



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Tim Murphy
Chairman
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

JUL 11 2013

Dear Mr. Chairman:

Thank you for providing the opportunity for the Food and Drug Administration (FDA or the Agency) to testify at the April 16, 2013, hearing before the Subcommittee on Oversight and Investigations entitled "A Continuing Investigation into the Fungal Meningitis Outbreak and Whether It Could Have Been Prevented." We provided a partial response to questions posed by certain Members of the Committee on May 22, 2013. This is our final response, incorporating responses to questions posed by Representatives Bill Johnson and Renee Ellmers.

If you have further questions, please let us know.

Sincerely,

A handwritten signature in cursive script that reads "Karen Meister for".

Michele Mital
Acting Associate Commissioner
for Legislation

We have restated each Member's questions below in bold, followed by FDA's responses.

The Honorable Tim Murphy

1. Please explain the new policy and process FDA has established to enhance communications with the State pharmacy boards.

Working with our state and local partners is a priority. We have been coordinating with the states during our inspections of pharmacies that may pose higher risks and are known to have produced sterile drug products in the past, and we are providing updated information regarding our inspections to appropriate regulators. FDA coordinated our inspections with state officials, who have accompanied our investigators in most cases, including 28 of 31 (90 percent) of the priority inspections, and all of the 26 for-cause inspections. Moreover, inspection observations on FDA Form 483s¹ and Warning Letters are being posted on our website for states and the public to see. This is important because many of these facilities ship across state lines.

In addition, we have conducted training for some states and are working on a plan for additional interactions, regardless of whether we do or do not get Federal legislation. We have had conversations with five state Boards of Pharmacy, attended the National Governors Association policy committee meeting, and held at least bi-weekly calls with the National Association of Boards of Pharmacy, and we intend to continue these state outreach efforts to improve our communications with states. We are also exploring other ways to provide useful information to state regulators.

2. Please explain what steps have been taken to ensure that Warning Letters and related correspondence are approved in a timelier manner.

Warning Letters are an important regulatory tool and serve as the Agency's principal means of achieving prompt voluntary compliance with the Federal Food, Drug, and Cosmetic Act (FD&C Act). FDA issues Warning Letters to address violations of regulatory significance and may follow with an enforcement action if the violations are not promptly and adequately corrected.

FDA takes very seriously the importance of approving and issuing Warning Letters and related correspondence in a timely manner, and we are taking steps to increase our timeliness and efficiency. For example, FDA is conducting a "Lean Project Improvement Initiative," aimed in part at improving the efficiency with which the Agency issues Warning Letters involving human drug products by identifying areas

¹ An FDA Form 483 is issued when investigators observe any significant objectionable conditions. It does not constitute a final Agency determination of whether any condition is in violation of the FD&C Act or any of our relevant regulations but the observations often serve as evidence of a violation of the FD&C Act and its implementing regulations.

for process improvement and working to standardize the process. This would include Warning Letters related to compounding.

In addition, with respect to pharmacy compounding, in several instances in the past, the issuance of Warning Letters and subsequent correspondence has been delayed by pharmacies' challenges to FDA's authority, court decisions, and other complexities and ambiguities in the law. Legislation that provides FDA with appropriate authority over firms that produce and ship interstate sterile drugs in advance of or without a prescription would help the Agency to issue Warning Letters and related correspondence and take appropriate enforcement action more efficiently.

- 3. Please explain what constitutes a “proactive inspection” versus a “for cause” inspection. Which official or employee at FDA made the decision to suspend “proactive” inspections of compounding operations and what was the threshold that needed to be crossed prior to FDA conducting such an inspection in 2011 and 2012?**

In the context of compounding pharmacy inspections, FDA typically considers conducting a “for cause” inspection in response to a report of a serious adverse event that is associated with a product quality issue or practice that may have caused the drug to be adulterated or misbranded. FDA may also consider conducting a for-cause inspection in response to a request from a State Board of Pharmacy.

FDA conducts “proactive” inspections when routine surveillance is appropriate in the absence of a specific reason to inspect.

We are not aware of the decision to suspend routine, proactive inspections of compounding pharmacies as having been made by any one individual.

The Honorable Michael C. Burgess

- 1. According to the recently released OIG report, *High-Risk Compounded Sterile Preparation and Outsourcing by Hospitals that Use Them*, 92% of hospitals produce sterile compounds and only about half had USP 797-compliant clean rooms. In addition, about one half of hospitals stated that cost and space will be major challenges to comply with 797. Furthermore, the report concludes that hospitals intend to increase the amount of sterile compounding they produce onsite in the wake of drug shortages. Therefore, will FDA include hospitals in the compounding framework that FDA is proposing?**

FDA's proposed framework would make a distinction between two categories of compounding: traditional and non-traditional. Traditional compounding would include the combining, mixing, or altering of ingredients to create a customized medication for an individual patient with an individualized medical need for the compounded product, in response to a valid patient-specific prescription or order from a licensed practitioner documenting such medical need. Under our proposal,

hospital pharmacies would be classified as traditional compounding pharmacies. Traditional compounding, while posing some risk, plays an important role in the health care system, and should remain the subject of state regulation of the practice of pharmacy. Health systems are entrusted with and liable for the care of their patients, and their compounding pharmacy activities are just one aspect of that care. That responsibility for patient care creates incentives that do not exist in the same way for pharmacies outside of hospital systems.

