

United States Senate

HEALTH, EDUCATION, LABOR, AND PENSIONS COMMITTEE

**The New England Compounding Center and
the Meningitis Outbreak of 2012: A Failure
to Address Risk to the Public Health**



Committee Staff Report

November 15, 2012

On September 26, 2012, as a result of the rapid work of the Tennessee Department of Public Health and the Centers for Disease Control and Prevention (CDCP), an outbreak of an unusual strain of fungal meningitis was identified. Preservative free methylprednisolone acetate (MPA), administered via spinal injection, was quickly identified as a likely source of the infections. The MPA was traced back to a compounding pharmacy in Framingham Massachusetts, the New England Compounding Pharmacy Inc., doing business as the New England Compounding Center (NECC). The Food and Drug Administration (FDA) subsequently determined that three separate lots of MPA, totaling over 17,000 doses produced by NECC between May 21, 2012 and August 10, 2012, were contaminated with the *exserohilum rostratum* fungus.ⁱ

To date, NECC's failure to produce a sterile and safe product has led to more than 30 deaths and over 450 serious illnesses requiring treatment with high risk anti-fungal medications. The efforts of the CDCP and the Tennessee Department of Public Health allowed public health officials in 23 states to rapidly track and begin monitoring the approximately 14,000 possible recipients of the contaminated drug. But thousands of people around the country continue to wait and see whether they will develop meningitis, joint infections, spinal abscesses, or arachnoiditis. Those treated will face the risk of kidney and liver damage from the powerful anti-fungal drugs.

While the quick work of the public health community has led to early identification and treatment of many cases of meningitis, and reduced the fatalities resulting from the administration of the contaminated MPA, the Committee's investigation demonstrates that this crisis should have, and could have, been avoided entirely.

Since its creation in 1998, inspections of NECC by state, federal, and independent investigators have identified and documented profound deficiencies in the company's production of sterile drugs. The company has also been cited on multiple occasions for improper use of prescription blanks to solicit orders and failure to comply with state regulations requiring patient-specific prescriptions for compounded drugs.

Moreover, the same drug at issue in the current outbreak, NECC-produced MPA, had previously been a suspected cause of at least two cases with bacterial meningitis-like symptoms. These reports triggered an FDA inspection of the facility ten years prior to the current outbreak, in August 2002.

While the FDA sampling of NECC-produced MPA proved sterile at the time, other MPA samples were found to contain bacteria.ⁱⁱ As an FDA employee stated in a power point presentation to the Massachusetts Board of Registration in Pharmacy (Board) at the time, "Sterilization techniques and aseptic practices continue to raise questions, despite no positive (nonsterile) results from latest samples. Absence of evidence is not evidence of absence."¹

ⁱ Testing of the third lot is ongoing.

ⁱⁱ An outbreak of fungal meningitis caused by MPA compounded by a South Carolina pharmacy also occurred in mid-2002.

Four years later in 2006, an independent evaluator reported to NECC manager and co-owner Barry Cadden that major areas of concern included “inadequate and incomplete documentation,” that “end product testing is often performed on ‘stock solutions’ and not the end product that is required,” “process controls including validation of sterilization cycles and media fills are inadequate,” and “in many cases the procedures are not in strict accordance with USP 795/797” as required by Massachusetts state law.²

In view of these repeated concerns with regard to the ability of NECC to safely produce compound drugs, it is difficult to understand why definitive action was never taken to either revoke its license or, at a minimum, closely monitor the company’s operations. Instead, the company was allowed to grow and expand operations, ultimately holding licenses to ship drugs to at least 45 states. The same owners were subsequently permitted to open the far larger Ameridose, which supplied compounded drugs to hospitals around the country. Also, that company now has been found to lack adequate procedures to ensure that the compounds produced are safe, uniform or sterile.

This report is based on information obtained in the course of the Committee’s investigation. It is intended to recount the known history of NECC, its related companies and their interactions with federal and state regulators as of November 15, 2012 to better understand the events leading to the current public health crisis.

The New England Compounding Company

NECC was created in 1998 by the Conigliaro family. Three Conigliaro siblings and their spouses own the company: Douglas and Carla Conigliaro; Barry Cadden and Lisa Conigliaro Cadden; and Gregory Conigliaro. Ownership and management of the company have remained essentially unchanged since 1998. Pharmacists Barry Cadden and Lisa Conigliaro Cadden own 25 percent of the company, Carla Conigliaro owns 65 percent, and Gregory Conigliaro owns 10 percent. Gregory Conigliaro also owns a neighboring recycling business. Barry Cadden was in charge of operations and significant amounts of the actual compounding at NECC during the entire period of operations. The three siblings and spouses also own Ameridose and Alaunus, two companies created in 2006, in similar proportions.

