising section out, the only part that any court said actually violated the Constitution and the whole issue was severability; wouldn't that have been the better thing to do from 2002 until 2012?

Dr. WOODCOCK. Yes, I think in retrospect that would have been better. I think there was a fear getting a worse——

Mr. GRIFFITH. Was there a fear of coming to Congress and asking for help when you needed it?

Dr. WOODCOCK. Well, you know, the late Senator Kennedy did develop a bill and asked around about it with some other Senators and there was so much opposition that they never introduced that. And I think that was——

Mr. GRIFFITH. Did the bill do anything other than clarify that the bill could be severed and that the only parts that weren't in place or should be in place were the advertising restrictions?

Dr. WOODCOCK. I am not familiar with what exactly it is.

Mr. GRIFFITH. Because I don't know what was in that bill and I suspect there was something other than clarifying the law was in there.

Dr. WOODCOCK. Oh, yes.

Mr. GRIFFITH. And I would have to say in the draft guidance that you all were about to propose the FDA defined a new framework for compounded drugs that would be administered in a health care setting and basically what you proposed was was that you could

compound for more than one patient in the hospital setting or in a medical practice setting as long as there was a prescription that followed if you knew you were going to use it in like in an ophthalmological setting or in a hospital setting as long as you could tie that later to a direct patient, isn't that correct?

Dr. WOODCOCK. That is my understanding.

Mr. GRIFFITH. And so under that reading of that, other than clarifying that the advertising section is no longer the law, you really didn't need any new authority to do that, did you?

Dr. WOODCOCK. To make that interpretation?

Mr. GRIFFITH. Yes or no? To make the interpretation.

Dr. WOODCOCK. I don't understand your question.

Mr. GRIFFITH. It is in your guidance request so I assume that is correct. Is that correct?

Dr. WOODCOCK. That is correct.

Mr. GRIFFITH. And I appreciate that. And I am looking up to see how much time I have left.

We also have this business about talking to the States. There is nothing that prohibited you in the law from talking to the States when you got complaints from say Colorado or Ohio, which actually happened in the NECC case, nothing prevented you from calling Massachusetts, did it?

Dr. WOODCOCK. No.

Mr. GRIFFITH. And, in fact, in the guidelines you are setting up a new way to make that work so it is efficient, isn't that correct?

Dr. WOODCOCK. The guidelines——

Mr. GRIFFITH. The guidelines of sharing information between the States and making sure that everybody is keeping an eye on these folks.

Dr. WOODCOCK. The guidance, hmm, yes.

Mr. GRIFFITH. So you didn't need any new authority to do that, did you?

Dr. WOODCOCK. We don't need authority to talk to the States. We do that all the time in many different areas of regulation.

Mr. GRIFFITH. But you failed to do that in the NECC matter, and I guess my concern is, is that while I too have learned to respect your veracity and think you are a great witness, much better than that other lady that came in here, we couldn't get anything straight out of her, so I do appreciate it—but I would have to say that one of my concerns is that the FDA had all these tools available to it, if it had chosen to do so and I understand people make mistakes, things happen, I understand that, I am not being critical, but instead of asking for new authority shouldn't we just clarify the fact that the advertising restrictions aren't the law, and that if there are areas that need to be clarified, not giving new authority but just clarifying some things, that we could follow your guidance proposal from August of last year and come up with a pretty good proposal, isn't that true? Yes or no.

Dr. WOODCOCK. No. I don't think so.

Mr. GRIFFITH. So that was a bad proposal that you all were putting guidelines out on?

Dr. WOODCOCK. The guidance——

Mr. GRIFFITH. Yes or no. Were those guidance proposals bad?

Dr. WOODCOCK. They were based on the 503, which is not really that workable for the current industry that we have. I am sorry I can't give you just a "no" answer. I don't think we have a good——

Mr. GRIFFITH. All right. I am out of time so if you could submit your recommendations I would greatly appreciate it.

Mr. Chairman, I yield back.

Mr. PITTS. The chair thanks the gentleman, and now recognize the gentleman from Texas, Mr. Green, 5 minutes for questions.

Mr. GREEN. Thank you, Mr. Chairman.

Dr. Woodcock, thank you for being here today, and I am concerned that the majority side has looked at this issue and said the FDA has the necessary authority to properly regulate. As Commissioner Hamburg explained at the last meeting, the current level of scrutiny being applied by the FDA is a result of the outbreak. The court case may be strengthened, but a favorable ruling on the authority over compounding manufacturers and non-traditional manufacturers is far from certain.

As a result, I think we must pass limited legislation that allows the FDA to regulate compounding manufacturers across State lines. The draft currently being debated in the Senate is a good first step, but I think there are some changes we could made to strengthen the bill.

In her testimony before the committee, and I won't judge on Commissioner Hamburg's testimony, asserted the agency needs greater authority over large compounding pharmacies that are essentially manufacturers. The Senate legislation would create a new category of compounding manufacturers that would be under FDA regulatory authority.

Commissioner Hamburg also told us that the FDA agrees that the regulation of a traditional pharmacy compounding should be left to the State legislators and State boards of pharmacy. We have laws in my home State of Texas that allow when medically necessary and in very limited circumstances a compounding of medications before the receipt of a patient specific prescription for administration in the office of the prescribing physician. Those are called office use compounding. It is my understanding a majority of States have these similar laws.

Dr. Woodcock, what do you recommend that Congress craft or how do you recommend that Congress craft language to give the FDA the necessary authority to regulate large, interstate compounding manufacturers while still preserving the ability of States to regulate the traditional compounders?

Dr. WOODCOCK. It is a complicated question. We want to make sure that the traditional compounders can flourish because they provide a valuable service but not that they don't go to 20 rooms or 50 rooms, right, and start making large scale. So there have to be boundaries there.

Traditional manufacturers, obviously, have to submit applications to FDA, pay user fees and then undergo review and frequent inspections for GNPs. The hospitals have told us, the hospitals in your district and all around the country have told us that they rely on this industry now for the compounding manufacturing industry, if you wish to call it that, for certain services that used to be done in the hospitals but are now outsourced. However, these operations

are proceeding under the rubric compounding right now but they are doing something quite different and in a larger scale. And so if Congress would see fit, what we are saying is not we want more regulation, we want regulation that would fit this new activity, right, and would be appropriate for that and allow them to flourish.

Mr. GREEN. I only have a couple minutes. For example, if a hospital in Houston wants to contract with a company in Massachusetts, that still should be under FDA authority.

Dr. WOODCOCK. For sterile products is what we are proposing, so if they want to get injectables from a New Jersey firm, they want to buy injectables and use it in their hospital or in their clinic, we think that should be under FDA authority if those are sterile products.

Mr. GREEN. OK. Do you agree that legislation should clarify the current law in the area and protect the ability of States and boards to decide what is the appropriate scope of practice for traditional pharmacies?

Dr. WOODCOCK. Absolutely.

Mr. GREEN. Including the areas of anticipatory and office use compounding?

Dr. WOODCOCK. Well, we have to make sure that it draws the line and doesn't allow them to produce, say, and how do you do that, is 17,000 vials, is that anticipatory compounding? You have to have some clarity on that.

Mr. GREEN. It seems like it would be. What is the FDA's position on office use compounding pursuant to State law where it occurs? Under the current Federal law, FDCA, and under the legislation being considered in the Senate?

Dr. WOODCOCK. Well, right now, under current Federal law it is blurry, all right, as far as how much you could make? You all are saying to me that you think you can tell what a manufacturer is but there is no bright line in the statute that says when you cross that line and become a manufacturer.

Mr. GREEN. And that is our job to define that.

Dr. WOODCOCK. That would be very useful.

Mr. GREEN. The other thing I am concerned about is traditional compounder in an area that is close to State boundaries. Again in Massachusetts with New England there is maybe a different problem whereas in Texas it is not that big a problem except along our border with other States.

How do we keep those traditional compounders from being classified if they work across State lines, geographically fairly close, from being classified as a compounding manufacturer?

Dr. WOODCOCK. Well, we think there are some Federal standards that ought to be in place, OK, that distinguish even a traditional compounder so that there are certain things that they are held to do and then they remain traditional compounders.

Mr. GREEN. Thank you, Mr. Chairman. I appreciate it and look forward to working on the legislation.

Mr. PITTS. The chair thanks the gentleman. I now recognizes the gentleman from Pennsylvania, Dr. Murphy, 5 minutes for questions.

Mr. MURPHY. Thank you for being here, Dr. Woodcock, I have the highest respect for you and I appreciate your candid conversations.

I want to cut to the chase here because I don't want this to be a political discussion and I think it is being mislabeled as that.

I held hearings in my Subcommittee on Oversight and Investigation and it was my impression we weren't getting clear answers about missteps within the FDA. And I just want to make sure that I know that the FDA is saying we have learned from our problems and here is how we change.

So let me run through a series of questions with you and help get that on the record.

First of all, the FDA has repeatedly cited the fact that the Fifth and Ninth Circuit Courts of Appeals have issued conflicting decisions on whether section 503A of the Food, Drug and Cosmetic Act remains valid, and in a written statement on November 14th of last year oversight committee hearing Commissioner Hamburg cited the Circuit Court's split as having "amplified the perceived gaps and ambiguity associated with FDA's authority over compounding pharmacies."

Now the Fifth Circuit Court decision was July 2008, is that correct?

Dr. WOODCOCK. Right.

Mr. MURPHY. In May 2009, just prior to Commissioner Hamburg being confirmed, a briefing was provided to Acting Commissioner Joshua Sharfstein proposing several paths forward in light of the Fifth Circuit's decision upholding 503A.

Do you recall participating in that briefing? Yes or no.

Dr. WOODCOCK. No.

Mr. MURPHY. The FDA produced to the committee an email chain from the Office of the Chief Counsel from July 2009. A copy of this document I think is now in front of you. The top email is from Michael Landa, FDA's Acting Chief Counsel at the time, and notes the plan is to enforce section 503A nationwide except in the Ninth Circuit and that, quote, Josh is on board, unquote.

Mr. Landa then notes that Dr. Sharfstein, quote, would touch base with Peggy but did not think she would have any objection, unquote. Do you know whether or not Commissioner Hamburg was consulted in the decision to proceed with enforcement of section 503A?

Dr. WOODCOCK. I do not know affirmatively, no.

Mr. MURPHY. Do you suspect that she did or——

Dr. WOODCOCK. I would suspect that she was.

Mr. MURPHY. Thank you. And if you turn to the second page of that email chain, the leader of the compounding team in FDA's drug center, your center, notes that Dr. Sharfstein and Deb Otter asked to chart the timeframe for each step we plan to do to implement the new plan.

Dr. Woodcock, this plan had yet to be implemented when the outbreak began in September, 2012, am I correct?

Dr. WOODCOCK. That is correct.

Mr. MURPHY. And yes or no, prior to announcing the new plan FDA felt as though it needed to draft a new guidance document detailing the approach it would be taking as well as various regulations that 503 required? Yes or no.

Dr. WOODCOCK. That is my understanding.

Mr. MURPHY. Thank you. And yes or no, during this time period inspections and enforcement actions came to a standstill.

Dr. WOODCOCK. My understanding is that it is not true, that we did certainly went for cause inspections.

Mr. MURPHY. Certainly with NECC.

Dr. WOODCOCK. I can't comment specifically on NECC. I am sorry.

Mr. MURPHY. Is that——

Dr. WOODCOCK. Due to the ongoing criminal investigation.

Mr. MURPHY. I understand. By August 2012 your center signed off on another draft guidance document that was going through final clearance, yes or no.

Dr. WOODCOCK. Yes, my understanding.

Mr. MURPHY. Thank and a briefing has been had, in fact been scheduled to discuss the new guidance documents with Commissioner Hamburg back in September 2012, is that correct.

Dr. WOODCOCK. That is correct.

Mr. MURPHY. And yes or no, Commissioner Hamburg testified before O&I that she was really not that aware of issues related to drug compounding until after the meningitis outbreak; therefore, would any additional changes to this draft document guidance have been made based on Commissioner Hamburg's input.

Dr. WOODCOCK. I don't know. That would be speculation.

Mr. MURPHY. OK. The point is the agency had a solution here that would have allowed it to conduct inspections was my understanding. But so the FDA failed to even acknowledge the existence of this guidance document until it produced it to this committee in March of 2013, well after the FDA promoted an entirely new regulatory paradigm.

Here is where I want you to help clarify this for all of us. My question is what does FDA now know about the compounding industry that it did not incorporate in this guidance document and is provided as a learning experience to make some changes? You may respond.

Dr. WOODCOCK. What we have seen as we have done inspections of this industry, we have focused on the highest risk areas and we have seen violations of aseptic processing, that basically mean that there is no insurance of sterility of the products coming out of these compounding pharmacies.

And this means that this outbreak that we have seen will happen again. Since the outbreak, we have had an instance of fungal bodies being observed in an IV bag ready to be given to a cancer patient, all right, that came from a compounding pharmacy. We have also had other instances of patients having eye infections and other instances of non-sterility of products. So we have had harm as well as the nonsterile practices that lead to the harm.

Mr. MURPHY. With regard to the way that FDA approaches these things and I understand you are looking for more authority to handle some things but what we really need to know is within the realm of the authority you already had—and I am not asking you to hang anybody out right now, that is not the purpose of this hearing—but are there internal lessons that the FDA has learned they could have handled some things differently that could have possibly

led to different results other than dealing with the lawyers' issues here.

Dr. WOODCOCK. Well, I think we should have been more aggressive. There was great concern about our, the limitations of our authority and that we would lose and then have even less ability to influence this industry. But in retrospect I think it would have been more important to simply go forward and see how it turned out in the courts, aggressively exert our current authority, which is primarily new drug authority.

Mr. MURPHY. Thank you. That is why I like hearing from a physician instead of a lawyer. I will need to submit these e-mails for the record if that is all right, Mr. Chairman.

Mr. PITTS. Without objection, so ordered.

Mr. MURPHY. Subject to redactions by staff.

Mr. PITTS. The chair thanks the gentleman and now recognizes the gentlelady from California, Mrs. Capps, for 5 minutes for questions.

Mrs. CAPPS. I believe—am I before Mr. Engel?

Mr. PITTS. Yes.

Mrs. CAPPS. Oh.

Mr. PITTS. We are going in order of appearance.

Mrs. CAPPS. OK, all right. I thank you. I just want to thank you for your testimony today, Dr. Woodcock, and I want to thank Mr. Pallone for holding this necessary hearing. This is an important issue and I believe needs to be revisited.

Under current statute, a great deal of uncertainty and variation exists between regulations. And this uncertainty creates gaps that can lead to compromised patient safety, as we have seen most recently with the meningitis outbreak. We cannot wait for another public health crisis to act, and what we have right now isn't working.

Dr. WOODCOCK. Right.

Mrs. CAPPS. I believe you would agree. Families don't have the peace of mind they are receiving effective drugs that they can trust and compounding pharmacies across the States are not on a level playing field. Many States are inadequately inspecting facilities. After a similar incident in my State of California almost a decade ago, regulations were enhanced and sterile compounding pharmacies now require an inspection or accreditation through a national agency. You know, this isn't good enough because many hospitals and clinics in California buy drugs from out of state, compounding pharmacies in other States, including the Massachusetts pharmacy. So hospitals and States don't exist in isolation. Hospitals have a great need to be able to buy large quantities of compounded drugs.

Mr. Migliaccio suggests in his written testimony that there should be no special regulatory program for these large scale drug compounders. Instead he implies that they should be treated like conventional drug manufacturers and should have to go through the new drug application process to manufacture and distribute any drugs.

My question now, Dr. Woodcock, could you explain to us why you believe requiring new drug applications for all drugs would not be

warranted and what the consequences would be particularly for hospitals if FDA were to take such an approach?

Dr. WOODCOCK. Well, that approach would be our current authorities. It is not that we don't have current authorities. Our current authorities require submission of applications, payment of a user fee, thanks to the user fee bill you all passed for generics recently, and we have had the new drug one for a while, and review of all the information, a large package submitted to the agency, and then we inspect those facilities frequently, including a preapproval inspection to make sure everything is OK before the product gets out on the market. So that is our current authorities.

Now many of these outsourcers, what they are actually doing is taking FDA approved products and putting them into convenience forms or putting them into, combining them, say for hyper alimentation or something like that, and then shipping them around the country based on patient need.

The industry has basically told us that they can't make all these different very patient specific forms and convenience forms. And there are questions of efficacy that are related because these are already FDA approved products. The key is, and this used to be done by the hospital pharmacy, by the clinic they would do this. I did this when I was an intern, all right, when the interns were able, had to be kind of worker bees. So we made up the chemotherapy, we put things into bags and the nursing staff would do this as well or the hospital pharmacy.

Now, with the very large scale of medicine they want to buy these, and many of the clinics are in office buildings, they don't have a pharmacy or clean room there. So they need to order these products, right.

Mrs. CAPPS. I want to get to another question.

Dr. WOODCOCK. I am sorry. It is so complicated. Let me finish then. So there isn't good regulatory fit right now. It isn't where we say we have to have all these broad new authorities, no, there is no fit for this industry that has grown up.

Mrs. CAPPS. All right. I want to make sure that I am able to enter a statement from the American Society of Health System Pharmacists which addresses this issue as well. Their statement details the many ways in which hospitals have come to rely on compounded medications from outside compounding pharmacies which you are alluding to.

And I want to ask that this statement that I am holding up be entered into the record.

Dr. Woodcock, if there is a time for you to address this, would a two-tiered regulation system that clarifies a uniform set of rules for compounding manufacturers while preserving the State's role in traditional pharmacy compounding be a practical thing?

I will just let you comment on that.

Dr. WOODCOCK. Yes. We have proposed something like that as something that would be practical but it would require a new regulatory scheme for this new industry that has evolved to make sure they are making the product safely. It is no good to have convenience products if they are contaminated or they are super potent or there are other things wrong with them. However, of course that is up to Congress whether they want this industry to persist be-

cause our current regulatory authorities require submission of application.

Mrs. CAPPS. I see. OK, thank you. I yield back.

Mr. PITTS. And did you want to submit that for the record?

Mrs. CAPPS. Yes, I would like to.

Mr. PITTS. Without objection so ordered.

The chair recognizes the gentlelady from North Carolina, Mrs. Ellmers, 5 minutes for questions.

Mrs. ELLMERS. Thank you, Mr. Chairman, and thank you, Dr. Woodcock, for being here today. I just want to clarify a few terms because we are putting terms out and I want to make sure I am understanding them. When we are talking about traditional compounders, who are we talking about?

Dr. WOODCOCK. We are talking about pharmacies, licensed pharmacies who react to a prescription for a specific individual patient and make a specialized dosage.

Mrs. ELLMERS. And right now that is under the authority of the State, not under FDA, correct?

Dr. WOODCOCK. Correct.

Mrs. ELLMERS. And when we are talking about the compounding manufacturers, how is that different from the term drug manufacturers.

Dr. WOODCOCK. Compounding manufacturers is a new term that is contained in the Senate bill, OK——

Mrs. ELLMERS. Right, so this is Senate language.

Dr. WOODCOCK [continuing]. To reflect this large scale industry. They are not usually reacting to a prescription. They are making things that hospitals need and order frequently so they make them at large scale like a drug manufacturer. But often they are not—a drug manufacturer starts from scratch. They start from what we call the active pharmaceutical ingredient, which often someone will buy from India or China, bring it in, test it and then make the product.

Mrs. ELLMERS. So sometimes it may be in a different form but is it not the same product, and you are saying that because products might be coming from somewhere else that that is the essential difference?

Dr. WOODCOCK. No, there are two different activities that are lumped under this compounding manufacturing. One is what we call the outsourcers, OK, they get generally outsource from a hospital or clinic, something the clinic or hospital pharmacy used to do, all right, and that is putting things in syringes, little IV bags, diluting chemotherapy, getting everything all right so they can just hang it on the patient rather than having to do that——

Mrs. ELLMERS. Rather than having to actually do it in house. Now——

Dr. WOODCOCK. That is one. And then the other is people who are doing larger scale compounding.

Mrs. ELLMERS. Larger scale. And that would currently fall under the jurisdiction of the FDA.

Dr. WOODCOCK. That is what kind of is under dispute.

Mrs. ELLMERS. And that is what we are trying to get to is when do we make that distinction between compounding pharmacy and compounding manufacturer.

Dr. WOODCOCK. And also a manufacturer who is already a pharmaceutical company has to submit an application to FDA and be under that regime.

Mrs. ELLMERS. Now, currently, so basically the compounders have the same regulations and requirements as the drug manufacturers? Yes or no?

Dr. WOODCOCK. No.

Mrs. ELLMERS. And I am not just talking about numbers but I am just talking about regulations again, is this State versus Federal, is that the main difference that we are talking about?

Dr. WOODCOCK. The States regulate pharmacies. They license pharmacies and these activities right now occur all in licensed pharmacies.

Mrs. ELLMERS. OK. What are the changes to compounding you propose making in order to prevent the meningitis outbreak last year to ensure compounded products are safe? If you can just quickly give us an idea of what you would like to see.

Dr. WOODCOCK. Well, limit the traditional compounding to more or less reaction to a prescription, OK, and compounding something for a specific patient, that is traditional compounding. And don't allow compounding of really complicated dosage forms that even the traditional manufacturers have trouble making. Then we are saying establish a new group, the compounding manufacturers is what the Senate called them. They don't get prescriptions, but they have to register and list with FDA. Tell us who they are, what they are making and where they are located, right, and then they have to submit adverse events to us. And they would be subject to proper GMP requirements to make sure they make safe products, OK, but they wouldn't have to submit applications to us.

Mrs. ELLMERS. But you did mention application process a moment ago. Can you repeat that?

Dr. WOODCOCK. Sure. Some of the members are talking we have current authorities, yes, we do have authorities. Our authorities are you are a new drug manufacturer or a generic drug manufacturer, you must submit an application to us. You must a pay user fee or you should not be producing drugs in the United States.

Mrs. ELLMERS. So once that application process is fulfilled, that, it is just so that you know that that particular facility exists and what their plan of action is?

Dr. WOODCOCK. I am sorry, it is really hard to do this. That is our current authorities. That is how we regulate generic drugs and new drugs in the United States, all right, through that process. That is not what compounding is.

Mrs. ELLMERS. OK. Now let me ask this question. The number and how much a parmacy is making seems to be the issue of where it falls, what jurisdiction. In your own words, where do you, where would you see that line of action? What do you see, how much product can a compounder make without being designated a manufacturer?

Dr. WOODCOCK. That is what we have been struggling with since the 503 was passed, OK, there is no line in there in the statute. And so what is an inordinate quantity? We don't know. Is it 10 units? Is it 1,000 units? Is it 17,000 units? So we have endeavored

to use other criteria to say, OK, when you would be subject to Federal jurisdiction.

Mrs. ELLMERS. Well, my time is expired but obviously that is the main question here. So thank you.

Dr. WOODCOCK. We would be happy to work with you.

Mr. PITTS. The chair thanks the gentlelady and now recognizes the gentleman from New York, Mr. Engel, 5 minutes for questions.

Mr. ENGEL. Thank you, Mr. Chairman.

Dr. Woodcock, thank you for the good work that you do. We appreciate it very much.

Dr. WOODCOCK. Thank you.

Mr. ENGEL. I want to first ask a New York question. New York, it is my understanding that New York has no licensing requirements specific to compounding pharmacies and according to the National Conference of State Legislatures there is no requirement that New York pharmacies comply with the U.S. Pharmacopeia chapter 795 or 797 compounding standards and according to the Pharmacy Compounding Accreditation Board, which accreditation is entirely voluntary, they say there are only 10 pharmacies in all of New York accredited for pharmacy compounding.

So that being said, I am pleased that no New York pharmacies were included as part of the FDA's most recent risk-based priority inspections of 31 sterile compounding pharmacies. So what I want to ask New York specific is, does the FDA know which pharmacies in New York are compounding medications?

Dr. WOODCOCK. We have no way of nothing in any State, OK, we have been told by the industry that there are 23,000 pharmacies that may engage in some form of compounding across the country, but we don't know who they are, where they are or what they are making, because they don't have to tell us.

Mr. ENGEL. So I assume then that the answer would be "no" to this, does the FDA currently have the authority to collect and test samples or examine the records of a compounding pharmacy in New York? And can you elaborate on why this information is critical for public health and safety?

Dr. WOODCOCK. Well, we do believe we have the authority to go in and get samples and look at records but it has been contested.

Mr. ENGEL. OK. Thank you. I am intrigued by the part of your written testimony which lays out a proposed risk-based framework for a new legislative approach to compounding to ensure patient safety and health.

First, you proposed dividing the world of compounding into non-traditional compounders which would be subject to FDA's jurisdiction and traditional compounders who would remain under State oversight.

Is there a concern that non-traditional compounders may create a category of pseudo drug manufacturers? And if so, how do you protect against that?

Dr. WOODCOCK. Well, there is a concern that traditional manufacturers could actually be drug manufacturers in disguise and that non-traditional manufacturers could be. And for traditional we really feel that prescription requirement and the statement of medical need for the patient is important, for non-traditional we have proposed a series of things, including that they would register and

list with us so we would not who they are and also not make copies of commercially available drugs.

Mr. ENGEL. You mentioned the need for sort of do not compound list as part of this framework. Can you explain why this is necessary and why you cannot do this using your current authority?

Dr. WOODCOCK. Yes. Well, we feel that products say we have withdrawn from the market for reasons of safety should not be allowed to be then compounded and U.S. citizens would then be exposed to them again. And we are seeing this now as you know in dietary supplements, we have to go after them because they sneak in drugs that have been pulled off the market, all right. So that is one category.

Another category might be very difficult to manufacture dosage forms where the pharmaceutical industry that has a lot of science available to them and a lot of engineers and scientists still have trouble making them reliably, some of the patches, some of the inhalers and so forth.

Mr. ENGEL. You sort of touched on this, but can you elaborate further on what steps the FDA is taking now utilizing the authority that you believe the that FDA has to conduct improved oversight over compounding pharmacies?

Dr. WOODCOCK. Well, it is more oversight on whether it has improved because we are having to go to the ones we read about or we know about or we have had prior actions and we are doing a risk-based approach and going to those pharmacies as well as going to pharmacies where you have had reports of problems recently, all right, and for cause type of inspections.

And as I said, we are going in with the States, the State board of pharmacy, their investigators, we often do an inspection together and we are taking very aggressive action. But we do not, for example, have recall authority, we cannot, we don't have the authority, we don't have recall authority for any drugs, right, and we do not have the authority to shut these pharmacies down, they are licensed by the State, but we have shared full information with the States, and they have shut 11 pharmacies down as a result of the findings in these inspections.

So that is improved oversight, but we will see about if we go to court like what kind of response we get from the courts as far as our authority.

Mr. ENGEL. Well, again thank you for the good work that you do. And I especially appreciate your testimony here this morning. It is concise, it is to the point. When we ask a question you respond very pointedly and it is very much appreciated. Thank you.

Dr. WOODCOCK. Thank you.

Mr. PITTS. The chair thanks the gentleman. The chair now recognizes the gentleman from New Jersey, Mr. Lance, 5 minutes for questions.

Mr. LANCE. Thank you, Mr. Chairman. And good morning to you, Doctor. You stated to Dr. Murphy that if you had it to do over, you might move more aggressively regarding the situation that, unfortunately, occurred, is that accurate?

Dr. WOODCOCK. Well, I think we would have moved aggressively as we are now against all pharmacies. There was no way to predict at any time which of these pharmacies will cause this problem.

And as I said, it will happen again because the conditions under which these sterile products are manufactured are not acceptable and the products are contaminated.

I have learned, what I have learned from this is the resilience of the human body to microbial invasion because we have cultured many samples from these pharmacies and we have grown organisms. And we haven't had outbreaks and that is because both the human body can repel them and because some of them aren't human pathogens.

Mr. LANCE. Thank you. This is a very complicated subject and certainly I think answers require more than "yes" or "no."

Dr. WOODCOCK. I am sorry.

Mr. LANCE. And you don't have to be sorry at all, I think that this is extremely complicated.

One of the difficulties as I read the background information is the split in the circuits.

Are you advised by attorneys at the Department of Justice on these matters or do you have attorneys at your own agency regarding the significant split between the Fifth and the Ninth Circuit and the Supreme Court decision?

Dr. WOODCOCK. We have our staff attorneys that belong to the Office of General Counsel at HHS and they are the FDA branch of that, and then they work with the Justice Department as well.

Mr. LANCE. Perhaps you are not the appropriate person to ask, but it seems to me, speaking as an attorney, that there needs to be much greater clarification so that there can be one standard across the Nation and not a split between the circuits, with the Supreme Court decision that did not answer the question fully.

Would that be your understanding?

Dr. WOODCOCK. That is my understanding. I am not a lawyer, but I appreciate clarity when I try to perform regulations.

Mr. LANCE. And I would hope moving forward in our responsibilities to protect the health of the Nation in conjunction with your responsibilities that we could work together to clarify the situation.

I have 2–1/2 minutes, and I defer to Dr. Burgess.

Mr. BURGESS. I thank the gentleman for that. Well, Dr. Woodcock, what is it about the Exserohilum fungus that rendered it such a bad actor? You said sometimes the human body actually can resist these things, sometimes they don't even register. But Exserohilum was a bad one.

Dr. WOODCOCK. Let me talk in general so I am not talking about NECC, but clearly it is the amount of bioburden of the contamination and that is why shipping these—bioburden means how many organisms are in there, OK, for the nonclinicians in the room—and so shipping something around unrefrigerated, which is happening a lot, OK, if you happen to get something in there, it gets a long chance to grow, all right. If you put it in a part of the body that is sort of protected from the immune system a little bit or is particularly vulnerable, if you inject with a steroid, we have had multiple outbreaks where there is an injection with a steroid and of course steroids suppress the immune system so then that weakens that part of the body and even systematically weakens the body's ability to respond to infectious attack because of the actual medi-

cine that has been given. But we have had sepsis from IV products. Nine people died in 2011.

Mr. BURGESS. Let me just stop you there because we could obviously could go on. But that is significant because you have a steroid which inhibits fighting infection, you have a space in the epidural space that is relatively protected from white blood cells and things that normally fight infection, it is preservative-free because it is going into the epidural space if you had preservatives that would be bad for nerves so.

Dr. WOODCOCK. High risk.

Dr. BURGESS. So it is the confluence of bad events. So you know this stuff is high risk.

On the issue of manufacturing, I just have to tell you looking at the notes compiled by the other subcommittee, Oversight and Investigations, going back to May 10, 2012, when the Colorado Board of Pharmacy issued to NECC a cease and desist order and the same day FDA's Denver office informed New England the cease and desist order, New England compliance officer responsible for NECC spoke to an optometrist with the U.S. Department of Veterans Affairs inquiring about whether or not they could use NECC to repackage Avastin. This communication is significant because once again it confirms that FDA understood that NECC was acting like a manufacturer not a traditional compounding pharmacy. An email response "I did not think they could use firms if profiles were unacceptable. NECC Framingham is profiled as a manufacturer because we determined that they are a manufacturer and not a compounding pharmacy," an email from the compliance officer for the New England district to FDA May 11, 2011.