2. The Committee is aware that FDA is currently inspecting pharmacies to GMP standards.

How are you determining whether to inspect as a manufacturer versus a compounding pharmacy and when does this analysis take place?

The fungal meningitis outbreak has caused us to re-examine our past practices with regard to our oversight of compounding pharmacies, and in coordination with state officials, FDA recently conducted its own risk-based inspections of sterile practices at certain compounding pharmacies that may pose higher risks and are known to have produced sterile drug products in the past. The objective of these inspections was to determine whether these compounding pharmacies posed a significant threat to public health from poor sterile processing practices.

To ensure a consistent approach, the Agency inspected against the current Good Manufacturing Practice (cGMP) standards. This avoided the use of different standards for pharmacies based on differences in state law or the application of the FD&C Act. In addition, the Agency has considerable experience with its cGMPs, a national standard that helps ensure the production of quality, safe, sterile drug products.

The decision to focus on Federal standards for sterile practices provides a consistent approach to reviewing the quality of sterile drug products made at different firms across the country. When we observed conditions that may constitute violations of the FD&C Act during any of the inspections, at the close of the inspection, we issued an FDA Form 483, listing our inspection observations. Whether FDA will take action based on these standards will depend upon the facts of each specific case. If a compounded drug product does not meet the exemptions under section 503A of the FD&C Act (to the extent they are applicable) or the conditions for exercise of enforcement discretion under FDA's Compounding Compliance Policy Guide, FDA could issue a Warning Letter or take enforcement action such as a seizure or injunction. If, based on information reviewed during the inspection and discussion with the firm, the firm's drug production activities appear more like those within the bounds of traditional pharmacy practice and not conventional manufacturing, FDA intends to refer the matter to the state that licensed the pharmacy for further action, noting the sterile processing deficiencies we observed.

Are you partnering with and in discussions with State Board of Pharmacies to determine if the pharmacy has exceeded state licensing authorities?

FDA is working closely with the states and will be providing updated information regarding our inspections to appropriate regulators. Inspection observations on FDA Form 483s and Warning Letters are being posted on our website for states and the public to see. This is important because many of these facilities ship across states. In addition, FDA coordinated our proactive inspections with state officials, who have accompanied our inspectors in almost all cases.

The Honorable Pete Olson

- 1. Currently, we understand there is a mechanism for compounding pharmacies to register with the FDA. What authority does this give FDA over the pharmacies that voluntarily register with the FDA? What standards are enforced on these registered pharmacies?**

Unlike conventional drug manufacturers, by law, compounding pharmacies are not required to register with FDA if they meet certain conditions. Pursuant to section 510(g) of the FD&C Act, pharmacies are exempt from registration if they comply with applicable local laws regulating the practice of pharmacy and medicine, regularly engage in dispensing drugs upon a prescription from a licensed practitioner, and do not manufacture, prepare or compound drugs for sale other than during the regular course of their business of dispensing or selling drugs at retail.

A pharmacy's voluntary registration may provide FDA with information about the facility, such as its name, location, and ownership structure, but voluntary registration alone does not give FDA additional authority over the pharmacy. In fact, a compounding pharmacy might register with FDA to give the impression that the Agency provides a higher level of oversight or approval of the pharmacy's activities than it actually does.

The Honorable Morgan Griffith

- 1. If an establishment refuses to allow FDA inspectors to enter, please explain the process for obtaining a warrant. In the past 5 years, how many times has this occurred? Has a judge ever refused? On average, how long has it taken FDA to get a warrant since the date FDA inspectors initially attempted to enter the facility?**

If an establishment refuses to allow FDA investigators to enter or permits the investigators to enter but refuses to permit access to information that the Agency needs, and believes it has authority, to review, the Agency can seek an administrative warrant. In some circumstances, FDA seeks an administrative warrant before attempting an inspection, if it has reason to believe that the firm will refuse an inspection.

Generally speaking, the process for obtaining a warrant involves the following steps: (1) the relevant FDA District Office recommends that a warrant be obtained and prepares a recommendation that describes the refusals investigators have encountered and the information sought; (2) the District Office's draft application is reviewed concurrently by the Division of Enforcement within the Office of Regulatory Affairs' Office of Enforcement and Import Operations and the relevant Center (e.g., the Office of Compliance in the Center for Drug Evaluation and Research for warrants related to compounding pharmacies); (3) the Agency's Office of the Chief Counsel reviews the draft warrant and application for legal sufficiency, and then provides the papers to the Division of Enforcement to transmit to the Department of Justice's (DOJ) Consumer Protection Branch for review; (4) following review by DOJ's Consumer Protection Branch, the local United States Attorney's Office receives the papers and assigns an Assistant United States Attorney, who then arranges a meeting with the investigator and a Magistrate Judge to get the warrant signed by the Magistrate Judge; (5) after the warrant is signed, arrangements are made in most cases for the U.S. Marshal's Service to accompany the investigators as they attempt to execute the warrant.