NECC was granted a special pharmacy license by the Board in June 1998. That license allowed the company to produce compounded pharmaceutical products without operating a full-service pharmacy, but still subject to the state requirement that the company to have an individual patient prescription for each dose compounded. Massachusetts also adopted United States Pharmacopeia Standard <797>, which sets forth standards for compounding pharmacies including requirements for clean facilities, specific training for operators, and air quality evaluations.³

The first enforcement action against NECC began just 10 months after issuance of the license. In April of 1999, the Board filed a complaint against NECC for including blank prescriptions in solicitations to practitioners, a practice that violated state law. Six months later, in November of 1999, the Board resolved the complaint by issuing a warning to NECC in a private non-disciplinary advisory letter.⁴

In June 2001, the Idaho Board of Pharmacy complained to the Massachusetts Board that NECC was, among other things, including unapproved prescription forms in its solicitations to Idaho practitioners. Documents are unclear regarding whether the Board took formal action on this complaint. In fact, as detailed below, it appears that the Board has a dysfunctional system for logging incoming complaints and evaluating whether a complaint warrants assignment to an inspector.⁵ Documents received by the Committee make clear, however, that NECC was investigated or warned for prescription-related concerns on at least 5 other occasions in the following 10 years.

Adverse Events

To the Committee's knowledge, the first time the safety of NECC's products was called into question was in early 2002. In March 2002, a prescribing doctor reported to the FDA that as many as five patients became ill following an epidural injection of NECC-produced betamethasone repositories.⁶ He reported the illnesses to the FDA, alerted NECC about the issue, and returned unused doses to NECC without taking samples.⁷ However, when the FDA arrived to inspect NECC on April 9, 2002, there were no records for the drugs in question.⁸

The FDA, joined for part of the inspection by the Board, spent three days inspecting NECC's facilities. When searching NECC's database, the FDA found a "date made" entry for the lot-number of drugs cited in the report but noted that "no associated records could be retrieved."⁹ The FDA inspection report recounts that Barry Cadden asserted that the lot had never been produced but could provide no documentation that the lot had been cancelled.¹⁰ Additionally, although the FDA contacted the physician making the report and confirmed he had returned the unused portion to NECC, FDA inspectors could find no record of the return.¹¹

In the course of the inspection, FDA inspectors were told by Barry Cadden that approximately 4 lots of product produced between March and April 2002 had tested positive for endotoxin and were awaiting disposal.¹² FDA inspectors documented that NECC had sampled betamethasone repositories immediately after sterilization in the autoclave, and then left the product for up to 7 to 10 days before placing it in individual vials.¹³ FDA inspectors reported an additional 8 areas of concern including a lack of procedures to ensure the operation of the autoclave, use of expired products, and inaccurate beyond use (i.e. expiration) dating.^{14, iii}

In August of 2002, another series of adverse events were reported to the FDA.¹⁵ These reports indicated that at least 2 patients were hospitalized for meningitis-like symptoms, and that the suspected sources of the infections were epidural injections of NECC-produced MPA, the same drug at issue in the current outbreak.¹⁶

The FDA, joined for part of the inspection by the Board, returned to NECC for a series of six days of inspections between October 2002 and February 2003. At that time Barry Cadden indicated to FDA inspectors that NECC was in the process of drastically expanding its operations. Since the FDA's prior inspection, NECC had doubled its square footage and hired

ⁱⁱⁱ Two days after the inspections, on April 18, 2002, the Nevada Board of Pharmacy submitted a complaint to the Board, alleging that NECC was selling non-FDA approved products in the state. It is unclear if the Board took any action as a result of this complaint.

additional staff. Further, NECC's manager stated his intent to expand sales to all 50 states, up from the 13 states in which it was then licensed.¹⁷

FDA tested unused vials of the MPA collected from the location of the adverse event report, and found that 5 of the 16 vials were contaminated with bacteria. The FDA also tested other vials obtained during inspections of NECC and found problems with super potent MPA and sub-potent betamethasone repositories.¹⁸ Investigators again documented the use of procedures insufficient to ensure safe compounding. Those concerns included a "lack of documentation to verify that the autoclave itself is maintained and calibrated to perform its intended function," as well as a concern regarding a lack of safe procedures to ensure that "the transfer of bulk drug product and equipment from the autoclave... to another room ... is not introducing contamination into the finished product."¹⁹ The FDA's inspectors concluded, "Sample results revealed that the firm has sterility and potency issues with injectable steroid suspensions (betamethasone repository USP and methylprednisolone acetate USP)."²⁰

In April 2002, prior to these inspections, the United States Supreme Court in *Thompson v. Western States Medical Center* ruled that section 503A of the Food Drug and Cosmetics Act included an impermissible restriction on commercial speech. The Supreme Court did not address provisions that clarified FDA's authority to regulate certain compound pharmacies, which the lower court held was not severable from the unconstitutional commercial speech restrictions. While NECC would likely have been subject to FDA regulation pursuant to section 503A of the Food Drug and Cosmetics Act, FDA's authority with regard to NECC under 503A was unclear after *Western States*, although FDA's general authority against unapproved new drugs, misbranded, or adulterated product was not in dispute. Despite the ambiguity regarding 503A, in May 2002 the FDA issued guidance which reasserted its authority to inspect compounding pharmacies and provided a non-exhaustive list of factors that the agency would consider in determining whether to take enforcement action when the scope and nature of a pharmacy's activities raise the kind of concerns ordinarily associated with drug manufacturing.

