



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

**STATEMENT
OF
MARGARET A. HAMBURG, M.D.
COMMISSIONER OF FOOD AND DRUGS**

**FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**BEFORE THE
COMMITTEE ON HEALTH, EDUCATION, LABOR AND PENSIONS
UNITED STATES SENATE**

**“PHARMACY COMPOUNDING: IMPLICATIONS OF THE 2012 MENINGITIS
OUTBREAK”**

NOVEMBER 15, 2012

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and Members of the Committee, I am Dr. Margaret Hamburg, Commissioner of Food and Drugs at the Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS). Thank you for the opportunity to be here today to discuss important issues related to the tragic fungal meningitis outbreak associated with compounded methylprednisolone acetate (MPA), a steroid injectable product distributed by the New England Compounding Center (NECC), and to discuss more broadly safety issues related to pharmacy compounding.

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

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

FDA'S RESPONSE TO THE CURRENT OUTBREAK

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

Let me briefly summarize the sequence of key events regarding the outbreak. On September 25, 2012, CDC notified FDA that it was working with the Tennessee Department of Health to investigate a cluster of meningitis cases at a single clinic, which might be associated with product contamination. When we learned of the potential contamination, we joined CDC in investigating. On September 26, NECC began a voluntary recall of three implicated lots of MPA and voluntarily ceased manufacturing of MPA. The Massachusetts Board of Registration in Pharmacy, which has primary oversight responsibility for pharmacies in its State, oversaw the recall, and initiated a one-day inspection of NECC's Framingham, Massachusetts, facility. FDA also began to coordinate with the Massachusetts Board of Registration in Pharmacy to plan for inspection of NECC. We coordinated closely with the State on this adverse event inspection, because the State has authority to compel certain actions where our authority is more limited.

FDA and the Massachusetts Board of Registration in Pharmacy initiated a joint inspection of NECC on October 1, 2012. On October 4, FDA and CDC held a joint press conference

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

announcing the investigation of the meningitis outbreak.² On October 5, after FDA had observed fungal contamination by direct microscopic examination of foreign matter taken from a sealed vial of MPA collected from NECC, FDA issued a MedWatch Safety Alert to 220,000 health professionals to notify them of the fungal contamination. Out of an abundance of caution, the Safety Alert took the additional step of recommending that health care professionals and consumers not use any product produced by NECC. FDA also requested that health care professionals retain and secure all remaining products purchased from NECC until FDA provided further instructions about how to dispose of these products. In addition, the Safety Alert encouraged health care professionals and patients to report to the Agency's MedWatch Safety Information and Adverse Event Reporting Program any adverse events or side effects related to the use of these products. On October 6, at FDA's recommendation, NECC agreed to recall all products.

As our investigation continued, on October 11, we announced our findings showing the presence of a fungal contaminant in multiple sealed vials of MPA injection, made at the NECC's Framingham, Massachusetts, site. CDC confirmed the specific type of fungus related to the patient disease – *Exserohilum* – in this briefing as well.³ On October 15, based on FDA's ongoing investigation and out of an abundance of caution, we further advised health care professionals to follow up with patients who were administered any NECC injectable product on or after May 21, 2012, including an ophthalmic drug that is injectable or used in conjunction with eye surgery or a cardioplegic solution. After working closely with the State on October 22, the Agency made available two lists of customers (consignees) who received products that were shipped on or after May 21, 2012, from NECC's Framingham, Massachusetts, facility, advising

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

those customers to check their stocks to identify whether they had any products from NECC, and if so, to immediately isolate any identified product from their drug supplies and contact NECC to obtain instructions on how to return products.

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

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

The Agency has been working closely with CDC, numerous state health departments, and the Massachusetts Board of Registration in Pharmacy to investigate the outbreak of fungal meningitis. This is a far-ranging investigation across the United States. FDA, in conjunction

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

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

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

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

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

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

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

FDA has communicated throughout this investigation with the media, Congress, state health officials, health care professionals, and the public to keep them apprised of important findings and developments as we move forward in our investigation. FDA's website is updated on a frequent basis to provide broad access to any new public information. This information is being further disseminated through the Agency's electronic listserves and through Twitter and

Facebook. Along with CDC, FDA is providing health care professionals with information they need on an ongoing basis, and as new information comes to light, to advise and treat patients affected by this situation.

Targeted alerts have been sent to 150 health care professional organizations, including the national specialty-specific societies that work with spinal injections, such as the American Society of Anesthesiologists, the American Academy of Physical Medicine and Rehabilitation, and the North American Spine Society, and also to all state medical, pharmacist, nursing, and physicians' assistant societies, as well as all state boards of pharmacy. Regular phone updates are provided to state health departments, in collaboration with CDC, and written updates are also distributed to national pharmacy and ophthalmology professional organizations. FDA also contacted patient and health care professional groups and consumer groups and worked with the American Hospital Association as part of our response.