Over the past five years, FDA has sought and obtained about six administrative warrants for compounding pharmacies. This figure does not include situations where the Agency was able to resolve a refusal by some other means (e.g., a conversation between FDA's Office of Chief Counsel and the firm's attorney). We have not identified a situation where a Judge refused to sign an administrative warrant sought by FDA, but we note that our records on administrative warrants are somewhat limited. Also, our records are not kept in a way that would enable us to readily calculate the average the length of time it takes for FDA to obtain an administrative warrant, and the length of time can depend on a variety of factors. We estimate that the average time to obtain a warrant is two weeks. In the most recent administrative warrant we sought for a pharmacy, 10 days passed between when the refusal was encountered and when the warrant was signed by the Magistrate Judge.

The Honorable Bill Johnson

- 1. For each Adverse Event Report FDA received associated with a product produced by NECC or Ameridose, please document what actions the agency took in response, including, but not limited to, whether FDA informed the Massachusetts Board of Pharmacy.**

While FDA is unable to comment specifically regarding NECC or Ameridose due to the ongoing investigations, we have listed below reports of adverse events associated with NECC and Ameridose products that FDA identified based on a search of readily available records, including the FDA Adverse Event Reporting System (FAERS) database. Thus, this listing of reports may not be an all-inclusive list. For each identified report, the list indicates whether FDA is able to confirm having communicated information about the report to the Massachusetts Board of Registration in Pharmacy (MA Board of Pharmacy).

NECC

A comprehensive search of the FDA Adverse Event Reporting System (FAERS) database identified 52 reports associated with NECC between 2002 and September 26, 2012. The MA Board of Pharmacy was notified about five of the 52 reports by FDA. Thirty-nine of the reports were related to a single product, and FDA's investigation did not identify evidence of a product quality deficiency. Two reports were isolated adverse events, and six reports did not raise a signal for product quality issues. These reports include:

- In March 2002, FDA received two reports describing dizziness, shortness of breath, diaphoresis, and drop in blood pressure following administration of betamethasone injection. The MA Board of Pharmacy was notified, and FDA and the MA Board of Pharmacy conducted simultaneous, but independent, investigations in April 2002. FDA investigators were unable to complete the investigation because NECC management contested FDA's authority to inspect and refused to provide necessary records.
- In July and August 2002, FDA received three MedWatch reports describing two cases (two of the reports described the same case) of meningitis in patients who received injections of methylprednisolone acetate prepared by NECC. The MA Board of Pharmacy was notified; FDA and the MA Board of Pharmacy conducted a joint inspection, and an FDA-483² list of inspectional observations was issued in February 2003. FDA lab analysis identified bacterial contamination. Based upon the evidence available to them, FDA and the MA Board of Pharmacy jointly determined that NECC at that time was operating as a compounding pharmacy and, therefore, the state would be in a better position to obtain compliance or take regulatory action as necessary. NECC recalled 15 lots of methylprednisolone acetate that were labeled with an incorrect expiration date; this included the lot that was found to be contaminated.
- In 2007, FDA received six reports associated with Avastin repackaged by NECC for patients enrolled in a Visudyne Registry Study of Age-Related Macular Degeneration (AMD) Therapy. Reports were submitted in accordance with the Visudyne Registry Study protocol. Four patients aged 77 or older died. The cause of death was reported as unknown. Product quality complaints for NECC's repackaged Avastin were not reported, and these reports do not raise a signal for product quality issues. The MA Board of Pharmacy was not notified by FDA.
- FDA received a report in June 2007 describing a case of endophthalmitis in a patient who received an injection of Avastin repackaged by NECC. This was an

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individual adverse event. For such isolated reports, it is rarely possible to know with a high level of certainty whether the event was caused by the product. The MA Board of Pharmacy was not notified by FDA.

- In December 2007, FDA received 39 reports that appeared to have been filled out by individual patients but all were submitted together in one batch. The reports described flu-like symptoms in fibromyalgia patients treated with betamethasone compounded by NECC, which the patients' physician attributed to lack of efficacy. FDA conducted an investigation at the office of the patients' physician and collected samples of betamethasone. FDA did not find any information to suggest that the adverse events were caused by deficiencies in the quality of the betamethasone made by NECC, and FDA laboratory analysis indicated that the samples met specifications for endotoxins, assay, and identification. The MA Board of Pharmacy was not notified by FDA.
- FDA received a report in September 2009 describing endophthalmitis in a patient who received an injection of Avastin repackaged by NECC. This was an individual adverse event. For such isolated reports, it is rarely possible to know with a high level of certainty whether the event was caused by the product. In addition, the report indicated that approximately 40-50 other patients had received Avastin from the same lot that was associated with this event, and that no other adverse events were reported. The MA Board of Pharmacy was not notified by FDA.

FDA also received an October 2008 report of an adverse event through its Consumer Complaints database. This report describes a patient who was treated for a bacterial infection and other symptoms after chelation therapy with phosphatidylcholine, prepared by NECC. FDA collected a sample, and laboratory analysis indicated that the product failed to meet label claims for potency, but tested negative for microbial contamination. A recall was not pursued because there was no evidence of contamination and the product lot had expired when the sample results were received. The MA Board of Pharmacy was not notified by FDA.