Dr. WOODCOCK. Well, I am not going to argue with you about this particular case because I can't talk about the case. But clearly the decision about whether a firm is making, is making product legally under 503A would be for the courts ultimately, all right, that is just how it was set up.

Mr. BURGESS. But under the Food, Drug and Cosmetic Act, if I may, you have the regulatory authority over manufacturers and your own compliance officers identified NECC is a manufacturer, acts like a manufacturer, walks like a manufacturer, they are a manufacturer.

Mr. Chairman, I will yield back.

Mr. PITTS. The chair thanks the gentleman and I now recognize the gentleman, Mr. Butterfield, for 5 minutes for questions.

Mr. BUTTERFIELD. Thank you, Mr. Chairman. And thank you, Dr. Woodcock, for your testimony today.

I will be brief. The hour is certainly getting late. But in studying this issue, Mr. Chairman, it seems that the FDA lacks clear direction and clear authority over what can be done once a compounding pharmacy is found to have failed to meet the standards.

And so, Dr. Woodcock, after the meningitis outbreak at the New England Compounding Center about a year ago, FDA increased its inspection of compounding pharmacies. I think that is true. The findings by Federal investigators have been alarming. And hopefully there will be more aggressive investigations.

I want to take you to the subject of sequestration. FDA is understaffed, underfunded and stretched very thin, at least that is what

we have been told. How are the cuts from sequestration hindering the FDA and your inspectors from conducting the thorough oversight that is critical to patient health?

Dr. WOODCOCK. Well, don't forget, the Energy and Commerce Committee overall have been very concerned that we haven't been to manufacturers overseas, traditional drug manufacturers, and that has been partly due to our resource limitations. Now we do have the user fee, the Generic Drug User Fee Act, and that will allow us to increase our inspectors who go overseas but my point is even the traditional industry we have difficulty covering that adequately. Now there are over 20,000 compounding pharmacies, and we don't know who is who. And so——

Mr. BUTTERFIELD. Can some of your lack of resources be attributable to sequestration?

Dr. WOODCOCK. Oh, yes, absolutely. Well, sequestration took another bite out of what was already a stressed agency, particularly as far as inspectional coverage and now, to give you perspective the whole drug industry has about 5,600 establishments, all right, and so we try to inspect those on a regular basis. To say now that there are 20,000, 26,000, 28,000 compounding pharmacies the question how do we get there, and then sequestration has reduced our funding, our user fee funding as well as our base appropriation funding.

Mr. BUTTERFIELD. And is that really having a negative impact on your work?

Dr. WOODCOCK. Absolutely.

Mr. BUTTERFIELD. Now does your agency fully understand that sequestration is not a 1 year process, it is a 10-year process so unless it is repealed or modified it is going to continue for some years to come.

Dr. WOODCOCK. We have grave concerns about our continued ability to operate our programs under the various financial stresses that we have and these new activities that we need to take on.

Mr. BUTTERFIELD. What is an FDA Form 483?

Dr. WOODCOCK. That is a form with the investigators' observations that is left with the firm at the end of the inspection.

Mr. BUTTERFIELD. Are these posted on the Web site?

Dr. WOODCOCK. Yes. They are public.

Mr. BUTTERFIELD. OK. And from what we can gather, some 48 form 483s that have been conducted are posted on the Web site?

Dr. WOODCOCK. Yes. We are posting them publicly to make sure that people understand what our findings are.

Mr. BUTTERFIELD. What are some of the worst conditions that have been observed by some of your inspectors?

Dr. WOODCOCK. Well, primarily, it relates to not keeping, not having practices that would assure the product would be sterile. Don't forget, these are going to be injected in people's bodies, into their eyes, around their spinal cord into their veins and the practices would allow fungal spores, mold, contamination from the body of a person so that would be bacteria, to actually get into the products and then multiply.

Mr. BUTTERFIELD. Finally, are there any tools other than money, of course, that Congress can provide to the FDA so the American people can feel more assured that the compounded drug they are taking is prepared in a safe and secure way?

Dr. WOODCOCK. We need clear lines of authority. We need to know what the States regulate, what the Feds regulate and what our authorities are. If we regulate part of the industry, I would like to know who they are, where they are located and what they are making so that then we can then prioritize where to go because we are not going to get to thousands and thousands of sites in the next several months.

Mr. BUTTERFIELD. Thank you. You have been very kind. I yield back.

Mr. PITTS. The chair thanks the gentleman. I now recognize the gentleman from Utah, Mr. Matheson, 5 minutes for questioning.

Mr. MATHESON. Thank you, Mr. Chairman. Dr. Woodcock, it is always good to have you before the committee. I have always appreciated my conversations with you and I appreciate your trying to highlight an issue where I think it is all important we take a hard look at this and figure out a better way to go forward. If I want to oversimplify this hearing, that is kind of where we are.

I fear my questions may be a bit repetitive for what you may have already covered that is the reality of being the last people asking questions.

But I was interested as I understand it when you were discussing, when the FDA discussed some informant actions back in 2006, after—can you tell me at that point what actions—can you elaborate what actions were discussed by the agency 7 years ago? Are you familiar with that discussion that took place? That is before your time. Maybe you can't answer that.

Dr. WOODCOCK. No. No. I wasn't. I wasn't head of Center for Drugs at that time either.

Mr. MATHESON. You present several policy options in your testimony, and it is going to provide FDA some different authorities for certain compounders. Can you describe how those options, how they might have played out, allowed the 2012 outbreak to play out differently than it did if you had those options at that time?

Dr. WOODCOCK. If we have clear Federal authority and a clear idea of what is traditional compounding and what is not traditional compounding because don't forget this industry maintained they are working within the scope of State pharmacy practice. That is what they have maintained all along, all right, and so we need a clear understanding of what is the scope of traditional pharmacy compounding practice which FDA has already supported as appropriate in providing individualized therapy for people, and what is beyond that and requires Federal oversight, and to make sure that is delineated. And I think you will hear from the other witnesses, that is delineated from people masquerading as one of these buckets who are actually drug manufacturers. So we need clarity in whatever.

And if Congress decides not to allow compounding manufacturing at all, all right, then we have heard from the hospitals and the clinics that that would be a tremendous burden on them because they would have to take back all this that they had outsourced.

Mr. MATHESON. Mr. Chairman, that is all I am going to ask now. I will yield back.

Mr. PITTS. The chair thanks the gentleman. I now recognize the ranking member of the full committee, Mr. Waxman, 5 minutes for questions.

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

Dr. Woodcock, your testimony states that the current legal framework does not provide FDA with the tools it needs to appropriately regulate the compounding industry in its current state. You explained that you are referring both to section 503A and other parts of the Federal Food, Drug, and Cosmetic Act.

I would like to start with section 503A. Obviously as you explained to Mr. Pallone, there are major questions about whether it would even remain in effect if challenged in most of the country apart from the Fifth Circuit. With regard to the circuit split, Representatives Barton and Griffith have asked why you could not fix this with guidance.

Can you explain what a guidance could or could not do to address the circuit split?

Dr. WOODCOCK. Certainly. A guidance says on every page that it is not binding either on FDA or the industry. That is what it says on every page. It is more or less an explanation of our thinking. It doesn't add new requirements or cannot solve differences in court opinions.

Mr. WAXMAN. But putting that aside you say that section 503A actually contains provisions that have impeded FDA's ability to effectively regulate pharmacy compounding.

Can you elaborate on what those provisions are and how they have impacted FDA's oversight of compounding pharmacies?

Dr. WOODCOCK. Yes, well, I think there are provisions in there that are vague, and so we need clarity about what is the line. So, for example, it says you shouldn't compound without a prescription in inordinate amounts. What is "inordinate?" That is in the eye of the beholder. The industry has maintained that all of their activities, regardless of their scale, are within the scope of traditional pharmacy compounding.

Mr. WAXMAN. The Oversight and Investigations Subcommittee of Energy and Commerce conducted a detailed investigation involving thousands of pages of FDA documents.

One thing we found in that investigation is that for years, going back to the Bush administration, key FDA decision makers have in numerous internal meetings and memoranda indicated that section 503A is inadequate and that new legislation is necessary.

Are you familiar with any of these documents or any of these internal discussions?

Dr. WOODCOCK. Well, I was present in the early 2000s when the court cases came down, all right. We had been preparing to try and implement 503A and making the preparations for that when the Circuit Court and then the Supreme Court ruled. So I am familiar with that set of discussions.

Mr. WAXMAN. Well, is it fair to say that the agency leaders going back to the Bush administration understood that they needed new legislation because of fundamental weaknesses in section 503A?

Dr. WOODCOCK. Yes, it was very difficult to implement in any reasonable manner.

Mr. WAXMAN. Mr. Chairman, the notion that FDA is asking for legislation simply to cover for past mistakes or in some sort of power grab is not correct. For years through two different administrations, agency leaders have known that there were problems with the underlying law.

Let's turn to the other provisions in the act apart from section 503A.

Dr. Woodcock, your testimony indicated that you are encountering difficulty when you attempt to inspect compounding pharmacies now using your current authorities. You mentioned that you actually had to seek a warrant in two cases after the pharmacies delayed or refused your access to records.

Can you describe in more detail exactly what has happened during those inspections and describe which current statutory provisions are contributing to the difficulties you have faced when attempting to conduct inspections?

Dr. WOODCOCK. Well, I probably can't speak to statutory provisions. I am sorry. But what has happened is we have gone in there and, as I said, the industry has long maintained that we do not have authority over these licensed pharmacies that are in States, right, and so we go in and we ask to either inspect or to inspect records. And they say under some of the court cases that have occurred we don't have to turn over records to you.

Mr. WAXMAN. So some might argue that there is no problem here since you were eventually able to conduct the inspections and obtain the records you were seeking. But can you——

Dr. WOODCOCK. Certainly.

Mr. WAXMAN [continuing]. Speak to that assertion?

Dr. WOODCOCK. The real problem is what is clarity? What is a compounding pharmacy? What is a traditional compounding pharmacy? What about the status of these large scale and how do you define a large scale operation? You might say, well, I know it when I see it. OK, but how do you——

Mr. WAXMAN. Well, I was amazed to hear during your responses to earlier questions that in order for FDA to begin conducting the more recent inspections, you had to actually look in the newspapers and at the television ads and Web sites to even know where the compounding pharmacies were.

Obviously, we don't ask you to search the Internet or watch TV to figure out where drug manufacturers are.

What is the difference here and do you need new authority to remedy the situation?

And before you answer that, not only are we uncertain as to the continued validity of FDA's authorizing statutes with respect to compounding pharmacies, but that statute itself is plagued by problems. And so I think we need to clarify the situation.

But why should you have to go on TV and the Internet to be able to do inspections?

Dr. WOODCOCK. Because they don't have to tell us who they are, where they are operating, and what they are making. They don't have to submit anything to us. They are operating under State law. And they don't have to send us adverse events if they occur, even deaths, and we would read about them in the paper, hear about

them from the CDC or State health department, or a consumer or doctor will call us.

And that is how we learn about this. And we don't know of all this universe of 28,000 firms. We don't know what they are doing. And so you might say, well, you should know about this. But when it happens, most of our actions have been reactive to things that we have heard about.

Mr. WAXMAN. Thank you very much. Thank you for your indulgence, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman.

We are voting now on the floor so we will again recess until the floor votes are concluded, and then we will come back and reconvene with the second panel.

I think all of the members have asked their questions. There may be some follow-up questions and we will ask you to please respond when we send you those.

Dr. WOODCOCK. Certainly.

Mr. PITTS. So at this point we will recess until conclusion of floor votes.

[Recess.]

Mr. PITTS. The time of our recess having expired, we will reconvene our hearing. At this time, I would like to request unanimous consent to enter a statement from the National Association of Chain Drug Stores into the record. Without objection, so ordered.

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

Mr. PITTS. At this point, I will introduce our second panel. Today on our second panel we have Dr. Scott Gottlieb, resident fellow, American Enterprise Institute. Mr. Joseph Harmison, owner, Harmison Pharmacies, on behalf of the National Community Pharmacist Association. Ms. Elizabeth Scott Russell, Government Affairs Manager of the National Association of Boards of Pharmacy. Ms. Gabrielle Cosel, Manager, Drug Safety Project, Pew Health Group at the Pew Charitable Trust. And Mr. Gerry Migliaccio, Quality Systems Consultant, Migliaccio Consulting.

Thank you all for coming. You each will have 5 minutes to summarize your testimony. Your entire written statement will be entered into the record.

So, Dr. Gottlieb, we will begin with you. You are recognized for 5 minutes for an opening statement.

STATEMENTS OF SCOTT GOTTLIEB, M.D., RESIDENT FELLOW, AMERICAN ENTERPRISE INSTITUTE; JOSEPH H. HARMISON, OWNER, HARMISON PHARMACIES, ON BEHALF OF NATIONAL COMMUNITY PHARMACIST ASSOCIATION; GERRY MIGLIACCIO, QUALITY SYSTEMS CONSULTANT, MIGLIACCIO CONSULTING; ELIZABETH SCOTT (SCOTTI) RUSSELL, GOVERNMENT AFFAIRS MANAGER, NATIONAL ASSOCIATION OF BOARDS OF PHARMACY; GABRIELLE COSEL, MANAGER, DRUG SAFETY, THE PEW CHARITABLE TRUSTS

STATEMENT OF SCOTT GOTTLIEB

Dr. GOTTLIEB. Thanks a lot, Mr. Chairman Pitts, Mr. Ranking Member Pallone, and members of the committee. Thanks for the opportunity to testify today. I have a longer statement for the

record. I would like to summarize a few key points for you this morning.

The tragic deaths of 55 Americans and the sickening of more than 740 resulting from contaminated steroid injections that were shipped by a disreputable firm have rightly focused public attention on a largely unfamiliar but prominent part of the drug supply chain, the practice of pharmacy compounding.

Before this Congress are proposals to tighten Federal regulatory oversight of these compounding pharmacies and the practice of pharmacy more generally. Observers are calling on Congress to give the FDA more oversight of these firms. New laws merit consideration. We should articulate clear and bright lines between a legitimate practice of pharmacy compounding and those firms operating illegally as large-scale manufacturers under the guise of a pharmacy license. Some key considerations should, in my opinion, guide this work.

First, there exists a practice of pharmacy. It was never intended that all compounding would create a new drug and be subject to FDA regulation but for the enforcement discretion or for the willingness of Congress to provide explicit exemption to certain pharmacists and certain activities that pharmacists undertake.

Second, FDA has authority to target compounders that cross the line between the practice of pharmacy and engage in drug manufacturing under the guise of a pharmacy license. What FDA largely lacks is ease of administering this authority. FDA is generally not able to force firms to submit advance information to the agency before the firm is suspected of any wrongdoing, and so that the agency is more efficiently able to identify firms engaged in wrongdoing and target its oversight.

Third, FDA generally lacks tools and resources to regulate a new class of firms that the agency has dubbed nontraditional compounders. I would argue that the firms in question here are not compounders, and calling them such confuses different issues. Rather, they are engaging in the bulk, large-scale repacking and manufacturing of sterile preparations of FDA-approved drugs, typically in advance of and often not in response to prescriptions for individual patients.

To the degree that these large-scale operations prepare sterile volumes of drugs in a bulk form and ship these units widely, they present some novel risks and they have the potential for what I would call distributed risks. The public health could benefit from applying additional oversight to these firms, especially requirements that they adhere to good manufacturing practices.

Fourth, as we address issues of supply, we must also address the policy decisions that have increased demand for products from some disreputable firms, from large-scale compounders who are breaking existing law and violating existing regulations. For example, the recent crackdown on manufacturing of generic drugs have shifted a lot of the demand for generic preparations to compounders. Likewise, decisions by FDA to suspend enforcement against compounders in certain select situations where the agency and policymakers had concerns about the high cost of FDA-approved drugs relative to the low costs of compounded versions has

also given greater license to certain compounders to bend, if not break existing law.

Consistent enforcement is going to be especially important if we create a new class of compounders that FDA has dubbed the nontraditional compounding. If FDA doesn't exercise its enforcement evenly and consistently, which means not allowing firms to compound identical versions of FDA-approved products, then the agency will give more incentive for drug makers to remask themselves as nontraditional compounders to skirt FDA's new drug requirements.

Finally, the market for compounding drugs is evolving very quickly. It is consolidating as other entities like distributors could well start buying out the large compounders. As this process unfolds, it will leave behind a much different compounding industry. This should serve as a cautionary tale to all of us. We should be mindful that the rules that we might write today would no longer be applicable to the market that we see tomorrow.

Thank you for the opportunity to testify this morning. I look forward to your questions.

Mr. PITTS. Thank you, Dr. Gottlieb.

[The prepared statement of Dr. Gottlieb follows:]

Examining Drug Compounding

Testimony before the House Energy & Commerce Committee
Subcommittee on Health
Thursday May 23, 2013

By Scott Gottlieb, MD
Resident Fellow
The American Enterprise Institute

Key Points:

1. There exists a practice of pharmacy. It was never intended that all compounding would create a new drug and be subject to Food and Drug Administration regulation but for the enforcement discretion of the FDA or for the willingness of Congress to provide explicit exemption to certain pharmacists and certain activities.

2. FDA has authority to target compounders that cross the line between the practice of pharmacy and engage in drug manufacturing under the guise of a pharmacy license. While legal precedents cited by other witnesses have created some ambiguity, what the FDA largely lacks is ease of administering its authority. FDA is generally not able to force firms to submit advance information to FDA (before the firm is suspected of any wrongdoing) so that the agency is able to more efficiently identify firms engaged in wrongdoing and target its oversight. In some cases, FDA doesn't know about these firms until a problem arises. In other instances, FDA is forced to make an affirmative case that a compounding pharmacy is violating the law before the agency is able to compel an inspection or take other measures.

3. FDA generally lacks tools and/or resources to regulate a new class of firms that the agency has dubbed "non traditional compounders". I would argue that the firms in question here are not compounders, and calling them such confuses different issues. These are firms that repackage sterile FDA approved products into new dosage forms to improve their administration and enable the drugs to be tailored to therapy – for example, breaking chemotherapy into pediatric volumes, mixing hyperalimentation, preparing IV fluids, and breaking hospital-volume anesthetics like propofol for use in appropriately supervised outpatient settings. These firms fall into a gray area right now where they are treated as compounders but are not engaging in traditional forms of compounding. Rather they are engaging in the bulk repacking and manufacturing sterile preparations of FDA approved drugs, in advance of (and often not in response to) prescriptions for individual patients. To the degree that these large-scale operations prepare sterile volumes of drugs in a bulk form and ship these units widely, they present some novel risks.

4. As we address issues of supply, we also must address the policy decisions that have increased demand for compounded products from large scale "non traditional" compounders. At times, FDA has exercised its authority unevenly, which has given more incentive to compounders to skirt the law. Also FDA's actions against generic firms have driven the market for many drugs to compounders. In law and regulation, we need to take a risk-based approach that encourages sourcing of drugs from the most competent parts of the market, not its least competent elements.

5. This is going to be especially important if we create a new class of compounders that FDA has dubbed "non traditional compounding". If FDA doesn't exercise its authority evenly, which means not allowing firms to compound identical versions of FDA approved products, then FDA will give incentive for drug makers to re-mask themselves as "non traditional compounders" to skirt the new drug requirements.

6. Part of the reason why FDA's oversight has been, at times, inconsistent is that the agency often had a product orientation -- not a facility-based orientation – to its enforcement activity. That needs to change. FDA often targeted products they believed were being inappropriately marketed for inappropriate uses, rather than firms that were not operating under sound conditions. Enforcement was often reactive as a result. The agency's enforcement needs to take on both considerations.

7. Finally, the market for compounded drugs is evolving quickly. It's consolidating, and other entities (distributors, generic manufacturers) could well start buying out the large compounders. To these ends, what we do today may be irrelevant to the market we see in the near future. It may pay to wait and see how things shake out, and also to see how FDA's recent enforcement activity impacts these markets.

The views expressed in this testimony are those of the author alone and do not necessarily represent those of the American Enterprise Institute.

Introduction

Mr. Chairman Pitts, Mr. Ranking Member Pallone, and members of the House Energy and Commerce Committee, Subcommittee on Health:

Thank you for the opportunity to testify today before this Committee.

The tragic deaths of 55 Americans and sickening of more than 740[1], resulting from contaminated steroid injections (methylprednisolone acetate) that were shipped by a disreputable "compounding pharmacy" located in Massachusetts, have rightly focused public attention and the work of this Committee on a largely unfamiliar, but prominent part of our drug supply chain – the practice of pharmacy compounding.

[1] CDC Statistics: http://www.cdc.gov/hai/outbreaks/meningitis.html

Before this House Committee, as well as the Senate, are proposals to tighten federal regulatory oversight of these compounding pharmacies, and of the practice of pharmacy more generally. Observers are calling on Congress to give the Food and Drug Administration (FDA) expanded oversight of these establishments.

New laws merit consideration. We should articulate clear and bright lines between the legitimate practice of pharmacy compounding, and those firms operating illegally as large-scale drug manufacturers under the guise of a pharmacy license.

I don't believe that it should be left to FDA's discretion to establish these boundaries as the agency goes about its work, or allow a fuzzy standard to persist. I believe that this would only add to uncertainty in the marketplace and create an undue burden on FDA to interpret vague authority. Ultimately it would result in uneven enforcement that would risk repeating some of the past mistakes.

Nor do I believe any pharmacy practice where drugs are compounded necessarily creates a new drug. There is such a thing as the practice of pharmacy that was, in my view, a sphere of medical practice that was never intended to be subject to FDA oversight. There are pharmacies that clearly practice within the scope of their profession, and are subject to state and professional regulation. And there are pharmacy compounders that are clearly crossing the line between the practices of pharmacy and taking on all the characteristics of a drug manufacturers and, as such, already fall squarely within FDA's existing oversight and authority.

But it seems illogical, inconsistent with prior statute, and administratively burdensome to declare that all pharmacy compounding – even done locally, for individual patients, and in response to valid prescriptions – creates a new drug and could be subject to FDA oversight but for Congress' willingness to exempt certain activity from new drug requirements, or FDA's exercise of enforcement discretion.

Instead, we should establish a clear boundary and objective tests for when pharmacies are engaging in legitimate compounding – and are subject to state regulation; and when establishments have crossed the line and are operating as drug manufacturers under the facade of a pharmacy license. When these lines are crossed, FDA has clear authority to assert – at the least – its Good Manufacturing (GMPc) standards to ensure the safety and effectiveness of products. This basic principle exists today, and should be part of any further clarification of existing law.

The merit in considering these issues is made urgent by the tragedy in Massachusetts and the apparent malfeasance at the New England Compounding Center (NECC). But it's also made necessary by the changing face of this industry.

These changes in the way compounding pharmacies operate, along with policy decisions (some made by FDA) that have increased demand for these compounded products, have strained FDA's existing resources and its policies in this area.

These challenges may call for a greater role for both state and federal regulators. But we need to be mindful of the reasons why the practice of pharmacy has traditionally been left to state regulation. When proper oversight demands that regulators examine the relationship between a provider and a patient (as proper oversight of the practice of pharmacy entails) then these endeavors are best left to state and professional authorities who have more proximity to the actual provision of care. Not every regulatory endeavor benefits from federal involvement.

In addition, we also need to be mindful of the policy decisions that drive more widespread – and sometimes inappropriate – use of compounded products. Finally, we need to be aware of the authority that FDA currently has that – with proper attention and perhaps additional resources – could provide better protections.

We need to take measure of these things before we enact new laws.

The recent problems didn't arise from traditional compounding, which is a legitimate part of the practice of pharmacy and an important part of medical care.

The traditional practice of pharmacy compounding is generally regarded as the combining or altering of ingredients by a licensed pharmacist, in response to a licensed practitioner's prescription for an individual patient. This activity produces a medication tailored to a patient's special medical needs. Compounding pharmacies mix or alter drug ingredients to adapt a medicine based on a doctor's prescription—for example by changing a pill into a formula, changing dosage forms, tailoring chemotherapy, or adding cherry flavoring to a child's medicine.

The practice of pharmacy compounding lets physicians customize drugs to individual patients. Traditional pharmacy compounding typically is performed on a small scale and is always performed in response to a valid patient prescription.

The FDA normally doesn't get involved with such practices because it isn't tasked with regulating the legitimate practice of pharmacy. Like the practice of medicine, pharmacy is largely left to professional and state oversight. But once pharmacies begin manufacturing and shipping medicines on a wide scale, and do so in a way that isn't in response to a valid prescription, these firms often become "drug manufacturers" and fall squarely under the FDA's extensive authority.[2]

In recent years, we have seen much more widespread use of compounded pharmacy products. Along with this increased use, we have seen the simultaneous expansion in the scope of the industry, and the advent of very large compounding pharmacies that commercialize and distribute drugs on a wide scale, without a doctors' prompting, and outside the boundaries of an individual patient encounter.

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[2] A compounding fracture at the FDA. Scott Gottlieb and Sheldon Bradshaw. The Wall Street Journal, November 14, 2012. A24.

These mega establishments stretch the traditional definition of what it means to be a compounding pharmacy. It's the intersection between the activities of these non-traditional establishments and existing state and federal regulation, that I believe bears closer scrutiny. With my testimony today I want to do three things:

First, I want to outline some policy decisions that I believe have increased demand and weakened oversight of compounding under FDA's existing authorities.

I believe these policy decisions merit scrutiny, and perhaps re-examination. The compounding industry has evolved significantly in recent years, in many cases magnifying old risks and creating new ones. Some of this evolution owes to changes in the market for these products. But in other cases, it stems from changes in regulation that have shifted the market away from traditional manufactures, and at times, emboldened compounders to expand production into gray areas.

All of these factors bear close scrutiny. Any solution to mitigate existing risks must address not only the supply of higher-risk products, but also the factors that create the demand for these products to be produced by lower-standard manufactures.

Moreover, if Congress does seek to give FDA clearer authority to regulate these so-called non-traditional compounders, who I believe already fall outside the traditional practice of pharmacy and are subject to FDA oversight today, there is an important consideration. This new authority has to go hand-in-hand with vigorous enforcement by FDA of rules that prohibit compounders from making copies of FDA-approved drugs. Otherwise, creating this third category of "compounding manufacturers" where the full brunt of FDA's requirements don't apply will create incentive for drug manufacturers to re-cast themselves as non-traditional compounders so that they can float into this new, regulatory-light category.

In recent years, FDA has been reluctant to stop compounders from copying FDA-approved drugs out of economic concerns that it would limit consumers to higher priced products. These economic concerns have to be addressed separately.

If the NDA process imposes costs that end up raising the price of finished goods, that has to be separately addressed, perhaps through thoughtful review of how the NDA process could be made more efficient when it comes to certain lower risk, better understood sterile products. But so long as FDA is going to create a new category of compounding manufactures, it needs to prevent traditional FDA approved products from moving into this new category and undermining the safety of products now being produced by reputable manufacturers to high standards. We also need to make sure that the intellectual property surrounding those NDA products is not deliberately undermined by a new category of FDA-sanctioned manufacturers.

Second, I want to outline where FDA has existing authority to regulate non-traditional pharmacy compounding, and try and give this committee a sense for

how, in my view, that authority has been exercised by FDA and why the agency has made certain choices in how it interpreted those rules. Much is made of FDA's concern that legal challenges to the existing statute and policies have left FDA's current authority muddled. While these complaints have merit, I believe that there are other considerations that also shape the strength of FDA's authority.

For example, FDA often targets specific products rather than troubled facilities. The FDA has also, at times, not enforced rules evenly out of concern that knocking certain violating products and firms out of the market might impose higher costs on consumers. All of these considerations and policy choices have merit. But they create a regulatory scheme that is at times reactive and can appear arbitrary.

Third and finally, I want to propose some ideas for how I believe that a clearer standard in policy and law could provide for more effective oversight in this area and create a clearer boundary between the legitimate practice of pharmacy compounding and those firms that are distorting that traditional custom.

FDA has noted that legal challenges to its existing policies have served to muddle its authority. We also need to consider the way that FDA's own actions have contributed to this haziness. The FDA's influence on stoking some of the challenges it now faces is instructive because as I will explain, it speaks to the need for FDA and Congress, to establish a clear line between the activities that fall within the FDA's scope and those that are traditional pharmacy left to state authority.

The Evolution of Large Scale Compounding

As FDA Commissioner Dr. Peggy Hamburg stated in recent testimony, the practice of pharmacy compounding has undergone an evolution in recent decades. We have seen the advent of very large scale compounding firms that operate with many of the characteristics of traditional drug manufacturers. In recent months, FDA has referred to this practice as "non traditional compounding."[3]

Part of this growth in compounding has been driven by greater sourcing of these products by hospitals. As Dr. Hamburg stated in recent testimony, to save costs, hospitals have outsourced compounding that they used to do in house.[4]

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[3] Pharmacy Compounding: Implications of the 2012 Meningitis Outbreak, Statement of Margaret A. Hamburg, M.D., Commissioner of Food and Drugs, Food and Drug Administration, Department of Health and Human Services, Before the Committee on Health, Education, Labor and Pensions United States Senate. November 15, 2012

[4] Statement of Margaret A. Hamburg, MD Commissioner of Food and Drugs, Food and Drug Administration, Before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives. "A Continuing Investigation Into the Fungal Meningitis Outbreak and whether it Could have Been Prevented." April 16, 2013.

Let me elaborate on this point. While I agree with the FDA's general analysis, I would cast the different pieces of this broader industry into different slices.

What have evolved are essentially three types of outfits when it comes to the area generally referred to as compounding.

First is traditionally compounding, where a pharmacy works in consultation with a physician to tailor a product based on a valid prescription.

This practice of pharmacy falls within professional and state purview and has not been the source of recent concerns.

Next, there are firms that masquerade as pharmacies, but engage in large scale manufacturing, often of unique products or drugs designed to compete with FDA approved medicines. These firms develop these drugs in bulk, without valid prescriptions or in anticipation of prescriptions, and do not adhere to good, sterile manufacturing techniques. These firms seem to be violating current federal law. Many are manufacturing new and unapproved drugs. In so doing, they are already subject to FDA's current and extensive oversight.

There is a third category of manufacturers that FDA has dubbed "non traditional compounding" but which I would offer is not compounding in its traditionally form, but another new and vital manufacturing service that has evolved over time.

Firms in this third category typically produce sterile products in bulk, usually to supply large medical practices and hospitals. In its most common form, these outfits will break down large volumes of FDA approved products into smaller units, for example taking large units of an anesthetic and breaking it into syringes to be more easily administered, taking a large unit chemotherapeutic and breaking it into smaller units to be dosed for a pediatric indication, or producing hyperalimentation for supplemental nutrition delivered by parental or enteral means.