FDA pharmacists are fielding calls from the public and we have extended their hours of availability for the last several weeks to help respond to the public's concerns. We also continue to respond to calls and e-mails from health care professionals, hospitals and clinics, and others with questions about the NECC and Ameridose recalls.

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

FDA's past activities with respect to NECC include: a 2002 inspection in response to adverse event reports (followed by a State inspection and action under Massachusetts' authority) and a 2006 Warning Letter focused on lower risk issues associated with copying approved drugs,

marketing and packaging. Throughout this time, NECC has repeatedly disputed FDA's jurisdiction over its facility.⁴ The Massachusetts Board of Pharmacy reinspected NECC in 2011 in response to a letter from the firm indicating that NECC was "updating its facility and moving into adjacent space"; that inspection included a tour of the facility, security review, licensing review, and inspection of NECC's sterile and non-sterile processing areas.⁵ The Massachusetts Board of Pharmacy inspection found the facility to be "Satisfactory."⁶

FDA'S LEGAL AUTHORITY OVER COMPOUNDED DRUGS

FDA regards traditional pharmacy compounding as the combining or altering of ingredients by a licensed pharmacist, in response to a licensed practitioner's prescription for an individual patient, which produces a medication tailored to that patient's special medical needs. In its simplest form, traditional compounding may involve reformulating a drug, for example, by removing a dye or preservative in response to a patient allergy. Or it may involve making a suspension or suppository dosage form for a child or elderly patient who has difficulty swallowing a tablet. FDA believes that pharmacists engaging in traditional compounding provide a valuable medical service that is an important component of our health care system. However, by the early 1990's, some pharmacies had begun producing drugs beyond what had historically been done within traditional compounding.

After receiving reports of adverse events associated with compounded medications, FDA became concerned about the lack of a policy statement on what constituted appropriate pharmacy compounding. In March 1992, the Agency issued a Compliance Policy Guide (CPG), section

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

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

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

7132.16 (later renumbered as 460.200) to delineate FDA's enforcement policy on pharmacy compounding. It described certain factors that the Agency would consider in its regulatory approach to pharmacies that were producing drugs.

The compounding industry objected to this approach and several bills were introduced, some with significant support, to limit the Agency's oversight of compounding.⁷ In May 1996, in a House Commerce Committee hearing on FDA reform legislation, FDA Commissioner David Kessler testified that the compounding provision being considered by the Committee was likely to encourage large-scale manufacturing under the guise of pharmacy compounding, and could allow for potentially dangerous compounding of sterile products, leading to serious safety problems or death.⁸

In November 1997, S. 830, the Food and Drug Administration Modernization Act of 1997 (FDAMA) was signed into law as Public Law 105-115.⁹ FDAMA added to the FD&C Act's Section 503A, which addresses FDA's authority over compounded drugs.¹⁰ Section 503A exempts compounded drugs from three critical provisions of the FDCA: the premarket approval requirement for "new drugs"; the requirement that a drug be made in compliance with current good manufacturing practice (cGMP); and the requirement that the drug bear adequate directions for use, providing certain conditions are met. These conditions include, among other things, that the compounding be performed by a licensed pharmacist or physician, that there be a

⁷ H.R. 5256, Pharmacy Compounding Preservation Act of 1994, introduced Oct. 7, 1994, 1 co-sponsor; H.R. 598, Pharmacy Compounding Preservation Act of 1994, introduced Jan. 20, 1995, 141 co-sponsors; H.R. 3199, Drug and Biological Products Reform Act of 1996, introduced March 29, 1996, 205 co-sponsors; H.R. 1060, Pharmacy Compounding Act, introduced March 13, 1997, 152 co-sponsors; H.R. 1411, Drug and Biological Products Modernization Act of 1997, introduced April 23, 1997, 16 co-sponsors

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

⁹ Public Law 105-115, FDAMA, 111 Stat. 2296 (Nov. 21, 1997), available at <http://www.gpo.gov/fdsys/pkg/PLAW-105publ115/pdf/PLAW-105publ115.pdf>

¹⁰ Id.

prescription for the compounded product for an individual patient, and that the compounded product be necessary for an identified patient. It allows FDA to restrict the compounding of certain categories of drugs (after notice-and-comment rulemaking), and limits the quantity of compounded drugs that a pharmacy could ship out of state to five percent of the total prescription orders, unless the state enters into a Memorandum of Understanding with FDA that addresses the distribution of “inordinate amounts” of compounded drugs out of the state, and the handling of complaints about compounded products shipped out of the state. Section 503A also contains restrictions on the advertising or promotion of the compounding of any particular drug, class of drug, or type of drug, and on the solicitation of prescriptions for compounded drugs from prescribers. These provisions were the subject of subsequent court challenges, which have produced conflicting case law and amplified the perceived gaps and ambiguity associated with FDA’s authority over compounding pharmacies. We look forward to working with Congress to address these issues.