Ameridose

FDA's search of FAERS for reports related to Ameridose identified 18 reports. Eleven of the reports describe adverse events and are listed below. Three of these reports (including two reports received from different sources describing the same incident) describe adverse events in patients receiving several drug products prepared by various firms, and Ameridose's product was not considered suspect. Three reports do not describe adverse events that are considered serious or unexpected, and five reports describe possible lack of efficacy of drug products made by Ameridose. None of these reports suggested sterility concerns. The MA Board of Pharmacy was not notified about these reports by FDA.

- In April 2008, FDA received a report indicating that succinylcholine supplied in prefilled syringes had an unpredictable clinical effect, at times producing inadequate or no muscle relaxation.

- FDA received a report in November 2008 describing intermittent lack of effect from phenylephrine syringes. The reporter indicated that several syringes were returned to the vendor, which reported back that the syringes were “fine.”
- In March and June 2010, FDA received two reports from different manufacturers describing the same incident, in which a patient’s arm turned white and needed to be amputated after several drugs, including midazolam, made by Ameridose, were infused into an artery instead of a vein. The reporter indicated that the adverse events were related to administration of a drug made by a different manufacturer.
- In June 2011, FDA received a report regarding a patient who was administered products, including a promethazine HCl and sodium chloride bag made by Ameridose, and Reglan, made by a different firm. She experienced decreased respirations, decreased blood pressure, and unresponsiveness after administration of Reglan (not supplied by Ameridose), which was considered suspect. The reporter considered the adverse events to be related to the combination of promethazine and Reglan.
- FDA received a report in November 2011 describing three patients who reported poor pain control from a ropivacaine + fentanyl epidural injection. The reporter indicated that Ameridose had been contacted.
- FDA received a report in March 2012 regarding a patient who was not adequately sedated with a dose of midazolam 1mg/mL and required an additional 4mg to achieve sedation. The report noted that Ameridose was contacted about the potential problem and was conducting an investigation.
- In July 2012, FDA received a report describing lack of muscle relaxation in a patient who received succinylcholine chloride made by Ameridose. The reporter suspected that the drug was not refrigerated properly and degraded.
- In September 2012, FDA received three reports from the same reporter describing “post-operative agitation and excitation” in patients who received methohexital during electroconvulsive treatment. The reports indicated that potency results and all other testing were within specification. Also, side effects such as restlessness and anxiety are included in the approved product labeling.

2. Please describe how Adverse Event Reports submitted to FDA’s MedWatch system are shared with the correct FDA offices and employees.

FDA implemented the MedWatch program to learn of adverse experiences that patients have encountered. FDA requires manufacturers to report adverse experiences to FDA and encourages voluntary reports from consumers and health professionals. FDA also accepts reports submitted electronically at www.fda.gov/medwatch/report.htm. FDA uses these MedWatch reports to identify problems in marketed products.

Voluntary reports are essential for ensuring the continued safety of FDA-regulated products. Reports submitted to MedWatch are added to existing data in our Adverse Event Reporting System database and reviewed by FDA's post-marketing safety staff for the appropriate product areas. The collected reports are monitored and observed for emerging patterns. One or two well-documented case reports may provide an early signal of unexpected safety issues and lead to additional evaluation. This may result in FDA actions that improve the safety of the products used in patient care each day. We carefully evaluate and analyze all reports that are available to us and make recommendations for possible actions, if the science-based risk evaluation warrants the actions.

- 3. In addition to the numerous Adverse Event Reports, FDA had received associated with Ameridose products harming patients, the agency received several alarming complaints from an employee at Ameridose, including the fact that there was mold growing in one of the sterile compounding rooms. Please explain what information FDA needed to receive about a company prior to conducting a “for cause” inspection during your tenure as Commissioner? What were the criteria used?**

Although we cannot comment on Ameridose specifically due to the ongoing FDA investigation, in the context of compounding pharmacy inspections, FDA typically considers conducting a “for cause” inspection in response to a report of a serious adverse event that is associated with a product quality issue or practice that may have caused the drug to be adulterated or misbranded. FDA may also consider conducting a for-cause inspection in response to a request from a State Board of Pharmacy.

The Honorable Rence Ellmers

- 1. Please submit a list of all complaints relating to NECC or Ameridose that FDA forwarded or reported to the Massachusetts Board of Pharmacy.**

FDA searched its readily available records for complaints related to NECC and Ameridose that the Agency received between 2002 and September 25, 2012, and did not identify any complaints that FDA is able to confirm having forwarded or reported to the Massachusetts Board of Pharmacy. However, some complaints were sent to both FDA and the Massachusetts Board of Registration in Pharmacy, and some were investigated jointly.

The Honorable Edward J. Markey

- 1. I recently released a report entitled “State of Disarray” that analyzed state oversight of compounding pharmacies and was based on information provided**

directly from the state boards of pharmacy.³ This report found that only 2 states, Mississippi and Missouri, routinely track compounding pharmacies in their state. And none of the states have requirements that its board of pharmacy be notified on the quantity of compounded drugs produced or whether a pharmacy is shipping drugs over state lines. Given the lack of information maintained by the states, do you think that states can currently do an adequate job of overseeing interstate commerce engaged in by compounding pharmacies within the state? Please explain.

