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PHARMACY COMPOUNDING: IMPLICATIONS OF THE 2012 MENINGITIS OUTBREAK

HEARING

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

UNITED STATES SENATE

ONE HUNDRED TWELFTH CONGRESS

SECOND SESSION

ON

EXAMINING PHARMACY COMPOUNDING, FOCUSING ON IMPLICATIONS OF THE 2012 MENINGITIS OUTBREAK

NOVEMBER 15, 2012

Printed for the use of the Committee on Health, Education, Labor, and Pensions

Available via the World Wide Web: http://www.gpo.gov/fdsys/

U.S. GOVERNMENT PUBLISHING OFFICE

94–198 PDF WASHINGTON : 2015

For sale by the Superintendent of Documents, U.S. Government Publishing Office
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PHARMACY COMPOUNDING: IMPLICATIONS OF THE 2012 MENINGITIS OUTBREAK

THURSDAY, NOVEMBER 15, 2012

U.S. SENATE,
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The committee met, pursuant to notice, at 9:53 a.m., in room SD–106, Dirksen Senate Office Building, Hon. Tom Harkin, chairman of the committee, presiding.

Present: Senators Harkin, Enzi, Mikulski, Casey, Hagan, Merkley, Franken, Bennet, Blumenthal, Alexander, and Roberts.

OPENING STATEMENT OF SENATOR HARKIN

The CHAIRMAN. The Senate Committee on Health, Education, Labor, and Pensions will please come to order.

We're meeting here today to better understand what caused one of the worst public health crises this country has experienced in recent years, the meningitis outbreak that has claimed the lives of 32 Americans and sickened at least 461 people. While those affected grapple with side effects and complications related to treatment, thousands more are waiting to see if they become ill. This outbreak has been traced back to pharmaceuticals produced at the New England Compounding Center in Framingham, MA, where it is now clear the owners and managers demonstrated a complete disregard for basic procedures to ensure that the products they were manufacturing were sterile.

The real question we will seek to answer today is: How could this have happened? How could 17,000 doses of a product so contaminated that, upon recall, black particles were visible to the naked eye in some of the samples, have been shipped to 23 States? How could a pharmacy that the FDA had described in 2003 as posing, and I quote,

> " . . . the potential for serious public health consequences if the compounding practices, in particular, those relating to specific sterile products, are not improved . . . "

How could they have been then licensed to ship drugs to 45 different States?

As we have learned over the course of our committee inquiry, NECC's shortcomings were well-documented. The FDA and the Massachusetts Board of Pharmacy repeatedly found significant deficiencies in their operations, including the suspected destruction of documents and contaminated lots; findings of bacterial contamination in compounded medications; findings of sterile injectable prod-

ucts that were both too weak or too strong in potency; and repeated complaints about the sale of compounded drugs without a patient-specific prescription in direct violation of State and Federal law.

Yet, despite the abundance of documentation, neither the Massachusetts Board nor the FDA appears to have taken the necessary steps to protect the public from these products.

I will dispense with the rest of my statement, and I will submit it in its entirety for the record.

[The prepared statement of Senator Harkin follows:]

PREPARED STATEMENT OF SENATOR HARKIN

The committee will come to order. We are meeting here today to better understand what caused one of the worst public health crises this country has experienced in recent years: the meningitis outbreak that has claimed the lives of 32 Americans and sickened at least 461 people.

While those affected grapple with side effects and complications related to treatment, thousands more are waiting to see if they become ill. This outbreak has been traced back to pharmaceuticals produced at the New England Compounding Company in Framingham, Massachusetts, where owners and managers demonstrated a complete disregard for basic procedures to ensure that the products they were manufacturing were sterile.

The question we will seek to answer today is: how could this have happened? How could 17,000 doses of a product so contaminated that upon recall, black particles were visible to the naked eye, have been shipped to 23 States? How could a pharmacy that the FDA had described in 2003 as posing,

> " . . . the potential for serious public health consequences if [the] compounding practices, in particular those relating to specific sterile products are not improved, . . . "

have been licensed to ship drugs to 45 different States?

As we have learned over the course of our committee inquiry, NECC's shortcomings were well-documented. The FDA and the Massachusetts Board of Pharmacy repeatedly found significant deficiencies in NECC's operations, including the suspected destruction of documents and contaminated lots; findings of bacterial contamination in compounded medications; findings of sterile injectable products that were *both* too weak or too strong in potency; and repeated complaints about the sale of compounded drugs without a patient-specific prescription, in direct violation of State and Federal law. And yet, despite the abundance of documentation, neither the Massachusetts Board nor the FDA appears to have taken the necessary steps to protect the public from these products.

Equally troubling is that fact that, when the owners and managers of NECC sought a license for a separate company, Ameridose, to compound drugs on scale perhaps 10 times the size of NECC, these same State and Federal regulators granted that license. They did so without referencing the checkered history of NECC, even though Ameridose would supply hospitals across the country under contract with the *largest group purchasing organization in the United States*. How could that history not been deemed relevant? How could NECC's owners have been allowed to expand

their operations, in light of their history? These are questions I am hoping to answer today.

In the face of such a tragedy it is natural to want to take action. And we will. This committee has a demonstrated ability to work to find bipartisan solutions that will take into consideration the needs of all stakeholders. The hearing today will explore not just what happened, but it will begin to help us determine how to prevent similar outbreaks in the future.

What is important to remember, however, is that drug compounding is essential and that most pharmacies that compound do so on a vastly smaller scale than NECC. We need to ensure that these pharmacists can continue to compound without a drastic increase in overhead.

We also know that to address drug shortages, compounding is occurring both in hospitals and in pharmacies to replenish supply of previously available drugs. Indeed, in the case of methylprednisolone acetate, the drug at issue in the outbreak, two manufacturers had ceased producing the drug in the last 2 years.

We know compounding is critical, and that the need for large scale compounding is increasing. But we do not know where or how much large-scale drug compounding is being conducted, or if these companies are compounding drugs in accordance with best practice standards. More importantly, we have no way of knowing which facilities are *not* in compliance. This is a problem and indicates to me the need for better Federal regulation in this area.

As a committee, we will work together to identify and plug any gaps in our regulators' authority. We want to ensure that any pharmacy that takes the kinds of risks with patient lives that NECC did will be shut down long before more patients get hurt. The only good that can come from a tragic situation like this outbreak is the momentum to make changes to prevent it from ever happening again. I look forward to hearing the thoughts of the panel on this topic and I promise the other members of this committee who I know have a history on this issue to working together with you to ensure that a problem like this cannot occur again.

In our first panel, we'll hear from Dr. Beth Bell of the Centers for Disease Control and Prevention about the public health impact of the meningitis outbreak and CDC's role in responding to it. Dr. Peggy Hamburg of FDA and Dr. Lauren Smith of the Massachusetts Department of Public Health will talk to us about the role of their agencies in regulating compounding pharmacies in general and in investigating NECC specifically. And we'll ask them about their views on what we can do to prevent future crises.

We invited the manager and co-owner of the New England Compounding Center, Mr. Barry Cadden, to appear on our second panel. We were informed by Mr. Cadden's attorney that he would decline to voluntarily appear, and if compelled to appear, would invoke his Fifth Amendment right against self-incrimination and refuse to answer our questions. I am disappointed by his failure to appear, but frankly, I believe this committee has amply demonstrated the extensive failures of Mr. Cadden and NECC, as the record of this hearing will make clear.

On our third panel, we will talk to the physician whose critical work led to the initial identification of the outbreak and who ably

worked with CDC to isolate NECC products as the source of the meningitis infections, Dr. Marion Kainer of the Tennessee Department of Health. We'll also talk with David Miller from the International Academy of Compounding Pharmacists and Dr. Kasey Thompson of the American Society of Health-System Pharmacists about the use of compounding in medical care, and the measures needed to ensure that compounded drugs are safe.

Before we begin, I'd like to submit to the record the documents that we have received from NECC, FDA, and Massachusetts in response to our investigatory letters.

The CHAIRMAN. But before we begin, I'd like to submit for the record the documents that we have received from NECC, the FDA, and Massachusetts in response to our investigatory letters. Without objection, they'll be submitted for the record.

[Editor's Note: Due to the large volume of documents and the high cost of printing, the information referred to is maintained in the committee file.]

And with that, I'll yield to Senator Enzi.

OPENING STATEMENT OF SENATOR ENZI

Senator ENZI. Thank you, Mr. Chairman.

Thirty-two Americans have died, out of 461 total, sickened after receiving contaminated steroid injections produced by the New England Compounding Center, or NECC. Additionally, approximately 14,000 patients in 23 States have been exposed to potentially contaminated injections produced by the same pharmacy.

This case represents a catastrophic failure by the regulatory agencies that are charged with protecting patients from unsafe drugs. Such a failure is unacceptable, and we're going to examine what happened in order to determine what needs to be done to prevent it from reoccurring.

The compounding pharmacy that caused these patients' deaths and illnesses has a long history of problems with product safety and compliance with State regulations. These problems began almost as soon as NECC first received its pharmacy license in the late 1990's, when complaints began to be made about the sterility of the products and its practices around the requirement for individual patient prescriptions.

Both the FDA and Massachusetts Board of Pharmacy became aware of the problems with NECC over a decade ago. They jointly inspected NECC's facility and held multiple meetings about the problems they discovered. The Massachusetts Board entered into a consent decree with NECC in 2006. Later that year, FDA also issued a warning letter to NECC.

Despite the multiple warnings, State and Federal regulators failed to continue to monitor NECC and take the steps that could have prevented the current situation. In particular, the Massachusetts Board should have known from its numerous inspections of NECC's facility that it was operating a large-scale drug manufacturing operation. That information, coupled with repeated complaints highlighting NECC's pattern of failing to require valid prescriptions for specific patients, clearly contravened Massachusetts regulatory requirements for compounding pharmacies.

Even after receiving multiple complaints about the sterility and safety of drugs compounded by NECC, there is no evidence that the Board made any effort to even followup and inspect NECC's facility from 2006 until 2011. State boards of pharmacy have explicit authority over the practice of pharmacy, including compounding products for individual patients. States like Massachusetts also have clear and unequivocal authority to inspect, suspend, and revoke pharmacy licenses.

While there have been litigation and conflicting court decisions around Federal legislation enacted in 1997 to differentiate between compounded and manufactured products, this ambiguity alone cannot be blamed for this tragedy. FDA can inspect any facility that manufactures, processes, packs, or holds products for interstate commerce and has authority over unapproved new drugs in interstate commerce. FDA also has the ability to take action against misbranded or adulterated products.

NECC was clearly operating outside its pharmacy license in violating State laws requiring individual prescriptions. NECC also looked like it was operating as a large-scale drug manufacturer, pretending to be a pharmacy in order to avoid FDA regulation. In every warning letter and legal brief the Food and Drug Administration has ever issued concerning this very type of conduct, including a 2006 warning letter to NECC, the agency said it had clear authority to regulate this very type of conduct.

I hope today we can find out why these State and Federal authorities were not used to prevent this tragedy. The committee is and will continue to investigate NECC's conduct and the oversight of both FDA and the Massachusetts Board of Pharmacy. We've sent letters to FDA, the Massachusetts Board, and NECC. We've received over 10,000 pages of documents, which show NECC has a history of not complying with State and Federal law. We expect to receive more documents in the coming weeks and will leave no stone unturned.

I want to take a moment to recognize the longstanding interest of my colleagues, Senators Roberts and Burr, regarding pharmacy compounding. They've been leaders in this area since the late 1990s and released a draft of pharmacy compounding legislation with former HELP Committee Chairman Kennedy in 2007.

Many other members of the HELP Committee also have a strong interest in this matter. Senator Alexander's home State of Tennessee has been hit particularly hard by the current outbreak. I know that Senators Franken and Blumenthal have strong views. Numerous members of the HELP Committee signed oversight letters requesting the information from the Food and Drug Administration, the Massachusetts Board of Pharmacy, and the New England Compounding Center.

The HELP Committee worked very effectively and in a bipartisan manner to reauthorize the FDA user fee legislation earlier this year. I am confident we can all work together to arrive at a common understanding of this problem and its solution.

I'm also interested in hearing from Dr. Kasey Thompson of the American Society of Health-System Pharmacists on our third panel. Many patient populations and specialties require compounded products, including pediatrics and hospice. Some State

pharmacy boards, like Wyoming's, also do their jobs effectively. I hope he can comment on the benefits of traditional pharmacy compounding and the strengths and weaknesses of pharmacy regulation by the States.

Last, I want to thank Dr. Bell from the CDC and Dr. Kainer for attending today. Without your hard work, I understand this could have been much worse. Patients all over the country owe you thanks for immediately acting upon hearing about only one case.

Thank you, Chairman Harkin, for holding this important hearing, and I look forward to learning more about how this tragedy occurred in order to see that it's not repeated in the future.

The CHAIRMAN. Thank you very much, Senator Enzi.

It has been a longstanding procedure of this committee that only the chair and the ranking member give opening statements. The chair, with the concurrence of the ranking member, would diverge from that for this hearing because of the long-time interest in and leadership by Senator Roberts on this issue and because he had been a leader on a bill that came up about 5 or 6 years ago. I would yield for no more than 5 minutes for an opening statement by Senator Roberts.

STATEMENT OF SENATOR ROBERTS

Senator ROBERTS. Thank you, Mr. Chairman, and Ranking Member Enzi. The reason I'm making this statement is very simple. I've been involved in this for 12 years. This is not a new story. I just appreciate you allowing me to make a short statement. I believe it's important to outline some of the previous actions that members of this committee and the Senate have taken in the past to review and take action on issues relating to compounding pharmacy.

I want to begin by thanking the Chairman and the Ranking Member for holding this hearing on a crisis that has gained significance and deserves attention over the past few weeks but is also an issue that many of us on the committee have worked on for many years and for some over a decade.

First and foremost, I want to start out by reiterating my support for pharmacy compounding. I know that compounding serves a very important role for patients, such as patients who are allergic to certain ingredients found in approved drugs or for children who need a pediatric dosage of a drug.

Legitimate pharmacy compounding occurs when a patient has a special medical need that cannot be met by an FDA-approved drug. Their physician writes a specific prescription for the patient, and then the individual pharmacist makes the medication for the individual patient. This type of compounding should continue. I want to work to ensure that we don't do anything to alter that practice.

However, and unfortunately, the more traditional pharmacy compounding is not why we are here today. We are here today because there have been bad actors who are using the good name of pharmacy compounding to mass produce products not approved by the FDA and provide them to patients. Compounding products are made for the individual patient and are, therefore, not FDA-approved.

However, under the guise of traditional compounding, some manufacturers have been mass producing and providing products with-

out the knowledge of the patient or their doctor. Regrettably, this is not a new issue. There have been many examples of injuries and deaths from unsafe compounded drugs that stretch across the country. In fact, it goes back over a decade or more. Throughout that time, I've had the privilege of working with many members on this committee, more especially Senator Burr, on issues relating to pharmacy compounding.

This is an issue that hit far too close to home in Kansas. Several years ago, a pharmacist in Kansas City was found to be diluting cancer drugs for his patients. Unfortunately, over 4,000 patients were affected before authorities could stop him. Senator Kit Bond and I worked together at that time to hold the first HELP Committee hearing on pharmacy compounding. We requested a GAO report on the status of pharmacy compounding to try to get some answers.

We sponsored what I always thought was a very simple amendment to the Medicare Modernization Act to have the FDA establish a committee to look into pharmacy compounding and make any recommendations to improve and protect patient safety. This committee was to terminate after 1 year. It was an amendment supported in the Senate. Unfortunately, it was stripped during the conference because some folks incorrectly thought that the States were adequately regulating such pharmacies and that additional Federal regulation would be an undue burden.

I must say I think every member here on this committee time and again has fought against additional Federal regulation and placing undue burdens on any constituent, including my local community pharmacists. I was amazed. Fast forward a few years later. With Chairman Kennedy and Senator Burr, we once again tried to take a closer look at the regulation and enforcement of pharmacy compounding. In an effort to be open and transparent, we produced a discussion draft along with Ranking Member Enzi and Senator Reed and requested comments and feedback.

While I don't think that discussion draft is anything that I would recommend signing into law today, the intent was to garner stakeholder feedback and apply it to our policymaking. Instead, rather than working with us, we were faced with a full grassroots effort to stop the discussion draft from moving forward. I said then, and I would repeat now, that my intent, and I believe the intent of others, was never to do away with pharmacy compounding. What we needed were answers. What we got was pushback.

Now, while it was ultimately Chairman Kennedy's decision not to move forward with the discussion draft, I had hoped then and continue to believe it is important today to revisit the regulation, oversight, and enforcement of pharmacy compounding at the Federal and State levels. There are obviously very serious patient safety concerns. I have my own opinions on where the cracks may be and ways to address these safety concerns. To that end, I am working with my colleagues on the HELP Committee to discover the appropriate measures we need to put in place to protect patient safety.

Let me be clear. I have not and will not introduce any sort of legislation to ban pharmacy compounding. However, the recent and repeated loss of life has reiterated the need for appropriate meas-

ures to be put in place to ensure that bad actors can no longer take advantage of patients. Patients have a right to know when they are receiving a product that is not FDA-approved and the risk that may come with using it. As I said during the last hearing we had on this subject, I fully recognize the benefits of compounding pharmacy and that they fill an important niche in the healthcare delivery system.

However, many questions need to be answered. How do we define manufacturing versus compounding? What are we doing at the State level to enforce regulations currently on the books? How can we get States that do not have adequate regulations on the books to improve? Are those who are inspecting properly trained? Should we have a means to test products once they have been compounded to ensure they are safe and accurate doses? Are schools of pharmacy properly training individuals to compound and what steps they should take to make sure they do so safely? Why is there not a system of adverse event reporting?

These questions were important a decade ago and, unfortunately, they continue to remain relevant today. My expectation from today's hearing is to answer some of these questions, learn more about the current state of regulation of pharmacy compounding, and I anticipate that all of our witnesses will commit to working fully with this committee to address any potential gaps in the regulatory structure that would potentially affect patient safety.

I thank the chair and my colleagues for their indulgence.

The CHAIRMAN. Thank you very much, Senator Roberts.

Now we'll turn to our first panel. We'll hear from Dr. Beth Bell of the Centers for Disease Control and Prevention about the public health impact of this outbreak and the CDC's role in responding to it. Second, we'll turn to Dr. Peggy Hamburg, Commissioner of the FDA, and then Dr. Lauren Smith of the Massachusetts Department of Public Health to tell us about the role of their agencies in regulating compounding pharmacies in general and in investigating NECC, specifically. We'll ask them about their views on what we can do to prevent future crises.

With that, all your statements will be made a part of the record in their entirety. I'd ask that you limit your opening statements to 5 to 7 minutes, and then we'll open it for questions. Welcome, all of you. Thank you for being here.

Dr. Bell, we'll start with you. Please proceed.

STATEMENT OF BETH BELL, M.D., MPH, DIRECTOR, NATIONAL CENTER FOR EMERGING AND ZOONOTIC INFECTIOUS DISEASES, CENTERS FOR DISEASE CONTROL AND PREVENTION, ATLANTA, GA

Dr. BELL. Chairman Harkin, Ranking Member Enzi, members of the committee, thank you for the opportunity to speak to you today about CDC's response and ongoing activities in the multistate outbreak of fungal meningitis and other infections. CDC disease detectives work 24/7 to save lives and protect Americans from harm. The fungal meningitis outbreak is a reminder of the importance of CDC's ability to rapidly respond to, to characterize, and to stop outbreaks of unexplained illness and death.

My remarks today will focus specifically on the public health response to the outbreak associated with injections of contaminated preservative-free methylprednisolone acetate produced by the New England Compounding Center, NECC. To begin, I want to give particular credit to Dr. April Pettit, an infectious disease doctor at Vanderbilt University, who identified the first meningitis case and notified the State health department. If Dr. Pettit had not acted, it is likely that many more patients would have been exposed.

We are also fortunate that Dr. Pettit reached out to Dr. Marion Kainer of the Tennessee Department of Health, who quickly identified similar cases, reached out to CDC for support, and identified the common exposures: three lots of methylprednisolone acetate produced by NECC. Dr. Kainer's quick response resulted in a voluntary national recall of the suspected NECC lots within days of the first case being reported. CDC then reached out to other State health departments to marshal an enormous nationwide effort, including rapidly contacting approximately 14,000 patients at risk.

The efforts of Dr. Kainer and the hundreds of other State public health officials who responded to this outbreak did not happen by chance. Despite trying economic times, we have worked hard to build and sustain a network of trained public health professionals that can rapidly detect and respond to outbreaks. As State budget cuts have forced public health personnel losses, we are fortunate to have been able to make a real difference with CDC's direct financial and in-kind support.

Many of the outbreak responders are directly supported through CDC's Epidemiology and Laboratory Capacity Cooperative Agreement. Dr. Kainer is a graduate of CDC's Epidemic Intelligence Service Training Program, and Tennessee is one of CDC's 10 emerging infections program sites that receive additional resources which supported their response in this outbreak. The resources available through the Prevention and Public Health Fund authored by this committee also made a tangible difference in detecting and responding to the outbreak.

I would also like to share information about some of the patients affected by the outbreak and what CDC has done to try to help them. As of November 14, a total of 461 cases, including 32 deaths, have been reported in 19 States. The approximately 14,000 people across the country who received the contaminated medication include people like Diana Reed and George and Lillian Cary.

Diana Reed of Brentwood, TN, was the primary caretaker of her wheelchair-bound husband, Wayne, who suffers from Lou Gehrig's Disease. Diana was healthy and physically active, but after a neck injury, she turned to steroid injections to help with her pain. Tragically, Diana received a contaminated injection and became the third Tennessean to die of fungal meningitis.

George Cary of Howell, MI, is husband of Lillian. Both received contaminated steroid injections in September. Lillian was the first to show symptoms and, tragically, lost her battle to fungal meningitis. While grieving the loss of his wife, George was also diagnosed with fungal meningitis himself and is in the process of undergoing the long and difficult treatment. These are just a few of the personal stories associated with this tragic event.

Because this infection is so rare and few doctors have ever treated it, CDC stepped in to ensure that patients were getting the best possible care. We convened a panel of the Nation's leading clinical fungal disease experts to work with CDC scientists to help develop diagnostic and treatment guidance. Even with treatment, we are seeing many patients return with new symptoms and new conditions. We also fear that more exposed patients will become ill before the outbreak is over.

Our focus going forward should be on preventing these outbreaks in the future and ensuring that all products, materials, and procedures used in healthcare are safe. We are fortunate in this case for the clinical and public health heroes like Drs. Pettit and Kainer in Tennessee.

I will end by again noting the thousands of patients and families who have been directly affected by this event. Diana, George, Lillian, and countless others put their faith in our healthcare system. Patients deserve to be safe whenever they receive their medical care.

Thank you.

[The prepared statement of Dr. Bell follows:]

PREPARED STATEMENT OF BETH BELL, M.D., MPH

Chairman Harkin, Ranking Member Enzi, members of the committee, thank you for the opportunity to speak to you today about CDC's response and ongoing activities related to the multistate outbreak of fungal meningitis and other infections. CDC works 24–7 to save lives and protect people from harm and this outbreak illustrates the power of public health in action both to identify serious health problems and to coordinate a targeted response that protects our Nation and its citizens from infectious disease threats.

I want to extend my sympathies to the patients affected by this outbreak. Our hearts go out to the patients and families impacted by the debilitation and death from these infections.

My remarks today will focus specifically on the identification of, and subsequent public health response to the outbreak associated with injections of contaminated preservative-free methylprednisolone acetate (MPA), an injectable steroid produced by the New England Compounding Center (NECC). Specifically, I will cover three critical areas related to the outbreak:

- a summary of the response by CDC and our partners in State public health agencies;
- a description of the fungal infections involved in this outbreak and how these infections are affecting patients; and
- a discussion of several early lessons learned.

As of November 14 at noon (EST), a total of 461 cases, including 32 deaths, have been reported in 19 States. The cases include fungal meningitis, stroke, or other central nervous system-related infections plus 10 peripheral joint infections (i.e., knee, hip, shoulder, elbow). CDC and our partners at State and local health departments marshaled an enormous effort nationwide to determine the source and scope of the outbreak, rapidly contact patients at risk, and enlist the individual input of leading experts to help us develop novel diagnostic and treatment guidance to achieve the best possible patient outcomes. In this outbreak, local infectious disease officials, including State epidemiologists, healthcare associated infection (HAI) prevention coordinators, and others whose positions are directly supported through CDC's Epidemiology and Laboratory Capacity (ELC) cooperative agreement and CDC's Emerging Infections Program (EIP) were pivotal in the original identification of the outbreak and the substantial patient notification that followed. Their efforts at the State and local level have been extraordinary and in many cases undoubtedly contributed directly to saving the lives of exposed patients.

I would like to highlight some specific efforts by CDC and State health agencies:

- The Tennessee Department of Health (TN DOH) identified and sounded the alarm on the initial cluster of cases. The TN DOH official who alerted others about these cases serves as the State's HAI Program Director and is a graduate of CDC's

Epidemic Intelligence Service (EIS) program. Tennessee also is one of CDC's 10 Emerging Infections Program (EIP) sites and as such receives additional resources that helped support their response in this outbreak.

• The Virginia Department of Health laboratory, whose staff had been trained by CDC in identifying fungi, was the first to identify the very rare fungal pathogen, *Exserohilum*. This discovery saved valuable time and provided the Nation with a critical piece of information to guide diagnostic and treatment recommendations.

• The Michigan Department of Community Health identified the first case of a joint infection associated with these products.

• Over 250 Federal disease control specialists have been working out of CDC's Emergency Operations Center to coordinate the multistate fungal outbreak response efforts with Federal, State, local, tribal, and territorial public health partners. CDC coordination was helpful to ensure patient notification, development and dissemination of treatment guidance, and rapid communication to the public and the health professions community.

- State and local public health departments, health care facilities, and CDC tracked down and contacted over 14,000 exposed patients in 23 States with facilities which received the implicated medication.
- CDC engaged the Nation's leading clinical fungal disease experts to receive their individual input on the development of diagnostic and treatment guidance appropriate for identifying and treating patients that develop infections. This panel has met repeatedly as the outbreak has evolved to adjust clinical advice to very complex and rare infections. CDC has educated over 4,200 clinicians through our clinician conference calls (COCA calls) on the interim diagnostic and treatment guidance.
- CDC has prioritized transparent and rapid communication with the public in this outbreak. To date, CDC's meningitis outbreak and fungal diseases web pages have been accessed over 1 million times and have sourced media outlets with direct links and resources to ensure accurate reporting and broad dissemination of health messages. CDC has used the Health Alert Network (HAN) to release multiple health advisories as the outbreak has unfolded. HANs are directly distributed to health care providers nationwide. CDC has also responded to over 4,500 calls to our public inquiry line (CDC–INFO).

• CDC's mutually reinforcing laboratory and surveillance systems have been critical in confirming the cause of the outbreak:

- CDC's fungus laboratory is the national reference laboratory and in this outbreak has served as an indispensable resource to public health and FDA laboratories to identify and confirm the variety of fungal species recovered from patient, product, and environmental samples. Because there were no available rapid diagnostic tests to identify the fungal organism(s) associated with this outbreak, CDC scientists developed and refined a real-time polymerase chain reaction (PCR) to detect fungal ribosomal DNA, and then performed DNA sequencing to identify the specific fungus by its DNA barcode.
- CDC's HAI laboratory is working with FDA to identify other microorganisms from sealed medication vials. Few laboratories nationwide have the technical expertise and capacity to perform such complicated and exact testing to assess the presence of any bacterial contamination.
- CDC's Infectious Diseases Pathology laboratory has been testing biopsy and autopsy samples from the outbreak. Information from these analyses provides vital clinical information on how this rare disease is affecting patients, and such information is used to inform development of CDC's interim clinical guidance.

EVOLUTION OF THE OUTBREAK

On September 18, an astute clinician alerts the Tennessee Department of Health (TN DOH) of a patient with culture-confirmed *Aspergillus fumigatus* meningitis after epidural steroid injection at an ambulatory surgical center (ASC).[1] The patient received an epidural steroid injection on July 30 and was admitted to the hospital in late August.

This type of infection is exceedingly rare, and we are extremely fortunate that the clinician chose to test the patient's cerebrospinal fluid (CSF) for a possible fungal infection (which is not a routine test ordered by clinicians) and then notify the State health department when those results came back positive. After further consultation with the clinician in Tennessee, the TN DOH contacts CDC on September 20 to ask

[1] *www.cdc.gov/mmwr/preview/mmwrhtml/mm61e1012a1.htm?s_cid=mm61e1012a1_w.*

if CDC has received similar reports of unexplained fungal meningitis infections. CDC relays that it had not received reports of unexplained fungal meningitis infections and recommends that the TN DOH conduct a site visit to the ambulatory surgical center where the epidural injection was administered.

On Friday, September 21, the TN DOH follows up with CDC about the results of the site visit. TN DOH relays that multiple products and exposures could be the source of the infection, including epidural injection tray kits, preservative-free contrast media, povidone-iodine, lidocaine, and preservative-free MPA from NECC.[2] External contamination of supplies in a common storage area at the ASC was also considered as a possible source of infection. CDC recommends that TN DOH continue to gather detailed information, including lot numbers on all of the products and sources of exposure, to facilitate further investigation. Over the weekend, the TN DOH works with the ASC and area hospitals to gather additional information and checks if there are any other *Aspergillus* or unexplained meningitis cases.

On Monday, September 24, CDC and TN DOH discuss the investigation. The discussion focuses on additional patients with meningitis from the same ASC with similar procedures and product exposures uncovered by the TN DOH over the weekend. CSF cultures from the additional patients with meningitis were negative, but all presented with a clinical picture similar to the index patient. CDC and TN DOH coordinate on next steps of the investigation. The TN DOH contacts the Massachusetts Department of Public Health (MA DPH) in an effort to obtain more information about NECC and its products. TN DOH notifies MA DPH about its cluster of meningitis cases following epidural steroid injections[3] and that use of MPA distributed by NECC is one of the common exposures under investigation.

On Tuesday, September 25, CDC notifies FDA that CDC and the TN DOH are investigating a cluster of meningitis cases in a single ASC in Tennessee that may be related to product contamination. CDC notes that they are investigating several product exposures as possible sources of infection. Also on Tuesday, the MA DPH and the MA Board of Pharmacy organize a call with NECC, the TN DOH, and CDC to inform NECC of the ongoing investigation and inquire about product information and adverse event reporting. Public health authorities learn about how the MPA steroid is prepared, request distribution lists for the three lots[4] identified by the TN DOH and inquire about any reports of illnesses related to MPA.[5] NECC states that it has not received reports of illnesses and that sterility testing, as well as environmental monitoring, has not demonstrated any concerning results. The MA Board of Pharmacy asks if NECC has a voluntary recall process in place if the investigation confirms contamination. NECC affirms that it does have a voluntary recall process in place.

The following day (September 26), the MA Board of Pharmacy initiates an inspection of NECC[6] and NECC issues a voluntary recall of the three lots of MPA identified by the TN DOH. Approximately 3,000 doses of MPA are quarantined or returned.[7] CDC is provided an invoice list of all facilities that received possibly contaminated lots and begins work with TN DOH and other State health departments to contact other clinics from the NECC distribution list to see if they are aware of any meningitis cases of unknown etiology. CDC also provides an update to FDA about the NECC call and informs FDA that NECC initiated a voluntary recall of the three lots of MPA though there was no specific evidence of product contamination. CDC asks FDA to query MedWatch reports for any related cases; the MedWatch query ultimately identifies the previously known cases from the Tennessee ASC. During this time, CDC continues to pursue other possible sources of the outbreak and contacts the New York Department of Health for assistance in contacting the company that produced the epidural injection trays used at the Tennessee ASC.

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[2] Kainer, M., et al. Outbreak of Neuroinvasive Fungal Infections Associated with Epidural Steroid Injections, Tennessee, 2012.

[3] Kainer, M., et al. Outbreak of Neuroinvasive Fungal Infections Associated with Epidural Steroid Injections, Tennessee, 2012.

[4] Lot #05212012@68, BUD 11/17/2012; Lot #06292012@26, BUD 12/26/2012; Lot #08102012 @51, BUD 2/6/2013.

[5] www.cdc.gov/mmwr/preview/mmwrhtml/mm61e1012a1.htm's__*cid=mm61e1012a1__w*.

[6] MA DPH NECC Preliminary Investigation Findings: ". . . investigators found NECC employees cleaning sterile compounding areas and conducting environmental testing. MA DPH investigators also detected signs of bleach decontamination in the compounding areas."

[7] MA DPH NECC Preliminary Investigation Findings.

On September 27, FDA and MA DPH begin coordination for a collaborative investigation of NECC.[8] A case is identified in another State[9] as North Carolina reports its first patient with meningitis of unknown etiology following epidural spinal injection to CDC late that evening. This is significant because it is the first evidence that the exposure may not be isolated to the TN ASC. CDC begins working with the TN DOH and NC DOH to identify common exposures in new cases from both States which include MPA from NECC as well as the same brands of povidone iodine and lidocaine. Of the patients identified thus far, only one has a culture-confirmed *Aspergillus* fungal meningitis infection. The additional patients have a similar clinical presentation of meningitis as the index case with *Aspergillus*, but no microbiological data yet link them together. The microbiological key comes later in the outbreak when the Virginia Department of Health (VA DOH) in consultation with CDC's infectious disease pathology laboratory links an unexplained death to the outbreak and identifies Exserohilium as the fungal pathogen related to that case.

On Friday, September 28, CDC requests all 23 States with clinics that received the three MPA lots from NECC begin contacting patients who received epidural injections to see if there are any other meningitis cases of unknown etiology. Through the weekend of September 29–September 30, CDC posts outbreak information to ClinMicroNet (a network of clinical labs) and the Emerging Infections Network (EIN, a network of infectious disease physicians) to help identify any additional *Aspergillus* meningitis cases or meningitis cases of unknown etiology.

On Monday, October 1, FDA and MA Board of Pharmacy initiate a joint inspection of NECC.[10] Investigators find violations of MA pharmacy regulations[11] and the MA DPH issues a formal quarantine notice.[12]

The following day, CDC initiates a call with the 23 States that received the three NECC lots of MPA to provide updates on the investigation and share information on meningitis cases of unknown etiology as well as common exposures. While NECC products are considered the likely source of the outbreak, the investigation does not find conclusive evidence of NECC product contamination until October 4 when FDA announces it has identified by microscopy visible fungal contamination of previously sealed vials of MPA from NECC from one of the three lots identified by TN DOH.

With conclusive identification of fungal contamination, CDC activates its Emergency Operations Center on October 4 and intensifies outreach to patients and clinicians to ensure appropriate patient diagnosis and treatment. CDC also launches a fungal meningitis outbreak Web site to provide continual updates to patients, clinicians, and the public, and by October 5, CDC posts the lists of the clinics that had received the three implicated lots of MPA to facilitate patient followup. Additionally, CDC and FDA laboratories work on pathogen identification in patient, product, and environmental samples. This combined laboratory effort ultimately recovers multiple bacterial and fungal contaminants from sealed NECC products labeled as sterile.

THE PATIENT EXPERIENCE WITH FUNGAL MENINGITIS AND RELATED INFECTIONS

We do not yet have a full picture of the extent of the impact of this tragic outbreak, which clearly has devastating impacts on patients and their families. Contaminated medication was administered by injection to thousands of people, resulting in an outbreak of fungal meningitis and other infections. *Exserohilum rostratum*, the predominant fungal species in this outbreak, is a common brown-black mold found in soil and on plants, especially grasses, that thrives in warm and humid climates. Fungal infection caused by *Exserohilum rostratum* is rare and when it does occur it has generally been documented as a cause of sinus and skin infections. Diagnosis of fungal meningitis, particularly with molds, is extremely difficult because traditional diagnostic methods such as culture have limited yield.

The clinical syndromes of these infections are rare and thus lack clinical trials or other experience that provide evidence for optimal treatment. Available treatments are not straight-forward because of potential adverse events and variability among

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[8] MA DPH NECC Preliminary Investigation Findings.

[9] *http://www.cdc.gov/mmwr/preview/mmwrhtml/mm61e1012a1.htm?s_cid=mm61e1012a1_w.*

[10] *http://www.cdc.gov/media/releases/2012/t1004_meningitis_outbreak.html.*

[11] MA DPH NECC Preliminary Investigation Findings—Investigators found that methylprednisolone products labeled as patient specific were not individual prescriptions but lists of patients generated by a clinic and provided to NECC to obtain the product which is a violation of MA pharmacy regulations.

[12] MA DPH NECC Preliminary Investigation Findings—"The Notice directed that all methylprednisolone acetate raw materials (chemicals), all non-sterile products located at NECC used in the compounding of methylprednisolone acetate, and all inventory on the premises prepared for dispensing and stored at the pharmacy, or received by recall should be quarantined and not disposed of without the express approval of the DPH."

patients. With little literature describing these types of infections and limited clinical experience available, CDC solicited the individual input of outside mycology experts to help develop novel diagnostic and treatment guidance for patients at risk for these fungal infections. CDC has worked with these experts throughout the outbreak to update our interim guidance as more information has become available about the clinical experience of patients. Adequate duration of antifungal treatment is unknown although we expect a minimum of 3 months' treatment be considered. CDC has sent staff to States and worked with State and local health departments to abstract medical charts and gather information on patients' ongoing clinical experiences. CDC has disseminated our treatment guidance through web postings, blast e-mails to professional societies, and multiple clinician-specific conference calls.

As of November 13, the median age of the patients is 65 years (range: 16–92 years) and over 60 percent are female. While most of the cases have presented with meningitis, we have also seen cases of stroke, epidural abscess (infection between the outer covering of the brain and spinal cord and the bones of the skull or spine), osteomyelitis (bone infection), and septic arthritis (joint infection). Many patients with meningitis had only a few mild symptoms, such as headache and/or nausea or vomiting.

The incubation period has ranged from 0 to 120 days with a median of 20 days. Based on current data, the highest risk is likely to be in the first 42 days (6 weeks) after last injection. Maximum incubation period for infection is not known, and the incubation period could be longer for some patients. Thus, asymptomatic but exposed patients should remain vigilant for symptoms and seek medical attention should symptoms develop. The clinical situation is still evolving. Even with treatment, we are seeing many patients return after being discharged from the hospital with new symptoms and other conditions such as arachnoiditis (inflammation of the membranes that surround nerves) and abscesses at the original injection sites. This suggests that there may be long-term complications for patients that have not yet become apparent.

To support ongoing clinical efforts, CDC has developed a Clinicians Consultation group consisting of a network of leading clinical infectious disease and fungal disease experts nationwide who have volunteered to provide consultation with clinicians providing direct patient care. CDC is also planning to continue to follow cases to help track the course of treatment and provide ongoing information on patient outcomes.

EARLY LESSONS LEARNED

Outbreak responses require skilled, trained public health personnel in State and local agencies. In this outbreak, we were fortunate that trained individuals were already "on the ground" in key positions, reinforced by already-established surveillance and laboratory capacity. Personnel cuts at the State and local levels have made CDC support to State infectious disease programs key to these efforts. CDC's Epidemiology and Laboratory Capacity (ELC) cooperative agreement and the Emerging Infections Program (EIP) support this critical infectious disease capacity and networking.

This outbreak is also a reminder of the importance of CDC's infectious disease epidemiologists and laboratories to rapidly respond to and characterize outbreaks of unexplained death and illness. This outbreak exemplifies the work of CDC's disease detectives to track down and solve public health problems. CDC's laboratory capacity for infectious diseases has been a critical element in the response, identifying rare or obscure pathogens and providing added capacity as a backstop to States. With declining local resources, many States have cut back on maintaining fungal testing and instead rely upon CDC's fungus laboratory. During the peak of laboratory testing, CDC's fungus laboratory was operating 7 days a week to test the hundreds of outbreak-related samples. This outbreak has also underscored the importance of bioinformatics and genomics technologies that can help CDC and States more rapidly and decisively detect, respond to, and control large outbreaks like this one.

CDC plays a vital role not only in responding to these outbreaks but in preventing them as well. For years, CDC and its State public health partners have been the first-responders to multiple outbreaks stemming from suboptimal practices in handling sterile medications in clinics and in pharmacies. We are learning that many of these outbreaks are the result of a widespread lack of knowledge of or adherence to well-recognized regulatory and professional standards for properly handling sterile medications.

CONCLUDING REMARKS

This outbreak demonstrates the essential role that public health plays in identifying and responding to infectious disease outbreaks large or small. Our national public health capacity is disseminated to State and local responders who work on a daily basis to keep our country safe from infectious diseases—whether they are from naturally emerging threats such as a new influenza pandemic or from human-made problems such as contaminated medicines. CDC will continue to work with State partners, national experts, front-line clinicians and others to respond to the critical public health needs related to this outbreak.

Fungal meningitis outbreak update

November 14, 2012*

461 fungal meningitis and joint infection cases, includes deaths

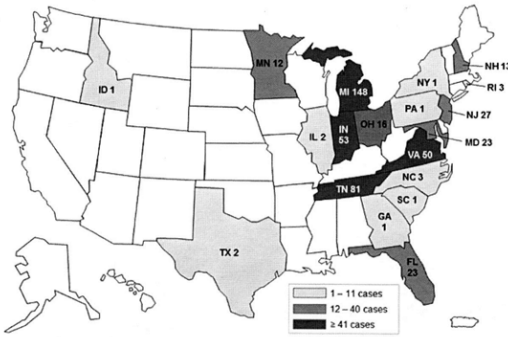
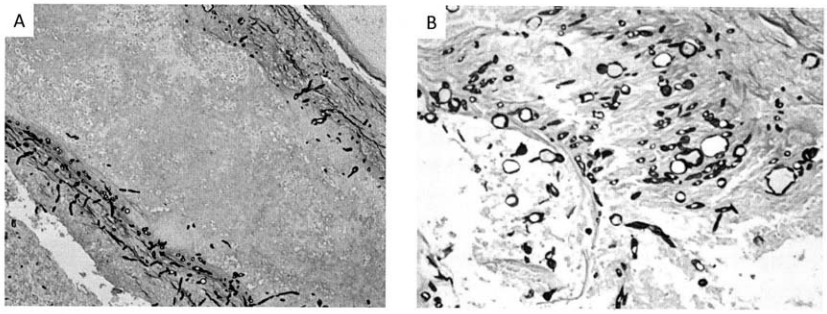


Table by State

State	Total Case Counts	Peripheral Joint Infections	Deaths
Florida (FL)	23	0	3
Georgia (GA)	1	0	0
Idaho (ID)	1	0	0
Illinois (IL)	2	0	0
Indiana (IN)	53	0	4
Maryland (MD)	23	0	1
Michigan (MI)	148	6	8
Minnesota (MN)	12	0	0
North Carolina (NC)	3	0	1
New Hampshire (NH)	13	4	0
New Jersey (NJ)	27	0	0
New York (NY)	1	0	0
Ohio (OH)	16	0	0
Pennsylvania (PA)	1	0	0
Rhode Island (RI)	3	0	0
South Carolina (SC)	1	0	0
Tennessee (TN)	81	0	13
Texas (TX)	2	0	0
Virginia (VA)	50	0	2
TOTALS	**461***	**10**	**32**

*Last day of online web posting



Here are microscopic images of biopsy tissue from CDC's pathology laboratory that show manifestation of disease. Fungal hyphae (black) can be seen here within blood vessel walls (A) and can be seen (B) necrotizing (killing) cells in the basilar artery, one of the arteries that supplies the brain with oxygen-rich blood.

The CHAIRMAN. Thank you very much, Dr. Bell.

Now we'll turn to Dr. Peggy Hamburg, the Commissioner of the Food and Drug Administration. Dr. Hamburg and Dr. Smith, I

know you were both at the House hearing yesterday. I hate to have you do double duty, but that's the way this system works. We wanted you over here also to be able to speak with us, so we could also engage you in questions about the role of both the FDA and the Massachusetts inspections.

Dr. Hamburg, please proceed.

