THE COMMONWEALTH OF MASSACHUSETTS
EXECUTIVE OFFICE OF HEALTH AND HUMAN SERVICES
Massachusetts Department of Public Health

New England Compounding Center (NECC)

Preliminary Investigation Findings

BOARD OF REGISTRATION IN PHARMACY REPORT

October 23, 2012

INTRODUCTION

Since September 24, 2012 a widespread outbreak of fungal meningitis has affected people in 17 states and caused 23 deaths at the time of this report. The outbreak originated from a medication compounded by New England Compounding Center (NECC), a facility licensed by the Massachusetts Board of Registration in Pharmacy (Board). The Massachusetts Department of Public Health (DPH) has taken immediate action to protect public health and safety. In collaboration with investigators from the U.S. Food and Drug Administration (FDA), DPH investigators have worked to identify the root causes of these events. While the complete scope and severity of this outbreak will not be fully understood for many weeks, to ensure the utmost transparency, DPH is releasing these preliminary findings from its ongoing investigation of NECC. This report constitutes early findings that may be subject to revision as the investigation unfolds.

Medication compounding involves the practice of taking commercially available products and modifying them to meet the needs of an individual patient pursuant to a prescription from a licensed provider. Nearly all retail pharmacies in Massachusetts perform compounding, however only 25 compounding pharmacies meet the standards necessary to produce sterile injectable products. By terms of their license with the Board, every Massachusetts pharmacy must comply with Massachusetts laws and regulations, including compliance with the United States Pharmacopeia Standards. Compounding pharmacies may only perform compounding upon receipt of a patient-specific prescription. These requirements and restrictions are consistent with the rules in place in other states.

Upon beginning the joint on-site investigation of NECC early in this outbreak, DPH and FDA investigators identified serious deficiencies and significant violations of pharmacy law and regulations that clearly placed the public's health and safety at risk.

KEY FACTS

DATE(S) OF INVESTIGATION: *September 26, 2012 to Present*
PHARMACY LICENSE NUMBER AND INITIAL ISSUE DATE: *DS2848; July 16, 1998*
LICENSE STATUS: *Voluntary Surrender, October 3, 2012*
CORPORATION NAME: *New England Compounding Pharmacy, Inc.*
DBA NAME: *New England Compounding Center (NECC)*
ADDRESS: *697 Waverly Road, Framingham, MA, 01702*
MANAGER OF RECORD AND LICENSE NUMBER: *Cadden, Barry J; PH21239*
DEA REGISTRATION NUMBER AND EXPIRATION DATE: *BNS927819, July 31, 2013*
PRACTICE SETTING: *Specialty Pharmacy*
PREVIOUS INSPECTION DATE: *May 24, 2011*
PREVIOUS INSPECTION DOCKET OR STAFF ASSIGNMENT NUMBER: *ISP-738*

INVESTIGATIVE METHODOLOGY

The NECC on-site investigation process consisted of DPH investigators obtaining documentary evidence (including photographs), reviewing and obtaining copies of Standard Operating Procedures, observational findings, reviewing and obtaining copies of all policies and procedures, reviewing batch records and interviewing NECC staff. The FDA conducted product testing and investigators took environmental samples of various areas of the facility to test for contaminants.

DPH investigators principally communicated with three NECC staff members during the on-site investigation (Barry J. Cadden, Glenn A. Chin and Lisa Conigliaro-Cadden) along with FDA investigators. After September 26, 2012, the majority of NECC employees were no longer on site. As has publicly been documented, NECC terminated many of their staff. The continuing investigation will include interviews of NECC employees.

SELECTED PRELIMINARY FINDINGS

During the facility inspections, investigators documented serious health and safety deficiencies related to the practice of pharmacy. All pertain to violations of 247 CMR 9.01(3) or 247 CMR 6.01(5)(a):

- NECC distributed large batches of compounded sterile products directly to facilities apparently for general use rather than requiring a prescription for an individual patient.
    - Records show that NECC had lists of potential patient names but did not have patient-specific prescriptions from an authorized practitioner when compounding and dispensing medication, as required by state law.
    - Manufacturing and distributing sterile products in bulk was not allowed under the terms of its state pharmacy license. If NECC was appropriately licensed as a manufacturer with the FDA the company would have been subject to additional levels of scrutiny.
    - NECC did not conduct patient-specific medication history and drug utilization reviews as required by regulations.