In this case, FDA took the position that the Board was better situated to take action against NECC. An FDA memo documenting a February 5, 2003, meeting between the FDA and the staff of the Board states that "a discussion was held to determine if NECC should be considered a manufacturer or a compounder" and that "current findings supported a compounding role."²¹ The memo concludes:

Mr. Elder [from FDA] concluded the meeting by summarizing the discussions and *emphasizing the potential for serious public health consequences if NECC's compounding practices, in particular those relating to specific sterile products are not improved.* The point was made that so long as a pharmacy's operations fall within the scope of the practice of pharmacy...FDA will generally defer to state authorities for regulatory oversight. In such cases FDA will seek to engage cooperative efforts aimed at achieving regulatory compliance and ensuring the safety and quality of compounded products.²²

The FDA then officially stated in the NECC Inspection Report issued February 10, 2003, "[R]eferral to Massachusetts State Board of Pharmacy. Recommend firm be prohibited from manufacturing until they can demonstrate ability to make product reproducibly and dependably.

If state is unwilling to take action, recommend firm be enjoined for [Good Manufacturing Practices] deficiencies.”²³

Despite the formal recommendation that the state take action, it is unclear whether the Board took any additional action for the next year.^{iv} It also does not appear that FDA conducted any follow-up to verify whether Massachusetts’ response was sufficient to protect public health and safety.

Finally, on February 20, 2004, the Board staff conducted a compliance inspection and noted that NECC had taken corrective actions for the safety concerns identified in 2002 and 2003.²⁴ Nonetheless, the Board’s staff recommended a public reprimand of NECC for its prior misconduct.²⁵

On September 21, 2004, more than two years after the first reported cases of meningitis and other adverse events, and apparently acting on the staff recommendation, the Board voted to seek a public censure and probation for NECC’s misconduct leading to the infections.^{26,v} As was the Board’s custom, they sent a consent decree to NECC that, if agreed to, would impose the relevant discipline and monitoring requirements for a three-year period.²⁷ The Board’s staff transmitted its proposed consent decree to NECC on October 4, 2004.²⁸

NECC did not agree to the proposed consent decree. NECC wrote to the Board asking it to instead consider non-public disciplinary action, to better protect NECC’s business interest.²⁹ Counsel for NECC wrote: “once disclosed, the reprimand will surely result in inquiries/investigations in [other] jurisdictions. Regardless of the derivative actions taken, the attendant legal and administrative costs will be devastating.”³⁰ The Board voted in November of 2004 to decline NECC’s request for modifications to the consent decree.³¹ Following that action by the Board, Committee interviews with Board staff suggest that the consent decree was referred for formal action to prosecuting attorneys within the Massachusetts Department of Public Health.³²

For over a year, the record shows no formal order was filed and no hearing was held. Instead, it appears that attorneys for the Department of Public Health negotiated a modified consent agreement approved by the Board with an effective date of January 10, 2006.³³ The revised consent decree required that NECC submit to two inspections over a six-month period by a third-party evaluator, as well as a series of written assurances that recommended improvements had been made, in exchange for a suspended period of non-public probation.³⁴ The agreement

^{iv} FDA’s investigation report also notes that Mr. Cadden, the manager of NECC, was serving on a committee for the state of Massachusetts, created to revise state regulations controlling compounding pharmacies. (FDA *Inspectional Observations*, Form FDA483, issued to Barry Cadden, R. Ph, Owner and Director of Pharmacy, New England Compounding Pharmacy, Inc., February 10, 2003.) The committee’s work, however, became moot after the release of USP 797, which then was adopted by Massachusetts. 247 CMR 9.01(3)

^v Between the Board staff report recommending censure and the Board vote to issue the consent decree, pharmacist Sophia Pasedis was appointed to the eleven-member Board. Ms. Pasedis appears to have been an employee of NECC in some capacity at the time of her appointment, and thus recused herself from the Board consideration of the consent decree. Ms. Pasedis is currently a manager of the Conigliaros’ other drug company, Ameridose.

was referred to as “non-disciplinary” and was “not reported to the National Association of State Boards of Pharmacy or other outside report agencies[.]”³⁵

Thus, almost four years after the two series of adverse events, including hospitalizations, likely caused by MPA, and three years after the FDA had stressed “the potential for serious public health consequences if NECC’s compounding practices, in particular those relating to specific sterile products are not improved,”³⁶ the Board merely required NECC to hire an outside monitor, and made no mention of suspension or revocation of NECC’s license.