STATEMENT OF MARGARET A. HAMBURG, M.D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION, WASHINGTON, DC

Dr. HAMBURG. Thank you very much, Mr. Chairman and members of the committee. I appreciate the opportunity to testify about this tragic fungal meningitis outbreak associated with an injectable steroid product distributed by NECC as well as to focus on the safety concerns related to compounding and legislation that is needed to prevent such incidents from happening again.

I want to, of course, begin by offering my sympathies to the patients affected by this outbreak and their families. This event has had devastating effects on patients across the country, many of whom were likely unaware that they were receiving a drug that was compounded, not reviewed or approved by the FDA.

Our foremost goal is the protection of the public health. Since the onset of this outbreak, we've targeted FDA resources, from experts in our headquarters to inspectors and scientists in district offices and labs across the country, to do everything we can to stem the toll of this terrible event.

Together, with CDC and the States, we've sought to identify potentially contaminated products and ensure that they are removed from market and don't reach patients. We've collected and analyzed hundreds of samples from the relevant firms, as well as from medical facilities and State and local agencies, to isolate the cause and determine the extent of the contamination. We're working daily to ensure that timely, clear, and accurate information is disseminated about the findings of our investigation, what products are affected, and what providers should do with any product still on their shelves. We're working to alleviate existing drug shortages that could be exacerbated by product recalls.

We've also been reviewing actions taken in the past with regard to NECC. In a tragedy of this magnitude, you always look back to see what more could have been done. Certainly, we should have sent the warning letter more swiftly and done the inspection originally planned. From our review thus far, we have no reason to believe that any of those specific actions in question, more timely issuance of the 2006 warning letter or inspectional follow-up, would have prevented this recent tragedy.

What we do know is that stronger, clearer authority would enable more effective regulation of the drug compounding industry, especially when it's been evolving so significantly. As it is, our authority over compounding is limited, unclear, and contested. In the face of differing views in Congress and the courts about FDA's authority and continuing challenges by industry, the agency has struggled with how to chart an effective course to protect the public health.

Like Senator Roberts, we recognize that traditional compounding provides an important service for patients who, for example, can't swallow a pill or are allergic to an ingredient in a drug product. The industry has evolved well beyond a neighborhood pharmacist. In particular, the movement by many hospitals to outsource pharmacy compounding has created a market for compounding operations that produce drugs that reach far larger numbers of patients.

When these facilities operate well, they may serve an important function in terms of safety and efficiency. However, when they fail to follow safety and quality standards, many patients may be harmed. Our best information is that there are thousands of other compounders out there producing what should be sterile products made to exacting standards, and thus many other firms with the potential to generate a tragedy like this.

The current oversight framework, in attempting to draw a bright line between compounders and manufacturers, fails to address the complex issues raised by the changing nature of the industry. Additionally, gaps and ambiguities in the law have hampered our ability to act to protect patients and to prevent rather than to react to safety problems.

I am committed to working with Congress and other stakeholders to design a system of rational, risk-based regulation that takes into account both the Federal and State rules. As I outlined in my testimony, we have developed a proposed framework that would tier the degree of oversight to the risk posed by the type of product and practices. Traditional compounding would remain the purview of the States.

The higher risk posed by nontraditional compounding would be addressed by Federal standards, including standards for quality control. Under this framework, certain products carrying the highest risk could not be compounded. They could only be produced by entities willing to meet the standards currently required of drug manufacturers.

We would also like to explore with you authorities that would be important to support this new regulatory paradigm, including clear authority to access records, mandatory reporting of adverse events, additional registration requirements to facilitate appropriate oversight and coordination with State regulators, clear label statements to allow prescribers and consumers the opportunity to make informed judgments, and adequate funding to support the inspections and oversight activities outlined in the framework.

Because a key piece of any plan involving oversight of pharmacy compounders will continue to be performed at the State level, we must work closely with our State partners as we develop the framework for new authorities. FDA will be inviting representatives from all 50 States to participate in a full-day meeting on December 19 to facilitate these important discussions and to strengthen our working relationship with the States.

We have a collective opportunity and responsibility to help prevent future tragedies. If we fail to act, this type of incident will happen again. It is a matter of when, not if, I'm afraid. If we fail to act now, it will only be a matter of time until we're all back in

this room asking why more people have died and what could have been done to prevent it.

I am happy to answer any questions you have and look forward to working with you on this very important public health issue.

[The prepared statement of Dr. Hamburg follows:]

PREPARED STATEMENT OF MARGARET A. HAMBURG, M.D.

INTRODUCTION

Mr. Chairman and members of the committee, 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 the tragic fungal meningitis outbreak associated with compounded methylprednisolone acetate (MPA), a steroid injectable product distributed by the New England Compounding Center (NECC), and to discuss more broadly safety issues related to pharmacy compounding.

I want to begin by offering my deepest sympathies to the patients affected by this outbreak and their families. This outbreak has had devastating effects on individuals and families across the country. The Centers for Disease Control and Prevention (CDC) has reported 32 deaths among 438 individual cases (428 cases of fungal meningitis and 10 cases of peripheral joint infections)[1] across 19 States. Approximately 14,000 patients may have received injections with MPA from three implicated lots. In addition, two other NECC products have been found to be contaminated with different bacteria. We have found no adverse health effects to date from these additional products, but continue to investigate the public health implications of this contamination.

Although the investigation is ongoing, we want to provide you with an update on the actions that FDA has taken, and is continuing to respond to this outbreak. We also want to suggest steps that Congress can take to strengthen FDA's authority to help prevent tragedies like this from happening in the future.

FDA'S RESPONSE TO THE CURRENT OUTBREAK

FDA's primary goal since the onset of this outbreak has been to protect the public health. With the State and Federal partners, we are conducting thorough investigations of the relevant facilities, monitoring the voluntary recalls associated with these products to ensure that contaminated and potentially contaminated product is off of the shelves, and ensuring that information is communicated promptly and clearly to health care professionals and patients.

Let me briefly summarize the sequence of key events regarding the outbreak. 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. When we learned of the potential contamination, we joined CDC in investigating. On September 26, NECC began a voluntary recall of three implicated lots of MPA and voluntarily ceased manufacturing of MPA. The Massachusetts Board of Registration in Pharmacy, which has primary oversight responsibility for pharmacies in its State, oversaw the recall, and initiated a 1-day inspection of NECC's Framingham, MA, facility. FDA also began to coordinate with the Massachusetts Board of Registration in Pharmacy to plan for inspection of NECC. We coordinated closely with the State on this adverse event inspection, because the State has authority to compel certain actions where our authority is more limited.

FDA and the Massachusetts Board of Registration in Pharmacy initiated a joint inspection of NECC on October 1, 2012. On October 4, FDA and CDC held a joint press conference announcing the investigation of the meningitis outbreak.[2] On October 5, after FDA had observed fungal contamination by direct microscopic examination of foreign matter taken from a sealed vial of MPA collected from NECC, FDA issued a MedWatch Safety Alert to 220,000 health professionals to notify them of the fungal contamination. Out of an abundance of caution, the Safety Alert took the

[1] Four-hundred and twenty-eight cases of fungal meningitis, stroke due to presumed fungal meningitis, or other central nervous system-related infection meeting the outbreak case definition, plus 10 peripheral joint infections (e.g., knee, hip, shoulder, elbow).

[2] "CDC and FDA Joint Telebriefing on Investigation of Meningitis Outbreak" (October 4, 2012); transcript available at *http://www.cdc.gov/media/releases/2012/t1004_meningitis_outbreak.html*.

additional step of recommending that health care professionals and consumers not use any product produced by NECC. FDA also requested that health care professionals retain and secure all remaining products purchased from NECC until FDA provided further instructions about how to dispose of these products. In addition, the Safety Alert encouraged health care professionals and patients to report to the Agency's MedWatch Safety Information and Adverse Event Reporting Program any adverse events or side effects related to the use of these products. On October 6, at FDA's recommendation, NECC agreed to recall all products.

As our investigation continued, on October 11, we announced our findings showing the presence of a fungal contaminant in multiple sealed vials of MPA injection, made at the NECC's Framingham, MA site. CDC confirmed the specific type of fungus related to the patient disease—*Exserohilum*—in this briefing as well.[3] On October 15, based on FDA's ongoing investigation and out of an abundance of caution, we further advised health care professionals to followup with patients who were administered any NECC injectable product on or after May 21, 2012, including an ophthalmic drug that is injectable or used in conjunction with eye surgery or a cardioplegic solution. After working closely with the State on October 22, the Agency made available two lists of customers (consignees) who received products that were shipped on or after May 21, 2012, from NECC's Framingham, MA facility, advising those customers to check their stocks to identify whether they had any products from NECC, and if so, to immediately isolate any identified product from their drug supplies and contact NECC to obtain instructions on how to return products.

On October 26, FDA released a copy of the FDA Form 483 (list of observations made during the on-site inspection) issued to NECC. FDA observed, and has since confirmed, that contaminated products were made at NECC's Framingham, MA facility, and listed a number of observations made during the course of the inspection regarding conditions in the clean room at this facility.

Most recently, on November 1, FDA and CDC laboratories announced that bacteria had been identified as present in three separate lots (batches) of NECC-supplied, preservative-free injectable betamethasone, with each lot producing different culture results (identifying different contaminants), and in a single lot of NECC cardioplegia solution. FDA stated that although final laboratory results on additional samples were still pending, the previous finding of fungal contamination of MPA and recent finding of bacterial contamination of injectable betamethasone and cardioplegia solution reinforced the Agency's concern about the lack of sterility in products produced at NECC's compounding facility and served to underscore that hospitals, clinics, and health care professionals should not use any NECC-supplied products.

The Agency has been working closely with CDC, numerous State health departments, and the Massachusetts Board of Registration in Pharmacy to investigate the outbreak of fungal meningitis. This is a far-ranging investigation across the United States. FDA, in conjunction with our State partners, is in the process of inspecting several facilities associated with this outbreak. This includes compounders, wholesale distributors, active pharmaceutical ingredient (API) suppliers, contract laboratories, and others. The Agency's first priority has been to detect any contaminated or potentially contaminated products, to prevent them from reaching U.S. consumers by ensuring they are effectively recalled and removed from the market, and, as discussed more fully below, to communicate key information about these products to the providers and patients who need it. In connection with this investigation, FDA has collected and analyzed hundreds of samples from firms associated with this outbreak, as well as from medical facilities and State and local agencies. In addition to staff at FDA headquarters, staff in FDA district offices in New England, New York, Dallas, Seattle, Chicago, Los Angeles, Detroit, Cincinnati, Kansas City, and Florida, and laboratory personnel in Denver, San Francisco, Atlanta, New York, and Boston, are assisting in this investigation.

FDA also inspected Ameridose LLC's facility in Westborough, MA as part of the Agency's ongoing fungal meningitis outbreak investigation. Ameridose and NECC share some of the same management. Ameridose entered into a voluntary agreement with the Massachusetts Board of Registration in Pharmacy to temporarily cease all pharmacy and manufacturing operations starting on October 10, 2012. After FDA's preliminary inspectional findings raised concerns about a lack of sterility assurance for products produced at and distributed by Ameridose's Westborough facility, the company voluntarily recalled all of its unexpired products in circulation. FDA completed its inspection on November 9, 2012.

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[3] "CDC, FDA, Massachusetts Department of Public Health: Joint Telebriefing Updating Investigation of Meningitis Outbreak" (Oct. 11, 2012); transcript available at *http://www.cdc.gov/media/releases/2012/t1011_meningitis_outbreak.html*.

FDA is currently conducting recall audit checks of NECC's customers. In an audit check, FDA contacts a subset of the firm's customers, which in this case were health care facilities, to confirm that they received notice of the recall and took the action requested in the recall notice.

In this case, the facilities were instructed to immediately segregate and quarantine the material and to work with NECC to coordinate return of the products. As of November 5, 2012, FDA had completed 587 audit checks of NECC's health care facility customers. FDA found no product remaining for use at any of the NECC customers that it audited, and all customers had knowledge of the recall. Ameridose commenced its product recall on October 31, 2012; FDA initiated its audit check process for the Ameridose recall on November 5, 2012.

FDA has identified six Ameridose products that were on the FDA drug shortage list prior to the recall (sodium bicarbonate injection; succinylcholine injection; atropine sulfate injection; bupivacaine hydrochloride injection; lidocaine hydrochloride injection and furosemide injection).

These six drugs were in shortage before the Ameridose shutdown due to manufacturing problems, delays, and discontinuations by commercial manufacturers. FDA's Drug Shortage Program is using every tool available to work with manufacturers to address these shortages. For five of the drugs, we expect the shortages to decrease based on all of the ongoing efforts of FDA and the manufacturers to address these shortages and do not anticipate the Ameridose shutdown to create additional issues. For sodium bicarbonate injection, we are continuing all efforts to address the shortage, including exploring temporary importation to assist with supplies until demand is being met by the U.S. manufacturers.

FDA has communicated throughout this investigation with the media, Congress, State health officials, health care professionals, and the public to keep them apprised of important findings and developments as we move forward in our investigation. FDA's Web site is updated on a frequent basis to provide broad access to any new public information. This information is being further disseminated through the Agency's electronic listserves and through Twitter and Facebook. Along with CDC, FDA is providing health care professionals with information they need on an ongoing basis, and as new information comes to light, to advise and treat patients affected by this situation.

Targeted alerts have been 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 are provided to State health departments, in collaboration with CDC, and written updates are 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 are fielding calls from the public and we have extended their hours of availability for the last several weeks to help respond to the public's concerns. We also continue to respond to calls and e-mails from health care professionals, hospitals and clinics, and others with questions about the NECC and Ameridose recalls.

The far-ranging investigation is ongoing and FDA will continue to update stakeholders as quickly as possible as information becomes publicly available.

FDA's past activities with respect to NECC include: a 2002 inspection in response to adverse event reports (followed by a State inspection and action under Massachusetts' authority) and a 2006 Warning Letter focused on lower risk issues associated with copying approved drugs, marketing and packaging. Throughout this time, NECC has repeatedly disputed FDA's jurisdiction over its facility.[4] The Massachusetts Board of Pharmacy re-inspected NECC in 2011 in response to a letter from the firm indicating that NECC was "updating its facility and moving into adjacent space"; that inspection included a tour of the facility, security review, licensing review, and inspection of NECC's sterile and non-sterile processing areas.[5] The Massachusetts Board of Pharmacy inspection found the facility to be "Satisfactory."[6]

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[4] Inspection Report for April 2002 inspection, at PP. 2, 3, 5; Establishment Inspection Report for 2002/2003 inspection, at p. 11; Inspection Memorandum for 2004 inspection, at p. 3; Warning Letter Response, at PP. 3–4.

[5] A copy of MABRP's May 24, 2011, Inspection Report for NECC is available on MABRP's Web site at *http://www.mass.gov/eohhs/docs/dph/quality/boards/necc/03-new-england-compounding-pharmacy-incnew-england-compounding-center-inspection-report.pdf*.

[6] See MABRP's May 24, 2011 Inspection Report for NECC, id., at p. 10.

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. 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. 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.[7] In May 1996, in a House Commerce Committee hearing on FDA reform legislation, FDA Commissioner David Kessler testified that the compounding provision being considered by the committee was likely to encourage large-scale manufacturing under the guise of pharmacy compounding, and could allow for potentially dangerous compounding of sterile products, leading to serious safety problems or death.[8]

In November 1997, S. 830, the Food and Drug Administration Modernization Act of 1997 (FDAMA) was signed into law as Public Law 105–115.[9] FDAMA added to the FD&C Act's Section 503A, which addresses FDA's authority over compounded drugs.[10] Section 503A exempts compounded drugs from three critical provisions of the FDCA: the premarket approval requirement for "new drugs"; the requirement that a drug be made in compliance with current good manufacturing practice (cGMP); and the requirement that the drug bear adequate directions for use, providing certain conditions are met. These conditions include, among other things, that the compounding be performed by a licensed pharmacist or physician, that there be a prescription for the compounded product for an individual patient, and that the compounded product be necessary for an identified patient. It allows FDA to restrict the compounding of certain categories of drugs (after notice-and-comment rulemaking), and limits the quantity of compounded drugs that a pharmacy could ship out of State to 5 percent of the total prescription orders, unless the State enters into a Memorandum of Understanding with FDA that addresses the distribution of "inordinate amounts" of compounded drugs out of the State, and the handling of complaints about compounded products shipped out of the State. Section 503A also contains restrictions on the advertising or promotion of the compounding of any particular drug, class of drug, or type of drug, and on the solicitation of prescriptions for compounded drugs from prescribers. 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 authority over compounding pharmacies. We look forward to working with Congress to address these issues.

Looking Ahead

FDA believes that there is a legitimate role for traditional compounding to provide needed drugs to patients that, for example, need a drug that is allergen free or have a medical need that cannot be met with an approved FDA product. However, we have grown increasingly concerned about certain compounding practices, and we

[7] 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.

[8] Statement by David A. Kessler, M.D., Commissioner of Food and Drugs, Dept. of Health and Human Services, before the Subcommittee on Health and Environment, Committee on Commerce, House of Representatives (May 1, 1996).

[9] 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*.

[10] Id.

have seen an increasing number of incidents related to compounded drugs. The NECC/meningitis situation is the latest, and most serious, incident. As described above, 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 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 prescription or order for an individual patient who has a documented medical need for the compounded drug.

Further, we recommend that the statute recognize 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 plays an important role in the health 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 based on one or more of the factors identified below. Non-traditional compounding would be subject to Federal standards adequate to ensure that the compounding could be performed without putting patients at undue risk. For example, enforcement could be by the FDA or by a State willing to effectively oversee the compounding activities, as determined by FDA.

Factors that could place a product into the "non-traditional compounding" category might include some statutorily specified combination of: the type of product/activity (e.g., sterile compounding); the amount of product being made; whether the production is being done before the receipt of a prescription or order for a particular patient (so-called "anticipatory compounding"); whether the compounded drug is being shipped interstate; or whether the drug is being dispensed to someone other than the ultimate user when it leaves the facility where it was produced.

Non-traditional compounding should, because of the higher risk presented, be subject to a greater degree of oversight, with the riskiest products subject to the highest level of controls, such as appropriate current good manufacturing practice ("cGMP") standards established by FDA. 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 cGMPs, along with other requirements applicable to manufactured drug products. We would seek to permit the Secretary to have sufficient flexibility in this area to make these exceptions necessary to address issues of public health.

FDA would like to explore with Congress 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.

FDA also believes that pharmacies engaged in non-traditional compounding should register with FDA so that FDA can maintain an accurate inventory of such pharmacies to facilitate appropriate oversight and coordination with State regulators. In addition, FDA would like to explore with Congress several other ideas

such as clear label statements identifying the nature and source of the non-traditionally compounded product, and requiring non-traditional compounders to report adverse events. The labeling statements would provide prescribers and consumers with valuable information about the products they are using or taking so that they can make informed judgments about their use. Requiring non-traditional compounders to report adverse events, as drug manufacturers are required to do, would allow FDA and the States to identify trends and to proactively take steps to curtail dangerous compounding practices. Other appropriate regulatory and enforcement tools might also be useful. Funding will be necessary 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 implemented in other settings.

In light of growing evidence of threats to the public health, the Administration urges Congress to strengthen Federal standards for non-traditional compounding. Such legislation should appropriately balance legitimate compounding that meets a genuine medical need with the reality that compounded drugs pose greater risks than those that are evaluated by FDA for safety and efficacy and subject to manufacturing controls to ensure consistently high product quality. We recommend that it recognize the appropriate State role in regulation of traditional compounding, while authorizing Federal standards and oversight for non-traditional compounders that produce riskier products. We look forward to working with Congress in striking the right balance.

CONCLUSION

Protecting Americans from unsafe and contaminated drugs is not just an important responsibility of FDA—it is part of our core mission. To fulfill our mission, we must be able to proactively identify dangerous practices before they result in actual harm, and when necessary, intervene to minimize the damage and to prevent future similar events. Tragically, there have been 32 deaths to date associated with this outbreak. However, we are hopeful that our actions thus far and the ongoing investigation are preventing unknown numbers of further deaths, which might have occurred had we and our partners not acted aggressively after we became aware of the outbreak.

We look forward to working with Congress on legislation that will balance the need to allow legitimate forms of traditional pharmacy compounding with the need for adequate Federal oversight of higher risk pharmacy compounding practices.

I am happy to answer any questions you may have.

The CHAIRMAN. Thank you, Dr. Hamburg.

Dr. Smith, welcome. Again, as I said, your statements will be made a part of the record in their entirety. If you could sum it up, I'd appreciate it.

STATEMENT OF LAUREN SMITH, M.D., MPH, INTERIM COMMISSIONER, DEPARTMENT OF PUBLIC HEALTH, BOSTON, MA

Dr. SMITH. Good morning, Senator Harkin and Ranking Member Enzi and members of the committee. Thank you for having me here today. My name is Dr. Lauren Smith, and I'm the Interim Commissioner for the Massachusetts Department of Public Health.

I must begin by saying that my thoughts are with the victims and their families of this tragic outbreak—some of the poignant stories described by Dr. Bell. I know that the numbers that represent those made ill and those who lost their lives actually represent real people with real stories. That only strengthens my resolve to ensure that no other families have to suffer the heartbreak that these have.

As a mother, a pediatrician, and a public health leader, I have devoted my life and career to protecting the health of others. These events invoke in me the same outrage that you and the rest of the public feel. For many of you, I know this hits very close to home.

For nearly 2 months, our department, along with the FDA, has conducted a joint investigation of the New England Compounding Center, the source of the devastating fungal meningitis outbreak. We have also investigated and shut down NECC's sister companies. NECC knowingly disregarded sterility tests, prepared medicine in unsanitary conditions, and violated their pharmacy license, which endangered thousands of lives as a result. NECC bears the primary responsibility for the harm that they have caused with these actions.

I was given the responsibility as interim commissioner less than 3 weeks ago to lead my department through this crisis. And like you, I have been trying to put together the pieces of the puzzle. First licensed by Massachusetts in 1998, NECC and its owner, Barry Cadden, have been the subject of numerous complaints resulting in a series of investigations by the State and the FDA.

These investigations led the Board of Pharmacy to propose reprimand and probation in 2004. This proposal was inexplicably weakened in 2006, allowing NECC to continue to operate without any disciplinary actions pending an independent evaluation of its progress under a consent agreement. The Board of Pharmacy's failure to take decisive disciplinary action in 2006 on these complaints contributed to these tragic events.

In addition, in April 2006, the Board of Pharmacy staff learned that the principal of PSI, the evaluator for NECC, had been convicted of Federal crimes that resulted in 18 people being blinded. However, the staff did not share this information with the Board members before they accepted the report from PSI indicating that NECC's compliance with the consent agreement had been completed. These same staff members failed to act on a July 2012 report from a Colorado Board of Pharmacy that NECC had violated both Colorado and Massachusetts pharmacy regulations. These staff members have been removed from their jobs.

Poor judgment, missed opportunities, and lack of action have allowed NECC to continue on this troubling path. We acknowledge that some of these lapses were preventable, but, clearly, all are unacceptable.

From the early days of this outbreak, the department has acted swiftly and decisively. We secured a surrender of NECC's license, shut down its operations, and secured a total recall of NECC products. We moved to permanently revoke NECC's license, as well as the licenses of the three principal pharmacists who oversaw their operations. We also secured the suspension of operations of Ameridose and Alaunus, which are two other drug manufacturers also owned by Barry Cadden, which, as I'm sure you know, have been found to have substandard practices.

While taking these strong and necessary actions, we have reexamined our own State regulations regarding compounding pharmacies. Although our regulations are comparable to those in most States, they clearly need to be strengthened to address the realities of this evolving industry. On November 1, Massachusetts enacted a series of emergency regulations to bring greater scrutiny to this industry and require sterile compounding pharmacies to report both volume and distribution information to us.

In addition, licensed pharmacies will also have to report when they are the subject of either a State or a Federal investigation. We have also begun unannounced inspections of all sterile compounding pharmacies. Teams are conducting those inspections even as we speak.

To further strengthen our oversight over sterile compounding pharmacies, we must also explore changes in State law. We have created a special commission to review best practices in other States and to identify stronger mechanisms of oversight of pharmacies such as these in Massachusetts.

As we work to raise our standards in Massachusetts, we urge Congress to act to strengthen the Federal oversight. Congressman Markey's leadership on this issue is laudable, and we hope this will address the regulatory black hole that exists currently between State and Federal oversight.

As a pediatrician who has cared for acutely ill children and their families for close to 20 years, I understand that patients place a significant amount of trust in our healthcare system. We must use these terrible events as an impetus to work together as public health leaders and legislators to institute reforms to restore this trust and ensure that something like this never happens again. I know that we will keep the victims and their families always in our thoughts as we work to identify responsibility and to implement policies and practices that will be both effective and lasting.

Thank you. I appreciate this committee's interest in this matter, and I commend you for moving so swiftly to bring us together to discuss it.

[The prepared statement of Dr. Smith follows:]

PREPARED STATEMENT OF LAUREN SMITH, M.D., MPH

SUMMARY

- For nearly 2 months, the Massachusetts Department of Public Health has conducted a joint investigation of New England Compounding Center (NECC) with our Federal partners at the Food and Drug Administration (FDA) to determine what caused the devastating fungal meningitis outbreak that has sickened hundreds and led to dozens of deaths across the country. DPH has also been jointly investigating sister companies Ameridose and Alaunus, Westborough, MA-based drug manufacturers.
- NECC knowingly disregarded sterility tests, prepared medicine in unsanitary conditions and unlawfully engaged in manufacturing, endangering thousands of lives as a result.
- This testimony provides a chronology of events based upon documents, reports, and e-mails recently reviewed, beginning with NECC's licensure in July 1998. It is a troubling history.
- The Massachusetts Department of Public Health has taken swift and decisive actions since we became aware of the outbreak.
  - DPH secured a surrender of NECC's license, shut down its operations and issued a total recall of NECC products.
  - Massachusetts sterile compounding pharmacies have been required to attest under penalty of perjury that they are meeting all State laws and regulations.
  - The Massachusetts Board of Pharmacy approved emergency regulations to enhance oversight of compounding pharmacies.
  - We have begun unannounced inspections of the State's 25 sterile compounding pharmacies to review how they function when they are not aware that an inspection is scheduled.
  - We have named Christian A. Hartman, an expert in pharmacy practice and patient safety, to chair a Special Commission on compounding pharmacies. We will look at best practices in other States, explore new ideas, and consider the interplay between State and Federal authority.

- We have removed three key employees from their jobs due to their failures to act at key junctures.
- Massachusetts will continue to do whatever we can, make any changes, and identify any areas of new law to make sure something like this never happens again.

Good morning, Chairman Harkin, Ranking Member Enzi, members of the committee, thank you for having me here today. My name is Dr. Lauren Smith, I am the Interim Commissioner of the Massachusetts Department of Public Health and I welcome the opportunity to have this discussion.

I want to say from the outset that my thoughts are with the victims and families affected by this tragic outbreak. As a mother, a pediatrician, and a public health leader, I have devoted my life and career to protecting the health of others. Have no doubt that these events invoke in me the same outrage that you and the rest of the public feel. The natural first question we all ask is "How could this possibly have happened?" The necessary second question is "What can we do to ensure that this terrible situation does not happen again?"

For nearly 2 months, our Department has conducted a joint investigation of New England Compounding Center (NECC), alongside our Federal partners at the Food and Drug Administration (FDA), to answer these questions.

NECC is a Framingham, MA-based pharmacy that compounds sterile medications. It was identified as the source of the devastating fungal meningitis outbreak that has sickened hundreds and led to dozens of deaths across the country. For many of you, and for those with cases among your constituents in particular, I know these losses hit close to home.

NECC knowingly disregarded sterility tests, prepared medicine in unsanitary conditions and unlawfully engaged in manufacturing, endangering thousands of lives as a result. NECC bears the primary responsibility for the harm they have caused with these actions.

I was given the responsibility as interim commissioner less than 3 weeks ago, to lead my department during this crisis. And like you, I have spent the last several weeks trying to put together the pieces of this troubling puzzle.

Although the majority of these events happened in the previous administration and well before I came to the Department, I offer the following chronology based on a review of documents and reports from the time.

Let me begin by noting that by statute, the Massachusetts Board of Registration in Pharmacy, supported by the Department of Public Health's Division of Health Professions Licensure, has primary responsibility for oversight of the practice of pharmacy in the Commonwealth.

The Board of Pharmacy is an independent body, with 11 members appointed by the Governor. The Board has the responsibility and legal authority to license and regulate pharmacies and pharmacists. DPH staff investigators, lawyers, administrators, and an executive director support the Board's operations.

The Massachusetts Board of Registration in Pharmacy's interaction with NECC began on July 16, 1998, when it obtained its initial license. On February 2, 1999, the Board received the first complaint against NECC, which alleged that the pharmacy had provided a prescriber with pre-printed prescriptions that specifically listed NECC medications. State law prohibits pre-printed prescriptions. Prescriptions are required to be patient-specific, and based upon the patient's diagnosis, medical history, allergies, tolerance, and the specific constellation of symptoms that the patient is presenting. This complaint was resolved in October 1999 with an informal reprimand letter, a non-disciplinary action.

In April 2002, working with the FDA, the Board visited NECC and obtained records related to a recent MedWatch report concerning betamethasone, a compounded steroid suppository. The FDA investigator met with Barry Cadden, owner of NECC, and conducted an inspection on April 9, concerning procedures, sterility and recordkeeping.

In October 2002, the Board initiated a joint investigation with the FDA at NECC related to the April 2002 betamethasone complaints as well as MedWatch reports associated with the use of methylprednisolone acetate, the injectable steroid medication implicated in this current outbreak. The MedWatch reports pertained to two patients who received the steroid and experienced pain and headaches and were hospitalized with meningitis-like symptoms. Laboratory tests from these investigations identified subpotency of betamethasone and superpotency of methylprednisolone acetate. The FDA also noted contamination of one lot of methylprednisolone acetate with bacteria. These investigations continued into 2003.

Also in 2002, Board of Pharmacy member Karen Ryle convened a Task Force to study Board oversight of the compounding pharmacy industry. Barry Cadden served on this Task Force, which met for nearly 2 years. The Task Force discussed proposals to change regulations around compounding, but records do not show whether formal recommendations were made, and the Board did not adopt new regulations.

In February 2004, the Board conducted a followup inspection of NECC and noted that all deficiencies surrounding sterility, safety, quality and procedures from the 2002–3 investigations had been resolved. Just weeks later, however, the Board received a complaint, from a pharmacist in Wisconsin, expressing concerns with the safety of a topical anesthetic product. The complaint alleged that NECC advised the pharmacy to unlawfully use a staff member's name rather than an individual patient's name in filling a prescription. The Board then in place resolved this complaint with a disciplinary warning letter on September 30, 2004.

Based on this series of investigations, in September 2004, the Board voted unanimously to sanction NECC with a reprimand, a 3-year probation, and a requirement that Barry Cadden obtain additional training in sterile compounding. NECC objected to these sanctions, but the Board reaffirmed this approach through an additional unanimous vote on November 23, 2004.

More than a year later, on January 10, 2006, NECC entered into a non-disciplinary consent agreement with the Board that was significantly weaker than the earlier version. The signed consent agreement stipulated a 1-year probation to be stayed with the condition that NECC hire an independent evaluator. The Board's staff identified Pharmaceutical Systems, Inc. (PSI) as the evaluator to conduct inspections of NECC's compounding practices.

Despite interviews with Board and staff members involved with these decisions and a thorough review of the limited records retained from this period, troubling questions remain about what influenced the more lenient consent agreement resolution, given NECC's track record. I will not be satisfied until we know the full story behind this decision.

What we know now is that from January to April 2006, the independent evaluator PSI conducted an assessment of NECC's compliance with United States Pharmacopeia Standards, and oversaw development of policies and procedures. PSI also issued recommendations for process improvement and provided training for NECC staff. An April 7, 2006 report from PSI described NECC's compliance with the evaluation.

Our investigation has revealed that in late April 2006, some Board of Pharmacy and Health Professions Licensure staff, including the Board's executive director and legal counsel, learned that PSI executives were convicted of Federal crimes related to defrauding the FDA and selling unapproved sterilization equipment to hospitals. However, we have found no evidence to indicate that the executive director or staff attorney of the Board provided this crucial information to the Board. Nor did they see fit to send inspectors back to NECC in 2006 to determine if they were fulfilling the requirements of the corrective action plan.

In May 2006, the Board voted to affirm that NECC was in compliance with the terms of the consent agreement, thus accepting PSI's findings in overseeing NECC's compliance.

Consistent with Board policy at the time, which was to inspect pharmacies only upon a change in licensure status or upon receipt of a complaint, the next time a Board investigator returned to the pharmacy was 5 years later on May 24, 2011 to inspect NECC following its renovation and expansion. This inspection included a full review of the facility space, operations, sterility protocols, and compliance with United States Pharmacopeia among other factors. The inspector found no evidence to suggest that NECC was violating patient-specific prescription requirements, and no deficiencies were cited.

In March 2012, the Board received a complaint pertaining to an insufficiently potent eye anesthetic distributed by NECC. This complaint focused on the potency of the medication but did not reference sterility concerns. This investigation continues.

In July 2012, some of the same staff members who failed to inform the Board of the issues surrounding PSI received a report from the Colorado Board of Pharmacy documenting violations of Colorado and Massachusetts pharmacy laws. The information provided to the Board executive director and legal counsel by Colorado showed that NECC had distributed bulk shipments of drugs to many hospitals in that State between 2010 and 2012 without patient/specific prescriptions, in violation of NECC's Colorado and Massachusetts licenses. The Colorado Board of Pharmacy issued a cease and desist order to stop NECC from engaging in the unlawful distribution of prescription drugs in the State in April 2011. Colorado informed the FDA of the adverse action, and provided them with the report, supporting evidence, and copy of

the order. However, there is no record of Colorado providing similar notice to the Board or DPH.

Colorado contacted Board staff in July 2012 because NECC was violating the April 2011 cease and desist order by continuing to prepare and dispense bulk shipments without patient-specific prescriptions. However, after receiving the July report, both the executive director and legal counsel failed to order an investigation, inform the Board of the complaint, or take any other action on the Colorado complaint.

The first two lots of contaminated methylprednisolone acetate linked to the meningitis outbreak were prepared in May and June 2012. The Colorado report was received 2 weeks prior to the production and shipping of the third lot of contaminated vials, which were prepared in August. Though issues of contamination with NECC products were not included in the Colorado report, given NECC's history and the evidence from Colorado that the company was violating Massachusetts pharmacy regulations, prompt action was warranted.

The individuals responsible for this failure to act have been removed from their jobs. These steps are consistent with the swift and decisive actions of DPH since we became aware of the outbreak.

Late in the evening of September 24, the Tennessee Department of Health notified our Department about a cluster of six exceedingly rare fungal meningitis cases. All six cases shared common risk factors, including an epidural injection of a steroid prepared by NECC. The Massachusetts DPH secured a list of medical facilities in 23 States that had received shipments of the steroids from three suspect lots identified by the Centers for Disease Control and Prevention. A day later, we secured a recall of those three lots, totaling 17,676 vials, and began our on-site investigation at NECC.

On October 1, we were joined on-site at NECC by the FDA and commenced our joint investigation. Among a list of troubling findings, investigators observed visible black particulate matter in sealed vials that had been returned to NECC through the recall. Several batches of the drugs had been shipped by NECC prior to the completion of internal sterilization tests. Investigators also found evidence that NECC had been dispensing medication in bulk shipments rather than filling a patient-specific prescription for each dose dispensed.

We secured a surrender of NECC's license, shut down its operations and issued a total recall of NECC products.

Our aggressive investigation not only focused on NECC, but also companies with shared ownership. On October 10, we secured the voluntary suspension of operations of Ameridose, a Westborough, MA drug manufacturer also owned by Barry Cadden. This closure allowed for a full investigation by DPH and the FDA, and eventually led to a total recall of Ameridose products. Ameridose remains closed as the investigation continues.

The Board of Registration in Pharmacy moved to permanently revoke NECC's license, as well as the individual licenses of the three principal pharmacists who ran NECC so they may never practice pharmacy in Massachusetts again. The Board also issued a cease and desist order to all pharmacy staff at NECC to bar them from any compounding activities.

While taking these forceful and necessary actions, we have also reexamined our own approach to regulating this industry.

It is clear that the compounding pharmacy industry has changed drastically from the days of neighborhood businesses that served a local clientele. We recognized that our State regulations needed to be strengthened to address the realities of this industry, which has evolved over time, and again we took action.

On November 1, Massachusetts enacted a series of emergency regulations to bring greater scrutiny to the industry and ensure that we have the tools to prevent such a tragedy from happening again.

Our new regulations stem from the lessons learned from this tragedy and require sterile compounding pharmacies in Massachusetts to report volume and distribution figures to the State, for the first time. This will alert us to any pharmacy that is acting like a manufacturer by producing medication on an industrial scale, which requires an FDA license and the additional scrutiny and adherence to high manufacturing standards for safety and quality that FDA oversight requires. We are also requiring all licensed pharmacies to report to the State when they are the subject of investigations by any other States or the Federal Government. This will allow us to know when other entities have identified issues with pharmacies in Massachusetts, including other States that issue non-resident licenses to pharmacies in Massachusetts.

The Board of Pharmacy's prior approach to inspecting pharmacies when they first apply for a license, and then again only if they move or if there is a complaint,

though not out of line with the approach used by most States, is no longer sufficient to keep pace with the changing nature of the industry. Since the outbreak we have begun unannounced inspections of the State's 25 sterile compounding pharmacies to review how they function when they are not aware that an inspection is scheduled. Teams are in the process of conducting additional inspections as we speak.

Massachusetts sterile compounding pharmacies have also been required to attest under penalty of perjury that they are meeting all State laws and regulations.

To further strengthen our oversight over sterile compounding pharmacies, we need to explore changes to State law. We created a Special Commission, and named Christian Hartman, an expert in pharmacy practice and patient safety, as its chairman. The Commission will include members of the Massachusetts' Legislature and experts in pharmacy practice, regulatory affairs, and patient safety. We will look at best practices in other States, explore new ideas, and consider the interplay between State and Federal authority. The first meeting of the Commission is scheduled for this month and this body will report its findings to the Governor by December 31.

As we work to raise standards in Massachusetts, we urge Congress to act to strengthen Federal oversight. It is clear that the patchwork of disparate State regulations is not enough to keep the public safe.

Congressman Markey's leadership in putting forward legislation is laudable and would help fill what he has aptly called a "regulatory black hole" that exists between State and Federal oversight. Congressman Markey's report also shows that at least 34 States have had deaths or illnesses stemming from violations at compounding pharmacies nationwide before this current meningitis outbreak. We join Congressman Markey in supporting immediate Federal action.

As a pediatrician who has looked into the faces of children and families at their most vulnerable moments, I understand the faith and trust that patients place in our health care system. I would never have contemplated that a medicine I might prescribe to my patients could actually be the source of such harm. We must use these terrible events as an impetus to work together, as public health officials and legislators, to reaffirm the trust that has been broken by the circumstances surrounding this outbreak.

I pledge to you that Massachusetts will continue to do whatever we can, make any changes, and identify any areas of new law to make sure something like this never happens again. We intend to identify responsibility but also focus on reforms that will be effective and lasting.

As the victims and their families remain always in our thoughts, we accept the challenge of reform that lies ahead.

Thank you. I am happy to take your questions.

The CHAIRMAN. Thank you, Dr. Smith, and thank you all. We'll start a round of 5-minute questions.

I wanted to have Dr. Bell here today. I know you weren't at the hearing in the House yesterday. I thought it was extremely important for us and for the public to know just how important the intervention of CDC was in this. I'm going to read your concluding remarks which I read last night.

> "The outbreak demonstrates the essential role that public health plays in identifying and responding to infectious disease outbreaks, large or small. Our national public health capacity is disseminated to State and local responders who work on a daily basis to keep our country safe from infectious diseases, whether they are from naturally emerging threats such as a new influenza pandemic or from human made problems such as contaminated medicines. CDC will continue to work with State partners, national experts, frontline clinicians and others to respond to the critical public health needs related to this outbreak."

Again, I think the public needs to be aware that we have an infrastructure in this country with CDC, with our State departments of public health, with our field epidemiologists who instantaneously can intervene, track these threats down, keep our public safe. That's why I thought it was so important for CDC to be here today,

both to outline—and I know we have another witness from Tennessee who will be here. You mentioned this person, Dr. Kainer—to let the public know that things happen, and we're never going to be 100 percent safe, either from human-made problems or infectious diseases, as you mentioned, like influenza pandemics.

I think it's also important for us to know that the more we constrain the budgets of the Center for Disease Control and Prevention and the budgets of our public health entities around the United States, the more we put the public at risk. We have for too long treated public health as sort of a stepchild of healthcare in America, something that, well, we just don't have to pay attention to. It's to our detriment, and people die, and people get sick if we don't continue our support for public health in the United States.

Senator Mikulski and I worked very closely in the Affordable Care Act to make sure that we had a strong component of public health in that bill. I just hope that my colleagues and others who are watching the proceedings will, again, note what has happened to public health funding in America. I know this is not an Appropriations Committee meeting, but I wear two hats, and I'm sorry, but I'm going to wear that one here right now.

In fiscal year 2009, CDC funding was $6.239 billion. Got that? In 2009, $6.239 billion. In fiscal year 2012, it's down to $5.644 billion, and yet we have more emerging diseases. We have more people. We have people moving more rapidly around the country. We have people moving from this country to other countries, back and forth, through commerce, through travel. Yet we continue to turn a blind eye to the need for public health infrastructure in this country.

Dr. Bell, thank you, and I look forward to our witness from the State of Tennessee also and what they did to intercede in this.

Dr. Hamburg, when I see the history of this and I read the history of this and I see the two court cases, Fifth Circuit and Ninth Circuit—I'm not going to go into all that. You understand it. I have some sympathy for the FDA not knowing exactly what its role is going to be. But that's OK. That's the past. We have to do something now. And, of course, I'm going to look to Senator Roberts and others who have been more involved in this in the past for some guidance and direction.

Why don't we just have a demarcation line? If a compounding pharmacy makes anything that goes outside the State boundaries, that's FDA jurisdiction—anything. If it stays within a State, it can be State or it can be dual, depending. But anything that goes beyond State borders, that must be under FDA purview.

Dr. HAMBURG. That isn't the way the law is currently written. You're asking a larger question of why don't we do that. The problem is——

The CHAIRMAN. I know that's not the way the law is, but I'm saying why don't we do that?

Dr. HAMBURG. The problem is that there is not a clear distinction between what is a compounder and what is a manufacturer, either in law or in practice. The industry is evolving in ways that can be very, very important to the healthcare system and the needs of patients.

For example, it used to be in a hospital that the hospital pharmacy in the basement would make up intravenous bags with potassium chloride or other substances added in to be used on the floor. Because of volume and because of concerns about making sure that this is actually done under the best and most safe and most efficient circumstances, hospitals have started outsourcing some of those kinds of activities where they're repackaging a drug or a medical product, and that can have real benefits.

If we treat all of those individuals as manufacturers, we'll have to have them submit drug applications for every one of those products. They'll be subject to user fees. We could hold them to stronger standards of compliance to good manufacturing practice, et cetera, and that would really have benefits. I think the challenge is we have to think about how to address this.

The CHAIRMAN. Dr. Hamburg, I understand. I get all that. But, really, the essential thing is what is in the best interest of protecting the public health.

Dr. HAMBURG. I think——

The CHAIRMAN. That's the essential question.

Dr. HAMBURG. Yes.

The CHAIRMAN. Now, if some people can't protect the public health by making things in their basement, maybe they shouldn't be making things in their basement.

Dr. HAMBURG. I guess what I would really propose is that we have an antiquated system, trying to fit a square peg into a round hole. What we have proposed in terms of a tiered system, I think, could get at these issues in a very responsible way. Traditional compounding on a small scale would remain under the purview of the States.

