STATE OF DISARRAY

How States' Inability to Oversee **Compounding Pharmacies** Puts Public Health At Risk

April 15, 2013

A report written by the staff of Congressman Edward J. Markey (D-MA) using the responses to an investigation launched by Reps. Edward J.Markey (D-MA), Henry A. Waxman (D-CA), John Dingell (D-MI), Frank Pallone (D-NJ) and Diana Degette (D-CO)

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EXECUTIVE SUMMARY AND RESULTS IN BRIEF

An outbreak of fungal meningitis that has thus far claimed the lives of 53 people and sickened 733 brought national attention to compounding pharmacies, the drugs they produce, and the potential risks from these drugs. At the center of this outbreak was the Massachusetts-based New England Compounding Center (NECC) that produced the preservative-free injectable steroid drug that caused the deadly outbreak. This drug, found later to be contaminated with mold, was shipped to 23 states and injected into more than 14,000 patients, resulting in the worst pharmaceutical-related public health crisis in U.S. history. The NECC tragedy was not the first incident of compounding pharmacies causing fatalities or illnesses. Over the last decade, compounding pharmacies have been responsible for at least 23 additional deaths and 86 serious illnesses across the nation.

Unlike drug manufacturers, which are subjected to rigorous Food and Drug Administration (FDA) oversight, there is no requirement for compounding pharmacies to register with the FDA or to follow any FDA-specified procedures to ensure that the drugs they produce are safe and effective. In fact, the oversight of all pharmacies typically falls under the purview of individual states. Attempts by the FDA and by Congress to address safety concerns by ensuring uniform federal standards for compounding pharmacies have led to numerous lawsuits and conflicting judicial rulings and according to the FDA, created "ambiguity associated with FDA's authority over compounding pharmacies." The agency has called on Congress to take action to prevent another such outbreak, stating that if FDA's authority remains unchanged, "this type of incident will happen again. It's a matter of when, not if."

> *"This type of incident will happen again. It's a matter of when, not if."*
> *-Food and Drug Administration*

In November 2012, Reps. Edward J. Markey (D-Mass.), Henry A. Waxman (D-Calif.), John Dingell (D-Mich.), Frank Pallone (D-N.J.) and Diana DeGette (D-Colo.) launched an investigation to examine how state boards of pharmacies oversee compounding pharmacies, requesting detailed information from all boards on their regulatory and information collection processes.[1] This report analyzes the information provided in response to this request. A summary of all state board responses can be found in Appendix B.

The results of this investigation reveal that most states are incapable of assuring the safety of compounded drugs that are prepared using even the riskiest sterile processes or that are shipped into their state from an out-of-state pharmacy. The investigation also found that poor record-keeping practices by the states make it difficult, if not impossible, for the states to identify compounding pharmacies with systemic, repetitive compounding safety problems. Instead of being able to proactively address safety problems, many states rely on public complaints made after a compounded drug is implicated in an injury or death before they can initiate an investigation and take steps to prevent harm to more

[1] Appendix C includes a copy of this request.

patients. Moreover, when problems are identified with compounded drugs from pharmacies located in another state, there is no uniform method by which the states notify the FDA or the state in which the problematic pharmacy is located. As a result, these unsafe pharmacies often continue to operate, potentially shipping dangerous or even deadly products across the nation, without increased oversight or penalties.

While most states do not separately track compounding pharmacy activities and the problems associated with them, some states also do a poor job of tracking and overseeing even traditional pharmacy activities. For example, in addition to failing to keep and track records of compounding pharmacy concerns, states including South Dakota, Illinois, Hawaii, New York, Ohio and Vermont, also generally do not routinely track the number of regular pharmacy inspections that are performed. New York, Ohio, Minnesota and Connecticut do not keep searchable records on the number of disciplinary actions that are taken against pharmacies for any reason. The inability of these states to maintain basic records on general pharmacy operations calls into question the capability of these states to oversee more complex and more risky compounding pharmacy activities.