- NECC distributed two of the recalled lots of methylprednisolone acetate (PF) 80 MG/ML prior to receiving results of sterility testing:
  - Lot *06292012@26* was prepared on June 29, 2012. Final sterility testing was completed on July 17, 2012. Two shipments of product were made prior to the final sterility tests results being received.
  - Lot *08102012@51* was prepared on August 10, 2012. Final sterility testing was completed on August 28, 2012. Eleven shipments of product were made prior to the final sterility tests results being received.
  - While NECC's records show the sterility tests found no contamination, the adequacy of NECC's sterility testing methods are currently under examination.

- Final sterilization of product did not follow proper standards for autoclaving (sterilization through high pressure steam) pursuant to United States Pharmacopeia Standard 797 (USP 797) and NECC's own Standard Operating Procedures:
  - Examination of NECC records indicated a systemic failure to keep products in the autoclave for the required minimum 20-minute sterilization period necessary to ensure product sterility.

- NECC did not conduct proper validation of autoclaves pursuant to USP 797:
  - NECC failed to test their autoclaves to ensure proper function.

- Visible black particulate matter was seen in several recalled sealed vials of methylprednisolone acetate from Lot *08102012@51*.

- Powder hoods, intended to protect pharmacists from inhaling substances during medication preparation, within the sterile compounding area were not thoroughly cleaned pursuant to USP 797.
  - Residual powder was visually observed within the hood during inspection. This contamination may subsequently lead to contamination of compounded medications.

- Condition of "Tacky" mats, which are used to trap dirt, dust, and other potential contaminants from shoes prior to clean room entry, violated the USP 797.
  - Mats were visibly soiled with assorted debris.

- A leaking boiler adjacent to the requisite clean room created an environment susceptible to contaminant growth:
    - A pool of water was visually observed around the boiler and adjacent walls, creating an unsanitary condition; the culture results of this potential contaminant are still pending.

CHRONOLOGY OF THE OUTBREAK & DEPARTMENT OF PUBLIC HEALTH ACTIONS

Monday September 24, 2012 – The Massachusetts Department of Public Health (DPH) was notified by Tennessee Department of Health in late evening about a cluster of six rare fungal meningitis cases, with onset of symptoms between July 30 and September 18, 2012. These patients had several risk factors in common, including an epidural injection of steroid (methylprednisolone acetate 80 mg/ml preservative free) compounded at New England Compounding Center (NECC) located in Framingham. Tennessee also reviewed three other products not made by NECC as potential contaminants.

Tuesday September 25, 2012 – DPH planned an investigation of NECC given growing concerns of linkage to infections. The DPH's Bureau of Health Care Safety and Quality, Board of Registration in Pharmacy (Board), and Bureau of Infectious Diseases began rapid response planning on September 25, and convened a multi-agency meeting between the Tennessee Department of Health, the U.S. Centers for Disease Control and Prevention (CDC), the U.S. Food and Drug Administration (FDA), and the New England Compounding Center (NECC). At the demand of DPH staff, Barry Cadden and Gregory Conigliaro, principal owners of NECC, immediately provided documentation of all facilities in the nation that had received medications from three lots of methylprednisolone acetate that were suspected by the CDC as being linked to the fungal infections ("suspect lots"). Distribution lists were provided to public health authorities across the country, including CDC and FDA. The suspected product was distributed to more than 14,000 patients in 23 states.