Nontraditional compounding that gets us into this area would be addressed in a different way. For one thing, they'd have to register with us, so we'd know who they were and what they were making. We would have Federal standards that they could be held to, either enforced by the States or by the FDA. We would have to, in statute, through a combination of factors, define what puts you into this category; what kinds of products you're making, like sterile products; what volume of products; are you shipping interstate; other issues about shipping directly to the user or through a third party. We can do that together.

Then there's some products that clearly should only be under the purview of a full-fledged manufacturer and that simply should not be compounded because of the nature of those products, biologics and transdermal patches, extended release, and other things. Then copying an FDA-approved drug is also clearly not appropriate.

The CHAIRMAN. OK. Thank you. I'm over my time. I will hold for Senator Enzi when he returns.

Next I would recognize—oh, he's not coming back? Then I would yield to Senator Roberts or Senator Alexander. This is in terms of how people appear on the committee. Senator Roberts appeared——

Senator ROBERTS. It looks like I have appeared first.

Dr. Hamburg, your past interactions with NECC, the New England Compounding Center, prior to the current crisis, which spanned over 6 to 10 years, depending on how you look at it—we

were taking a look at your testimony before the House. Were you Dingellized over there or, did you get around all that?

Dr. HAMBURG. That's a term I'm not familiar with.

Senator ROBERTS. There are a lot of us that are very much familiar with it.

[Laughter.]

You said that NECC has repeatedly disputed FDA's jurisdiction over its facility. You cited a number of times during your interactions that NECC had done so. Isn't it also true that each time the NECC disputed the FDA authority, the FDA responded, reasserting its authority to regulate the NECC? Now, that culminated in the final communication between the FDA and the NECC in 2008 prior to the current crisis.

The FDA wrote to the NECC to outline in no less than four pages—and we don't need to get into reading the four pages, I hope—the numerous reasons why the FDA did have the authority to regulate and, furthermore, use its enforcement authorities with the NECC. I think that's correct.

Now, in fact, that letter went on to tell the NECC not only to clean up its act or there would be specific consequences, but also to confirm future inspections would occur to ensure the firm's compounding practices are consistent with the policies articulated in the compounding guidelines. If this is correct, then I think we need a yes or no answer from you. That didn't come in the House. One more time, did the FDA actually have the authority to regulate and engage in enforcement actions against the NECC? Can you give us a yes or no?

Dr. HAMBURG. I'll make you mad the same way I made Dingell mad in terms of it's not a yes or no question, per se. We have authority, but it's limited and——

Senator ROBERTS. I think you said it was a gray area. I don't want a gray area. I want a black or white answer. Do you have that authority? Did you have that authority?

Dr. HAMBURG. We have limited—we have authority, but it is limited and unclear and contested.

Senator ROBERTS. That's a hell of an authority. In May 2011, from the Colorado Board of Pharmacy, the FDA was informed of a cease and desist letter and related report accusing the NECC of illegal distribution of compounded drugs. FDA officials, including Bruce Ota, the signatory to the 2008 FDA letter I was referring to, to the NECC threatening enforcement for such conduct and asserting jurisdiction over NECC, was individually notified according to the May 2011 email that was introduced into the record.

The FDA then waited until July 2012, over a year, to suggest to Colorado they contact the Massachusetts Board of Pharmacy. I don't know how you can explain this, with over a year. The State of Massachusetts fired and suspended the individuals who ignored the Colorado complaint about the NECC. By the time the FDA suggested in July 2012 that Colorado contact the Massachusetts Board for action, the NECC had already compounded some of the drugs that led to this tragedy.

Indeed, if the FDA had acted in 2011, according to their letter, either to investigate or to notify Massachusetts of the NECC's continued violation, 30 lives could have been saved. Did the FDA take

any action against the FDA personnel who ignored this problem for over a year?

Dr. HAMBURG. Obviously, in the context of the situation, looking at that, questions are raised. When the communication came from Colorado, it was around an issue of NECC acting out of compliance with the Colorado Board of Pharmacy Registration and Licensure and the question of whether they were, in fact, registered with us as a manufacturer.

I wish, in retrospect, that we had alerted the Massachusetts Board of Pharmacy at that time. It's also important to underscore that that communication really was not about the kinds of sterility concerns and safety quality issues that underlie this ongoing outbreak.

Senator ROBERTS. OK. I appreciate that. My time is almost up. If you had inspected upon receipt of the Colorado complaint in the summer of 2011 and found the unsanitary conditions and the scale of production that existed at NECC, is it your position that you could not have shut the operation down despite a decade of evidence that NECC was a bad actor? That's the first part.

Last part: If that is the case, why do you assert the authority to cease, enjoin, or otherwise prosecute the recipients of your warning letters? Why in the hell send the warning letters if you can't act on them? That's just an empty threat. Why do we even have an FDA and why do you have a job if the FDA can't stop back-alley, large-scale drug manufacturing that it knows about and writes letters about?

Dr. HAMBURG. If we had gone in in 2011, as you had suggested, and found unsanitary conditions and contaminated product, we could have acted with the full force of FDA authority as we have acted in other cases of compounding failures that have resulted in contaminated products. However, in terms of our routine oversight responsibility of NECC, that does rest with the State board of pharmacy if they are behaving as a compounder.

Massachusetts was actually in that facility in 2011 and found that the conditions were satisfactory. It speaks to the fact that inspections are only one piece of what can make a difference. What we are really trying to seek is a legislative framework that would enable us to hold these kinds of large-scale, nontraditional compounders to a set of standards, proactively in a preventive way, rather than using authority——

Senator ROBERTS. That's what you want us to provide, a legislative framework to really define that you do have the authority to act on your own letters?

Dr. HAMBURG. At the present time, our authority, because it is limited and unclear and contested, really forces us into a position of being reactive rather than proactive. With drug manufacturers, we can require and hold them to a different set of standards in terms of compliance with good manufacturing practice and the requirement of preapproval review for safety, quality, and manufacturing controls.

Senator ROBERTS. Thank you. I'm done.

The CHAIRMAN. We've got to go around. Thank you.

Senator Mikulski.

STATEMENT OF SENATOR MIKULSKI

Senator MIKULSKI. Mr. Chairman, thank you very much for holding this hearing. I, too, wish to express my condolences to the families who have passed away—one in Maryland. Today, their Sun paper reports a constituent whose name I can use because it's already in a public domain—Mr. Gerald Cohen, 71, retiree, filling his free time with gardening, enjoying the company of his grandchildren, and being active in the community. Treated with steroids, he now is so sick from nausea, fever, and he eventually had a stroke. He told his wife, "I thought I was dying."

This is why we are here today, to look for the right regulation. Also, at the same time, regulation without resources is a hollow exercise, and then resources without a workforce—the fact that we have to recruit people in science and train them to enforce these also needs to be part of this discussion.

Mr. Chairman and colleagues, I hope this is the first of a series of hearings on not only regulatory reform but also on resource need and also on workforce need. I would hope today, too, we would look at not only what is not working but what did work. Obviously, Tennessee was really doing their public health job. Obviously, Colorado was really doing their job, because they sent an alert. So, we need to do those lessons learned.

In the area of regulation, I'm very interested in the black hole of when do we go from the traditional role of compounding—with Senator Roberts we all agree exists—to where they're now manufacturers. Even when they do do traditional compounding, when are they just sloppy, dilatory, or dangerous? How do we get to that? The other is then the resources that Senator Harkin talked about and referenced.

Dr. Hamburg, I'd like to come back to you. Do you feel that what you are suggesting with your two-tiered system would get us to the problem, or would you also think that there needs to be—that this would be a down payment on getting to this? As the market is evolving, market forces are evolving on compounding, and then our tendency in Congress is to be anti-regulatory, dump everything on the States, until there is a problem. Then we pound our chests and want the Federal Government to be involved.

We've got a lot of convergent forces, even within this institution. Do you think your framework would get us to this, or do you think also we need additional work, say, through a commission, as suggested by Senator Roberts, or through the Institute of Medicine to go for an even more deep dive in this?

Dr. HAMBURG. I think that the tiered approach that we are proposing would make an enormous difference. Right now, really, what is a compounder versus a manufacturer is very unclear. 503A was Congress' attempt to really clarify it, but it doesn't define compounding anywhere. It doesn't set an absolute limit on volume. It doesn't set an absolute prohibition on compounding in advance of getting a prescription.

Senator MIKULSKI. That's the methodology. What would be the outcome achieved?

Dr. HAMBURG. What would be the outcome achieved?

Senator MIKULSKI. In other words, if we go your way, yes.

Dr. HAMBURG. Oh, I think there would be many, many benefits. We would, No. 1, be able to really know what the landscape looks like, who's out there doing what. We would have a set of Federal standards that would be strong and really support quality. We would have authorities for adverse event reporting and an ability to have labels so people would know whether the product was compounded or not. We would clarify the issue around inspections so that when we went in, we'd be able to get access to the records that we need.

Senator MIKULSKI. OK. Thank you. I want to go to Dr. Bell and Dr. Smith for my next set of questions.

Dr. Bell, you referred consistently in your testimony about something called the Epidemic Intelligence Service, and then how also those people trained in that service are working in a variety of States, one of which was Tennessee that, again, did such a superb job.

Senator Alexander, we'd like to compliment the public health people in Tennessee.

Could you, then, talk about the role of CDC, not only in this, but this Epidemic Intelligence Service, and how it would be of use in terms of ultimately bio surveillance at the local level which acted so quickly, because we can't be in every place, everywhere, all the time? And it must go through the States.

Dr. BELL. Yes. Thank you, Senator. The Epidemic Intelligence Service is a training program that CDC has had in place for actually many decades. Many of us—and I hazard to say maybe most of us, even me with the gray hair—who have been at CDC for decades started our careers in CDC in the Epidemic Intelligence Service. There is a very, very large cohort of epidemiologists in the State and local health departments who also trained at CDC.

This is an extremely important resource that we have. There are other aspects——

Senator MIKULSKI. Just tell me what it does.

Dr. BELL. Basically, it's a training program, so——

Senator MIKULSKI. What do you train them to do?

Dr. BELL. We train them to do field epidemiology. We train them to investigate outbreaks. We train them in how to work with the laboratories. We train them in how public health works.

Senator MIKULSKI. Then they don't stay at CDC. Some do.

Dr. BELL. That's correct.

Senator MIKULSKI. Like the ones who were so pioneering in the work on early detection of Legionnaire's Disease and others. But then they go to States.

Dr. BELL. That's right.

Senator MIKULSKI. Then they work in State health departments or in a variety of other areas of the public health human infrastructure.

Dr. BELL. That's right. In fact, we have some Epidemic Intelligence Service officers that are assigned to State health departments during their training. For example, this outbreak is a good example of how this EIS program works.

Senator MIKULSKI. I have limited time, Dr. Bell.

Dr. BELL. OK. Just to say that we have done what we call Epi-Aids. These are, in outbreaks, assistants that we provide. In this

situation, we've sent EIS officers out five or six times to help quickly—including to Tennessee very early on in the outbreak—to help the State health departments quickly identify the problem.

Senator MIKULSKI. Now, tell me how much these people get paid, and what is their education?

Dr. BELL. I can't tell you how much they get paid. They generally——

Senator MIKULSKI. Are they GS–15s? Do they get paid $180,000 a year? Do they get paid $45,000 a year?

Dr. BELL. I think it depends on their level of training. They have to have an advanced degree. It could be a Ph.D., an M.D., or they could be a nurse with a master's degree. They could be a veterinarian. They could be a pharmacist. They have many different ways of entering CDC.

Senator MIKULSKI. Thank you. My time is up.

I would like to say to my colleague, Mr. Chairman, with your indulgence—to my colleague from Kansas, Senator Roberts—I would like, really, Mr. Chairman, to work with you to—we have the FDA recommendations. We have the Roberts Commission. I remember when you did that during the Affordable Care Act, and it was an impressive piece of work.

We're possibly going to IOM, the Institute of Medicine, where we have the appropriate regulation, where we don't over-regulate so we strangulate. But at the same time, we have to really move on it. While we're working to pass legislation, perhaps we need a process to get us to the right legislation and maybe a down payment on what we need to do, while we also look at the resources, which you identified, Mr. Chairman, and then these workforce needs, because if you have the right roles without the right people, you don't have anything.

Thank you, and I appreciate this hearing.

The CHAIRMAN. I want to reassure you, Senator Mikulski, and others on this committee that I have asked my staff to work with Senator Enzi's staff and other staff on this committee to get a good bipartisan process going, to work together to achieve exactly the end that you say. That is ongoing right now. I want to reassure you of that.

Senator Alexander.

STATEMENT OF SENATOR ALEXANDER

Senator ALEXANDER. Thanks, Mr. Chairman, for the hearing, and thanks to Senator Roberts for your leadership in the area. I certainly intend to work with Senator Harkin and Senator Roberts, Senator Mikulski and others.

I hope it's our first order of business to answer these questions, not just whose job was it to prevent this tragedy, but whose job will it be to make sure it doesn't happen again. That's our job here today. This has been a nightmare for Tennesseans, as it has been for any Americans affected. We've had 32—13 Tennesseans died, 81 Tennesseans are sick, and 1,000 more exposed.

All of us are shaken, because we live in this country where we have this miracle that we walk into one of our 60,000 drug stores or pharmacies or go to our doctor or our pain clinic, and we get medicine, and we don't think about it. We just assume it's safe.

And then to suddenly go home and find that you've got fungal meningitis and you may die or be permanently disabled is a nightmare, not just for the families involved, especially them, but for all of us. I want to do everything I can to help solve this problem.

Now, my experience as Governor, Mr. Chairman, was that whenever I gave a job to more than one person, sometimes it came back not done. When I put somebody on the flagpole, it was surprising to see how fixing that responsibility got it done. Let's start on what went right.

Obviously, we had incompetence in the Massachusetts State Board of Pharmacy. We had confusion at the FDA. We had a textbook case of A-plus excellence at the CDC, the Centers for Disease Control, and at the State of Tennessee and at Vanderbilt University, their partner, where they uncovered this within literally a matter of a couple of days, and in a few more days were able to alert everybody about it.

Dr. Bell, whose job is it? Is it your job at CDC, once something like this is discovered, to let the world know about it? Is that your job, or is that the job of a lot of different people?

Dr. BELL. Senator, that's our job.

Senator ALEXANDER. So it's clear. If that hadn't been done, that would have been your responsibility, really. Right?

Dr. BELL. Yes, sir. It's our responsibility to let the world know about public health threats.

Senator ALEXANDER. Right. And you did a superb job. Let's go back. What we're hearing from the FDA is they had some authority, but it was confusing. We hear from Massachusetts—or I'll just say it. Massachusetts—well, let me ask Dr. Smith.

Massachusetts clearly had the authority to regulate this compounding pharmacy. Correct?

Dr. SMITH. That's correct.

Senator ALEXANDER. So Massachusetts clearly had the authority. FDA had some authority, but there was confusion. It seems to me that one guiding principle in terms of working this out is let's stop this dual responsibility. Let's put either the State board of pharmacy on the flagpole or the FDA on the flagpole and get the other one out of it.

Now, I'll give you an example of that. In surface mining, we have a procedure in the State where the EPA and the Department of Interior may delegate to States the whole responsibility for regulating surface mining, or they may take it back. If something bad goes wrong, and Tennessee has that responsibility, it's Tennessee's fault. If Tennessee gave it back to the Federal Government, it's the Federal Government's fault. At least everybody knows who's on the flagpole for that.

Dr. Hamburg, would you be in favor of a system that would say to a State like Massachusetts that for 10 years has been incompetent in managing a compounding facility like this that it should take over completely compounding of pharmaceutical drugs?

Dr. HAMBURG. There are many different models that——

Senator ALEXANDER. No. I'm asking you would you be in favor of that model? Do you think it makes sense to have a model where you may delegate to Massachusetts or any State, for example, the

responsibilities for even sterile compounding or advanced compounding, or you may keep it?

Dr. HAMBURG. I think first——

Senator ALEXANDER. But if you kept it, it would be your responsibility, and you couldn't say you were confused about it.

Dr. HAMBURG. Traditional compounding on the local level should remain the responsibility of States. Nontraditional compounding——

Senator ALEXANDER. How much of that goes on? Traditional compounding, as I understand it, happens in most pharmacies. Is that right?

Dr. HAMBURG. Most pharmacies. We don't know the numbers because they don't register with us. There are many, many, many, many thousands.

Senator ALEXANDER. I've heard an estimate of 60,000 pharmacies or drug stores.

Dr. HAMBURG. Yes.

Senator ALEXANDER. That's traditional compounding. Advanced compounding—how much of that is there?

Dr. HAMBURG. We think there are about 7,500 pharmacies doing so-called advanced compounding, and then about 3,000 that are doing sterile processing. For those, we should have Federal standards that could be enforced by the State or by the Federal Government.

Senator ALEXANDER. Now, that's my problem. Why would you say "or by the Federal Government?" Then we have a hearing 5 years from now, and we have another tragedy, and the State says, "Well, we could have done it," and you say, "We could have done it." I'd like to see one of you say, "It was our job," just like Dr. Bell said.

Dr. HAMBURG. I guess I'm saying that's a subject for discussion. Some States are very strong in terms of their boards of pharmacy. Others are much weaker.

Senator ALEXANDER. How do we pick and choose? If I'm sitting down in Gainesboro, TN, I don't care which one it is. Whether it's the Federal Government or the State government, I want the one that's going to do the job. How do you decide that?

Dr. HAMBURG. I think it should be made explicit.

Senator ALEXANDER. So you agree that one person should have——

Dr. HAMBURG. I do think we should make it explicit.

Senator ALEXANDER. With advanced compounding, either Federal or State should be in charge. Is that right?

Dr. HAMBURG. For nontraditional compounding, there should be Federal standards that apply to certain types of practices that go to issues of quality and safety.

Senator ALEXANDER. Instead of telling somebody else what to do, why don't you just do it? Is it too big a job to put all here?

Dr. HAMBURG. It would certainly enormously expand what we do presently. We've got about 5,600 drug manufacturers and facilities that we routinely are responsible for oversight of and inspection.

Senator ALEXANDER. Let me answer my own question and say it's too big a job to put it all here. Would you then certify State

agencies as adequate to do sterile compounding or inadequate to do it? And what if they fail to do it?

Dr. HAMBURG. We need to discuss the range of options. That would certainly be one model that could work. I would like to see, though, some consistency of the standards applied, and I think a Federal standard would enable us to do that.

Senator ALEXANDER. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you. I just want to say we will have a second round here for this panel.

Senator Hagan.

STATEMENT OF SENATOR HAGAN

Senator HAGAN. Thank you, Mr. Chairman, and thank you and Senator Enzi for holding this hearing today and the continued bipartisan leadership of this committee. I also want to thank our witnesses for coming today, and I certainly have heartfelt and sympathy condolences to all of the families and individuals who have gotten sick from this, ultimately have died, and then all of the other people who are very worried about what might happen.

Confronting this outbreak is a pressing national concern. Over 451 people in 19 different States have developed fungal meningitis, and 32 people have died, one of those individuals in my State, a woman, Elwina Shaw. I actually had an opportunity to speak with her son and with her husband. She was 77 years old. She was very active. Her husband said you couldn't slow her down. She was busy from the morning until she went to bed—active. She loved to garden. She had back pain this summer. She went to get treated and had three steroid injection shots. When she ended up getting a migraine headache, she just didn't know what to do. She had nausea, and she really just wanted to stay in bed.

She went to the hospital, and they treated her for migraines. The headaches returned. Her family took her back, and that's when they diagnosed the fungal meningitis. She stayed at the hospital for over a month. She then had two strokes. She was left without speech and motor functions. Her son, Scott, said this was a horrible death, that she had black fungus that had to be swabbed from her mouth and suctioned, and it was just a horrible situation.

Fifty-two days after the injection to relieve her back pain, she passed away. What is really ironic about today—today would have been her 78th birthday. We all know that these are terrible situations, and we are committed to acting to be sure that something like this never happens again in the United States.

Dr. Hamburg, what I'm trying to understand is—if you can help give some thought and guidance to—why in February 2003 the FDA designated the New England Compounding Center a pharmacy rather than a manufacturer? The investigation then was into the same pharmacy compounding the same drug that led to the same result of fungal meningitis. I'm just wondering if this scenario could have been avoided 10 years ago.

Dr. HAMBURG. We were actively involved in the investigation beginning in 2002 of the contaminated products, working to get the products off the shelves and limit the damage. In terms of the ongoing efforts to remediate the sterility concerns, we were working with the State board of pharmacy. Together we determined that

NECC—as I understand it. I, of course, wasn't commissioner at the time, so I'm relying on records and what I've been told.

As I understand it—and I've looked at the notes, the minutes of the meeting—there was a determination that NECC was behaving as a compounding pharmacy, and under the existing legal framework, that is the appropriate authority of the State board of pharmacy for regulatory oversight. They took the lead and began a series of steps with NECC to address the sterility concerns. We tried to be as helpful as we could be. It was clearly determined that it was the Massachusetts Board of Pharmacy's responsibility to work with NECC on this important issue.

Senator HAGAN. We certainly see what has happened in the interim. That's why we're obviously holding this hearing and looking at the actions that we need to take. And I know we're on a short timeframe today.

Dr. Smith, I wanted to also thank you for coming. I know you recently became the interim commissioner. Given the integral role that the Massachusetts Board of Pharmacy has played in the current outbreak, I want you to shed some light on its failure to properly discipline the New England Compounding Center over a longer period of time.

Yesterday, when I spoke to Elwina Shaw's son, Scott, he said, "These companies are allowed to make drugs in the back end of a recycling facility?" The disturbing thing is—and this is his quote—is that "someone in this Nation thought that was a good idea. It makes no sense."

I have to ask you, Dr. Smith, why in April 2011 did the NECC receive a permit to expand its facilities when the FDA later found out that its building was 100 feet from the mattress and plastics recycling plant, and that black particulate matter near the HVAC system was contaminating sealed vials of the steroid now causing this current meningitis outbreak? When the Board granted that request, did it know that the same family that owns NECC also owns that recycling plant? Any comments?

Dr. SMITH. Certainly. When the board of pharmacy did the on-site inspection that you're referring to, it was in the situation of NECC requesting an expansion or a change in its physical plant. The inspector at the time did the on-site inspection, looked at about 10 or 12 different areas, including sterility, quality assurance, staff training, among a number of others. At that time, the inspector's report, which I know we've shared with this committee, indicated that there were no issues.

Now, it is not a specific aspect of the report to look at the broader outside environment and the siting of the facility. However, going forward, that is certainly something that we can look at.

Senator HAGAN. But in the FDA report, it did show that this black particulate matter was close by and, obviously, could have tainted some of the medicine.

Dr. SMITH. There were a number of substandard practices that NECC had, including the interior contamination that you're discussing, as well as a disregard for their own policies and procedures regarding sterility, and, obviously, their disregard of Massachusetts pharmacy law.

Senator HAGAN. Obviously, there are many issues that we have to determine, and I appreciate you holding this hearing. Thank you.

The CHAIRMAN. Thank you, Senator Hagan. As I said, we'll have an extra round for Senators to followup on.

Senator Blumenthal.

STATEMENT OF SENATOR BLUMENTHAL

Senator BLUMENTHAL. Thank you, Mr. Chairman. I want to join in my thanks to you and Senator Enzi for holding this hearing as I suggested and urged that you do in the wake of this tragedy and express my sympathy to the families and individuals who have been affected by it, and also my respect for Commissioner Hamburg and the excellent institution that you lead.

Unfortunately, having reviewed many of these documents, having spoken to experts in the field, having reviewed the history here, the conclusion is inescapable that this tragedy could and should have been prevented by more effective enforcement of existing laws. NECC was a known risk to both Federal and State regulators, but both failed to take any dispositive and effective action to stop this kind of tragedy, action that could have been taken against both NECC and Ameridose. In effect, they were disasters waiting to happen. In fact, they waited to happen for about a decade.

Going through the history, I understand your view that the FDA's authority was, as you have said—and I think you've used this formulaic expression a number of times—contested, limited, and unclear. But so is a lot of Federal authority and State authority, and it's used effectively to prevent wrongdoing and law breaking by companies like NECC that cannot only imperil the health of people but actually kill them, as this company did through its contaminated product.

I think that a lot of the questioning that you're seeing here reflects a skepticism on the part of Congress and the public about whether the FDA will use this enhanced authority more effectively than it has used the authority that it has had to date. I think that the assurance that the FDA now has to give is that it will be vigorous and zealous in using new authority, if it's given that authority, and I think that that is a challenge for the agency at this point.

It's a challenge for the Federal Government and certainly for State authorities as well. We don't have jurisdiction over them. I would suggest to you that the jurisdictional question ought to be resolved very simply and starkly. If a company manufactures drugs, you regulate them now, do you not?

Dr. HAMBURG. Drug manufacturers we regulate, yes.

Senator BLUMENTHAL. Correct. In other words, if a company produces pharmaceutical drugs without a specific patient prescription, they are regulated by the Federal Government. That ought to be the rule.

Dr. HAMBURG. As I understand it, that is not currently, in fact, in the law.

Senator BLUMENTHAL. It certainly was the intent of Congress. Those decisions that so swayed the FDA to avoid asserting its authority and jurisdiction were also unclear, limited, and contested.

An enforcer knows, in that situation, the only way to protect the public is to use what authority he or she has.

Dr. HAMBURG. Yes.

Senator BLUMENTHAL. In this instance, whether it's in 2004, the inspection report that involved the FDA; 2006, where a warning letter was issued and NECC never responded until 2007 and then the FDA never got back to them until 2008, the FDA failed to use its existing authority. I'm suggesting to you that the jurisdiction ought to be asserted as widely and effectively as possible and that there be no ambiguity in the law as there is now.

To the extent you use a multi-tiered, complicated, differentiated approach, you will embark on the same kind of perilous voyage that you have in the past.

Dr. HAMBURG. If I can make two quick points, one is I completely agree with what you're saying. Frankly, I wasn't there, but I wish that the responses had been more timely, there had been better communication with the States, and that the outcome had been different. As far as using our existing authorities, during my tenure, we have tried to be proactive or aggressive in responding to problems that come before us.

There have been a series of incidents where we've had problems with contaminated products for intraocular injection or problems with other compounded products, and we have moved in quickly, as soon as we heard about the cases, done the inspections, gotten the companies to recall the products. In some cases—in most of the cases, in fact, they've stopped compounding sterile products.

In one instance that was actually a veterinary case that occurred right before I became commissioner, we decided to go after the compounding pharmacy after 21 horses were killed because of super potent medication that they were provided with by a compounding pharmacy. We lost in court. Later, we had a problem with that same compounding pharmacy for an important human medical product, and there was serious injury as a result. We went back in, we recalled the product, we got them to stop practices, and they're not compounding now.

We have tried to use the authority that we have, but it is reactive. What I would like would be to have a system in place that was statutorily defined, that would assign roles and responsibilities, that would define standards of quality practice, that would help us to prevent problems from happening in the first place. Just looking at the map in terms of how the statute governing our oversight of compounding pharmacies currently exists, it applies in some parts of the country and it doesn't in others, and there's a big gray area. That can't be good for anyone.

What I'm saying is that—as Senator Roberts said, this is certainly the most tragic of the events that we've seen. For more than a decade, there have been problems in this area, and there will be more problems unless we really work together, to make sure that we have the overriding, legal authorities that are strong and clear and explicit. I just think we can do better.

Senator BLUMENTHAL. I agree.

And I apologize, Mr. Chairman, because my time has long expired.

Overriding is the key word, overriding local authorities that may be reluctant to enforce. Your job—and it is uniquely and always the job of the Federal Government to establish standards that protect the public health and safety where there is a national impact, and, clearly, there is a national impact here. When a drug compounding pharmacy—whatever terminology you want to use, traditional, non-traditional, big, small—if they manufacture a drug, if they make it without a specific individual prescription, that's manufacturing. You do that now. Why not for these as well?

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you very much, Senator Blumenthal.

I will, for the record, say that the first phone call I received after this outbreak occurred was from Senator Blumenthal, urging us and urging this committee to really engage in this. Based on that, we got our committee staff involved in it immediately.

I thank you for your diligence and being on top of this, Senator Blumenthal.

Senator BLUMENTHAL. Thank you, Mr. Chairman.

The CHAIRMAN. Senator Bennet.

STATEMENT OF SENATOR BENNET

Senator BENNET. Thank you, Mr. Chairman. I want to thank you and the Ranking Member for holding this hearing.

This may be the most needless tragedy that I've seen since I've been here. I've appreciated the work that we've done over the last several years with the FDA to try to figure out how we get a drug supply in this country that's actually safe. When I learned, for example, that 80 percent of the active ingredients in our pharmaceuticals are coming from abroad and there was no regulatory framework in place, we all went to work on that. We're working together, and I appreciate the chairman's leadership on a track-and-trace system in this country.

This was an event that never had to happen. I wanted to ask a question to Dr. Smith and Dr. Hamburg about this.

Thank you for being here today. Thank you all for your testimony.

Dr. Smith, as you relayed in your testimony, the Colorado Board of Pharmacy issued a cease and desist letter to the New England Compounding Center in both April 2011 and July 2012, twice, because NECC had continued to violate its licensure in both Colorado and Massachusetts by issuing numerous compounded drugs without patient-specific prescriptions. Both times, our board of pharmacy in Colorado also informed the Massachusetts Board of Pharmacy, as well as the local Denver office of the FDA.

I've been informed that upon receipt of both complaints, the executive director of the Massachusetts Board failed to assign an investigator to this complaint. After the outbreak, they also failed to alert the Massachusetts Department of Public Health officials of this complaint. Obviously, our State had the diligence and resources to be on the lookout for NECC products. Others, for some reason, did not and as a result this tragedy occurred all over the United States of America.

Dr. Smith, I want to know whether you felt the response to the Colorado Board of Pharmacy was adequate, and, if not, how you're going to fix this problem going forward.

And, Dr. Hamburg, I'd like to ask you about when a State board of pharmacy serves in its good actor role by issuing these cease and desist letters and notifies the Massachusetts Board and their local FDA office, how we can better prioritize this at the Federal level. As Senator Alexander said, how can we better strengthen the role of either the States or the Federal Government to take responsibility in a circumstance like this one?

Dr. Smith, I'll turn it to you.

Dr. SMITH. Thank you. Just to be clear, while the executive director of the Board of Pharmacy did receive notification from the Colorado Board of Pharmacy regarding the cease and desist that was done in April 2011, we have not found any record that there was any communication from the Colorado Board of Pharmacy at that time back in 2011.

Now, that said, clearly, when we got the information from the Colorado Board of Pharmacy in July——

Senator BENNET. I don't think I understood what you just said. Can you say that again?

Dr. SMITH. I'm sorry. If I heard you correctly, you indicated that back in 2011 and then again in 2012, the Colorado Board of Pharmacy communicated with the Massachusetts Board of Pharmacy. What I was saying is that we haven't found any record of a communication between Colorado and the Massachusetts Board until July 2012.

Now, that said, it is clear that it was a serious and, grave lapse of judgment executed by the board's executive director not to followup on what Colorado sent. The report was clear. It indicated with sufficient detail that NECC was clearly operating outside of Massachusetts pharmacy laws. The board certainly knew of NECC at that time and that it had issues. It should have been a red flag that was followed up on, and it wasn't. That clearly was, frankly, a mistake, a grave one, and we have acted since then to remove that employee.

Senator BENNET. It's one of those things where it doesn't even feel like it's a gray area. It feels to us like it was a flashing red light.

Dr. SMITH. I agree. What I can say is when I learned of this email exchange and the fact that we, the board of pharmacy, knew this in July 2012, I was astounded, baffled, and incredibly angry, because that was something we should have acted on.

Senator BENNET. Dr. Hamburg.

Dr. HAMBURG. In retrospect, clearly, I would have hoped that there would have been greater communication. That speaks to the issue that was raised about ensuring the appropriate level of back and forth communication and coordination with our State partners. When this email was received, it was in the context of a violation of State pharmacy registration and licensure. While there was an indication that they had sent product in the absence of specific patient prescriptions, there was no indication of a safety or quality concern that was being raised.

We really felt that it was—as I understand, those kinds of issues are often handled by the State board of pharmacy. We should have made sure that Massachusetts was aware, and it underscores the need for greatly enhanced communication and coordination. The other aspect speaks to the larger question that we really need to work on clarifying and trying to figure out how to address this issue of compounding versus manufacturing and when does one authority kick in and when does the other apply.

Senator BENNET. I think Senator Alexander hit the nail on the head. It's a question of clarity, of what the roles and responsibilities here really are, so that what, at the best, is bureaucratic in difference—and it's probably worse than that, I suspect—causes this kind of thing.

Mr. Chairman, thank you for holding this hearing.

The CHAIRMAN. Thank you, Senator Bennet.

I'm starting another round. I don't know how many Senators would like to have more questions. I just have a couple.

Dr. Hamburg, unlike NECC, where there is a lack of clarity, as we now know, regarding the FDA's authority, there's another company called Ameridose.

Dr. HAMBURG. Yes.

The CHAIRMAN. Owned by the same people, run by the same people, closely aligned. Ameridose is registered with the FDA. Although it is essentially a large-scale compounder—it is a large-scale compounder—it provides products to hundreds of hospitals all over the country. Now, given that the two companies are owned and run by the same people, that the FDA inspectors documented many similar serious problems at Ameridose and NECC, could the contamination just have easily occurred at Ameridose?

For example, in 2008, the regional inspector for the FDA recommended a warning letter to be issued to Ameridose, but it never got sent. I'm wondering whether what you're recommending is clarifying enough, that compounders like NECC are subject to FDA's authority. Is that really enough, if FDA already had the authority with regard to Ameridose?

Dr. HAMBURG. I can't speak to the specifics of Ameridose because it is the subject of an ongoing investigation. It speaks to this issue of these hybrids of compounding pharmacies that are merging more into manufacturing, and the fact that we do need a system that is clearer.

Registration with the FDA does not necessarily mean that they become a drug manufacturer. People register with us for all kinds of reasons and never even are putting anything into commerce. It means, we get their name and address. We never got listings of products that Ameridose was manufacturing, but we were engaged with them in terms of inspections and responding to some specific complaints and concerns.

I really think we need to work together to figure out how to address this evolving field of nontraditional compounding, because it can serve an important need. We need to be able to define it more and be able to really apply the right enforcement approaches.

The CHAIRMAN. I got it. I got that. I just keep saying that FDA had authority over Ameridose but didn't exercise that authority. This was clear.

Dr. HAMBURG. We were in Ameridose and took some actions related to some specific concerns in the facility. In 2010, I think it was, we were in there around an issue with a particular product, nicardipine, I believe.

The CHAIRMAN. I will take a look at that. I just know that in 2008——

Dr. HAMBURG. There was a—my colleague was just reminding me—a recall of a super potent——

The CHAIRMAN. Oh, this.

Dr. HAMBURG [continuing]. Fentanyl product.

The CHAIRMAN. That's very true. One was super potent and one was subpotent.

Dr. HAMBURG. There was one that was dramatically super potent and one that was less potent. We were in there and we did take actions. Again, I can't speak to all the specifics because we're still investigating, looking at that internally as to what we should have done, and it's part of a broader investigation.

The CHAIRMAN. OK. I got that. I'll look at Ameridose, but it seems to me that that was a clear cut case but we still weren't exercising authority.

I did have one more question, Dr. Smith. You know, I look at this history, and I'm pointing it out not just to point a finger at something and to chastise, but to understand that certain structures don't accomplish what people think they accomplish. In 2003, staff from the FDA met with the staff from the Massachusetts Board of Pharmacy to discuss,

> " . . . the potential for serious public health consequences if NECC's compounding practices, in particular, those relating to sterile products, are not improved."

That was in 2003.

At that meeting, consensus was reached that primary jurisdiction over NECC rested with the board, Massachusetts. The board then took 1 year to get a staff investigator to recommend censure, 6 months to actually issue a censure in the form of a draft consent decree, another whole year to arrive at a signed consent decree which then lasted for all of 6 months.

In all, it took the board 4 years from the time MPA-caused meningitis was reported to make NECC hire a third party to review and improve its sterility procedures. Again, this is not effective oversight.

Maybe I'm making a statement more than a question. I'm saying that sometimes we set up these structures, and we people them with the very people that they're supposed to be policing. In this case, I'm informed that a member of this board is a person who actually works for Ameridose, and his or her paycheck—I forget the gender of the person—their paycheck comes from the very company that they're supposed to be overseeing.

We see this happening in a lot of different States, where boards are set up but they're peopled with the very people that they're supposed to be policing. They're all friends. They go to the same clubs. They belong to the same this and the same that, and it's sort of a wink and a nod and a pat on the back. Sometimes that's why I think that for effective oversight, you need the expertise of people

in the field, but only to inform a board, not to actually exercise that kind of jurisdiction.

Dr. SMITH. You bring up very important points. The Board of Pharmacy in Massachusetts, by statute, indicates who is allowed to be on the board. Certainly, in evaluating as part of this review the function of the board, that's something that's also going to be taken up by the special commission that we've established to be able to really provide us with best practices about what kind of board makeup might be better suited or better balanced to be able to perform the oversight function that is so crucial.

If I could just say one other thing about the lapses that you clearly point out, I would say that the emergency regulations that we issued on November 1st include two that I think are very important. One would be to require pharmacies in Massachusetts who are the subject of State or Federal investigations to disclose that and make that known to us. That would get at the issue that Senator Bennet raised of Massachusetts not being aware at the time that Colorado issued a cease and desist letter. That would be very important.

The other would be that sterile compounding pharmacies must supply information about volume and distribution patterns to the State board. Right now, that is not required. And, clearly, compounding pharmacies like NECC who are acting in a *de facto* manufacturing-like role would then have to tell us information about how much they're making, what they're making, and where they're shipping it to.

That would allow us to identify pharmacies that are doing that kind of practice, as opposed to the neighborhood compounder that's doing that necessary compounding or the ones that are doing it within State law, which is one prescription at a time. NECC was violating that as well.

The CHAIRMAN. Got it. Thank you.

Senator Roberts.

Senator ROBERTS. Thank you, Mr. Chairman, and thank you for citing the timeframe that is most frustrating to this.

Doctor, you said that if there were sterility issues, you could have shut the manufacturer down. I'm having a lot of trouble here with this. On 4/16/2002, FDA report cited sterility issues and lack of accountability by NECC and Mr. Cadden as the former CEO or director, he took the Fifth over in the House yesterday, we asked him to appear and he did not.

I might add that this timeline was prepared by our staff, the committee staff, the chairman's staff. We asked for a timeline from you in regards to any actions that you have taken against any compounding manufacturer. We have yet to receive that, and I would hope that we could get it.

But this is 2002. Mr. Chairman, we go through 2002—a complaint, 2002 adverse event, FDA inspections, FDA 483. By the way, the 483 is like a 1099 in regards to your taxes. You don't want to get a 483. That says you're in trouble, and you've got to answer. I have the answer by the New England Compounding Center. Then I have the warning letter back.

I could go down all of the things that have happened here—investigation, complaint, board action, board action, inspection. We

go clear down here, another whole page of it—letter, board action, board consent, board compliance, compliance, other licensing, advisory letters, licensing. Finally, in 2006, a warning letter. Finally, we get something done.

Here's the warning letter. In the warning letter—and here, by the way, is the 483 that says you're in trouble—2002. Finally, after all of these things happen, in 2006, we have a warning letter. All right. What happens with a warning letter? And then New England Compounding Centers respond, and then you respond to them about the warning letter. So this is a warning letter after the response to the warning letter.

And you say,

> "Your firm must promptly correct the violations noted in December 4, 2006, warning letter and establish procedures to assure that such violations do not reoccur. Its failure to do so will result in enforcement action, including seizure of the firm's products and an injunction against the firm and its principals. In a future inspection, we will confirm the commitments that you made in your response and verify that your firm's compounding practices are consistent with the policy articulated,"

et cetera, et cetera, et cetera.

That's a pretty strong response. What happened? Actually, nothing happened until 2008, and then there was another 483. I'm not going to go through all that. We went through that. That involved Colorado. And, finally, we get to a 483 of October 26, 2012, finding multiple sources of contamination and air sampling showing contaminants 6 months prior to compounding of MPA. This has been going on since 2002. This is amazing.

These are steroid injections, by the way, that when there was an inspection, there were vials of the product and there was black fungus in the vials. Who on earth would put an injection needle into a vial with black fungus to put into somebody's knee or shoulder or whatever? Maybe that's the problem I have with my knees. Hell, I don't know.

I'm just saying it took all that time, Mr. Chairman, and nobody did anything. You say that you have the ability to shut down somebody if they have sterility issues. I have two or three 483s here and letters back and forth from 2002 until now, and the thing that shut the manufacturer down was 30 lives. Holy mackerel.

Senator Alexander is precisely correct. I don't know whether you need a State flagpole or a Federal flagpole or something to get us off the dime here so that if somebody gets into this kind of a problem and you feel that you have to issue a 483, you can shut them down. Now, what am I missing here, other than I'm over time and I made a long statement and I didn't allow you to have a question. By the way, thank you for wearing purple because Kansas State is rated No. 1 in the BCS poll.

Dr. HAMBURG. Obviously, it's a very long answer and we're out of time. Just quickly, the 2002 contaminated product issues were responded to very swiftly in terms of going in and inspecting. We worked with the Massachusetts Board of Pharmacy. The products, in fact, were taken off the shelves. A decision was made, as we discussed earlier, that because this was a compounding pharmacy, it

was under the purview of the Massachusetts Board of Pharmacy who licenses and oversees the day-to-day operations.

They took on that responsibility of working with the company to resolve the sterility issues, including the consent decree in 2006, which turned out to have serious flaws, as Dr. Smith indicated. The belief was that the company had made progress, working with the Massachusetts Board of Pharmacy, to address the sterility issues.

The 2006 warning letter from the FDA actually concerned a completely different set of issues at the facility. It had to do with three specific products where we did have very real concerns with the practices at NECC. It didn't have to do with sterility failures. It had to do with basically copying FDA-approved drugs or making unapproved drugs. They were things that were taken seriously.

As I said earlier, I wish that we had been much prompter in the followup on that, and perhaps we should have been more aggressive. The response to those warning letters—and had we taken the legal action that you indicated that we were citing authority to take, it would have been on a set of issues involving these specific products, and it probably—maybe we would have been successful and it would have made a difference. Maybe we wouldn't have been.

I wasn't at the agency at the time. I know that there was a lot of internal debate about how to proceed. That's why it was slowed, because of the ambiguity in the law and the fact that there was ongoing litigation and differing opinions about the scope of our authority coming in. I think that doesn't fully answer your question, and I think we all wish that we had done more. It is complicated.

Senator ROBERTS. OK. I've gone over and it's my fault, not your fault—3 minutes. You're just saying basically that your statement was erroneous. You do not have the authority to shut people down if there's a sterility issue because you don't know whether it's State, whether it's Federal, or whether it's specific to this product or that product, and all of the laundry list of things that went on here with staff and everything else. Then you have a crisis on your hands, and that's what happened.

It's a pretty sad situation, Mr. Chairman.

Can we get your timeline?

Dr. HAMBURG. We will get you the timeline. We are still collecting information, going through documents. This did happen at a time when many of the people involved are no longer at the agency. We're working hard to respond to the ongoing public health crisis, and many of the same people that we need to pull the documents are involved in that.

We are very focused on it. We recognize the work that you need to do. We want to work with you, and we appreciate your patience.

The CHAIRMAN. Thank you, Senator Roberts.

Senator Blumenthal.

Senator BLUMENTHAL. Thank you, Mr. Chairman. I'd like to pursue, Mr. Chairman, your questions at the very outset here about the Ameridose matter, which, for me, in many respects, is more serious even than the NECC from a Federal enforcement standpoint.

I have reviewed all the documents, 483s, and inspection reports. Clearly, serious, egregious violations of basic standards were found

by your inspectors in 2008 and then again in 2010. Now, I take it that the recommendation was made for a warning letter to be issued. There is no evidence in the documents submitted to this committee that any warning letter was ever sent. Do you disagree?

Dr. HAMBURG. That is my understanding.

