

ONE HUNDRED THIRTEENTH CONGRESS
Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
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WASHINGTON, DC 20515-6115
Majority (202) 225-2927
Minority (202) 225-3641

February 1, 2013

Margaret A. Hamburg, MD
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Hamburg:

Pursuant to Rules X and XI of the U.S. House of Representatives, the Committee on Energy and Commerce is continuing its investigation into the facts and circumstances surrounding the recent outbreak of fungal meningitis and whether it could have been prevented. It is a top priority of the Committee as we begin the 113th Congress. Contaminated injectable steroid products made and distributed by the New England Compounding Center (NECC) are responsible for killing 45 individuals and sickening almost 650 others across 19 States. This is one of the deadliest public health crises in U.S. history.

The Committee has a long history of conducting bipartisan oversight of the nation's drug supply. When drug-related outbreaks have occurred in the past, we have deliberately and exhaustively investigated their causes and surrounding circumstances. We have done so not to cast blame, but to ensure that history does not repeat itself. If any gaps or uncertainties in the ability of the Food and Drug Administration (FDA) to protect the public health are identified pursuant to such investigations, the Committee has worked with FDA to fill or clarify them.

During the November 14, 2012, hearing, Members of this Committee attempted to begin to do just that. We invited you to explain your understanding of FDA's authority over compounding pharmacies and to identify the specific gaps in that authority. For example, Subcommittee Chairman Tim Murphy asked you to simply provide the definition of "compounding pharmacy" versus "manufacturer," and explain which FDA official is responsible for defining it. You acknowledged that FDA had "many discussions" about the definitions of compounding pharmacy and manufacturer, that the FDA chief counsel's office participated in those discussions, and that the issue was "complex." However, you refused to explain with any particularity the difference between the two. Congressman Lee Terry asked you to point to the specific parts of the Food, Drug, and Cosmetic Act that need to be revised or lack clarity. In response, you stated that "[t]he problem is that, with this evolving industry, there is a gray area." Again, you did not offer this Committee any specifics as to what authority FDA

has over compounding pharmacies nor has FDA provided any legal memoranda on this issue as requested by the Committee on November 16, 2012.

The Committee has also sought to understand FDA's history with the NECC and how the agency exercised its authority over the company. Before the Committee can consider any proposals related to FDA's authority over compounding pharmacies, we must fully understand what happened with NECC. Unfortunately, FDA has failed to provide the requested documents in a timely manner. On December 20, 2012, Subcommittee Chairman Murphy and Ranking Member DeGette called you to discuss the Committee's concern with FDA's inadequate production of internal communications responsive to the Committee's requests. We note that the Massachusetts Board of Pharmacy, a much smaller entity than the FDA that is not accustomed to congressional oversight, produced *all* of its responsive emails prior to the November 14, 2012, hearing. Chairman Murphy requested that FDA complete its production by January 7, 2013—over two months after the initial deadline given in the Committee's bipartisan letter of October 17, 2012. The Committee was optimistic, based on your assertions, that substantial compliance would have been achieved by that date and that any outstanding issues could be addressed in a subsequent meeting. Over a month has passed since that telephone call and nothing significantly has changed.

In fact, in the three months since this Committee first requested documents relevant to the outbreak and the agency's history with the NECC, FDA has produced past inspection reports and formal correspondence with the company, most of which had already been made publicly available. With regard to the Committee's request for internal FDA communications relating to NECC, the agency has produced emails from only one FDA district office employee (now retired), without including any attachments such as memoranda or complaint reports. Even that production is markedly incomplete, as all but a small batch of these emails from this individual's account relate to NECC's sister company, Ameridose – not NECC – and are from 2008 to 2010. To date, FDA has produced no communications from the critical time period of 2002 through 2006, when FDA conducted three separate inspections of NECC's facilities, documented numerous public health and safety concerns, and considered enforcement actions against the firm. FDA has produced no communications from staff and officials at FDA headquarters, who were actually making the decisions about how to address the situation at NECC. In addition, FDA took three months to produce a one-and-a-half-page timeline of its involvement with the company, a document Committee staff requested on October 12, 2012, during its first teleconference with FDA related to the outbreak. (See Attachment A.)

At the time you testified on November 14, 2012, documents produced to the Committee showed that FDA had issued a Warning Letter to the NECC on December 4, 2006; that NECC objected to the Warning Letter on January 5, 2007; and that FDA finally issued a response to those objections almost two years later on October 31, 2008. Members of this Committee asked you to explain why, given NECC's record, FDA failed to re-inspect NECC after issuing the 2006 Warning Letter. In response, you repeatedly highlighted that the violations included in the Warning Letter were not germane to the recent outbreak. You stated that “the Warning Letter and the inspection it was based on had to do with a different set of concerns than sterility failures” and that FDA had “no reason to believe that any of the specific actions in question –

more-timely issuance of the 2006 warning letter or inspectional follow-up – would have prevented this recent tragedy.”