PSI Monitoring

Pursuant to the revised consent decree, a third-party auditor, Pharmacy Support, Inc. (PSI) was selected to evaluate NECC’s compliance with United States Pharmacopeia Standard 797, which the Board had recently adopted as the governing standard for Massachusetts.³⁷ PSI inspected NECC in January 2006 and noted multiple concerns, including sterility concerns. Among them, PSI noted a range of fundamental problems, including:

- NECC had “no requirements for donning proper attire or hand washing” when compounding medicines;
- “Mixing instructions are not specific and do not always indicate time and temperature;”
- “No quality control procedures are defined;”
- “Non-sterile 70% IPA is used to sanitize;”
- “Beard covers not worn;”
- “Hairnets and beard covers were not worn properly;”
- “Environmental monitoring procedures are inadequate;”
- “Calibrations are not performed properly;”
- “Floors in the unclassified/hybrid buffer area have not been sanitized in 3 months of use;”
- “[Beyond use dates] assigned incorrectly;”
- “There are no written procedures for receipt, storage, and accountability of controlled substances;”
- “[Standard Operating Procedures] are inadequate or not followed;”
- “Complaint forms were not available for some complaints logged in the complaint log;”
- “Most sections of complaint forms are not complete;”
- “Lot numbers are not assigned appropriately;”
- “4 out of 8 gloves observed had holes while CSP was compounded;” and
- Dry heat “sterilization equipment has not been verified.”³⁸

NECC took significant corrective measures, including replacing deficient equipment, conducting several training sessions for staff, and adopting a wide range of new standard operating procedures.³⁹ PSI submitted a final report on April 7, 2006, stating that NECC was largely compliant with pharmaceutical standards.^{40,vi} In April and May, the Board received two

^{vi} Six days later, at the end of an 8-week jury trial and three-year indictment, both PSI’s CEO and Chief Compliance Officer were criminally convicted on 19 counts including fraud, mail fraud, and a violation of the Food and Drug Control Act. *US v. Caputo*, No. 03 CR 0126 (N.D. Ill. Oct 16, 2003). It is unclear how PSI was selected as the Massachusetts Board of Pharmacy has been unable to identify or produce documents discussing the selection of PSI in detail. Documents do show that PSI submitted a proposal to

more cursory letters from NECC assuring compliance with its remaining open issues.⁴¹ On June 2, 2006, the Board informed NECC that it had fulfilled the requirements of its consent decree and that it considered the matter closed.⁴²

Additional NECC Complaints

At the time the Board acted to send the initial consent decree to NECC, it also acted to resolve three additional complaints against NECC in September 2004.⁴³ Despite ongoing investigations relating to serious adverse events, the Board issued three *non-disciplinary* private advisory letters to NECC resolving complaints submitted during the prior two years from practitioners in South Dakota, Texas, and Wisconsin.⁴⁴ While the advisory letters fail to spell out the specifics of the complaints, and the original complaints have not been reviewed by the Committee to date, it appears that NECC may have been soliciting bulk orders rather than patient-specific prescriptions, conduct that NECC was initially reprimanded for in 1999. A Board inspection report from around that time specifically notes that NECC “continues to reduce to writing orders on bulk purchase order forms and not on the approved prescription blanks. An issue previously addressed with Mr. Cadden.”⁴⁵

Additionally, in April 2004, five months before issuance of the advisory letters, the Board received a new complaint from a practitioner regarding the safety of NECC compounded triple anesthetic cream. The complaint states “My second concern is that [redacted] related to the purchasing technician that he would need a prescription for the product and that we could use the name of a staff member if we wanted to. He said ‘other’ institutions have used a nurses name....He assured her that it was legal. He indicated that after we received the product it was up to us how we used it and whom it was administered to.”⁴⁶ It appears that this complaint triggered a Board inspection on November 2004. When questioned about the use of false names, Cadden responded “a review of the same documentation provided to you does show what would appear to be incorrect or repetitive names being provided by several of our prescribing physicians.”⁴⁷ Yet the Board staff again recommended issuance of yet another non-disciplinary advisory letter dismissing this complaint.

On November 7, 2012, Department of Public Health officials informed the Committee that a July 2012 complaint against NECC, from the Colorado Board, for producing drugs in the absence of a patient-specific prescription had been discovered in the email of the Board’s Executive Director. The complaint, which was received while the contaminated lots of MPA were still being produced by NECC, provided clear photographic evidence that NECC was shipping products in the absence of patient-specific prescriptions.⁴⁸ Further, Colorado had issued a cease and desist order to NECC in 2011 regarding this practice.⁴⁹ Board staff never acted on the July 2012 complaint, and it is unclear that the Board itself was aware of the complaint.^{vii}

While Massachusetts state law requires that a compounding pharmacy possess a patient-specific prescription before preparing a compound drug, it appears that NECC has been

the Massachusetts Board and the prosecutor negotiating the consent agreement provided contact information to NECC’s counsel.