Senator BLUMENTHAL. There was no warning letter ever sent.

Dr. HAMBURG. No.

Senator BLUMENTHAL. Despite findings about the lack of potency in the drugs, the lack of proper sterility standards, the basic cleanliness, and other kinds of minimal standards in a company that is many times the size of NECC manufacturing hundreds of different kinds of products sent across the Nation, no warning letter was issued. Is that correct?

Dr. HAMBURG. The product was recalled, however. My understanding is no warning letter was sent.

Senator BLUMENTHAL. Why was no warning letter issued?

Dr. HAMBURG. We are looking into that. As I said, some of the specifics are part of an ongoing investigation internally and more broadly.

Senator BLUMENTHAL. There's no question in your mind, is there—because there wasn't in any of the inspectors who did these reports—that FDA had full and complete authority over Ameridose?

Dr. HAMBURG. As I said, it was something of a hybrid in terms of being a repackager-pharmacy. It wasn't a drug manufacturer, like Merck or Pfizer, but——

Senator BLUMENTHAL. You're telling the committee it was not a drug manufacturer?

Dr. HAMBURG. It was not a drug manufacturer in the sense of a drug manufacturer that we have the oversight of in terms of new products that undergo product review and approval before licensure, that are subject to all that that entails.

Senator BLUMENTHAL. Your inspector in the jurisdiction section of the report in 2010 said the firm currently repacks and manufactures prescription drug products which are FDA-regulated drug products.

Dr. HAMBURG. As I said at the outset, Ameridose is actually the subject of an ongoing investigation, and you understand what that entails. I have been asked not to try to characterize Ameridose at this time as we're looking into those very questions that you're asking.

Senator BLUMENTHAL. Let me ask you a broader question which looks to the future rather than the past. I want to reiterate that much of the documents and issues that have been brought to the committee relate to a time before you took over the position that you have now, and we're asking both you and Dr. Smith to answer questions about institutional performance well before your responsibility.

Looking to the future, if there is an NECC and an Ameridose continuing to operate out there, do you know who they are? In other words, if you had that authority today, do you know where you would go in terms of where the problems are, the future tragedies waiting to happen?

Dr. HAMBURG. We do not know the universe of compounding pharmacies that might fit into this category of activity because they are not required to register.

Senator BLUMENTHAL. Shouldn't you know?

Dr. HAMBURG. I do think that we should know, and I would like to see that as part of new legislation if we would do it.

Senator BLUMENTHAL. You can begin that task right now, can't you?

Dr. HAMBURG. We are beginning to reach out to our colleagues at the State level to learn more information. We are enhancing our activities around some of the large compounding facilities that we know about to really make sure that we have as much information about what they're doing and how they're doing it.

Senator BLUMENTHAL. Let me just suggest—and I don't mean to sound simplistic, because I know your task is resource challenged and we haven't really discussed the resource issue. I know it's one that is very much a challenge for the FDA at this point.

Dr. HAMBURG. Absolutely.

Senator BLUMENTHAL. The Congress really should be meeting its obligation to provide those resources that are necessary for the tasks that we're all implying you should have been carrying out.

I would suggest very respectfully that the FDA ought to make it a priority to scrutinize the 3,000 compounding pharmacies, the documents that are public—and most of these documents are public right now, as we've seen from the media. They're available to folks who want to go into the records to find them—and where are the next tragedies going to occur; who will cause them; what kind of standards are they failing to meet—so that when you're provided with that authority that is not as limited, unclear, and contested, as you say it is now, you can swoop down on them and shut them down or at least require that they correct the problems that exist.

Dr. HAMBURG. I really appreciate your observations, including the one on resources, because that is a huge challenge. We have enormous responsibilities for the protection of the public health across a huge domain of areas of activity. I hope that I can work with you to address the crazy quilt of regulatory oversight that we currently have, because that will enable us to act in a much more efficient and targeted way.

I also do think that the more we can be preventive, as you say, rather than reactive, using our authorities that are clearly in the law to address a contaminated product—but we don't want to have to wait until there's a contaminated product. We want to be able to make sure that these facilities are operating with the kind of preventive controls and standards of quality that the American people expect and deserve.

Senator BLUMENTHAL. I would just suggest that you be preventive with a capital P, and that you regard these renegade, outlier drug manufacturers as the threat to public health which, clearly, they are.

Dr. HAMBURG. Yes.

Senator BLUMENTHAL. Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Senator Blumenthal.

Senator Alexander.

Senator ALEXANDER. Mr. Chairman, I'd like to ask to place in the record statements from the Tennessee Department of Health, the Tennessee Board of Pharmacy, the Tennessee Hospital Association, the Tennessee Pharmacists Association, and the Tennessee Medical Association, all of which I asked for this hearing.

[The information referred to may be found in Additional Material.]

Senator ALEXANDER. As much as I would like to focus my time on whose fault it was, I think the families of those who were hurt in Tennessee would like me to find out how we can make sure this doesn't happen again. I'd like to pursue the line of questioning that Senator Blumenthal and I and others have asked about, for lack of a better word, the flagpole theory.

As I listen to this—and the reason I haven't asked Dr. Smith many questions is she said, and we know, that the Massachusetts State Board of Pharmacy had the clear authority to deal with this problem. They just were incompetent in dealing with it. And if anybody's going to be shut down, I think they should be shut down. That would be where I would go.

Now, as we move over to the FDA, thinking about looking ahead, I'm not sure—listening to the FDA's confusion and reading their record about this, I wouldn't trust the FDA more than I would trust the Tennessee Department of Public Health to keep our medicines safe. In fact, the evidence that we've heard already and that we're going to hear from the second panel is that an example of doing things well in part of this area came because of the alliance between Vanderbilt University and the Tennessee Department of Health.

It leads me back to this solution, Mr. Chairman, to how we fix accountability here. I'm trying to think through different ways we do things in the Federal Government. I'm thinking of our nuclear program. Admiral Rickover in the 1950s set up our nuclear submarines, and he had a very novel idea. He interviewed every single captain, and he told them their career depended upon whether or not there was ever an accident on the reactors on their submarines.

Since the 1950s, there's never been a death in connection with any activity on a nuclear submarine, and I'm pretty sure the reason is because if there's an accident on a nuclear submarine, that captain's career is basically over or seriously diminished. There's clear responsibility. It's the captain's responsibility.

I'd like to be able to come back to a testimony 6 months from now, after we've worked together to pass a law, and hear representatives of State boards of pharmacy say, "This is my responsibility, and this is what we're doing about it," and hear the FDA say, "This is our responsibility." I don't want to hear this joint responsibility that "they were supposed to do it, and we could have done it, but nobody did it."

Let me narrow it down a little bit. As I understand it, Senator Blumenthal was focusing in on manufacturing, and the estimate I have is that there are about 5,600 manufacturers of drugs. Is that about right?

Dr. HAMBURG. There are about 6,500 facilities that are manufacturing active pharmaceutical ingredients or drugs.

Senator ALEXANDER. You have the total responsibility for that. Right?

Dr. HAMBURG. We do provide ongoing oversight, yes.

Senator ALEXANDER. That's your job. That's not the Massachusetts Board of Pharmacy——

Dr. HAMBURG. Yes, absolutely.

Senator ALEXANDER. You're on the flagpole for them. And then you've said and others have said that the compounding actually goes on, traditional compounding, in thousands of pharmacies across the country, and we're not talking about that. That's under State boards of pharmacy.

What we're really talking about—and the estimates I have may or may not be right—is that there are about 7,500 pharmacies that specialize in advanced compounding services and about 3,000 in sterile compounding. It's somewhere within those facilities, where State boards of pharmacy have responsibility, and you have some responsibility. Is that right?

Dr. HAMBURG. Yes. That's the area that in our proposed framework we'd really like to focus on as needing clarification.

Senator ALEXANDER. Would you like to take over the responsibility, the total responsibility, for a certain number of those pharmacies?

Dr. HAMBURG. That might well be the best outcome.

Senator ALEXANDER. How many of those would that be? Is that a few hundred, or is that a few thousand, or do you know?

Dr. HAMBURG. We don't know, because at the present time, many of those facilities are not reporting information to us or are not registered with us. We need to understand—and those numbers are not our numbers because they don't——

Senator ALEXANDER. No, they're my numbers, and I'm not sure they're right. I'm just trying to get a rough idea. If you already have 6,500 manufacturers, if you were to take over several thousand more or several hundred more, it would make a difference. Maybe you don't have the capacity to do that.

Dr. HAMBURG. It would be a real challenge. Of course, for our other inspectional activities over drug manufacturers, we have user fees that help to support our budget. Senator Harkin well knows, as we just worked so hard——

Senator ALEXANDER. Right. I'm trying to get to a point. Would it be conceivable that there could be a system where you have the responsibility, but you're able to delegate that responsibility to some States that are willing to meet standards, and your job would be more like, say, the Nuclear Regulatory Commission? You'd go around and check and make sure that—it wouldn't be your job to regulate—you wouldn't regulate the facilities, but you would basically be regulating the States who took on that function in addition to their supervision of traditional pharmacies.

Dr. HAMBURG. That would be one model, and we could——

Senator ALEXANDER. Is that a possibility?

Dr. HAMBURG. Also lay out clear Federal standards for practice.

Senator ALEXANDER. Could that be done in a way that made it clear that while you were—what that might mean, for example, in a case like this, is that you would go to Massachusetts—you'd have the authority to go to Massachusetts and take away their authority

completely to deal with sterile manufacturing or sterile compounding because of incompetence or failure to meet Federal standards, under that model.

Dr. HAMBURG. That would be a possible model. It's well worth exploring all the different ways that we could improve the system and make sure that it is fully coordinated and provides a safety net to protect health.

Senator ALEXANDER. Mr. Chairman, as you can tell, my general drift here is that looking to the future, if the definition already is not for these advanced compounding units—if they're not already manufacturing—and Senator Blumenthal was suggesting they may already be—if they already are, then they're under the FDA.

If they're not, I would suggest we make it clear that either the Federal Government or the State government through a set of certification from the Federal Government be on the flagpole, have the full accountability and responsibility for doing it. If they fail to do it, they lose their opportunity to do that. That's one model that I would suggest.

The CHAIRMAN. Thank you very much, Senator Alexander. I would just say that as part of this ongoing effort, Senator Enzi and I and the committee will be sending a letter to each State board of pharmacy to learn more about their oversight practices in this area, including just how many large-scale sterile compounders are operating today and who they are. We don't know. We are preparing a letter, and I hope that I can get all of the signatures on both sides of the aisle here to send that letter out. It's being prepared by our staffs right now.

I will close this panel where I started with Dr. Bell. I talked about the need for public health and the funding. We've heard a lot about FDA and about the necessity for FDA to take more oversight responsibility here. Again, I remind you of what Dr. Hamburg just said. This comes down to resources.

We continually ask the Food and Drug Administration to do more and more and more. We ask them to do more in healthcare. We ask them to do more in food inspections, more for imports coming from overseas, and, to a certain point, the resources are going to have to be there. So, I hope that when appropriations time comes around—and we're looking at funding for both of these, both for CDC and for the FDA—that we can meet our obligations in making sure that they're adequately funded to carry out the responsibilities we keep asking them to do.

Thank you all very much.

Now we'll turn to our second panel. I guess we won't turn to our second panel. The second panel was Barry Cadden, the manager and co-owner of the New England Compounding Center. He declined our invitation. We decided not to issue a subpoena. He was subpoenaed by the House committee yesterday and showed up and continually took the Fifth Amendment. There was no reason to go through that charade here today with him.

On our third panel, we have—and I'll ask them to come up—David G. Miller, the executive vice president and CEO of the International Academy of Compounding Pharmacists, an association which represents individual pharmacists involved in the compounding industry.

Then we have Dr. Kasey Thompson, who serves as the vice president of the Office of Policy, Planning, and Communications at the American Society of Health-System Pharmacies, an organization which advises its members on the responsible use of compounded medications. Dr. Thompson has extensive knowledge regarding the safe use of compounded drugs, as he previously served as ASHP's director of the Center of Patient Safety and director of the Practice Standards and Quality Divisions.

Our third witness is one who has been referenced earlier, Dr. Marion Kainer. I will yield to my distinguished friend and Senator from Tennessee for purposes of introducing Dr. Kainer from Tennessee.

Senator ALEXANDER. Thank you, Mr. Chairman.

I'd like to welcome Dr. Marion Kainer. Our previous witness from the Centers for Disease Control mentioned her. She'll tell more about this, and we'll talk about it at the time. An astute clinician at Vanderbilt University, who has a partnership with the State of Tennessee where Dr. Kainer is director of Healthcare Associated Infections and Antimicrobial Resistance Program, reported something suspicious to Dr. Kainer. Within a matter of a few days, this report led to a recall of the material that was being spread around the United States from this New England facility, undoubtedly saving many lives and helping many others.

It was called by the executive director of the Association of State and Territorial Health Officials, who said this, Mr. Chairman:

> "By the time we learned this was a problem around the country, the information from Tennessee had already narrowed it down to what the problem was. It was a textbook case of how to do it right."

Dr. Kainer obtained her medical degree and master of public health in Melbourne. She's had a distinguished career in Australia and the United States, with over 20 years of experience in infection control. I compliment her for her astuteness, her leadership, and welcome her to the panel, and I thank the chairman for inviting her.

The CHAIRMAN. Thank you, Senator Alexander.

We welcome you all. All of your statements will be made a part of the record in their entirety. We'll proceed in reverse order of the introductions. We'll start with Dr. Kainer.

Dr. Kainer, I'm sure I speak for all the committee. You have our highest praise, and we thank you for your diligence—for being on top of this immediately and for doing exactly what needed to be done in getting it to the Center for Disease Control. I'll just echo what Senator Alexander said. Your timely action and professionalism undoubtedly saved many lives.

Thank you very much and please proceed. Welcome to the committee.

STATEMENT OF MARION KAINER, M.D., MPH, FRACP, DIRECTOR, HEALTHCARE ASSOCIATED INFECTIONS & ANTIMICROBIAL RESISTANCE PROGRAM, TENNESSEE DEPARTMENT OF HEALTH, NASHVILLE, TN

Dr. KAINER. Thank you. On behalf of the Tennessee Department of Health, I would like to thank Senator Alexander for the oppor-

tunity to comment on the fungal meningitis outbreak. I'm the director of the Healthcare Associated Infections and Antimicrobial Resistance Program.

In Tennessee, we now report 81 cases and 13 deaths. Our concerns and prayers for patients, families, and loved ones affected by this preventable tragedy are ongoing. There are many heartbreaking stories. Some have been reported in the media. Diana Reed's death devastated her family. Her husband has Lou Gehrig's Disease and Diana was her husband's arms, legs, and voice and kept his accounting business going.

Fungal meningitis is extremely rare. One of our greatest challenges was knowing just what we were dealing with as more and more patients fell ill. Even though we were looking for fungus, because the initial patient reported to us had been diagnosed with fungal meningitis, none of the diagnostic tests yielded confirmed results until October 3d, 15 days after we initiated our investigation of the first case. My written remarks include a detailed chronology.

I would like to direct your attention to some early lessons learned from this outbreak. First, compounding of medications must be performed safely. Patients and healthcare providers should expect safe and effective medications. Compounding pharmacies do provide a needed service. If compounded products are unavailable to meet the unique needs of some patients, providers may perform compounding or repackaging themselves at the bedside and may also put patients at risk.

Second, recent investments in public health infrastructure through cooperative agreements from the CDC have supported building public health capacity. This capacity was critical in identifying and responding to this outbreak, determining the cause resulting in product recall only 8 days after initial notification, saving lives and limiting the number of patients exposed.

Six members of our Healthcare Associated Infections or HAI team are funded through the Prevention and Public Health Fund Epidemiology and Laboratory Capacity grant and the Emerging Infections Program. In addition, the team has a CDC/CSTE fellow. I am the only person on the HAI team not funded by the CDC.

Our HAI team had the expertise to conduct on-site visits, to ask the right questions, create a database, and enter and analyze the data swiftly to determine the cause of the outbreak and those at highest risk of getting sick. We did an analysis to assess the potential impact if there had been a delay in the recall from NECC by 9 days. In Tennessee alone, we estimate by now, we would have seen an additional 59 cases and at least five additional deaths.

To prevent healthcare associated infections, our team has built close relationships with infection preventionists. These relationships are built on mutual trust and have been invaluable in promoting open communication. Surge capacity was provided by staff funded under the Epidemiology and Laboratory Capacity and the Public Health Emergency Preparedness grants.

These staff reviewed clinical information and helped track down over 1,000 exposed patients. Contact by phone or in person was made by local public health staff funded by the State of Tennessee. Outreach included frequent telephone calls and knocking on doors.

Our nurses tracked down one patient by contacting a tour operator in Yellowstone Park.

Third, this outbreak illustrates the tremendous importance of inter-facility communication when patients may seek medical services in multiple facilities for complications that arise from treatment at another facility. It also illustrates the critical importance of astute clinicians in alerting public health.

In conclusion, this has been a devastating outbreak for patients, their families and friends, healthcare providers and clinics. In Tennessee, we still have many patients hospitalized and suffering from complications and others who are exposed and frightened that they may become affected.

Sustained commitment to funding from CDC for emergency preparedness and reduction of healthcare associated infections has supported our productive relationships with partners and healthcare providers across the State. These preexisting relationships allowed us to respond quickly because we trusted each other. We all need to work together to do our best to prevent such a tragedy from occurring again and to ensure that we have a public health capacity to detect and rapidly respond to any future outbreaks.

Thank you for your time and attention.

[The prepared statement of Dr. Kainer follows:]

PREPARED STATEMENT OF MARION KAINER, M.D., MPH, FRACP

SUMMARY

Communication and coordination among healthcare providers and public health in Tennessee was unusually strong thanks to major Federal grants to the State that have supported tracking and improving rates of hospital-acquired infections. Years of close collaboration between public health staff in the federally funded healthcare associated infection program and hospital-based infection preventionists in the State resulted in relationships and mutual trust that permitted easy collaboration during the investigation and response to this crisis.

Despite this close relationship, cracking this investigation was difficult because of the significant technical challenges in definitively diagnosing fungal meningitis. We had to take actions days in advance of being able to confirm that we were definitely dealing with a fungus. With CDC's help, we have been able to diagnose people much more easily since the early days of the outbreak. A timeline of the major events in this investigation is provided in the attached written testimony.

Recent investments in public health infrastructure through cooperative agreements from the CDC have built public health capacity at the TDH. This capacity was invaluable in identifying and responding to the outbreak, determining the cause resulting in product recall only 8 days after initial notification, saving lives and limiting the number of patients administered the contaminated injections. In Tennessee, if the recall from NECC had been delayed by 9 days, we estimate that at this time we would have seen an additional 59 cases and at least 5 additional deaths. If treatment guidance from CDC had been delayed, the number of deaths would be even higher. Of the 33 Tennessee patients who sought medical care before October 3, 9 (27.3 percent) died. Of the 48 patients who sought medical care on, or after October 3, when the first CDC treatment guidance was issued, four (8.3 percent) died.

Six members of the Healthcare Associated Infections (HAI) team are funded through the Prevention and Public Health Fund Epidemiology and Laboratory Capacity Cooperative agreement and the Emerging Infections Program. In addition, the team has a CDC/Council of State and Territorial Epidemiologists (CSTE) fellow. The only person not funded by CDC is the director of the HAI program, Dr. Kainer. The team had the expertise to ask the right questions, conduct on-site visits, create relevant standardized investigation forms, create a data base, enter and analyze the data swiftly to determine the cause of the outbreak and those at highest risk of getting sick. Surge capacity was provided by staff funded under the Epidemiology and Laboratory Capacity (ELC) grant and the Public Health Emergency Preparedness

(PHEP) cooperative agreements as well as an additional CDC/CSTE fellow and an Epidemic Intelligence Service (EIS) officer assigned to Tennessee. State-funded public health nurses in the field were mobilized to contact hard to reach patients, going door to door when necessary, and maintaining regular phone and in person contact with patients for weeks.

This has been a devastating outbreak for patients, their families and friends, healthcare providers and clinics. In Tennessee we still have many patients hospitalized and suffering from complications and others who are exposed and frightened that they may become infected. Sustained commitment to funding for emergency preparedness and reduction of healthcare associated infections through cooperative agreements from the CDC has supported our productive relationships with our partners and healthcare providers across the State. These pre-existing relationships allowed us to respond quickly because we trusted each other. We all need to work together to do our best to prevent such a tragedy from occurring again and to ensure that we have the public health capacity to detect and rapidly respond to any future outbreaks.

On behalf of the Tennessee Department of Health, I would like to thank Senator Alexander for the opportunity to comment on the recent fungal meningitis outbreak. I hope to provide some insights from this tragic outbreak to the Health, Education, Labor, and Pensions (HELP) Committee which I hope will assist the committee to gain an understanding of potential opportunities to prevent and respond to such devastating outbreaks in the future.

As of November 13, Tennessee reported 81 cases and 13 deaths. Behind each one of these numbers is a lot of suffering of the patients affected, their loved ones and the communities in which they participated. One example: The death of Diana Reed who, according to her brother, was her husband's arms, legs and voice, has been devastating. Her husband has Lou Gehrig's Disease and Diana was instrumental in keeping his accounting business going and in helping her husband get in and out of bed, the shower and his wheelchair. The family is trying to figure out how they will carry on and enable her husband the ability to maintain his dignity and to keep his work without her; they shared their story with the *New York Times*.

Fungal meningitis is extremely rare. One of our great challenges was knowing just what we were dealing with as more and more patients fell ill. Even though we were looking for a fungus because the initial patient reported to us had been diagnosed with a fungal meningitis, none of the diagnostic tests yielded confirmed results until October 3, 15 days after we initiated our investigation of the first case.

Below is an outline of the timeline of major events of this outbreak and the role of the Tennessee Department of Health in this investigation. I will also discuss lessons learned in the context of this investigation.

Timeline of Major Events

Date	Major events	Case count as known at that time
Day 1: Tuesday, Sept. 18	Dr. Marion Kainer, Director of the Tennessee Department of Health (TDH) Healthcare Associated Infections and Antimicrobial Resistance Program, receives an email sent by Dr. April Pettit, Infectious Diseases Physician, Vanderbilt University Medical Center (VUMC) about a patient with meningitis caused by a fungus, **Aspergillus fumigatus**, who had a recent epidural injection at a pain clinic. Dr. Kainer and Dr Pettit discuss the case ..... Dr. Kainer speaks with Ms. Candace Smith, infection preventionist (IP) at St Thomas Hospital (STH), which is organizationally affiliated with the St Thomas Outpatient Neurosurgical Center (STONC) where the patient received the injection. Dr. Kainer requests details of the procedure, states that the infection is a sentinel event of concern, which deserves a careful investigation and requests that Ms. Smith commence an inspection of the pain clinic (e.g., evidence of any construction, water damage) and to inquire about any potential additional cases.	1 case of Aspergillus meningitis

Timeline of Major Events—Continued

Date	Major events	Case count as known at that time
Day 3: Thursday, Sept 20	IP from STH contacts Dr. Kainer and confirms that index case had an epidural steroid injection (ESI) at STONC; provides details of the procedure. Because the facility manager of STONC is on vacation, the IP at STH continues to help in the investigation. Dr. Kainer contacts Dr. Perz at the Division of Healthcare Quality Promotion (DHQP), Centers for Disease Control and Prevention (CDC) to ask whether any cases of Aspergillus meningitis had been reported to CDC from any other ambulatory surgery centers (ASC) or pain clinics. Fungal meningitis is rare, but is not required to be reported to the CDC. Even without any requirement, clinicians or States often contact CDC about unusual infections; however, no one had recently contacted the Mycotics Branch at CDC to report any cases of Aspergillus meningitis. STH reports two additional patients with meningitis with high levels of white blood cells but no known cause. Both had undergone ESIs at STONC. Diagnoses were complicated because the patients appeared to be getting better and the cause of their meningitis was unknown. Dr. Kainer worked with clinicians to request exhaustive diagnostic tests. They also had ESI performed by same anesthesiologist at STONC. The preservative-free methylprednisolone acetate used in their ESIs was obtained from New England Compounding Center (NECC). Arrange for one on Dr Kainer's staff to visit STONC the next morning, with the IP and the ID physician from STH.. ***On this day, STONC closes voluntarily, sequesters supplies and orders new supplies from other distributors***.	1 case of Aspergillus meningitis 2 cases of meningitis, unknown cause, both seeming to be improving No national reports of Aspergillus meningitis
Day 4: Friday, Sept 21	Visit to STONC by TDH staff for a careful review of all procedures and the physical environment: no evidence observed of environmental conditions that would have led to fungal contamination of procedures. TDH contacts CDC and describes findings of site visit. TDH asks CDC to help with laboratory testing of patients with meningitis of unknown cause (because fungus is very hard to diagnose) and also for testing of environmental samples from the clinic, if needed. Another patient with meningitis and stroke with a history of ESI at STONC is identified, while VUMC also reports yet another patient who had a stroke and had an epidural injection, but at the time it was not clear where the ESI was done (it was confirmed as STONC on Day 7). TDH sent out a Health Alert using our TN Health Alert Network (THAN), asking clinicians to look for and report any cases of meningitis following epidural injection to the TDH. At this time, the leading suspected causes of meningitis were the contrast media and methylprednisolone acetate (MPA) from NECC because both were used in each patient (and are commonly given together for an ESI). Other less likely possibilities included local anesthetic, local skin preparation and needles used for the injection.	1 case of Aspergillus meningitis 2 cases of meningitis of unknown cause 1 case of stroke and meningitis, unknown cause 1 case of stroke, no spinal tap was done
Day 6: Sunday, Sept 23	IP at STH contacts Dr. Kainer about one new patient and one patient re-admitted with meningitis; both had ESI at STONC.	

Timeline of Major Events—Continued

Date	Major events	Case count as known at that time
Day 7: Monday, Sept 24	Facility manager from STONC has returned from vacation and provides additional information on the facility practices. TDH staff arrange to begin collecting data on patients to try to find out what distinguishes the case patients from those who did not get sick. TDH and CDC communicating closely. Dr. Kainer contacts State epidemiologist at Massachusetts Department of Health, Dr. Al DeMaria, to request a conference call with TDH, CDC, MA staff and NECC to obtain distribution list of clinics that got MPA from NECC in order to look for other cases of meningitis among patients who received ESI with MPA compounded by NECC.	1 case Aspergillus meningitis 4 cases of meningitis unknown cause 1 case of stroke, but no spinal tap done
Day 8: Tuesday, Sept 25	2 new cases of meningitis reported to TDH. Both had ESI using MPA from NECC at STONC; however, one of the patients did not receive the suspected contrast and the procedure was done by a different anesthesiologist. Conference call with TDH, CDC, Massachusetts Department of Health and Board of Registration in Pharmacy (MABRP) and NECC. NECC stated no adverse events reported, no new suppliers of ingredients or changes in procedures. TDH described severity of cases and that preservative free MPA was leading hypothesis. TDH requested distribution list and verified that voluntary recall procedures were in place. TDH staff begin collecting all the medical information needed to conduct their epidemiologic studies. STONC starts contacting potentially exposed patients ..... A new patient who had an ESI at STONC was admitted to STH with numbness and bowel/bladder control problems, but no headache or fever. Her spinal tap shows signs of meningitis of unknown cause, but with a much lower white blood cell count than the other cases of meningitis.	1 case Aspergillus meningitis 6 cases of meningitis unknown cause 1 case of stroke, but no spinal tap done 1 case of other neurologic problems and abnormal spinal tap (unknown cause)
Day 9: Wednesday, Sept. 26	**NECC issues voluntary recall for three lots of preservative free MPA and provides distribution list of consignees to MABORP and FDA**. TDH and CDC draft an Epi-X Alert (national emergency alert system for public health professionals) to report cases of meningitis related to epidural injections. TDH continues to followup on patients who received ESI at STONC to look for any other unusual illnesses or complications. CDC helps TDH by making available a medical doctor with expertise in treating fungus to assist TN clinicians in caring for patients.	
Day 10: Thursday, Sept. 27	TDH staff complete first round of epidemiologic studies; preliminary findings supports that MPA is a likely source.. TDH asks STONC to contact all patients who had procedures since July 30. Analysis of the NECC distribution list shows two other clinics in TN received MPA. These clinics are contacted and all MPA is sequestered. Both clinics cease performing ESIs. The first clear evidence that the meningitis cause is not related to the STONC clinic: North Carolina (NC) reports a patient with meningitis exposed to MPA from NECC.	

Timeline of Major Events—Continued

Date	Major events	Case count as known at that time
Day 11: Friday, Sept. 28	It is still not absolutely clear that the MPA from NECC is the only possible source of contamination: the NC case patient had also received lidocaine and povidone iodine from the same manufacturers used by STONC. The lidocaine was the same lot number. CDC notifies all State Health Departments of situation and urges them to contact clinics who do ESIs to ask them to contact and check on the health of recipients of MPA using a script prepared by CDC. They ask that this be done immediately, not waiting until after the weekend. CDC issues another national Epi-X alert indicating that this now is a multistate outbreak and requesting reports of meningitis, other neurological infections, and stroke. TDH sends its own alert through THAN to clinicians and hospitals in TN to look for and report meningitis, stroke and focal infections in patients who have had epidural injections. Still, all diagnostic tests on these cases remain negative. The only patient with a confirmed diagnosis remains the first case patient reported. This highlights the difficulty of diagnosing a fungal infection, even when one is looking very hard to find it. TDH continues to work on epidemiologic studies to learn more about these patients, despite not yet having a confirmed diagnosis. TDH requests assistance from CDC to abstract clinical data from patient records (help arrives on Day 14).	
Day 13: Sunday, Sept 30	TDH and STONC staff continue to abstract data on patients who had procedures since July 1.	
Day 14: Monday, Oct 1	TDH holds its first press conference and initiates a daily scheduled press briefing. TDH partners with the State Poison Control Center to assist in responding to questions from the general public. Other TN clinics continue to contact patients exposed to MPA from NECC. CDC and TDH staff work on gathering patient data to continue studies. TDH participates on call with expert fungal clinical panel convened by CDC, discuss need for CDC to provide interim suggestions/advice to clinicians on diagnosis and treatment.	11 cases, 2 deaths
Day 15: Wednesday, Oct 3 ...	CDC issues interim guidance on diagnostics and clinical management using input from an expert fungal clinical panel convened by CDC. **For the first time since the initial report, a tissue biopsy from a case patient shows a fungus.** However, the fungus looks different than Aspergillus. More tests must be done to identify it. TDH issues another alert through THAN to clinicians to help them identify, diagnose and treat ill persons exposed to MPA from NECC. TDH analysis of STONC patients suggests that one particular lot of the three NECC MPA lots present at STONC is the most likely to make patients sick: Lot 06292012.	18 cases, 2 deaths

Timeline of Major Events—Continued

Date	Major events	Case count as known at that time
Day 16: Thursday, Oct 4	A final identification of the fungus causing illness is still not made, but a specimen from another patient who died shows a fungus that is not Aspergillus. **FDA announces fungus was seen on microscopic examination of an unopened vial of MPA from Lot 08102012.** This now is very strong evidence that MPA is the cause of the outbreak. TDH alerts TN healthcare facilities using THAN to cease use of all medications and products from NECC.	
Day 17: Friday, Oct 5	TDH opens State health operations center to assist in case tracking, active surveillance (contacting, reaching out to all persons who received MPA from NECC at any of the three Tennessee clinics—a total of 1,009 persons). Mobilize regional health operations centers and use public health nurses to contact hard to reach patients, going door to door when necessary. Public health nurses maintained regular phone and in person contact with affected patients for weeks, changing messaging as required to adjust to a fluid and constantly changing scientific understanding and related patient needs. The CDC has another meeting of its expert fungal panel	29 cases, 3 deaths
Day 18: Saturday, Oct 6	NECC announces voluntary recall of all NECC products .. FDA issues Medwatch alert asking providers to stop using any NECC products.	29 cases, 3 deaths
Day 24: Friday, Oct 12	MMWR (CDC publication) is published on clinical presentation of cases.	50 cases, 6 deaths
Day 26: Sunday, Oct 14	FDA call with States and CDC on concerns about sterility of any product from NECC.	53 cases, 6 deaths
Day 27: Monday, Oct 15	FDA issues Medwatch alert ..... TDH works with the Tennessee Hospital Association (THA), the TN medical association (TMA), the ambulatory surgery center association and the TN pharmacist association to assist in alerting hospitals, providers and clinics to identify and notify patients who received NECC products.	53 cases, 6 deaths
Day 29: Wednesday, Oct 17	TDH identifies that patients who received older vials are much more likely to get sick. Questions begin about whether or not to test these patients even if they are not sick, if testing might prevent serious illness such as stroke.	61 cases, 8 deaths
Day 30: Thursday, Oct 18	TDH works with CDC experts to develop a mathematical model used for decision analysis by CDC about what to do for high risk patients. **For the first time, CDC and FDA confirm presence of *Exserohilum rostratum* in unopened vials from Lot 0810210@51**. This is now definitive evidence that contaminated MPA is the cause of the outbreak.	63 cases, 8 deaths
Day 35: Tuesday, Oct 23	MA Board of Registration in Pharmacy issues report of initial preliminary findings.	70 cases, 9 deaths
Day 38: Friday, Oct 26	FDA releases copy of FDA form **483**. All 50 vials of MPA tested showed contamination (likely fungal).	74 cases, 10 deaths
Day 48: Tuesday, Nov 6	The New England Journal of Medicine publishes an article written by TDH and CDC investigators on this outbreak: ***http://www.nejm.org/doi/full/10.1056/NEJMoa1212972***.	78 cases, 13 deaths
Day 51: Friday, Nov 9	TDH invited to provide testimony to the Senate HELP committee. TDH requests on-site assistance again from CDC to describe later complications of fungal infection, such as epidural abscess, arachnoiditis and risk factors. Two EIS officers will arrive on-site on Nov 13.	81 cases, 13 deaths

LESSONS LEARNED

1. Compounding and/or repackaging of medications must be performed safely. Patients and healthcare providers should expect safe and effective medications. Compounding pharmacies provide a needed service. If compounded products are unavailable to meet the unique needs of some patients, providers may perform compounding or repackaging themselves at the bedside and may also put patients at risk.

2. Recent investments in public health infrastructure through cooperative agreements from the CDC have supported building public health capacity at the TDH. This capacity was invaluable in identifying and responding to the outbreak, determining the cause resulting in product recall only 8 days after initial notification saving lives and limiting the number of patients administered the contaminated injections. Specific examples are provided below:

a. Six members of the Healthcare Associated Infections (HAI) team are funded through the Prevention and Public Health Fund Epidemiology and Laboratory Capacity Cooperative agreement and the Emerging Infections Program. In addition, the team has a CDC/Council of State and Territorial Epidemiologists (CSTE) fellow. The only person not funded by CDC is the director of the HAI program, Dr. Kainer.
    i. The team had the expertise to ask the right questions, conduct on-site visits, create relevant standardized investigation forms, create a database, enter and analyze the data swiftly to determine the cause of the outbreak and those at highest risk of getting sick.
    ii. In Tennessee, if the recall had been delayed by 9 days, we estimate that at this time we would have seen an additional 59 cases and at least 5 additional deaths. If treatment guidance from CDC had been delayed, the number of deaths would be even higher.
    iii. To prevent healthcare associated infections, the team has built very close relationships with infection preventionists at hospitals, the Tennessee Hospital Association and is building relationships with the ambulatory surgery center community. These relationships are built on mutual trust and have been invaluable in promoting open communication.

b. Surge capacity was provided by staff funded under the Epidemiology and Laboratory Capacity (ELC) grant and the Public Health Emergency Preparedness (PHEP) cooperative agreements as well as an additional CDC/CSTE fellow and an Epidemic Intelligence Service (EIS) officer assigned to Tennessee.
    i. These staff-funded provided assistance in reviewing clinical information on suspect and confirmed cases, and in tracking down 1,009 exposed patients. Contact by phone or in person was made by local public health department staff, funded by the State of Tennessee, sometimes with assistance from law enforcement. Outreach included frequent telephone calls and door to door tracking, including home visits whenever necessary. Some exposed patients were living in or traveling in other States or were overseas when they developed symptoms.
    ii. The State Health Operations Center provided the necessary infrastructure to coordinate activities among the 170 public health staff in Tennessee.
    iii. The alert network (THAN) connecting TDH with clinicians and staff at hospitals was invaluable in rapidly getting information out.
    iv. We were able to use a database designed for tracking persons in shelters to track patients who were exposed.

3. Relationships with Federal partners were critical in the response to this outbreak.

a. CDC provided invaluable assistance throughout the outbreak including weeknights and weekends. Some examples include:
    i. Laboratory support: CDC developed a diagnostic test to assist in the outbreak investigation and provided laboratory support for confirming the identities of fungal isolates. The infectious diseases pathology branch has been providing valuable insights on how this fungus behaves and the type of damage it does to tissues. This has greatly assisted the clinicians on the fungal expert working group.
    ii. Clinical support: TDH was fortunate to have CDC Epidemic Intelligence Service Officers on-site to assist in clinical data abstraction. CDC regularly convenes the expert fungal panel to develop diagnostic

and management guidance that has been constantly updated with the latest clinical information. This has been very helpful to clinicians, many of whom have never treated fungal meningitis before, and this guidance without a doubt saved a lot of lives. Of the 33 Tennessee patients who sought medical care before October 3, 9 (27.3 percent) died. Of the 48 patients who sought medical care on, or after October 3, when the first CDC treatment guidance was issued, four (8.3 percent) died.

iii. Communications: CDC has provided relevant, up-to-date information on case counts, diagnostic and treatment guidance, case definitions, etc, . . . on their Web site, through EPI–X alerts and the Health Alert Network. They have hosted regular conference calls with State partners and other Federal partners to ensure accurate dissemination of information.

iv. Epidemiologic support: CDC has provided technical support (e.g., reviewing logistic regression models, running survival analyses) as well as coordinated the aggregation of data across multiple States to provide a complete national picture. Examples of critical information include distribution of incubation periods. CDC provided expertise in mathematical modeling to review whether guidance needed to be changed for asymptomatic patients at high risk of infection in order to prevent strokes or death.

v. Coordination: CDC has coordinated the national response with other States and the FDA.

vi. Funding through cooperative agreements—please see above note #2 on how these funds were used to build capacity at the TDH.

b. FDA provided valuable information on local inspection findings, as well as laboratory testing of products

i. The information provided by FDA was extremely helpful. It also would have been helpful if FDA had shared interim findings with TDH and other State health departments to allow them a better understanding of the extent of the problem at the compounding pharmacy. This type of information is very helpful as State health departments attempt to gauge the level of risk and consider surveillance strategies.

4. Relationships and Infrastructure

a. By focusing on emergency preparedness and on reducing healthcare associated infections, we have made much progress in enabling rapid communication between public health and hospitals; however challenges remain, especially with providers who do not work in hospitals (e.g., ambulatory surgery centers) and with medical specialists who are not traditional emergency response partners.

b. Use of electronic health records allowed tremendous savings in time in allowing us to monitor the clinical progress of patients and saved time and resources at the affected hospitals.

c. This outbreak illustrated the tremendous importance of inter-facility communication when patients may seek medical services in multiple facilities for complications that arise from treatment at another facility. Reporting to public health is critical, as Dr. Pettit's email illustrated.

d. Communication with exposed patients during periods of great uncertainty was very important. Public health played a vital role in finding exposed patients that were difficult to reach and when clinic staff were overwhelmed with the task at hand.

e. Communication with media: Frequent press-briefings allowed TDH to effectively communicate important public health messages in a dynamic and rapidly evolving outbreak while allowing staff to continue to do critical work.

CONCLUSION

This has been a devastating outbreak for patients, their families and friends, healthcare providers and clinics. In Tennessee we still have many patients hospitalized and suffering from complications and others who are exposed and frightened that they may become infected. Sustained commitment to funding for emergency preparedness and reduction of healthcare associated infections through cooperative agreements from the CDC has supported our productive relationships with our partners and healthcare providers across the State. These pre-existing relationships allowed us to respond quickly because we trusted each other. We all need to work together to do our best to prevent such a tragedy from occurring again and to ensure

that we have the public health capacity to detect and rapidly respond to any future outbreaks.

Thank you for your time and attention.

The CHAIRMAN. Thank you, Dr. Kainer.

Now we'll turn to you, Mr. Miller, for your statement.

STATEMENT OF DAVID G. MILLER, R.Ph., EXECUTIVE VICE PRESIDENT AND CEO, INTERNATIONAL ACADEMY OF COMPOUNDING PHARMACISTS, MISSOURI CITY, TX

Mr. MILLER. Thank you, Chairman Harkin. I also thank the members of the committee. My name is David Miller. I am the executive vice president and I am proud to serve also as the CEO of the International Academy of Compounding Pharmacists.

We are a professional association that represents pharmacists in a wide variety of practices, local community pharmacies, hospitals, nursing homes, hospice centers. Each one of those pharmacists and the pharmacy technicians and the student pharmacists that belong to our organization actually specialize in the development of customized medication solutions that patients need in order to meet their particular health needs.

The tragedy of New England Compounding Center, NECC, is quite simple to us as an organization. They were a pharmacy that was essentially hiding behind that license and, in reality, acting as an illegal drug manufacturer. Plain and simple, what NECC did was to violate the trust that every member of the public has, specifically, in their local pharmacist, but even more so tainted the reputation of pharmacists in every practice setting throughout the country and placed their trust in jeopardy.

We know that NECC now acted with impunity. They failed to adhere to the quality standards that our organization, our profession, and our government require of us at both the State and Federal level. We know also that NECC ignored State laws and Federal laws as they manufactured illegally and distributed bulk quantities of prescription drugs throughout the country.

We know what NECC did. We do not yet know fully the extent of what allowed them to do that. It is clear that the State Board of Pharmacy of Massachusetts failed to do their job. They failed to protect the citizens of Massachusetts and, most importantly, because other States relied upon their action, their inspections, and their follow-through, permitted NECC to continue its illegal activities and distribute tainted medications into States throughout the United States.

More importantly, we also know that the FDA knew, as we heard on the previous panel, of the problems with NECC. One of the things that we find particularly appalling, not only as a profession but, specifically, a professional association, is that there is no question whether or not the Food and Drug Administration had regulatory authority over this particular business. They were engaged in illegal manufacturing of drugs. The FDA is empowered through the FDCA and this Congress to stop illegal manufacturing.

I have heard for 2 days and have seen a map that actually was created by IACP being referred to by the agency as a crazy quilt. There are questionable overlaps in the regulation of compounding pharmacy. Let me reiterate that there is no question who has the

authority to immediately shut down an illegal prescription drug manufacturer. That rests with the FDA.

That is something that we find particularly disturbing, that the agency, who knew that NECC was distributing drugs without patient-specific prescriptions throughout the United States, did nothing to stop them.

Last, one of the things that we have to ask ourselves as a healthcare system is what prompted clinicians, hospitals, facilities throughout the United States to obtain medications from a pharmacy. We know in this particular case of methylprednisolone acetate, the medication at issue, and others that NECC produced was a product that was manufactured and available in the marketplace.

What prompted, what allowed, and what permitted physicians, hospitals, et cetera, to purchase from an illegal manufacturer? As one of the members from the State of Tennessee asked me when this first issue came to light, why did a hospital in Tennessee buy medicine from a pharmacy outside of Boston? Why did they not turn to a local accredited sterile compounding pharmacy? Why did they do that?

That's a question, Mr. Chairman and members of the committee, we don't yet know. There's much we don't know. What I can tell you is this, as an organization representing and comprised of pharmacists and pharmacy technicians, we are absolutely committed to making sure this never happens again. No compounding pharmacist should be able to hide behind their license as a pharmacy or a pharmacist when, in reality, their actions are illegal drug manufacturing. We have to stop that.

I thank the committee, and I look forward to working with you as we attempt to solve this problem as expeditiously as possible.

Thank you, sir.

[The prepared statement of Mr. Miller follows:]

PREPARED STATEMENT OF DAVID G. MILLER, R.PH.