Looking Ahead

FDA believes that there is a legitimate role for traditional compounding to provide needed drugs to patients that, for example, need a drug that is allergen free or have a medical need that cannot be met with an approved FDA product. However, we have grown increasingly concerned about certain compounding practices, and we have seen an increasing number of incidents related to compounded drugs. The NECC/meningitis situation is the latest, and most serious, incident. As described above, FDA’s ability to take action against compounding that exceeds the bounds of traditional pharmacy compounding and poses risks to patients has been hampered by gaps and ambiguities in the law, which have led to legal challenges to FDA’s authority to inspect pharmacies and take appropriate enforcement actions.

The Administration is committed to working with Congress to address the threat to public health from gaps in authorities for effective oversight of certain compounding practices. To that end, FDA has developed a framework that could serve as the basis for the development of a risk-based program to protect the public health.

Risk-based Framework

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

Further, we recommend that the statute recognize two categories of compounding: traditional and non-traditional. “Traditional compounding” would include the combining, mixing, or altering of ingredients to create a customized medication for an individual patient with an individualized medical need for the compounded product, in response to a valid patient-specific prescription or order from a licensed practitioner documenting such medical need. Traditional compounding plays an important role in the health system and should remain the subject of State regulation of the practice of pharmacy.

“Non-traditional compounding” would include certain types of compounding for which there is a medical need, but that pose higher risks based on one or more of the factors identified below.

Non-traditional compounding would be subject to Federal standards adequate to ensure that the compounding could be performed without putting patients at undue risk. For example, enforcement could be by the FDA or by a State willing to effectively oversee the compounding activities, as determined by FDA.

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

Non-traditional compounding should, because of the higher risk presented, be subject to a greater degree of oversight, with the riskiest products subject to the highest level of controls, such as appropriate current good manufacturing practice (“cGMP”) standards established by FDA.

In addition, FDA believes that with noted exceptions, certain products are not appropriate for compounding under any circumstances. These products would include: 1) what are essentially copies of FDA-approved drugs, absent a shortage justification based on the drug appearing on FDA’s shortage list; and 2) complex dosage forms such as extended release products; transdermal patches; liposomal products; most biologics; and other products as designated by FDA. Producing complex dosage forms would require an approved application and compliance with cGMPs, along with other requirements applicable to manufactured drug products. We would seek to permit the Secretary to have sufficient flexibility in this area to make these exceptions necessary to address issues of public health.

FDA would like to explore with Congress other authorities that would be important to support this new regulatory paradigm. For example, FDA should be given clear, full authority to collect and test samples of compounded drugs and to examine and collect records in a compounding

pharmacy, just as the agency does when inspecting other manufacturers. FDA should have clear statutory authority to examine records such as records of prescriptions received, products shipped, volume of operations, and operational records such as batch records, product quality test results, and stability testing results. Such inspections are necessary to determine when a pharmacy exceeds the bounds of traditional compounding, to respond to public health threats, and to enforce Federal standards.

FDA also believes that pharmacies engaged in non-traditional compounding should register with FDA so that FDA can maintain an accurate inventory of such pharmacies to facilitate appropriate oversight and coordination with State regulators. In addition, FDA would like to explore with Congress several other ideas such as clear label statements identifying the nature and source of the non-traditionally compounded product, and requiring non-traditional compounders to report adverse events. The labeling statements would provide prescribers and consumers with valuable information about the products they are using or taking so that they can make informed judgments about their use. Requiring non-traditional compounders to report adverse events, as drug manufacturers are required to do, would allow FDA and the States to identify trends and to proactively take steps to curtail dangerous compounding practices. Other appropriate regulatory and enforcement tools might also be useful. Funding will be necessary to support the inspections and other oversight activities outlined in this framework. We look forward to working with Congress to explore the appropriate funding mechanisms to support this work, which could include registration or other fees, as Congress has authorized and FDA has implemented in other settings.

In light of growing evidence of threats to the public health, the Administration urges Congress to strengthen Federal standards for non-traditional compounding. Such legislation should

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

CONCLUSION

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

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

I am happy to answer any questions you may have.