^{vii} The Board also informed the Committee that it had terminated the Executive Director and placed the Board’s Counsel on administrative leave as a result of this discovery.

consistently preparing and shipping batch products either in the absence of a prescription or to false prescription recipients since 1998. No regulatory entity appears to have undertaken a serious investigation of this ongoing practice, and the Board instead routinely dismissed and/or failed to act upon these repeated complaints.

Additional FDA Action

Two days after the Board finally voted to issue the consent decree in September 2004, the FDA and the Board returned to NECC, this time pursuant to a complaint regarding the company's improper production of an injectable dye used in ophthalmic procedures, Trypan Blue.⁵⁰ After Barry Cadden initially denied that any Trypan Blue was in stock, FDA inspectors located 189 vials of the product. Trypan Blue is commercially available and should not be compounded.⁵¹

This inspection led to the issuance of a December 4, 2006 FDA Warning Letter to NECC. The Warning Letter details issues including: the sale of compounded drugs without a patient-specific prescription; compounding copies of commercially-available drugs; selling misbranded compounding drugs; and compounding standardized non-approved drugs, with associated public health risks, on a large scale. It specifically notes that NECC "has reportedly told physicians' offices that using a staff member name on a prescription would suffice."⁵²

While the FDA Warning Letter seeks corrective action within 15 days and threatens that failure to correct could result in further regulatory action including seizure or injunction, it does not appear that any further action was contemplated or that any efforts to ensure that corrective action were sought by the agency. Moreover, FDA chose to issue this Warning Letter without having learned from the Board what, if any, disciplinary actions had been taken in response to the inspections from October 2002-February 2003.⁵³ In January 2007 NECC responded to the Warning Letter, and in October 2008 the FDA re-asserted its authority to take "enforcement action, including seizure of the firm's products and/or an injunction against the firm and its principals" if violations noted in the Warning Letter were not corrected. The FDA also stated that "[i]n a future inspection, we will ... verify that your firm's compounding practices are consistent with the policy articulated in the [Compliance Policy Guidelines]."⁵⁴ This response came two years from the date of FDA's initial Warning Letter and four years from the date of the relevant inspection. FDA took no further action until the recent outbreak.

Further, a May 2011 email exchange shows that FDA staff, including the signatory to the October 2008 letter re-asserting FDA inspection authority, received a copy of a Colorado Cease and Desist Order issued to NECC in 2011 as the result of distribution of non-patient specific compounded drugs to hospitals in the Denver area. FDA staff apparently did not share the Cease and Desist order with the Massachusetts Board, or suggest that the Colorado Board do so until Colorado inspectors again discovered NECC stock compound drugs in another Colorado hospital in July 2012.⁵⁵

Inspection Findings Subsequent to the Outbreak

Unfortunately the long history of concerns was borne out in inspections by FDA and the Board following the 2012 fungal meningitis outbreak. The Massachusetts Board began a series

of inspections of NECC on September 26, 2012. The Board and/or the FDA continued inspecting NECC from that date until October 26, 2012. The findings demonstrate a basic lack of compliance with USP <797> or with safe compounding as evidenced most clearly by the fact that “[v]isible black particulate matter was seen in several recalled sealed vials of Methylprednisolone Acetate.”⁵⁶ Perhaps most critically, the FDA inspection found that NECC’s environmental monitoring system documented 61 instances between January and August 2012 when either bacteria or mold was detected in concentrations exceeding action-level thresholds.⁵⁷

The inspection reports found that while sterility testing conducted on the contaminated lots did not reveal unacceptably high levels of endotoxins, the sample provided was insufficient relative to the batch size. In fact when FDA sampled 50 vials of returned MPA it determined all fifty were contaminated with microbial growth despite the fact that sterility tests on one sample from the same lot in August 2012 has proven clear.⁵⁸ The FDA and Board inspections unsurprisingly again document a basic lack of procedure to ensure sterile products were being compounded safely including:

- Inspectors observed “greenish yellow discoloration” lining one of two autoclaves used to sterilize various components and equipment;⁵⁹
- Inspectors observed “yellow residue lining the rear return of Weigh Station 2 Hood and greenish residue lining the rear return of Weigh Station 3 Hood...used to weigh active ingredients and other raw materials;”⁶⁰
- “Residual powder was visually observed within the [powder] hood during inspection;”
- “[Tacky] mats, which are used to trap dirt, dust, and other potential contaminants from shoes prior to clean room entry...were visibly soiled with assorted debris;”⁶¹ and
- “A leaking boiler adjacent to the requisite clean room created an environment susceptible to contaminant growth.”⁶²

The inspections also documented a continued disregard for the requirements of a patient-specific prescription for each compounded product. The state’s preliminary investigation report noted: “NECC distributed large batches of compounded sterile products directly to facilities apparently for general use rather than requiring a prescription for an individual patient.”