SUMMARY*

IACP Vice President of Government Affairs Sarah Dodge said,

> "IACP appreciates the opportunity to provide input as the U.S. Senate HELP Committee seeks to better understand current Federal and State oversight of pharmacy compounding and explore the possibilities for a legislative solution to the tragedy surrounding New England Compounding Center (NECC) business practices."
>
> "We believe we share similar goals: an understanding of how this tragedy happened, what can be done to prevent it from ever happening again, and ultimately how do we assure that compounding pharmacists are able to practice their professional expertise without overly burdensome regulations which inhibit quality patient care."

The State and Federal regulatory scheme for pharmacy compounding is complex—IACP members have valuable experience and technical understanding of the laws that govern our industry. IACP stands ready to help legislators and regulators to assist in conducting a thorough and complete assessment of State and Federal laws governing the practice of pharmacy. We believe this assessment must also examine how regulators exercise their jurisdiction and discretion in enforcement. IACP strongly believes that, in Massachusetts as well as other States, many laws and regulations exist that—if they had been followed and compliance had been enforced—would have severely mitigated the potential for the tragic meningitis infections and the needless deaths that have occurred.

*The Summary was provided by the International Academy of Compounding Pharmacists, of which, David G. Miller, R.Ph., is Executive Vice President and CEO.

The apparent and tragic results of NECC's alleged behavior undermine the fundamental principal of pharmacists' practice—preserve patient health by doing no harm. We are determined to help find the gaps in the practice, regulatory, and enforcement system which permitted this problem to happen and produce real solutions to prevent it from occurring in the future. Our profession stands ready to work with leaders from across the Federal and State governments to make sure that what happened at NECC never happens again.

Not only does Massachusetts have State sterility requirements and United States Pharmacopeia (USP) Standard compliance requirements, but it retains the right to pull a pharmacy's license, if that pharmacy is practicing outside the scope of its licensing requirements.

By all current indications, the operations of NECC were clearly outside of the scope of their own and other States' licensure requirements and their license should have been pulled long ago. The Massachusetts Board of Pharmacy had the authority to do so. The FDA also had the authority to do so once they identified NECC as engaging in the illegal manufacturing and distribution of a prescription drug.

At a minimum, knowing what they did, both the State and the FDA should have worked together to force the pharmacy to register as a manufacturer and to comply with Current Good Manufacturing Practice Guidelines (cGMP). Unfortunately, NECC showed a blatant disregard for existing rules and regulations (no matter what the law was or might have been, their behavior suggests that they would not have followed it).

Additionally, and still to be answered by both regulatory agencies, is this fundamental question: If both the State and the FDA knew of problems at NECC—and we know that they did, based on publicly disclosed documents—why did they fail to followup or take action? New regulations or new laws are meaningless if the regulatory agencies charged with upholding them simply turn a blind eye to problems and fail to do their job.

IACP supports the following State actions, at a minimum, to help mitigate further problems with sterility and other potential patient hazards:

- All Boards of Pharmacy must be adequately funded by State legislatures in a manner sufficient to hire trained/educated pharmacists to conduct regular inspections of all pharmacies. Too many Boards have been "de-funded" by legislatures that have funneled revenue from the Boards into the States' general funds leaving administrative gaps;
- Board inspectors conducting compounding pharmacy inspections in both community and institution settings must receive training in both the State regulations pertaining to compounding as well as the practice itself;
- All States must adopt mandatory compliance with USP <795> and <797> standards. Only 17 currently mandate that in their laws. All pharmacies providing compounding services—regardless of practice setting—*must* be held accountable to those standards;
- State Boards must "police" themselves and provide the necessary assurances to other State Boards which depend upon them for conducting inspections for non-resident pharmacies in a regular and consistent manner. Massachusetts's Board obviously failed to execute its responsibilities both to its citizens as well as patients in other States in which NECC was licensed by not conducting regular inspections.

IACP looks forward to the opportunity to testify before the Senate HELP Committee on November 15, 2012 to further address these critical issues.

The International Academy of Compounding Pharmacists (IACP) appreciates the opportunity to provide input to the Senate HELP Committee as the committee and legislators seek to better understand current Federal and State oversight of pharmacy compounding and explore the possibilities for a legislative solution to the tragedy surrounding New England Compounding Center (NECC) business practices.

IACP is an international, professional association established in 1991 to protect, promote and advance the art and science of pharmacy compounding. IACP provides support to more than 2,700 members through programs and services including reimbursement/third-party advocacy, government representation, regulatory analysis, public relations support, referral services and a fellowship program. IACP also represents more than 164,000 patient and practitioner advocates as part of our P2C2 grassroots network.

IACP members are individuals; IACP does not represent or advocate on behalf of specific pharmacies, businesses or companies. Compounding pharmacists work directly with prescribers including physicians, nurse practitioners and veterinarians to create customized medication solutions for patients and animals whose health

care needs cannot be met by standardized medications manufactured by the pharmaceutical industry.

IACP believes we share similar goals: an understanding of how this tragedy could happen, and how to ensure the safest possible practice of compounding in the future.

The State and Federal regulatory scheme for pharmacy compounding is complex—IACP members have valuable experience and technical understanding of the laws that govern our industry. IACP stands ready to help legislators and regulators to assist you in conducting a thorough and complete assessment of State and Federal laws governing the practice of pharmacy. We believe this assessment should also examine how regulators exercise their jurisdiction and discretion in enforcement.

The apparent and tragic results of NECC's alleged behavior undermine the fundamentals of pharmacy, which include doing no harm. We are determined to help find the problem and solve it. Our profession stands ready to work with you and leaders from across the Federal and State governments to make sure that what happened at NECC never happens again.

IACP strongly believes that, in Massachusetts and other States, laws and regulations currently exist that—if they had been followed and compliance had been enforced—would have severely mitigated the potential for the tragic meningitis infections that have occurred. Not only does Massachusetts have State sterility requirements and United States Pharmacopeia (USP) Standard compliance requirements, but it retains the right to pull a pharmacy's license, if that pharmacy is practicing outside the scope of its licensing requirements.

By all current indications, the operations of NECC were clearly outside of the scope of the State's licensure requirements and their license should have been pulled long ago. The State and the FDA should have worked together to force the pharmacy to register as a manufacturer, but also to comply with Current Good Manufacturing Practice Guidelines (CGMP). Unfortunately, NECC showed a blatant disregard for existing rules and regulations (no matter what the law was, their behavior indicates that they would not have followed it).

Millions of Americans have unique health needs that off-the-shelf prescription medicines cannot meet. For them, customized medicines—prescribed or ordered by licensed prescribers and mixed safely by trained, licensed compounding pharmacists—are the only way to better health.

By definition, compounded medicines are different than commercial pharmaceuticals; they are prepared at the direction of licensed prescribers to meet patients' individual needs that are not met by manufactured pharmaceuticals. As a result, Federal requirements designed for large-scale manufacture of uniformly dosed drugs do not apply to compounding pharmacies.

Many patients depend on compounded medicines, including children, those with allergies, cancer patients, children with autism, senior citizens, menopausal women, hospice patients and those who rely upon discontinued drugs. For patients who are unable to take medications orally or as injections—the traditional dosage forms for manufactured drugs—compounding pharmacists can create alternate methods of delivery, like ointments, solutions or suppositories, to fit their unique health needs.

Many, if not most, of the lifesaving intravenous drugs given in hospitals and clinics are compounded. Because hospital patients are often on multiple medications, compounding them into one treatment saves the hospital personnel time and the patient multiple injections or administrations.

Additionally, compounded medications are often used by veterinarians and pet owners for the care of their pets. Animals come in all shapes and sizes, so one-size-fits-all pharmaceuticals do not always meet their needs. In many cases, a compounded medication may be necessary for a non-food animal to be satisfactorily treated.

In 2003, IACP established a 501(c)(3) foundation to further research and educational initiatives for the advancement of pharmacy compounding. Its mission is to conduct and publish research studies, establish academic alliances, and institute educational programs and issue forums.

In 2004, IACP joined a coalition of eight leading pharmacy professional and regulatory organizations in the creation of a voluntary accreditation program for pharmacy compounding. The Pharmacy Compounding Accreditation Board (PCAB) helps to assure quality and raise awareness of the profession.

To begin with, IACP would support the following State actions to help mitigate further problems with sterility and other potential patient hazards:

- All Boards of Pharmacy must be adequately funded by State legislatures in a manner sufficient to hire trained/educated pharmacists to conduct regular inspections of all pharmacies. Too many Boards have been "de-funded" by legislatures that

have funneled revenue from the Boards into the States' general funds leaving administrative gaps;

• Board inspectors conducting compounding pharmacy inspections in both community and institutional settings must receive training in both the State regulations pertaining to compounding as well as the practice itself;

• All States must adopt mandatory compliance with USP <795> AND <797> standards. Only 17 currently have that on their books; and State Boards must "police" themselves and provide the necessary assurances to other State Boards which depend upon them for conducting inspections for non-resident pharmacies in a regular and consistent manner.

Massachusetts's Board obviously failed to execute its responsibilities both to its citizens as well as patients in other States in which NECC was licensed by not conducting regular inspections.

Many States address specific compounding standards either through existing State laws and regulations and/or through the State's adoption of USP standards for compounding pharmacy practices. IACP has submitted this information to the committee as part of its responses to committee questions issued to stakeholders prior to this hearing.

Uncertainty about the application of section 503A does not affect oversight of pharmacy compounding. As mentioned, the States do address compounding, specifically, and provide appropriate governing compounding standards. Moreover, some States already (and all should) require mandatory compliance with USP <795> AND <797> standards. To reiterate, IACP supports adoption of mandatory compliance with USP 795/595 by all States.

From the Federal standpoint, the FDCA's existing inspection provision, section 704, allows FDA oversight when a pharmacy is not operating in conformity with governing State laws, or akin to a drug manufacturer. FDCA section 704 contains two very important components:

1. Pursuant to the first sentence of section 704(a), FDA is permitted to inspect "all pertinent equipment, finished and unfinished materials, containers, and labeling therein" of any pharmacy. FDA can glean the information it needs to determine whether a pharmacy is engaged in manufacturing through its inspection of these items.

2. FDA gains enhanced inspection authority to inspect a pharmacy that is operating as if it were a manufacturer. This authority exists whenever a pharmacy:

(a) is not operating in conformity with State laws regulating the practice of pharmacy;

(b) is not regularly engaged in dispensing prescription drugs upon the prescriptions of licensed practitioners; and

(c) is compounding drugs for sale other than in the regular course of its business at retail. See section 704(a)(2)(A).

Notably, the enhanced authority granted to FDA under these circumstances is the same inspection authority FDA possesses with regard to drug manufacturers. Thus, existing FDCA section 704 allows FDA to inspect a noncompliant pharmacy such as NECC as a manufacturer, subjecting it to inspection for "all things therein (including records, files, papers, processes, controls, and facilities) bearing on whether prescription drugs . . . which are adulterated or misbranded within the meaning of [the FDCA] . . . have been or are being manufactured, processed, packed, transported, or held in any such place, or otherwise bearing on violation of [the FDCA]. (Section 704(a) (sentence three).

IACP strongly believes that the States have laws and regulations in place that regulate the professional practice of pharmacy, and they have for hundreds of years. State laws, for example, govern anticipatory compounding (appropriately based on a history between the pharmacy and the physician or patient to ensure adequate supply) and beyond-use dates for drugs, both of which necessarily limit how much of a drug may be compounded in advance.

Anticipatory compounding is also a required component of most States' laws to ensure timely patient access to drugs and thereby prevent wait-time and/or unavailability that may be harmful to the patient's health. States similarly regulate such things as standards for active pharmaceutical ingredients (APIs) used in compounding; ability to compound commercial copies; and percentage of compounded preparations that may be shipped out of State, i.e., many of the things existing section 503A simply attempts to reiterate.

Notably, when a pharmacy operates outside the scope of its State laws and regulations governing the professional practice of pharmacy, that pharmacy subjects itself to FDA inspection and oversight, and full FDCA application to the same extent as a drug manufacturer. NECC serves as a prime example of a pharmacy that

both breached State pharmacy regulatory laws and that should have been held accountable as a manufacturer by FDA. Such a non-State law compliant pharmacy no longer operates within the professional practice of pharmacy, which has always been effectively and traditionally regulated by the States through statutes and regulations developed over the course of more than a century.

IACP believes that, since the practice of pharmacy (much like the practice of medicine, veterinary medicine, nursing, etc.) is already regulated at the State level, the majority of policy and oversight is best if implemented/addressed/enforced at the licensure level. States have the ability to remove a pharmacy's license if that pharmacy is not operating within its licensure requirements.

States also already have in place levels of licensure, depending on the function and scope of practice. The Federal Government has clear oversight and jurisdiction if that pharmacy is acting as a manufacturer. Should a pharmacy be acting in a manufacturing fashion, they should be licensed as a manufacturer and subject to CGMP, as are all other manufacturers.

Again, IACP believes that all States must adopt mandatory compliance with USP <795> AND <797> standards. Only 17 States currently have adopted USP standards.

With regard to "manufacturing," IACP has long maintained and continues to maintain, that volume, percentage of sales, use of "commercial" equipment, or interstate sales should not be the determining factor in what constitutes a manufacturing practice. A pharmacy that focuses much of its practice upon compounding gains even greater experience with the activity, and thus has heightened expertise and experience that benefit, rather than harm, recipient patients. By analogy, an experienced heart surgeon is far more preferable than a surgeon who performs heart surgery only sporadically. IACP thus believes that rather than indicators such as volume, percentage of sales, interstate shipment, etc., it is the *activity* of the pharmacy with regard to what they do with medicines they dispense that must be scrutinized to determine whether or not they are engaged in manufacturing.

IACP strongly believes that the current statutory definition of manufacturing (as it reads in the Controlled Substances Act) (CSA) sufficiently defines, and distinguishes manufacturing from the practice of pharmacy compounding (see citation) Notably, the CSA definition dovetails nicely with existing FDCA section 704, as described above. Both hinge on the status of "pharmacy" or, conversely, "manufacturer," of whether the company preparing the drug operates in conformity with applicable State laws governing the practice of pharmacy and as an incident to dispensing such drug in the course of professional pharmacy practice.

Should Congress believe it is appropriate, it may be helpful to reiterate (mirror) the CSA definition in the Federal Food, Drug and Cosmetic Act (FDCA) as an appropriate standard for distinguishing between drug manufacturing and the medical practice of pharmacy compounding. Such inclusion also promotes uniformity between the two Federal acts. The CSA, (21 U.S.C. Sec. 802 (112–90) TITLE 21—FOOD AND DRUGS, SUBCHAPTER I—CONTROL AND ENFORCEMENT Part A (15) states:

> "(15) The term "manufacture" means the production, preparation, propagation, compounding, or processing of a drug or other substance, either directly or indirectly or by extraction from substances of natural origin, or independently by means of chemical synthesis or by a combination of extraction and chemical synthesis, and includes any packaging or repackaging of such substance or labeling or relabeling of its container; except that such term does not include the preparation, compounding, packaging, or labeling of a drug or other substance in conformity with applicable State or local law by a practitioner as an incident to his administration or dispensing of such drug or substance in the course of his professional practice. The term "manufacturer" means a person who manufactures a drug or other substance."

Additionally, the CSA States the following in terms of differentiating between interstate and intrastate commerce (21 USC Sec. 801 (112–90), TITLE 21—FOOD AND DRUGS. SUBCHAPTER I—CONTROL AND ENFORCEMENT Part A (5):

> "(5) Controlled substances manufactured and distributed intrastate cannot be differentiated from controlled substances manufactured and distributed interstate. Thus, it is not feasible to distinguish, in terms of controls, between controlled substances manufactured and distributed interstate and controlled substances manufactured and distributed intrastate."

Any changes to the statutory definitions of "manufacture" in either the CSA or the FDCA, or any changes to related regulations and/or agency policies, should be consistent as they apply to compounding pharmacies. For example, under either the FDCA or the CSA, a pharmacist should, with a prescription from a licensed physi-

cian, be able to compound patient-specific medications, controlled substance or not, sterile or unsterile, and deliver them directly to the prescribing physician for office administration when medically necessary as determined by the physician.

This alone should not trigger a requirement that the pharmacist register with either the DEA or the FDA as a "manufacturer." However, under current DEA policy, based on the agency's interpretation of the CSA, unless the drug (controlled substance) is delivered directly to the "end user," (i.e. the patient), registration as a "manufacturer" is required, even when the pharmacist is compounding the drug pursuant to a valid prescription and delivering the drug to the prescribing physician for medically necessary office administration.

This is a particularly troubling policy by the DEA as it relates to sterile, injectable compounds, which often must be surgically implanted and delivered via intrathecal pain pump. As the recent tragedy involving the NECC has shown, maintaining sterility throughout the compounding process and the administration of injectable compounded drugs is critical to patient safety.

DEA's current policy runs counter to both their stated goal of preventing diversion of controlled substances, and to standard medical practices intended to maintain sterility of the drugs. This has put compounding pharmacists in the untenable position of following universally accepted medical practice and risking enforcement action by the DEA; or, undergoing an expensive and burdensome manufacturer registration process that does not accurately reflect the status of their traditional pharmacy practice.

Alternatively, they could refuse to fill prescriptions for controlled substances for office administration, which could jeopardize patient access to critical medications. Again, changes to the FDCA or CSA should be consistent in what actions trigger manufacturer licensing requirements and should not impede traditional pharmacists from compounding patient-specific medications for office administration when medically necessary.

With regard to standards for sterile and non-sterile compounding, IACP feels that these issues are sufficiently addressed by State laws and regulations. Where it is not, IACP strongly urges that States adopt rules and regulations similar to those in Iowa (Iowa regulations are attached). IACP again encourages that the USP <795> and <797> standards and practices be adopted by every State, as further safeguard.

State Boards must "police" themselves and provide the necessary assurances to other State Boards which depend upon them for conducting inspections for non-resident pharmacies in a regular and consistent manner. Massachusetts Board obviously failed to execute its responsibilities both to its citizens as well as patients in other States in which NECC was licensed by not conducting regular inspections.

Additionally, virtually every State requires an out-of-state pharmacy to register as such with the recipient State (with one notable exception being Massachusetts). In this regard, the pharmacy dispensing compounds across State lines is subject to heightened (not diluted) oversight and regulation because it must abide by the laws of both its home State and the out-of-state recipient.

With regard to the Active Pharmaceutical Ingredients (APIs) used in the profession of compounding, there already exists in Federal statute language that requires all drugs compounded in the United States to use only active pharmaceutical ingredients (APIs) from FDA registered facilities. (See section 510). IACP regularly reminds its members to require a bill of lading. This provision was included in the PDUFA reauthorization legislation signed into law this year. Please see below for statutory language:

> P.L. 112–144, Section 713, The "Food and Drug Administration Safety and Innovation Act".
>
> SEC. 713. STANDARDS FOR ADMISSION OF IMPORTED DRUGS.
>
> Section 801 (21 U.S.C. 381) is amended—
>
> (1) in subsection (o), by striking "drug or"; and
>
> (2) by adding at the end the following:
>
> (r)(1) The Secretary may require, pursuant to the regulations promulgated under paragraph (4)(A), as a condition of granting admission to a drug imported or offered for import into the United States, that the importer electronically submit information demonstrating that the drug complies with applicable requirements of this Act.
>
> (2) The information described under paragraph (1) may include—
>
> (A) information demonstrating the regulatory status of the drug, such as the new drug application, abbreviated new drug application, or investigational new drug or drug master file number;

(B) facility information, such as proof of registration and the unique facility identifier;

(C) indication of compliance with current good manufacturing practice, testing results, certifications relating to satisfactory inspections, and compliance with the country of export regulations; and

(D) any other information deemed necessary and appropriate by the Secretary to assess compliance of the article being offered for import.

(B) PROCEDURE.—In promulgating a regulation under subparagraph (A), the Secretary shall—

(i) issue a notice of proposed rulemaking that includes the proposed regulation;

(ii) provide a period of not less than 60 days for comments on the proposed regulation; and

(iii) publish the final regulation not less than 30 days before the regulation's effective date.

(C) RESTRICTIONS.—Notwithstanding any other provision of Federal law, in implementing this subsection, the Secretary shall only promulgate regulations as described in subparagraph (B).

(3) DISCONTINUANCE OF REGISTRATION.—The Secretary shall discontinue the registration of any commercial importer of drugs that fails to comply with the regulations promulgated under this subsection.

(4) UNIQUE FACILITY IDENTIFIER.—The Secretary shall specify the unique facility identifier system that shall be used by registrants under paragraph (1). The requirement to include a unique facility identifier in a registration under paragraph (1) shall not apply until the date that the identifier system is specified by the Secretary under the preceding sentence.

(5) EXEMPTIONS.—The Secretary, by notice in the Federal Register, may establish exemptions from the requirements of this subsection.

(c) MISBRANDING.—Section 502(o) (21 U.S.C. 352) is amended by inserting "if it is a drug and was imported or offered for import by a commercial importer of drugs not duly registered under section 801(s)," after "not duly registered under section 510."

(d) REGULATIONS.—

(1) IN GENERAL.—Not later than 36 months after the date of the enactment of this Act, the Secretary of Health and Human Services, in consultation with the Secretary of Homeland Security acting through U.S. Customs and Border Protection, shall promulgate the regulations required to carry out section 801(s) of the Federal Food, Drug, and Cosmetic Act, as added by subsection (b).

(2) PROCEDURES FOR PROMULGATING REGULATIONS.—

(A) IN GENERAL.—In promulgating a regulation under paragraph (1), the Secretary shall—

(i) issue a notice of proposed rulemaking that includes the proposed regulation;

(ii) provide a period of not less than 60 days for comments on the proposed regulation; and

(iii) publish the final regulation not less than 30 days before the regulation's effective date.

(B) RESTRICTIONS.—Notwithstanding any other provision of Federal law, in implementing section 801(s) of the Federal Food, Drug, and Cosmetic Act, as added by subsection (b), the Secretary shall promulgate regulations only as described in subparagraph (A).

On the issue of where and with whom a pharmacy should be registered, pharmacies are already required to register with their State Board of Pharmacy and the Drug Enforcement Administration (DEA). Adding an additional registration requirement for pharmacies would do nothing to further the goal of keeping patients safe—it would amount to a paperwork requirement/administrative step that would produce no particular positive outcome due to an already overstrained FDA budget and the existing broad categories of oversight the agency has to prioritize.

The FDA may inspect an establishment—including pharmacies—to ensure that drugs are appropriately handled and stored. In other words . . . they can look at what's on the shelf, in the refrigerator, in the inventory, etc.

The FDA may not inspect records and files (e.g., prescriptions, compounding formulas, etc.) unless either (a) the pharmacy in noncompliant with its State laws, see supra section 704 discussion, or (b) FDA has an administrative warrant that demonstrates a sufficient cause to do so. A pharmacy may decline such an inspection if it believes it is operating in full compliance with the State law unless there is some sort of court document authorizing the FDA to do so.

However, if the pharmacy is registered as a manufacturer, the FDA has much broader authority to inspect and cite such a manufacturing entity. As a manufacturer, they would also have to comply with CGMP and the FDA has clear injunctive authority over them, should they not remedy violations. In short, a pharmacy engaged in manufacturing is subject to the same laws, inspections, restrictions, and penalties as a commercial drug manufacturer.

There are many patients (both human and animal) needing products in various medical scenarios requiring physician input and judgment based upon the needs of their patient. States already have limitations to this in their regulations and laws as necessary for their particular State for citizens/citizens' pets. Pharmacists are required, by State law, to have sufficient drugs and preparations on their shelves to enable them to service their clients in a timely manner. Any requirement that a pharmacist must wait on each and every prescription thus works counter to public interest and patient health and safety.

Regarding the prescription, moreover, there is no need for a physician to explicitly order a compounded drug. If a physician orders a name brand commercial product, the pharmacy will fill the prescription with it. If, however, the physician's prescription is specific as to active ingredient, dosage, and/or delivery format, it enables the pharmacy to create the medication as needed for the particular patient, and as a prescribed physician, without need of express direction to compound by the physician.

IACP acknowledges that many States have already addressed this issue through "office use" specifications in their laws and regulations (IACP has supplied the committee with a state-by-state office use regulation guide). Should a State NOT have such standards in place, IACP would urge the State to adopt clear and concise guidance for the compounding of medications for "office use." IACP adds that compounds prepared for office stock are no different than a singular compounded drug prescription in terms of pharmacy preparation. The same State law remains applicable to each and every one of these compounds. Finally, regarding labeling, please see the enclosed IACP statement regarding suggested labeling for office use.

Ultimately, the decisionmaking with regard to what a script requires is left to the medical practitioner who writes the scripts in the first place. The doctor or veterinarian is best educated and best suited to make these determinations on medicines to be used and in what dose and dosage form. IACP does not believe the volume of prescriptions involved necessarily is the issue. Instead, the issue is one of (a) drug preparation—which is the same regardless of number, and (b) fulfilling the medical judgments of the practitioner by following the practitioner's directions, as determined for the practitioner's patient.

IACP believes that the FDCA's existing inspection provision, section 704, which was outlined supra, allows FDA the necessary authority and oversight it needs to determine whether a pharmacy is operating as a pharmacy or, instead, akin to a drug manufacturer, thus subjecting it to full inspection and FDCA application.

By way of further example, FDA may inspect the equipment, drug materials, containers and labeling of any pharmacy. See section 704(a) (sentence one). State law requires pharmacy labeling to include, inter alia, the name and strength of the active ingredient, the lot number, the beyond-use date, the quantity or amount in the container, the pharmacy's name, and the physician's name.

Through this information, FDA can assess the professionals' licensure, the exact prescription for the patient, and exactly what the patient will receive. Moreover, all this information must be included on the label or the pharmacy violates its State's law, thus triggering the FDCA section 704 enhanced inspection (sentence three) that applies to drug manufacturers. (See section 704(a)(2)(A)).

It has not been IACP's experience that the FDA has had difficulty collaborating with the States. The opposite appears to be true. FDA often collaborates with both the State boards of pharmacy and the DEA, both of which have full inspection authority over pharmacies. See e.g., *Wedgewood Village Pharmacy, Inc.* v. *U.S.*, 421 F.3d 263, 271 (2005) (noting FDA collected all the evidence it needed regarding whether a pharmacy was operating as a pharmacy or more akin to a manufacturer through collaboration with the State board and DEA); and *Medical Center Pharmacy* v. *Mukasey*, 451 F.Supp.2d 854 (W.D.Tex. 2006) (noting same).

IACP stresses the importance of communicating important health information to patients whenever any medication is dispensed through labeling on the medication. IACP supports State regulations that require information on labeling that informs the patient that the medication has been compounded.

With regard to adverse event reporting, IACP argues that MedWatch is the Food and Drug Administration's reporting system for an adverse event or sentinel event, founded in 1993. This system should also be used for compounded medication.

An adverse event is any undesirable experience associated with the use of a medical product. The MedWatch system collects reports of adverse reactions and quality problems, primarily with drugs and medical devices, but also for other FDA-regulated products (e.g., dietary supplements, cosmetics, medical foods, and infant formulas).

Voluntary reporting by healthcare professionals, consumers, and patients is conducted on a single, one-page reporting form (Form FDA 3500). Reporting can be conducted online, by phone 1–800–FDA–1088, or by submitting the MedWatch 3500 form by mail or fax 1–800–FDA–0178.

Rather than replicating The MedWatch system, IACP contends that there already exists a reporting system for all in the Triad of care. MedWatch is intended to detect safety hazard signals for medical products. If a signal is detected, the FDA can issue medical product safety alerts or order product recalls, withdrawals, or labeling changes to protect the public health. Important safety information is disseminated to the medical community and the general public via the MedWatch Web site and the MedWatch E-list.

On the issue of communication between agencies, IACP would support a notification system that requires States to notify the FDA (within 14 days of such action) when a pharmacy's license has been revoked. Additionally, the FDA should notify States when they believe a pharmacy is acting as a manufacturer and may be operating outside of its registration status allowances.

Additionally, Congress might want to consider assessing civil penalties when a pharmacy owner/operator has willfully misled authorities as to the nature of their business.

IACP appreciates this opportunity to provide input on this critical outbreak to the committee and looks forward to further discussing this issue. IACP will be happy to respond to any additional questions the committee may have.

The CHAIRMAN. Thank you, Mr. Miller.

Now we'll turn to Dr. Thompson.

Dr. Thompson, please proceed.

STATEMENT OF KASEY K. THOMPSON, PHARM.D., M.S., B.S., VICE PRESIDENT, OFFICE OF POLICY, PLANNING AND COMMUNICATIONS, AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS, BETHESDA, MD

Mr. THOMPSON. Thank you, Chairman Harkin and distinguished members of the committee, for holding this hearing. My name is Kasey Thompson. I am vice president for Policy, Planning, and Communications with the American Society of Health-System Pharmacists. I am here today to provide ASHP's perspective on the recent meningitis outbreak and to explore potential policy options to help prevent similar events from occurring ever again in the future.

First and foremost, on behalf of ASHP and our more than 40,000 members practicing in hospitals, health systems, and ambulatory clinics, I want to express our sympathy for the victims and their families who were harmed by this terrible tragedy. The patients who relied on these medications deserved much better.

Unfortunately, the New England Compounding Center appeared to have been operating in a manner that falls far short of standards for compounding sterile preparations. Further, the scale and scope of NECC's operations more nearly resembles pharmaceutical manufacturing than traditional pharmacy compounding.

U.S. hospitals prepare a vast array of compounded sterile preparations every day in order to meet the needs of patients. In fact, the majority of compounded medications hospitals utilize are prepared in-house by pharmacy departments. The compounded medications that hospitalized patients need include simple intravenous admixtures to complex customized medications that are not avail-

able off the shelf, such as multi-ingredient solutions for heart surgery, epidural pain medication, and adult medications prepared with concentrations that can be safely administered to babies and children.

However, hospitals also enlist the help of qualified compounding pharmacies for some compounded preparations for several reasons. For example, they may not have the necessary equipment or facilities to prepare some high-risk preparations, or they may face medication shortages from commercial products.

Hospitals prepare or purchase compounded medications based on specific patient needs and individual medication orders or in anticipation of needs for patients under their care. Importantly, medications that are purchased from outside compounding pharmacies are not commercially available from brand or generic manufacturers in the individualized form needed for specific patients.

ASHP has dedicated itself to developing the highest standards for compounding sterile products in hospitals. We began publishing guidelines on sterile and non-sterile compounding in the early 1990s. In 2010, ASHP published the ASHP Guidelines on Outsourcing Sterile Compounding Services to advise pharmacy departments on how to conduct due diligence when selecting outsourcing vendors. All of our guidelines have always been available as a free public service to the healthcare community and to others.

However, even with the availability of these useful resources, we cannot rely solely on the diligence of purchasers to take the place of proper licensing, inspection, and oversight of entities producing compounded medications, especially those entities that are manufacturing in large quantities and shipping across the country. Pharmacists and other healthcare providers should not be expected to perform the jobs of regulators by visiting and inspecting pharmacies and manufacturers that they do business with.

The distinction between traditional pharmacy compounding and manufacturing appears to be a regulatory gray area between State boards of pharmacy and the FDA. As we have seen, however, the implications of this gray area are serious.

We recognize the regulatory challenges of defining the activities in this gray area. We firmly believe that specific definitions are essential so that mass production of the scope and scale done by NECC falls clearly within the regulatory jurisdiction of FDA rather than State boards of pharmacy. To this end, we have developed policy recommendations for the committee, FDA, and other stakeholders to consider as we explore ways to address this gap in oversight.

A number of variables make distinguishing between compounding and manufacturing difficult. Therefore, both functions might be better viewed as a continuum of activities stratified by the potential risk for patient harm, each requiring defined procedures, equipment, training, and quality controls. At one end of the continuum, oversight of traditional compounding is clearly within the purview of States and the oversight of pharmaceutical manufacturing within the purview of the FDA.

Once compounding activities advance along the continuum to manufacturing, the risk to patient safety and public health increases. There may be a need for a special category of FDA over-

sight that falls between compounding and manufacturing but does not require a drug approval.

For example, if a compounding pharmacy sells to other organizations and not directly to patients, there may be a need to be regulated by the FDA. Doing so would allow hospitals, clinics, and physician offices to purchase sufficient quantities of compounded product as is necessary to meet patient needs, while doing so under the assurance that they are making those purchases from appropriately regulated entities.

ASHP recommends stronger communication and collaboration between State boards of pharmacy and the FDA to accomplish this goal. We also believe that State boards of pharmacy should be able to work with FDA to inspect an entity suspected of engaging in large-scale drug production beyond the scope of traditional pharmacy compounding.

Finally, we strongly believe the FDA must be provided with the resources it needs to perform oversight of compounding entities that are potentially engaged in manufacturing.

Thank you for the opportunity to provide the perspectives of the pharmacists who practice in hospitals and health systems. ASHP remains committed to working with Congress, the FDA, and other stakeholders to ensure that an event like this never occurs again.

[The prepared statement of Mr. Thompson follows:]

PREPARED STATEMENT OF KASEY K. THOMPSON, PHARM.D., M.S., B.S.

SUMMARY

U.S. hospitals prepare a vast array of compounded sterile preparations every day in order to meet the needs of patients. However, hospitals also enlist the help of qualified compounding pharmacies for some compounded preparations for several reasons.

ASHP has dedicated itself to being a leader in developing the highest standards for compounding and sterile product preparation in hospitals. We have developed an assessment tool based on our guidelines that helps pharmacists in hospitals and health systems comprehensively evaluate sterile compounding service providers and use comparative date for their vendor selection process.

However, we cannot solely rely on the due diligence of purchasers to take the place of proper licensing, inspections and oversight of entities producing compounded medications. The distinction between traditional pharmacy compounding and manufacturing appears to be a regulatory gray area between State boards of pharmacy and FDA. As we have seen, however, the implications of this gray area are serious.

ASHP recommends stronger communication and collaboration between State boards of pharmacy and the FDA. We also believe that it may be necessary to revisit previous attempts to further define pharmacy compounding from large scale, mass-produced medications. Finally, we strongly believe that FDA must be provided the resources it needs to perform serious and meaningful regulatory oversight.

Good morning and thank you Chairman Harkin, Ranking Member Enzi, and distinguished members of the committee, for holding this hearing. My name is Kasey Thompson and I am vice president of Policy, Planning and Communications for the American Society of Health-System Pharmacists (ASHP). I am here today to provide ASHP's perspective on the recent meningitis outbreak, and to explore potential policy options to help prevent similar events from occurring in the future.

First and foremost, on behalf of ASHP and our more than 40,000 members practicing in hospitals, health systems, and ambulatory clinics, I want to express our sympathy for the victims and their families who were harmed by this tragedy. The patients who relied on these medications deserved much better. Unfortunately, the New England Compounding Center appeared to have been operating in a manner that falls far short of standards for compounding sterile preparations. Further, the

scale and scope of NECC's operation more nearly resembles pharmaceutical manufacturing rather than pharmacy compounding.

U.S. hospitals prepare a vast array of compounded sterile preparations every day in order to meet the needs of patients. In fact, the majority of compounded medications hospitals utilize are prepared in-house by pharmacy departments. The compounded medications that hospitalized patients need span from simple intravenous admixtures to complex customized medications that are not available off the shelf, such as multi-ingredient cardioplegia solutions for heart surgery, precisely measured combinations of epidural pain medication and adult medications prepared in concentrations that can be safely administered to babies and children.

However, hospitals also enlist the help of qualified compounding pharmacies for some compounded preparations for several reasons. For example, they may not have necessary equipment or facilities to prepare some high-risk preparations, or they may face medication shortages for commercial products that can only be replicated by a compounding pharmacy.

Hospitals prepare or purchase compounded medications based on specific patient needs and individual medication orders or in anticipation of needs for patients under their direct care. Importantly, medications that are purchased from outside compounding pharmacies are not commercially available from brand or generic manufacturers in the individualized form needed for a specific patient or patients, unless manufacturers cannot supply them.

ASHP has dedicated itself to developing the highest standards for compounding and sterile product preparation in hospitals. Through our peer-reviewed publication, the *American Journal of Health-System Pharmacy*, we began publishing guidelines on sterile and non-sterile compounding in the early 1990s. In 1993 we published the *ASHP Technical Assistance Bulletin on Quality Assurance for Pharmacy-Prepared Sterile Products*. This was revised in 2000, and is currently in the final stages of revision.

These guidelines formed the basis for the three-tier risk assessment structure later incorporated by the United States Pharmacopeia into Chapter 797, its standards for compounding sterile products. In 2010, ASHP published the *ASHP Guidelines on Outsourcing Sterile Compounding Services* to advise pharmacy departments on how to conduct due diligence when selecting outsourcing vendors. In addition, we have developed an assessment tool based on our guidelines that helps pharmacists in hospitals and health systems comprehensively evaluate sterile compounding service providers and use comparative data for their vendor selection process. Our guidelines and assessment tool are and have been available free as a public service to the health care community and others.

POLICY OPTIONS

We cannot rely solely on the due diligence of purchasers to take the place of proper licensing, inspections and oversight of entities producing compounded medications, especially for those entities that are manufacturing in large quantities and shipping across the country. Pharmacists and other health care providers should not be expected to perform the jobs of regulators by visiting and inspecting pharmacies or manufacturers that they do business with.

The distinction between traditional pharmacy compounding and manufacturing appears to be a regulatory gray area between State boards of pharmacy and FDA. As we have seen, however, the implications of this gray area are serious.

We recognize the regulatory challenges of defining the activities in this gray area, but we firmly believe that specific definitions are essential so that mass production of the scope and scale done by NECC falls within the regulatory jurisdiction of FDA, rather than State boards of pharmacy. To this end, we have developed policy recommendations for the committee, FDA and other stakeholders to consider as we explore ways to address this gap in oversight.

Previous attempts to define compounding in Federal law contained certain elements that should be examined in light of practice changes since 1997. Recent legislative proposals merit further discussion and exploration, since they may reflect those practice changes and allow for the regulatory flexibility among State boards of pharmacy and the FDA that would ensure that hospitals continue to be allowed to obtain compounded medications in anticipation of patient need.

Compounding pharmacies range from small pharmacy operations that compound medications for individual patients directly under their care to large-scale operations that prepare compounded medications in the volumes required to serve the needs of patients under the care of health systems or physician offices. A number of variables make distinguishing between compounding and manufacturing difficult. Therefore, both functions might be better viewed as a continuum of activities strati-

fied by the potential for risk of patient harm, each requiring defined procedures, equipment, training, and quality controls. At one end of the continuum, oversight of traditional compounding is clearly within the purview of States, as is FDA regulation at the other end of the continuum with pharmaceutical manufacturing. As legislative proposals are considered, it will be important to reaffirm the role of State boards of pharmacy to license and regulate traditional compounding while recognizing that large-scale compounding of sterile products may require oversight by the FDA in cooperation with State boards of pharmacy.

Once compounding activities advance along the continuum to manufacturing and the risk to patient safety and public health increases, there may be a need for a special category of FDA oversight that falls between compounding and manufacturing but does not require a drug approval (e.g., an NDA). For example, if a compounding pharmacy sells to other organizations and not directly to patients, then they may need to be regulated by the FDA. Doing so would allow hospitals, clinics, and physician offices to purchase sufficient quantities of compounded product as is necessary to meet patient needs, while doing so under the assurance that they are making those purchases from appropriately regulated sources.

ASHP recommends stronger communication and collaboration between State boards of pharmacy and the FDA to accomplish this goal. We also believe that State boards of pharmacy should be able to work with FDA to inspect an entity suspected of engaging in large-scale production beyond the scope of pharmacy compounding. Previous court rulings have made FDA's authority to inspect these facilities unclear and subject to legal action.

Finally, we strongly believe that FDA must be provided the resources it needs to perform serious and meaningful regulatory oversight of entities that are potentially engaged in manufacturing. Not to do so now will only hinder the agency in implementing legislation.

CONCLUSION

To summarize, we are profoundly saddened by what we believe should have been an avoidable tragedy. ASHP remains committed to working with Congress, FDA and other stakeholders to address these regulatory gaps and reduce the likelihood of similar outbreaks from compounded sterile products in the future.

The CHAIRMAN. Thank you very much, Dr. Thompson. We'll begin a round of 5-minute questions.

Mr. Miller, do you believe Congress should clarify the legal status of section 503A given the current split between the Ninth and Fifth Circuits?

Mr. MILLER. Mr. Chairman, there is definitely clear confusion about authority based upon the judicial decisions in the Fifth and the Ninth. We also know based upon the *Medical Center* v. *Thompson* decision in the Supreme Court that actually struck down sections of the original FDA FDAMA law as being unconstitutional. So, yes, we need to go back and revisit this, especially in light of this tragedy.

The CHAIRMAN. Let me ask that question one more time. Do you believe Congress should clarify the legal status of section 503A?

Mr. MILLER. Yes.

The CHAIRMAN. Thank you. That's all I wanted to hear. We know the background and stuff. We're trying to get a clarification of this. So you think that we should give that kind of clarification whether it's the flagpole type or some kind of clarification on section 503A?

Let me ask this. I may tend to disagree with you a little bit on your sort of absolute statement that FDA had jurisdiction in this. I still think that's sort of a gray area. But let's assume that they did.

Mr. MILLER. Yes, sir.

The CHAIRMAN. Assuming we agree that they should have jurisdiction when a pharmacy like NECC operates in a manner and scale that is essentially a manufacturer, shouldn't the FDA have

access to records such as prescription records to help it determine whether the operation is really a compounder or a manufacturer?

Mr. MILLER. That's a complex question, and the answer is it does. The FDA has the ability to obtain a court order, subpoena, or administrative warrant to obtain any records within a pharmacy. They also have the ability to work in collaboration with a board of pharmacy. The board of pharmacy in every State has the ability to look at all documentation and materials in any of its licensed sites.

If the FDA felt compelled, in addition to its Form 482 on-site inspection of materials, that it needed additional information, that's a simple collaboration with a State board of pharmacy. We know based on testimony that occurred between the FDA and the Massachusetts Board of Pharmacy, and yet that system still failed. Does the FDA—should they—actually, Senator, although it's not specific, they do have that ability currently.

The CHAIRMAN. They do have to go through a lot of hoops. They've got to go to court. They've got to get all kinds of things before they do that. That takes, obviously, a lot of resources. It takes a lot of time. I'm just saying that if we agree that FDA should have this jurisdiction, shouldn't they have access to records to help them determine whether it's a compounder or a manufacturer, because sometimes—as Dr. Hamburg kept saying, sometimes they don't know.

Mr. MILLER. Yes. One of the things that also has to be addressed—and it's very important—is that as we distinguish between a pharmacy engaged in compounding, which more than 50 percent of all pharmacies in the country do, versus manufacturing, we have to look at what they are doing, not necessarily how, but what are they doing.

The CHAIRMAN. I know you were here for the first panel. You may have heard me say something about State lines.

Mr. MILLER. Yes.

The CHAIRMAN. I don't know if that's right or not. What are the features that distinguish NECC from what you would view as a legitimate large-scale compounding pharmacy? Again, we heard about volume. I mentioned interstate shipment, prescription records. Again, do we have some guidelines? What features would distinguish that as a legitimate large-scale compounding pharmacy?

Mr. MILLER. Mr. Chairman, I am a pharmacist. I tend to think black and white. The answer is pretty simple. When I receive a prescription, regardless of whether it's a compound or an off-the-shelf commercially manufactured drug, that is coming from an authorized prescriber in my State. I'm empowered to fill it for a patient, or, depending upon the order, I may be filling it for a clinic associated with a hospital down the street. I fill prescriptions.

The difference between NECC and a compounding pharmacy was they weren't filling prescriptions. They were bulk manufacturing and selling. A company like Pfizer creates and sells medications. They don't fill prescriptions. A company like Ameridose, associated with NECC, creates and sells medications. Pharmacies fill prescriptions.