- 2. As you are aware, sterile compounding, particularly using non-sterile components, carries the greatest danger to public health. Yet only a handful of states (13 states) know which pharmacies are providing sterile compounding services, and even fewer of these states (5 out of 13 states) have inspectors that are specifically trained for identifying problems with sterile compounding. The current system allows any state to come up with their own regulatory framework for sterile compounding, resulting in a patchwork of standards across the nation.**
 - a. Do you think that FDA should impose a mandatory, enforceable and uniform standard for sterile compounding applied across all 50 states, to ensure consistency in the safe production of sterile drugs? Please explain.**
 - b. Do you think FDA should play a role in ensuring that all sterile compounding pharmacies are held to this same standard and enforced against uniformly? Please explain.**
- 3. A recurring theme that came up in responses provided by the state boards of pharmacy was that when issues arise with out-of-state pharmacies, states do not consistently inform the state where the pharmacy is physically located or other states where the drugs were shipped. As a result states are unable to effectively police compounding pharmacy activities in other states because they are simply not aware of what occurs outside their borders. Do you think FDA should be responsible for policing the interstate commerce associated with all compounding pharmacies? Please explain.**

In response to Questions 1, 2, and 3, we note that of compounded products, sterile compounded products made in advance of or without a prescription and shipped interstate pose the highest risks to the most people if they are not made in accordance with strict quality standards. FDA is proposing to define non-traditional compounding based on factors that make the product higher risk, such as any sterile compounding in advance of or without receiving a prescription, where the drug is distributed out of the state in which it was produced. Under this proposal, FDA would hold these compounders to Federal quality standards adequate to ensure that the compounding could be performed without putting patients at undue risk; conduct proactive inspections; ensure that the firms comply with required adverse event reporting and labeling; and take appropriate enforcement action when necessary to protect the public health.

³ <http://markey.house.gov/press-release/markey-report-compounding-pharmacies-going-untracked-unregulated-under-inspected-coast#overlay-context=>

Likewise, the states must assume more responsibility in monitoring the compounding of sterile products that are made in response to patient-specific prescriptions and those that are distributed only in a single state, as well as the compounding of non-sterile products. States have a variety of different laws and regulations and varying levels of resources and expertise to oversee compounding pharmacies. They apply different standards and enforce them differently. At the 50-state meeting, we heard from states that while they feel comfortable regulating pharmacies that operate within their states, they have concerns about pharmacies located out of their state that ship into the state and that may not be tightly regulated, placing their citizens at risk. FDA's proposal to regulate interstate shipment of the highest-risk, sterile-compounded products should alleviate some of these concerns.

FDA is willing to assist the states in developing and implementing appropriate product quality standards. FDA already has conducted training for some states and is working on a plan for additional interactions with the states, regardless of whether new Federal legislation is or is not enacted.

4. The report indicated that states do not have the requirement that compounding pharmacies report the volume of drugs they are providing in advance of a prescription, or in response to prescriptions. Given this lack information on the state level, it would be impossible for states to focus enforcement activities on facilities that are the largest producers of compounded drugs.

a. Would FDA support the requirement that compounding pharmacies provide information on the volume of drugs to FDA or the states?

A requirement for firms engaging in non-traditional compounding; i.e., those that produce and distribute interstate sterile products in advance of or without a prescription—to report information regarding the volume of drugs they compound to the Agency would be helpful. In addition, states could consider whether a state requirement for pharmacies engaging in traditional compounding to report such information to the states may assist states' regulation of these entities. Reporting the volume of compounded drugs to FDA or the states would help regulators to identify those pharmacies that are the largest producers of compounded drugs and help to prioritize inspection and surveillance resources.

b. Would FDA find it helpful to have this information, for purposes of determining which of these facilities may be manufacturing drugs and are all therefore subject to the requirements of drug manufacturers?

Information regarding volume would be helpful; it would provide data on high-producing pharmacies so that the Agency could prioritize inspections and use its resources to best protect the public health. For example, FDA is particularly concerned about the large-scale distribution of compounded sterile drug products to

health care facilities nationwide, when compliance with appropriate standards for large-scale production has not been met.

However, determining whether a firm is acting as a manufacturer or a pharmacy compounder is very fact-specific. Sometimes a state-licensed pharmacy may be simultaneously engaging in some activities that are considered traditional compounding while other activities are more like typical manufacturing, further complicating the determination of the facility's regulatory status. Therefore, while volume information is helpful, it is critical that FDA have clear authority to examine pharmacy records.

For all compounders, traditional and non-traditional, FDA should have clear authority to examine records, such as records of prescriptions received, products shipped, volume of operations, and operational records such as batch records, product quality test results, and stability testing results. Such inspections are necessary to determine when a pharmacy exceeds the bounds of traditional compounding, to facilitate FDA's response to public health threats, and to enforce Federal standards when appropriate.