Some states have initiated administrative or legislative improvements to their compounding safety efforts. Despite these efforts, however, deficiencies associated with state record-keeping, communication, resources, and specialized expertise combined with the inability of any single state to monitor the adequacy of compounding pharmacy safety in 49 other states appear to be systemic barriers to relying solely on the states to assure the safety of compounded drug products. The FDA needs clear, unambiguous authority that would enable it to set and enforce safety standards for the riskiest and largest compounding pharmacies, as well as those that sell compounded drugs across state lines.

FINDING 1: State boards of pharmacy generally do not know which pharmacies engage in compounding, do not know whether pharmacies ship compounded drugs across state lines, and do not know which pharmacies manufacture large quantities of compounded drugs. In many cases, states are incapable of even providing accurate information regarding the numbers of registered pharmacies in their states.

- Only two states, Mississippi and Missouri, routinely track the number of compounding pharmacies in their state.
- Only thirty-two states were able to provide historical data on the number of licensed pharmacies in their states.
- None of the state boards have requirements for pharmacies to disclose the volumes of compounded drugs they produce or whether compounded drugs are being sold across state lines.

FINDING 2: Only thirteen state boards of pharmacy know which pharmacies are providing sterile compounding services and only five of these states have inspectors that are trained to identify problems with sterile compounding.

- Thirty-seven state boards of pharmacy (74% of respondents) do not routinely track which pharmacies are providing risky sterile compounding services

- Only 19 state boards of pharmacy provide their inspectors with special training to identify problems with sterile compounding.

FINDING 3: States typically do not maintain pharmacy inspection records that enable them to identify systemic and repeated compounding pharmacy safety problems that originate either in-state or out-of-state.

- Twenty-two state boards of pharmacies do not keep any historical inspection records for compounding pharmacies.

FINDING 4: States are unable to effectively police compounding pharmacy activities in other states. Moreover, when issues arise with out-of-state pharmacies, states do not consistently inform the origination state or the FDA.

FINDING 5: Despite general increases in state board of pharmacy budgets, the number of pharmacy inspectors has remained consistently low. Furthermore, states usually do not distinguish between inspections of traditional and compounding pharmacies.

- On average, states employ just 5 inspectors (a range of 1-30 inspectors was reported) with responsibility to inspect all pharmacies.
- Only 5 state boards of pharmacy were able to provide an estimation of the number of inspections occurring at compounding pharmacies.

BACKGROUND

NECC and the Outbreak of Fungal Meningitis

On September 21, 2012 the Centers for Disease Control and Prevention (CDC) was notified by the Tennessee Department of Health (TDH) of a patient who had developed a rare type of fungal meningitis 19 days after receiving an epidural steroid injection at an ambulatory surgical center in Nashville. Less than a week later, the CDC and TDH had discovered several other infected patients and linked the outbreak to the same preservative-free injectable steroid produced by the New England Compounding Center (NECC) in Framingham, Massachusetts.

Once identified as the likely culprit of the infections, NECC initiated a voluntary recall of the suspected lots, identifying more than 17,000 doses shipped to customers in 23 states. By the time the voluntary recall was initiated, more than 14,000 patients had already received a potentially contaminated injection. To date, these tainted drugs have been responsible for 53 deaths and 733 serious illnesses across 20 states.

Following the identification of NECC as the source of the fungal meningitis outbreak, the Massachusetts Department of Public Health and the Food and Drug Administration (FDA) inspected the NECC facility and identified significant problems with cleanliness and sterilization processes at the facility.[2] These problems included observing mold and other foreign material on surfaces of areas in the facility that should have been kept sterile.[3] FDA also found that NECC's own monitoring systems had identified unsafe levels of bacteria and mold, but the company had taken no action.[4]

In addition to the contamination, investigators also found evidence that the NECC had not been compounding drugs for patient-specific prescriptions, as is required of licensed pharmacies under both state and federal regulation. Instead, the NECC accepted patient lists generated by out-patient medical centers, clinics, hospitals, and pain management facilities and provided to NECC for the purpose of obtaining its products. Despite NECC selling contaminated drugs in this manner to at least 23 states, only Colorado had identified NECC as being involved in producing drugs in the absence of a patient-specific prescription two months before the outbreak occurred.[5] At the time of the discovery, the Colorado board notified the Massachusetts board of pharmacy director, who was subsequently fired for never acting on this information.