One of the things that we've heard from conversations with many boards of pharmacy is how do I distinguish this? It's relatively simple. Any pharmacy inspector, specifically one who is a pharmacist and trained, can tell you, based on the paperwork in that pharmacy, is this pharmacy filling a prescription, or are they essentially creating bulk quantities? And those bulk quantities, whether they're 100 or 100,000—are they being sold as opposed to being dispensed?

It's a function of what we do as pharmacists that really differentiates between pharmacy practice and manufacturing. That's where I think we really went awry here with NECC, because it was quite apparent that they were not filling prescriptions. They were selling stuff, and that's what manufacturers do.

The CHAIRMAN. OK. I'll try to absorb all that.

Senator Roberts.

Senator ROBERTS. I want to be a little insistent here, and I apologize for that. In the first place, in my opening statement, I said that I hoped that the witnesses today would offer their commitment to work with us—and I think you've done that—and to do so in good faith—and I know you'll do that—with the intent to be transparent and forthcoming with your thoughts and your suggestions and your concerns. That came from my opening remarks.

Is this something that you are both willing to do, remembering that during the early days of trying to get something done, we wanted answers and all we got was pushback. Could you speak to that, please?

Mr. MILLER. Senator Roberts, as a pharmacist and as an organization representing pharmacists, the worst possible thing has happened. We have more than 30 people dead. We have 461 people ill. Right now, the focus must be on working collaboratively—professional associations, regulators, legislators—to prevent this from ever happening again. IACP and all the other pharmacy associations, State and national, will be working with you, this committee, and everyone else to make sure that we protect the public from organizations, businesses, entities like an NECC. You have my commitment on that, Senator.

Senator ROBERTS. I appreciate that.

Dr. Thompson, I know that you are providing a legislative blueprint to be of help to us, which I appreciate. Is that criteria voluntary, or is that mandatory?

Mr. THOMPSON. The blueprint that we suggested?

Senator ROBERTS. Yes.

Mr. THOMPSON. We think that's mandatory. Basically, it's to clarify the jurisdiction of the FDA over manufacturing of these compounding entities. I call them entities for a reason, because it is a gray area—and I'm speaking as a practitioner and for our members—in trying to understand who they're doing business with out there. And we do believe there are some gray areas.

We think that this is something that would give the FDA the authority it needs to regulate these entities that fall between the Pfizers and the Mercks and the large-scale manufacturers that are manufacturing under approved drug applications and abbreviated new drug applications for generic drugs and these entities that are compounding medications in large amounts.

Senator ROBERTS. In your opinion, either one of you, do you think that NECC is a manufacturer? If you do, do you believe that FDA has the current oversight and enforcement authority to appropriately regulate manufacturers?

Mr. THOMPSON. I believe that they were behaving as a manufacturer, without question. It's become clear to me, or perhaps unclear, whether FDA had the authority or not. This registration that compounding pharmacies do with the FDA is not the same as what a commercial manufacturer that is manufacturing under a new drug application and is licensed to manufacture under that application. I do believe it's a regulatory gray area that must be confirmed by Congress.

Mr. MILLER. No question, Senator. NECC was engaged in illegal manufacturing. They did not have a license in the State of Massachusetts as a manufacturer. All States oversee that, in addition to the FDA. They were not registered with the FDA. They were shipping products nationwide without prescriptions, without official authorized orders from prescribers. Bottom line, that's manufacturing.

Senator ROBERTS. I appreciate that. I have no further questions, Mr. Chairman.

The CHAIRMAN. Senator Alexander.

Senator ALEXANDER. Thanks, Mr. Chairman.

Thank you for being here and for your testimony. You make the solution sound pretty simple, that you just take these large facilities that are in the gray area, and some of them are manufacturers and they're regulated by the FDA, and the rest of them aren't. They're filling prescriptions and they're regulated by State boards of pharmacy. Am I hearing you right?

Mr. MILLER. From—go ahead, Kasey.

Mr. THOMPSON. I'm sorry. Yes, you are hearing me correctly in that respect. We do believe that traditional pharmacy compounding is the filling of a prescription and dispensing that to a patient. These entities that are preparing large amounts of medications and not necessarily dispensing those to patients but selling those to various entities, whether it's hospitals, physician offices or others, are manufacturing.

Senator ALEXANDER. There are some—let's take Tennessee. Maybe we've got 1,000 to 1,200 pharmacies. Let me just guess at it. And based upon your testimony, maybe 500 of them do compounding.

Mr. MILLER. That's correct.

Senator ALEXANDER. Now, apparently, there must be a number of other larger compounding pharmacy facilities in Tennessee, for example. Would that be true? Anybody know? I have some suggestions here that there may be 7,500 pharmacies that specialize in advanced compounding, 3,000 that provide sterile compounding. Are these just large drug stores that we're talking about, or are these large entities or companies that fill prescriptions, that do advanced sterile compounding and still fill prescriptions? How many are we talking about here?

Mr. MILLER. Senator, thank you. I can answer that. Those statistics actually come from the International Academy of Compounding

Pharmacists. The 7,500 and 3,000 you've heard mentioned are actually our statistics.

There are compounding pharmacies, sterile compounding pharmacies, in the State of Tennessee, actually, quite a few of them. Some are large. Some are relatively small. One of the things I don't want us to get too hung up on is the issue of size, because size does not necessarily mean that you're a manufacturer. It's actually what you do—Senator Harkin, to what I was saying before.

Senator ALEXANDER. There might be 40 or 50 in Tennessee, roughly. We're usually 2 percent of everything, so if there are 3,000 sterile manufacturers, there might be 40, 50 or 60 of varying sizes. Is that right?

Mr. MILLER. Sterile compounding pharmacies, not manufacturers.

Senator ALEXANDER. Sterile compounding pharmacies.

Mr. MILLER. Yes, sir. What we have to recognize is they may be part of a hospital. They may be part of a home infusion company that specializes in outpatient, a nursing home, long-term care, or it could be affiliated with one of our major chains. It could be a standalone, community-based pharmacy.

Senator ALEXANDER. These are the ones we're talking about here. We're not talking about the 1,000 pharmacies that are doing traditional compounding, or we're not talking about manufacturers who are selling in bulk. We're talking about, in my State, maybe 40, 50, or 60 entities of various sizes which are compounding pharmacies, some of them doing sterile work.

Mr. MILLER. Actually, you have more than that in terms of compounding, in general. That estimate for sterile compounding in your State—I would say that's extremely accurate. Those are the pharmacies we would want to make sure are identified by your State.

Senator ALEXANDER. That's where the potential trouble is, insofar as this incident is concerned. Is that right?

Mr. MILLER. My hesitation isn't because I don't agree. I'm concerned that that may be too narrow of an interpretation.

Senator ALEXANDER. Let me ask it this way, then. The trouble is the lack of clarity about who's on the flagpole.

Mr. MILLER. Yes, sir.

Senator ALEXANDER. If I can understand—let's just narrow it down to these, let's say, 50 advanced compounding facilities in Tennessee. That gets rid of most of the drug stores in Tennessee, and it gets rid of all the manufacturers. We're talking about 50. How do we decide who regulates those 50? Does the State board of pharmacy do it, or does the FDA do it?

Mr. MILLER. Right now?

Senator ALEXANDER. Well, no. How should it be? How should it be going forward?

Mr. MILLER. To identify them, I would send the State board of pharmacy in to inspect all of them. That State board inspector should be able to determine is this pharmacy a pharmacy, or is this pharmacy actually engaged in manufacturing.

Senator ALEXANDER. What if they're as incompetent as the State Board of Pharmacy of Massachusetts seemed to be over the last 10 years?

Mr. MILLER. Then we have a very significant problem. Fortunately, that doesn't seem to be the case in most States. One of the recommendations our organization has at the State level is we need to adequately fund our boards and provide them with inspectors who are trained and kept up-to-date so they can go in and review a pharmacy so that we can identify and prevent an NECC——

Senator ALEXANDER. I interrupted you. You were saying you would send the State board of pharmacy in to decide, first, are they pharmacies, or are they manufacturers?

Mr. MILLER. That's correct.

Senator ALEXANDER. Then what?

Mr. MILLER. If they are identified as being a manufacturer outside of the practice of pharmacy and the rules and regulations within the State, the State board has the ability to shut them down, discipline them, revoke their license, suspend it, if they believe—the State board, just as Colorado did with NECC—if they identify that pharmacy as a manufacturer, they can cross-file that complaint, specifically, with the FDA, who has the ability to shut down an illegal manufacturer.

Senator ALEXANDER. Yes.

Mr. MILLER. So it's a combination of both——

Senator ALEXANDER. Well, this is helping me. Sometimes when we get these large, difficult questions, getting it down to a quantifiable level helps. We're really talking about, in a State like ours, what to do about 30, 40 or 50 institutions. How do we identify them, and then how do we regulate them. If we don't trust the State in every case, or don't trust the FDA in every case—I would trust the Tennessee Board more than I'd trust the FDA to identify them, to tell you the truth, based on what I've heard today. But not Massachusetts.

So there we have the dilemma. I suppose with that smaller number, you could allow the FDA to go in and make its own judgment about whether they're manufacturers or not. If they are, regulate them. You're saying have the State board go in and decide it.

Mr. MILLER. Senator, first off, the FDA can go into those facilities, those pharmacies, at any time. No question about that. If we wish to, from a policy standpoint, require that the FDA inspect all potentially identified sterile compounding pharmacies, that's a decision we could make as a policy.

Senator ALEXANDER. That wouldn't be so many that it would be an overwhelming number, would it? Or would it?

Mr. MILLER. I can't answer that for the FDA. My biggest concern would be——

Senator ALEXANDER. We're just talking about identification.

Mr. MILLER. Yes. The agency would need to not only identify them, but also then deal with the fact that each State has conflicting compounding guidelines. For example, in the State of Tennessee, your board of pharmacy said clearly to all licensees in January, "No non-patient-specific prescriptions in our State." Other States do permit that.

Senator ALEXANDER. Why is that?

Mr. MILLER. Why is that? Because the individual State board of pharmacy makes a decision as to what is needed and how it needs to be regulated to protect the citizens within their State.

Senator ALEXANDER. Well, I'm running a little bit over my time here, Senator Harkin. It helps us, in terms of developing a policy to solve the problem looking forward, to narrow it down to the number of entities we're talking about. Perhaps we could agree to exclude manufacturers and people who are illegally manufacturing. They're just illegally manufacturing. And then traditional compounding, we understand, exists.

To identify the number of entities that fall into this gray area, how do we identify them, and then how do we regulate them? One of the things I'm experimenting with in my mind is an idea for these areas, such as sterile compounding, that sort of area, where the FDA may have standards, and actually certify a State to handle that narrow area of compounding and be able to take it away.

For example, in the case of Massachusetts, had there been such a structure existing, based upon what we've heard today, I would say if the FDA had the authority, it should jerk the ability of Massachusetts to deal with these sorts of entities at least until Massachusetts cleaned up its act. On the other hand, it should give Tennessee an award for working with the CDC to move quickly to eliminate the spread.

Anything you could submit to the committee, to the chairman, Senator Enzi, Senator Roberts, those of us who are interested, identifying exactly the number of entities we're dealing with and a practical way for identifying, with the end result being that we have some agency clearly on the flagpole, so when we come up here 6 months from now, we don't have one saying, "Yes, I had responsibility," and the other one saying, "Well, I had some, too"—I want one to say, "It was my fault, my job, my responsibility," or the other one saying, "No, that's my fault," just as the head of the CDC said when I asked her—I said, "Whose job was it to let the world know what happened?" She said, "That was my job."

The CHAIRMAN. Thank you, Senator Alexander. We're preparing this letter, as I mentioned earlier, to go out to all the State boards of pharmacy. Please take a good look at that, and if you've got some suggestions for other things that you might want to go into that letter, please let us know. I'd like to get it out as soon as possible.

Senator ALEXANDER. Good. I'll look at it today.

The CHAIRMAN. Some of the things you brought up may not be in there, and I want to have you take a look at that to see if we need to put——

Senator ALEXANDER. Thank you. Good.

The CHAIRMAN. I appreciate that very much.

I just wanted to ask Dr. Thompson—I read through your testimony yesterday, and I'll just refer to it again, just reviewing it. I know you're saying that hospitals and large entities like that can't really ensure the inspections to make sure that they're getting the right kind of products that are sterile and everything like that.

It seems to me if hospitals are outsourcing compounding, can't they take steps to ensure that they're buying from suppliers who utilize sterile practices? It seems like—don't take this wrong, but it seems like in your testimony you're shoving it all off on the compounding pharmacies. Don't the hospitals also, especially large entities, have a responsibility? Can't they take steps to ensure who

they're buying from and that they're meeting good manufacturing practices?

Mr. THOMPSON. Yes, sir, and I believe that many of them do. They verify that they're licensed by the State board of pharmacy. They look to see whether or not they're registered with the FDA as a manufacturer, which is a regulatory gray area. I've spoken with many pharmacists that do go out and visit facilities.

As you can imagine, Senator Harkin, a small hospital in Iowa with 25 beds or less——

The CHAIRMAN. Can't do that, no.

Mr. THOMPSON [continuing]. You know, flying to Massachusetts. That's where the challenge comes in. I think many do that. But, at the end of the day, they have to be able to count on the regulatory apparatus, whether it be the State or the FDA, to do their part. We don't inspect Pfizer to make sure that their products—so that's sort of the point I was trying to make.

The CHAIRMAN. I understand a small hospital in Tennessee or Iowa can't do that. There are some big hospital chains, and they buy a lot of product. A lot of the smaller hospitals would rely upon their ability to make sure that from whom they're buying is practicing good manufacturing practices.

Mr. THOMPSON. Oh, sure, absolutely. Many of them do that. I've spoken with many hospital pharmacists that go out and look at compounding pharmacies. It gets a little difficult when they go into these manufacturing operations, because that's sort of a different type of expertise—that somebody needs to inspect a manufacturer. But many of them do that, to your point.

The CHAIRMAN. I also want to again say forthrightly about compounding products that we think a lot about it as meeting specific needs of individuals. It has to be prescription-based, rather than just producing mass products. Compounding pharmacies also fill a real niche in our society for meeting a drug shortage that might happen at some time. They can step in and do things right away and help us meet certain drug shortages. That's just another valuable service that they provide.

Dr. Kainer, I didn't ask you any questions, but, again, more than anything, you illustrate the diligence and the professionalism of our public health professionals in the United States and the close cooperation between the State departments of health and the CDC. To me—and I have looked at different health systems around the world—our public health system in this country, in terms of prevention and in terms of immediate diagnosis—that's the wrong word—immediately finding things that are happening—detection and response, beats anything anywhere in the world.

We have to make sure that we continue to have adequate funding so that we employ and hire the best possible epidemiologists and other professionals. You exemplify that, and I appreciate it very, very much.

Mr. Miller, thank you very much. The two responses that I liked hearing from you today were, No. 1, on the clarification on 503A, and in response to Senator Roberts that your association will, indeed, work with us as opposed to what happened a few years ago.

Mr. MILLER. Absolutely, Senator.

The CHAIRMAN. That's good news.

Senator ALEXANDER. Mr. Chairman.

The CHAIRMAN. Yes.

Senator ALEXANDER. Mr. Chairman, something you said, might provide an opportunity for Dr. Kainer to respond. I thought you made a very good point. The hospitals and the clinics and the physicians, particularly after this, who buy compounded medicines will be on alert. Maybe there's something else that the CDC or its associates could do to create a warning system.

For example, was there anything that went on over the last 10 years that we've heard about in Massachusetts with the New England Compounding Center that could have been put up as a yellow flag that a hospital, like the Saint Thomas pain clinic might have known about before they bought that, just by checking the internet?

Is there a system like that, Dr. Kainer? I thought Senator Harkin's question was a very good one.

The CHAIRMAN. That's interesting.

Dr. KAINER. I'm not specifically aware of such a system that occurs right now that is in the public, specifically on identifying or having a warning signal for a hospital. They have the 483 inspection reports that people can do. It's not necessarily user-friendly or easy for hospitals.

If I may add, many of the physicians who ordered these medications did not realize that they were ordering from a compounding pharmacy. They actually thought that they were purchasing things from a manufacturer. Alerting clinicians as to what is the difference between a compounding pharmacy and a drug manufacturer, what's the difference between a generic medication versus a brand name medication, and compounded products are not the same.

There's a lot of confusion among those providers. Perhaps there's an opportunity here to educate the providers that there is a difference between compounded products and manufactured products.

The CHAIRMAN. That's very interesting. We should pursue that, too. I was just told by my staff that many of the documents that came out of the board in Massachusetts were not public. There was no way for anybody out there, a hospital or someone, to know that there were these indications. Maybe that's something else we should look at.

Is there anything else that any of you want to impart to the committee at all before we close it down? No?

Thank you all very, very much, each of you, for your diligence, for being here, for adding to our deliberations. You can sense that this is truly a bipartisan effort. This committee will forge ahead in developing legislation, and, toward that end, we again seek your input and your advice and work with you to develop this legislation. Hopefully, we'll have something soon next year that we'll be able to move ahead on and put this sad chapter behind us.

Thank you all very much. I request that the record stay open for 10 days to allow Senators to submit statements and questions for the record.

With that, the committee will stand adjourned. Thank you all very much.

[Additional material follows.]

ADDITIONAL MATERIAL

PREPARED STATEMENT OF SENATOR CASEY

Chairman Harkin, Ranking Member Enzi, I would like to thank you for convening this investigative hearing. As members of the Health, Education, Labor, and Pensions Committee, many from States affected by this terrible tragedy, I believe we have a duty to exercise our investigative and oversight authority, and to make sure that we take every step possible to ensure that a tragedy like the ongoing meningitis outbreak does not happen again.

Like you, I am deeply disturbed by the long history of problems at the New England Compounding Center, and concerned that it took an event of this magnitude, with over 400 people infected with a potentially lethal strain of meningitis and over 30 having succumbed to its effects, to alert us to the dangers of this company's practices.

In the face of this crisis, Pennsylvania has seen only one case, compared to dozens of cases in the home States of some of my colleagues on the committee. This outbreak has alerted us all to the dangers to public health posed by bad actors in the pharmacy compounding arena.

I know there are many good compounding pharmacists, and I recognize the important role they play in ensuring that patients have access to the drugs they need, when they need them, and in the right form. Something went wrong at NECC, and now over 30 people are dead as a result. We are here to learn what led to this situation, and what we need to do to ensure it never happens again.

There are many questions we have yet to answer, and we are not sure what the best path forward will be. It is clear that NECC was operating outside the bounds of Federal and State law. Do we need greater Federal oversight of compounding pharmacies? Do we need to require the FDA to work more closely with State boards of pharmacy, and improve their communication? How have the split district court decisions affected the FDA's ability to take action with regard to compounding pharmacies?

There appears to be a lot of confusion surrounding the regulation and oversight of these larger compounding pharmacies that operate in the middle ground between traditional, small-scale compounding pharmacies and large manufacturers. I believe that everyone would benefit by reexamining current Federal law and reevaluating whether our existing regulatory system is appropriate for an industry that is changing and addressing new challenges in our health care system. I know that this issue has been contentious in the past, and I hope that all of the interested parties will come together in good faith to protect the public from future tragedies.

I look forward to hearing from our witnesses, I thank them for sharing their expertise, and I thank Chairman Harkin and Ranking Member Enzi for their commitment to protecting the public from harm. I look forward to working with the other members of the committee to clarify the law as it pertains to compounding pharmacists.

PREPARED STATEMENT OF JOHN J. DREYZEHNER, M.D., MPH, FACOEM, COMMISSIONER, TENNESSEE DEPARTMENT OF HEALTH, NASHVILLE, TN

Please accept my sincere appreciation for your investigation into a matter that has, regrettably, impacted thousands of Americans. Our concerns and prayers for the patients, families and loved ones affected by this preventable tragedy are continuing. On behalf of those who have died or suffered physical and mental anguish, and their families and friends who have also endured loss and anxiety, I thank you for your work and assure you the Tennessee Department of Health is firmly committed to working with you, our State legislators, the healthcare community and other stakeholders to take this clear opportunity to do all we can to assure this never occurs again.

As you know, healthcare and public health professionals in Tennessee were the first in the Nation to detect, investigate and understand what had gone horribly wrong in our clinics as a result of a compounding pharmacy that now appears to have been acting as a manufacturer in another State. Our investigation began Tuesday, September 18, when an astute clinician provided the first indication of something unusual in a patient's presentation and subsequent laboratory evaluation. The finding of fungal meningitis launched a rapid investigation that soon identified contaminated methylprednisolone acetate (MPA) from the New England Compounding Center in Massachusetts as the cause of an outbreak of meningitis, stroke and death for patients who had received epidural steroid injections with the egregiously tainted product at three facilities in our State.

I am proud of the work done in Tennessee to expeditiously identify the contaminated medication which within 8 days of that first report September 18th sparked a national recall of the three contaminated lots of MPA. I am equally proud of work by the Tennessee Department of Health, our central and local health department teams and our many healthcare partners to rapidly find, reach out and provide close assistance and regular contacts to more than 1,000 at risk individuals and their families. I'm also proud of the cooperation among many States in addressing this most serious outbreak. None the less, because this whole tragic episode was preventable, I am not just saddened by the occurrence, I am angered.

This does not appear merely to have been an unfortunate lapse or error in pharmacy judgment or practice. It appears to have been a cascade of increasingly serious and obvious omissions and commissions that were persistently not addressed for reasons currently unknown. The people who compounded these medications knew they were being relied upon to be sterile by patients and clinicians—real people who trusted them. This was a blatant disregard for health and safety by pharmacists who should understand the potential consequences of the final catastrophic failure that ultimately occurred. This was, at root, a fundamental breach of an ethical duty and sacred obligation by the New England Compounding Center to first, do no harm.

As a physician, my colleagues and I rely on a long-standing foundation of trust and confidence in the drugs we administer to patients, believing these materials are safe and effective and will help, not hurt, an individual. I've talked with doctors who unknowingly administered contaminated NECC products to the people they were trying to help, and the impact to them is devastating. The men and women in the medical community who trusted NECC products are among the victims in this tragedy. We are angered by a few who failed to uphold the integrity of critical processes, protocols and procedures, resulting in harm to those we have pledged not to harm.

I turn now to the committee's specific questions. It is important to retain the ability to compound medication. Compounding pharmacies play a vital role in the practice of medicine. While the national attention has focused on major compounding operations, most family pharmacists across America are occasional compounding pharmacists, attested to by the mortar and pestle that are symbols of pharmacy practice. These pharmacists help patients who need smaller doses or different forms or formulations of medications than may be readily available from manufacturers. Children may need medication in a different form to use it. If a child cannot swallow a pill, for example, he or she may need a liquid. Similar considerations apply to hospice patients who may be unable to receive medication by its traditional route. Dermatologists often prescribe compounded products because of the unavailability of certain drug combinations; others are allergic to dyes and preservatives used in medications they need.

It is vital to preserve this traditional compounding, maintaining the value provided to patients, but we must make sure manufacturing of pharmaceuticals is not done under the guise of drug compounding.

Tennessee's laws and regulations, as do most States, provide that the practice of pharmacy includes compounding. In Tennessee, there is not a separate license for

pharmacies who do drug compounding; therefore Tennessee regulates pharmacies under its general pharmacy laws and regulations. It is important to note Tennessee also has a similar license category that encompasses and regulates manufacturers/ wholesalers/ distributors of drugs. The same regulations apply to out-of-state pharmacies, although we necessarily must rely upon the pharmacy's home State and/or Federal entities to inspect and provide "on the ground" regulation. There is always room for improvement. Attention to both regulatory and industry standards are necessary, complimented by a robust and adequately resourced regulatory effort to achieve these improvements. We are actively reviewing our own processes—and in partnership with our Boards, including our Board of Pharmacy, professional associations and other stakeholders—we are considering how we can improve our own regulatory posture, efficiency and effectiveness in Tennessee to assure the safety of patients and the confidence of our public, as well of the people outside our borders who rely on us to regulate their suppliers.

We understand in this situation we can be vulnerable to over-reacting but at the same time we do not want to do too little. Clearly the status quo is not acceptable. While our State is also a victim of these bad actors in another jurisdiction, that does not relieve us of our responsibility to look at our own processes with a critical eye and make them better. When events like this contaminated medication tragedy occur or when we identify a "near miss" we must take the opportunity to see how we can prevent a similar event from occurring again. We are committed to doing just that. In my 15 months as Commissioner of Health in Tennessee and more than two decades in public health, the need to do so has never been more clear.

As an example, we acquire information about non-resident compounding pharmacies from the pharmacy's home State through reciprocity. We could require more information be provided with respect to a pharmacy's operation, so we can more readily identify issues which require investigation or action by State regulators. We also believe information can be collected that will help draw a distinction between traditional compounding and mass-compounding pharmacies. Our review of these issues has led us to believe the factors which the FDA stated it would consider in determining when it would take enforcement action are generally appropriate. We believe a regulating body should:

- Determine whether the pharmacy is compounding drugs in response to or anticipation of receiving prescriptions for individual patients.
- Determine whether the pharmacy is compounding drugs that were withdrawn or removed from the market for safety reasons;
- Determine whether the pharmacy is compounding finished drugs from bulk active ingredients that are not components of FDA approved drugs;
- Determine whether the pharmacy is receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance was made in an FDA-registered facility; and for substances intended for sterile compounding, is sterile upon receipt.
- Determine whether the pharmacy is receiving, storing, or using drug components not guaranteed or otherwise determined to meet official compendia requirements;
- Determine whether the pharmacy is using commercial scale manufacturing or testing equipment for compounding drug products;
- Determine whether the pharmacy is 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; and
- Determine whether the pharmacy is compounding drug products that are commercially available or that are essentially copies of commercially available FDA-approved drug products.

We don't believe any adverse event reporting requirement that exists will capture every occurrence that could lead to harm. Additionally, some errors are not easily detected and therefore not likely to be identified or reported. In the subject outbreak, the fungal meningitis, was not a reportable disease and may have gone undetected as an adverse medication event had we not had robust and trusting relationships with healthcare professionals through our CDC funded healthcare associated infection team and the astute clinicians and scientists that identified a concerning occurrence. In this same case, strokes occurred that were not initially recognized as being linked to the injection of tainted epidural steroids.

We believe it is important for the Federal Government to respond to this issue because many drugs are introduced into interstate commerce, and it is the proper role of the Federal oversight agencies to regulate these drugs and those producing the drugs. In addition to appropriate Federal regulation, however, the Tennessee Department of Health would like to take this opportunity to stress the importance

of our State-Federal partnerships. The capacity building funding for emergency preparedness and training has ensured our ability to marshal resources, particularly people and expertise, to respond correctly and rapidly and to be able to mount a surge of effort in an emergency situation. The prior existence and availability of those resources and excellent communication with Federal partners in this outbreak made a significant difference in the speed and thoroughness of our response. It is crucial these resources remain available to the States for any such future event of public health significance.

In summation, the Tennessee Department of Health is supportive of strengthening the regulatory process for compounding pharmacies through fact-based initiatives that ensure what happened at New England Compounding Center will not happen again. Compounding pharmacies have provided safe, reliable medications for many years, and we shouldn't allow the aberration of a few to negate the value of many who serve admirably. We would also note that regulation is necessary but not sufficient to ensure safe and effective medications. We must also rely on the professionals who do the work every day to keep their sacred obligations to the patients and clinicians they serve in the forefront at all times. We encourage the committee to make sure existing laws and regulatory practices are rigorously enforced, and to consider any additional authorities deemed necessary to ensure all Americans that the drugs they receive through interstate commerce meet all applicable quality standards including safety and effectiveness.

Thank you for your work in this critical area.

STATE OF TENNESSEE, DEPARTMENT OF HEALTH,
BUREAU OF HEALTH LICENSURE AND REGULATION,
DIVISION OF HEALTH RELATED BOARDS,
NASHVILLE, TN 37243.

Hon. LAMAR ALEXANDER,
U.S. Senate,
Washington, DC 20510.

SENATOR ALEXANDER: I wanted to thank you for the opportunity to submit testimony for the upcoming hearings related to compounding pharmacy. The magnitude of the fungal meningitis outbreak has reinforced the need to improve regulation of facilities performing high volume sterile product preparation, both pharmacies and manufacturers. My answers to the questions posed are delineated below.

Question 1. What is the appropriate role of compounding pharmacies in providing medicines to patients?

Answer 1. Compounding is a cornerstone of the practice of pharmacy. Compounding pharmacists prepare custom medicines for patients who may be allergic to a particular ingredient, require a smaller (or larger) dose, or need specialized or rare pharmaceuticals. Compounding has traditionally been limited to these sorts of activities. Compounding requires a high level of pharmacological expertise, as well as close coordination with other health care providers and patients. However, in recent years the practice of compounding has been expanded to include the large-scale repackaging, mixing, and fabrication of drugs. This practice, which under certain circumstances could be considered "drug manufacturing," varies from the traditional practice of compounding. A complex set of factors has led to the rise of this practice, and it is therefore difficult to lay the blame at the feet of any party. While these sorts of organizations have played a valuable role in ensuring the stability of our drug supply, steps should be taken to ensure the continued existence of traditional pharmacy compounding.

Question 2. What is Tennessee's experience with licensing, regulating, and overseeing in-state compounding pharmacies operating within Tennessee's borders? Out-of-state compounding pharmacies? Are there areas that need improvement?

Answer 2. Tennessee law recognizes that compounding is an integral part of the practice of pharmacy. Compounding pharmacies in Tennessee are regulated under the same standards applied to retail pharmacies; there are not distinct licenses for each type of practice. Periodic inspections are carried out by pharmacist investigators to ensure compliance in all areas of pharmacy practice, including compounding.

Out-of-state compounders are judged by the same standards as out-of-state retail pharmacies. The same regulations apply to each, but we have to rely upon regulators in each pharmacy's home State to inspect and ensure that out-of-state pharmacies comply with the law. It would not be practical to inspect all out-of-state

pharmacies that hold Tennessee licenses, nor would it be practical to inspect all drug products shipped into the State from out-of-state pharmacies.

Specific legislation targeted at sterile compounding practices, as well as legislation or regulation that makes a distinction between traditional compounders and manufacturers are two areas to consider. Additional resources could also be helpful.

Question 3. Where do you obtain information about non-resident compounding pharmacies? What solutions would you recommend to improve the availability and understanding of that information?

Answer 3. We acquire information about non-resident compounding pharmacies from regulators in each pharmacy's home State. We could require that more information be provided with respect to a pharmacy's operation, so that we could readily see if there are issues which require investigation or action by State regulators. We could also increase our cooperation and information sharing with Federal entities such as FDA and DEA when the regulatory boundaries blend or crossover.

Question 4. Is there a way to draw a distinction between traditional compounding pharmacies and mass-compounding pharmacies similar to what NECC was doing?

Answer 4. The FDA uses several factors to differentiate between traditional compounding and NECC-type operations. These factors are very helpful in drawing this distinction, and are set out below:

- Determine whether the pharmacy is compounding drugs in anticipation of receiving prescriptions, except in limited quantities;
- Determine whether the pharmacy is compounding drugs that were withdrawn or removed from the market for safety reasons;
- Determine whether the pharmacy is compounding finished drugs from bulk active ingredients that are not components of FDA approved drugs;
- Determine whether the pharmacy is receiving, storing, or using drug substances without first obtaining written assurance from the supplier that each lot of the drug substance was made in an FDA-registered facility;
- Determine whether the pharmacy is receiving, storing, or using drug components not guaranteed or otherwise determined to meet official compendia requirements;
- Determine whether the pharmacy is using commercial scale manufacturing or testing equipment for compounding drug products;
- Determine whether the pharmacy is 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; and
- Determine whether the pharmacy is compounding drug products that are commercially available or that are essentially copies of commercially available FDA-approved drug products.

Question 5. How do Tennessee providers using an out-of-state compounding pharmacy evaluate and determine to use that pharmacy?

Answer 5. This aspect is part of the practice of medicine in Tennessee. It is the facility or provider's ultimate choice to pick a supplier.

Question 6. Do you believe that existing adverse event reporting is adequate to capture any event that may occur as the result of a compounded prescription drug?

Answer 6. It is difficult to determine what sort of adverse event reporting structure could have prevented this tragedy. It is hard to develop event reporting requirements that cover enough ground, but aren't overly burdensome to our health care providers. Given the rapidly changing nature of the healthcare and pharmaceutical industries, event reporting criteria would likely need to be constantly updated. While it is important that health care providers report adverse events to the appropriate bodies, it also ensures that the regulators have the necessary tools to work with the private sector in the event of an emergency.

Question 7. Do you think there should be a Federal response to clarify how compounding pharmacies are regulated in light of the actions of NECC?

Answer 7. Yes, clarification is highly important as it pertains to the differentiation between manufacturing and compounding pharmacy and the resulting variances in regulation. Federal leadership would also be beneficial to develop communication channels that will increase transparency and facilitate interstate and interagency information exchange, resulting in more informed regulation by individual States or regulating bodies.

Thank you for your willingness to take on the daunting task of regulatory reform. With thoughtful input from a variety of sources, we are more likely to find a fitting solution to the challenges that we face.

Sincerely,

ANDREW C. HOLT, *Pharm.D.*,
EXECUTIVE DIRECTOR,
Tennessee Board of Pharmacy.

PREPARED STATEMENT OF CRAIG BECKER, PRESIDENT, TENNESSEE HOSPITAL ASSOCIATION (THA), NASHVILLE, TN

On behalf of the Tennessee Hospital Association and its member hospitals, I would like to thank Senator Alexander for the opportunity to comment on the recent meningitis outbreak in Tennessee and the impact on the patients we serve. It is my intention to provide the Health, Education, Labor, and Pensions (HELP) Committee with a chronological description of events, the role of THA and finally with lessons learned from this tragedy.

First and foremost, THA and its members' primary concern is over the health of the patients impacted by this tragedy. Once the problem had been identified by the Tennessee Department of Health (TDH) and the Center for Disease Control (CDC), THA members stopped using the tainted product. Once the cause of the outbreak and a course of action had been determined, THA and its members took every appropriate action to deal with this unprecedented crisis.

We hope and pray that there never will be another incident like this, but we feel the systems in place to notify members, pull the tainted product off the shelves and treat the infected patients, worked. We cannot thank enough the TDH, Commissioner John Dreyzehner, M.D., MPH, Marion Kainer, M.D., MPH, Director, Healthcare Associated Infections and Antimicrobial Resistance program and the rest of the TDH staff for its prompt actions and for its succinct directions to the provider community.

THA's role in this event was primarily to act as a conduit for information to our members and non-members alike, as it was made available from the TDH and other Federal agencies. THA has a data base of all key administrative and clinical people in Tennessee's hospitals. At various times, at the direction of the TDH, THA provided hospitals, both members and non-members, with critical information about the crisis and more important, actionable directions on how to treat, or not treat those affected patients.

CHRONOLOGY

I believe it would be instructional for the committee to know the chronology of events THA has developed from our combined notes and calendars. It should be understood this is based on THA material and not others, who may differ with our view.

September 18, 2012—Dr. April Pettit, an infectious disease specialist at Vanderbilt University Medical Center, treats the first (index) case, realizing this type of spinal meningitis was extremely rare. Dr. Pettit alerted TDH to the potential problem. Dr. Kainer immediately implements surveillance procedures to determine if there were other cases.

September 20, 2012—TDH identifies two other possible cases. Dr. Kainer notifies CDC.

September 24, 2012—After surveying the clinic where the outbreak had occurred, TDH traces tainted product back to New England Compounding Center (NECC) and requests from Massachusetts Department of Health (MDH) a distribution list of all products shipped to Tennessee.

September 25, 2012—Tracing records back, TDH determines "Clinic A" as the likely location for several of the patients. It should be noted that the provider community acted immediately, closing the suspected clinic and totally supported the TDH investigation. The clinic identified and gave all patient information to TDH and provided full access to clinical records.

September 26, 2012—NECC issues a voluntary recall of steroid products.

September 28, 2012—CDC declares the problem a multi-state outbreak.

October 30, 2012—At the direction of Commissioner Dreyzehner, THA began acting as a conduit of information to get information to all key staff in hospitals and clinics, noting the clear connection to NECC.

October 5, 2012—Federal Drug Administration (FDA) confirms a sealed vial is contaminated and issues a national recall and order to cease using NECC products.

October 8–10, 2012—THA and TDH work together providing constant timely information to providers on findings and treatment recommendations.

October 15, 2012—THA hosts a conference call with TDH and key hospital staff.

October 16, 2012—THA staff follows up with personal calls to same key staff of all hospitals and clinics that received NECC product to be sure the product has been pulled from all clinical areas, including crash carts, ambulatory units, etc.

October 17, 2012—THA briefs FDA on the situation and requests guidance on who our providers should contact, what they should say, what patient prioritization (surgery, topical, etc.) should providers use, and guidance on how to deal with the pediatric population. FDA took our request under advisement.

October 18, 2012—THA, working with TDH, sends out sample notification letters, which includes guidance from FDA and CDC. Again, THA personally contacts those impacted hospitals and clinics.

October 19, 2012—THA provides additional information received from TDH on media responses, patient letters. This became a burden for hospitals not NECC. Also, a flood of "worried well" patients began showing up in hospital ERs. Hospitals had to take critical staff away from patient care to staff call centers to field calls from the "worried well."

October 20, 2012—To present TDH determines 42 days is the critical time for incubation of the disease, and flood of patients begins to ease. THA and TDH continue to be in constant contact and alerts are sent as needed.

LESSONS LEARNED

As in any crisis, it is always important to review lessons learned to be prepared for the future disaster. The following represent the significant findings from THA's perspective.

1. The Tennessee Health Alert Network, (THAN), developed after 9/11 was invaluable. Even with THA having an extensive list of key staff, THAN alerted providers about the problem much faster than we could have otherwise.

2. Having a transparent and open line of communication with TDH, THA and the provider community was the most important element of dealing with the crisis. Drs. Dreyzehner and Kainer are to be commended for keeping in constant contact and for being willing to utilize a non-government entity such as THA to transmit accurate and timely information. We found it discouraging that Federal agencies weren't aware of the role non-governmental entities could play in such an emergency.

3. There needs to be a better system of contacting smaller ambulatory care and physician office settings. Getting the information to them was mostly through the media.

4. Better and timelier guidance from Federal agencies is critical. There were many questions around whether or not products such as eye drops should be given priority status and what providers should tell patients. It appeared to those of us in the field that coordination among agencies was lacking. One suggestion would be to designate a lead agency in a crisis like this and to empower the appropriate staffs to give out information to providers and their representatives instead of having to "run it up the flag pole."

5. As a follow up to No. 4, a national spokesperson speaking out on the crisis would have been very helpful. In Tennessee, Dr. Dreyzehner was the very effective face of the crisis. He was transparent, open and didn't avoid the tough questions.

6. This was a supplier issue, not a provider issue. Hospitals, doctors and nurses worked on the assumption these drugs were safe; however when the crisis erupted, it became their problem, not NECC's. It would have been helpful for a Federal agency to make it clear to the public that it was NECC's problem, not the provider community. In some ways, our doctors and nurses feel as much a victim as our patients.

CONCLUSION

This was a tragedy to our patients, to the trust in the safety of our drugs from both the provider and patient perspective and to the providers who injected what they thought was safe product. I have personally talked with doctors and nurses who have said they are devastated by what happened.

Again, I cannot express enough appreciation to Drs. Dreyzehner and Kainer and the entire TDH staff for its support, quick action and openness, all of which no doubt saved lives. We have learned from this tragedy and will be better prepared

for the next one. It is our greatest hope that hospitals, doctors and nurses can be assured we have safe and adequate medications, to serve the American people.

Thank you for your time and for allowing me to thank those who acted so courageously in dealing with this outbreak.

TENNESSEE PHARMACISTS ASSOCIATION (TPA),
NASHVILLE, TN 37219,
November 15, 2012.

Hon. LAMAR ALEXANDER,
U.S. Senate,
455 Dirksen Senate Office Building,
Washington, DC 20510.

Re: Response to Request for Testimony Regarding Pharmacy Compounding in Tennessee

DEAR SENATOR ALEXANDER: The Tennessee Pharmacists Association appreciates the opportunity to submit testimony for the record to the U.S. Senate Health, Education, Labor, and Pensions (HELP) Committee for your November 15, 2012, hearing entitled "Pharmacy Compounding: Implications of the 2012 Meningitis Outbreak." We thank you for your service to the citizens of Tennessee and our country.

The Tennessee Pharmacists Association (TPA) is a professional organization representing pharmacists, student pharmacists, pharmacy technicians and others interested in improving medication use and patient care in Tennessee. TPA members provide care in all practice settings, including community pharmacies, hospitals, long-term care facilities and other settings. TPA and its members are deeply concerned about the tragic situation that has occurred as a result of what appears to be large-scale manufacturing by a pharmacy in Massachusetts, and we are prepared to work with legislators and regulators to assure public safety and access to quality medications that meet patients' needs. We extend our deepest sympathy to patients and families affected by this tragic event.

RESPONSES TO SPECIFIC QUESTIONS

The questions you posed demonstrate a sincere desire to understand the complexities of the issue, and Tennessee's pharmacists appreciate your commitment. Our responses are provided after surveying TPA member pharmacists and reviewing their responses to the questions. In some instances, responses are provided that are specific to hospital/health-system pharmacy practice settings and are so noted.

To assure a clear understanding of the answers below, we are providing the definitions for "compounding" and "manufacturer" found in the Tennessee Pharmacy Practice Act, §TCA 63–10–204:

Compounding

(4) "Compounding" means the preparation, mixing, assembling, packaging or labeling of a drug or device:

(A) As the result of a prescription order or initiative based on the prescriber-patient-pharmacist relationship in the course of professional practice,

(B) In anticipation of prescription orders based on routine, regularly observed prescribing patterns; or

(C) For the purpose of, or as an incident to, research, teaching or chemical analysis and not for sale or dispensing;

Manufacturer

(21) "Manufacturer" means any person, except a pharmacist compounding in the normal course of professional practice, engaged in the commercial production, preparation, propagation, conversion or processing of a drug, either directly or indirectly, by extraction from substances of natural origin or independently by means of chemical synthesis, or both, and includes any packaging or repackaging of a drug or the labeling or relabeling of its container and the promotion and marketing of such drugs or devices;

Question 1. What is the appropriate role of compounding pharmacies in providing medicines to patients?

Answer 1. Compounding has been and continues to be an essential and integral part of the profession of pharmacy and was the major component of pharmacy practice for many years prior to large-scale pharmaceutical manufacturing. Compounding allows pharmacists to meet specific patient medication needs, including veterinary needs. Pharmacists are educated, trained and qualified to provide these services for their patients.

Generally speaking, compounding of a pharmaceutical product occurs when a particular patient has a specific need and the medication dosage form or concentration required to treat that need is not available from a commercial manufacturer, or is not available due to a shortage. Many patient populations require medications that may not be available for a variety of reasons. For example:

1. Pediatric patients, particularly neonates, may require small dosages or customized dosage forms that aren't manufactured by an FDA-approved manufacturer.
2. Geriatric patients may need a dose in an oral liquid that can be administered via nasogastric tubes.
3. Patients undergoing anesthesia, such as women in labor, require medications that must be sterile and free of preservatives in order to be safely administered through an epidural injection.

Increasingly, compounded pharmacy products are also purchased to fulfill patient needs for prescription drugs that are not available due to manufacturers' shortages or back-order situations. When certain drug products cannot be purchased through the routine inventory chains, the critical product may only be available through compounding pharmacies. Critical shortages continue to contribute to medication safety issues, and compounding pharmacies are often the only source of these agents.

Compounding is a necessary component of the professional practice of *all pharmacies*. Many community pharmacies routinely engage in preparation of non-sterile pharmaceuticals. The simple mixing of two commercially manufactured products into a new product—such as adding a customized flavoring agent—is compounding, as is mixing two creams together. Preparing of any intravenous admixture or creating specialty pediatric or geriatric dose formulations is also compounding, in that a manufactured product is altered for specific patient needs. All pharmacists must have the right to compound and prepare a product for an individual patient need.