These outfits are really sterile repackaging and re-mixing firms – not compounders in the traditional, local sense. Hospitals used to do this sort compounding of work in house, in their own pharmacies. When it was a hospital-based pharmacist working on a small scale under a sterile hood, there was manageable risk and a lower likelihood of wide contamination. But to save costs and improve quality and efficiency (in part, as a response to the tightening of the hospital industry's regulations) the hospitals have outsourced this work to these new, large firms.

The firms now performing this role are doing it on a wide scale, and are not compounders in the traditional sense. FDA confuses the issues by referring to these firms as "non traditional compounders". I would call these firms sterile preparation manufacturers or sterile prep manufacturers. These firms are a new, and important category of drug suppliers. They are now a vital part of the drug supply chain for hospitals and large outpatient practices. And their work creates certain risks.

If generic drug firms were engaging in this activity, FDA would require separate drug applications for each dosage firm. FDA would require the generic firms to do stability studies, container closure studies, and pay separate user fees, among other things. This is one of the reasons why the generic drug makers do not supply drugs in the full range of dosage forms and packaging – and why the hospitals have to turn to these "sterile prep manufacturers" (or non-traditional compounders).

This begs the question: Should these sterile prep manufacturers be subject to the same oversight as a generic drug firm engaging in the same activity?

It's a relevant question, but I think the answer is no. Because these hospital preps and repackaged drugs have a shorter dating period, it might be reasonable to subject them to a lighter regulatory touch.

The firms doing this sort of "non traditional compounding" (to borrow FDA's poorly suited lexicon) generally do a good job. But they have been the source of some problems, including some fatal contaminations in recent years. A review of FDA's recent oversight work has found that these products are not uniformly produced under sterile techniques, and in some cases have some significant contaminations. To the degree these "sterile" products are being used in hospitalized patients, who often have a lot of co-morbid illness, this can create public health risks.

It is reasonable to consider whether these outfits should be subject to GMP requirements to make sure they adhere to sterile techniques.

I would offer that these firms should be the focus of the present discussion.

Traditionally compounding should continue to be the domain of state and professional oversight. And the compounders like NECC engaged in manufacturing new drugs already fall under FDA's current scrutiny. As for the sterile prep manufacturers (or "non traditional compounders") since the sterile preps and re-packaged goods are often produced and shipped on a wide scale, an inadvertent contamination in one lot could have widely distributed risks before a product could be recalled by an overlapping patchwork of state and federal authority.

Policy Choices and the Rising Demand for Compounded Products

To exam why the industry has grown and evolved in recent years, also requires a closer examination of the policy measures that I believe have contributed to these circumstances. Some of these recent policy decisions have driven demand away from traditional manufacturers like generic drug firms, and to compounders.

In at least some cases, providers are turning to a small number of unreliable compounders because they cannot sources these products elsewhere.

To begin, a recent tightening in FDA's oversight of generic drug firms that made nearly identical versions of the same sterile injectable drugs produced by many compounders (including NECC) has prompted providers to source more products from large scale compounders. This tightening was rooted in some legitimate concerns that FDA had about the reliability of the generic manufacturing facilities. But it has created a contradictory set of policies that at has had the effect of shifting purchases from more reliable sources to firms with more questionable practices.

A key question is this: Even assuming that the FDA's concerns around the generic drug makers were all proven correct, would the continued production of drugs from these facilities – under close FDA supervision – been preferable to the alternative outcome -- closing these generic facilities and driving some providers to source products that were in shortage from compounders. By driving the generic firms to close their facilities while they underwent remediation, it left the market to be supplied by the only outfits still capable of operating – the compounders. This fueled further growth of these compounded products. But one must also ask whether the overall risk to the public was increased as a result of the fact that so much of the utilization had shifted to these more lightly regulated outfits.

This question is important is because it gets to the heart of the kinds of considerations that a risk-based approach to regulating these products should take up, and to how we make sure clinical needs are met with the most reliable products available. This same challenge has played out in other contexts where the decisions that FDA took may have served to increase demand for compounded drugs.

For example, Congress intended for FDA's enforcement over compounding to take into consideration when drugs were being manufactured by compounders that competed directly with FDA approved medicines, and therefore didn't offer any unique tailoring or differentiation that was a key clinical characteristic of the practice of pharmacy and the traditional role of compounding.

To these ends, the FDA has historically asserted its authority when compounding pharmacies were supplying their own versions of drugs that were also available commercially -- as FDA-approved branded and generic products. In these circumstances, the FDA held that these compounding firms were guilty of distributing unapproved new drugs. Among other things the New England Compounding Center, the outfit behind the tainted steroid shots, was cited for this sort of activity in that 2006 warning letter that FDA sent to the troubled firm.

However, a policy change made in recent years curtailed some of the exercise of this authority. This policy change gave greater economic incentive and political license to compounders to engage in more widespread production of drugs that exist as FDA approved products and compete directly with FDA regulated medicines.

In particular, FDA changed a longstanding guidance document that stipulated that the agency would clear the market of compounded drugs once a drug went through the new drug approval process and earned FDA approval for the same indication.

The guidance was changed to read that FDA would use its discretion in such cases, and only take action to remove the compounded products in cases where it had specific public health concerns. While I understand the agency's economic concerns around the potential for drug costs to rise when compounders are forced to exit the market, these considerations should not factor into the consistency by which the agency applies its policy. There are other avenues to address these economic concerns. FDA could also give greater consideration to the cost of the NDA process and ways to make that more efficient, especially in the case of old, well-understood drugs seeking FDA approval to sell approved versions of compounded drugs.

But the policy of removing the older, unapproved drugs remains controversial, and expectations that FDA would enforce it were largely squashed after FDA said it would not step in when the company KV Pharma, sought and received FDA's nod for Makena, an approved form of a type of progesterone that's widely compounded.

The FDA decided not to take action out of a well-publicized concern about the high cost of Makena relative to the compounded formulations. This political decision undermines the incentive for other companies to run registration trials to get FDA approval for drugs that are widely compounded. It emboldened compounders. The company that got FDA approval for Makena, KV Pharma, went into bankruptcy.

What kind of incentive does that give to other firms to invest in the development of FDA-approved versions of drugs that are being widely compounded?

The intervention in the KV Pharma case sends a message to would-be violators that the pricing of products could factor into how the FDA can enforce its own safety rules. The New England Compounding Center was also among the compounding firms distributing an unapproved version of the KV Pharma product. Does this committee believe that it's a good outcome that the active ingredient in Makena is now being widely used in woman who are pregnant, and made by firms like NECC?

Or would an FDA approved version of that medicine be preferable?

It's hard to have it both ways when it comes to these matters. That's why it was important that FDA lay out clear lines and enforces them vigorously and consistently to reduce the incentive of firms to skirt the law by operating as new drug manufacturers under the guise of a pharmacy license.

This is especially true if Congress creates a third category of "non traditional compounders". If FDA doesn't vigorously and consistently enforce a clear boundary between drugs that must be compounded because of the way they are made, and those that have gone through the NDA process and exist in the market as FDA

approved new drugs, then the agency will create a clear and improper incentive for some drug manufacturers to re-cast themselves as "non traditional compounders" to skirt the new drug requirements of the Act. Congress should be aware that there are significant, competing tradeoffs as a result of this approach. For example, there's the potential for new policies to drive compounders out of certain popular markets.

The Exercise of FDA's Existing Authorities

Even while we consider new legislation, we should first look for avenues to help FDA make better use of its existing authority to regulate non-traditional pharmacy compounding. As FDA has shown with its recent, robust actions, the agency has some clear authority in this space and the ability to exert considerable oversight.

Indeed, by FDA's account, it targeted 29 firms for inspections based on their sterile processing practices and took stern actions against some of those firms. In most cases FDA was able to exercise its oversight without interference. In a few instances FDA needed to seek a court's backing to get access to the records. While this may have imposed some brief delays, the agency seems to have fulfilled its mission.

Much is made of FDA's concern that legal challenges to the existing statute and to the agency's policies have left FDA's current authority muddled.

While these complaints have some merit, I believe there are other considerations that also shape the exercise of FDA's authority. Considering these can provide a fuller understanding of the challenges that FDA faces, and potential policy solutions.

In particular, I believe that the FDA has historically taken a product approach to its enforcement of its compounding oversight, rather than a facility based approach. What I mean by this, more specifically, is that the enforcement actions were often taken in response to individual products that the FDA was concerned with – either because the products carried inappropriate claims, or were being used for circumstances where FDA didn't believe that the benefits justified the risks.

For example, in 2006 FDA sent a series of warning letters to compounders who were formulating topical lidocaine for use as a pre-treatment in electrolysis, to help numb peoples' legs before they had the sometimes-painful procedure.

FDA was rightly concerned that using large amounts of topical lidocaine in this way could cause systemic side effects, and was an inappropriate use of the drug.

I use this example to illustrate a simple point: That the enforcement activity often targeted the products rather than the facilities. This often made the agency's enforcement a reactive process, rather than a pro-active assessment of risk. While products being used in inappropriate ways create risks, and deserve regulatory scrutiny, the FDA can probably get as much, if not more bang for its public health dollar by bringing equal or even greater focus on the facilities that are

inappropriately compounding products in ways that are unsterile and cross the line between traditional compounding and the wholesale manufacture of new drugs.

It's a difference of where the enforcement mindset emanates from – whether it flows from the drug reviewers in charge of reviewing products, or facility inspectors in charge of overseeing the quality of facilities, or some combination of each.

In the past, a lot of the enforcement activity emanated from the drug review divisions and the drug center's office of compliance. This let to an orientation that sometimes targeted products, rather than facilities. FDA would bring enforcement actions in cases where FDA found drugs that were being compounded for uses that the agency believed created risk, or misled consumers.

I believe an equal focus should be placed on targeting unsafe, unsanitary facilities whose business practices violate existing law. This requires a greater role for the FDA field in doing actual inspectional work that focuses on unsafe facilities as much as it requires a focus by drug review staff on the products themselves, and the indications they are used for.

Establishing Bright Regulatory Lines

Above all else, the inspectional activities must be targeted in a way that creates a clear delineation between the protected practice of pharmacy, and those firms that are creating new, unapproved drugs, or the sterile prep manufacturers I spoke of.

FDA has outlined a number of key factors that establish the boundary between traditional and "non traditional" compounding pharmacy. So it has historically articulated where a boundary could rest. These principles should guide policy.

It's these factors that have been the basis of FDA's recent vigorous and successful oversight efforts in this area. The agency's recent enforcement work demonstrates that the agency is able to enforce its supervision when firms fall outside of these boundaries. Moreover, some of these factors have already formed the basis of Congressional statute in section 503(A). These factors should form one basis of FDA's enforcement going forward and any re-articulation of that policy.

It's noteworthy that size, as well as shipping across state lines, alone, are not reliable criteria. There are good reasons why some products may be produced on a large scale even in response to physician prescriptions. For example, it may not be possible to develop a single dose from a bulk ingredient.

So a pharmacy producing a drug for a single physician in response to a single prescription may be forced to produce extra volumes of the same finished product.

There are equally good reasons why some pharmacies might ship products interstate. It could be as simple as a pharmacy that resides close to a state border. Proper criteria involve more than just one or several factors, but a multi-part test.

FDA has expressed some of the factors that would be part of a multi-part test in its prior guidance documents that addressed its enforcement. They include:

1. Compounding of drugs in anticipation of receiving prescriptions, except in very limited quantities that are done in close relation to the amounts of drugs that will need to be compounded after receiving valid prescriptions.
2. Compounding drugs that were already withdrawn by FDA or removed from the market for safety reasons.
3. Compounding finished drugs from bulk active ingredients that are not components of FDA approved drugs without an FDA sanctioned investigational new drug application (IND) in accordance with 21 U.S.C. § 355(i) and 21 CFR 312.
4. Receiving, storing, or using drug substances (for use in compounding) without first obtaining written assurance from the supplier that each lot of the drug substance has been made in an FDA-registered facility.
5. Receiving, storing, or using drug components not guaranteed or otherwise determined to meet official compendia requirements.
6. Using commercial scale manufacturing or testing equipment for compounding drug products.
7. Compounding drugs for third parties who resell to individual patients or offering compounded drug products at wholesale to other state licensed persons or commercial entities for resale.
8. Except in certain narrow circumstances, compounding drug products that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products.
9. Failing to operate in conformance with applicable state law regulating the practice of pharmacy.

Conclusion

FDA has rightly noted that non-traditional compounding should, because of the higher risk presented, be subject to a greater degree of oversight. The large scale compounding we've seen in the marketplace, where firms manufacture large volumes of sterile products, and do so in advance of (and sometimes without) a proper physician prescription, and then ship these finished products across the country, should be subject to a higher level of manufacturing controls.

"Compounders" operating in this manner are not operating as pharmacies. Let's make no mistake. They are making new sterile dosage forms on a mass scale.

Other "compounding pharmacies" operating with these same characteristics, and making unapproved new drugs (like NECC) already fall outside the traditional practice of pharmacy and make themselves subject to FDA's oversight.

FDA's main complaint, in my opinion, isn't that these entities aren't subject to the agency's regulation under the existing law. The FDA's main complaint, when you boil it down, is that the existing legal framework puts too much burden on FDA (in the agency's opinion) to have to make the affirmative case that these firms are operating in a way that places them under the agency's jurisdiction. That's a valid complaint, but it' a different concern than the one commonly reported.

At its core, the issues we are talking about here aren't issues of whether or not FDA has proper authority. They do. The issues are whether or not FDA has the legal and regulatory tools to make its role in these regulatory endeavors administratively easier, more consistent and anticipatory, and less resource intensive.

FDA's traditional regulatory posture is to compel the submission of information to the agency that allows FDA to target its regulatory oversight. In the case of compounding pharmacies, FDA – at the margins – needs to often make the affirmative case that certain firms are not acting as pharmacies but as drug manufacturers and are therefore subject to the agency's oversight.

What FDA wants, in my view, is the means to compel the submission of certain information that would enable FDA to more easily demonstrate when compounders are no longer acting as compounders. But we should be candid about this key fact. Legislation could be narrowly tailored to address the real problems here. I believe that some of the proposals address issues that are peripheral to the key challenge.

In closing, I wish to make one final point. The market for compounding is changing very rapidly, not only as a result of the tragedy in Massachusetts, but the stepped up oversight that FDA has exerted in recent months, as well as the activity on Capitol Hill. It's also driven by issues in the marketplace itself, where certain lower margin businesses are looking to get into higher margin work in drug manufacturing.

To these ends, we're seeing compounders consolidate, and get acquired by more reputable manufacturers. It's my belief that this industry will undergo an evolution in the next few years, where many of the large-scale compounders will either consolidate or close because they can't meet the current scrutiny, and reputable manufacturers and maybe drug distributors will acquire many others.

We may also benefit from seeing the culmination of FDA's recent enforcement activity, and get a better sense of the contours of FDA's existing influence.

As this process unfolds, it will leave behind a much different compounding industry. This should serve as a cautionary note to all of us. The rules that we might write today may no longer be applicable to the market that we see tomorrow.

The market forces that are transforming this industry may accomplish many of the public health goals that we seek to address through legislation.

# # #

Dr. Scott Gottlieb is a physician and Resident Fellow at the American Enterprise Institute. From 2005-2007 he served as the FDA's Deputy Commissioner for Medical and Scientific Affairs, and before that as the agency's Director of Medical Policy Development and as a Senior Advisor to the FDA Commissioner. Dr. Gottlieb consults with and invests in biopharmaceutical companies and serves as a director to several life science companies. Scott Gottlieb is a member of the policy boards to the Leukemia and Lymphoma Society and the Society of Hospitalist Medicine.

Dr. Gottlieb can be reached at Scott.Gottlieb@gmail.com

Mr. PITTS. Mr. Harmison, you are recognized for 5 minutes for opening statement.

STATEMENT OF JOSEPH H. HARMISON

Mr. HARMISON. Thank you, Mr. Chairman. I wish I could speak as quickly——

Mr. PITTS. Poke the button on that. If you will push the button, speak into the mike, please. Thank you.

Mr. HARMISON. OK. Excuse me.

Chairman Pitts, Ranking Member Pallone, Vice Chairman Burgess, thank you for the opportunity to be here today. As stated, I am Joe Harmison. I am a practicing pharmacist, pharmacy owner, and past president of the Texas Pharmacy Association and the National Community Pharmacists Association. NCPA appreciates the opportunity to share the community pharmacist's perspective regarding issues relating to drug compounding. NCPA represents the views of community pharmacists, including 23,000 independently owned community pharmacies. According to an NCPA member survey, 86 percent of our members do some kind of compounding. This can range from flavoring pediatric liquids to changing dosage forms to pay for patients that can't take oral solids to topicals to injections. In my practice, we mainly emphasize pain medications. And we are U.S. Pharmacopeial 797 standard compliant.

Our hearts go out to the families who have suffered from the tragic events surrounding New England Compounding Center, and NCPA is committed to working with Congress on the issues of practice that exceed State-regulated compounding. NCPA commends the committee for taking a closer look at those actions and inactions that led to the tragic NECC event. We believe the committee is taking the proper steps to address this tragedy by focusing its investigations on what steps should have been taken and oversight that ensures that the proper regulatory bodies are exercising their full authority.

Compounding is the backbone of pharmacy. It goes back to the time of the alchemist. For centuries, pharmacy only did compounding, until World War II, then commercially prepared medicines became more prevalent, which is still the thing today. But it did start dawning on people a couple of decades ago that there are people that need something that just isn't commercially available. So compounding came back into being an important part of the pharmacy practice.

Another thing, compounding serves to bridge a gap which we are experiencing more and more when commercial products are not available. Patients must be assured that they are not forced to go without medicines or their treatment because medications are unavailable and compounding for that medication is prohibited or tied up in a bureaucracy. It is important to reiterate that pharmacist compounding is an integral part of pharmacy profession and meets patients' needs in hospitals, long-term care, home infusion, hospice, every community setting I can think of.

NCPA has always and will continue to advocate that pharmacy compounding is best regulated by the State boards of pharmacy while manufacturing oversight is the purview of the FDA. Pharmacy compounding medication is an important part of the medical

care and allows dispensing custom-made medications and should continue to be related by State boards of pharmacy, as all other medical profession licenses are.

State boards of pharmacies currently oversee all aspects of pharmacy and in most cases their records are public. So it is not hard to obtain who is doing what. If the FDA has concerns about appropriate licensed pharmacy, then the FDA currently has the authority to ask the State board of pharmacy to work with them to address the issues. If it is found that they have an entity that is acting under the guise of a pharmacy and is exceeding its State-regulated authority, then the States board of pharmacy should suspend the license of that pharmacy until it complies with the State regulations or meets the FDA regulations to be a manufacturer.

All parties involved must make certain that the State boards of pharmacy are adequately staffed, trained, and funded to effectively regulate compounding. NCPA encourages the State boards of pharmacy to acquire uniform compliance with USP 797 standards in order to provide more uniform product standards. As such, every State will be assured that resident and nonresident pharmacies alike are all in compliance with the USP standards.

In most cases, compound medication must originate from a prescription for a specific patient. There are times that we may do things in advance, but we have to be able to prove that we use historically a certain amount in a very short period of time.

I see I am out of time. Compounding should not be defined by nuance, such as types of product, whether it is sterile or nonsterile, as risk of complexity of compounding is not solely dependent on the product type. Neither is quantity of the product made in a pharmacy of bearing because we can make many different things and they are all safe. And interstate commerce should not be—because we, was stated earlier, we are a border State to 5 different States, and, being rural, there are places that just have to go across State lines. But if it is the issuance of a prescription for a specific patient for a specific malady, this should be allowed and under the purview of the States.

Thank you for the opportunity to be here. NCPA pledges to work with Congress to put this to rest.

Mr. PITTS. Chair thanks the gentleman.

[The prepared statement of Mr. Harmison follows:]

United States House of Representatives
Committee on Energy and Commerce
Subcommittee on Health Hearing on
"Examining Drug Compounding"
Thursday, May 23, 2013 - 10:00am

Chairman Pitts, Vice-Chairman Burgess, Ranking Member Pallone and Members of the Subcommittee, my name is Joe Harmison and I am a pharmacist, owner of DFW Prescriptions and past president of the National Community Pharmacists Association (NCPA). NCPA appreciates the opportunity to share the community pharmacy perspective regarding issues relating to drug compounding. NCPA represents the interests of America's community pharmacists, including the owners of more than 23,000 independent community pharmacies. According to a NCPA member survey, almost 86% of independent community pharmacies compound medications. Our members perform a wide variety of compounding services including hormone replacement medications, making suspensions palatable for pediatric patients, different dosage forms for patients suffering from intractable nausea and vomiting, and medications for cystic fibrosis patients, to name a few. Specific to my practice, I compound medications primarily used in the treatment of pain that help patients and their physicians treat their conditions. We are compliant with U.S. Pharmacopeial Convention (USP) <797> Pharmaceutical Compounding—Sterile Preparations standards.

Our hearts go out to the families who have suffered from the tragic event surrounding the New England Compounding Center (NECC), and NCPA is committed to working with Congress on the issue of practices that exceed state regulated compounding. NCPA commends the Committee for taking a closer look at what actions and inactions led to the tragic NECC event. We believe the Committee is taking the proper steps to address this tragedy by focusing on investigations into what steps should have been taken and oversight to ensure that the appropriate regulatory bodies are exercising their full authority.

Importance of access to compounded medications

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 in accordance with a prescription based on the patient's individual needs. Compounding services can help bridge the gaps during times of prescription drug shortages. Drug shortages have nearly tripled, according to the FDA, and their impact can be devastating. Patients must be assured that they are not forced to go without needed medications or treatments because their medication is unavailable and compounding of that medication is prohibited or tied up in bureaucracy.

It is important to reiterate that pharmacist compounding is an integral part of the pharmacy profession and meets patients' needs in hospitals, long-term care and assisted living facilities, home infusion settings, and many community settings.

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. These state Boards of Pharmacy currently oversee all aspects of a pharmacy from licensure, oversight of pharmacists and technicians, the process of filling prescriptions, records, documents, and compliance with the state's laws and regulations. If the FDA has a concern about an appropriately-licensed pharmacy, then the FDA currently 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 exceed 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 for manufacturing and registers with the FDA. All parties involved must make certain that the state Boards of Pharmacy are adequately staffed, trained, and funded to effectively regulate compounding.

NCPA encourages state Boards of Pharmacy to require uniform compliance with USP 797 in order to provide more uniform production standards. As such, every state will be assured that resident and non-resident pharmacies alike are all in compliance with these USP standards.

Compounds are prepared based on prescriptions or on anticipation of demand

In most cases, compounded medications must originate from a prescription for a specific patient from a health care professional and are made specifically for an individual patient's needs. In other instances, pharmacists participate in anticipatory compounding where they anticipate a demand that a physician might have for a compounded drug based on historical prescribing patterns. In order to preserve access to these vital compounded medications, pharmacies should not be hindered in their ability to engage in anticipatory compounding as long as it is reasonable and based on a historical pattern of prescriptions received by that pharmacy or for specific patients served by that pharmacy.

Compounding should not be defined by the quantity of medications produced or to where the medications are shipped. Compounding should be defined as the preparation of medications upon receipt of a prescription, or, where in reasonable quantities, in anticipation of need for a medication based upon historical patterns.

To the contrary, compounding should not be defined by nuances such as type of product (i.e. sterile and non-sterile) as risk and complexity of compounding is not solely dependent upon product type; quantity of product made as a pharmacy can produce a significant number of compounded medications and not be a manufacturer as long as the pharmacy is making these medications based on individual prescriptions or in anticipation of need based on historical patterns; or interstate commerce as a pharmacy may legitimately ship to more than one state as long as the pharmacy makes the medications being shipped based on individual prescriptions or in anticipation of need based on historical patterns.

Clear lines of communication between the FDA and State Boards of Pharmacy are needed

The FDA should share all inspection data in a timely fashion with state Boards of Pharmacy. Furthermore, FDA should communicate to state Boards of Pharmacy whether the response from the entity inspected addresses all concerns and is sufficient without necessary further action or whether further action is needed to address these concerns. The FDA should strengthen the communication between its regional offices and the states. In addition, FDA should utilize all existing authority and resources in developing and sharing data with states. In order to address the failure in communication in the past, FDA must utilize, and strengthen if necessary, all existing portals and resources in order to produce the needed data sharing to increase communication between the states and FDA.

In conclusion

While discussing what new regulations should be undertaken to prevent this tragedy in the future, before expanding federal authority it is imperative that Congress look at whether current laws and regulations are being properly enforced. NCPA urges the Committee to preserve the authority of state Boards of Pharmacy over compounding by defining any new category with FDA oversight in a very limited and narrowly targeted manner. In addition, any legislation must not be used to facilitate a broad expansion of FDA power over the historically state-regulated practice of pharmaceutical compounding.

NCPA is committed to working with Members of Congress in order to make certain that a tragedy such as the New England Compounding Center does not occur in the future while also preserving patients' access to customized and safe compounded medications. Thank you for inviting me to testify and to share the viewpoints of independent community pharmacy.

Mr. PITTS. Ms. Russell, you are recognized for 5 minutes for opening statement.

STATEMENT OF ELIZABETH SCOTT (SCOTTI) RUSSELL

Ms. RUSSELL. Thank you. Good afternoon, Chairman Pitts, Ranking Member Pallone, and members of the subcommittee. The National Association of Boards of Pharmacy appreciates the opportunity to appear before you today and provide information related to pharmacy compounding. I am Elizabeth Scott Russell, government affairs manager for the association.

As part of a comprehensive action plan that assists States following the meningitis outbreak, NABP partnered with the Iowa Board of Pharmacy to begin conducting inspections of all of its approximately 609 resident pharmacies, focusing first on those delivering compounded drugs into Iowa. Our inspections confirmed that the activities that occurred with NECC were also occurring in other facilities in other States.

To date, NABP has inspected approximately 165 pharmacies and is in discussions about similar inspection programs with other States. We are building a system of proactive information exchange for all pharmacies that will include verifications of licensure, disciplinary checks, and assurances of a timely and robust inspection that meets uniform standards at no cost to boards to assist them in making licensure and registration determinations for nonresident pharmacies.

NABP does believe that Federal legislation is needed to provide the needed distinction between compounding and manufacturing to address critical concerns and provide a safe and equitable environment for both to occur in the best interest of the patient. NABP supports the major concepts of the legislation proposed by the Senate HELP Committee and welcomes the proposed clarifications to the regulatory uncertainties that currently exist, uncertainties that were a primary factor leading to the recent meningitis tragedy.

In particular, NABP affirms that the regulation of the practice of pharmacy remains the responsibility of the State boards of pharmacy and agrees with the language in the proposed Senate legislation that defines traditional pharmacy compounding as part of the practice of pharmacy to be regulated by State boards of pharmacy. NABP also supports the establishment in legislation of a new category for the preparation of nonpatient-specific sterile products that would be registered and regulated by FDA and a clear distinction between this new category and traditional pharmacy compounding.

Although we understand that some terminology must be employed to describe this new category, we would prefer that the term "compounding" not be included in the name because of potential confusion with traditional pharmacy compounding.

NABP supports Federal legislation prohibiting entities that fall into this new category also being licensed as a pharmacy by the State, as this separation is essential to addressing the ambiguous authority that currently exists between the States and FDA; that is, who is responsible. Our experience affirms the importance of a clear separation between manufacturing and compounding and clarifying what activities fall under Federal jurisdiction and what

fall under State jurisdiction. Not having a clear separation could also provide a veil for unscrupulous entities to hide their activities.

NABP does not believe that the interstate distribution of non-patient-specific sterile products should be a required criteria for meeting this definition, this new category, as is in the Senate proposal. We understand the need to establish a delineation point, but such differentiation between intrastate and interstate distribution could create patient safety concerns by allowing large-scale intrastate entities to avoid Federal regulation. NABP could still support proposed legislation that exempts intrastate distributions from the definition for this new category provided the situation is monitored for any additional future action that may be necessary.

In conclusion, NABP believes there is a need for Federal legislation that addresses the safe preparation of compounded medications for patients, that distinguishes between compounding and manufacturing, defines a new category of manufacturers under FDA regulation, balances effective regulation with reality, and carefully constructs the scope and activities of this new category to meet patient needs while maintaining necessary protections. We appreciate this opportunity for input and are available to discuss our comments and any legislative solution in greater detail. Thank you.

Mr. PITTS. Chair thanks the gentlelady.

[The prepared statement of Ms. Russell follows:]

Testimony

on behalf of the
National Association of Boards of Pharmacy

to the

House Energy and Commerce Committee
United States House
May 9, 2013

presented by:

Elizabeth Scott Russell, RPh
Government Affairs Manager
National Association of Boards of Pharmacy

Good morning Chairman Pitts, Ranking Member Pallone, and members of the Committee. I am Elizabeth Scott Russell, Government Affairs Manager for the National Association of Boards of Pharmacy (NABP). NABP appreciates the opportunity to appear before you today and provide information related to pharmacy compounding.

NABP is the impartial organization founded in 1904 whose members are the state agencies that regulate the practice of pharmacy. NABP supports the state boards of pharmacy by developing, implementing, and enforcing uniform standards for the purpose of protecting the public health. NABP also helps state boards of pharmacy to ensure the public's health and safety through its pharmacist license transfer, pharmacist competence assessment, and accreditation programs.

Following the tragic meningitis outbreak caused by contaminated injectable drugs, several states implemented compounding pharmacy inspections or conducted surveys of pharmacies, focusing especially on those engaged in sterile compounding. As part of the NABP Compounding Action Plan that was developed in November 2012 and implemented in December 2012, NABP partnered with the Iowa Board of Pharmacy and other states to begin conducting inspections of all nonresident pharmacies delivering compounded drugs into Iowa. Our initial inspections confirmed that what occurred at the New England Compounding Center (NECC) was also occurring at other facilities in other states. To date, NABP has inspected approximately 165 pharmacies across the states and will continue our inspections until all of Iowa's approximately 600 nonresident pharmacies are inspected.

NABP is also in discussions about similar inspection programs with a number of other states and has plans to establish an e-Profile for each pharmacy in the United States. These e-Profiles will include verifications of licensure, disciplinary checks, and verification that a timely and robust inspection has occurred for each pharmacy, including those performing sterile and non-sterile compounding. The information in the e-Profiles for pharmacies will be sent proactively to boards for use in making licensure and registration determinations for nonresident pharmacies.

In the event that a board of pharmacy has been unable to perform a timely or robust inspection, NABP will conduct an inspection on behalf of the states to ensure relevant laws and pharmacy practice standards are being met. In addition, once an inspection has been completed, NABP will make all publicly available documents, including inspection reports and disciplinary actions, available at no cost to consumers, boards, and Food and Drug Administration (FDA) through a user-friendly and searchable console.