Ameridose

One month after the terms of NECC’s 2006 consent decree were deemed satisfied, the Board approved a license for a new company, Ameridose, owned by the Conigliaro family.^{63, viii} Massachusetts Board Member Sophia Pasedis has been a manager of record for the company.⁶⁴ According to media reports, Douglas Conigliaro, although not listed as an owner or manager, plays a significant role at Ameridose.⁶⁵

^{viii} The ownership distribution is essentially the same with Carla Conigliaro owning 65 percent, Barry and Lisa Cadden owning 25 percent and Gregory Conigliaro owning 10 percent. (11-9-12 HELP Committee staff interview with NECC attorneys.)

Ameridose is also a sterile compounding company, but because it produces batch drugs for hospitals rather than patient-specific prescriptions, it is registered as a manufacturer with the FDA as well as with the Massachusetts Board.⁶⁶ The company does not manufacture any FDA approved product but rather is exclusively a large-scale compounder.

Until the outbreak, Ameridose contracted with Novation, the largest group purchasing organization in the country. Thus, Ameridose products were available to Novation's 3,000 hospital members as well as 22,000 other providers and facilities. Despite the history of problems with NECC and the joint ownership of the two companies, neither the licensure of Ameridose nor the large scale of its operations appears to have raised any concerns amongst the Board or the Board staff. Documents suggest that Ameridose was subject to routine pre-announced inspections by the Board in 2008 and 2011.⁶⁷

However, the FDA had serious concerns with Ameridose. The FDA inspected the company in 2008 and found serious problems with the company's operations. Despite the large scale of Ameridose's operations even in 2008, investigators documented that products were shipped immediately without waiting for the results of sterility testing, that testing for potency and dose uniformity is not routinely performed and procedures were insufficient, and that the company was generally not in compliance with the requirements of USP 797 as required by Massachusetts law. As an example, management could not locate test results for 3 of 17 active ingredients inspected. Results of sampling tests taken at the August 2008 inspection returned a finding of superpotent Oxytocin, resulting in a recall of the product and an additional inspection in September 2008.⁶⁸ FDA staff placed Ameridose on the work plan for high risk facilities and recommended that a warning letter be issued to the company although no such letter was actually issued.⁶⁹

While Ameridose was also the subject of at least 9 reports to the FDA of adverse events, faulty products, or medication errors, it is unclear that any of these triggered an inspection or investigation.⁷⁰ Following NECC's identification as the source of the fungal meningitis, the Board secured a temporary stop of Ameridose operations, though the company continues to hold a valid license. After the FDA began inspections on October 31, 2012, Ameridose issued a voluntary recall of all products.⁷¹

On November 12, 2012, the FDA issued a preliminary inspection report for Ameridose, finding startlingly similar problems to those they found NECC. Although the FDA has not reported any findings of contaminated drugs from Ameridose, the agency's preliminary findings "raised concerns about a lack of sterility assurance for products produced at and distributed by this facility."⁷²

The FDA's inspection found that, like at NECC, there were clear problems with ensuring that drugs were sterile, or that doses were uniform. The FDA found that batches of drug product were not tested to ensure sterility, and that procedures were not established, written, or followed to prevent microbiological contamination of sterile drug products. What procedures were available did not include adequate validation of sterilization. The report also notes that the company failed to write or follow procedures detailing other aspects of their business.⁷³

Moreover, the FDA found that testing of Ameridose's product did not include appropriate laboratory determination of conformance to the identity and strength of each active ingredient. And there were no written procedures for production and process controls to assure that the drug products had the identity, strength, quality and purity they purported to possess.⁷⁴

Additionally, the FDA found that the buildings were not in good repair, that equipment and utensils were not cleaned, maintained, and sanitized at appropriate intervals to prevent contamination. The company further lacked suitable procedures to facilitate cleaning and maintenance, lacked equipment for adequate control over air pressure, and were infested with vermin.⁷⁵

Conclusion

Given the history of NECC, the fact that the company produced and shipped a contaminated product that has led to 32 deaths and 461 infections to date is not a surprise. The surprise is that they were allowed to continue to engage in drug compounding for over a decade with this record.

Both federal and state regulators were well aware that NECC and its owners posed a risk to the public health. Both had documented that the company routinely flouted requirements that it compound products only when a patient specific prescription was received, compounded unapproved and commercially available products, potentially destroyed documents and samples relevant to adverse events, and most critically, repeatedly failed to demonstrate that the company could safely compound sterile products. There were a number of authorities and mechanisms for both federal and state regulators to address this issue, but bureaucratic inertia appears to be what allowed a bad actor to repeatedly risk public health.