5. **The report also indicated that states generally do a poor job maintaining historical records. For example, only 64 percent of the boards of pharmacy that responded to the investigation were able to provide the number of pharmacies that were licensed in their state over the decade. Furthermore, state licensing practices differ greatly; as some states compile community pharmacies with drug dispensers, distributors and wholesalers and others license these categories separately. Moreover, typically the states do not maintain pharmacy inspection records that enable easy searching and compiling of statistics and data, making it impossible for many of these states to identify issues pertaining to safety, cleanliness, sterility and other issues that came to light in the NECC tragedy. Do you think the current licensing and record keeping practices of the states would enable them to solely and effectively identify systemic and repeated compounding pharmacy safety problems?**

As noted above, FDA is proposing to define non-traditional compounding based on factors that make the product higher risk such as any sterile compounding in advance of or without receiving a prescription, where the drug is distributed out of the state in which it was produced.

Likewise, the states must assume more responsibility in monitoring the compounding of sterile products that are made in response to patient-specific prescriptions and those that are distributed only in a single state, as well as the compounding of non-sterile products. States have a variety of different laws and regulations and varying levels of resources and expertise to oversee compounding pharmacies. They apply different standards and enforce them differently. At the 50-state meeting, we heard from states that while they feel comfortable regulating pharmacies that operate within their states, they have concerns about pharmacies located out of their state that ship into the state and that may not be tightly regulated, placing their citizens at risk.

FDA's proposal to regulate interstate shipment of the highest-risk, sterile-compounded products should alleviate some of these concerns. Likewise, the states must assume more responsibility in monitoring the compounding of all products that are marked intrastate.

The Honorable G.K. Butterfield

- 1. Will sequestration impact FDA's ability to inspect compounding facilities and adequately address complaints associated with compounded drugs? Will sequester increase the possibility that a contamination situation could occur again?**

Sequestration will reduce FDA funding, which will have a variety of adverse impacts on FDA's programs, including the Agency's ability to inspect compounding facilities, and address complaints associated with compounded drugs to the extent we could with more funds.

- 2. Does reassigning investigators who would normally be conducting inspections at conventional drug manufacturers divert resources from other areas including pharmaceutical approval?**

Yes, the funding to conduct the 31 proactive inspections, as well as the 26 recent for-cause inspections comes out of existing funding for drug manufacturing inspections—including pre-approval inspections—and pulls from the same inspection force. The number of investigators who have the training to conduct these inspections is limited, and the investigators conducting the compounding inspections also conduct pre-approval and other types of inspections. The current staffing of compounding inspections is not sustainable in the longer term, without harming our ability to oversee the 5,600 conventional manufacturers we regulate. It is also important to note that the proactive inspections FDA has conducted are a fraction of the compounding pharmacy industry. As we have previously said, we do not know how many pharmacies there are since they do not register; however, according to the International Academy of Compounding Pharmacists, an estimated 28,000 pharmacies do some degree of compounding. Even with a limited group of 500-1000 non-traditional compounding pharmacies over which FDA has proposed that it would have proactive authorities, at current funding levels, FDA projects that it would inspect each pharmacy only once every 25-50 years.

- 3. In the risk-based framework recommended by FDA, would the Agency have the appropriate resources to test samples of compounded drugs and examine records of compounding pharmacies?**

As Dr. Hamburg noted in her testimony, we look forward to working with Congress to explore the appropriate funding mechanisms to support this work, which could include registration or other fees, as Congress has authorized and FDA has successfully implemented in other settings. Providing establishment and reinspection

fees to help defray the cost of enhanced oversight would significantly improve the current oversight of compounders.

- 4. It is my understanding that there is a mechanism for compounding pharmacies to register with FDA. What authority does this give FDA over the pharmacies that voluntarily register with FDA? What standards are enforced on these registered pharmacies?**

Unlike conventional drug manufacturers, by law, compounding pharmacies are not required to register with FDA if they meet certain conditions. Pursuant to section 510(g) of the FD&C Act, pharmacies are exempt from registration if they comply with applicable local laws regulating the practice of pharmacy and medicine, regularly engage in dispensing drugs upon receiving a prescription from a licensed practitioner, and do not manufacture, prepare or compound drugs for sale other than during the regular course of their business of dispensing or selling drugs at retail.

A pharmacy's voluntary registration may provide FDA with information about the facility, such as its name, location, and ownership structure, but voluntary registration alone does not give FDA additional authority over the pharmacy. In fact, a compounding pharmacy might register with FDA to give the impression that the agency provides a higher level of oversight or approval of the pharmacy's activities than it actually does.

- 5. What improvements in communication and oversight have been implemented by FDA in response to meetings with State Pharmacy boards?**

Working with our state and local partners is a priority. We have been coordinating with the states during our inspections of pharmacies that may pose higher risks and are known to have produced sterile drug products in the past, and we are providing updated information regarding our inspections to appropriate regulators. FDA coordinated our inspections with state officials, who have accompanied our investigators in most cases, including 28 of 31 (90 percent) of the priority inspections, and all of the 26 for-cause inspections. Moreover, inspection observations on FDA Form 483s and Warning Letters are being posted on our website for states and the public to see. This is important because many of these facilities ship across state lines.

In addition, we have conducted training for some states and are working on a plan for additional interactions, regardless of whether or not new Federal legislation is enacted. We have had conversations with five state Boards of Pharmacy, attended the National Governors Association policy committee meeting, and held at least bi-weekly calls with the National Association of Boards of Pharmacy, and we intend to continue these state outreach efforts to improve our communications with states. We are also exploring other ways to provide useful information to state regulators.