NABP supports the legislation proposed by the United States Senate Committee on Health, Education, Labor, and Pensions (HELP), with some minor modifications. The proposed legislation addresses the critical concerns identified by the states and validated by NABP through its inspections of compounding pharmacies. We welcome the Senate legislation's clarifications to the regulatory uncertainties that currently exist – uncertainties that were a primary factor leading to the recent meningitis tragedy. Most importantly, the clarifications provide the needed distinction between compounding and manufacturing and provide a safe and equitable environment for both compounding and manufacturing to occur in the best interest of the patient.

Authority of the States

As provided in the proposed Senate legislation, NABP agrees that the regulation of the practice of pharmacy, which includes traditional pharmacy compounding, remains the responsibility of the state boards of pharmacy. NABP supports the establishment of the new category of "compounding manufacturing" regulated by FDA, and the clear distinction between this new category and traditional pharmacy compounding. Although we would prefer that "compounding" not be included in the proposed designation because of the inference to traditional compounding and the confusion that could result, we understand that some terminology must be employed that describes the activity being regulated.

The separation of compounding from manufacturing is also critical to maintain the present authority of the states and address one of the contributing factors to the NECC crisis, specifically, the ambiguous authority between the states and FDA. The provision of the proposed legislation that specifies a compounding manufacturer cannot be licensed as a pharmacy is essential to distinguishing between state-regulated compounding and FDA-regulated manufacturing. Our experience, and most recently our inspections of compounding pharmacies, affirms the importance of this prohibition in clarifying what activities fall under federal jurisdiction (FDA) and what entities can engage in compounding and operate under state jurisdiction (state boards of pharmacy).

If a compounding manufacturer is allowed to hold dual licensure or registration, it will be more difficult to separate the two enterprises and could provide a veil for unscrupulous entities to obfuscate their activities. NABP supports FDA receiving authority to access any and all documents and records required for the oversight and regulation of compounding manufacturers. We are concerned, however, about allowing FDA access to pharmacy records for activities that are regulated by the states. If an entity is manufacturing or compound manufacturing, then under the proposed legislation and current authority, FDA will have access to all documents and records concerning these activities. Authorizing FDA access to pharmacy records could create jurisdictional conflicts with the states and impede the states from investigating or prosecuting a case because FDA has seized evidence or information needed by the state(s). What is needed in lieu of allowing such access is increased communication between the states and FDA.

Intrastate Exemption from Definition of Compounding Manufacturer

NABP discussed with the Senate HELP Committee concern with the proposed exemption for intrastate distribution of non-patient-specific sterile compounded products. We understand the logic of establishing a delineation point to more readily identify and regulate large-scale operations that conceivably pose more risk to patients than smaller operations. However, as we explained to the Senate HELP Committee, it is our finding that non-patient-specific, sterile prepared products distributed within a state bear the same risk levels to patients as products that are introduced into interstate commerce. The differentiation between intrastate and interstate activities to define a compounding manufacturer could create patient safety concerns by allowing large-scale intrastate entities to avoid federal regulation. We indicated to the Senate HELP

Committee that although this is a critical concern for the states, NABP would support the proposed legislation absent this revision, if our concern is noted and the situation monitored for any additional future action that may be necessary.

Conclusion

As stated earlier in our statement, NABP supports the proposed Senate legislation, as it addresses the safe preparation of medications and products for patients and aligns well with the approaches suggested and recommended by the states. NABP supports legislation that distinguishes between compounding and manufacturing, defines a new category of manufacturing that balances effective regulation with reality, and carefully constructs allowances and prohibitions on the scope and activities of a compounding manufacturer in order to meet patient needs while maintaining the necessary protections. NABP appreciates this opportunity for input and is available to discuss our comments and any legislative solution in greater detail.

Thank you.

Mr. PITTS. Ms. Cosel, you are recognized for 5 minutes for an opening statement.

STATEMENT OF GABRIELLE COSEL

Ms. COSEL. Thank you. Chairman Pitts, Ranking Member Pallone, Vice Chairman Burgess, and members of the subcommittee, thank you for the opportunity to testify on the need for Federal legislation to improve the safety of compounded medicines. My name is Gabrielle Cosel. I work on pharmaceutical quality and safety at the Pew Charitable Trusts, which is an independent research and public policy organization.

Pharmacists have always compounded medicines. But many of the activities we refer to as compounding today are far removed from traditional pharmacy practice. In recent months, this committee has stressed the responsibility of FDA to ensure the safety of activities that depart from traditional compounding and are more akin to manufacturing. Today I will focus on a regulatory framework that clarifies the agency's role, ensures that limited resources are used wisely, and sets clear expectations for the industry.

First, though, it is important to look over the risks. The fungal meningitis epidemic illustrates how patients can be harmed by substandard compounded drugs. But it is far from an isolated incident. My written testimony describes 19 additional pharmacy compounding errors from the past decade that have caused serious injuries and deaths in at least 29 different States. The list includes meningitis, blood stream infections, and at least 38 patients who suffered partial or complete vision loss.

Recent history raises further concern. Two months ago, a New Jersey compounder recalled all of its products because of mold contamination. When a drug is produced in mass quantities, the potential harms from a quality failure also multiply. There are companies today that compound thousands of packages of vials of medicines and ship them to buyers all over the country. These activities have outgrown the State regulatory structures established to oversee them. Federal law already regulates some aspects of compounding, and today we urge you to make changes to ensure clarity and effective oversight.

First, large-scale compounding should be subject to higher quality standards, specifically applicable good manufacturing practices. Second, the FDA is the appropriate agency to oversee GMPs, and States should not exercise redundant oversight. And finally, patients must be protected by ensuring that compounders do not undermine gold standard FDA-approved drugs.

Compounding quality standards are currently set by the States, and they are variable. Pew recently joined with the American Hospital Association and the American Society for Health System Pharmacists to host a summit on sterile compounding, and experts at that meeting emphasized that pharmacy compounding standards were never intended and are not suitable for large-scale production. Compounding high volumes or repeat batches of medicines involves standardized processes and should be subject to applicable GMPs. The FDA is best placed to enforce these standards, but resources should be focused on activities that pose the highest public health

risk. Facilities that produce large volumes of sterile products that may reach many patients or that carry out particularly high-risk compounding, such as creating sterile products from a nonsterile bulk ingredient, should be required to register with the FDA.

FDA should issue regulation clarifying the criteria for registration. As with pharmaceutical manufacturing, FDA should inspect compounding facilities on an ongoing basis with a frequency based on risk. And facilities should pay fees to ensure FDA is adequately resourced to provide this oversight.

Under this framework, States may continue to require FDA-registered compounding facilities to hold pharmacy licenses, but State enforcement of quality standards should be preempted for these facilities. To exercise effective oversight, the FDA must have access to the records of facilities it regulates or that it believes fall under its jurisdiction. This requires a fix to current law. Even today, compounders continue to challenge FDA's access to records. Key safety requirements should also be set at the Federal level, such as a "do not compound list," and this should apply to all compounding facilities.

It is important to state that large-scale compounding cannot be addressed simply by requiring these facilities to submit new drug applications. Some large compounders fill a niche in our health system, such as for hospitals that don't have sufficient capacity to mix drugs in-house. However, any new regulatory scheme must not undermine the approvals process and encourage compounding at the expense of traditional manufacturing. While the goal is to ensure the quality of compounded medicines, patients, doctors, and pharmacists should prefer FDA-approved products whenever possible. Only the latter go through pre-market review to establish safety, efficacy, and bioequivalence, along with pre-approval of manufacturing methods and facilities. Legislation should be clear that a compounder may not make a copy or a variation of a marketed drug except when that drug is in shortage or to address a specific medical need of a specific patient.

In conclusion, I thank you for your leadership, and I urge you to create a clear, workable framework to protect patients. I welcome your questions.

Mr. PITTS. Chair thanks the gentlelady.

[The prepared statement of Ms. Cosel follows:]

Testimony before the Committee on Energy and Commerce
Subcommittee on Health
United States House of Representatives
May 22, 2013

The Pew Charitable Trusts

Dear Chairman Pitts, Ranking Member Pallone and members of the Subcommittee,

Thank you for the opportunity to testify on the need for federal legislation to improve the safety of compounded medicines.

My name is Gabrielle Cosel. I work on pharmaceutical quality and safety at the Pew Charitable Trusts, an independent, nonpartisan research and public policy organization.

Pharmacists have always compounded medicines – it is the origin of the profession – but many of the activities we refer to as compounding today are far removed from the traditional practice of preparing individualized medicines for one patient at a time. Some compounders today produce large volumes of drugs and ship them to clinics and hospitals across the country.

In recent months, this committee has repeatedly stressed the responsibility of FDA to ensure the safety of activities that depart from traditional compounding and are more akin to manufacturing. I will focus today on a regulatory framework that clarifies the Agency's role, ensures that limited resources are used wisely, and sets clear expectations of the industry. First, though, it is important to understand the risks we face.

Examining the risks

The epidemic caused by the New England Compounding Center highlights the dangers to patients from compounded drugs. As of May 6, that outbreak has been associated with 55 deaths and 741 serious infections in 20 states.

But what happened at NECC is not an isolated incident. I have included with my testimony a Pew summary that describes 19 additional pharmacy compounding errors since 2001.[1]

These errors caused serious injuries and deaths in at least 29 different states. The list includes 22 additional deaths, as well as serious infections – meningitis, bloodstream, and at least 38 patients who suffered partial or complete loss of vision. It also includes patients harmed by sub-potent or super-potent doses. For example, three people in Oregon and Washington who died after receiving drugs from Texas – intravenous injections for back pain that were *eight times* the labeled strength.[2]

Recent inspections of compounders raise further concern: For example, two months ago, the FDA announced a recall of all of the products manufactured by a New Jersey compounder because of potential mold contamination. The FDA press release referred to "visible particulate contaminants" in what was supposed to be a sterile product.[3] Also this year, a Georgia compounder conducted a nationwide recall of sterile products after reports of serious eye infections.[4]

Compounding errors can cause exponentially greater harms if the product has been produced in mass quantities. There are companies today that compound thousands of packages or vials of medicine and ship them to buyers all over the country, going well beyond the traditional practice of a pharmacist making a single drug in response to a specific prescription for a specific patient. These activities have outgrown the state regulatory structures established to oversee them.

Congress, through section 503(A) of the Food, Drug and Cosmetic Act, already recognizes FDA's responsibility to oversee some compounding activities. Today, we urge you to amend certain elements of this provision to ensure its effectiveness and provide greater clarity on state and federal roles. We urge the following elements:

1. **When appropriate, large-scale compounding should be subject to higher quality standards – specifically applicable Good Manufacturing Practices (GMPs),**
2. **FDA is the appropriate agency to oversee GMPs, and states should not exercise redundant oversight,**
3. **Patients must be protected by ensuring that compounders do not undermine "gold standard" FDA-approved drugs.**

Today, compounding quality standards are set by states. Some states incorporate United States Pharmacopeia standards for sterile and non-sterile compounding (USP chapters 797 and 795, respectively), but experts at a recent pharmacy compounding summit co-hosted by Pew, the American Hospital Association (AHA), and the American Society of Health-System Pharmacists (ASHP) stressed that USP compounding standards were developed for use in pharmacies and are not suitable for larger-scale production.

Compounding large volumes of repeated batches of medicines implies standardized processes that should be subject to appropriate quality standards such as those outlined in current Good Manufacturing Practices (cGMPs) for drug manufacturers.

For example, cGMP requires manufacturers to validate systems and processes to ensure that medicines meet consistent quality and safety standards. Process validation becomes increasingly important as the same drug is compounded in repeat batches. In addition, USP 797 does not require the testing of a drug's starting ingredients, while cGMP does. And expiration dates are set for a manufactured drug based on extensive stability testing. But a beyond-use date for a compounded medicine may in some cases be set by referencing published studies of drugs that may not conform exactly to the compounded product.[5,6] GMPs are developed by the FDA, and the agency is best placed to enforce them.

Facilities that produce large volumes of sterile products, or carry out particularly high-risk compounding, such as manufacturing from a non-sterile bulk ingredient, should be required to register with the FDA. FDA should issue a regulation clarifying the criteria for registration. As with pharmaceutical manufacturing, FDA should inspect compounding facilities on an ongoing basis, with a frequency based on risk.

To avoid an unfunded mandate, the FDA will need adequate resources to conduct ongoing inspections of registered facilities. These resources should be provided through facility fees.

It is important to state that large-scale compounding cannot be addressed simply by asserting these facilities are making unapproved new drugs and requiring them to submit to the New Drug Approval or Abbreviated New Drug Approval process. For example, some large compounders have become a source of intravenous and epidural therapies for hospitals and health systems that do not have the capacity to compound them in-house. Entities that play a role in our health care system should not be left to default or ad-hoc application of full requirements of the FDCA. The regulatory oversight system for these entities should be clearly defined. However, as addressed below, it is important to ensure that compounding does not encourage the sector to produce new drugs that undermine the FDA-approval paradigm.

Under this framework, states may continue to require FDA-registered compounding facilities to hold state pharmacy licenses, but state enforcement of quality standards should be preempted for these facilities. The section 704 provision that exempts pharmacies from the requirement to provide records access to FDA should be removed for registered facilities. Without this authority the FDA will be challenged when it attempts to investigate a facility that should be under its jurisdiction. Such challenges have been well documented. In the wake of deadly meningitis outbreak a Congressional investigation clearly showed that even when the FDA had access to a facility its ability to access records was challenged.[7] Additionally, in March of 2013 the FDA reported that compounders denied FDA investigators access to records in a number of recent cases.[8]

Key safety requirements should also be set at the federal level, such as a "do not compound" list. Congress has already recognized that certain products are not suitable for compounding (frequently cited examples include transdermal delivery systems, biologic products and sustained release formulations) and has given FDA the authority to establish a "do not compound" list. This authority should be maintained and should apply to both FDA-registered and non-registered facilities, as it does now. The section 704 records exemption should also be removed for purposes of enforcing the do not compound list.

It is important to emphasize that compounded drugs do not go through the pre-market approval process that brand and generic drug companies go through to demonstrate safety, efficacy and bioequivalence, along with pre-approval of manufacturing methods and facilities. These are critical systems to protect patients. Because they do not apply to compounders, compounded medicines can never be an adequate substitute for FDA-approved drugs.

Any new federal regulatory scheme must not encourage compounding at the expense of conventional manufacturing. Legislation should be clear that a compounder may not make a copy or a variation of a marketed drug, except when that drug is in shortage or to address specific medical needs of a specific patient. Congress should also prohibit the wholesale of compounded drugs.

Another important safeguard against circumvention of the approvals process is limiting compounding from bulk to only well-characterized and already in-use active ingredients, such as those described by a USP monograph, or those in an existing drug application. These concepts are not new, but are part of current 503A language.

Conclusion

We thank you for your leadership on this important issue. Congress has long recognized the role of FDA in providing oversight of compounding. It is time to update the Food, Drug and Cosmetic Act to remove ambiguities and create a clear, workable framework to address patient safety.

Thank you for the opportunity to testify, and I welcome your questions.

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PEW CHARITABLE TRUSTS

U.S. Illnesses and Deaths Associated With Compounded Medications (2001-Present)

APPENDIX B

The Pew Charitable Trusts has identified 20 pharmacy compounding errors associated with 1022 adverse events, including 75 deaths, since 2001. Contamination of sterile products was the most common compounding error, though some incidents were the result of pharmacists' and technicians' miscalculations and mistakes in filling prescriptions.

Year	States	Reported cases	Reported deaths	Adverse events	Compounding error	Product
2012	FL, GA, ID, IL, IN, MD, MI, MN, NC, NH, NJ, NY, OH, PA, RI, SC, TN, TX, VA	733	53	Fungal meningitis and other infections	Contamination[1]	Spinal injections: preservative-free sterile methylprednisolone acetate
2012	CA and six other states	33		Fungal eye infection; 23 cases of partial to severe vision loss	Contamination[2]	Eye injections: Brilliant Blue-G (BBG) retinal dye and triamcinalone
2011	FL, TN	21		Bacterial eye infection; one case of meningitis and encephalitis; four cases of loss of eyesight; three patients had eye removals	Contamination[3]	Eye injections: intravitreal bevacizumab (Avastin) injections
2011	CA	5		Blindness	Unintended presence of another medication[4]	Eye injections: intravitreal bevacizumab (Avastin) injections
2011	AL	19	9	Bacterial bloodstream infection	Contamination[5]	Parenteral nutrition solution
2010	IL	1	1	Fatal overdose	Dose of sodium 60 times stronger than ordered[6]	IV solution: sodium chloride
2007	WA, OR	3	3	Fatal overdose	Dose of colchicine eight times stronger than labeled concentration[7]	IV solution: colchicine
2007	MD, CA	8		Bacterial bloodstream infection	Contamination[8]	IV solution: fentanyl

U.S. ILLNESSES AND DEATHS ASSOCIATED WITH COMPOUNDED MEDICATIONS 2001-PRESENT

Year	States	Reported cases	Reported deaths	Adverse events	Contributing factor	Product
2004-2006	MI, MO, NY, SD, TX, WY	80		Bacterial bloodstream infection	Contamination[9]	IV flush syringes: heparinized saline
2006	OH	1	1	Fatal overdose	Dose of sodium chloride stronger than ordered[10]	Chemotherapy infusion
2006	NV	1	1	Fatal overdose	Dose of zinc 1,000 times stronger than ordered[11]	Neonatal parenteral nutrition solution
2005		2		Bacterial bloodstream infection	Contamination[12]	IV flush vials: preservative-free heparinized saline
2005	MN and one other state	6		Bacterial eye infection; all cases had partial or complete loss of vision; two patients had eye removals	Contamination[13]	Eye solution: trypan blue
2005	VA	5	3	Systemic inflammatory response syndrome	Contamination[14]	Heart infusion: cardioplegia
2005	CA, NJ, NC, NY, MA	18		Bacterial bloodstream infection	Contamination[15]	IV solution: magnesium sulfate
2004	CT	2		Bacterial bloodstream infection	Contamination[16]	IV flush syringes: heparin-vancomycin
2004	MO, NY, TX, MI, SD	64		Bacterial bloodstream infection	Contamination[17]	IV flush syringes: heparinized saline
2002	NC	5	1	Fungal meningitis and sacroiliitis	Contamination[18]	Spinal injections: methylprednisolone acetate
2001	CA	11	3	Five cases of bacterial meningitis; five cases of epidural abscess; one patient had an infected hip joint	Contamination[19]	Spinal or joint injections: betamethasone
2001		4		Bacterial bloodstream infection	Contamination[20]	IV infusion: ranitidine
TOTAL		1022	75			

Pew's drug safety project works to ensure a safe, reliable pharmaceutical manufacturing and distribution system. For more information, visit www.pewhealth.org/drugsafety.

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Mr. PITTS. Mr. Migliaccio, you are recognized for 5 minutes for opening statement.

STATEMENT OF GERRY MIGLIACCIO

Mr. MIGLIACCIO. Thank you, Chairman Pitts and Ranking Member Pallone, for inviting me here to speak today. My name is Gerry Migliaccio. I am a consultant in the area of pharmaceutical quality systems. In 2012, I retired from Pfizer, Incorporated, after a 33-year career in pharmaceutical manufacturing and quality operations. For 11 of those years, I served as the head of the Global Quality Organization at Pfizer. So this experience has provided me with quite an intimate knowledge of the quality requirements and regulatory framework applicable to manufacturing medicines for the United States public.

Patient safety is the highest priority for pharmaceutical manufacturers. Companies comply with the gold standard of quality manufacturing as defined by FDA's current Good Manufacturing Practice regulations and the associated guidance documents. These regulations apply to all prescription drugs approved for sale in the United States, wherever they are made, and extend to all components of a finished drug product, including the active pharmaceutical ingredients.

FDA's regulations are based on the fundamental principle that you cannot inspect or test quality into a finished product. Quality must be designed into the manufacturing process and designed into the product. The regulations also drive manufacturers to establish a quality systems approach to assure consistent quality.

In pharmaceutical manufacturing, quality systems and GMP requirements begin at the investigational stage. FDA requires that a new drug application describe the quality safeguards for the proposed manufacturer of a new medicine in the Chemistry, Manufacturing, Control section of the application. Part of the evidence required by FDA to demonstrate safety and efficacy is the requirement that a manufacturer provide, and I quote, "a full description of the methods used in and the facilities and controls used for the manufacture, processing, and packing of a new drug."

The manufacture of medicines, whether by NDA holders or large-scale compounders, involves similar activities and similar potential for risk. Large-scale compounding can involve mixing of active and inactive ingredients, as well as other manufacturing steps. Therefore, in order to assure the safety of the American public, the manufacture of medicines, whether by manufacturers or by pharmacies, should be regulated in a consistent risk-based manner. Large-scale commercial manufacturing of prescription medicines, whether the producer is designated as a pharmacy or as a manufacturer, should be governed by the same high standards currently in effect for pharmaceutical manufacturing and subject to the same inspection and enforcement actions by FDA.

Moreover, large-scale compounders should be required to prove that they can manufacture medicines consistently and safely by submitting an application to FDA containing a Chemistry, Manufacturing, and Control section, and submitting to both pre-approval and routine GMP inspections.

Let me give you a personal perspective on the importance of GMP regulations. During my career, I considered the regulatory framework in the United States as the blueprint for assuring safety and efficacy. Whether you are a small startup company or a large multinational manufacturer, the regulations and guidance documents provided a template for success. From designing quality into a manufacturing process to the selection of material suppliers to construction of facilities, the selection of equipment, the training of employees, all the way to the final approval to distribute the product, the regulations and guidance documents provide for a consistent risk-based approach to assure quality. The regulations have also evolved to encourage innovation and continuous improvement and to help support the justification of new technology to further enhance quality assurance.

Therefore, it is just very logical to me that any large-scale manufacturer of medicines, including compounders, should comply with these same regulations. A manufacturer in full compliance will have a high degree of assurance that the medicines they produce will be of consistently high quality. A large-scale company making thousands of doses of medicine with the name "Pharmacy" on the door and another with the name "Pharmaceutical Company" on the door should be regulated in a similar manner when they perform similar manufacturing steps and present similar risks to patients.

Thank you for your attention.

Mr. PITTS. Chair thanks the gentleman.

[The prepared statement of Mr. Migliaccio follows:]

Oral Statement of Gerry Migliaccio
Quality Systems Consultant
Retired Senior Vice President of Global Quality
Pfizer Inc

House Energy and Commerce Committee
Health Subcommittee
Examining Pharmacy Compounding

May 23, 2013

I would like to thank Chairman Pitts and Ranking Member Pallone for inviting me to speak today. My name is Gerry Migliaccio. I am a consultant in the area of pharmaceutical quality systems. In 2012, I retired after a 33-year career in pharmaceutical manufacturing and quality operations at Pfizer. For eleven years I served as the head of Pfizer's Global Quality Operations. This experience has provided me with an intimate knowledge of the quality requirements and regulatory framework applicable to manufacturing medicines for the United States public.

Patient safety is the highest priority for pharmaceutical manufacturers. Companies comply with the "gold standard" of quality manufacturing as defined by FDA's current Good Manufacturing Practice (cGMP) regulations

and associated guidance documents. These regulations apply to all prescription drugs approved for sale in the United States, wherever they are made, and extend to all components of a finished drug product including active pharmaceutical ingredients. FDA's regulations are based on the fundamental principle that quality cannot be inspected or tested into a finished product. Quality must be designed into the manufacturing process and product. The regulations also drive manufactures to establish a quality systems approach to assuring consistent quality.

In pharmaceutical manufacturing, quality systems and cGMP requirements begin at the investigational stage. FDA requires that a new drug application (NDA) describe the quality safeguards for the proposed manufacture of a new medicine in the Chemistry, Manufacturing, and Controls (CMC) section of the application. Part of the evidence required by FDA to demonstrate safety and effectiveness is the requirement that a manufacturer provide "a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of [a new] drug...."[1]

[1] See 21 U.S.C. 355(b)(1).

The manufacture of medicines – whether by NDA holders or large-scale compounders – involves similar activities and the potential for risk. Large-scale compounding can involve mixing of active and inactive ingredients as well as other chemical and even biological manufacturing steps. Therefore, in order to assure the safety of the American public, the manufacture of medicines, whether by manufactures or pharmacies, should be regulated in a consistent, risk-based manner. Large-scale commercial manufacturing of prescription medicines, whether the producer is designated as a "pharmacy" or as a "manufacturer" should be governed by the same high standards as biopharmaceutical manufacturing, and subject to the same inspection and enforcement actions by FDA.

Moreover, large-scale compounders should be required to prove that they can manufacture medicines consistently and safely by submitting an application to FDA containing a CMC section and submitting to both pre-approval and routine cGMP inspections.

Let me give you a personal perspective on the importance of the cGMP regulations. During my career, I considered the regulatory framework in the US as the blueprint for assuring safety and efficacy. Whether you are a

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It is logical to me that any large-scale manufacturer of medicines, including compounders, should comply with these same regulations. A manufacturer in full compliance will have a high degree of assurance that the medicines they product will be of consistent high quality. A large-scale company making thousands of doses of medicines with the name "pharmacy" on its building and another with the name "pharmaceutical company" should be regulated in a similar manner when they perform similar manufacturing steps and present similar risks to patients.

Thank you for your attention.

Mr. PITTS. I will begin the questioning. And I recognize myself for 5 minutes for that purpose.

Dr. Gottlieb, the FDA has proposed creating a new category of, quote, "nontraditional compounders," end quote. Do you believe this has the potential to add confusion rather than clarity to regulated industry?

Dr. GOTTLIEB. I do believe there is this category of companies, large companies, that have grown up that basically do the outsourced work of the hospitals. And it is not really traditional compounding in the sense that we understand that word. What they are really doing is sterile preparations of drugs, breaking down FDA-approved products into different formulations that make it easier to administer to patients, and it is a completely different thing than what traditional compounding is.

I do think it creates the potential that traditional manufacturers might have a temptation to recast themselves into this new category if we don't have very equal enforcement and very aggressive enforcement of the existing law because there will be an incentive to go into this pathway because it will be sort of a regulatory light pathway.

The reason why Teva Pharmaceuticals doesn't, you know, manufacture all the formulations of Propofol that doctors might want is because if they went about doing that they would have to file an ANDA for each one and pay a user fee for each one. So if we create this category, it could be an incentive for traditional manufacturers to try to move back into this new category, and that wouldn't serve the public interest.

Mr. PITTS. To follow up, impact on intellectual property rights. How would this new category potentially impact intellectual property rights?

Dr. GOTTLIEB. Well, again, I think it could create an avenue for people to try to game around the new drug regulations to create products that would fit into this category. And it is not an argument for not trying to think about how we could apply GMP regulations to this emerging, this new category of manufacturers. But it is an argument for trying to make sure that we enforce existing law against compounders who, for example, compound versions of FDA-approved products.

In recent years, the FDA has backed off enforcement that was put into place to crack down on people who are engaging in the compounding of drugs that exist in FDA-approved formulations. And so that creates an incentive to try to obviate existing intellectual property.

Mr. PITTS. Mr. Migliaccio, Director Woodcock mentioned on the previous panel that the agency could not require compounders to register with the FDA. However, the FDA has the full authority to require manufacturers operating under the guise of compounders to register with the FDA, like NECC. Isn't that correct?

Mr. MIGLIACCIO. Yes. Well, every manufacturing establishment within a pharmaceutical company has to have an establishment registration with the FDA.

Mr. PITTS. Hasn't the FDA recently used its manufacturing inspection authority to inspect manufacturers acting under the guise of compounding recently?

Mr. MIGLIACCIO. I believe they have used their inspection authority to attempt to inspect compounding manufacturers. And I understand that they have been turned away in certain cases.

Mr. PITTS. Please explain the similar scope of risk between NDA holders manufacturing drugs and large-scale compounders.

Mr. MIGLIACCIO. Well, pharmaceutical manufacturers make pharmaceutical products at very different scales. I mean, we make small volume, we make large volume. Compounders are doing the same thing. We are following similar manufacturing steps. We are taking active ingredients and inactive ingredients, combining them, trying to yield a product that has the potency and purity required by the patient.

Compounding the problem with sterile products is the risk around sterility. Sterility is not something that you can test into a product. Yes, you do a sterility test, but it is not a reliable measure of sterility. You have to have a very robust system to assure sterility. And the GMPs require that we actually prove that to the FDA before we can market the product. We have to prove that we can assure sterility to a very high degree before we can put a product on the market. That is not the case, the risks are the same for compounding pharmacies, but they don't have to provide that same evidence.

Mr. PITTS. Could legislation that applies different standards adversely affect the quality of drugs made available to patients?

Mr. MIGLIACCIO. Oh, I believe that compounding pharmacies making product at large volume are manufacturers and should be regulated according to the manufacturing regulations, the GMPs, which have proven to be very successful in protecting the American public.

Mr. PITTS. Let me squeeze one more question in here, Mr. Harmison. What safety precautions are you required to comply with?

Mr. HARMISON. I comply with USP 797 and State laws and rules and regulations of the State of Texas.

Mr. PITTS. And can you briefly describe the importance of traditional compounding that occurs in independent pharmacies across the country?

Mr. HARMISON. Mr. Chairman, that is a very broad subject. If we are talking about somebody making a cream, there is one thing. If I am making a sterile injection, that is quite another thing. I am making a capsule for somebody. We still strive, basically, we are not going to make anything we wouldn't give to our children or grandchildren.

Mr. PITTS. Thank you.

My time has expired. Recognize the ranking member 5 minutes for questions.

Mr. PALLONE. I wanted to start with Ms. Russell. In your testimony, you cite the need for FDA to be given new and better authority over drug compounding. Obviously, your organization is made up of State agencies that regulate the practice of pharmacy, so you are in a unique position to have insight into whether FDA needed new authority in this area.

So, Ms. Russell, your testimony describes the fact that there were regulatory uncertainties that were a major factor leading to

the NECC meningitis tragedy. Can you elaborate on what those—I always hate to say elaborate—but can you tell us what those uncertainties were and how they contributed to the meningitis outbreak?

Ms. RUSSELL. Sure. I think that there are a number of entities in the United States, across the United States, that would tell boards of pharmacy that they were distributing nonpatient-specific sterile products as an FDA manufacturer. And they may have actually gone on FDA's Web site and registered as a manufacturer and State boards of pharmacy didn't think they had jurisdiction over those particular activities. FDA didn't necessarily recognize them as an approved manufacturer because they hadn't filed an NDA. So there were uncertainties and ambiguities in who had responsibility over these particular firms.