While this most recent public health nightmare has garnered wide public attention, it isn't the first time that a compounding pharmacy has been at the center of a

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[2] Food and Drug Administration, *Form 483 Issued to Barry Cadden* (Oct. 26, 2012) and Massachusetts Department of Public Health, Board of Registration in Pharmacy Report, *New England Compounding Center: Preliminary Investigation Findings* (Oct. 23, 2012).
[3] The Committee on Energy and Commerce Hearing on "The Fungal Meningitis Outbreak: Could it Have Been Prevented?" Majority Memorandum. November 12, 2012.
[4] Food and Drug Administration, *Form 483 Issued to Barry Cadden* (Oct. 26, 2012)
[5] Colorado Board of Pharmacy also discovered NECC engaging in illegal distribution of compounded drugs to hospitals in April 2011, but did not notify the Massachusetts Board of Pharmacy at this time.

contamination crisis. On October 29, 2012, Rep. Markey released a report entitled "Compounding Pharmacies, Compounding Risk"[6] that documented more than a decade of violations and problems at compounding pharmacies throughout the country. This report revealed that even before the current meningitis outbreak, compounding pharmacies were responsible for at least 23 deaths and 86 serious illnesses in at least 34 states. Many of the violations at these compounding pharmacies mirrored the issues revealed at NECC, including selling drugs without a valid prescription, manufacturing large quantities of drugs, and preparing sterile drugs in facilities that were visibly dirty leading to contaminated drug products.

Regulation of Compounding Pharmacies-Federal Role

The 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, to produce a medication tailored to that patient's special medical needs.[7] In its simplest form, the practice has been used to provide a patient with a medication that is not commercially available, such as adding flavor to a child's dose or removing a dye or preservative for a patient who has specific allergies.

Unlike drug manufacturers, which are required to register with the FDA to make, distribute and sell drugs, there is no requirement for compounding pharmacies to register with the FDA. Furthermore, drug manufacturers are subject to FDA inspections and are required to follow specified safety procedures known as good manufacturing practices (GMPs), as well as report to the FDA any adverse events that are associated with use of their drug products. Compounding pharmacies do not have to follow these same requirements, and like all pharmacies, the oversight of the practice of pharmacy compounding has largely been left to the states.

However, over the last several decades the practice of compounding has expanded and evolved. Today, compounding pharmacies produce injectable medications and other sterile drug products that require the utmost sterility and sophisticated processes and equipment. Internet pharmacies provide mail-order medications to patients in different states whom they will never examine or counsel. Hospitals have moved from in-house to outsourcing pharmacy services for drugs used throughout the hospital. Pharmacies have also expanded their operations to produce thousands of identical drug products, sometimes in advance of prescriptions for easy distribution to medical facilities across the country. In many ways, the activities of these types of pharmacies are more akin to drug manufacturers or distributors, even though the regulatory framework that governs them requires far less regulatory oversight and far less rigorous safety practices.

[6] October 29, 2012 Compounding Pharmacies, Compounding Risk. See: http://markey.house.gov/press-release/new-markey-report-reveals-current-outbreak-least-23-deaths-86-serious-illnesses

[7] November 12, 2012. Statement of Dr. Margaret Hamburg, Commissioner of Food and Drugs before the Subcommittee on Oversight and Investigations Committee on Energy and Commerce.