Suspect Lots of Methylprednisolone Acetate (PF) 80 mg/ml Injection identified by TN DOH:

Lot #05212012@68 prepared by NECC on 5/21/2012
Lot #06292012@26 prepared by NECC on 6/29/2012
Lot #08102012@51 prepared by NECC on 8/10/2012

17,676 total doses

Wednesday September 26, 2012 – DPH began an onsite investigation of NECC and instituted a recall of all suspect lots of methylprednisolone acetate. Investigators confirmed that all non-distributed methylprednisolone products were quarantined, and that methylprednisolone acetate was no longer being produced. Approximately 3,000 doses were quarantined or returned through recall. Upon arriving at NECC, investigators found NECC employees cleaning sterile compounding areas and conducting environmental testing. DPH investigators also detected signs of bleach decontamination in the compounding areas.

Thursday September 27, 2012 to Sunday September 30, 2012 – DPH coordinated with FDA to plan a collaborative investigation of NECC.

Monday October 1, 2012 – DPH and FDA began a joint investigation at NECC. Findings supported by the epidemiological work of the CDC prompted DPH to issue a formal Quarantine Notice pursuant to M.G.L. c. 94C, §§ 13 and 189A, and M.G.L. c. 112, §§ 30 and 42A. This legally formalized the September 26 quarantine action. The Notice directed that all methylprednisolone acetate raw materials (chemicals), all non-sterile and sterile products located at NECC used in the compounding of methylprednisolone acetate, and all inventory on the premises prepared for dispensing and stored at the pharmacy, or received by recall should be quarantined and not disposed of without the express approval of the DPH. Investigators were shown examples of methylprednisolone products that were labeled as patient specific. The associated documents were not individual prescriptions but lists of patients generated by a clinical facility and provided to NECC to obtain the product. NECC stated the list of names was considered to be an authorized prescription by the physician. This practice is not in accordance with Massachusetts regulations.

Tuesday October 2, 2012 – DPH and FDA observed visible black particulate matter in sealed vials (of purportedly sterile methylprednisolone acetate) returned to NECC. Inconsistencies in sterilization processes of materials were identified through review of NECC's records. The Board voted to obtain a Voluntary Surrender of NECC's license or to initiate action to issue a Temporary Order of Summary Suspension.

Wednesday October 3, 2012 – DPH secured voluntary surrender of NECC's license, effective 12 pm (noon), and instituted a voluntary recall of all intrathecal products (those injected into the area around

the spinal cord or brain). DPH also notified Massachusetts providers to cease use of all NECC products.

Thursday October 4, 2012 – DPH and FDA publicly announced that black particulate matter, tentatively identified by microscopy as fungal contamination, was seen in a sealed, purportedly sterile vial of methylprednisolone acetate from a suspect lot. CDC and FDA recommended that all health care professionals cease use and remove from their pharmaceutical inventory any material produced by NECC. Massachusetts State Epidemiologists contacted nine Massachusetts health care facilities that received non-implicated lots of methylprednisolone acetate, instructing them to contact recipient patients to determine whether there were any unusual infections or other complications. No infections from the non-implicated lots sent to Massachusetts facilities have been identified at this time. DPH and FDA investigators continued with their on-site investigation and evaluated standard operation procedures and batch records related to sterile compounding. FDA investigators took environmental samples of various areas of the facility to test for contaminants.

Friday October 5, 2012 – DPH and FDA investigators noted visible contaminants in additional sealed recalled vials of methylprednisolone acetate. The particulate matter was noted in vials labeled in conformance with Massachusetts pharmacy regulations with patient-specific information. Additionally, particulate matter was noted in recalled vials that were labeled without patient-specific names, in clear violation of Massachusetts regulations. DPH and FDA each issued an alert to providers and facilities across the country stating the identification of particulate matter.

Saturday October 6, 2012 – DPH secured an immediate recall of all NECC products.

Monday October 8, 2012 – At the request of DPH, Barry Cadden and Glenn Chin, leaders at NECC, voluntarily ceased practice as pharmacists pending completion of the investigation.