What you failed to mention – and what the few communications FDA has produced to the Committee show – is that after the Warning Letter was issued in 2006, FDA received additional complaints about NECC that directly called into question the safety of the company’s products. Further, certain district office employees were eager to re-inspect NECC based on these new developments. In fact, one district office official stated on October 27, 2008, “We are starting to get a lot of complaints involving products produced at NECC, we are going to need to go out there real quick to follow up on them.”

It is apparent from the emails that follow-up inspections were considered which extended beyond the issues raised in the Warning Letter, but that officials at FDA headquarters were hesitant to return to NECC prior to issuing a response to the company’s January 2007 reply to the Warning Letter. For example, after discussing a particular complaint, one FDA district office official stated on October 17, 2008, “We need to make sure the investigator follows up on this. . . . We have a pending CDER assignment to re-inspect NECC as a follow up to a [Warning Letter] *and other issues*. We are still waiting for [Center for Drug Evaluation and Research] (CDER)/[Office of the Chief Counsel] (OCC) to respond to the firm’s response . . . OCC expects a response to the firm in a few weeks. Then we will conduct the reinspection.” (Emphasis added.) Although FDA ultimately sent NECC a response on October 31, 2008, the agency never went back to re-inspect NECC to ensure that the past violations were corrected or to investigate the new complaints that were made to FDA after the 2006 Warning Letter.

In early 2009, documents produced to the Committee show that FDA district office staff was again prepared to inspect NECC, this time for a “possible injunction,” after additional adverse event reports were submitted to FDA’s MedWatch system. That inspection was ultimately cancelled. Three years later, in 2012, FDA staff again considered inspecting NECC. In May 2011, the Colorado Board of Pharmacy notified FDA that NECC had continued its illegal practice of shipping large quantities of drug products across the country without patient-specific prescriptions. Based on this evidence, the Colorado Board issued a cease and desist order to NECC in April 2011, which NECC subsequently violated in July 2012. After this violation, the Massachusetts Board of Pharmacy was first made aware of these violations by the Colorado Board. Though FDA knew about these violations in 2011, it did not conduct an inspection or confer with Massachusetts authorities in either May 2011 or July 2012. However, on July 17, 2012, after hearing of NECC’s violation, an FDA district office employee emailed individuals in CDER’s Office of Compliance and asked, “Based on past conversations that we may start enforcing compounding pharmacies at the end of this year do you want us to wait until you issue an [inspection] assignment to go to [NECC]?” No substantive reply to this question has been produced to the Committee.

The few communications FDA has produced to the Committee from the account of one district office employee raise new and troubling questions about the agency’s oversight of NECC after the December 2006 Warning Letter up until the recent outbreak, including why FDA failed to re-inspect the company’s facility. FDA’s repeated inaction is even more troubling in that it runs counter to remarks you gave early in your tenure during a speech entitled, “Effective

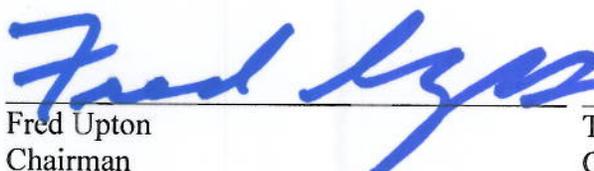
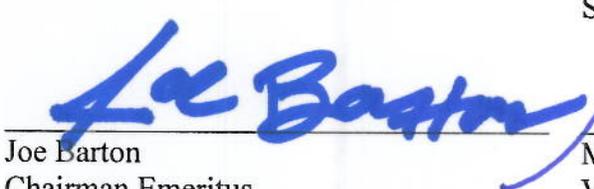
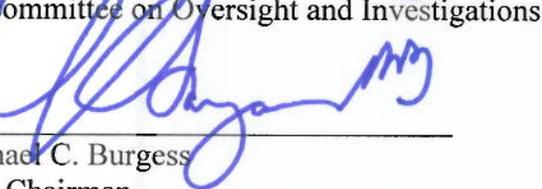
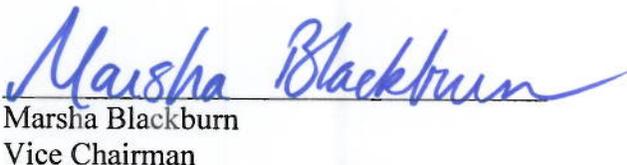
Enforcement and Benefits to Public Health.” In that speech, you noted the need to “follow-up on signals indicating problems” and promptly “assess whether or not a company has made required changes in its practices.”¹ In order for the Committee to fully understand why FDA never re-inspected NECC or took any meaningful enforcement action against the company, despite repeatedly asserting that it could and would do so, the agency must cooperate with the Committee’s investigation and fully respond to our request for internal communications and memoranda. Producing a selection of emails from one retired employee’s account in three months is not cooperation.

Forty-five lives have been lost and hundreds of lives have been jeopardized. The public has a right to know what role FDA played with regard to the NECC so that the Committee can answer the question posed by our November 14, 2012, hearing: could this tragedy have been prevented?