Mr. PALLONE. So you also indicate that NABP is supportive of the Senate legislation clarifying the distinction between compounding manufacturers and traditional compounders. And you further indicate that your recent inspections of compounding pharmacies has underscored the importance of getting this clarity through Federal legislation. So can you explain more about what you have done in your inspection's undertaking? I am curious about why, if any BP in the States have been able to conduct such widespread inspections recently, that isn't enough. In other words, what would be achieved by FDA through new Federal legislation that can't be accomplished by the State boards of pharmacy?

Ms. RUSSELL. Maybe I wasn't clear. We do think traditional pharmacy compounding should remain the purview of State boards of pharmacy. But we do think that there are these entities that are engaged in large-scale activities that more resemble manufacturing and that FDA should have jurisdiction to inspect and investigate those.

Our initial inspections that we have been involved in for the State of Iowa, part of it has been trying to determine which of these large-scale entities are engaged in these more resembling manufacturing-type processes, and those are not condoned by the Iowa Board of Pharmacy, nor most other States. And we don't think that State boards of pharmacy have the resources to be able to adequately inspect basically manufacturing operators that are operating under the guise of legitimate pharmacy practice.

Mr. PALLONE. Thank you.

Let me ask Ms. Cosel. I would like to ask you a question that we heard a little about during the first panel. That has to do with hospital use of compounding medications. As we heard, hospitals have increasingly come to rely on compounded medicines that they obtain from large-scale pharmacies, and Dr. Woodcock talked some about how FDA's authorities to oversees these large-scale facilities are not appropriately tailored to the task. So I wanted to ask you, do you agree that hospitals do have a legitimate need for drugs from these large-scale pharmacies? Can you explain more about why they have come to rely on them? And what are your views on whether the FDA has the right authorities to handle regulation of that type of entity.

Ms. COSEL. Yes. And I think the question is very astute, because it hits on just what is at hand today. There is a question about bad

actors and if they cross a certain line whether they should be shut down. Yes. But there is also a question of entities that do fill a niche in our healthcare system, such as the outsources you reference, sir. And it has become clear over the years that hospitals have increasingly looked to outsourced operations to provide them sterile mixed products, mixed variations of finished FDA drugs.

And the simple answer can't just be calling these entities manufacturers and requiring them to submit a new drug approval. We need to make absolutely clear that when you are compounding on a large scale and filling this niche for the health system you should be held to high quality standards, GMPs, as my colleague Mr. Migliaccio testified on as well.

Mr. PALLONE. Mr. Harmison, I have got a little time. Your testimony can be summarized as follows: States always have and always should regulate compounders with no role for the FDA. But we know that numerous failure by Massachusetts regulators led to the NECC tragedy. In light of this tragedy, is it still your view—and I don't mean—you tell me if I am wrong—is it still your view that States are capable of regulating large-scale compounders?

Mr. HARMISON. Yes, Mr. Pallone. I think if they have the willpower to do it, they have the ability.

Mr. PALLONE. So you don't think there is a role for FDA in the regulation of large-scale compounders like NECC.

Mr. HARMISON. I think the rule of the FDA is oversight. If they think that there is a problem, they should go talk to the State boards of pharmacy, say, come, go with me, let's inspect this. If it is in violation of the State law, then the State should take action on them. If they say, we don't have this, somebody decide if they are a manufacturer. If they are a manufacturer, certainly they are under the purview of the FDA.

Mr. PALLONE. I don't know. It just seems to me that what you are proposing sounds nice in theory, but I think much of the testimony seems to indicate it doesn't work out practically. But whatever, I don't want to put words in your mouth. Thanks a lot.

Mr. PITTS. Chair thanks the gentleman.

Now recognize the vice chair of the committee, Dr. Burgess, for 5 minutes for questions.

Mr. BURGESS. Mr. Harmison, let's continue on that line for a moment, because when another subcommittee of the Energy and Commerce Committee, the Oversight and Investigations Subcommittee first started this investigation, we were joined by the brand new head of the Massachusetts Board of Pharmacy. And the reason she was the brand new head was because the old head had been recently dismissed because of the problems that occurred.

We have heard from the FDA this morning that, no, we are not going to replace anyone in our organization. And looks to me like the Massachusetts Board of Pharmacy acted. Although there may have been problems leading up to the crisis, their response to the crisis and after seems much more reasonable than what I have seen under the Federal regulatory agency. Is that a fair assessment that I am making?

Mr. HARMISON. As an employer, if I were in that position, somebody wouldn't be in my employ anymore.

Mr. BURGESS. Well, that is, you know, this was so baffling about all of this. I mean, again, the poor individual who was the head, the brand new head of the Massachusetts Board of Pharmacy had to come here and answer some pretty tough questions and some for which she no answer, and simply said those people are no longer working for us. And you have to wonder if whether or not there are civil or even criminal activities are going to follow them for a while. I wouldn't be surprised to learn that.

But, again, you have a large Federal regulatory agency, and they are immobile. And not only are they immobile, after they find out that there is a problem, but the months and years leading up to this. Well, we are going to have to have guidance, and, well, it is bound up in some stuff.

And I read you the email chain. From 18 months before this crisis hit, they recognized that it was manufacturing, that they were required to list these compounds, they were required to submit to GMP. The people in the FDA understood that. And for whatever reason it didn't translate to the street level to get it done. In fact, I don't think the people that were working in the agency, again, I just—the mental image, they must be tearing their hair because they keep coming up to this point waiting for someone to say "go" and no one ever said "go."

And that is the problem I see if we divested away from the State agencies. Bad news at Massachusetts Board of Pharmacy. You know, bad news at what happened. But at least they have reacted in what I would consider a sensible way. I can't say the same to the FDA. That is painful for me to say that.

Mr. HARMISON. Well, if I can go back to an old Paul Newman movie, it appears what we have is a failure to communicate between regulatory agencies and enforcement agencies.

Mr. BURGESS. Dr. Gottlieb, let me just ask you because you have some experience working within the agency. Is that not correct?

Dr. GOTTLIEB. Look, I think NECC was breaking existing law. They were acting as a large-scale manufacturer under the guise of a pharmacy license. They were compounding identical versions of FDA-approved products, they were doing it in bulk, they weren't doing it in response to prescriptions. They had had previous GMP violations. So they were known bad actor.

I think the issue isn't necessarily what is FDA's authority. FDA has extensive authority. I think that the challenge is that they don't have ease of administrating authority because they don't have the ability to compel the submission of certain information. And it is not the posture by which they typically regulate.

In the case of compounding, in many cases FDA is forced to have to make an affirmative case before it could go in and start to do its work. Typically, the FDA doesn't regulate that way. Typically, the FDA regulates from a posture where they compel submission of information to the agency and then they are able to target their activities based on that information. You know, under existing law they have extensive authority, in my view, but it is authority that makes it administratively more burdensome for them in this area than others.

Mr. BURGESS. But, you know, the concept of an affirmative case, and for heaven sakes, the system was blinking red for years. For

years. You had whistleblowers, you had people bringing brochures in, you had people showing up saying, this is what we heard at a conference. These guys were clearly skating way beyond the edge, way beyond the fringe. And, OK, well, it may not be the normal FDA posture to take an affirmative case, when the evidence is laid in front of you, it shouldn't take——

Dr. GOTTLIEB. Well, this one was obvious.

Mr. BURGESS [continuing]. It shouldn't take years to come to the conclusion of filing the action that eventually closed the NECC. Is that correct?

Dr. GOTTLIEB. This was a known bad actor over a long period of time—including, frankly, the time in which I was at FDA, we sent out a warning letter to this firm in 2006.

Mr. BURGESS. OK.

Thank you, Mr. Chairman. I will yield back.

Mr. PITTS. Chair thanks the gentleman.

And now recognize the ranking member emeritus, Mr. Dingell, for 5 minutes for questions.

Mr. DINGELL. Mr. Chairman, I thank you.

First question is for Ms. Russell of the National Association of Boards of Pharmacy and also Ms. Cosel of the Pew Charitable Trusts.

Ladies, do you believe that there is regulatory uncertainty regarding the FDA's role in overseeing compounding pharmacies? Yes or no?

Ms. RUSSELL. Yes.

Ms. COSEL. Yes.

Mr. DINGELL. Now, these next two questions are for Ms. Russell. In your testimony, you mentioned that NABP partnered with the Iowa Board of Pharmacy to inspect pharmacies which deliver compounded drugs into Iowa. Is that correct?

Ms. RUSSELL. Yes.

Mr. DINGELL. Now, in your testimony also, you also mention that your inspections found that what occurred at NECC was happening elsewhere. Is that correct?

Ms. RUSSELL. Yes.

Mr. DINGELL. Could you briefly describe what you found at some of the facilities where you found a repeat of this kind of situation?

Ms. RUSSELL. We found large-scale operations similar to what NECC was doing where they were allegedly compounding or producing bulk quantities of sterile injectable products, some that were essentially copies of commercial products. We found issues with compliance with standards for sterility compounding and basically that they were shipping nonpatient-specific drugs into the State of Iowa in violation of Iowa State law.

Mr. DINGELL. What did the Iowa agency do about this?

Ms. RUSSELL. Iowa is in the process of—they have got three attorneys now working on the inspections that we provided. And they have issued notices of regulatory hearing for 5 of the first 6 pharmacies that we went in, which were some of the larger-scale operations. Those hearings I believe will be held in June this year, next month.

Mr. DINGELL. They seem to be in great haste. Am I correct?

Ms. RUSSELL. Pardon?

Mr. DINGELL. They seem to be in great haste to get around to processing this matter. Yes or no?

Ms. RUSSELL. Yes.

Mr. DINGELL. I don't see it that way.

Would you submit also for the record other details of the events that you found, if you please?

Now, in your testimony you mentioned there has been 19 significant compounding errors since 2001. Is that correct?

Ms. COSEL. Yes, 20, including NECC.

Mr. DINGELL. OK. Would you for the record submit the details of those events, please, to us?

Ms. COSEL. Yes, sir.

Mr. DINGELL. Now, how many people died as a result of these incidents?

Ms. COSEL. Not including NECC, there were 22 deaths associated with these incidents, and including NECC there were 77.

Mr. DINGELL. Could you submit for the record the details on these things, if you please?

Ms. COSEL. Yes, sir.

Mr. DINGELL. Now, as far as you know, have there been further problems with compounding pharmacies after the NECC outbreak? Yes or no?

Ms. COSEL. Yes. We have seen a number of recalls related to quality problems with compounded drugs this year.

Mr. DINGELL. Could you submit again for the record what you found in those matters?

Ms. COSEL. Certainly.

Mr. DINGELL. Could you give us a brief perhaps picture of what you found done in these instances and whether this was the responsibility of the State agencies or the Feds?

Ms. COSEL. Well, I can give one example. There was a recall by a Georgia compounder this year, I believe in March, of all sterile products, because there were serious eye infections in at least 5 patients associated with a contaminated eye injection. In this case, this was a nationwide recall. So if we are—if Congress is considering a new regulatory system that is clear that large-scale compounding of high-risk sterile products would be explicitly under FDA oversight, I think we would have had a much better chance of ensuring the safety of those processes.

Mr. DINGELL. Particularly since they are shipping all across the United States and this is touching many agencies, many States, and people in many States and agencies. Is that right?

Ms. COSEL. Yes.

Mr. DINGELL. And, by the way, thank you for your patience. It lets me get a lot more questions in.

Would you for the record please submit the information that you have on these instances?

Ms. COSEL. Yes.

Mr. DINGELL. Now, in your opinion, is the outbreak at NECC an exception to the rule or do you believe that it is but one example of a larger problem?

Ms. COSEL. It is certainly an extremely horrific example, but it is just one of the larger issues we face. We acutely need greater clarity on oversight structures for large-scale compounding.

Mr. DINGELL. And one of the things we have do is to clarify it so that everybody knows who is supposed to and who can do what. Is that right?

Ms. COSEL. Yes.

Mr. DINGELL. Because we have the court cases that have screwed up the interpretation by both State and Federal agencies on this matter. Is that right?

Ms. COSEL. Legal uncertainty is one problem, as is changes with the industry and the emergence of the large-scale sector.

Mr. DINGELL. I have used more than my time. Thank you, Mr. Chairman.

Mr. PITTS. Chair thanks the gentleman.

Now recognize the gentleman from Virginia, Mr. Griffith, 5 minutes for questions.

Mr. GRIFFITH. Thank you, Mr. Chairman.

I have to tell you all, and I appreciate all of you being here, that I think part of the problem is, is that we have a clash of two worlds, the legal world and the medical world. Because when I look at the authority granted to the FDA under the code, with the exception of the advertising overreach, which was stricken down, there is plenty of authority already there to get to every problem that you all have raised today. And that is my concern.

And I asked the doctor earlier, and she was very kind, you know, this happened, the Supreme Court case came down that dealt with the Ninth Circuit in 2002. Where was the request to Congress to clarify? Because the only clarification is that the rest of the authority granted, with the exception of the advertising provision, should have been reenacted by Congress.

Now, can we tweak it a little bit and make it a little bit better? I am sure we can. And I am certain that we will work on that, because none of us want to see this problem happen again. But I heard one of the witnesses, and I don't remember which one now, say that they understood that there had been problems, you know, getting the records and getting into things. And, in fact, I think because the medical world—and I was a courtroom attorney, and so maybe it is a little different, not attorneys, but courtroom attorneys, they see things differently.

So I asked legal counsel who was here at a previous hearing, for the FDA, do you have any trouble getting warrants? And I expressed that my opinion always was as a defense attorney, criminal defense attorney, that the government didn't have too much trouble getting warrants. He said, that wasn't my experience. And I asked him to get me information. Yesterday, we received that information.

And, sure enough, FDA cannot point to a single example of where they requested a warrant where they were denied that warrant. So while the common belief is they have a hard time getting this information, the data would indicate otherwise.

I also asked, how long does it take you to get the warrant? And they said, in the most recent administrative warrant we sought for a pharmacy, 10 days passed between when the refusal was encountered and when the warrant was signed by the magistrate judge.

I have got to believe that if, as somebody said earlier, the blinking light, the red light warning, warning had been going off for

years, that if instead of being timid and being afraid of the law, the medical folks had burst in, as often police officers have to do—if they think somebody has a DUI, they may not win the case in the end, but they get that person off the road, at least temporarily, to see what is going on—that is what should have happened in this situation.

Would you agree with that, Mr. Harmison, that that is probably what should have happened, instead of coming in, trying to rewrite the law.

Mr. HARMISON. Yes, sir. If there is public safety at risk, the State board of pharmacy absolutely has the power to come in and say, wait a minute, you are shut down.

Mr. GRIFFITH. Yes. And I think that the guidelines that were worked on, never fully finalized, but that were worked on in the draft guidelines of August of last year that we didn't learn about until March of this year, make that clear as well. Because it goes through and when it talks about distinguishing between, as you all have called them different names, large-scale producers or production of compounded drugs, large-scale manufacturers, I think they are manufacturers. And I said in one of the earlier hearings, you know, I can call myself the Duke of Earl if I want to, but that doesn't mean I am getting diplomatic immunity.

And that is where I think we run into this problem. But when they did that draft, they said, when you are looking at whether or not somebody is doing a compounded drug product that qualifies for the exemptions, they came up with 10 guidelines. And they are all significant and important, but I noted with interest two of those. Number 8 says the licensed pharmacist or licensed physician does not compound regularly or in inordinate amounts any drug products. Number 10 says that you should have a memorandum of understanding with the States so that you can work out these areas that aren't clarified or in a State where they have not entered into a memorandum of understanding the pharmacists shouldn't be sending to another State more than 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician.

These seem to me to be reasonable restrictions, and it makes the definition that I think each one of the witnesses here today is looking for, distinguishing between the traditional pharmacy that is doing some things for their patients and their customers and these large-scale manufacturers who are, in fact, in my opinion, they are not compounders in the traditional pharmacy sense, but they are, in fact, manufacturers.

I look forward to trying to make sure that we clarify some of that because I do think that part of the problem is, is not having some street lawyers at the FDA who know that sometimes you have got to go in and kick the courthouse door down and say here is what we are doing. And when the judge sees the risk to the public he will say, OK, I will sign the warrant, OK, we will shut them down at least until we can find out whether or not they are a risk to the public. I think the authority already exists for that. I just think there has been some timidity in the legal department at the FDA.

And when you talk about registration, when you look at the rules in section 510 of the act, I think it is pretty clear that unless you

are a small town pharmacist you are supposed to be registering anyway. Does anybody disagree with that?

Dr. Gottlieb, do you disagree with that?

Dr. GOTTLIEB. No, 510 has a requirement for registration. And I think 503A actually lays out some criteria to try to distinguish, you know, these illegitimate compounders from the legitimate ones. So the language does exist and this could—even 503A could be better interpreted in regulation. But I think the compliance policy guide which you just quoted is a very good start for that.

Mr. GRIFFITH. I think they did a nice job in that guidance. I am not going to say I would agree with every word of it, but most of it is pretty good stuff and it indicates the FDA had the authority to move forward even under the rules that they now say they don't have the authority to do.

With that, I see my time is up and I yield back. But I do appreciate all of you all staying through two vote series on a long day. Thank you.

Mr. PITTS. The chair thanks the gentleman.

And with that, we again thank the witnesses for your patience.

That concludes the questions of the members who are present. There are other questions I am sure that other members who are not here will also like to submit to you and we will ask that you please respond promptly once you receive those questions.

And I will remind members that they have 10 business days to submit questions for the record, and Members should submit those questions by the close of business on Thursday, June the 6th.

Very informative and important hearing. Thank you very much for your attendance.

Without objection, the subcommittee is adjourned.

[Whereupon, at 1:50 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

JOHN D. DINGELL
15TH DISTRICT, MICHIGAN
COMMITTEE ON
ENERGY AND COMMERCE
CO-CHAIR
HOUSE GREAT LAKES
TASK FORCE
MEMBER
MIGRATORY BIRD
CONSERVATION COMMISSION

Congress of the United States
House of Representatives
Washington, DC 20515–2215

October 9, 2012

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The Honorable Margaret Hamburg
Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Commissioner Hamburg:

I write to you regarding the recent fungal meningitis outbreak thought to be related to epidural steroid injections.

As you know, this is not the first case of fungal infection as a result of contaminated methylprednisolone acetate produced by a compounding pharmacy, nor is this the first case of contamination and adverse events resulting from compounded sterile injectable products. In this more recent case, it is my understanding that an investigation into the source of the outbreak is still ongoing; however, the New England Compounding Center (NECC) in Framingham, Massachusetts, has voluntarily recalled preservative-free methylprednisolone acetate products produced and distributed from this facility. I am aware of the fact that U.S. Food and Drug Administration (FDA) have recommended that none of the facility's compounded products be used, and further, NECC has voluntarily shut down.

While these actions may help to prevent a larger outbreak from occurring, I am deeply concerned that this outbreak may be due to a contaminated pharmaceutical produced by a company that has not been properly regulated by federal or state authorities. Therefore, I respectfully request the answers to the following questions.

1. Although the investigation is still ongoing, FDA has discovered fungal contamination of sealed vials of methylprednisolone acetate collected at NECC. How many vials of this steroid has NECC produced? How many vials of this steroid produced by NECC have been distributed? How many facilities have received vials of this steroid produced by NECC? Where are these facilities located? When were the vials linked to the outbreak distributed? How many patients have received injections of this steroid produced by NECC thus far?

2. Who first discovered the contamination of vials of methylprednisolone acetate? When was the contamination first discovered? Where was the contamination first discovered? How was contamination discovered? When was the contamination first reported to FDA? How did this contamination occur?

3. NECC has issued a voluntary recall of the methylprenisolone acetate products and has voluntarily shut down. When was the voluntary recall first initiated? How many lots have been recalled? How many doses were included in the recall? When did NECC shut down its facility?

4. Are any vials of methylprednisolone acetate from NECC still available on the market? If yes, how many vials remain on the market?

5. What alerts regarding methylprednisolone acetate has FDA issued to health professionals? What alerts regarding methylprenisolone acetate has FDA issued to consumers? How have these alerts been transmitted to these parties?

6. With what federal and state agencies has the FDA been working on this investigation?

7. It has been reported that Massachusetts's Board of Registration in Pharmacy has had at least four previous complaints about the sterility of NECC's products – in 2002, 2003, 2011, and one complaint is currently being investigated. Were these complaints shared with the FDA? If yes, when were these complaints shared?

8. What has been the inspection history of the NECC facility? When was the NECC facility in Framingham last inspected? What were the results of that inspection?

9. Does FDA have the authority to inspect compounding pharmacies? If yes, when was the last time FDA officials have inspected NECC's facility? What were the results of that inspection?

10. It has been reported that more than 17,000 vials compounded by NECC have been recalled thus far. What does FDA consider to be legitimate forms of pharmacy compounding? What volume does FDA consider to be legitimate uses of pharmacy compounding?

11. Do compounding pharmacies, like NECC, register with FDA? If yes, how many compounding pharmacies are currently in operation?

12. Do compounding pharmacies list their products with FDA? If yes, how many products produced by compounding pharmacies are currently on the market?

13. Does FDA approve drug products produced through compounding pharmacies? Are drug products made through pharmacy compounding required to meet the safety and efficacy standard set by FDA?

14. Does FDA have sufficient authority to oversee compounding pharmacies, such as NECC, now? If so, please explain why. If no, please explain why.

15. Does FDA need additional authority to oversee compounding pharmacies? If yes, please explain why and list the authorities needed. If no, please explain why.

While I recognize that compounding serves an important purpose and provides pharmaceuticals for individual patients with unique needs, I am concerned that NECC was operating at such a volume to be outside of what may be considered traditional pharmacy compounding. Further, I am concerned that a facility with a long history of sterility complaints was allowed to operate at such margins and endanger the lives of thousands of patients. I urge FDA to use its enforcement authority to the fullest extent possible to ensure that NECC cannot again distribute contaminated compounded drug products and to swiftly identify what other authorities are needed to ensure such an incident cannot occur again. I will be sending you further inquiry as to what FDA can do with existing regulatory authority and what additional statutory authority is needed by FDA.

Given the serious nature of this outbreak, I respectfully request that a response be sent to my office no later than October 22, 2012. Should you or your staff have any questions, please do not hesitate to contact me or Kimberlee Trzeciak of my staff at (202) 225-4071.

With every good wish,

Sincerely,

John D. Dingell
Member of Congress

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

APR 26 2013

The Honorable John D. Dingell
House of Representatives
Washington, D.C. 20515-2215

Dear Mr. Dingell:

Thank you for your letter of October 9, 2012, concerning the fungal meningitis outbreak associated with methylprednisolone acetate, a steroid injectable product distributed by the New England Compounding Center (NECC). This outbreak has had devastating effects on individuals and families across the country.

The Food and Drug Administration (FDA or the Agency) believes that pharmacists engaging in traditional compounding provide a valuable medical service that is an important component of our health care system. The history of this issue shows that there is a need for appropriate and effective oversight of this evolving industry. It is clear that the industry and the health care system have evolved and outgrown the law, and FDA's ability to take action against compounding that exceeds the bounds of traditional pharmacy compounding and poses risks to patients has been hampered by gaps and ambiguities in the law, which have led to legal challenges to FDA's authority to inspect pharmacies and take appropriate enforcement actions.

The fungal meningitis outbreak has caused the Agency to review our past practices with regard to our oversight of compounding pharmacies. We have established an Agency-wide steering committee to oversee and coordinate our efforts, and we have taken several important steps to identify and inspect high-risk pharmacies that are known to have engaged in production of sterile drug products.

The Administration is committed to working with Congress to address the threat to public health from gaps in authorities for effective oversight of certain compounding practices. To that end, FDA has developed a framework, discussed below, that could serve as the basis for the development of a risk-based program to protect the public health.

We have restated your questions below in bold, followed by our responses.

1. **Although the investigation is still ongoing, FDA has discovered fungal contamination of sealed vials of methylprednisolone acetate collected at NECC. How many vials of this steroid has NECC produced? How many vials of this steroid produced by NECC have been distributed? How many facilities have received vials of this steroid produced by NECC? Where are these facilities located? When were the vials linked to the outbreak distributed? How many patients have received injections of this steroid produced by NECC thus far?**

As part of the public health investigation into the outbreak, FDA has learned that, among the three suspect lots of methylprednisolone acetate (MPA) produced by NECC, there are 17,676 total vials. These lots were distributed to facilities in 23 states (California, Connecticut, Florida, Georgia, Idaho, Illinois, Indiana, Maryland, Michigan, Minnesota, North Carolina, New Hampshire, New Jersey, Nevada, New York, Ohio, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Virginia, West Virginia), between the date of preparation of the first lot (May 21, 2012) and the date on which the suspect lots were recalled (September 26, 2012). After the recall of NECC steroid medications on September 26, state and local health departments identified almost 14,000 people in 23 states who were potentially exposed to the implicated MPA; of these, an estimated 11,000 individuals received spinal or paraspinal injections.

2. **Who first discovered the contamination of vials of methylprednisolone acetate? When was the contamination first discovered? Where was the contamination first discovered? How was contamination discovered? When was the contamination first reported to FDA? How did this contamination occur?**

As part of the public health investigation into the outbreak, FDA has learned that, on September 21, 2012, the Centers for Disease Control and Prevention (CDC) was notified by the Tennessee Department of Health of a patient with the onset of meningitis approximately 19 days following epidural steroid injection at a Tennessee ambulatory surgical center. On September 25, 2012, CDC notified FDA that it was working with the Tennessee Department of Health to investigate a cluster of meningitis cases at a single clinic, which might be associated with product contamination. On October 18, 2012, FDA and CDC announced that "CDC and FDA have confirmed the presence of a fungus known as *Exserohilum rostratum* in unopened medication vials of preservative-free methylprednisolone acetate (80mg/ml) from one of the three implicated lots from NECC (Lot #08102012@51, BUD 2/6/2013). The laboratory confirmation further links steroid injections from these lots from NECC to the multistate outbreak of fungal meningitis and joint infections."

Due to the ongoing criminal investigation, FDA cannot comment further.

3. **NECC has issued a voluntrary recall of the methylprenisolone acetate products and has voluntarily shut down. When was the voluntary recall first initiated? How many lots have been recalled? How many doses were included in the recall? When did NECC shut down its facility?**

As part of the public health investigation into the outbreak, FDA worked with NECC to initiate a voluntary recall of the suspect lots of MPA on September 26, 2012. At the time, three lots (17,676 vials) were included in the recall; however, since that time, the recall was expanded to include all products made by NECC. FDA was notified that NECC ceased production on October 3, 2012, and has not recommenced production.

4. **Are any vials of methylprednisolone acetate from NECC still available on the market? If yes, how many vials remain on the market?**

As of October 6, 2012, all products compounded and distributed by NECC were recalled by the firm. NECC posted notice of the recall on their website, *www.neccrx.com*. As of January 30, 2013, as part of the public health investigation into the outbreak, FDA had completed 1,155 audit checks with customers who received NECC products. FDA found no unexpired product remaining for use with any of the customers, and all customers had knowledge of the recall either through NECC, CDC, state health departments, the media, or other sources.

5. What alerts regarding methylprednisolone acetate has FDA issued to health professionals? What alerts regarding methylpredinsolone acetate has FDA issued to consumers? How have these alerts been transmitted to these parties?

As part of the public health investigation into the outbreak, FDA issued two MedWatch alerts in October 2012 (with updates through November 2012), advising health care professionals and consumers of the risks associated with drug products produced by NECC, including MPA acetate, and providing updates as FDA's investigation progressed. Links to the MedWatch alerts on FDA's website are provided below.

FDA issued an alert on October 5, 2012 (updated on October 6, 2012), advising that FDA had observed fungal contamination in a sealed vial of methylprednisolone collected from NECC, and recommending that health care professionals and consumers not use any product produced by NECC. The alert indicated that although the investigation into the source of the outbreak was ongoing, it was possibly associated with preservative-free MPA acetate produced and distributed by NECC. This alert is available at *http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm322849.htm.*

FDA issued another MedWatch alert on October 15, 2012, which was updated multiple times. The initial alert dated October 15, 2012, advised of a patient with possible meningitis associated with triamcinolone acetonide, and two transplant patients (revised on October 16, 2012, to one transplant patient) with *Aspergillus fumigatus* infections following administration of cardioplegic solution made by NECC. The alert was updated on October 18, 2012, noting that CDC and FDA confirmed the presence of *Exserohilum rostratum* in unopened vials of preservative-free MPA acetate made by NECC. Further updates, dated October 22, 2012, informed that FDA was making available lists of customers who received products shipped on or after May 21, 2012, from NECC, and dated October 24, 2012, was to provide an updated list of customers. The final update, dated November 1, 2012, advised that two additional products recalled by NECC, preservative-free betamethasone and cardioplegia solution, tested positive for bacterial contamination. This alert is available at *http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm323946.htm.*

FDA communicated throughout its investigation with the media, Congress, state health officials, health care professionals, and the public to keep them apprised of important findings and developments as our investigation proceeded. FDA's website was updated on a frequent basis to provide broad access to any new public information. This information was further disseminated through the Agency's electronic listservs and through Twitter and

Facebook. Along with CDC, FDA provided health care professionals with information they needed on an ongoing basis, and as new information came to light, to advise and treat patients affected by this situation.

Targeted alerts were sent to 150 health care professional organizations, including the national specialty-specific societies that work with spinal injections, such as the American Society of Anesthesiologists, the American Academy of Physical Medicine and Rehabilitation, and the North American Spine Society, and also to all state medical, pharmacist, nursing, and physicians' assistant societies, as well as all state boards of pharmacy. Regular phone updates were provided to state health departments, in collaboration with CDC, and written updates were also distributed to national pharmacy and ophthalmology professional organizations. FDA also contacted patient and health care professional groups and consumer groups and worked with the American Hospital Association as part of our response.

FDA pharmacists fielded calls from the public and extended their hours of availability for several weeks to help respond to the public's concerns. We also continued to respond to calls and e-mails from health care professionals, hospitals and clinics, and others with questions about the NECC and Ameridose recalls.

6. **With what federal and state agencies has the FDA been working on this investigation?**

FDA cannot comment at this time.

7. **It has been reported that Massachusetts Board of Registration in Pharmacy has had at least four previous complaints about the sterility of NECC's products- in 2002, 2003, 2011, and one complaint is currently being investigated. Were these complaints shared with the FDA? If yes, when were these complaints shared?**

FDA received three adverse event reports in 2002 suggesting sterility concerns associated with MPA acetate compounded by NECC. These reports came directly to FDA via the MedWatch reporting system from the hospital that treated the patients. The Agency is not aware that the Massachusetts Board of Registration in Pharmacy (MBRP) provided any report of these adverse events to FDA. FDA's investigations of these reports were, however, communicated to the Massachusetts' Board of Registration in Pharmacy (MBRP). The inspection beginning in 2002 regarding the adverse event reports associated with methylprednisolone was conducted jointly by FDA with MBRP.