The Committee will continue its investigation to determine how this tragic failure of oversight occurred, and how it can best be prevented in the future.

¹ FDA Internal Memorandum, February 24, 2003, re: *February 5, 2003 Meeting with Massachusetts Board of Pharmacy / Division of Professional Licensure (239 Causeway Street, Boston, MA 02114)*, p. 10 of Attachment 1.

² Letter from Pharmacy Support, Inc., to New England Compounding Center, January 30, 2006, and enclosure: *Compounding Sterile and Non Sterile Preparations Observations and Recommendations Final Report*.

³ 247 CMR 9.01(3).

⁴ Committee staff interview with Board inspectors 11/9/12.

⁵ Senate HELP Committee staff interviews of Massachusetts Department of Public Health staff, October and November, 2012.

⁶ FDA *Investigative Report*, re: FACTS 298826, New England Compounding Pharmacy Inc. EI 4/9, 4/10, 4/16/02; FDA *Inspectional Observations*, Form FDA483, issued to Barry Cadden, R. Ph, Owner and Director of Pharmacy, New England Compounding Pharmacy, Inc., April 16, 2002.

⁷ FDA *Investigative Report*, re: FACTS 298826, New England Compounding Pharmacy Inc. EI 4/9, 4/10, 4/16/02.

⁸ *Id.*

⁹ FDA *Inspectional Observations*, Form FDA483, issued to Barry Cadden, R. Ph, Owner and Director of Pharmacy, New England Compounding Pharmacy, Inc., April 16, 2002, p. 4.

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- ¹⁰ Id. at 4.
- ¹¹ Id. at 4.
- ¹² Id. at 7.
- ¹³ Id. at 7.
- ¹⁴ Id. at 8.
- ¹⁵ FDA *Establishment Inspection Report and Continuation Sheet*, re: FACTS 332851, New England Compounding Pharmacy Inc., EI Start: 10/24/02, EI End: 2/10/03; FDA *Inspectional Observations*, Form FDA483, issued to Barry Cadden, R. Ph, Owner and Director of Pharmacy, New England Compounding Pharmacy, Inc., February 10, 2003, p. 5.
- ¹⁶ FDA *Establishment Inspection Report and Continuation Sheet*, re: FACTS 332851, New England Compounding Pharmacy Inc., EI Start: 10/24/02, EI End: 2/10/03, pp. 4-5.
- ¹⁷ Id.
- ¹⁸ Id.
- ¹⁹ FDA *Inspectional Observations*, Form FDA483, issued to Barry Cadden, R. Ph, Owner and Director of Pharmacy, New England Compounding Pharmacy, Inc., February 10, 2003, p. 1.
- ²⁰ Id. at 2.
- ²¹ FDA Internal Memorandum, February 24, 2003, re: *February 5, 2003 Meeting with Massachusetts Board of Pharmacy / Division of Professional Licensure (239 Causeway Street, Boston, MA 02114)*, p. 2.
- ²² Id. at 3-4.
- ²³ FDA *Establishment Inspection Report*, re: FACTS 332851, New England Compounding Pharmacy Inc., EI Start: 10/24/02, EI End: 2/10/03, p. 1.
- ²⁴ Massachusetts Department of Public Health – Division of Health Professions Licensure, *Investigation Report*, Re: New England Compounding Center, DS 03 055, and Barry Cadden, PH 03 066, March 4, 2004, p. 9.
- ²⁵ Id. at 9.
- ²⁶ Massachusetts Board of Registration in Pharmacy, *Pharmacy Board Meeting Minutes: Tuesday, September 21, 2004*, p. 9.
- ²⁷ Letter from the Massachusetts Board of Registration in Pharmacy to New England Compounding Center, re: *Docket Number DS-03-055/PH-03-066/ New England Compounding Center (Permit #2848) and Barry Cadden, R.Ph., License No. 21239*, October 4, 2004; Massachusetts Board of Registration in Pharmacy, *Consent Agreement re: Docket No. DS-03-055, PH-03-066*.
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- ³² Senate HELP Committee staff interviews of Massachusetts Department of Public Health staff, October and November, 2012.
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- ³⁶ FDA Internal Memorandum, February 24, 2003, re: *February 5, 2003 Meeting with Massachusetts Board of Pharmacy / Division of Professional Licensure (239 Causeway Street, Boston, MA 02114)*, p. 2.
- ³⁷ Letter from Pharmacy Support, Inc., to New England Compounding Center, January 30, 2006, and enclosure: *Compounding Sterile and Non Sterile Preparations Observations and Recommendations Final Report*.
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⁴⁰ Id.