FDA has not provided a valid reason to the Committee for continuing to withhold these documents. If FDA does not produce all responsive documents by 5:00 p.m. on February 25, 2013, the Committee will move forward with a business meeting to compel their production.

If you have any questions, please contact Karen Christian or John Stone with the Committee staff at (202) 225-2927.

Sincerely,

 Fred Upton Chairman	 Tim Murphy Chairman Subcommittee on Oversight and Investigations
 Joe Barton Chairman Emeritus	 Michael C. Burgess Vice Chairman
 Marsha Blackburn Vice Chairman	

¹ Margaret A. Hamburg, MD, “Effective Enforcement and Benefits to Public Health,” Aug. 6, 2009, available at <http://www.fda.gov/NewsEvents/Speeches/ucm175983.htm>.

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cc: The Honorable Henry A. Waxman, Ranking Member

The Honorable Diana DeGette, Ranking Member
Subcommittee on Oversight and Investigations

Attachment

Timeline of FDA Interactions with NECC and Ameridose

Background

Please find below an overview of certain facts related to the Food and Drug Administration's (FDA, or the Agency) past interactions with the New England Compounding Company (NECC) and Ameridose. No information related to FDA's ongoing investigations of these companies is included. The information in these timelines is representative of our current understanding, based upon the records and information we have been able to review to date. We continue to collect information related to our history with these companies. We would be pleased to provide additional information if and when it becomes available.

Timeline for NECC

- According to the records FDA has reviewed to date, our earliest record of contact with NECC was an April 2002 inspection to follow-up on two adverse event reports submitted to FDA associated with betamethasone compounded by NECC. On April 16, 2002, FDA issued a Form FDA 483, which included three observations voicing concerns regarding NECC's process for producing sterile drugs.
- From October 24, 2002, until February 10, 2003, FDA and the Massachusetts Board of Pharmacy (MABP) conducted a jointly coordinated inspection to follow-up on adverse event reports received in July and August 2002 of bacterial meningitis associated with methylprednisolone compounded by NECC.
- In a meeting held on February 5, 2003, toward the end of the 2002-2003 inspection, FDA and MABP jointly decided that MABP would take the lead in enforcement and inspections of NECC's compounding operations since NECC was functioning as a compounding pharmacy. On February 10, 2003, FDA issued a 483 closing out its inspection. The firm responded on February 26, 2003, and supplemented its response on May 20, 2003, describing the corrective steps the firm was taking in response to the 483.
- FDA inspected NECC from September 23, 2004, until January 19, 2005, in a focused inspection related to a competitor's complaint that NECC had compounded a drug using bulk active ingredients that were not a component of an FDA-approved drug. FDA subsequently approved another firm's application to market the drug, and FDA issued a Warning Letter in December 2006 to NECC stating the firm was compounding copies of commercially available products; compounding standardized anesthetic drug products, which was outside the scope of traditional pharmacy compounding; and repackaging Avastin. The Warning letter charged that the copies of the FDA approved drugs and the anesthetic cream were misbranded and that the repackaged Avastin was an unapproved new drug. The Warning Letter did not pertain to sterility failures at NECC. During the 2004-05 inspection, FDA reviewed NECC's procedures in light of the February 10, 2003 483 and concluded that corrective actions had been implemented.
- In January 2006, NECC entered into a consent agreement with the Commonwealth of Massachusetts related to inadequacies in the firm's sterile and non-sterile compounding

practices. The consent agreement required NECC to hire a consultant and take corrective actions, which would be verified by the consultant. In June 2006, MABP notified NECC that the firm had fulfilled the terms of the consent decree.

- In January 2007, NECC responded to the 2006 Warning Letter.
- FDA responded to NECC's Warning Letter response in October 2008.

Timeline for Ameridose

- Ameridose first registered with FDA in September 2006, but never listed any drugs.
- FDA and MABP conducted a jointly coordinated inspection of Ameridose in December 2007 to follow-up on a complaint related to the company making IV solutions without receipt of patient-specific prescriptions and to gather facts since the firm had recently registered with FDA. FDA advised the firm to validate and verify its aseptic processes since it was making sterile products.
- FDA performed a second inspection of Ameridose seven months later (July-Aug. 2008). This was an inspection to review the firm's "good manufacturing practices." The agency issued the firm a 483 on August 6, 2008, citing several observations, such as not confirming the sterility of products before distribution. Ameridose responded in August 2008 stating that it would take corrective actions to address FDA's observations in the 483.
- During the 2008 inspection, FDA also collected samples of Fentanyl (a strong pain medication), which was found to be super-potent, leading to a Class I recall in September 2008.
- In September 2008 and November 2008, FDA returned to the firm to review shipping records specific to the super-potent Fentanyl, to review the firm's corrective and preventative actions since the September 2008 recall, and to follow-up on questions discussed during the prior inspection.
- In June 2010, FDA received a commercial complaint related to the compounded product nicardipine and conducted at the same time as MABP a limited inspection in response. In January 2011, FDA was informed that the complainant and Ameridose reached an amicable resolution. Massachusetts officially dismissed the complaint in June 2011.