Additional Comments From the Health-System/Hospital Pharmacy Community

While not every community pharmacy is equipped for sterile compounding, it is a necessary component in the daily routine of every hospital pharmacy. Compounding pharmacies provide a significant service to hospital patients. They formulate therapeutic and diagnostic products, make noncommercial formulations, customized preservative-free and dye-free formulations, and are essential to meet the needs created by national pharmaceutical shortages. Compounding pharmacies fill a niche with high-risk compounding, such as non-sterile to sterile IV admixtures like cardioplegia solutions or IV Continuous Renal Replacement Therapy solutions. Most inpatient hospital pharmacies in Tennessee do not have IV rooms that meet structural USP 797 regulations, nor the equipment, expertise, or testing processes to perform this level of compounding safely. Compounding pharmacies can provide this service at an extremely high quality. With the critical shortages of sterile injectibles, especially medications that are used in code or emergency situations, compounding pharmacies also perform sterile transfer from larger size injectibles to the size and dosage form that is readily available. This prevents serious medication errors from occurring and prevents delays in emergency therapy.

Question 2. What is Tennessee's experience with licensing, regulating, and overseeing in-state compounding pharmacies operating within Tennessee's borders? Out-of-state compounding pharmacies? Are there areas that need improvement?

Answer 2. The Tennessee Board of Pharmacy has successfully regulated all pharmacies providing patient care services in Tennessee, including both hospital- and community-based pharmacies that compound. Additionally, the Board of Pharmacy regulates manufacturers, wholesalers and distributors located in Tennessee. State law requires all Tennessee Board of Pharmacy investigators to be pharmacists licensed in Tennessee. The Tennessee Board of Pharmacy routinely inspects all licensees located in-state to verify compliance with laws, rules and standards of practice.

Tennessee law requires any pharmacy, regardless of whether located in-state or out-of-state, providing services to a Tennessee resident to be licensed by the Tennessee Board of Pharmacy. Regarding out-of-state pharmacies, the Tennessee Board of Pharmacy relies on the Boards of Pharmacy in other States for regulation of the pharmacies in their respective States. The Tennessee Board does not and cannot conduct on-site inspections of out-of-state pharmacies to verify compliance with Tennessee law and Board regulations. Inspections by out-of-state agencies, if conducted at all, may vary widely from State to State, as do State rules and regulations. The qualifications of the inspectors in other States may vary as well.

Inspections of pharmacies by qualified personnel are critical. Visual, on-site inspection of the premises, the culture of the pharmacy staff, and operations are im-

portant in assessing the appropriate actions of the pharmacy being inspected. We believe all States must have requirements for routine and thorough inspections of pharmacies. It is imperative that all Boards of Pharmacy be provided sufficient resources to employ optimal numbers of pharmacists as inspectors and to provide the ongoing training needed by those pharmacist inspectors.

Question 3. Where do you obtain information about non-resident compounding pharmacies? What solutions would you recommend to improve the availability and understanding of that information?

Answer 3. From a regulatory perspective, information on non-resident compounding pharmacies comes from the Tennessee Board of Pharmacy or, if information is shared, from the Board of Pharmacy in the State where the pharmacy is originally licensed.

Most information regarding sources of compounded products comes either from hospital pharmacy buying groups or as "word of mouth" or recommendations from colleagues. Marketing materials or advertisements may also be a source of information. Small hospitals would rely heavily on such materials, while larger institutions with greater resources at their disposal may conduct on-site visits at out-of-state pharmacies.

Question 4. Is there a way to draw a distinction between traditional compounding pharmacies and mass-compounding pharmacies similar to what NECC allegedly was doing?

Answer 4. It is very difficult to definitively differentiate between compounding and manufacturing in all circumstances. While it is easy to determine that a traditional pharmacy practice providing patient-specific, small-volume services as described in the definition of compounding is "compounding," the provision of compounded medications may be of significant volumes and still be compounding as opposed to manufacturing. Manufacturing occurs when individual patient needs are not part of the process. Altering drug products in large quantities for resale that are not prepared and labeled for specific patient use in the final State is manufacturing. Current State and national laws need to be enforced to protect our citizens.

Whatever proposals are considered, we believe it is important that State Boards of Pharmacy continue to license and regulate traditional compounding, while recognizing that large-scale production of sterile products that are not for specific patients may require oversight by the Food and Drug Administration (FDA) in cooperation with State Boards of Pharmacy. A process for better collaboration and cooperation between State Boards of Pharmacy and the FDA would be a step forward.

Question 5. How do Tennessee providers using an out-of-state compounding pharmacy evaluate and determine to use that pharmacy?

Answer 5. The Tennessee Department of Health has an on-line resource that allows healthcare providers to research the licensure of all entities through a web portal: http://health.state.tn.us/HCF/Facilities_Listings/facilities.htm.

Pharmacists also use an evaluation tool published by the American Society of Health-System Pharmacists. This tool can be located at: http://www.ashpfoundation .org/sterileproductstool.

In addition, pharmacists receive information through hospital buying groups and from marketing information received. Again, word of mouth or positive recommendations by colleagues can have a major influence on selection of out-of-state compounding pharmacies.

Availability and pricing may be considered in these decisions.

Question 6. Do you believe that existing adverse event reporting is adequate to capture any that may occur as the result of a compounded prescription drug?

Answer 6. The Tennessee Board of Pharmacy rule 1140–03–.14(14) states:

> "The designated pharmacist in charge shall report to the board any situation in which a medical or prescription order has caused serious personal injury or death."

In Tennessee, reporting of adverse events that occur at this level is not an option but a requirement.

The current national system of voluntary reporting adverse medication reactions is probably underutilized for both compounded and manufactured medications. While pharmacists support the concept of actively reporting adverse reactions to compounded and commercially available preparations, the existing system—FDA MedWatch program—is designed in such a manner as to actually impede pharmacists' participation. There needs to be additional collaboration between the FDA and compounding pharmacists, so this system can be widely and meaningfully used.

Additional Comments From the Health-System/Hospital Pharmacy Community

The existing FDA adverse event reporting mechanism commonly referred to as MedWatch (https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm) is cumbersome and time-consuming. Furthermore, it is an entirely voluntary process. We believe that the vast majority of providers/prescribers are unaware of this reporting process. We also believe that many reports are never made due to a fear of reprisal.

Question 7. Do you think there should be a Federal response to clarify how compounding pharmacies are regulated in light of other actions of NECC?

Answer 7. We believe that if NECC had been properly categorized as a manufacturer (instead of a compounding pharmacy), existing regulations as enforced by the FDA would have been adequate to prevent this tragedy from taking place. We believe there is a need for more stringent oversight and a clearer distinction between compounding and manufacturing. The FDA does require clear authority, adequate funding and staffing in order to properly inspect and oversee manufacturers of pharmaceuticals.

Unfortunately, there are no laws that will absolutely prevent unethical behavior or operations that fall short of recognized standards. Thorough and routine inspections by qualified and trained individuals and stringent oversight by regulatory personnel are the best approaches to prevent these types of situations.

TPA remains committed to working with Congress, State legislators, national and State regulators, and other stakeholders to address any regulatory gaps that may exist and reduce the likelihood of any problems from compounded products in the future.

Please contact me if you have questions or need additional information regarding the comments that TPA has submitted. Again, thank you for requesting input from pharmacists and other health care professionals in Tennessee.

Sincerely,

BAETEENA M. BLACK, D.PH.,
Executive Director.

TENNESSEE MEDICAL ASSOCIATION (TMA),
NASHVILLE, TN 37212,
November 14, 2012.

Hon. LAMAR ALEXANDER,
U.S. Senate,
455 Dirksen Senate Office Building,
Washington DC 20510.

Re: Meningitis Outbreak

DEAR SENATOR ALEXANDER: Thank you for the opportunity to make comments on the recent nationwide meningitis outbreak. First and foremost, our hearts go out to the thousands of patients who sought care from physicians for chronic back pain, only to later learn that the medication administered was contaminated. Whether the patients were diagnosed with fungal meningitis or were fortunate enough not to be affected, they all were placed in an unfortunate position that was probably preventable had there been more oversight of the Massachusetts compounding pharmacy.

For background purposes, members of the Senate Health, Education, Labor, and Pensions Committee should be aware that chronic pain and its treatment has become an increasingly visible part of medical treatment over the last 20 years. Well-educated and appropriately trained physicians will almost always initiate other, less aggressive forms of treatment, such as pharmaceutical or physical therapy, before initiating spinal injections or even more invasive surgical procedures. A provider treating chronic back pain should be somewhat passive when starting spinal injections and, if the patient does not get relief, stop the treatment regimen.

Compounding pharmacies, both local to the State of Tennessee and those that are external to the State of Tennessee doing business in our State, are overseen and licensed by the Tennessee Board of Pharmacy. Tennessee physicians believe that our Pharmacy Board performs these duties with great care and diligence. We have no reason to believe that any patient seen and cared for at any of the three centers which received the tainted medication here in Tennessee was provided anything but the appropriate standard of care. Our pain physicians in the State tell us that they do use compounded drugs for those hard to get drugs or for repackaging. Prior to this outbreak, the prevailing perception among the physician community in Tennessee was that compounding pharmacies were as regulated as manufacturing phar-

macies and that generally the products they marketed met the necessary quality control standards for safety and efficacy.

We now know differently and believe that Congress can assure the development of a transparent and accountable regulatory system, whether that be Federal or on a State level, over the production and distribution of compounded drugs. It is our understanding that, if the company had been licensed as a manufacturer, they would have come under the aegis of the FDA. Regulatory gaps should be filled so physicians can once again feel safe about the compounded drugs they order. Should Congress determine that the Food and Drug Administration is the proper entity to oversee this facet of the health care system, we would ask you to provide the agency with the necessary authority and resources to effectively regulate the industry.

In terms of the adverse event reporting, existing mechanisms are in place to report adverse outcomes. The elusive component of any reporting system is "recognizing" an event as adverse and related to a medication, compounded or not. Fortunately, a very perceptive Vanderbilt physician was able to identify the cause of a very bad outcome and reported it immediately to State officials. Once recognized, capturing and reporting is reasonably straight-forward.

Since the outbreak was publicized, we have heard from some individual physicians specializing in pain care that patients have expressed a real reluctance to undertake spinal injections. For some, other treatment options may be available but for many the injections represent the best long-term hope for relief of their pain. Although their reluctance is certainly understandable, such a response limits the options available to the treating physician and ultimately will mean less-than-acceptable care to the patient. Whatever Congress can do to assure consumers that this outbreak represents an opportunity to make real change that will minimize the possibility of future reoccurrences would be a significant step forward.

Thank you again for the opportunity to make comments on this issue.

Sincerely,

WILEY ROBINSON, M.D., FHM,
President.

THE COMMONWEALTH OF MASSACHUSETTS,
BOSTON, MA 02108–4619,
January 23, 2013.

U.S. SENATE,
Committee on Health, Education, Labor, and Pensions,
Attn: Pamela J. Smith, Staff Director; and
Frank J. Macchiarola, Republican Staff Director,
428 Senate Dirksen Office Building,
Washington, DC 20510–6300.

DEAR MS. SMITH AND MR. MACCHIAROLA: Thank you for the opportunity to respond to your member's inquiries regarding compounding pharmacy oversight and the New England Compounding Center (NECC)—the company primarily responsible for the meningitis outbreak that has claimed dozens of lives across the country. As the Massachusetts Department of Public Health continues to take aggressive actions to protect public safety, our ongoing collaboration with your committee is important to ensure that this type of tragedy never happens again.

In Massachusetts, we have taken significant actions to enhance our regulations, increase inspection schedules and hold pharmacies accountable following this tragic outbreak. And this month, Governor Patrick filed strong legislation to further increase oversight of pharmacies, including regulation of out-of-state pharmacies and reconstitution of our Board of Pharmacy. As we work to raise standards in Massachusetts, we urge Congress to act to strengthen Federal oversight to address the regulatory grey areas that exist between State and Federal regulation.

The Department is committed to our continued and close collaboration with the committee, the Centers for Disease Control and Prevention (CDC), the U.S. Food and Drug Administration (FDA), and other States' public health officials to investigate the exact cause of an outbreak to take the necessary actions to enhance policies and adopt best practices both here and across the Nation.

I welcome the opportunity to continue this work with you, your fellow committee members, and the U.S. House Energy and Commerce Committee to address these critical needs.

Below you will find answers to your specific questions. Please do not hesitate to be in touch with me or my staff. We thank you for your continued leadership.

Sincerely,

LAUREN A. SMITH, M.D., MPH,
Interim Commissioner.

Question 1. Why did the Massachusetts Board of Pharmacy enter into a weakened consent agreement with NECC, even after forwarding the original, stronger consent agreement (which included a public reprimand) to the prosecuting attorneys within the Department of Public Health?

Answer 1. These actions were taken in 2006 during a previous Administration and are deeply troubling. An extensive file-by-file and e-mail review conducted by staff has yet to uncover any documentation, information or communications that clearly describe what transpired between the initial consent decree in 2004 and the final actions taken by the Board in 2006.

While NECC bears the primary responsibility for this tragic outbreak, it is apparent that Board staff displayed poor judgment, missed opportunities and failed to take appropriate action to hold NECC accountable. Those individuals who were responsible have been removed from their jobs.

Question 2. Did the Department of Public Health ever consider legal action as an alternative to either of the consent agreements?

Answer 2. As stated above, the lack of documentation related to these decisions is troubling. In the absence of such information, we cannot clearly establish the array of options that may have been considered.

Question 3. What steps are you currently undertaking to improve oversight of compounding pharmacies in Massachusetts?

Answer 3. Following my testimony before the committee on November 15, 2012, the Commonwealth has taken significant actions to this effect, which I am happy to share with you.

We advanced emergency regulations that went into effect immediately on November 1, 2012, to enhance our ability to monitor the sterile compounding industry. The new regulations require sterile compounding pharmacies in Massachusetts to report, for the first time, volume and distribution figures to the State, which will alert the Board of any pharmacy that is acting like a manufacturer, which requires an FDA license.

The regulations also require all licensed pharmacies and pharmacists to report to the Board when they are the subject of any disciplinary action by any State or Federal agency. This will allow the Board to know when other entities have identified issues with Massachusetts-licensed pharmacies.[1]

Nearly 40 pharmacies have been inspected since Governor Patrick directed the Board of Pharmacy to begin checks of compounding pharmacies that produce sterile injectable medications. These inspections identified problems in several pharmacies for which new cease and desist orders have been issued and corrective plans have been put into place.

Other pharmacies that have been inspected have come back with minor deficiencies that have since been corrected, or are currently being addressed. Unannounced inspections of compounding pharmacies that produce sterile injectable medications will continue until all have been inspected.

We also announced changes at the Massachusetts Board of Pharmacy, with three new members who work across diverse health care settings filling seats on the Board.

In October 2012, the Governor established a Special Commission on Pharmacy Compounding as part of the Administration's comprehensive response to the outbreak. The Commission met regularly, looking at best practices in other States and exploring changes to the law to help address the regulatory gray area surrounding compounding pharmacies. A final report was issued on January 4, 2013.

Building on the recommendations identified by the Commission, on January 4, 2013 Governor Patrick also announced the filing of legislation to reform the Board of Pharmacy and strengthen the Commonwealth's oversight of the compounding pharmacy industry in Massachusetts. Specifically, the legislation:

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[1] Please note that the Massachusetts Board of Pharmacy voted on final regulations as described on January 8, 2013. These regulations will become final once published within the Massachusetts Register on February 1, 2013.

1. Requires a special license for sterile compounding that will enable regulators to better track and hold pharmacies accountable for their practices;

2. For the first time, authorizes the Board to assess fines against Massachusetts-licensed pharmacies that violate Board of Pharmacy policies, regulations, or statute; and establishes whistleblower protections for pharmacists and pharmacy staff;

3. Requires licensure for out-of-state pharmacies that deliver and dispense medications in the Commonwealth;

4. Establishes a clear process to restructure and reorganize the composition of the Board of Pharmacy, ensuring more balanced representation of background of Board members to improve oversight of the industry. The Board will include more members not practicing in the industry they are responsible for regulating. Under the legislation, the eleven (11) member Board would be comprised of four pharmacists, one pharmacy technician, one nurse, one physician, one quality improvement expert, and three public members who have experience in healthcare delivery or consumer advocacy.

Question 4. FDA inspectors released recently a report last week from their recent investigation of Ameridose—a company owned and managed by the same families as the New England Compounding Center. This report included the following description of the conditions they found—I quote:

> " . . . insects were observed to be located in the unclassified area where finished sterile product is packaged and stored. The insects were also located within approximately 3 to 10 feet of the controlled area where sterile products are manufactured. At least one bird was observed flying in the unclassified area where sterile finished product is packaged and stored."

How do you explain the fact that Ameridose was shipping products all over the country that had been manufactured under these circumstances, given the years of complaints about both the New England Compounding Center and Ameridose?

Answer 4. In the course of its licensure in Massachusetts, Ameridose had been subject to one complaint, pertaining to potential patent infringement. This issue was settled between Ameridose and the complainant.

During previous licensure inspections, Board staff did not identify any findings similar as those witnessed during the joint inspection with the FDA. As soon as we learned of these issues, we took action to suspend operations at Ameridose and NECC's other sister companies. The FDA secured a recall of all Ameridose products and the company remains closed.

These events have clearly indicated that the complaints-driven inspection policies that were used by Massachusetts and continue to be used by many States are insufficient to provide comprehensive oversight to compounding pharmacies. It is important to know how a pharmacy is operating when they are not scheduled for an inspection. That is why Massachusetts now has unannounced inspections of all pharmacies compounding sterile injectable substances and we have advanced new regulations to enhance our inspection schedules.

Question 5. Many State Boards of Pharmacy rely on the Board of Pharmacy in the State where a pharmacy is physically located to conduct inspections, since most Boards of Pharmacy do not have the capacity to inspect pharmacies across the country. Given the current crisis, how do you think Minnesota's Board of Pharmacy can make sure that a pharmacy in Massachusetts is shipping safe products into Minnesota? Does the current system work?

Answer 5. As you have pointed out, limited, geographic-bound resources require greater, more consistent and streamlined communications between States, as well as our Federal partners. Although we have taken great strides to increase oversight in Massachusetts, similar progress is needed at the Federal level. The Federal Government's role in oversight of interstate commerce is essential to our shared success. Likewise, the FDA must fulfill its obligation to ensure that manufacturers declare themselves as such and abide by all Federal laws and regulations. In Massachusetts, our Board of Pharmacy has adopted emergency regulations that require every pharmacy to report within 7 business days all adverse events relating to the preparation of medications in that pharmacy. Additionally, pharmacies in Massachusetts are now required to share all disciplinary actions taken by other States and the FDA on receipt. While this does not substitute for clear, regular and streamlined communications between all parties, I believe these to be important steps forward to ensure this never is allowed to happen again.

As outlined in the Department's response to Question 3, through the Governor's filed legislative reform, the Board will now have the authority to regulate out-of-state compounding pharmacies that ship medications into Massachusetts through the development of an out-of-state oversight process. The Board will also gain the

authority to create an alternate licensure category for pharmacies that pose a higher risk to the public, and to levy fines against these licensees where appropriate. Additionally, Massachusetts is working with our Commission on compounding pharmacies as well as the National Association of Boards of Pharmacy (NABP) to further address these issues and make enhancements where necessary.

Question 6a. In addition to the report from the FDA of infestations of insects, vermin, and even a bird in Ameridose's facility, according to the FDA's inspection report, Ameridose did not adequately test sterility or log complaints from patients and reports of adverse events. Can you clarify the requirements of a compounding pharmacy in the Commonwealth of Massachusetts regarding sterility testing and the reporting of complaints and adverse health events?

Answer 6a. The Massachusetts Board of Pharmacy regulation 247 CMR 9.01(3) requires that "a pharmacist shall observe the standards of the current United States Pharmacopoeia." Briefly, United States Pharmacopoeia ("USP") requires the following testing:

- Viable particle testing must be done every 6 months at a minimum and when certifying new equipment, following any servicing of facilities or equipment, and in response to issues of compounded sterile preparations (CSPs).
- Sampling of compounding personnel glove fingertips, at least annually.
- Media fill test, at least annually.
- All high-risk level CSPs that are prepared in groups of more than 25 identical single dose packages or multi-dose vials must meet sterility tests before they are dispensed/administered. (They also have to be tested for bacterial; endotoxins (pyrogens)).

Additionally, the emergency regulation, 247 CMR 6.15(5), adopted on November 1, 2012 requires pharmacies to attest to compliance with USP <797>. In the Spring of 2012, the Board began requiring new pharmacies that engage in sterile compounding to complete a USP <797> Gap Analysis. Presently, inspections of pharmacies engaged in sterile compounding focus on compliance with USP <797>.

The emergency regulation, 247 CMR 6.15(6), adopted on November 1, 2012, requires every pharmacy to report within 7 business days all errors that occur during the preparation of medications in that pharmacy, building on previously established reporting requirements for medication errors that led to patient harm.

Question 6b. Had these requirements been fully implemented, would they have been sufficient? Does the State have the capacity to enforce these requirements?

Answer 6b. Massachusetts has the authority to enforce its regulations, which require compliance with USP <797> and reporting of adverse events, and to impose disciplinary action for any violation of its regulations. 247 CMR 6.15(5);247 CMR 9.01(3); 247 CMR 10.03.

Question 6c. Does the State have the capacity to enforce these requirements for compounding pharmacies located in other States that are shipping into Massachusetts—for example, the statewide requirement that Minnesota also has on the books that sterile products be compounded according to the United States Pharmacopea?

Answer 6c. The Governor's proposed legislation introduces an out-of-state licensure category, currently not in existence in Massachusetts. Through comprehensive requirements on all pharmacies that seek to ship medications to the Commonwealth, we will gain the authority to enforce requirements in the quality and safety of compounding processes.

Question 7. After reviewing the documents and looking at the timeline, it is clear that NECC had multiple violations of Massachusetts pharmacy law. What, in addition to the multiple violations and inspection reports, would prompt the Board to suspend or revoke a pharmacy license?

Answer 7. Under my leadership, the Board and DPH will continue to act swiftly to hold pharmacies and pharmacists sufficiently responsible for their actions. While I was not at the Department during the deliberations around NECC's 2006 consent agreement, it is my position that the action was insufficient given the severity and volume of deficiencies from their initial licensure in 1998 through 2004. Since we learned of this crisis, we secured suspension of operations at NECC and its sister companies and launched unannounced inspections of all pharmacies compounding sterile injectible substances, which have also resulted in additional cease and desist orders and corrective plans.

Question 8. How often do you suspend or revoke licenses, and what factors are considered when deciding between different disciplinary actions? What is the proc-

ess to suspend or revoke a license, both when you have the consent of the company and you do not?

Answer 8. Inspections and resulting disciplinary actions by the Board, including but not limited to suspensions and revocations of a pharmacy's retail license, constitute a complaint-driven process. As defined with the Board of Pharmacy, a "complaint" is a formal proceeding and does not refer to the colloquial use of the word. The Board receives approximately 300 complaints per year. The Board opens a "complaint" after receiving information about issues with a licensee, and establishing that an investigation is warranted.

Complaints that warrant disciplinary action are often a result of identified deficiencies found in the course of an inspection. Historical data is readily available for the 6 years of the Patrick-Murray Administration (January 2007 through December 2012). During this time period, the Board identified deficiencies during its inspections of the self-identified sterile compounding pharmacies on eight occasions. In seven of these instances, the deficiencies were resolved without the need for further Board action; however, Board action was required in one case. (*See* CIVAS complaint history, appended and referenced as **Attachment A**.) While Attachment A provides a thorough summary of the history, below are examples of types of deficiencies noted:

- Failures to maintain required documentation (e.g., perpetual inventory for controlled substances);
- Unregistered technician observed working in control room;
- Failure to maintain appropriate supervisory ratios;
- Equipment lacking and having outdated seals and/or certification (e.g., balance);
- Broken equipment (e.g., thermometer in ante room);
- General concerns regarding cleanliness;
- Refrigeration concerns (e.g., refrigeration logs with temperature readings below recommended level);
- Expired drugs on shelves; and
- Inadequate security (e.g., door left ajar).

Should a complaint warrant Board action, the Board can choose to take either a disciplinary or non-disciplinary action. The Massachusetts General Laws grant the Board the authority to take various disciplinary and non-disciplinary actions. Disciplinary actions are intended for those described in our regulations that result in a permanent mark on a licensee's record that is publicly reported and available to consumers on our Web site. Disciplinary actions may include: suspension, revocation of personal registration, pharmacy permit, license or controlled substance registration, reprimand or censure of the registrant or licensee, cease and desist notice, consent agreement or probation. Non-disciplinary actions may include a non-disciplinary warning letter, advisory letter, a consent agreement with non-disciplinary actions, or dismissal of the complaint. The actions available to the Board are summarized with the corresponding statutory authority (*See* **Attachment B**). It should be noted that Governor Patrick's recently filed legislation authorizes the Board to assess fines against Massachusetts-licensed pharmacies that violate Board of Pharmacy policies, regulations, or statute.

From 2002–12, the Board recorded sixty-eight (68) disciplinary actions taken against Massachusetts retail pharmacies:

Year 2002—No. of Disciplinary Actions: 1
Year 2003—No. of Disciplinary Actions: 4
Year 2004—No. of Disciplinary Actions: 2
Year 2005—No. of Disciplinary Actions: 4
Year 2006—No. of Disciplinary Actions: 2
Year 2007—No. of Disciplinary Actions: 4
Year 2008—No. of Disciplinary Actions: 9
Year 2009—No. of Disciplinary Actions: 9
Year 2010—No. of Disciplinary Actions: 11
Year 2011—No. of Disciplinary Actions: 17
Year 2012—No. of Disciplinary Actions: 5

Question 9. Please briefly discuss past situations in which the Board has revoked a license. What violations were evident in those facilities? Was the revocation communicated to other State boards or the FDA?

Specifically, were any revoked for violations of the patient-specific prescription rule? What were the circumstances?

Answer 9. Since January 1, 2000, the Massachusetts Board of Pharmacy has taken action against 14 pharmacies, to revoke, suspend, or summarily suspend licensure, or enter into a consent agreement for surrender of licensure. None of the

14 instances involved violation of the patient-specific prescription rule. The circumstances varied, and include: Medicaid fraud (false claims to MassHealth), improper storage or handling of drugs; failure to maintain proper sanitation; repackaging and redispensing medications that had been returned; issues involving sample medications; sale of drugs to an unlicensed entity; and failing to keep medications properly labeled leading to dispensing errors.

Staff formerly employed to support the Board of Pharmacy did not maintain sufficient records to clearly delineate when actions were shared with either the FDA or other relevant State Boards. Going forward, the Department is conducting an extensive audit of all operational policies and procedures in all nine (9) health professions licensure boards supported by DPH staff. These efforts will facilitate alignment of these entities, ensuring uniformity and enhanced quality control of these critical functions.

Question 10. Please describe any standard operating procedures that were put in place since September 25 to facilitate communication and coordination with other boards of pharmacy. How is any disagreement with another board of pharmacy resolved?

Answer 10. *See* response to Questions 3 and 5.

Question 11. How often do you contact other State boards of pharmacy? Do you know which of your pharmacies ship out-of-state, and do you ever get requests to inspect those facilities? How do you respond to such requests?

Answer 11. On November 1, 2012, the Massachusetts Board of Registration in Pharmacy adopted emergency regulations that include the following provision:

> "Every pharmacy licensed pursuant to M.G.L. c. 112, §39, that performs central intravenous admixture services (CIVAS), or engages in sterile compounding, shall report to the Board every 6 months, or upon request by the Board, at a minimum, the following information:
>
> (a) total number of prescriptions dispensed, distribution data identifying the States in which the prescriptions were distributed, status of any non-resident licenses issued by other States, hood certifications required by 247 CMR 6.01(5)(c) 5, status of CIVAS approval is) where applicable, and any other information required by the Board.
>
> (b) All such report shall be accurate and comply with the Board's reporting requirements.
>
> (c) All reports shall be accompanied by an affidavit attesting compliance with all laws and regulations pertinent to sterile compounding. This attestation shall be made under pains and penalties of perjury, and include attestation to the following: "this registrant/licensee only prepares and dispenses medication pursuant to a valid prescription as defined in M.G.L.
>
> c. 94C for a single patient, regardless of whether the medication is prepared for a Massachusetts or out-of-state patient."—247 CMR 6.15(5).

Prior to enactment of these regulations, there was no formal mechanism for designating which pharmacies shipped their products to other States.

Question 12. I am concerned that if a State board wants to know the history of a facility, not all the information is reported and it is hard to know the full compliance history. I understand the National Association of the Boards of Pharmacy keeps a database with this information. Could you describe which of the numerous actions against NECC in the past 14 years were reported to NABP, or how the actions were made known to other State boards of pharmacy?

Answer 12. All of the dispositions taken against NECC were non-disciplinary. As a result, none of the Board actions would have likely been reported to the Healthcare Integrity Protection Data Bank (HIPDB) and the National Practitioner Data Bank (NDBP). These actions included the 1999 informal reprimand (against both NECC and Barry Cadden, the co-owner and head pharmacist of NECC, as an individual), the September 30, 2004 advisory letters to NECC, the January 2006 consent agreement (specifically agreed not to report), and the 2010 Ameridose complaints.

This highlights what I have said before: that poor judgment, missed opportunities and a lack of appropriate action allowed NECC to continue on this troubling path.

The Division of Health Professional Licensure (DHPL) reports disciplinary actions against its licensees in several ways. First, the Board reports disciplinary actions with respect to pharmacists and pharmacy technicians to the HIPDB. The Board also reports disciplinary actions with respect to pharmacies to the NPDB. In both instances, Board staff prepares an internal report that Division staff use to enter into the Federal databases within a day of action. The reported disciplinary actions

include not only the initial discipline imposed (e.g., suspension of license), but also subsequent changes (e.g., reinstatement of licensure, with probationary status).

In addition to the foregoing, the Board maintains a spreadsheet, listing the disciplinary licensing actions reported to HIPDB and NPDB. As I mentioned before, under previous Board policy, non-disciplinary actions were not reported publicly, something both the Board and the Commission are actively reexamining. This spreadsheet is cumulative for the period beginning in calendar year 2005 (fiscal year 2006) to the present. During the first week of each month, Board staff updates this spreadsheet with the NPDB and HIPDB reports made during the preceding months. The spreadsheet is then emailed to individuals or entities on a distribution list. The distribution list includes the National Association of Boards of Pharmacy (NABP), specifically, *clearinghouse@nabp.net*. DPH cannot comment on NABP policy as to how this information is then reviewed and shared more broadly.

Question 13. In general, what actions do you report to NABP regarding pharmacies in Massachusetts? Could you describe the line between what you must report, and what is not reported?

Answer 13. These tragic events have made one thing clear: timely information and communication, acted on swiftly is critical in ensuring public health and safety. As I have described in answering Question 12, there are clear policies in place for Board staff to report these incidents to NPDB and HIPDB.

ATTACHMENTS

SUMMARY OF COMPLAINT HISTORY AND BOARD ACTION AGAINST FACILITIES ENGAGED IN STERILE, INJECTABLE COMPOUNDING AS IDENTIFIED THROUGH ATTESTATION OR CIVAS CERTIFICATION

Through the attestation process, four pharmacies included on the preliminary list of CIVAS facilities self-identified as no-longer providing sterile compounding:

- *Conlins Pharmacy Inc (DS2135)* confirmed that they are no longer engaged in sterile compounding;
- *Integrity Pharmacy Services (DS89643)* – DPH believes this pharmacy closed without notifying the board. The facility has not responded to email or phone, provided no attestation and has no website – a visit will be made in the near future to confirm closure;
- *Littles ISC Pharmacy (DS2551)* - Board staff received an email on 10/24/12 that the pharmacy is not doing any sterile compounding and will not be doing so until further notice;
- *Southcoast Pharmacy* – Board staff received an email on 10/24/12 confirming that the pharmacy does not engage in any sterile compounding. This facility is located within a hospital system.

	DS #	Pharmacy Name	City	Complaint History
1	DS89820	*Apothecare South Shore*	Brockton	**SA-INV-2968 OPEN CASE** Allegation: failure to deliver Asmanex inhaler on time. Opened 8/24/12 **Pending Investigation**. **SA-INV-2970 OPEN CASE:** Allegation: failure to deliver Vitamin D when ordered; not enough supply dispensed. Opened 8/24/12 **Pending Investigation.** Complaint under previous ownership: PH-2010-0119 Opened 7/19/10 following an inspection on 5/20/10 which identified violations of regulations related to security and accountability of narcotic following a complaint that a pharmacy technician-trainee had diverted and taken narcotics and subsequently expired from drug overdose. Inspection found the pharmacy failed to maintain a perpetual inventory of Schedule II controlled substances received, dispensed or disposed of, with reconciliation performed at least every 10 days; no biannial inventory. Consent Agreement for one year Probation effective 2/9/11.
2	DS2943	*Boulevard Pharmaceutica Compounding Center*	Worcester	None
3	DS89801	*CarePoint Partners (Parenteral Infusion Associates)*	Plymouth	None
4	DS3327	*Optical Care Systems*	Braintree	None

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5	DS3330	Critical Care Systems	Shrewsbury	DS-06-018 Opened 8/29/07 Allegation: Pharmacy failed to dispense a prescription properly; on or about 3/3/07 and 6/8/07 the pharmacy dispensed intravenous Vancomycin and/or substituted of containing Morphine rather than intravenous Vancomycin for two patients as prescribed. Dismissed due to lack of sufficient evidence 9/15/06. DS-PHA-2011-0115 opened 4/29/11 Allegation: Pharmacy failed to adhere to proper standards of professional practice; the pharmacy dispensed a prescription for a Total Parenteral Nutrition (TPN) that may have resulted in or contributed to an adverse medical event for a patient. Hospitalized patient admitted to Boston Hospital was found to have a TPN bag from Baxter that grew bacteria. Dismissed with Advisory Letter on 12/8/11.
6	DS3592	Home Infusion Solutions	Falmouth	None
7	DS8161	Brightview Drug Inc	Hampshire	DS-05-039 opened 10/12/2004 Allegation: Pharmacy failed to adhere to proper standards of pharmacy practice; on diverse occasions the pharmacy compounded and dispensed a non-FDA approved drug product namely Dexmedetomidine; allowed pharmacy technicians to work without proper job supervision; and the pharmacy operated in unsanitary conditions. An inspection was conducted on or about 7/28/2004. (Note this record has been destroyed in error during with record retention schedule). Advisory Letter issued 12/22/04. DS-06-078 opened 4/4/06 Allegation: Pharmacy failed to adhere to professional standards of pharmacy practice. The complaint alleges that on or about 3/15/2005 the pharmacy not limited compounding and mixing activities in a sterile manner. Unannounced inspection conducted on 4/14/2005 found that the pharmacy was under renovation and pharmacy was taking appropriate steps to ensure clean environment. Complaint dismissed lack of sufficient evidence 7/22/06. DS-07-042 opened 3/7/07 Allegation: Pharmacy failed to fill a prescription properly; on or about 10/28/2006 the pharmacy dispensed Carbamazepine 100mg chewable tablets rather than regular 100mg tablets as prescribed. Complaint dismissed 6/12/07. SA-MV-1035 opened 2/18/10 Allegation: Pharmacy failed to adhere to standard of practice; on or about 2/4/2010 the pharmacy failed to deliver a compounded medication in a timely manner. Complaint dismissed due to lack of sufficient evidence 1/10/11.

				PHA-2013-0180 opened 8/2/13 OPEN CASE: Allegation: Medication Error. Pharmacy failed to compound/dispense a prescription properly; on or about 3/4/10 the pharmacy dispensed a prescription written for ethosuximide liquid 50 mg/ml with backorder 20 mg/ml to a 3 year old patient, resulting in hospitalization. UNDER INVESTIGATION
8	DS8972B	Integra Scripts Pharmacy	West Springfield	None
9	DS3418	North Shore Pharmacy Services, LLC	Wakefield	DS-07-025-006; DS-08-017; 393-08-014; DS-08-018; DS-09-042; DS-08-043; DS-08-093; 2009SD8010; PHA-2013-0286; PHA-2011-0028 The Board of Registration in Pharmacy (Board) entered into a Consent Agreement (Effective Date: June 3, 2011) with North Shore Pharmacy Services (parent company: Omnicare, Inc. (Covington, KY) largest provider of pharmaceutical care to long-term care facilities), a Massachusetts pharmacy licensed to operate at 381 A Main Road in Wakefield, Massachusetts (Pharmacy Reg. No. 3408), in resolution of two complaints filed with the Board involving medication dispensing errors (seven complaints) and multiple violations of Board regulations 247 CMR (various sections). The Consent Agreement sums include a minimum 24 month Probationary Status (commencing June 3, 2011); the engagement of an independent consultant to complete an assessment of regulatory compliance and implementation of multiple specific corrective actions by specified dates, including such areas as limited Drug Pharmacopeia (USP) Standard 795 and 797 compliance, self-audits and in-service trainings. The Board approved the Institute for Safe Medication Practices (ISMP), a non-profit organization located in Horsham, Pennsylvania with expertise in medication error prevention and safe medication use (also contract as a Patient Safety Organization (PSO) by the Agency for Healthcare Research and Quality), to be the independent evaluator required by the North Shore Pharmacy Services Consent Agreement. Resolution of the complaints by agreement followed an extended period of complaint investigation and negotiation by counsel for North Shore Pharmacy Services. The Consent Agreement terms have been complied with by North Shore Pharmacy Services to date. North Shore Pharmacy Services is permitted to petition the Board for termination of Probationary Status on or about June 3, 2013 (end of two year period), such petition to include demonstration of compliance with all Consent Agreement terms. PHA-2010-0104 opened 8/24/10 Allegation: Pharmacy failed to dispense a prescription/order properly; on or about 5/27/10 the pharmacy dispensed a prescription/order with nortriptyline 20mg rather than amitriptyline 20mg as

				prescribed to a patient in a residential facility; which prescription/order was transcribed incorrectly by a facility nurse. **Dismissed with Advisory Letter 1/28/11.** **DS-06-015** opened 8/28/07 Allegation: Pharmacy failed to dispense a prescription properly; on or about 5/22/07 the pharmacy received a physicians order to increase the patients Trilisate TO 750mg P) BID. The complainant alleged that on or about 7/11/07 the patients was prescribed Trileptal 600 mg in the p.m. and Trileptal 450 mg in the a.m. but the pharmacy dispensed Trileptal 750 mg (twice daily). **Dismissed with Advisory Letter 7/26/08.**
10	DS3419	*Partners Pharmacy of MA*	Marlborough	**DS-06-137 opened 4/6/06** Allegation: Pharmacy failed to properly secure Schedule II inventory as well as failed to participate in electronic data transmission reporting PMP. **Dismissed with Advisory letter 7/3/06.** **DS-07-013** opened 10/3/06 Allegation: Pharmacy failed to dispense a prescription properly; the pharmacy dispensed Depakote 125 mg tablets instead of the prescribed Artcept 10 mg. **Dismissed with advisory letter 12/18/06.**
11	DS3055	*Pharmahealth Pharmacy*	New Bedford	None
12	DS3335	*Sullivan's Health Care, Inc.*	Rosindale	None
13	DS2838	*The Medicine Store*	Hyannis	None
14	DS3587	*The Whittier Pharmacist, Inc.*	Bradford	None
15	DS89799	*Western Mass Compounding Center, Inc.*	West Springfield	**SA-INV-2610** opened 2/8/12 Complaint that pharmacy would not compound a medication at a strength requested by the patient; pharmacy was following laws and regs and appropriately refused to compound a drug product that is a copy of a commercially available drug; situation explained to patient. **No further action required.**
16	DS3300	*Baystate Home Infusion & Respiratory Services*	Springfield	**DS-05-079** opened 4/26/05 Allegation: Pharmacy failed to dispense a prescription properly on two separate occasions; on or about 12/20/04 for an incorrect dose of trinotracan IV dispensed and on 3/18/05 for an incorrect dose of Dexamethasone dispensed. **Dismissed with an Advisory Letter 2/24/06.** **PHA-2012-0158 OPEN CASE** Allegation: Failure to fill Rx properly opened 8/1/2012 and **pending investigation**. The complaint refers to a hospice patient whose narcotic pain medication order delivery was significantly delayed and when delivered did not contain the appropriate medication so had to be reordered. (note, same complainant as PHA-2012-0157 vs West River Pharmacy).

17	DS89783	*BioRx LLC*	Woburn	None
18	DS2623	*Boston Home Infusion*	Dedham	None
19	DS3312	*Central Admixture Pharmacy Services, Inc.*	Woburn	None
20	DS3601	*Coram Healthcare Corporation of Mass.*	Norwood	None
21	DS3325	*Critical Care Systems*	Burlington	None
22	DS89700	*Diamoto Medical, Inc.*	Shrewsbury	None
23	DS89717	*Freedom Fertility Pharmacy*	Byfield	**SA-INV-2818 opened 8/29/12 OPEN CASE** Allegation: During on-site inspection on 2/24/12 Board inspectors observed that pharmacists and pharmacy technicians at this pharmacy which specializes in fertility medications were entering medication prescription orders and conducting other pharmacy related activities in common area; activities like insurance verification, data entry label preparation, etc. outside of the designated licensed pharmacy space; Board is awaiting corrective action – blue prints, etc. from the pharmacy. **UNDER INVESTIGATION** **PRIOR ADDRESS (DS3435) DS-08-121 opened 6/27/08 Allegation: Pharmacy failed to adhere to proper standards of professional practice; permitted pharmacy technicians to continue to practice after respective pharmacy technician registrations lapsed without timely renewal in violation of 247 CMR 8.07. Dismissed with Advisory Letter 1/13/09.**
24	DS3344	*Healthstar Pharmacy IPO, BBAI Lenox Village Pharmacy*	Lenox	**DS-05-083** opened 5/19/2005 Allegation: the Pharmacy failed to dispense prescription properly on two separate occasions; on or about 7/17/04 to 2/9/05 the pharmacy dispensed Hydrochlorothiazide 50mg rather than Hydrochlorothiazide 12.5 mg as prescribed, and the pharmacy dispensed Fosamax 70mg rather than Fosmax 35mg as prescribed on one occasion during the period of 6/25/02 to 9/3/04. **Dismissed with Advisory Letter 7/18/2005.**
25	DS89639	*Home Solutions*	Canton	None
26	DS89704	*Infusion Resources*	Waltham	None
27	DS3579	*Johnson Compounding and Wellness Center*	Waltham	None
28	DS3184	*Long Term Pharmacy Solutions, Inc.*	Lowell	None
29	DS3309	*MHHP Acquisitions Co. LLC – McClelland Health System*	West Springfield	**PHA-2010-0201 and PHA 2011-0005 are OPEN CASES** in Prosecution; Order to Show Cause issued December 12/8/2011. **See attached copy of the OTSC.** Allegations: On or about 9/8/10 the pharmacy improperly filled and dispensed a prescription for Seroquel 300 mg instead of the

		This pharmacy is under the same ownership (Omnicare) as North Shore Pharmacy, which is under stringent monitoring from ISMP.		prescribed ranitidine 300 mg., resulting in two hospitalizations for a 91 year-old patient at a nursing facility serviced by the pharmacy. In addition inspection violations cited on 3/16/2011. Violations include: failure to maintain pharmacy records and conduct inventories; to have two balances tested and sealed by the state or local sealer of weights and measures annually, failure to comply with USP standards for NON-STERILE Compounding Standards 795; failure to maintain adequate staff in pharmacy department; failure to investigate and collect pertinent data in response to quality related events. **OPEN CASE in LITIGATION.** **OS-09-031** Opened 11/30/07 Allegation: Pharmacy failed to dispense a prescription properly; on or about 10/1/07 the pharmacy dispensed tramadol 50 mg half tablets rather than trazodone 50 mg half tablets as prescribed. **Dismissed with Advisory Letter 7/25/08.** **PHA-2009-0150** opened 9/8/09 Allegation: Pharmacy failed to dispense a prescription properly; on or about 4/3/09 the pharmacy dispensed a prescription labeled with the incorrect prescriber's name as required. **Dismissed with Advisory Letter 12/3/09.**
30	DS3486	*New England Home Therapies*	Southborough	None
31	DS3513	*New England Life Care*	Woburn	None
31	DS89832	*Northeastry, Inc. d/b/a Cape Cod Home Infusion Services*	North Falmouth	**None for current DS89832** Prior location DS359: PHA-2011-0118 Failure to fill Rx Properly; Dismissed with advisory about 2/2/12
32	DS89702	*Oncolified Pharmaceutical Services*	Waltham	None
33	DS3498	*Pallimed Pharmacy*	Woburn	**SA-INV-2220 opened 6/9/11 OPEN CASE** Allegation: from national manufacturer that the Pharmacy is compounding Viagra (sildenafil) by obtaining active ingredient from unauthorized/unapproved FDA source. Pfizer states that they have exclusivity in the US and have provided documentation of same. Requested Alabama Board of Pharmacy to inspect repackager (located in Alabama), from whom Pallimed is obtaining sildenafil powder. Awaiting documentation from Alabama. **Under investigation.** **PHA-2011-0286 opened 10/18/11 OPEN CASE** Allegation: Pharmacy compounded and dispensed a prescription for HCG chorionic gonadotropin 10,000 units #2 vials on 09/19/11 that resulted in a pyrogenic reaction due to "impurities". Refills dispensed on 10/3/11. New information recently obtained.