⁴¹ Letters between Board and NECC, April 12, 2006, April 19, 2006, May 10, 2006, and May 22, 2006.

⁴² Letter from MA Board to NECC, June 2, 2006.

⁴³ Massachusetts Board of Registration in Pharmacy, *Pharmacy Board Meeting Minutes: Tuesday, September 21, 2004*.

⁴⁴ Letter from the Massachusetts Board of Registration in Pharmacy to New England Compounding Center, re: *In the matter of DS-03-038 and PH-03-042 – New England Compounding Center (Permit #2848)*, September 30, 2004; Massachusetts Board of Registration in Pharmacy, *Advisory Letter re: Docket No. DS-03-036, PH-03-042*, September 30, 2004; Letter from the Massachusetts Board of Registration in Pharmacy to New England Compounding Center, re: *In the matter of DS-03-060 and PH-03-070 – New England Compounding Center (Permit #2848)*, September 30, 2004; Massachusetts Board of Registration in Pharmacy, *Advisory Letter re: Docket No. DS-03-060, PH-03-070*, September 30, 2004; Massachusetts Board of Registration in Pharmacy, *Advisory Letter re: Docket No. DS-04-062, PH-04-161*, September 30, 2004.

⁴⁵ Massachusetts Department of Public Health – Division of Health Professions Licensure, *Investigation Report*, Re: New England Compounding Center, DS 03 055, and Barry Cadden, PH 03 066, March 4, 2004 at 7.

⁴⁶ Email from [redacted] to Massachusetts Board of Registration in Pharmacy, re: *New England Compounding Center Activity in the State of Wisconsin*, April 27, 2004.

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⁴⁹ Id.

⁵⁰ FDA Internal Memorandum, Re: *Inspection/Investigation of New England Compounding Center*, January 26, 2005.

⁵¹ Id. at 2.

⁵² FDA Warning Letter to NECC, Dec 4, 2006.

⁵³ FDA Internal Memorandum, Re: *Inspection/Investigation of New England Compounding Center*, January 26, 2005 at 4.

⁵⁴ Letter from FDA to NECC, Oct 31, 2008.

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⁵⁶ Massachusetts Board of Registration in Pharmacy Report, *NECC Preliminary Investigation Findings*, October 23, 2012, at 4.

⁵⁷ FDA *Inspectional Observations*, Form FDA483, issued to Barry Cadden, Owner, New England Compounding Pharmacy, Inc., d/b/a/ New England Compounding Center, October 26, 2012.

⁵⁸ FDA *Inspectional Observations*, Form FDA483, issued to Barry Cadden, Owner, New England Compounding Pharmacy, Inc., d/b/a/ New England Compounding Center, October 26, 2012.

⁵⁹ Massachusetts Board of Registration in Pharmacy Report, *NECC Preliminary Investigation Findings*, October 23, 2012 at 1.

⁶⁰ Id. at 7.

⁶¹ Massachusetts Board of Registration in Pharmacy Report, *NECC Preliminary Investigation Findings*, October 23, 2012 at 4.

⁶² Id. at 5.

⁶³ Ameridose, LLC, *Application for a New Store – 50 Fountain Street*, 2006.

⁶⁴ *Id.*

⁶⁵ Abby Goodnough *et. al.*, “Spotlight Put on Founders of Drug Firm in Outbreak,” *New York Times*, October 24, 2012, <http://www.nytimes.com/2012/10/25/health/with-meningitis-outbreak-a-spotlight-on-family-behind-compounding-pharmacy.html?pagewanted=all> (accessed November 14, 2012).

⁶⁶ *See, e.g.* FDA *Establishment Inspection Report, Ameridose, LLC*, January 16, 2008, p. 1; Ameridose, LLC, *Application for a New Store – 50 Fountain Street*, 2006.

⁶⁷ The Commonwealth of Massachusetts, Division of Health Professions Licensure, *Inspection Report*, 11/19/08; The Commonwealth of Massachusetts, Division of Health Professions Licensure, *Inspection Report*, 11/7/11.

⁶⁸ FDA *Establishment Inspection Report, Ameridose, LLC*, EI Start: 09/17/2008, EI End: 09/18/2008.

⁶⁹ FDA *Establishment Inspection Report, Ameridose, LLC*, August 22, 2008, p. 1.

⁷⁰ FDA, *FAERS search results for suspect drugs labeled as Ameridose, New England Compounding Center or Alaunus, Reports initially received by FDA from 1/1/02 to 9/25/12*, provided to Committee on November 8, 2012; *See also*, Letter from Wiley Rein, LLP to Massachusetts Board of Registration in Pharmacy, re: *Complaint Against Ameridose LLC for Unlawful Manufacturing and Distribution of Pre-Mixed Nicardipine Injection Products*, June 30, 2010 (the resulting investigation was administratively closed).

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⁷² *Id.*

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⁷⁵ *Id.*