A Historic View of the Federal Regulation of Compounding Pharmacies

In the early 1990's, after receiving reports of several adverse events associated with compounded medication, the FDA issued a Compliance Policy Guide (CPG) to clarify what constituted appropriate and legitimate pharmacy compounding. The CPG made clear that the agency would use its authority to regulate new drugs in commerce to stop the operation of pharmacies whose activities raise the kinds of concerns normally associated with a drug manufacturer.

In 1997, in order to "clarify the status of pharmacy compounding under federal law,"[8] Congress included provisions to regulate the practice of pharmacy compounding in the Food and Drug Administration Modernization Act (FDAMA).[9] Section 503(A) of the law exempted compounded drugs from the other requirements of the Federal Food, Drug, and Cosmetic Act (FFDCA), most notably the requirements to apply for a new drug approval and follow good manufacturing practices, as long as the pharmacy was licensed in a state, made the drug pursuant to a valid prescription for an individual patient, made the drug using approved ingredients and endorsed standard compounding processes, did not compound inordinate amounts or copies of commercially available drugs, and did not engage in advertising or promotion.[10] Additionally, the exemption from requirements of FFDCA would only hold in states that had entered into a memorandum of understanding (MOU) with the FDA addressing the manner in which the state regulators would investigate and address complaints about compounding pharmacies that were distributing outside the state. In states that did not enter into such an MOU, the exemptions from the provisions of FDAMA only applied if the compounding pharmacy limited its distribution of drugs outside of the state to no more than five percent of its sales.

Before the law took effect, compounding pharmacies challenged the advertising and promotion restrictions of Section 503(A) in federal court.[11] The Ninth Circuit Court found that the Section 503(A) ban on advertising and promotion was an unconstitutional limit on free speech. It also found that the unconstitutional provisions could not be severed from the remainder of Section 503(A), rendering the entire section of law void.[12] Subsequently, the Supreme Court affirmed the lower court rulings that the speech restrictions were unconstitutional, but did not rule on the Ninth Circuit ruling that the unconstitutional provisions could not be severed from the remainder of Section 503(A).

In 2002, FDA issued a new Compliance Policy Guide (CPG), which in large part was very similar to the 1992 CPG and outlined how the agency intended to use its enforcement discretion. FDA stated in its CPG that it would rely heavily on state oversight of compounders and focus its enforcement on compounding pharmacies that were producing large quantities of drugs without valid prescriptions, producing commercially available products, selling drugs wholesale or to third parties for resale, or otherwise violating the new drug, adulteration, or misbranding provisions of the FFDCA.

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[8] Conference Report H.Rept. 105-399 at 94. November 9, 1997.
[9] Pub.L. No.105-115, (1997)
[10] Pub.L. No.105-115, §503(A) (1997).
[11] *Western States Medical Center, et al. v. Shalala*, 69 F. Supp. 2d 1288 (D. Nev. 1999).
[12] *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002).

In 2003, amid rising concerns about compounded drug products, the FDA issued a report entitled "Limited FDA Survey of Compounded Drug Products,"[13] which examined 12 compounding pharmacies that allowed Internet orders. The FDA found that ten of the 29 products it sampled failed one or more standard safety or efficacy tests that were performed on them. A second similar FDA report was issued in 2006.[14] This time the FDA analyzed 36 samples, of which 12 (33%) failed analytical testing using "rigorously defensible testing methodology." The report also mentioned that in the 15 years between 1990 and 2005, "the FDA learned of at least 240 serious illnesses and deaths associated with improperly compounded products."[15]

In 2004, 10 compounding pharmacies brought suit against FDA, challenging more broadly FDA's authority to regulate compounded drugs.[16] The companies charged that compounded drugs were not "new drugs" and were therefore exempt from all of FDA's authority governing new drugs under the FFDCA. In 2008, the Fifth Circuit Court of Appeals found that compounded drugs were in fact "new drugs" and were subject to the FDA's drug approval, adulteration, and misbranding requirements. The Court went further and disagreed with the Ninth Circuit's view on the severability of Section 503(A), effectively reinstating Section 503(A) within the Fifth Circuit's jurisdiction - Texas, Louisiana, and Mississippi.