6. How are patients notified about recalls of compounded drugs they have been prescribed? Are patients made aware of symptoms of defective compounded drugs and treatment options if infected?

It is important to note that a drug recall is a voluntary action; FDA does not have mandatory drug recall authority. Firms that produce drug products, including compounded drugs, may decide to recall products that are defective or potentially harmful. In such cases, as part of the recall, the firm would notify those who have received the product, including consumers and health care professionals. When the Agency is advised of a firm's intent to recall, FDA's role is to monitor the company's strategy, including its communication strategy, and to assess the adequacy of the recall.

FDA works with industry and our Federal and state partners to issue public notices about recalls of drug products that may present a significant or serious risk to the consumer or user of the product. Not all recalls rise to the level of issuing press releases. FDA seeks publicity when the recalling firm does not adequately alert the public to recalls of products that pose a serious hazard. In such cases, FDA can hold press conferences, issue press releases, and post updates to its website.

FDA posts information pertaining to recalls on its website. For example, FDA's weekly "Enforcement Report" (<http://www.fda.gov/Safety/Recalls/EnforcementReports/default.htm>) lists all recalls overseen by FDA, including those that have been classified by FDA and those that are pending classification (these are reposted with their classification in the Enforcement Report once that determination has been made). FDA also has a "major recalls" webpage (<http://www.fda.gov/Safety/Recalls/MajorProductRecalls/default.htm>), which includes details of FDA's involvement in investigating recalls, a means to search recalled products, and information for consumers and industry representatives.

FDA's MedWatch program may also publish drug safety alerts that provide timely new safety information on FDA-regulated products and contain actionable information that may affect both treatment and diagnostic choices for healthcare professionals and patients. When indicated, FDA also publishes drug safety communications in both English and Spanish on its website to provide the public with access to important drug safety information. The webpage contains the most recent Drug Safety Communications (which may include advice to healthcare providers and patients as well as questions and answers) and links to pertinent safety information, such as Early Communications, Follow-Up Early Communications, Information for Healthcare Professional sheets, and Public Health Advisories. (<http://www.fda.gov/Drugs/DrugSafety/ucm199082.htm>).

In addition, FDA Drug Safety Podcasts are produced by FDA's Center for Drug Evaluation and Research (CDER). They provide emerging safety information about

drugs in conjunction with the release of Public Health Advisories and other drug safety issues.

Many of these communications are further disseminated through electronic distribution lists and through Twitter and Facebook.

7. What additional legal framework would provide FDA with the tools needed to identify and adequately regulate pharmacies to prevent product contamination?

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

Further, there should be a distinction between two categories of compounding: traditional and non-traditional. Traditional compounding would include the combining, mixing, or altering of ingredients to create a customized medication for an individual patient with an individualized medical need for the compounded product, in response to a valid patient-specific prescription or order from a licensed practitioner documenting such medical need. Traditional compounding, while posing some risk, plays an important role in the health care system, and should remain the subject of state regulation of the practice of pharmacy.

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

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

In addition, with noted exceptions, certain products are not appropriate for compounding under any circumstances. These products would include: 1) what are essentially copies of FDA-approved drugs, absent a shortage justification based on the drug appearing on FDA's shortage list; and 2) complex dosage forms such as extended-release products; transdermal patches; liposomal products; most biologics; and other products as designated by FDA. Producing complex dosage forms would

require an approved application and compliance with GMP standards, along with other requirements applicable to drug products made by conventional manufacturers.

There are other authorities that would be important to support this new regulatory paradigm. For example, FDA should have clear ability to collect and test samples of compounded drugs and to examine and collect records in a compounding pharmacy, just as the Agency does when inspecting other manufacturers. FDA should also have clear 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.

An accurate inventory of pharmacies engaged in non-traditional compounding would facilitate appropriate oversight and coordination with state regulators. In addition, FDA looks forward to working with Congress on potential improvements that may include label statements and adverse event reporting that have proven useful in other areas.

The Honorable Peter Welch

- 1. Currently, we understand there is a mechanism for compounding pharmacies to register with FDA. What authority does this give FDA over pharmacies that voluntarily register with FDA? What standards are enforced on these registered pharmacies?**

Unlike conventional drug manufacturers, by law, compounding pharmacies are not required to register with FDA if they meet certain conditions. Pursuant to section 510(g) of the FD&C Act, pharmacies are exempt from registration if they comply with applicable local laws regulating the practice of pharmacy and medicine, regularly engage in dispensing drugs upon a prescription from a licensed practitioner, and do not manufacture, prepare or compound drugs for sale other than during the regular course of their business of dispensing or selling drugs at retail.

A pharmacy's voluntary registration may provide FDA with information about the facility, such as its name, location, and ownership structure, but voluntary registration alone does not give FDA additional authority over the pharmacy. In fact, a compounding pharmacy might register with FDA to give the impression that the Agency provides a higher level of oversight or approval of the pharmacy's activities than it actually does.