Wednesday October 10, 2012 – Based on their shared ownership and leadership with NECC, DPH requested that Ameridose and Alaunus Pharmaceutical cease all pharmacy operations and any dispensing, manufacturing or wholesale distribution of any products starting at 3 p.m. on October 10 and continuing until 5 p.m. on October 22. DPH and FDA staff began an on-site investigation of Ameridose, a pharmacy, distributor and wholesaler regulated by the FDA. At the demand of DPH, Barry J. Cadden agreed to immediately resign as manager, director and from any other management

position at NECC, Ameridose, and Alaunus. DPH began working with the Massachusetts Hospital Association to ensure that the supply chain of medications would not be disrupted. The Board issued an advisory to all pharmacies and pharmacists in Massachusetts emphasizing that all of their actions must be performed in accordance with the United States Pharmacopeia. The advisory also reiterated that state law requires compounding pharmacies and
pharmacists to have a patient-specific prescription from an authorized practitioner when compounding and dispensing medication. Compounding pharmacies and pharmacists were required to submit an affidavit asserting that they are following state law in this regard.

Sunday October 14, 2012 – DPH staff began on-site investigation of Alaunus Pharmaceuticals, a wholesale distributor affiliated with Ameridose and NECC.

Monday October 15, 2012 – FDA issued an advisory that a patient may have acquired fungal meningitis from a different NECC steroid injection, triamcinolone acetonide. DPH epidemiologists began outreach to all 192 facilities in Massachusetts who received any NECC injectable products and supported providers in patient outreach. In addition, the FDA reported a transplant patient with an *Aspergillus fumigatus* infection who received a NECC cardioplegic solution during surgery. The CDC is actively working to confirm the presence of fungal contaminants in cardioplegic solutions. DPH asked Massachusetts providers to contact any patients who received any injectable product, including ophthalmic drugs or cardioplegia solutions prepared by NECC after May 21, 2012.

Thursday October 18, 2012 – FDA released definitive laboratory confirmation of the presence of fungal contaminants in sealed vials of methylprednisolone acetate in a suspect lot prepared by NECCDPH and FDA collected samples from sealed vials of completed product at Ameridose. Results are currently pending with the FDA.

Friday October 19, 2012 – DPH and FDA investigators scrutinized business practices of Alaunus Pharmaceuticals, and potential for inappropriate distribution of NECC or Ameridose products. At the request of DPH, Ameridose and Alaunus Pharmaceuticals extended their cessation of operations until November 5, 2012.

Monday October 22, 2012 – The Board authorized DPH staff to request voluntary permanent surrender of the licenses of Barry J. Cadden, Glenn A. Chin, and Lisa Conigliaro-Cadden, as well as

NECC. If the three pharmacists and NECC do not comply, the Board authorized staff to proceed with permanent revocation. All three individuals are currently prevented from practicing as pharmacists, and would be so prohibited throughout the appeal process.

ONGOING INVESTIGATION

The Department's collaborative investigation with the FDA is comprehensive and will continue until investigators have all information needed to determine what, if any, further action should be taken against NECC and its leadership. This investigation also extends to NECC's business practices and environmental conditions surrounding the business, including the presence of a nearby recycling center that shares ownership with NECC. Investigators are also looking into NECC's corporate entity, including, but not limited to, corporate ownership and governance structures at both NECC and sister companies, Ameridose and Alaunus. DPH will analyze and incorporate all evidence and information gathered by the FDA and the Board of Registration in Pharmacy into a final, comprehensive report. This report will be presented to the Board of Registration in Pharmacy, which will determine appropriate regulatory sanctions under administrative law. DPH will also assist with any investigation, federal or state, that explores the actions of NECC and its principals. DPH will continue to support and cooperate with federal policymakers in addressing gaps in oversight of compounding pharmacies, including leaders on the U.S. Senate Health, Education, Labor, and Pensions Committee, and the U.S. House of Representatives Energy and Commerce Committee, and members of the Massachusetts Congressional delegation, including Congressman Ed Markey. DPH will also work closely with the Massachusetts General Court to explore state-specific policy solutions. Findings of these investigations will be used to inform these state and federal actions to address regulatory gaps within the quickly evolving compounding industry.