FDA does not have a record of having received from MBRP reports of any complaints or adverse events in 2002, 2003, or 2011, regarding sterility of NECC's products.

8. **What has been the inspection history of the NECC facility? When was the NECC facility in Framingham last inspected? What were the results of that inspection?**

See enclosed document entitled "Timeline of FDA Interactions with NECC and Ameridose" that was provided to the House Energy and Commerce Committee on January 4, 2013.

9. Does FDA have the authority to inspect compounding pharmacies? If yes, when was the last time FDA officials have inspected NECC's facility? What were the results of that inspection?

Under FDA's current inspection authority in section 704 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), FDA's authority to inspect records at a pharmacy depends upon knowing certain facts about the pharmacy's operations that oftentimes can only be determined through inspection of records. The first of three criteria for being exempt from having records inspected is whether the pharmacy is operating in conformity with state law, a determination most readily made by a state and, in any case, likely dependent upon examining certain records. The second criterion is whether the pharmacy is dispensing prescription drugs without a prescription, but in many cases, FDA must be able to inspect records to determine that fact. Similarly, the third criterion is whether the pharmacy is compounding drugs for sale other than in the regular course of its retail business, which is also something that would be difficult to determine without a full inspection of the facility, including an inspection of appropriate records. So the authority is circular, and compounding pharmacies have cited this language in opposing FDA's efforts to inspect.

In addition, the records exemption for pharmacies can present an obstacle to FDA in determining the source of a complaint or outbreak associated with a compounded drug that may be adulterated or misbranded under the FD&C Act. FDA's ability to inspect in a timely manner any firm producing drugs is critical for effective oversight and regulation. Therefore, FDA strongly recommends that the provision in section 704 of the FD&C Act that limits the Agency's ability to inspect a pharmacy's records be removed. It is critical that FDA have clear authority to inspect pharmacies to determine the scope and nature of their operations to determine whether they are operating as compounding pharmacies or conventional drug manufacturers. The determination of whether a compounding pharmacy is engaging in conventional drug manufacturing is fact-specific, and FDA must be able to fully inspect pharmacies, and review their records, to gather the facts to make this determination.

Therefore, FDA should have clear ability to examine records such as records of prescriptions received, products shipped, volume of operations, and operational records such as batch records, product quality test results, and stability testing results. Such inspections are necessary to determine when a pharmacy exceeds the bounds of traditional compounding, respond to public health threats, and enforce federal standards.

See enclosed document entitled "Timeline of FDA Interactions with NECC and Ameridose," which was provided to the House Energy and Commerce Committee on January 4, 2013, for additional information.

10. It has been reported that more than 17,000 vials compounded by NECC have been recalled thus far. What does FDA consider to be legitimate forms of pharmacy compounding? What volume does FDA consider to be legitimate uses of pharmacy compounding?

Due to the ongoing criminal investigation, FDA cannot comment on NECC specifically.

With regard to compounding generally, FDA issued a Compliance Policy Guide (CPG) in 2002 (CPG Sec. 460.200) that describes the factors FDA considers in determining whether to take enforcement action against a compounding pharmacy. The CPG recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of human drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner, and states that this traditional activity is not the subject of the CPG. In its simplest form, this compounding may involve reformulating a drug, for example, by removing a dye or preservative in response to a patient allergy. Or it may involve making a suspension or suppository dosage form for a child or elderly patient who has difficulty swallowing a tablet. FDA believes that pharmacists engaging in traditional compounding provide a valuable medical service that is an important component of our health care system.

Section 503A of the FD&C Act, added to the law in 1997, also attempts to draw a line between pharmacy compounding and conventional manufacturing using different but similar factors to draw the line. That statute was challenged in court and the compounded product, consistent with the factors set forth in section 503A, is exempt from three key provisions of the FD&C Act: the requirement of premarket review for safety and effectiveness, the requirement to provide adequate directions for use, and the requirement that the drug meets Current Good Manufacturing Practice standards. The statute contains some ambiguous provisions that make it difficult to draw a clear line between compounded drugs that are subject to exemptions from the above provisions of the Act and those compounded drugs which are not.

Further, regulating certain types of compounding pharmacies as conventional manufacturers is not a good fit for the evolving category of outsourcer pharmacy, which provides drugs for hospitals and other health care entities. The Administration is committed to working with Congress to address the threat to public health from gaps in authorities for effective oversight of certain compounding practices. To that end, FDA has developed a framework that could serve as the basis for the development of a risk-based program to protect the public health.

FDA has suggested that legislation be enacted to create a new framework for regulating compounding. FDA suggests Congress create a new category of non-traditional compounding, subject to appropriate federal standards, which may be based on certain Current Good Manufacturing Practice (CGMP) requirements in 21 *Code of Federal Regulations* (CFR) Parts 210 and 211, and oversight to ensure consistent product quality standards are applied to sterile compounding done in advance of or without a pharmacy receiving a prescription where the compounded product is then shipped across state lines. FDA believes that there are other authorities that would be important to support this new regulatory paradigm. For example, FDA should be given clear, full authority to collect and test samples of compounded drugs and to examine and collect records in a compounding pharmacy, just as the Agency does when inspecting other manufacturers. FDA should have clear statutory authority to examine records, such as records of prescriptions received, products shipped, volume of operations, and operational records such as batch records, product quality test results, and stability testing results. Such inspections are necessary to

determine when a pharmacy exceeds the bounds of traditional compounding to respond to public health threats and to enforce federal standards.

11. Do compounding pharmacies, like NECC, register with FDA? If yes, how many compounding pharmacies are currently in operation?

Generally, pharmacies are exempt from registration under section 510 of the FD&C Act, provided they meet certain conditions (510(g) of the Act). Such conditions include operating under applicable local laws regulating the practice of pharmacy and medicine, regularly dispensing drugs upon a valid prescription, and not compounding drugs other than in the regular course of dispensing drugs at retail. As a result, FDA does not know all of the compounding pharmacies in the United States, and FDA does not conduct regular surveillance inspections of pharmacies as it does with typical drug manufacturers.

According to the International Academy of Compounding Pharmacists (IACP), there are an estimated 28,000 pharmacies that compound, including 7,500 pharmacies that specialize in compounding. About 3,000 of these pharmacies compound sterile products.

An accurate inventory of pharmacies engaged in non-traditional compounding would facilitate appropriate oversight and coordination with state regulators. Under FDA's proposed framework, certain sterile compounding facilities should be subject to federal oversight to ensure that the compounding of sterile drug products at those facilities can be done without putting patients at undue risk. These requirements would include federal registration of the compounding facilities that will be subject to federal quality standards, so that FDA knows where they are and what drug products they are making.

12. Do compounding pharmacies list their products with FDA? If yes, how many products produced by compounding pharmacies are currently on the market?

Because pharmacies that meet certain criteria generally are not required to register or list, FDA does not have a list or count of marketed compounded products.

An accurate inventory of pharmacies engaged in non-traditional compounding would facilitate appropriate oversight and coordination with state regulators. Under FDA's proposed framework, requirements would include federal registration of the compounding facilities that will be subject to federal quality standards, so that FDA knows where they are and what drug products they are making,

13. Does FDA approve products produced through compounding pharmacies? Are drug products made through pharmacy compounding required to meet the safety and efficacy standard set by FDA?

Under section 503A of the FD&C Act, compounded drugs that meet certain criteria are provided an exemption from three key provisions of the Act, including the drug approval requirements of section 505. The CPG on pharmacy compounding, CPG Sec. 460.200 Pharmacy Compounding, sets forth factors that FDA considers in determining whether to

exercise enforcement discretion in applying the drug approval requirements of section 505 of the FD&C Act. Thus, under either section 503A or the CPG, compounded drugs are not approved by FDA and lack an FDA finding of safety and efficacy.

14. Does FDA have sufficient authority to oversee compounding pharmacies, such as NECC, now? If so, please explain why. If no please explain why.

With regard to compounding generally, FDA is working with Congress, states, industry, and other interested stakeholders to develop a basic framework to help the Agency effectively oversee firms engaged in widespread distribution of sterile compounded drug products in advance of or without receiving a prescription. In the proposed framework, FDA believes that certain sterile compounding facilities should be subject to federal oversight to ensure that the compounding of sterile drug products at those facilities can be done without putting patients at undue risk, including requiring:

- Compliance with federal quality standards that are appropriate for the compounding of riskier products and exposure of larger numbers of patients
- Federal registration of the compounding facilities that will be subject to federal quality standards, so that FDA knows where they are and what drug products they are making; and
- These higher-risk compounding pharmacies to report to FDA serious adverse reactions to their drugs, of which they become aware, so that we can act quickly on potential problems that may be associated with compounded drugs.

And for all pharmacy compounding, FDA believes certain basic protections should be in place. These include:

- Clear authority to examine a pharmacy's records to more quickly locate the cause of an outbreak or other violations of the law
- Requirements for clear label statements that identify the nature and source of compounded products, providing prescribers and consumers with valuable information about the products they are using, so that they can make informed judgments about their use; and
- Prohibiting compounding of the most complex and highest-risk products—drugs and biologics that should only be made for patients by an FDA-registered drug manufacturer under an approved new drug application in which the manufacturer has demonstrated that the product is safe and effective and that it can be safely made according to the highest-quality standards.

This proposed framework requires legislative action. We look forward to continuing to work with Congress to enact an oversight framework to protect the public health before an outbreak.

15. Does FDA need additional authority to oversee compounding pharmacies? If yes, please explain why and list the authorities needed. If no, explain why.

There is a need for appropriate and effective oversight of this evolving industry. It is clear that the industry and the health care system have evolved and outgrown the law, and FDA's ability to take action against compounding that exceeds the bounds of traditional pharmacy compounding and poses risks to patients has been hampered by ambiguities in the law, which have led to legal challenges to FDA's authority to inspect pharmacies and take appropriate enforcement actions. The Administration is committed to working with Congress to address the threat to public health from limitations in authorities for effective oversight of certain compounding practices. To that end, FDA has developed a framework that could serve as the basis for the development of a risk-based program to protect the public health.

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

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

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

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

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

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

An accurate inventory of pharmacies engaged in non-traditional compounding would facilitate appropriate oversight and coordination with state regulators. In addition, FDA looks forward to working with Congress on potential improvements that may include label statements and adverse event reporting that have proven useful in other areas.

Thank you, again, for contacting us concerning this important matter. If you have further questions please let us know.

Sincerely,

Michele Mital

Michele Mital
Acting Associate Commissioner
for Legislation

Enclosure

Timeline of FDA Interactions with NECC and Ameridose

Background
Please find below an overview of certain facts related to the Food and Drug Administration's (FDA, or the Agency) past interactions with the New England Compounding Company (NECC) and Ameridose. No information related to FDA's ongoing investigations of these companies is included. The information in these timelines is representative of our current understanding, based upon the records and information we have been able to review to date. We continue to collect information related to our history with these companies. We would be pleased to provide additional information if and when it becomes available.

Timeline for NECC

- According to the records FDA has reviewed to date, our earliest record of contact with NECC was an April 2002 inspection to follow-up on two adverse event reports submitted to FDA associated with betamethasone compounded by NECC. On April 16, 2002, FDA issued a Form FDA 483, which included three observations voicing concerns regarding NECC's process for producing sterile drugs.

- From October 24, 2002, until February 10, 2003, FDA and the Massachusetts Board of Pharmacy (MABP) conducted a jointly coordinated inspection to follow-up on adverse event reports received in July and August 2002 of bacterial meningitis associated with methylprednisolone compounded by NECC.

- In a meeting held on February 5, 2003, toward the end of the 2002-2003 inspection, FDA and MABP jointly decided that MABP would take the lead in enforcement and inspections of NECC's compounding operations since NECC was functioning as a compounding pharmacy. On February 10, 2003, FDA issued a 483 closing out its inspection. The firm responded on February 26, 2003, and supplemented its response on May 20, 2003, describing the corrective steps the firm was taking in response to the 483.

- FDA inspected NECC from September 23, 2004, until January 19, 2005, in a focused inspection related to a competitor's complaint that NECC had compounded a drug using bulk active ingredients that were not a component of an FDA-approved drug. FDA subsequently approved another firm's application to market the drug, and FDA issued a Warning Letter in December 2006 to NECC stating the firm was compounding copies of commercially available products; compounding standardized anesthetic drug products, which was outside the scope of traditional pharmacy compounding; and repackaging Avastin. The Warning letter charged that the copies of the FDA approved drugs and the anesthetic cream were misbranded and that the repackaged Avastin was an unapproved new drug. The Warning Letter did not pertain to sterility failures at NECC. During the 2004-05 inspection, FDA reviewed NECC's procedures in light of the February 10, 2003 483 and concluded that corrective actions had been implemented.

- In January 2006, NECC entered into a consent agreement with the Commonwealth of Massachusetts related to inadequacies in the firm's sterile and non-sterile compounding

practices. The consent agreement required NECC to hire a consultant and take corrective actions, which would be verified by the consultant. In June 2006, MABP notified NECC that the firm had fulfilled the terms of the consent decree.

- In January 2007, NECC responded to the 2006 Warning Letter.

- FDA responded to NECC's Warning Letter response in October 2008.

Timeline for Ameridose

- Ameridose first registered with FDA in September 2006, but never listed any drugs.

- FDA and MABP conducted a jointly coordinated inspection of Ameridose in December 2007 to follow-up on a complaint related to the company making IV solutions without receipt of patient-specific prescriptions and to gather facts since the firm had recently registered with FDA. FDA advised the firm to validate and verify its aseptic processes since it was making sterile products.

- FDA performed a second inspection of Ameridose seven months later (July-Aug. 2008). This was an inspection to review the firm's "good manufacturing practices." The agency issued the firm a 483 on August 6, 2008, citing several observations, such as not confirming the sterility of products before distribution. Ameridose responded in August 2008 stating that it would take corrective actions to address FDA's observations in the 483.

- During the 2008 inspection, FDA also collected samples of Fentanyl (a strong pain medication), which was found to be super-potent, leading to a Class I recall in September 2008.

- In September 2008 and November 2008, FDA returned to the firm to review shipping records specific to the super-potent Fentanyl, to review the firm's corrective and preventative actions since the September 2008 recall, and to follow-up on questions discussed during the prior inspection.

- In June 2010, FDA received a commercial complaint related to the compounded product nicardipine and conducted at the same time as MABP a limited inspection in response. In January 2011, FDA was informed that the complainant and Ameridose reached amicable resolution. Massachusetts officially dismissed the complaint in June 2011.

JOHN D. DINGELL
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COMMITTEE ON
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CO-CHAIR
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October 16, 2012

The Honorable Margaret Hamburg
Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Commissioner Hamburg:

I write to you in regards to the most recent update on the U.S. Food and Drug Administration's (FDA) investigation of the contaminated products at the New England Compounding Center (NECC).

On Monday, FDA noted that additional products produced at NECC may have sterility issues. This includes a patient with possible meningitis that was injected with triamcinolone acetonide and two transplant patients who received cardioplegic solution during surgery who now have *Aspergillus fumigatus* infection. FDA has also cautioned against the use of any ophthalmic drugs that are injectable or used in conjunction with eye surgery. While I understand that FDA's investigation is still ongoing, I am greatly concerned that additional contaminated NECC products may still remain on the market and could cause harm to thousands more Americans.

Given this latest update, I respectfully request the answers to the following questions:

1. Please provide a complete list of the products produced at NECC, including the proprietary name, the nonproprietary name or common name, the quantity of doses produced, dosage forms, strengths, route of administration, and proposed indication for each of the products. How many of these products were prepared based on a prescription for a specific patient?

2. How many facilities, in how many states, have received NECC products?

3. Please provide an estimate of how many patients are at risk from infection or meningitis from the use of NECC products. How does FDA intend to notify patients that may have been treated with NECC products?

4. Do any of NECC's products remain on the market? If so, which products remain on the market? Of those that remain on the market, how many doses remain on the market?

As the meningitis outbreak continues to grow and now newer fungal infections are reported, I remain concerned that FDA and state regulators have not collected full and accurate information about the activities of NECC. It is clear that NECC willfully disregarded state regulations and did not properly address the concerns laid out by FDA in previous warning letters. This company's actions have shown that new authority and further oversight over compounding pharmacies is needed. I will be sending you further inquiry as to what authority, personnel, and funding is needed by FDA to better oversee compounding pharmacies.

Given the serious nature of this outbreak, I respectfully request that a response be sent to my office no later than October 30, 2012. Should you or your staff have any questions, please do not hesitate to contact me or have a member of your staff contact Kimberlee Trzeciak in my office at (202) 225-4071.

With every good wish,

Sincerely,

John D. Dingell
Member of Congress

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable John D. Dingell
House of Representatives
Washington, D.C. 20515-2215

APR 26 2013

Dear Mr. Dingell:

Thank you for your letter of October 16, 2012, concerning the fungal meningitis outbreak associated with methylprednisolone acetate, a steroid injectable product distributed by the New England Compounding Center (NECC).

We have restated your questions below in bold, followed by our responses.

1. **Please provide a complete list of the products produced at NECC, including the proprietary name, the nonproprietary name or common name, the quantity of doses produced, dosage forms, strengths, route of administration, and proposed indication for each of the products. How many of these products were prepared based on a prescription for a specific patient?**

   The list of products subject to NECC's voluntary recall is available on NECC's website, *www.neccrx.com*. Due to the ongoing criminal investigation, we are not able to provide additional information at this time.

2. **How many facilities, in how many states, have received NECC products?**

   A list that includes this information as received by FDA is available on FDA's website at *http://www.fda.gov/downloads/Drugs/DrugSafety/FungalMeningitis/UCM325466.pdf.*

3. **Please provide an estimate of how many patients are at risk from infection or meningitis from the use of NECC products. How does FDA intend to notify patients that may have been treated with NECC products?**

   As part of the public health investigation, FDA has learned that approximately 14,000 patients have been exposed to methylprednisolone acetate from the suspect lots of product. CDC and the departments of health in the affected states have been working together to notify those patients who were treated with the suspect product after May 21, 2012. A notice from the Centers for Disease Control and Prevention (CDC), "Notice to Clinicians: Continued Vigilance Urged for Fungal Infections among Patients Who Received Contaminated Steroid Injections," is available on CDC's website at *http://emergency.cdc.gov/HAN/han00342.asp*. Through active notification by clinics with assistance from states and CDC in early October, nearly all of these exposed persons were contacted at least once and informed of their risk for fungal infection as a result of receiving

injections with contaminated medication. FDA has also advised health care professionals to follow up with patients who have been treated with NECC injectable products shipped after May 21, 2012.

4. **Do any of NECC's products remain on the market? If so, which products remain on the market? Of those that remain on the market, how many doses remain on the market?**

   As of October 6, 2012, all products compounded and distributed by NECC were recalled by the firm. NECC posted notice of the recall on their website, *www.neccrx.com*. As of January 30, 2013, as part of the public health investigation into the outbreak, FDA had completed 1,155 audit checks with customers who received NECC products. FDA found no unexpired product remaining for use at any of the customers and all customers had knowledge of the recall either through NECC, CDC, state health departments, the media, or other sources.

Thank you, again, for contacting us concerning this important matter. If you have further questions, please let us know.

Sincerely,

Michele Mital
Acting Associate Commissioner
for Legislation

NACDS NATIONAL ASSOCIATION OF CHAIN DRUG STORES

Statement

Of

The National Association of Chain Drug Stores

For

U.S. House of Representatives
Subcommittee on Health

Hearing on:

"Examining Drug Compounding"

May 23, 2013
10:00 a.m.

2322 Rayburn House Office Building

National Association of Chain Drug Stores (NACDS)
1776 Wilson Blvd Suite 200
Arlington, VA 22209
703-549-3001
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The National Association of Chain Drug Stores (NACDS) thanks Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee on Health for consideration of our statement for the hearing "Examining Drug Compounding." We look forward to our continued work with you on ensuring that Americans receive safe and effective compounded prescription drugs.

NACDS commends the Committee for your efforts to better understand issues related to the compounding of prescription drugs. NACDS represents traditional drug stores, supermarkets, and mass merchants with pharmacies – from regional chains with four stores to national companies. Chains operate more than 41,000 pharmacies and employ more than 3.8 million employees, including 132,000 pharmacists. They fill over 2.7 billion prescriptions annually, which is more than 72 percent of annual prescriptions in the United States. The total economic impact of all retail stores with pharmacies transcends their over $1 trillion in annual sales. Every $1 spent in these stores creates a ripple effect of $1.81 in other industries, for a total economic impact of $1.81 trillion, equal to 12 percent of GDP. For more information about NACDS, visit www.NACDS.org.

Introduction

NACDS supports the mission and work of FDA in ensuring that Americans receive only safe and effective prescription drugs. Safeguarding the health and welfare of our patients remains our highest priority. Pharmacist compounding services are the only source of critical medications for millions of patients who each have their own unique health care needs. For these patients, there are no commercially-manufactured preparations available. Accordingly, we agree with FDA that prescription drug compounding services are a valuable and important part of our nation's healthcare system.

Background on Compounding

Prescription drug compounding has been a traditional function of the practice of pharmacy ever since the beginning of the profession. Compounding is an important component of patient care because many patients need prescription products that are not made commercially by drug manufacturers. Compounding by pharmacists is the only way to meet these patients' needs. Traditional prescription drug compounding is based on individual prescription orders for individual patients for products that are not commercially available. Because of these patient needs compounding continues to be an integral function of pharmacy practice.

Pharmacists are trained to prepare compounded medications and are tested on this competency. State boards of pharmacy license pharmacies after ensuring, among other things, that they have the proper tools and equipment to compound prescription drug medications.

The definition of what constitutes "compounding" is consistent from state to state. Generally, it involves the mixing of two or more drug substances together to deliver to the patient a product that is not commercially available. Most retail pharmacies engage in the compounding of skin creams, lotions, ointments, liquids, or suppositories. For example, chain pharmacists helped to meet the need for liquid Tamiflu during the 2009 H1N1 flu outbreak through their ability to compound the liquid product from Tamiflu capsules – and at the request of FDA. In other cases, a pharmacist may be called on to compound a liquid form of a medication for a patient battling cancer, when that patient is not able to swallow the pill form of the medication.

Some chain pharmacies may have a local or regional central compounding facility that they use to compound frequently-ordered products that are not commercially available, which are then distributed to individual retail stores in the chain. These compounded products are made in anticipation of prescriptions for these products based on the prescribing patterns of physicians.

Preserving State Board Authority

NACDS believes that state boards of pharmacy should retain sole jurisdiction over traditional prescription drug compounding. This is a proper role for state pharmacy boards. Prescription drug compounding has been an integral function of the practice of pharmacy since the early days of the profession. State boards of pharmacy have the experience and expertise to continue to regulate this integral function. We urge the Committee to continue to maintain this policy. We believe that state boards of pharmacy should continue to regulate functions that are the practice of pharmacy, while FDA should regulate the manufacturing of prescription drugs. FDA should not be granted authority over traditional pharmacy functions. FDA would not have the resources, ability or expertise to regulate pharmacies and the practice of pharmacy. Moreover, concurrent state and federal jurisdiction over pharmacies would cause unnecessary confusion for FDA, state boards of pharmacy, and pharmacies. All would be unsure as to where federal authority ends and state authority begins.

State and Federal Collaboration

We support efforts among FDA and the state boards of pharmacy to work together to investigate any questionable practices so that prescription drug compounding is regulated in the best interests of patients. To prevent future tragedies, there must be a close collaboration among FDA and the boards of pharmacy. Despite best efforts, there still may be entities that seek to circumvent patient safety measures as well as federal and state regulation. We support state and federal joint efforts to root out rogue entities that seek to use a state pharmacy license as a shield from federal oversight.

Conclusion

NACDS thanks the Committee for consideration of our comments. We look forward to working with policy makers and stakeholders on these important issues.

Central Admixture Pharmacy Services, Inc.
2530 Meridian Parkway, Suite 200
Research Triangle Park, NC 27713
Telephone: (919) 806-4448
Fax: (484) 821-9420

May 21, 2013

The Honorable Joe Pitts
House Committee on Energy and Commerce
Health Subcommittee
420 Cannon House Office Building
Washington, DC 20515

Re: "Examining Drug Compounding"

Dear Chairman Pitts,

On behalf of Central Admixture Pharmacy Services, Inc. (CAPS), I am writing to provide comments and insights that are relevant to current discussions regarding pharmacy compounding. CAPS appreciates the opportunity to work with the House Committee on Energy and Commerce to ensure that compounding pharmacies produce safe compounded sterile preparations.

Compounding pharmacy has a storied history in the provision of pharmaceutical care, from a time when essentially all prescriptions were compounded (estimated at 80% in the 1920's) to a period in which only a very small percentage are compounded (estimated at <1% in the 1970's). Today, the definition of pharmacy compounding is unclear and encompasses a host of practices ranging from adding simple flavorings to commercially available oral pharmaceuticals to the preparation of sterile injectables from approved pharmaceutical ingredient (API) powders.

In recent years pharmaceutical compounding has grown rapidly in the acute care setting. The hospital segment of the health care industry is facing extraordinary pressure to provide better patient care, improved patient outcomes and cost reductions. Hospital pharmacies have adapted their practices to be harmonized with these priorities and in doing so have appropriately focused on the provision of pharmaceutical care models to optimize outcomes. One such strategy is to contract sterile injectable compounding to outsourcing partners thus allowing scarce pharmacy resources to be focused on direct patient care activities. Over the last several years severe drug shortages have forced physicians and hospitals to seek compounded alternatives to otherwise commercially available products. The pharmacy compounding community continues to adapt their practices to meet the growing demands and needs of the market.

CAPS was founded in 1991 with seven original pharmacies to serve as an intravenous (IV) outsourcing partner to hospital and health system pharmacies. We work closely with our clients to identify compounded sterile preparations (CSPs) and services that add value to their pharmaceutical care model. Our activities and the CSPs we provide are an extension of the activities routinely performed onsite at the host hospital pharmacy. Centralization of these compounding activities allows CAPS to focus on associated quality systems, compounding processes, facilities, environmental controls, qualification practices and validation activities not commonly associated with traditional pharmacy practice.

- Today we have grown into a network of 25 pharmacies serving more than 1500 hospital pharmacies with clients and patients in all 50 states.
- In 1994 CAPS voluntarily registered all of our pharmacies with the FDA.
- Today our pharmacies that perform compounding activities beyond fulfilling patient specific prescriptions remain registered with FDA.
- Our business model focuses on both acute care and out patient care market segments.
- Our core business is comprised of patient specific parenteral nutrition formulations for those patients unable to meet nutritional needs orally.
- Other business components consist of non-patient specific compounded CSPs prepared in anticipation of a prescription in limited quantities based on historic ordering patterns. These formulations range from complex multi-ingredient admixtures such as cardioplegic solutions to single component admixtures such as standard antibiotic doses.

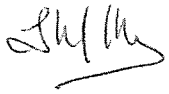
Recent discussions within the pharmacy community have sought to better define pharmacy compounding, clarify regulatory authority over the variations in practice, identify the appropriate rules and regulations to govern the practice, and establish minimum standards for all stakeholders who wish to engage in the practice. CAPS is of the belief that there are several key concepts that should be adopted when considering governance of compounding manufacturing.

- Language in the Federal Food, Drug, and Cosmetic Act should be revised to remove loopholes that permits pharmacies to "manufacture" under the guise of "Anticipatory Compounding":
    - Define traditional pharmacy compounding as a compounding activity resulting in a CSP specifically made for an identified individual patient and dispensed only upon receipt of said patient specific prescription. Defining the practice in this way does not prohibit compounding in anticipation of a prescription in limited quantities and based on historic ordering patterns. It does however impose a requirement that all CSPs be dispensed only upon receipt of the patient specific prescription.
- State Boards of Pharmacy should be responsible for governing the practice of traditional pharmacy compounding.
- Define compounding manufacturing as a compounding activity resulting in CSPs that are sold and distributed to identifiable clients without patient specificity. Such activities should be construed as compounding manufacturing regardless of distribution in interstate or intrastate commerce. Third party distribution or reselling should not be permissible.
- The FDA should be responsible for governing the practice of compounding manufacturing and has such authority within the existing framework.
- The FDA should be required to clearly define the applicable standards on which compounding manufacturers will be evaluated for compliance.
- An exemption for hospital pharmacies should be considered that will allow them to compound and distribute CSPs within their institution without patient specificity, at the time of distribution, to meet the needs of the patients within their institution.
- Such hospital pharmacy exemption should not extend beyond the care of patients within that specific institution. If a hospital or health system wishes to distribute non-patient specific CSPs to other entities under common ownership or otherwise, they should be required to register and meet the requirements of a compounding manufacturer.

- To this end, compounding manufacturers should be permitted to hold a pharmacy permit in addition to registration with FDA. Such hybrid practices should meet all requirements for a compounding manufacturer and the standards set for pharmacies within the states in which they are registered. The FDA and Boards of Pharmacy have demonstrated the ability to conduct joint inspections and focus on the component of business within their respective enforcement areas.
- Any CSP designated for office use that is compounded and distributed in advance of a patient specific prescription should be considered compounding manufacturing and the pharmacy engaged in such a practice held to that standard.
- A provision for intracompany transfer of compounded sterile preparations produced by a compounding manufacturer and designed to be used as components of finished doses (e.g. parenteral nutrition electrolytes) should be a permissible act. This is especially true during this period of significant drug shortages.

CAPS appreciates the opportunity to comment on this issue that is a vitally important to public health today. We look forward to supporting your efforts and are most willing to be available and serve as a resource to you during this process.

Sincerely,



Thomas Wilverding
President
Central Admixture Pharmacy Services, Inc

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED THIRTEENTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON ENERGY AND COMMERCE

2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515–6115

Majority (202) 225–2927
Minority (202) 225–3641

June 13, 2013

Dr. Janet Woodcock
Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Woodcock:

Thank you for appearing before the Subcommittee on Health on Thursday, May 23, 2013, to testify at the hearing entitled "Examining Drug Compounding."

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.

Also attached are Member requests made during the hearing. The format of your responses to these requests should follow the same format as your responses to the additional questions for the record.

To facilitate the printing of the hearing record, please respond to these questions and requests by the close of business on Thursday, June 27, 2013. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to **Sydne.Harwick@mail.house.gov**.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachments

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

MAR 07 2014

Dear Mr. Chairman:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the May 23, 2013, hearing before the Subcommittee on Health, Committee on Energy and Commerce, entitled "Examining Drug Compounding." This letter is a response for the record to questions posed by certain Members of the Committee, which we received on June 13, 2013. We are also responding to questions posed at the hearing by you and other Members.

If you have further questions, please let us know.

Sincerely,

Sally Howard
Deputy Commissioner
Policy, Planning, and Legislation

We have restated each Member's questions below in bold, followed by our responses.