The Honorable Gene Green

- 1. During the first round of questions you said there are certain drugs that neighborhood compounders should not be making. Is that something FDA wants to be able to forbid with new authority?**

Yes. With noted exceptions, certain products are not appropriate for compounding under any circumstances. These products include: 1) what are essentially copies of FDA-approved drugs, absent a shortage justification based on the drug appearing on FDA's shortage list; and 2) complex dosage forms such as extended release products; transdermal patches; liposomal products; most biologics; and other products as designated by FDA. Producing complex dosage forms would require an approved application and compliance with cGMP standards, along with other requirements applicable to manufactured drug products.

- 2. Does FDA currently not have authority to regulate what drugs can be compounded?**

FDA currently has some authority to regulate what drugs can be compounded. For example, under section 503A, FDA can, through rulemaking, establish a list of drugs that may not be compounded because the drugs or their ingredients have been withdrawn or removed from the market because the drugs or their ingredients "have been found to be unsafe or not effective." FDA can also establish a list of drugs that present "demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness" of the drug and, therefore, may not be compounded. However, due to the Ninth Circuit decision in *Western States*, this would not be a national standard. Furthermore, FDA's authority to regulate compounded drugs is more limited than our authority over conventional manufacturers and has been challenged in the past. And, as we have previously stated, our present authorities are not well-suited to appropriately and effectively regulating this evolving industry.

- 3. Additionally, to clarify from earlier, you seemed to be saying that FDA did not currently have the capacity to address all of the oversight and it would like to cover compounders, is that correct?**

As Dr. Hamburg noted in her testimony, we look forward to working with Congress to explore the appropriate funding mechanisms to support this work, which could include registration or other fees, as Congress has authorized and FDA has successfully implemented in other settings. Providing establishment and reinspection fees to help defray the cost of enhanced oversight would significantly improve the current oversight of compounders.

- 4. FDA has said in the past that they did not have regulatory authority to further investigate NECC in advance of the outbreak. However, FDA has inspected 31 facilities since the outbreak. In your testimony, you outside several other incidents, including one in Texas, which were the result of unsanitary compounds, what else has changed that FDA believes it has inspection authority now, but did not previously?**

FDA's authority over compounding pharmacies is more limited but not non-existent. And the existing framework is not the right fit for effectively regulating outsourcers who compound drugs in advance of or without receiving a prescription for an individually identified patient.

The fungal meningitis outbreak has caused us to review our past practices with regard to our oversight of compounding pharmacies. Using a risk-based model, we identified 29 firms for priority inspections focused on their sterile processing practices. During these 29 inspections, in two instances, FDA identified secondary firms associated with the priority inspections, for a total of 31 firms. While we are exercising our current authorities to protect public health, our authorities are still being challenged. Notably, even in light of recent events, and even though we are often working with the state inspectors, our investigators' efforts are being delayed because they are denied full access to records at some of the facilities they are inspecting. Just during the recent inspections, several pharmacies delayed or refused FDA access to records and FDA had to seek administrative warrants in two cases. And although we have been able to eventually conduct the inspections and collect the records that we have sought, our ability to take effective regulatory action to obtain lasting corrective action with regard to substandard sterility practices remains to be seen.

For example, FDA may inspect a pharmacy and find issues with that pharmacy's sterile processes, but, depending upon the facts of the case, may lack the authority to take legal action needed to ensure that the pharmacy corrects those issues.

5. Have all of the compounders that you have inspected willingly opened their doors to FDA or, even in light of the recent tragedy, have there been some compounders that have challenged FDA's authority?

As noted above, even though we are often working with the state inspectors, our investigators' efforts were delayed because, among other things, they were denied full access to records at some of the facilities they are inspecting. Just during the recent inspections, several pharmacies delayed or refused FDA access to records and FDA had to seek administrative warrants in two cases. And although we have been able to eventually conduct the inspections and collect the records that we have sought, our ability to take effective regulatory action to obtain lasting corrective action with regard to substandard sterile practices remains to be seen.

6. I'd like to hear more on the specifics of how FDA will be able to use its new authority. Will it require user fees or some other type of fee paid by compounders in order to facilitate this authority?

As noted above, we look forward to working with Congress to explore the appropriate funding mechanisms to support this work, which could include registration or other fees, as Congress has authorized and FDA has successfully implemented in other settings. Providing establishment and reinspection fees to help defray the cost of

enhanced oversight would significantly improve the current oversight of compounders.

- 7. Can we draw a bright line at whether the entity ships over state boundaries as the determining factor for FDA to enter?**
- 8. If we use other criteria in addition to interstate commerce, will that leave large loopholes or inadvertently exempt some compounders who should not be?**

In response to Questions 7 and 8, under FDA's proposal, interstate shipment would be one of three factors that would subject certain compounders to Federal quality standards adequate to ensure that the compounding could be performed without putting patients at undue risk. The other two factors are 1) sterile compounding and 2) compounding in advance of or without receiving a prescription. Under our proposal, FDA could also exercise its authority to take action against any compounder that is, for example, making misbranded or adulterated products, making copies of FDA-approved drugs, or making certain products that should not be compounded under any circumstances. In addition, for all compounders, traditional and non-traditional, FDA should have clear ability to examine records such as records of prescriptions received, products shipped, volume of operations, and operational records such as batch records, product quality test results, and stability testing results. Such inspections are necessary to contain an outbreak or other public health threat, determine when a pharmacy exceeds the bounds of traditional compounding, and enforce the other provisions of the law.