				Under investigation. **PHA-2012-0046 opended 3/12/12 PHA-2012-0171 James Nahill (PH21521)-MOR; PHA-2012-0157 OPEN CASE** Michael Costanzo (PH233143) - Verification RPH: Allegation that two patients were admitted to the hospital after receiving lidocaine in a private physician office (specializing in urology) for a routine, biopsy procedure. Initially the first patient was thought to be having an unrelated medical episode, possibly a stroke. When the second patient, 30 minutes later, began exhibiting similar symptoms, the lidocaine was suspected to be the trigger. The second patient was 60-years-old. (See related docket PHA-2012-0046.) Analysis by an independent laboratory (provided by the complainant) revealed that the vial labeled as lidocaine 2% (20 mg/ml) contained lidocaine 18 % (180 mg/ml) Both patients were treated in the emergency department and admitted to the hospital. Both patients were discharged one day later as their symptoms had fully resolved. **Case remains under investigation. PHA-2012-0046 PHA-2012-0170 Michael Costanzo (PH233143) - Verification RPH OPEN CASE** Allegation: two patients were admitted to the hospital after receiving lidocaine in a private physician office (specializing in urology) for a routine, biopsy procedure. This complaint is in reference to the second patient. Analysis by an independent laboratory (provided by the complainant) revealed that the vial labeled as lidocaine 2% (20 mg/ml) contained lidocaine 18 % (180 mg/ml). **Case remains under investigation.** SA-INV-1462 opened 7/21/10 Allegation: On or about 10/27/10 the pharmacy offered to ship bulk Rupranex (Schedule 3 controlled substance) to a veterinary clinic without a patient (species) specific prescription. Pursuant to M.G.L.C.94C patient (species) not required for veterinary prescription. **Dismissed 4/6/11.**
34	DS89765	*Royal Palm Specialty Pharmacy* *The Board received notification on 10/26 that this pharmacy would no longer be preparing sterile compounded medications.*	Webster	**PHA-2011-0399** **Related Complaint Docket Nos. PHA- 2012-0004 Karen A. Blakely, RPh (PH21868) Closed PHA-2012-0005 Mark J. Rubin, RPh (PH233459) PHA- 2102-0006 Agnes S. Rubin, RPh (PH25022) PHA-2012-0060 Joanne Blain, Pharmacy Tech (PT315) PHA-2012 0061 Angel Figueroa, Pharmacy Tech (PT3937) PHA-2012-0064 Pharmacy Tech (PT1566)** The Board opened a complaint on 11/28/11 regarding **Royal Palm Specialty Pharmacy** (Pharmacy), as well as an open complaint regarding the Pharmacist/Co-Pharmacy Owner/Manager of Record (Agnes S. Rubin - opened 1/9/12) and a Pharmacist/Co-Pharmacy owner/involved pharmacist (Mark J. Rubin – consulted with Karen Rubin by telephone regarding the "recipe" to be used to compound the medication). The Board has resolved a related complaint regarding involved pharmacist Karen A. Blakely by Consent Agreement (Reprimand). The

				Board has voted to dismiss the above-listed complaints regarding three pharmacy technicians (letters to be sent). The complaint (filed by mother of 19 year old patient) relates to the improper dispensing of a prescription for T3 (liothyronine – a thyroid hormone) 10 mcg SR #30 capsules compounded/verified/dispensed as T3 10 MG #30 capsules. Pharmacists Blakely and M. Rubin were both involved in the preparation of the medication. The Board inspected the Pharmacy on 12/20/11 and 4/24/11 and observed multiple violations of Board regulations. On 8/13/12 the Board proposed a Consent Agreement for the Pharmacy with a minimum two year Probationary Status, with terms that include, but are not limited to, application for compounding accreditation, re-training and United States Pharmacopeia (USP) analysis. Counsel for the Pharmacy commenced representation 8/23/12 and requested an extension for response was permitted; On 10/15/12 the Board received a counterproposal, which has not yet been reviewed by the Board, from the Pharmacies Counsel proposing a non-disciplinary resolution. Next regularly scheduled Board meeting is 11/13/11. The Board has proposed a Consent Agreement (Reprimand) regarding involved pharmacist/owner Mark J. Rubin. Counsel for this pharmacist has proposed on 8/13/12 that the Board dismiss the complaint, which response has not been reviewed by the Board. Next regularly scheduled Board meeting is 11/13/11. The Board has proposed a Consent Agreement regarding Owner/Manager of Record Agnes Rubin by Consent Agreement (Censure) on 8/13/12 related to her failure to appoint a new manager of record while she was on maternity leave and failure to report the error to the Board (247 CMR 6.14 and G.L. c. 112, s. 39D). Counsel for this pharmacist has proposed on 10/15/12 that the Board dismiss the complaint, which response has not been reviewed by the Board. Next regularly scheduled Board meeting is 11/13/11.
35	DS89068	*Village Fertility Pharmacy*	Waltham	None
37	DS3584	*Walgreens Infusion Services*	Southborough	None
38	DS3572	*West River Pharmacy, Inc.*	Marlborough	**PHA-2012-0157 opened 8/1/12 OPEN CASE** Allegation: Pharmacy failed to deliver needed medication to a hospice patient in a timely manner. **Under Investigation.** An inspection occurred on 9/19/12, identifying a series of deficiencies. There is no

				plan of correction in the file (this is not uncommon given the time-frame, this is quite possibly in process at DHPL and has not reached the file). Regulation requires filing by the licensee within 15 days of noted deficiencies. Findings included: Scale not sealed in controlled substances room; The refrigerator temperature was off; Compounding residue was seen on walls and fixtures; Pharmacist's daily prescription logs were not available; Insufficient pharmacist oversight over techs. **SA-INV-2356** – not a complaint just an assignment for evening inspection **PHA-2011-0084** - Inspectional deficiencies on 3/31/11 and 6/9/11: failed to maintain pharmacy records and conduct and maintain inventories; failed to report the loss of significant amount of controlled substances within 7 days; failed to comply with USP compounding (795 and 797) failed to handle Schedule II controlled substances; failed to conduct pharmacy operations in a clean and sanitary manner, failed to comply with required supervisory ratio of pharmacist to pharmacy interns, etc. *Disciplinary Action Imposed*, Probation for minimum of two years effective 12/20/11. **PHA-2009-0022 opened** 2/2/09 Allegation: Pharmacy failed to dispense a prescription properly on or about 10/13/08 the pharmacy dispensed Oxcarbazepine 150mg rather than Oxybutynin ER 10mg as prescribed. Dismissed with Advisory Letter 4/22/09.

AUTHORITIES TO DISCIPLINE LICENSEES

M.G.L. c. 112, § 24E	Authority to fine or punish with a term of imprisonment any person acting or purporting to act as a pharmacy technician without being registered to practice by the Board.
M.G.L. c. 112, § 28	Authority to suspend the certificate of registration as a pharmacist for such term as it fixes. Authority to reconsider its actions where it has suspended or revoked the license or certificate of registration of a pharmacist, and change its determination as justice requires.
M.G.L. c. 112, § 29	By a majority vote of all members, after hearing, the Board has the authority to suspend the certificate of registration of a registered pharmacist, who, in its judgment, is a menace to the public by reason of the improper use of intoxicating liquor or drugs.
M.G.L. c. 112, § 36D	Authority to punish by a fine of not more than $1,000 or by imprisonment in jail for not less than 30 days or more than one year for engaging in the sale, distribution, or delivery, at wholesale, of drugs or medicines without being licensed as provided in §§ 36A and 36B.
M.G.L. c. 112, § 40	Authority to suspend or revoke any registration made under §§ 39 – 39B and any permit issued there under for any violation of the law pertaining to the drug business or the sale of alcoholic beverages or for any violation of the rules and regulations established by the board. Before such suspension or revocation the board shall give notice and a hearing. Authority to require the attendance of persons and compel the production of documents.
M.G.L. c. 13, § 25	Authority to direct agents to file criminal complaints against all violators of such laws, rules, and regulations.
M. G. L. c. 112, § 52F	The board may, without a hearing, suspend or refuse to renew a registrant's license if the board finds that the health, safety or welfare of the public warrants such summary action; provided, however, that the board shall, within seven days of such summary action, afford the registrant the opportunity of a hearing pursuant to chapter thirty A. Any suspension imposed by the board shall remain in effect until the conclusion of the proceedings including judicial review thereof, unless sooner dissolved by a court of competent jurisdiction or withdrawn by the board.

ATTACHMENT B

RESPONSE OF MARION KAINER TO QUESTION OF SENATOR WHITEHOUSE

Question. Dr. Kainer, your testimony notes that electronic health records allowed "tremendous" savings in time and resources. How were electronic health records used by health care providers and the Tennessee Department of Health? Are there best practices you would recommend for other State health departments regarding the use of electronic health records during a public health crisis?

Answer. All of the hospital systems caring for patients in Tennessee used an electronic health record to record most of their health information when they were inpatients. At the beginning of our investigation and response, as in past responses to other outbreaks, we sent staff to the facilities to review key records on site and requested faxed copies of other records. This approach provides access to the needed records, but it is slow and involves many staff to process all the requests. In general, these are the same hospital staff who are needed at the healthcare facility as part of their response, so their availability is limited.

In the context of an evolving outbreak, when the number of cases is increasing rapidly and our understanding is evolving quickly, the questions being asked are also rapidly changing. This leads to repeated requests for additional records on both old and new patients. The process of obtaining vital information can become very slow.

Early in this outbreak response, the Tennessee Department of Health worked with all five hospital facilities caring for case patients to obtain remote electronic access to inpatient medical records from Health Department computers. This allowed our staff to quickly gather additional information on existing patients and to initially review new patient records, without having to visit the facilities or take the time of medical staff to assist with access. This provided more immediate and complete access to information than ever before.

As a result, we reduced the time to completing our analyses substantially, leading to better information for patients and clinicians in Tennessee, and the CDC. Rapid access to source data also allowed us to quickly compose a detailed summary of our findings, which was published in the *New England Journal of Medicine** much more quickly than if we had not had access to electronic records. This allowed a

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*A summary of the findings mentioned may be found at *www.nejm.org/doi/full/10.1056/NEJMoa1212972*.

broader audience to receive detailed information about the outbreak they could use to guide patient evaluation and care.

RESPONSE OF DAVID G. MILLER, R.PH., TO QUESTIONS OF SENATOR ENZI, SENATOR CASEY, AND SENATOR FRANKEN

SENATOR ENZI

Question 1. How do you define traditional compounding? What, if any, additional regulations should be placed on pharmacies that ship large quantities of products interstate? Is there a larger Federal role?

Answer 1. IACP does not have a definition of "traditional" compounding nor does one exist within our profession. We are very concerned that this term has been referenced by numerous individuals, organizations, and agencies and is both broad and subject to significantly variable interpretation depending upon who is referencing "traditional."

We believe the focus should not be on the creation of a definition of traditional vs. non-traditional but a more close examination of what constitutes compounding—the preparation and issuance of a medication upon receipt of a valid prescription from an authorized prescriber—and what constitutes manufacturing—the preparation, promotion, selling and distribution of a medication when no authorized prescriber is involved.

The manufacture of a medication cannot be judged, therefore, on the basis of quantity. It is not the amount or even the process of compounded medicine that is produced. Rather, it is an examination of the transaction in and of itself. A very busy, very large pharmacy can legitimately and appropriately compound and dispense medications intra- or interstate based upon the receipt of valid prescriptions from authorized prescriber and still remain a pharmacy. On the other hand, a small pharmacy can be engaged in manufacturing if the preparation and issuance of a compounded medication is done without a prescription or medical order from an authorized prescriber.

We believe that an immediate area to be addressed is the communication link between the State Boards of Pharmacy and the Food and Drug Administration. State Boards are in the best position to determine whether their license or permit holding pharmacies are exceeding the scope of pharmacy practice and engaging in manufacturing-like activities. In those instances, the State Board should have a liaison or communication channel to the FDA for followup inspection and action as the Federal agency has jurisdictional authority over manufacturing including illegal manufacturing by pharmacies or other entities.

Question 2. Are there basic standards that all sterile compounding facilities should be held to, such as USP 797? How would that be enforced?

Answer 2. IACP supports enactment of legislation or regulations which mandates the compliance with USP <797> standards by any practitioner or practice site involved in the preparation of sterile compounds. That includes all pharmacists as well as physicians, veterinarians or any other health care practitioner who compounds sterile preparations. Additionally, all settings including hospitals, home infusion companies, long-term care facilities, hospices, etc., should be held to the same accountability of adherence to these industry-wide standards.

IACP also supports enactment of legislation or regulations which mandates compliance with USP <795> standards by any practitioner or practice site involved in the preparation of non-sterile compounds as well.

Since States issue the licenses and permit for operation to a pharmacy, they are the first enforcement agency that should be responsible for conducting regular, unannounced inspections of all sterile compounding facilities.

Should you have any further questions or wish clarification on our responses, please do not hesitate to contact us. In the meantime, please accept our best wishes for a wonderful holiday season.

SENATOR CASEY

Question 1. How many prescriptions are filled annually by compounding pharmacists, and of those, how many are filled in a non-hospital/outpatient setting?

Answer 1. Unfortunately, no database exists which tracks all prescriptions filled in the United States—compounded preparations included. It has been estimated by the *International Journal of Pharmaceutical Compounding* that 1–3 percent of all *outpatient* prescriptions are compounded on an annual basis.

Question 2. When a compounding pharmacist ships drugs interstate in response to a valid prescription, are the products shipped directly to the patient or to the patient's provider? Does it depend on the type of product?

Answer 2. It depends upon the prescription itself (the actual order from the authorized prescriber), the type of medication ordered, the directions given by the prescriber, and the express request of the patient.

Some patient-specific medications can be delivered directly to the patient or, if requested to do so by either the patient or the prescriber, be delivered to the prescriber. In the latter case, that is often done when the administration of the medication is done by the prescriber him/herself. An example of that would be intrathecally administered medicines. Because those drugs are infusions, the integrity and stability of the medicine must be maintained. Minimizing steps in transport (e.g., pharmacy to patient then patient to physician) and controlling such things as temperature or security is one means of assuring that integrity.

Question 3. How many of your members are accredited by the Pharmacy Compounding Accreditation Board? Have these numbers been increasing?

Answer 3. As a professional society, IACP's membership is comprised of individuals: pharmacists, pharmacy technicians, student pharmacists and others involved in the specialty practice of compounding. The Pharmacy Compounding Accreditation Board accredits pharma*cies*—the physical business in which pharmacists practice. PCAB does not accredit individual practitioners; therefore, no IACP member is accredited by PCAB. As of December 1, 2012, PCAB currently accredits 168 pharma*cies*. According to their staff, there are approximately 40 additional pharmacies in various stages of the accreditation process. Since the NECC crisis, PCAB has seen a 400 percent increase in applications by pharmacies to begin the accreditation process.

Question 4. What is IACP doing to encourage its membership to pursue accreditation and take other steps to ensure their compounded products are safe?

Answer 4. IACP is a founding member of the Pharmacy Compounding Accreditation Board (PCAB) and has many members serving on its standing committees as well as providing a representative to its eight-person board of directors. IACP provides PCAB with complimentary exhibits at its national meetings and advertising space in its publications to raise awareness of the Board. All new members of IACP also receive PCAB information upon joining the Academy. Our most recent issue of our electronic magazine—*Custom Rx Connection*—featured an extensive article for the PCAB executive director. Additionally, our bi-weekly electronic newsletter also announces all newly accredited and re-accredited PCAB pharmacies as part of our efforts to promote accreditation.

IACP conducts both live and web-based accredited continuing education programs for its members and non-members on compounding standards and safety. The Academy began a collaboration with the United States Pharmacopeia (USP) earlier in 2012 which brings their seminars on standards and safety to all pharmacists through our educational portal.

Question 5. Dr. Hamburg discussed a possible risk-based framework for the regulation of compounding, recognizing that certain compounded products inherently pose a greater potential risk to patients should they be handled improperly. Could you share your comments on FDA's proposed framework?

Answer 5. Neither IACP nor its colleague professional associations have been provided sufficient details to determine whether or not the FDA's concept of a "risk-based framework" will lead to a meaningful change in their enforcement of regulatory authority. We continue to have a dialog with the agency to find solutions that will prevent a future NECC-like catastrophe; however, as outlined by Commissioner Hamburg, the proposed framework raises significant questions about scope and intent.

Question 6. Do you feel that taking risk into account is inappropriate? If so, what alternatives would you suggest?

Answer 6. IACP does not believe that the proposed framework from the FDA fully defines the concept of "risk" as it is understood in the professional practice community. Healthcare professionals are trained to assess risk of therapy but the agency's definition is not consistent with that commonly understood definition. Some medicines are *technically* difficult to compound because of the nature of the drug chemical or procedures necessary to obtain a finished preparation while others are *clinically* risky and inappropriate because they are known to have significant side effects and may cause harm to patients. Our Academy believes that developing a consensus-based definition between the pharmacy and medical practice communities in

conjunction with State and Federal regulatory authorities must be undertaken before any framework can be addressed.

Question 7. How do you propose drawing a clear line between traditional compounding for individual patients and large-scale compounding that much more closely resembles manufacturing? Clearly, there is confusion as to where this line is currently and where it should be.

Answer 7. IACP's position is that there is a clear demarcation between compounding and manufacturing. The issue is not whether a pharmacy is compounding in "large-scale" amounts—a term that is nearly indefinable—but whether they are compounding pursuant to a valid prescription or medical order from an authorized prescriber. Pharmacists dispense prescription drugs only when instructed to do so through the form of a prescription or medical order. Manufacturing is substantially different. A manufacturer is permitted to sell medications to a facility, hospital, wholesaler, pharmacy or directly to a prescriber *without* a prescription or medical order. Compounding and dispensing is driven by prescriber decisionmaking. Manufacturing is a purchase decision made without any prescriber input. All States define what constitutes a "valid prescription" and also designate which persons are considered "authorized prescribers." IACP believes that existing Federal statutory and regulatory language defines what constitutes a manufacturer and that the Food and Drug Administration has clear oversight authority in that arena.

SENATOR FRANKEN

Question 1. In a report on meningitis in 2002, the Centers for Disease Control and Prevention reported that "some health-system pharmacists might not realize that they are purchasing injectables prepared through compounding." The CDC report continues by stating that "purchasers of pharmaceuticals should determine if supplies are provided from a compounding pharmacy that is licensed in their State and that follows appropriate measures to ensure that injectable products are free of contamination." What responsibility do you believe that purchasers of compounded products should have to make sure that the products they're giving to their patients are safe?

Answer 1. IACP believes that all purchasers of compounded preparations are as equally responsible for assuring the quality and safety of the medications they obtain as they are for products purchased from pharmaceutical manufacturers. That is a responsibility which all pharmacists in the medication supply chain have been trained to do and should do.

When it comes to compounded preparations, the responsibility is even greater. Last year and in light of the ongoing drug shortage situation, IACP developed a tool to assist physicians and pharmacists in making informed decisions about professional partnerships with compounding pharmacies. This tool includes a step-wise checklist that includes such things as verification of licensure status, accreditation status, standards and processes for regular testing and validation, as well as recommendations to conduct an on-site interview and inspection. Called the *Compounding Pharmacy Assessment Questionnaire (CPAQ™)*, IACP distributed that tool to State and national medical, hospital, and pharmacy associations upon its release in October 2011. A copy of the *CPAQ™* is included for your review and is also available for download at the Academy's Web site *http://www.iacprx.org*.

ATTACHMENTS

[International Academy of Compounding Pharmacists (IACP™), October 5, 2011]

IACP Provides Meaningful Solution With Compounding Pharmacy Assessment Questionnaire

RISING MEDICATION SHORTAGES AFFECT PATIENT HEALTH—NEW IACP TOOL HELPS EVALUATE PHARMACIES FOR NEEDED COMPOUNDED MEDICATION SERVICES

HOUSTON.—As hospital medication shortages continue to increase by the day within the North American healthcare system, the International Academy of Compounding Pharmacists (IACP) has developed a new assessment questionnaire to assist hospitals, practitioners and non-compounding pharmacies identify and evaluate compounding pharmacies as they seek alternative sources for medications that currently are in limited to complete shortage status.

IACP's Compounding Pharmacy Assessment Questionnaire (CPAQ™) provides a comprehensive checklist of what to look for in a compounding pharmacy practice and is based upon United States Pharmacopeia (USP) standards which compounding pharmacists are obligated to follow according to State board of pharmacy regulations or standards of practice. Collaboration between licensed compounding pharmacists and their colleagues in hospitals and institutions is a long-standing solution to back-orders and shortages but the current shortage situation is at a crisis point for many health-systems. The expertise of a compounder with access to APIs (Active Pharmaceutical Ingredients—the pure, raw drug ingredient) can mean the difference between continued or initiation of much-needed medicines or an unnecessary delay in patient care.

IACP's Compounding Pharmacy Assessment Questionnaire (CPAQ™) includes evaluation points in the following areas:

- Regulatory compliance
- Licensing—permits
- Internal controls and quality assurance
- Testing & verification
- Site visits

Linda F. McElhiney, PharmD, R.Ph., FIACP, FASHP, compounding pharmacy operations coordinator, Indiana University Health, says,

> "Drug shortages have been an ongoing problem for healthcare facilities and the number of drug products that are unavailable due to manufacturer backorders and discontinuation is on the rise. These facilities are often trying to find substitutions for the drug products or alternative treatments and there is often a delay in the patients' treatment. Compounding pharmacies may be able to prepare these medications using bulk active pharmaceutical ingredients; however, it may be difficult for the healthcare pharmacy administrators to know if the compounding pharmacy can provide quality compounded medications to meet their facilities' needs because they are unfamiliar with the USP standards for compounding sterile and non-sterile preparations. The International Academy of Compounding Pharmacists (IACP) has developed a checklist of standards and criteria to assist the administrators in finding a suitable compounding pharmacy to meet these needs."

Scott Karolchyk, R.Ph., FIACP, IACP president-elect, says,

> "IACP leadership recently participated in FDA's conference on prescription drug shortages. While there were many good intentions expressed during the conference, there were no real solutions for *now*. Each day, pharmacists and physicians are grappling with making sure our patients get the medicines they need. What was clearly overlooked was how compounding pharmacists are providing solutions today as they work with U.S. hospitals, surgery centers, and practitioners to make those medicines available."

John Herr, R.Ph., IACP president, asked, "What better solution to this problem than pharmacists working intraprofessionally to take care of patients?"

> "The CPAQ tool is compounding pharmacy's way of stimulating that relationship. Given that compounders have an outstanding track record for preparing quality medications on a per-prescription basis, we know that working together will lessen the need to use the so-called 'gray market' of suppliers, distributors and others which are taking advantage of people in need."

ABOUT IACP

The International Academy of Compounding Pharmacists (IACP) is a professional association founded in 1991 to protect, promote and advance personalized medication solutions. The association represents more than 2,100 pharmacists and pharmacist technicians licensed and regulated by their individual State boards of pharmacy and located throughout North America, South America, Europe, Australia and Asia. In addition, IACP represents more than 154,800 patients, physicians, nurse practitioners and veterinarians through its ally grassroots organization, Patients & Professionals for Customized Care (P2C2). IACP is committed to ensuring the rights of physicians to prescribe, of pharmacists to prepare, and of patients to take personalized medication solutions that meet their unique, individual health needs.

IACP offers a free Compounding Pharmacy Locator Service which can be accessed toll free at (800) 927–4227 or via IACP's Web site at *www.iacprx.org*.

Compounding Pharmacy Assessment Questionnaire [CPAQ™]

The International Academy of Compounding Pharmacists represents more than 2,700 pharmacists and other professionals who specialize in the provision of customized medication solutions for patients who have unique therapeutic or health needs. IACP developed this *Compounding Pharmacy Assessment Questionnaire (CPAQ™)* to facilitate discussions and the establishment of collaborative and referral relationships between prescribers, clinics, hospitals, other pharmacies and its members.

IACP provides a free Pharmacy Locator Service to assist consumers and health professionals in identifying local compounders. Visit IACP's website at www.iacprx.org or call (800) 927-4227.

LICENSES - PERMITS				
CRITERIA	YES	NO	N/A	COMMENT
1. Is the pharmacy licensed and in good-standing with the state board of pharmacy? 2. Has the pharmacy ever been disciplined for any infractions related to its compounding services?	1.___ 2.___	1.___ 2.___	1.___ 2.___	
1. If the pharmacy is in a different state than the purchasing institution, is the pharmacy licensed to dispense/distribute/provide medications in this state as well? 2. What is the license number? 3. Is the permit in good standing? 4. Will the pharmacy become licensed? 5. Has the pharmacy ever been disciplined for any infractions related to its compounding services in those states in which it currently or formerly had a license/permit?	1.___ 2.___ 3.___ 4.___ 5.___	1.___ 2.___ 3.___ 4.___ 5.___	1.___ 2.___ 3.___ 4.___ 5.___	
1. If the pharmacy is in a different state than the purchasing institution, is the pharmacist-in-charge or another full-time pharmacist licensed in the state as well? 2. What is the license number(s)? 3. If not, will the pharmacy agree to have one of its staff pharmacists become licensed? 4. Has the pharmacist ever been disciplined for any infractions related to his/her compounding services?	1.___ 2.___ 3.___ 4.___	1.___ 2.___ 3.___ 4.___	1.___ 2.___ 3.___ 4.___	
1. Has the pharmacy demonstrated it meets national quality standards by earning accreditation by the Pharmacy Compounding Accreditation Board (PCAB)? Current accreditation can be verified at http://www.pcab.org. 2. Is the pharmacy accredited by any other accrediting bodies? If so, which ones?	1.___ 2.___	1.___ 2.___	1.___ 2.___	
1. Are the pharmacist(s) and/or its staff members of the International Academy of Compounding Pharmacists (IACP)? 2. Of the American Society of Health-System Pharmacists?	1.___ 2.___	1.___ 2.___	1.___ 2.___	
COMPOUNDING SERVICES PROVIDED				
1. What types of dosage forms does the pharmacy prepare (e.g., injectables, capsules, troches, oral liquids, suppositories, topicals, ophthalmics, inhalations)? 2. How long has the pharmacy compounded these various dosage forms?	1.___ 2.___	1.___ 2.___	1.___ 2.___	
1. Does the pharmacy provide sterile compounding services? 2. If so, what level of complexity?	1.___ 2.___	1.___ 2.___	1.___ 2.___	
INTERNAL CONTROLS AND QUALITY ASSURANCE				
Does the pharmacy have written and active Standard Operating Procedures (SOPs) in place for all compounding activities?				
1. Does the pharmacy obtain its pharmaceutical ingredients from an FDA- and DEA-registered Pharmaceutical Ingredients supplier? 2. How is that documented? 3. Are SOPs in place to demonstrate verification of supplier registration status?	1.___ 2.___ 3.___	1.___ 2.___ 3.___	1.___ 2.___ 3.___	
1. Does the pharmacy obtain Certificates of Analysis (CoA) for all formula ingredients from its suppliers? 2. Are those available for verification?	1.___ 2.___	1.___ 2.___	1.___ 2.___	

1. Does the pharmacy have an SOP in place in case of a recall? 2. Has the pharmacy had a recall in the last 24 months?	1. 2.____	1. 2.____	1.____ 2.____	
Does the pharmacy have an SOP on how a customer can report problems to the pharmacy?				
1. Has the pharmacy staff been trained and evaluated in proper aseptic technique, gowning and clean room procedures? 2. What SOPs exist that show performance compliance with those procedures?	1.____ 2.____	1. 2.____	1.____ 2.	
1. Does the pharmacy compound sterile preparations? 2. What level of sterile compounding is performed by the pharmacy using the commonly named "low-risk, medium-risk, and/or high-risk" categories?	1.____ 2.____	1.____ 2.____	1.____ 2.____	
1. Does the pharmacy comply with current *USP* <797> standards for sterile compounding? 2. How is that compliance documented through SOPs?	1.____ 2.____	1.____ 2.____	1.____ 2.____	
1. Does the pharmacy compound non-sterile preparations? 2. Are the preparations simple, medium and/or complex?	1.____ 2.____	1.____ 2.____	1.____ 2.____	
1. Does the pharmacy comply with the current *USP* <795> standards for non-sterile compounding? 2. How is that compliance documented through SOPs?	1.____ 2.____	1.____ 2.____	1.____ 2.____	
TESTING & VERIFICATION				
1. Does the pharmacy use published information or stability studies to establish the preparations' beyond use dating? 2. What sources are used?	1.____ 2.____	1.____ 2.____	1.____ 2.____	
1. Does the pharmacy have in place quality-assurance and continuous quality-improvement programs? 2. Give an example.	1.____ 2.____	1.____ 2.____	1.____ 2.____	

Does the pharmacy staff participate in ongoing training and continuing education that is specific to compounding pharmacy practice?				
1. Does the pharmacy have its compounded preparations regularly tested for potency to ensure the concentration on the container is what is stated on the label? 2. Which laboratories does the pharmacy use for potency assessments? 3. How frequently are batches tested for potency? 4. What SOPs are in place governing the frequency of testing?	1.____ 2.____ 3.____ 4.____	1.____ 2.____ 3.____ 4.____	1.____ 2.____ 3.____ 4.____	
1. Do the pharmacy's preparations meet the +- 10% of stated concentration that is required from USP? 2. How is that documented?	1. 2.____	1.____ 2.	1.____ 2.____	
Will the pharmacy provide written documentation of all testing results to the purchasing institution?				
1. Has the air quality in the pharmacy's designated compounding areas been independently tested and/or certified? 2. Please provide details.	1.____ 2.____	1.____ 2.____	1.____ 2.____	
1. Does the pharmacy perform or contract with an analytical lab to perform sterility testing according to *USP* <71> Sterility Tests and *USP* <85> Bacterial Endotoxin (Pyrogen) Tests? 2. Which laboratories does the pharmacy use for sterility assessments? 3. How frequently are batches tested for sterility? 4. What SOPs are in place governing the frequency of testing?	1.____ 2.____ 3. 4.	1.____ 2.____ 3.____ 4.____	1.____ 2.____ 3.____ 4.____	
1. How are the compounded preparations delivered or shipped? 2. Does the pharmacy assure proper storage conditions are maintained through delivery?	1.____ 2.____	1.____ 2.____	1.____ 2.____	
What is the turn-around time for delivery once the order has been placed?				

1. What information is on the labeling of the preparation? 2. How does the labeling look? 3. Does the pharmacy color code labels?	1.____ 2.____ 3.____	1.____ 2.____ 3.____	1.____ 2.____ 3.____	
How are the preparations packaged? 1. Unit-dose or multiple-dose? 2. Tamper-evident? 3. Protected from light? 4. Overwrapped?	1.____ 2.____ 3.____ 4.____	1.____ 2.____ 3.____ 4.____	1.____ 2.____ 3.____ 4.____	
1. Does the pharmacy accept site visits? 2. How can a site visit be arranged?	1.____ 2.____	1.____ 2.____	1.____ 2.____	

Date of Interview or Visit _____ **Conducted By** _____

Additional Info: _____

_____

_____

Pharmacy Approval (circle one) **YES NO Comment:**_____

The International Academy of Compounding Pharmacists (IACP) invites comments, questions, and suggestions for improving our *Compounding Pharmacy Assessment Questionnaire* (CPAQ™). Contact IACP at (281) 933-8400 or visit our website at www.iacp.org. The information contained in this *Compounding Pharmacy Assessment Questionnaire* is constantly evolving because of ongoing research and improvements in technology and is subject to the professional judgment and interpretation of the involved healthcare professionals. The International Academy of Compounding Pharmacists and its committee members have made reasonable efforts to ensure the accuracy and appropriateness of the information presented. However, any reader of this information is advised that the International Academy of Compounding Pharmacists, its advisory panel, and its committee members are not responsible for the continued currency of the information, for any errors or omissions and/or for any consequences arising from the use of the information in the *Compounding Pharmacy Assessment Questionnaire* in any and all practice settings. Any reader of this document is cautioned that the International Academy of Compounding Pharmacists makes no representation, guarantee or warranty, express or implied, as to the accuracy and appropriateness of the information contained in this *Compounding Pharmacy Assessment Questionnaire* and will bear no responsibility or liability for the results or consequences of its use.

RESPONSE BY KASEY K. THOMPSON TO QUESTIONS OF SENATOR ENZI, SENATOR CASEY AND SENATOR FRANKEN

SENATOR ENZI

Question 1. USP updated their standards for sterile compounding 5–10 years ago. Since then, have you seen an increase in outsourcing of sterile compounding?

Answer 1. USP 797 became official in 2004 and underwent a major revision in 2008 that included additional requirements.

Below are results from ASHP's May 2011 survey demonstrating increased outsourcing:

• In 2011, 70.9 percent of hospitals reported partially or completely outsourcing some drug preparation activities. A greater percentage of larger hospitals outsource some preparation activities compared with smaller hospitals. For example, 96.9 percent of hospitals with 600 or more staffed beds out-sourced some part of preparation activities, compared with 49 percent of hospitals with fewer than 50 staffed beds. The outsourcing of some preparation activities has increased over time, from 21 percent of hospitals in 2002 to 31 percent in 2005 and 42 percent in 2008.

• Of hospitals that out-sourced some part of preparation activities, 73 percent out-sourced patient-controlled analgesia (PCA) and epidural analgesia preparations, 65 percent out-sourced oxytocin preparations, and 38 percent out-sourced some i.v. admixtures and minibags (Table 10). About 25 percent of hospitals out-sourced syringe-based anesthesia medications, total parenteral nutrition (TPN) preparations, and flushes. Hospitals less frequently out-sourced cardioplegia preparations, unit dose drug repackaging, and unit dose repackaging for bar coding. The percentages of hospitals outsourcing PCA and epidural analgesia preparations, i.v. admixtures or minibags, and flushes have increased during the past 9 years, while the outsourcing of TPN preparations has declined.

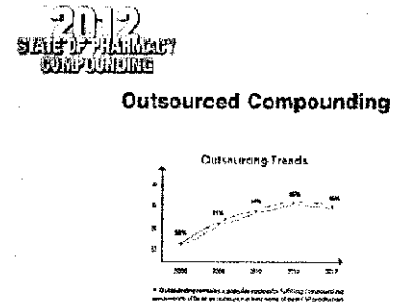
Table 10.—Preparation Activities That Are Either Partially or Completely Outsourced, Excluding Services Through a Contract Pharmacy Services Provider

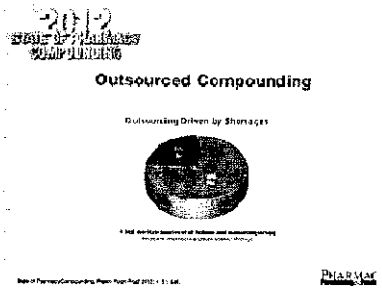
Characteristic	n	Patient-controlled analgesia and epidural analgesia preparations	Oxytocin	I.V. Admixtures and small-volume I.V. solutions	Syringe-based anesthesia medications	Total parenteral nutrient solutions	Flushes	Cardioplegia solutions	Unit dose repack-aging (drug only)	Unit dose repack-aging for bar coding
No. Staffed Beds:.										
<50	51	70.6	52.9	27.5	11.8	21.6	25.5	3.9	11.8	3.9
50–99	56	73.2	60.7	42.9	16.1	16.1	21.4	3.6	16.1	10.7
100–199	63	68.3	66.7	42.9	23.8	17.5	22.2	15.9	12.7	6.3
200–299	69	76.8	76.8	39.1	30.4	29.0	21.7	23.2	15.9	11.6
300–399	54	77.8	63.0	40.7	38.9	31.5	16.7	37.0	22.2	24.1
400–599	86	79.1	81.4	44.2	38.4	32.6	18.6	41.9	20.9	19.8
≥600	62	88.7	72.6	40.3	41.9	45.2	25.8	64.5	40.3	22.6
All hospitals—2011	441	73.3	65.2[1]	38.3	24.1[2]	23.6	22.2	18.3[3]	16.0	10.4[4]
All hospitals—2008[3]	270	64.0	[5]	37.3		32.8	13.9		13.4	14.6
All hospitals—2005[6]	186	40.2		31.4		39.8	12.8		11.6	9.6
All hospitals—2002[9]	137	16.7		15.7		52.4	9.1		12.1	8.9

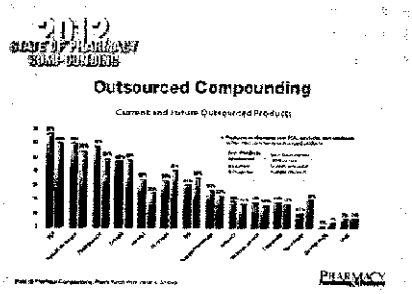
[1] Uncorrected $x^2 = 16.4578$, df = 6, designed-based $F(4.17, 1810.24) = 3.0517$, $p = 0.0147$.
[2] Uncorrected $x^2 = 24.0577$, df = 6, designed-based $F(4.19, 1817.03) = 4.2945$, $p = 0.0015$.
[3] Uncorrected $x^2 = 71.3848$, df = 6, designed-based $F(4.21, 1825.56) = 12.4305$, $p = 0.0001$.
[4] Uncorrected $x^2 = 20.8045$, df = 6, designed-based $F(4.20, 1824.14) = 3.5927$, $p = 0.0055$.
[5] Not surveyed.

In April 2012, Pharmacy Purchasing and Products published its own survey.

In general these results demonstrate a gradual increase (from 56 percent to 65 percent) in outsourcing since the establishment of USP 797 standards for compounding sterile products in 2008. While 76 percent of respondents reported outsourcing in response to a drug shortage, safety and the ability to provide a ready to administer dosing form were equally significant reasons as demonstrated by outsourced patient controlled analgesia (67 percent), epidural injections (48 percent), controlled substances (35 percent) and pre-filled OR medications (34 percent). (See graphs below.)







SENATOR CASEY

Question 1. Do you believe that hospitals and health systems that outsource their compounding to external compounding pharmacies are sufficiently able to determine whether those pharmacies are producing safe products?

Answer 1. Pharmacists have the expertise to help evaluate if compounding is being conducted in accordance with Federal and State definitions and standards established by the U.S. Pharmacopeia in Chapter 797. However, the ability of hospitals to conduct routine inspections of compounding entities is limited by resources, which is why it is important to have a Federal and State oversight system that en-

sures that these entities are capable of producing safe products in accordance with Federal and State laws. The American Society of Health-System Pharmacists also has guidelines and assessment tools available to help hospitals evaluate outside entities that provide compounded formulations. ASHP Guidelines on Outsourcing Sterile Compounding Services *http://www.ashp.org/DocLibrary/Bestpractices/MgmtGdlOutsourcingSterileComp.aspx*; ASHP Foundation: Outsourcing Sterile Products Preparation Contractor Assessment Tool *http://www.ashpfoundation.org/MainMenuCategories/PracticeTools/SterileProductsTool/SterileProductsAssessmentTool.aspx*.

Most pharmacists are not trained to evaluate manufacturing-level facilities where Current Good Manufacturing Practices (cGMPs) are applicable. Examples are bulk compounding of sterile preparations from (1) nonsterile ingredients or (2) from sterile ingredients using aseptic processing* and storing these medications for periods beyond those associated with compounding.

Question 2. Do you think that the compounded products typically used in a hospital or in-patient setting are different from other products typically used in outpatient settings, and if so, do you think that they should be subject to additional or different regulation?

Answer 2. The environment in which these medications are used is less important than the environment in which they must be prepared. The difference is whether the compounded product is a sterile preparation, such as an injectable, or ophthalmic medication. The preparation area is highly controlled to prevent contamination using methods that include in-process and final product quality assurance procedures. The applicable standards, USP 797, are adequate for compounding sterile preparations in hospitals.

Question 3. Under the current patchwork system of State and Federal regulation, do you think products compounded in a hospital pharmacy are safer or less safe than products compounded at freestanding compounding pharmacies?

Answer 3. Compounded sterile products from pharmacies that are made pursuant to or in anticipation of a medication order or prescription and according to USP 797 standards are equally safe, whether the pharmacy is in a hospital or community setting.

However, a sterile compounding business entity that does not fill prescriptions for individual patients is not a pharmacy. Regulatory oversight of these entities should be dependent on the scope and scale of their operations, which may range from patient-specific small batches to large-scale production of commonly used drugs or dose forms based on historical demand. The beyond use date (BUD) or shelf life these entities assign to final products as well as the risk level (low, medium, high) of the compounding activity are also factors.

These entities are neither a pharmacy nor a manufacturer, but fall somewhere in between into a regulatory gray area. An intermediate category of drug establishment with criteria for inclusion and clarification of regulatory oversight should be developed.

SENATOR FRANKEN

Question 1. In a report on meningitis in 2002, the Centers for Disease Control and Prevention reported that "some health-system pharmacists might not realize that they are purchasing injectables prepared through compounding." In your experience, is this sometimes the case? If so, what responsibility do you believe that purchasers—including health systems—have to ensure that they are providing their patients with safe medicines?

Answer 1. Lack of clarity regarding the nature of drug establishments that register with the FDA may in fact mislead pharmacists to believing they are purchasing products from a legitimate manufacturer, rather than a compounding pharmacy. Compounding businesses advertise that they are "registered with FDA," and are listed on FDA's Web site, however, their registration categories are not disclosed. Thus, pharmacists may not be aware they are contracting with a retail pharmacy, a regional admixture pharmacy, or a manufacturing pharmacy, rather than an entity with FDA oversight.

Pharmacists are accountable for the safety and quality of the products they dispense, including those obtained from contracted services. It should be recognized, however, that pharmacists have little control over how these businesses are oper-

*Aseptic processing uses sterile components to make a sterile final product. Sterility must be maintained through multiple manipulations which introduces more variables than formulation of products that are terminally sterilized.

ated. Regardless of State or Federal oversight, a licensed business subject to statutory and regulatory requirements and offering products or services for sale should not be allowed to shift liability for its products to the end users.

Question 2. In your written testimony, you state, "Previous court rulings have made FDA's authority to inspect these facilities unclear and subject to legal action." Would you expand on this statement?

In order to determine whether a pharmacy is acting like a manufacturer, should FDA have the authority to inspect the records and processes of pharmacies that they believe may be acting improperly?

Answer 2. It is our understanding that FDA has limited authority to inspect large scale compounding entities since most are essentially operating as pharmacies. We believe that FDA's authority needs to be clarified or new authorities given to FDA to regulate compounding businesses that produce large amounts of compounded products, and sell those products to entities other than the end user. We believe that FDA and State boards of pharmacy will need to work together more closely to determine when a compounding pharmacy should be placed into a new or clarified category of FDA oversight.

[Whereupon, at 12:51 p.m., the hearing was adjourned.]

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