The Honorable Joseph R. Pitts

1. **In your testimony, you reference nine separate incidents where compounded products caused deaths and serious injuries. Please explain the actions that the FDA took following each incident. What happened to the pharmacies where these contaminated products originated?**

   Below are descriptions of the actions that FDA took in response to the nine incidents described in Dr. Woodcock's testimony. We note that most, but not all, of these adverse events were associated with product contamination:

   • *"In 1997, two patients were hospitalized with serious infections after administration of contaminated riboflavin injection prepared by a Colorado pharmacy."*

   In 1997, Riboflavin Injection made by College Pharmacy in Colorado Springs, Colorado, was administered intravenously to two patients who subsequently developed septicemia. FDA laboratory analysis of an intact vial of this drug product confirmed the presence of *Pseudomonas aeruginosa* gram-negative bacteria and a bacterial endotoxin level greater than 1,250 Endotoxin Units per milligram of riboflavin.

   In April 1999, FDA issued a Warning Letter to College Pharmacy that addressed these findings and included adulteration [§§ 501(a)(1) and 501(b)] and misbranding [§§ 502(a) and 502(j)] violations of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

   FDA's Office of Criminal Investigations (OCI) later initiated a criminal investigation into the owner and operator of College Pharmacy, Thomas Bader, and referred its case to the Justice Department. In January 2010, Bader was convicted on 31 counts related to the distribution of human growth hormone (HGH) that was smuggled into the United States from China, and the distribution of an anabolic steroid to customers with no legitimate relationship to physicians. He was found guilty on two counts of conspiracy, including conspiracy to facilitate the sale of misbranded and unapproved Chinese-made HGH, and conspiracy to manufacture, distribute, dispense, and possess with intent to distribute anabolic steroids; 27 counts of distribution of HGH; one count of facilitating the sale of smuggled HGH; and one count of possessing with intent to distribute HGH. In June 2010, Bader was sentenced to serve 40 months in Federal prison and was ordered to forfeit $4.8 million and the pharmacy building. College Pharmacy remains in operation, but under different ownership.

• *"In 2001, 13 patients in California were hospitalized and 22 received medical care following injections from contaminated vials of a steroid solution. Three patients died as a result."*

In May 2001, FDA was notified that Doc's Pharmacy of Walnut Creek, California, shipped vials of betamethasone injection that were contaminated with *Serratia marcescens* to six health care facilities in California. Thirty-eight patients received the contaminated steroid; 13 patients were hospitalized, 22 received follow-up medical care, and three patients died. FDA needed to obtain an Administrative Warrant to complete an inspection of Doc's Pharmacy and documented several deficiencies in the firm's processes for the production of sterile drugs. In July 2001, an administrative law judge ordered the pharmacy to halt all compounding operations. The owner violated the Order, and the California Board of Pharmacy suspended his Pharmacist License in November 2001. The owner surrendered his license in March 2002, and Doc's Pharmacy was sold.

• *"In 2002, five patients in North Carolina suffered from fungal meningitis resulting from contaminated methylprednisolone acetate made by a South Carolina pharmacy. One person died."*

This incident refers to five cases of fungal infections, including one death, resulting from methylprednisolone acetate contaminated by Urgent Care Pharmacy in Spartanburg, South Carolina. FDA and the South Carolina Board of Pharmacy (SC BOP) conducted a joint inspection, and the SC BOP imposed a Cease and Desist Order. FDA recommended an immediate recall of all injectable drug products made by this facility, and although the firm initially refused to comply with this recommendation, it ultimately agreed to voluntarily recall all methylprednisolone acetate sterile injectables. FDA issued an alert warning the public about Urgent Care's injectable drugs, and the pharmacy subsequently closed permanently.

• *"In 2005, contaminated cardioplegia solution, made by a firm located in Maryland, resulted in five cases of severe systemic inflammatory infections; three of these patients died."*

Five patients were hospitalized with severe systemic inflammatory infections and three of these patients died after receiving cardioplegia solution during open heart surgery that was made by Central Admixture Pharmacy Services (CAPS) in Lanham, Maryland. After FDA laboratories identified gram-negative rods in two lots of the firm's cardioplegia solution, CAPS recalled all injectable drug products made at this facility, and FDA posted a Medical Products Safety Alert on its website notifying health care professionals about the product recall. FDA also inspected the CAPS' facility in Lanham, Maryland, and several other CAPS facilities, and then met with CAPS' management to discuss the Agency's concerns regarding CAPS' compounding activities. In 2006, FDA issued a Warning Letter to CAPS' parent company, B. Braun, which addressed this incident and other deficiencies in the firm's processes for the

production of sterile drugs that FDA identified during inspections of several CAPS' sites. CAPS subsequently hired a consultant to improve its processes.

• *"In 2007, three people died from multiple organ failure after a Texas compounder sold superpotent colchicine that was as much as 640 percent the labeled strength."*

In 2007, ApothéCure, Inc. in Dallas, Texas, prepared and dispensed 72 vials of injectable colchicine, some of which were 640 percent superpotent, resulting in the deaths of three patients. FDA obtained an Administrative Warrant to complete an inspection of the firm and identified several deficiencies in the firm's processes for the production of sterile drugs. FDA's OCI investigated the incident and referred the case to the Department of Justice for criminal prosecution. In April 2012, ApothéCure and its owner pleaded guilty to two misdemeanor counts of introducing a misbranded drug into interstate commerce. In addition, the Texas Attorney General's Office brought a civil case against ApothéCure, asking for a permanent injunction and civil penalties related to the firm's compounding activities, which include misbranded, adulterated, and unapproved drug products; misbranded foods; and false advertising of drugs and dietary supplements under Texas law. Before trial in November 2012, ApothéCure's owner signed a Consent Decree with the state of Texas, enjoining his firm from distributing adulterated or misbranded drugs.

In April 2013, FDA inspected and issued an FDA Form 483[1] list of inspectional observations to ApothéCure and its related company, NuVision, reflecting deficiencies in the firms' processes for the production of sterile drugs. On April 15, 2013, ApothéCure recalled all lots of sterile products compounded, repackaged, and distributed due to sterility assurance concerns, and on April 17, 2013, ApothéCure indicated in its response to the FDA-483 that it decided not to continue doing business, effective May 31, 2013. NuVision recalled all compounded lyophilized products due to sterility assurance concerns on April 15, 2013, and FDA issued a press release on May 18, 2013, alerting health care providers about lack of sterility assurance of all sterile drug products from this facility.

• *"In 2010, FDA investigated a cluster of* Streptococcus endophthalmitis *bacterial eye infections in patients who received injections of Avastin repackaged by a pharmacy in Tennessee."*

FDA attempted an inspection of Health and Wellness Compounding Pharmacy in Nashville, Tennessee, after learning of a cluster of *Streptococcus endophthalmitis* bacterial eye infections in patients who received injections of Avastin repackaged by this pharmacy. FDA needed to obtain an Administrative Warrant after the pharmacy's owner refused to allow FDA to inspect. Based on findings from the inspection, FDA determined that the firm was, at that time, operating as a pharmacy, and therefore, referred the incident to the Tennessee Board of Pharmacy.

[1] An FDA Form 483 is issued when investigators observe any significant objectionable conditions. It does not constitute a final Agency determination of whether any condition is in violation of the FD&C Act or any of our relevant regulations, but the observations often serve as evidence of a violation of the FD&C Act and its implementing regulations.

• *"In 2011, there were 19 cases of* Serratia marcescens *bacterial infections, including nine deaths, associated with contaminated total parenteral nutrition products."*

In 2011, Advanced Specialty Pharmacy dba Meds IV (Meds IV), located in Bessemer, Alabama, prepared and dispensed total parenteral nutrition (TPN) drug products contaminated with *Serratia marcescens*, which resulted in 19 infections, including nine deaths. After learning of this incident, FDA, the state, and the Centers for Disease Control and Prevention (CDC) inspected, and the firm recalled, all intravenous drug products that it produced in 2011. FDA issued a Warning Letter to Meds IV, including adulteration [§ 501(a)(2)(A)] and misbranding [§§ 502(a) and 502(j)] violations of the FD&C Act. Meds IV subsequently surrendered its pharmacy license to the Alabama Board of Pharmacy.

• *"In 2012, 43 patients developed fungal eye infections from contaminated sterile ophthalmic drug products. At least 29 of these patients suffered vision loss."*

FDA and the Florida Department of Health conducted a joint inspection of Franck's Lab in Ocala, Florida, after receiving reports of fungal endophthalmitis in patients who were administered ophthalmic injections of Brilliant Blue G and triamcinolone made by this firm. Franck's Lab subsequently ceased sterile compounding operations and after FDA's environmental sampling of the firm's clean room revealed the presence of microorganisms and fungal growth, the firm announced a recall of all sterile human and veterinary prescriptions distributed from November 21, 2011, to May 21, 2012. FDA issued MedWatch statements warning health care providers of the infections and alerting them to the recalls. FDA issued a Warning Letter to the firm, including adulteration [§§ 501(a)(2)(A) and 501(c)] and misbranding [§ 502(a)] violations of the FD&C Act. The owner of Franck's Lab sold the facility to Wells Pharmacy Network, but he still owns an infusion pharmacy, Trinity Healthcare, in Ocala, Florida.

• *"Recently, in 2013, FDA investigated reports of five cases of eye infections in patients who received Avastin repackaged by a pharmacy in Georgia. The Avastin was contaminated with bacteria."*

After learning of eye infections in patients who received Avastin repackaged by Clinical Specialties Compounding Pharmacy in Augusta, Georgia, FDA inspected and issued to the firm an FDA-483 list of inspectional observations reflecting deficiencies in the firm's processes for the production of sterile drugs. Clinical Specialties voluntarily recalled all lots of sterile drug products repackaged and distributed by the firm between October 19, 2012, and March 19, 2013, due to lack of sterility assurance. In its response to the FDA-483, Clinical Specialties indicated that it was permanently discontinuing the production of sterile drug products at its facility, effective March 8, 2013, and that it did not intend to prepare or sell sterile products in the future.

2. **More likely the FDA has gone through extensive self-evaluation to fully comprehend every single regulation related to compounding. You are likely more**

knowledgeable now about the current compounding regulations than you were six months ago. It would be invaluable for this subcommittee to know exactly what the FDA can do before we determine what you cannot do. So, please explain the tools you currently have.

Under the law as it existed as of the date of the hearing, section 503A of the FD&C Act provided FDA some authority to regulate what drugs can be compounded. For example, under section 503A, FDA could, through rulemaking, establish a list of drugs that may not be compounded because the drugs or their ingredients have been withdrawn or removed from the market because the drugs or their ingredients "have been found to be unsafe or not effective." FDA could also establish a list of drugs that present "demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness" of the drug and, therefore, may not be compounded. However, due to legal challenges regarding constitutionality of the law, under the law as it existed as of the date of the hearing, section 503A did not apply nationwide. Furthermore, FDA's authority to regulate compounded drugs is more limited than our authority over conventional manufacturers. For example, under section 510 of the FD&C Act, if certain criteria are met, compounding pharmacies are not required to register with FDA or report adverse events. As a result, FDA has limited knowledge of pharmacy compounders and limited ability to oversee their activities.

In 2002, the U.S. Supreme Court had held the advertising, solicitation, and promotion provisions in section 503A unconstitutional, and, at the time of the hearing, there were conflicting court decisions on whether the unconstitutional provisions could be severed from the remainder of the statute.

On November 27, 2013, the President signed Public Law 113-54, the Drug Quality and Security Act (DQSA), which removes certain provisions from section 503A of the FD&C Act that were found to be unconstitutional by the U.S. Supreme Court in 2002. The new law removes uncertainty regarding the validity of section 503A, which will be applicable to compounders nationwide. The DQSA also creates a new section 503B in the FD&C Act. Under section 503B, a compounder can become an "outsourcing facility." Outsourcing facilities will register under section 503B; however, the legislation did not change the exemptions from registration for pharmacies under section 510 of the FD&C Act.

3. **Between 2002 and 2012, NECC was the subject of a least 52 adverse event reports. Numerous offenses were documented throughout investigations at NECC undertaken by both the FDA and state regulators. Why did the Agency not shut down NECC after these inspections? Did NECC challenge the FDA's authority to inspect?**

FDA is unable to comment specifically on NECC due to the ongoing investigations.

The Honorable Marsha Blackburn

1. **I am concerned about the growing incidence of skin cancer in the United States and the significant delay in proving the latest sunscreen technology to help address this risk from exposure to the sun's harmful rays. According to the Skin Cancer Foundation, Americans are diagnosed with more than 3.5 million cases of skin cancer each year and 1 American dies every hour from Melanoma, the most deadly form of skin cancer.**

   I understand that the FDA created the Time and Extent Application (TEA) process in 2002 to streamline applications for over-the-counter applications, such as sunscreens, however FDA has not made a final decision on any product through the TEA process. In fact, eight new sunscreen ingredients have been waiting for FDA review, some for over 10 years. The TEA process is clearly broken and needs to be reformed.

   a) **In light of the public health epidemic regarding skin cancer, please explain significant delay in making a final decision on any of the 8 pending sunscreen applications.**

   b) **Please also explain why taking final action on the 8 pending sunscreen applications has been on the FDA's Unified Agenda as a priority since 2008, however no action has been taken.**

   In the 1970s, sunscreens were used primarily on a seasonal basis to prevent sunburn among consumers with the fairest skin coloration, and sunscreen active ingredients were not thought to penetrate beyond the skin surface. Today, sunscreens are used routinely by a large percentage of the population and in large amounts covering a much greater body surface area, with the result that the extent and duration of consumers' exposure to sunscreen ingredients is orders of magnitude greater than it was in the 1970s. There is also increasing evidence that some sunscreen ingredients can be absorbed through the skin, leading to systemic exposures to these agents that were not previously anticipated or evaluated. These shifts in sunscreen usage, together with advances in scientific understanding and safety evaluation methods, have given rise to new questions about what information is needed and available to support general recognition of safety and effectiveness for both currently marketed sunscreens and ingredients seeking inclusion in the monograph via the Time and Extent Applications (TEA) process.

   Within FDA, there has been an active examination of these important scientific questions, one result of which was significant new rulemaking in 2011 that focused primarily on updated efficacy testing and related labeling issues. We also are engaged in an ongoing internal evaluation of current sunscreen safety issues and evidentiary standards, which is directly informing our evaluation of all sunscreen active ingredients, including the eight TEA ingredients.

The TEAs ask FDA to include eight new sunscreen active ingredients in the Over-the-Counter (OTC) Drug Review, also known as the OTC drug monograph system. In brief, TEA reviews are regulatory proceedings that are inherently complex and must compete for resources and priority with other OTC monograph reviews and proceedings, among other FDA activities. As noted above, FDA is currently evaluating important scientific questions relating to OTC sunscreen ingredients. Because of the public health importance of OTC sunscreens, FDA is actively working to complete our review of these TEA ingredients and expects to take action on them in the near future. We are committed to finding ways to facilitate the marketing of additional OTC sunscreen products, but we must ensure their safety, effectiveness, and overall risk-benefit profile.

To elaborate, the pace of FDA's ongoing review of the sunscreen TEAs is best understood in the context of the overall OTC drug monograph system, of which the TEA process is a part. In brief, the FD&C Act requires FDA review and approval of a new drug application (NDA) for all new drugs before they may be marketed in the United States. To avoid "new drug" status, as defined in the FD&C Act, a drug must be generally recognized as safe and effective (the GRAS/E standard), and must also have been marketed to a material extent and for a material time under the conditions described in its labeling (the material time-and-extent standard). The OTC Drug Review is a multi-step notice-and-comment rulemaking procedure that was established in 1972 to review the safety and effectiveness of OTC drugs then or previously marketed in the United States (which were presumed to satisfy the material time-and-extent standard) and provide a regulatory mechanism (the OTC monograph system) allowing OTC drug products that were found to be GRAS/E to be marketed under an applicable OTC monograph rather than product-specific NDAs. OTC drug monographs are FDA regulations that describe conditions, including specified active ingredients, for marketing various categories of OTC drugs (such as sunscreens).

The TEA process (21 CFR § 330.14) was established in 2002 to provide a pathway to OTC monograph status for additional active ingredients and other conditions not marketed in the United States for OTC use prior to the establishment of the OTC Drug Review, by enabling sponsors to establish that a condition satisfies the material time-and-extent requirement based on historic marketing data other than the date of U.S. market entry. This is done by submitting a TEA containing the required marketing data, which is reviewed by FDA to determine whether or not the condition is eligible to be considered for inclusion in an OTC monograph (eligibility determination).

TEA ingredients and other conditions must satisfy the same GRAS/E standard and evidentiary requirements that apply to other active ingredients and conditions under the general OTC monograph process. And, consistent with the general monograph process, ingredients found eligible for review under TEA applications are subject to multi-step notice-and-comment rulemaking procedures before they may be included in a final OTC drug monograph. FDA has issued eligibility determinations for all TEAs submitted to date, and all eight sunscreen TEAs were found eligible to continue to the next stage of the TEA process, the GRAS/E determination, which is now ongoing.

c) **Will you commit to work with Congress and stakeholders to enact reforms to the TEA process that will ensure that sunscreen products receive a transparent review and a predictable timeline for consideration?**

FDA is willing to work with Congress and stakeholders on this issue.

2. **As you may know, on January 1, 2013, CMS made a technical change to its billing methodology for compounding pharmacies providing drugs used in implanted pain pumps. This change requires pharmacies to sell these compounded medications to physicians who then re-sell then to the patient and bill Medicare. Prior to January 1st, pharmacies were not required to sell drugs to the physician and instead could bill Medicare directly. To further complicate the matter, the Tennessee Board of Pharmacy does not allow pharmacies to sell these compounded medications to physicians for resale to patients. This practice is also illegal in Mississippi, and other state Boards of Pharmacy are assessing the impact of CMS' change on pharmacy practice. I am concerned that this technical change has jeopardized access to necessary pain medications for some of Medicare's most vulnerable beneficiaries. Even more, this change – prohibiting pharmacies from billing Medicare directly – eliminates an important accreditation requirement designed to protect patient safety. Pharmacies billing Medicare directly for these drugs must comply with Medicare supplier standards and federal regulations, such as U.S. Pharmacopeia 797. These standards provide an additional layer of quality promotion and patient safety for pharmacies compounding and dispensing sterile products for use in implanted pain pumps.**

Saying all of this, do you find it concerning the CMS – in the wake of the tragic out break, in spite of state pharmacy law, and in spite of stakeholder opposition – is encouraging pharmacies to sell drugs directly to physicians as opposed to billing Medicare directly and complying with quality accreditation standards?

For at least 20 years to 2013, pharmacies had billed Medicare directly for these patient specific compounded medications, and the National Home Infused Association supports legislation sponsored by Congressman Harper (HR 232) which would restore access to these therapies for beneficiaries. Saying all of this, do you find it concerning that CMS – in the wake of a tragic outbreak, in spite of state pharmacy law, and in spite of stakeholder opposition – is encouraging pharmacies to sell drugs directly to physicians as opposed to billing Medicare directly and complying with quality accreditation standards?

As these questions relate to CMS' reimbursement policies, we recommend contacting CMS with these questions.

3. **As you may or may not know, the State of Tennessee recently passed legislation that allows pharmacies to compound products for use in a practitioner's office for**

administration to that prescribing practitioner's patients – a practice known as "office use" compounding. It is my understanding that 43 other states also allow for office use compounding.

a) **What is the Agency's position regarding traditional compounding taking place in an office setting?**

b) **Should this be regulated by the FDA or State Board of Pharmacies? Please explain.**

In light of recent outbreaks associated with sterile drugs produced by pharmacies, the Agency has taken a critical look at our surveillance and enforcement approach to pharmacies that produce compounded drugs. Over the past year, FDA has conducted numerous for-cause and proactive inspections of firms that produce compounded drugs. The Agency continues to evaluate the information obtained during the inspections.

Since the hearing, the President signed the DQSA. Under the DQSA, hospitals and health care professionals can purchase compounded drugs without a prescription from a compounder that is registered as an outsourcing facility under section 503B. Section 503A requires, among other things, that, to qualify for the exemptions under section 503A, there be a prescription for an identified individual patient. The Agency intends to exercise its authority, as appropriate to protect the public health, against compounded drugs that do not qualify for the exemptions in section 503A or section 503B, and drugs that are adulterated or misbranded or otherwise violate Federal laws.

The Honorable Renee Ellmers

1. **Are compounders making the same products that drug-manufacturers make? I know it may be in a different form, but is it the same product?**

Compounders sometimes take FDA-approved products and dilute them to achieve a different strength, or they may make a liquid or suppository. They may also make drugs from bulk active ingredients. This may be done, for example, to make a product without an allergen, such as peanut oil, that some patients cannot tolerate. Many compounders do make products that appear to be only slightly different from those made by traditional drug manufacturers. For example, they might make an 8 mL vial of a product when the FDA-approved product is available in 10 mL vials. Although these products may appear to be similar to FDA-approved drug products, it is important to remember that compounded drugs do not undergo the same premarket review as FDA-approved drugs and thus lack an FDA finding of safety and efficacy, as well as manufacturing quality. The active ingredients may come from sources that have not been reviewed by FDA, and the methods by which they are made have not been reviewed to determine whether they are adequate to produce a safe, pure, and potent product.

2. Currently, do compounders have the same regulations and requirements that drug manufacturers have? Why or why not?

Under current Federal law, when certain conditions are met, compounding pharmacies are not subject to the same requirements as drug manufacturers. For example, compounding pharmacies, but not drug manufacturers, are exempt from certain requirements under the FD&C Act, as described below.

These disparate requirements derive from the FD&C Act. Section 503A, added to the FD&C Act in 1997 as part of the Food and Drug Administration Modernization Act of 1997 (FDAMA), describes the conditions under which certain compounded human drug products are entitled to exemptions from three sections of the FD&C Act requiring:

- Compliance with CGMP requirements (section 501(a)(2)(B));
- Labeling with adequate directions for use (section 502(f)(1)); and
- FDA approval prior to marketing (section 505).

Drugs produced by compounders must meet the conditions of section 503A to qualify for the exemptions specified in that section. All other applicable provisions of the FD&C Act remain in effect for compounded drugs, even if the conditions in section 503A are met. For example, a compounded drug cannot be contaminated or made under insanitary conditions (see sections 501(a)(1) and 501(a)(2)(A)). And if a compounded drug does not qualify for the exemptions under section 503A of the FD&C Act, the compounded drug would be subject to all of the requirements of the Act that are applicable to drugs made by conventional manufacturers, including the new drug approval, CGMP, and adequate directions for use.

However, at the time of the hearing, the validity of section 503A of the FD&C Act was uncertain. Section 503A FD&C Act had been challenged in court, and there were conflicting court rulings regarding the validity of this section. Since the hearing, President Obama signed the DQSA, which removes certain provisions from the FD&C Act that the U.S. Supreme Court held unconstitutional. By removing the unconstitutional provisions, the new law removes uncertainty regarding the validity of section 503A, which will be applicable to compounders nationwide.

3. What are the changes to compounding you propose making in order to prevent the meningitis outbreak last year and ensure compounded products are safe?

On April 16, 2013, FDA Commissioner Margaret Hamburg outlined the Agency's proposed framework for improving oversight of compounding in testimony before this Committee. Please see attached document (*April 16, 2013, Statement of Dr. Margaret Hamburg Before the Subcommittee on Health, Committee on Energy and Commerce*).

4. Is there a limit to how much product a compounder can make?

Under current Federal law, there is no limit to how much product a compounding pharmacy can make. Section 503A of the FD&C Act places a limit on the volume of drugs that may be shipped interstate. Under that provision, a pharmacy may only distribute interstate compounded drugs in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician, unless the state in which the pharmacy is located has entered into a memorandum of understanding (MOU) with the Agency that addresses the distribution of inordinate amounts of compounded drugs interstate and provides for an appropriate investigation by the state of complaints related to compounded products. FDA published a draft MOU in 1999, and received over 6,000 comments. However, due to the conflicting court rulings that had resulted in uncertainty regarding the validity of section 503A, the template MOU was never finalized, and FDA has not been implementing the provision.

However, on November 27, 2013, the President signed DQSA, which removes the provisions from section 503A of the FD&C Act that were found to be unconstitutional by the U.S. Supreme Court in 2002. By removing the unconstitutional provisions, the new law removes uncertainty regarding the validity of section 503A, which will be applicable to compounders nationwide. FDA has initiated actions to implement the new law.

5. **You testified before the Senate HELP committee regarding their legislation on May 9, 2013. Under this legislation, would compounded drugs manufactured by the new entity (compounding manufacturer) be subject to the same requirements as current manufacturers under the Federal, Food, Drug, and Cosmetic Act?**

    a. **If yes, can you describe those requirements?**
    b. **If no, how are those standards – different – and why are they different?**

As of the time of the hearing, the legislation proposed by the Senate HELP committee, S. 959, would have placed several requirements on "compounding manufacturers" that are similar to those imposed on traditional manufacturers. For example, as drafted, S. 959 would have:

- Required compounding manufacturers to meet FDA-established product quality standards, to register with FDA, and to list the products they produce.
- Required compounding manufacturers to report serious adverse events, of which they become aware, to FDA and to label their products with important information for physicians and consumers.
- Provided FDA with the clear authority to access records of compounding manufacturers during an inspection to more effectively oversee their compounding activities.

- Put in place several restrictions—applicable to both traditional compounders and compounding manufacturers—on the types of bulk drug substances that can be used to compound a drug and would prohibit the compounding of copies of marketed FDA-approved drugs, unless they appear on FDA's drug shortage list.

- Provided that compounding of other categories of drug products, such as complex dosage forms and biologics, would be prohibited because they are particularly difficult to make.

- Required compounding manufacturers to pay establishment fees and, when appropriate, re-inspection fees, to help defray the costs of this increased oversight.

Not all requirements imposed on manufacturers under the FD&C Act, however, would have applied to compounding manufacturers under S. 959. For example, compounding manufacturers would not be required to submit an NDA for compounded products.

6. How do drug manufactures today assure the raw materials (or Active Pharmaceutical Ingredient "API") used to create a drug are safe? What is the certification process?

For finished dosage forms (FDFs) required to have an application approved before marketing, FDA reviews API production processes before granting marketing approval of an FDF using the API. In addition, the FD&C Act requires producers of APIs (and excipients, or inactive ingredients) and producers of the FDF to follow CGMP requirements appropriate to the manufacture of the drug (API, excipients, or FDF). FDA regulates the manufacture of APIs under internationally harmonized CGMP guidance for industry, known as ICH Q7. The CGMP requirements, if followed, ensure that APIs have the safety, identity, quality, and purity as labeled. FDA inspects API production facilities referenced in approved applications to verify conformance with ICH Q7 and CGMPs.

FDA requires conventional manufacturers of the FDFs (e.g., tablets, capsules, injections) to exercise additional controls over the quality of APIs before use in FDF manufacturing. Specifically, the CGMP regulations for finished pharmaceuticals (primarily at 21 CFR parts 210-211) require FDF manufacturers to examine the integrity of each API shipment and to test samples verifying each ingredient's identity before it can be released for FDF production. FDA regulations, however, do not require FDF manufacturers of non-application drug products (e.g., OTC drugs covered by a published monograph at 21 CFR 330-358) to know who actually manufactures the API, and some APIs are purchased from wholesalers and brokers. For those products requiring an approved new drug application, FDA also reviews FDF production processes before marketing approval, and inspects FDF production facilities on a risk-based schedule to verify conformance with 21 CFR 211 and CGMPs.

Drug compounders, which are not subject to FDA application approval and CGMP requirements, may not routinely evaluate the quality of the APIs they use in compounding. Compounders that do not check each shipment or that do not verify their API supply chain are at significant risk of producing a finished product that does not contain the API they intended, does not function as intended, or contains harmful impurities.

7. **How do compounders access the API they use? Is their API FDA-approved?**

The Agency does not generally approve bulk APIs used in the manufacture or compounding of drug products, nor are the APIs used in compounding required to be FDA-approved.

8. **Don't drug manufacturers pay much more than a compounding manufacturer would under the User Fee structures? Why aren't compounders paying more if they are making the same product? Or more importantly, if I'm an FDA – licensed drug maker, why don't I just become a compounder? It would be cheaper and a lot less paper work?**

As you note, the user fees paid by drug manufacturers are significantly higher than those a compounding manufacturer would pay under the legislation under consideration as of the time of the hearing or that an outsourcing facility will pay under the DQSA. Pharmacies compounding drugs under the conditions in section 503A will continue to pay no user fees at all. However, there are a number of reasons that drug manufacturers would not opt to become a compounder. For example, only state-licensed pharmacists or physicians may qualify for the exemptions in section 503A of the FD&C Act, and the pharmacists or physicians must compound the drugs consistent with the conditions of section 503A. Under section 503A, a pharmacy may not compound regularly or in inordinate amounts any drug products that are essentially copies of a commercially available drug product. Further, under section 503A a pharmacy may only distribute interstate compounded drugs in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician, unless the state in which the pharmacy is located has entered into an MOU with the Agency that addresses the distribution of inordinate amounts of compounded drugs interstate and provides for an appropriate investigation by the state of complaints related to compounded products.

9. **There is some talk that compounding manufacturers could be utilized to help end drug shortages. Currently, how are drug shortages determined? Are there different levels of drug shortages?**

The CDER Drug Shortage Staff (DSS) utilizes information from manufacturers, other FDA offices, external entities, and market-share data to determine or verify that a shortage exists.

Consistent with FDASIA, DSS defines a drug shortage, with respect to a drug, to mean a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug.

The severity of the drug shortage situation for a given product may vary depending on certain circumstances, such as the length of the potential shortage/supply interruption and the number of other available manufacturers for that product, and whether they are also experiencing a shortage situation or whether they are able to increase production to meet the anticipated market shortfall.

10. Is the FDA drug shortage list the only list used?

The American Society of Health-System Pharmacists[2] (ASHP) lists drug shortages and additional information on its website. Although both ASHP and FDA maintain drug shortage lists, the information received and displayed regarding drug shortages varies between the two lists. For example, FDA's drug shortage list focuses mainly on drugs that are considered medically necessary,[3] while ASHP's list includes more drugs; some that are not medically necessary because there are suitable alternatives available.

11. How does a drug get off the drug shortage list? Who determines that?

For the drug products listed on the drug shortage list, DSS is in regular communication with relevant manufacturers regarding their current and projected drug supply and utilizes this information to help determine the supply status and potential path forward, if applicable. DSS may also consider information from other FDA offices, external entities, and market-share data. Once a drug product is available from the involved manufacturers and supply is sufficient to meet the demand or projected demand, DSS removes the drug product listing from the current drug shortage list and places it in the resolved drug shortage list, which is also on the FDA drug shortage website.[4]

12. For products on the drug shortage list, many of which are sterile injectable drugs, should a compounder be held to the same level of standards and requirements as the current manufacturers?

Patients expect and deserve high-quality drugs. Patients should have access to compounded medicines that are safe, pure, and potent.

FDA's testimony referenced a series of adverse events associated with compounded drugs, primarily sterile injectables, over the last 10 years, and FDA is concerned about

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[2] *http://www.ashp.org/*

[3] A medically necessary drug product is a product that is used to treat or prevent a serious disease or medical condition for which there is no other alternative drug in adequate supply that is judged by medical staff to be an adequate substitute. Off-label uses are taken into account when making medical-necessity determinations. FDA's drug shortage list includes all shortages that the Agency has been informed of and verified, which are mostly shortages of medically necessary drugs.

[4] *http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm314739.htm*

compounders that produce such high-risk sterile drugs without the necessary controls to ensure quality.

Under FDA's proposed framework (please see attached document, *April 16, 2013, Statement of Dr. Margaret Hamburg Before the Subcommittee on Health, Committee on Energy and Commerce*), as presented at the time of the hearing, pharmacies that produce sterile drugs in advance of or without a prescription and ship those drugs interstate would be subject to Federal oversight and uniform quality standards. These types of sterile compounding operations pose higher risks and, therefore, should be subject to uniform quality standards, established by FDA and appropriate to the activity, including when they are making drugs on the drug shortage list.

Since the hearing, President Obama signed the DQSA, which created a new section 503B in the FD&C Act. Under section 503B, a compounder can become an outsourcing facility and can compound drugs in shortage, so long as certain criteria are met, including compliance with CGMPs.

13. How many drug shortages would be relieved if compounders mass-manufactured product?

The Agency cannot estimate the number of drug shortages that may be relieved if compounders produced drug products in shortage. However, we note that under the recently enacted DQSA, which added section 503B to the FD&C Act, outsourcing facilities may now begin to play a role in compounding drug products that are in shortage. (Please see Question #6, from Ms. Ellmers, for additional information on requirements for APIs in FDA-approved products.)

With respect to drug shortages generally, it is often difficult to forecast the drug product(s) that may become in short supply or the duration of such shortages, since immediate and projected supply from drug manufacturers can change rapidly and unexpectedly due to many factors. FDA works hard, within its legal authority, to address and prevent drug shortages, which can occur for many reasons, including manufacturing and quality problems, delays, and discontinuations.

14. How would the safety of these compounded drugs be assured? What are the testing processes?

Under the legislation being considered at the time of the hearing, compounded drugs produced by compounding manufacturers would have been subject to Federal standards to help ensure that the compounding could be performed without putting patients at undue risk, and FDA would inspect against and enforce these Federal standards.

To further ensure the safety of compounded drugs, FDA proposed that it have clear ability to collect and test samples of compounded drugs and to examine and collect records in a compounding pharmacy, just as the Agency does when inspecting other

manufacturers. FDA also proposed that it have clear authority to examine records, such as records of prescriptions received, products shipped, volume of operations, and operational records such as batch records, product quality test results, and stability testing results. Such inspections are necessary to determine when a pharmacy exceeds the bounds of traditional compounding, to respond to public health threats, and to enforce Federal standards.

15. Will there be any differences between the standards and regulations of the compounding manufacturer and today's manufacturers?

As of the time of the hearing, the legislation proposed by the Senate HELP committee, S. 959, would have created a new category of drug producers called "compounding manufacturers." The recently enacted DQSA created a new category of drug producers called "outsourcing facilities." Among other significant differences, unlike conventional manufacturers, outsourcing facilities are not required to obtain an approved new drug application (NDA) for their compounded drugs, provided they meet certain conditions.

16. Can you provide more clarity/detail on the differences between the two levels of standards between today's manufacturers and the compounding manufacturer?

FDA cannot provide more clarity or detail on what the differences in the standards applicable to conventional manufacturers and compounding manufacturers would have been under the legislation being considered at the time of the hearing, because that legislation was never enacted or implemented.

Under the recently enacted DQSA, outsourcing facilities are subject to section 501(a)(2)(B) of the FD&C Act, which requires compliance with CGMPs. FDA is looking at its CGMP regulations to determine what requirements are appropriate for outsourcing facilities.

17. If the full requirements and standards are different for products on the drug shortage list produced by a compounding manufacturer than those of today's manufacturers, how will this ensure the greatest level of confidence and safety in the products?

As stated above, under the legislation being considered at the time of the hearing, compounded drugs produced by compounding manufacturers would be subject to Federal standards to help ensure that the compounding could be performed without putting patients at undue risk, and FDA would inspect against and enforce these Federal standards.

18. Do doctors and hospitals tell a patient that the drugs they are receiving are manufactured by a compounding manufacturer?

Health care providers and patients often are unaware that they administered or received a compounded product, which limits their ability to associate any adverse events with a compounded product. This hinders FDA's ability to effectively identify adverse events for compounded products in our adverse event reporting system. At the time of the hearing, FDA was working with Congress on its proposed framework, which included potential improvements such as label statements for compounded products to help patients and providers make more informed choices.

19. **Should hospitals and providers require a patient to sign a release for any liability if the hospital or provider gives a compounded drug that is not manufactured under the same safety requirement of the drug manufacturers?**

FDA does not have a position on this.

Additional Information for the record

During the hearing, Members asked FDA to provide additional information for the record. Descriptions of the requested information, based on the relevant excerpts from the hearing transcript regarding these requests, are provided below. We have restated each Member's questions below in bold, followed by our responses.

The Honorable Joseph R. Pitts

1. **You testified during the hearing that several companies have challenged your authority while the FDA was conducting inspections. Please provide a list to the committee of companies that the FDA inspected those that challenged your authority, and the grounds by which the companies challenged your authority.**

The response below was e-mailed to Representative Pitts' Health Policy Analyst on July 16, 2013, in response to this question.

In a sample of 226 pharmacy inspections[5] between 2002 and 2012 that FDA has conducted on practices related to pharmacy compounding of human and veterinary drugs, pharmacies have refused at least one FDA request in more than 25 percent of inspections. For example, 4 percent of firms refused FDA entry into their facility, and of those firms that did grant entry, 12 percent refused FDA access to records (e.g., shipping records, dispensing records, product formulas, and/or standard operating

[5] These 226 inspections represent the number of inspections recorded under the human and veterinary pharmacy compounding Program Assignment Codes (PAC Code) between 2002 and September 25, 2012, that FDA has conducted of pharmacies based on practices related to pharmacy compounding of human and veterinary drugs. Not all compounding pharmacy inspections were recorded under this PAC Code, in part, because some firms engage in multiple types of activities. In addition, some inspectional activities may have been coded as "investigations" rather than "inspections" and, therefore, not captured in this figure. Thus, we know that FDA conducted additional inspections of firms that could be classified as compounding pharmacies that are not accurately reflected in our databases.

procedures). Other refusals include the ability to observe drug production processes, collect samples, access portions of the facility, or take photographs.

FDA encountered refusals of at least one FDA request during inspections of the following compounding pharmacies between 2002 and September 25, 2012. This may not be an exhaustive list:

2002
- Lee and Company, Inc. dba Lee Pharmacy, Fort Smith, AR (July 2002)
- Med-Mart Pacific Pulmonary Services Pharmacy, Bakersfield, CA (November 2002)

2003
- Plum Creek Pharmaceuticals, Inc., Amarillo, TX (February 2003)
- Med 4 Home Pharmacy, Kansas City, MO (March 2003)
- Med-Mart Pacific Pulmonary Services Pharmacy, Bakersfield, CA (May 2003)
- Unique Pharmaceutical, Ltd., Temple, TX (August 2003)
- Monument Pharmaceutical Co., Inc., Winchester, VA (September 2003)

2004
- Keyes Drug, Newton, MA (April 2004)
- Reliant Pharmacy, Southaven, MS (May 2004)
- Reliant Pharmacy, Southaven, MS (June 2004)
- Essential Pharmacy Compounding, Omaha, NE (August 2004)
- Pet Script, Inc., Paris, TX (August 2004)
- University Rx Specialties, Inc. (September 2004)
- ApothéCure, Inc., Dallas, TX (September 2004)
- Kubat Custom Healthcare, Omaha, NE (September 2004)

2005
- PharMEDium Services, Sugar Land, TX (March 2005)
- Pulmo-Dose Inc., Murray, KY (August 2005)
- Civic Center Pharmacy, Scottsdale, AZ (October 2005)
- Pharmacy Creations, Randolph, NJ (October 2005)
- Wedgewood Village Pharmacy, Swedesboro, NJ (October 2005)
- Alchemist Shoppe, P.C., Denville, NJ (November 2005)
- Spoonamore Drug Co., Inc., Louisville, KY (December 2005)

2006
- Pharmacy Creations, Randolph, NJ (February 2006)
- D.R. Pharmacy, Inc., Midland, TX (March 2006)
- Oakdell Pharmacy, Inc., San Antonio, TX (April 2006)
- Hopewell Pharmacy and Compounding Center, Hopewell, NJ (October 2006)

2007
- Newman Inc. dba Medi-Stat, Mobile, AL (February 2007)
- ApothéCure, Inc., Dallas, TX (May 2007)
- Advanced Physician Solutions, Inc., North Hollywood, CA (July 2007)
- Leiter's Pharmacy, San Jose, CA (September 2007)
- Calvert-Gamble Pharmacy, Inc. dba Southern Meds Joint Venture, Biloxi, MS (October 2007)
- Delta Pharma, Inc., Ripley, MS (October 2007)
- Wellness Pharmacy, Birmingham, AL (November 2007)
- Bellevue Pharmacy Solutions, Inc., Saint Louis, MO (November 2007)
- Spoonamore Drug Co., Inc., Louisville, KY (December 2007)

2008
- PharMEDium Services LLC, Cleveland, MS (January 2008)
- AnazaoHealth Corporation, Tampa, FL (May 2008)
- Hopewell Pharmacy and Compounding Center, Hopewell, NJ (June 2008)
- Specialty Pharmacy of Saint Louis, Saint Louis, MO (July 2008)
- National Respiratory Services LLC, Louisville, KY (July 2008)
- Precision Pharmacies, LLC, Bakersfield, CA (August 2008)
- Advanced Physician Solutions, Inc., North Hollywood, CA (August 2008)
- University Pharmacy, Salt Lake City, UT (November 2008)

2009
- Medaus, Inc., Birmingham, AL (February 2009)
- Lee and Company, Inc. dba Lee Pharmacy, Fort Smith, AR (February 2009)
- Prescription Lab Compounding Pharmacy, Tucson, AZ (February 2009)
- Franck's Lab, Inc. dba Franck's Compounding Lab, Ocala, FL (May 2009)
- Franck's Lab, Inc. dba Franck's Compounding Lab, Ocala, FL (June 2009)
- Central Admixture Pharmacy Services, Inc., Chicago, IL (August 2009)
- Franck's Lab, Inc. dba Franck's Compounding Lab, Ocala, FL (December 2009)

2010
- Preckshot Professional Pharmacy, Peoria Hill, IL (June 2010)
- Health & Wellness Compounding Pharmacy, Nashville, TN (August 2010)
- Delta Pharma, Inc., Ripley, MS (September 2010)
- Alwan Pharmacy, Peoria, IL (December 2010)

2011
- Infupharma LLC, Hollywood, FL (September 2011)

2012 (January 2012 through September 25, 2012)
- Weatherford Compounding Pharmacy LLC, Weatherford, TX (February 2012)
- Franck's Lab, Inc. dba Franck's Compounding Lab, Ocala, FL (May 2012)

In addition, between 2002 and October 2012, FDA sought administrative warrants in 25 cases, of which nearly half were for compounding pharmacies. This covers all product areas, not just firms producing drugs. Below are some specific examples of situations in which FDA needed to obtain warrants to inspect compounding pharmacies. Although FDA was ultimately able to obtain warrants to inspect, in many of these cases, the firms' refusals hindered FDA's ability to rapidly investigate reports of serious patient injury, including infections and death. This is not an exhaustive list:

Lee Pharmacy (2002)
FDA initiated an inspection of Lee Pharmacy on July 17, 2002, to investigate a complaint from a physician reporting foreign material in a preservative-free sterile injectable drug product made by this firm. Lee Pharmacy's owner refused to provide records, including distribution information identifying consignees of this product, reportedly based on advice from his attorney. Because of these refusals, FDA's inspection ended prematurely on July 18, 2002. FDA attempted another inspection on December 2, 2002, and again was refused. FDA obtained an Administrative Warrant on December 10, 2002, to complete the inspection.

ApothéCure, Inc. (2007)
FDA initiated an inspection of ApothéCure, Inc. on April 26, 2007, to investigate reports of three deaths following administration of injectable colchicine that was later found to be 640 percent superpotent. When the scope of FDA's inspection went beyond the firm's preparation of colchicine, the owner refused to provide records or allow further access to the facility, causing the inspection to conclude prematurely on May 3, 2007. On August 3, 2007, FDA obtained an Administrative Warrant to complete its inspection. OCI investigated the incident and referred the case to the Department of Justice for criminal prosecution. On April 24, 2012, ApothéCure and its owner pleaded guilty to two misdemeanor counts of introducing a drug that was misbranded into interstate commerce.

Health and Wellness Compounding Pharmacy, LLC (2010)
FDA attempted an inspection of Health and Wellness Compounding Pharmacy on April 28, 2010, after learning of a cluster of *Streptococcus endophthalmitis* infections in patients who received injections of Avastin repackaged by this firm. The owner asserted that his firm was not under FDA's jurisdiction and refused to allow FDA to inspect. On August 2, 2010, FDA obtained an Administrative Warrant to inspect the firm.

Infupharma, LLC (2011)
FDA attempted to inspect Infupharma, Inc. beginning on July 18, 2011, after receiving reports of 12 cases of *Streptococcus endophthalmitis* infections following intravitreal injections of repackaged Avastin. After a few days, the owner asserted that his firm was not subject to FDA regulations and, although he agreed to suspend repackaging of Avastin, he would not agree to cease sterile operations. The owner refused FDA access to observe processing of sterile injectable drugs, and, therefore, FDA's inspection ended prematurely on July 22, 2011. After receiving sample analysis

results confirming microbial contamination and information suggesting that Infupharma intended to resume repackaging of Avastin, FDA obtained an Administrative Warrant on September 15, 2011, to complete the inspection and later issued a Warning Letter citing the firm for adulteration, unapproved drug, and misbranding violations.

Notably, despite recent events, and although we are often working with the state inspectors, our investigators' efforts are being delayed because they are denied full access to records at some of the facilities they are inspecting. For example, during both of our recent proactive and for-cause pharmacy compounding inspections, several pharmacies delayed or refused FDA access to records. FDA encountered refusals of at least one FDA request during recent inspections of the following firms and had to seek Administrative Warrants in three cases as noted:

- Wedgewood Pharmacy, Swedesboro, NJ (November 2012) (obtained warrant)
- JCB Labs, Wichita, KS (February 2013)
- Triangle Compounding Pharmacy, Cary, NC (February 2013)
- University Pharmacy, Salt Lake City, UT (February 2013)
- Avella, Phoenix, AZ (February 2013)
- Foundation Care, Earth City, MO (March 2013)
- Olympia Compounding Pharmacy, Orlando, FL (March 2013) (obtained warrant)
- MedQuest Pharmacy, North Salt Lake, UT (March 2013)
- Pine Pharmacy, Williamsville, NY (July 2013) (obtained warrant)

The Honorable Michael Burgess

1. **There was a discussion regarding the level of difficulty of obtaining an injunction from a judge. Please provide a list of how many times you have not prevailed in obtaining an injunction? (pg. 35)**

In general, the decision whether to pursue an injunction or a seizure is a fact-specific determination that is made by FDA on a case-by-case basis. In considering an injunction or a seizure, FDA will evaluate factors such as pending and adjudicated actions involving the same charges, the seriousness of the offense, the actual or potential impact of the offense on the public, whether other possible actions could be as effective or more effective, whether a voluntary recall by the firm was refused or would be inadequate to protect the public, whether violative practices have not been corrected through use of voluntary or other regulatory approaches, and/or whether FDA would be able to demonstrate the likelihood of the continuance of the violation in the absence of a court order. Additional information is available in FDA's Regulatory Procedures Manual, Chapter 6. Due to the many legal challenges at the time of the hearing (questions regarding the validity of section 503A of the FD&C Act), identifying and pursuing civil enforcement actions against compounding pharmacies has been difficult.

Between 2002 and September 25, 2012, FDA brought one injunction against a compounding pharmacy. In 2009, 21polo ponies died after being administered a compounded animal drug made by Franck's Lab in Florida. In 2011, the U.S. District Court denied FDA's requested injunction, stating that FDA's "statutory authority to regulate traditional state-licensed veterinary pharmacy compounding was questionable." FDA appealed that decision to the 11th Circuit Court of Appeals. In October 2012, the parties filed a joint motion to dismiss the appeal and vacate the 2011 U.S. District Court decision because it was moot after Franck's sold its assets and stopped engaging in animal drug compounding. On October 18, 2012, the 11th Circuit Court of Appeals granted this motion, dismissing the appeal and vacating the lower court's decision.

Although FDA did not bring additional civil injunction cases against compounding pharmacies, since 2002, FDA has criminally investigated at least six pharmacies regarding their compounding practices, which resulted in successful prosecutions by the Department of Justice, including:

- On April 24, 2012, ApothéCure, a compounding pharmacy, and its owner pleaded guilty to two misdemeanor counts of introducing a misbranded drug into interstate commerce. The government's charges were based on ApothéCure's February 2007 shipment of 72 vials of compounded colchicine. FDA testing of the vials revealed that some of the vials were superpotent, containing 640 percent of the level of colchicine declared on the label. Other vials were determined to be subpotent and contained less than 62 percent of the declared levels on the labels. Three patients who were administered colchicine from ApothéCure died shortly afterward, and the cause of death for all three patients was determined to be colchicine toxicity.

- In February 2012, the former Vice President of National Respiratory Services, LLC (NRS), a compounding pharmacy, pleaded guilty to charges of misbranding and adulterating drugs and to committing healthcare fraud. The government's charges were based on NRS providing compounded medications to patients, but leading both Medicare and patients' doctors to believe that NRS was providing FDA-approved, commercially manufactured products. The government also alleged that the former Vice President of NRS, aided and abetted by others, misbranded inhalation drugs because the labeling misrepresented the strength and potency of their active ingredients, or the type of drug actually provided and adulterated inhalation drugs, because their strength differed from what it was purported or represented to possess and because the drugs were contaminated and non-sterile.

- In January 2010, the owner and operator of College Pharmacy, a compounding pharmacy, was convicted on 31 counts related to the distribution of human growth hormone (HGH) that was smuggled into the United States from China, and the distribution of an anabolic steroid to customers with no legitimate relationship to physicians. He was found guilty on two counts of conspiracy, including conspiracy to facilitate the sale of misbranded and unapproved Chinese-made HGH and conspiracy to manufacture, distribute, dispense, and possess with intent to distribute

anabolic steroids; 27 counts of distribution of HGH; one count of facilitating the sale of smuggled HGH; and one count of possessing with intent to distribute HGH.

- In January 2006, the owner of City Pharmacy, a compounding pharmacy, pleaded guilty to health care fraud and misbranding drugs. The government's charges were based on findings that the pharmacy dispensed compounded inhalation solutions to Medicare patients in different strengths than the commercially available drugs prescribed, while leading Medicare and the patients' physicians to believe that the pharmacy was providing the FDA-approved, commercially manufactured products.

- In August 2004, pharmacists of Tricare Pharmacy Network, a compounding pharmacy, were convicted of misbranding of a drug after receipt in interstate commerce. This was based on evidence that the pharmacy dispensed drugs bearing fictitious patient and doctors' names or that were invoiced to disguise the drug that was shipped. In addition, the pharmacy did not receive or require prescriptions for drug products dispensed.

- In July 2002, the owner of The Medicine Shoppe was convicted on three counts of manufacturing a Schedule II Controlled Substance without a prescription, two counts of misbranding and adulterating drugs, and one count of health care fraud. The government's charges were based on evidence that the pharmacy dispensed compounded drugs instead of commercially available, FDA-approved drugs to numerous patients without their knowledge and without authorization from their physicians, as well as laboratory results indicating that samples of drug products collected at the firm were ineffective.

The Honorable John D. Dingell

1. **Please explain the authority the FDA needs to require all compounding pharmacies to register with the agency.**

2. **Please explain the authority the FDA needs to require all compounding pharmacies to report adverse events.**

3. **Please explain the authority the FDA needs to require all compounding pharmacies to follow good manufacturing practices.**

4. **Please explain the authority the FDA needs to require nontraditional compounders to be subject to appropriate good manufacturing practices the way manufactures are.**

5. **What authority does the FDA need to ensure risked-based inspection schedules are appropriate for non-traditional compounders?**

6. **Please explain the authority the FDA needs to see all records when inspecting a compounding pharmacy.**

7. **Please explain the authority the FDA needs for a fee system for the approval of pharmaceuticals and medical devices.**

8. **Please explain the need for a strong user fee program.**

Please see attached document (*April 16, 2013, Statement of Dr. Margaret Hamburg Before the Subcommittee on Health, Committee on Energy and Commerce*), provided in response to all of Representative Dingell's questions.

The Honorable H. Morgan Griffith

1. **The FDA was prepared to release guidance proposals in August of 2012. Please explain why this guidance does not adequately address pharmacy compounding.**

The needed clarity, predictability, and transparency for effective regulation of this industry should be set through clear requirements in statute, particularly given the size and public health impact of this industry and affected stakeholders, including the hospitals, patients, physicians, and states. At the time of the hearing, conflicting court decisions had created uncertainty with regard to the validity of section 503A. The DQSA removed the provisions of section 503A that had been held unconstitutional and removed uncertainty with regard to the validity of section 503A, which will now be applicable to compounders nationwide.

Under the legislation being considered at the time of the hearing, compounded drugs produced by compounding manufacturers would have been subject to Federal standards to help ensure that the compounding could be performed without putting patients at undue risk, and FDA would inspect against and enforce these Federal standards.

News & Events

"A Continuing Investigation into the Fungal Meningitis Outbreak and Whether it Could Have Been Prevented"

Statement of

Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs
Food and Drug Administration
Department of Health and Human Services

Before the

Subcommittee on Oversight and Investigations
House Committee on Energy and Commerce
U.S. House of Representatives

April 16, 2013

INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Margaret Hamburg, 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 be here today to discuss important issues related to pharmacy compounding.

We are at a critical point where we must work together to improve the safety of drugs produced by compounding pharmacies. As the compounding industry has grown and changed, we have seen too many injuries and deaths over many years caused by unsafe practices. I testified in front of this Subcommittee on November 14, 2012, soon after the emergence of a tragic fungal meningitis outbreak associated with compounded methylprednisolone acetate (MPA), a steroid injectable product distributed by the New England Compounding Center (NECC). To date, that outbreak has resulted in 51 deaths and over 730 people sickened in 20 States. Sadly, NECC was not an isolated incident. Indeed, over the past 20 years we have seen multiple situations where compounded products have caused deaths and serious injuries. For example, in 2001, 13 patients in California were hospitalized and 22 received medical care following injections from contaminated vials of a steroid solution. Three patients died as a result. In 2005, contaminated cardioplegia solution resulted in five cases of severe system inflammatory infections; three of these patients died. In 2007, three people died from multiple organ failure after a Texas compounder sold superpotent colchicine that was as much as 640 percent the labeled strength. In 2011, there were 19 cases of *Serratia marcescens* bacterial infections, including nine deaths, associated with contaminated total parenteral nutrition products, and in 2012, 43 patients developed fungal eye infections from contaminated sterile ophthalmic drug products. At least 29 of these patients suffered vision loss. These incidents are emblematic of long-standing issues associated with the practice of compounding and the public health concerns that can result from unsafe practices in compounding pharmacies.

Since the NECC outbreak, there have been seven additional recalls of sterile compounded and repackaged drug products by different pharmacies. In one very recent incident, the presence of floating particles, later identified to be a fungus, was reported in five bags of magnesium sulfate

intravenous solution, resulting in a nationwide recall of all sterile drug products produced by the pharmacy (over 100 products). Fortunately, we have not received reports of patient injury from these products. In another recent recall, all sterile drug products (approximately 60 products) from a second pharmacy were recalled as a result of reports that five patients were diagnosed with serious eye infections associated with the use of repackaged Avastin. Moreover, we believe that presently, there are hundreds of other firms operating as compounding pharmacies, producing what should be sterile products and shipping across State lines in advance of or without a prescription. However, the current legal framework does not provide FDA with the tools needed to identify and adequately regulate these pharmacies to prevent product contamination.

The history of this issue shows that there is a need for appropriate and effective oversight of this evolving industry. It is clear that the industry and the health care system have evolved and outgrown the law, and FDA's ability to take action against compounding that exceeds the bounds of traditional pharmacy compounding and poses risks to patients has been hampered by gaps and ambiguities in the law, which have led to legal challenges to FDA's authority to inspect pharmacies and take appropriate enforcement actions.

The fungal meningitis outbreak has caused the Agency to review our past practices with regard to our oversight of compounding pharmacies, and has led to some preliminary conclusions. In my view, even in the face of litigation and continuous challenges by industry to our authorities, we can nonetheless be more aggressive in pursuing enforcement actions against compounding pharmacies within our current limited authority. I can assure you that we are being more aggressive now. We have established an Agency-wide steering committee to oversee and coordinate our efforts, and we have taken several important steps to identify and inspect high-risk pharmacies that are known to have engaged in production of sterile drug products.

Using a risk-based model, we identified 29 firms for priority inspections focused on their sterile processing practices. During these 29 inspections, in two instances, FDA identified secondary firms associated with the priority inspections, for a total of 31 firms. We have taken investigators who would normally be doing inspections of conventional drug manufacturers and assigned them to conduct inspections of those pharmacies whose history suggests a greater risk of potential quality issues with their compounded products. We have coordinated our inspections with State officials, who have accompanied our investigators in most cases. At the same time, we have also continued to conduct for-cause inspections, often at the request of our State counterparts who invited us to accompany them on the inspections. When we identified problems during any of the inspections, at the close of the inspection, we issued an FDA Form 483 [1] listing our inspection observations. Thus far, we have issued an FDA-483 at the close of 43 of the 55 inspections we have conducted since last fall. We have seen some serious issues, including quality concerns that have led to product recalls. Observations have included: lack of appropriate air filtration systems, insufficient microbiological testing, and other practices that create risk of contamination.

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

As we have noted in the past, our ability to take action against inappropriate compounding practices has been hampered by ambiguities regarding FDA's enforcement authority, legal challenges, and adverse court decisions, and we have learned that the law is not well-suited to effectively regulate this evolving industry. For example, hospitals have come to rely on compounding pharmacies that function as "outsourcers" producing sterile drugs previously made by

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

In my last appearance before this Subcommittee, I presented a framework that could serve as a basis for the development of a risk-based program to better protect the public health, improve accountability, and provide more appropriate and stronger tools for overseeing this evolving industry. We have since met with over 50 stakeholder groups, including pharmacy, medical, hospital, payer, and consumer groups, and State regulators, to help further our understanding and inform our framework. Today, I will first provide background on FDA's current legal authority over compounded drugs, then provide additional details about the framework and suggest specific actions that Congress can take to help us better do our job and prevent future tragedies like this one.

FDA's Legal Authority over Compounded Drugs

FDA regards traditional pharmacy compounding as the combining or altering of ingredients by a licensed pharmacist, in response to a licensed practitioner's prescription for an individual patient, which produces a medication tailored to that patient's special medical needs. In its simplest form, traditional compounding may involve reformulating a drug, for example, by removing a dye or preservative in response to a patient allergy. It may also involve making an alternative dosage form such as a suspension or suppository for a child or elderly patient who has difficulty swallowing a tablet. FDA believes that pharmacists engaging in traditional compounding provide a valuable medical service that is an important component of our health care system. However, by the early 1990s, some pharmacies had begun producing drugs beyond what had historically been done within traditional compounding.

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

The compounding industry objected to this approach and several bills were introduced, some with significant support, to limit the Agency's oversight of compounding.[2] In November 1997, S. 830, the Food and Drug Administration Modernization Act of 1997 (FDAMA), was signed into law as Public Law 105-115.[3] FDAMA added Section 503A to the FD&C Act, to address FDA's authority over compounded drugs.[4] Section 503A exempts compounded drugs from three critical provisions of the FD&C Act: the premarket approval requirement for "new drugs"; the requirement that a drug be made in compliance with current good manufacturing practice (cGMP) standards; and the requirement that the drug bear adequate directions for use, provided certain conditions are met. These provisions were the subject of subsequent court challenges, which have produced conflicting case law and amplified the perceived gaps and ambiguity associated with FDA's enforcement authority over compounding pharmacies. In 2002, immediately after a Supreme Court ruling that invalidated the advertising provisions of Section 503A, FDA issued a revised compliance policy guide on compounding human drugs. Several additional legal challenges and court decisions then followed. More recently, FDA made significant progress toward issuing

another CPG. In fact, FDA was on track to publish a revised draft CPG in the fall of 2012, but the fungal meningitis outbreak intervened and we are now reevaluating the draft. It is important to note, however, that a CPG is not binding on industry and updating the CPG would not alleviate all issues with Section 503A.

A look at FDA's attempts to address compounding over the last 20 years shows numerous approaches that were derailed by constant challenges to the law. As a result, presently, it is unclear where in the country Section 503A is in effect, and Section 503A itself includes several provisions that have impeded FDA's ability to effectively regulate pharmacy compounding practices including those relating to prescription orders, medical need, and copying FDA-approved products.

Apart from Section 503A, there are additional provisions in the statute that have impeded effective pharmacy compounding regulation. For example, if certain criteria are met, the FD&C Act exempts compounding pharmacies from registration and the obligation to permit access to records during an inspection. As a result, FDA has limited knowledge of pharmacy compounders and compounding practices and limited ability to oversee their activities.

Looking Ahead

The Administration is committed to working with Congress to address the threat to public health from gaps in authorities for effective oversight of certain compounding practices. To that end, FDA has developed a framework that could serve as the basis for the development of a risk-based program to protect the public health.

Risk-based Framework

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

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

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

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

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

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

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

CONCLUSION

Given our experiences over the past 20 years and the recent fungal meningitis outbreak, we must do everything we can to clarify and strengthen FDA's authority in this area. We recommend that Congress recognize the appropriate State role in regulation of traditional compounding while authorizing clear and appropriate Federal standards and oversight needed for non-traditional compounders that produce riskier products. We look forward to working with Congress in striking the right balance.

I am happy to answer any questions you may have.

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

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

[3] Public Law 105-115, FDAMA, 111 Stat. 2296 (Nov. 21, 1997), available at *http://www.gpo.gov/fdsys/pkg/PLAW-105publ115/pdf/PLAW-105publ115.pdf*[1]

[4] Id.

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