Throughout the rest of the country not covered by the Fifth or Ninth Circuit decisions, it remains unclear whether the remaining provisions of Section 503(A), that were not ruled unconstitutional, remain in force. FDA has therefore continued to exercise its authority under the FFDCA in accordance with its 2002 Compliance Policy Guide.

However, FDA's 2002 Compliance Policy Guide cannot set binding legal standards. As noted in a recent report by the nonpartisan Congressional Research Service:[17]

> "In contrast to agency rules, which have the force and effect of law, guidance documents are merely considered to be a general statement of policy. Congress has passed requirements specific to FDA guidance documents, which state that such documents 'shall not create or confer any rights for or on any person, although they present the views of the Secretary on matters under the jurisdiction of the Food and Drug Administration.' Under regulations prescribing FDA good guidance practices, it is stated that 'guidance documents do not establish legally enforceable rights or responsibilities' and 'do not legally bind the public or the FDA.'"

[13] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm155725.htm
[14] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm204237.htm
[15] Ibid.
[16] Med. Ctr. Pharmacy v. Mukasey, 536 F.3d 383 (5th Cir. 2008).
[17] FDA's Authority to Regulate Drug Compounding: A Legal Analysis. Jennifer Staman, October 17, 2012.

Ambiguity of Agency Authority and Industry Litigation has led to Regulatory Confusion

As a result of this ambiguity in law and the non-binding nature of FDA's CPG, when the agency has attempted to utilize its enforcement discretion on a compounding pharmacy, its authority to do so has often been challenged in court. A prime example of this occurred in 2003 when FDA attempted to inspect Wedgewood Village Pharmacy after complaints alleged the pharmacy was making large quantities of drugs without prescriptions.[18] Wedgewood took the agency to court alleging that since they were a licensed compounding pharmacy, FDA had no authority to inspect the facility. Although the court ultimately disagreed with Wedgewood, it took more than a year for the judgment to be issued, and in the meantime the FDA could not collect the evidence necessary to take enforcement action against this pharmacy. On several other occasions when the FDA has been concerned about large quantities of drugs in interstate commerce, it has attempted to inspect the compounding pharmacies in question and has been challenged by the pharmacy and forced to obtain a court-ordered warrant, delaying the agency's ability to address a potential public health crisis.[19]

The FDA has also attempted to rein in the activities of compounding pharmacies through the issuance of dozens of warning letters since 2001 sent to pharmacies believed to have violated federal law governing the production of drugs .[20] While several pharmacies that received these letters ceased problematic activities, some instead challenged FDA's authority to oversee any activities that occur in pharmacies.[21]

The FDA has stated that the multiple court challenges "have produced conflicting case law and amplified the perceived gaps and ambiguity associated with FDA's authority over compounding pharmacies."[22] The agency has called on Congress to take action to prevent another fungal meningitis outbreak and compounded drug tragedy, stating that in the absence of legislation that provides clear authority to the FDA, "this type of incident will happen again, it's a matter of when, not if."

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[18] In the Matter of Establishment Inspection of Wedgewood Pharmacy, 421 F.3d 263 (3rd Cir. 2005) See: http://www.fda.gov/downloads/iceci/enforcementactions/enforcementstory/enforcementstoryarchive/ucm091066.pdf

[19] See for example In the Matter of Establishment Inspection of Wedgewood Pharmacy, 421 F.3d 263 (3rd Cir. 2005).

[20] See FDA's database on warning letters: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm

[21] *See*: Warning Letter (NEW-06-07W) from Gail T. Costello, Dist. Dir., New England Dist. Office, FDA, to Barry J. Cadden, Dir. of Pharmacy, New England Compounding Center (Dec. 4, 2006) and Letter from Barry J. Cadden, Dir. of Pharmacy, New England Compounding Center, to Compliance Officer, New England Dist. Office, FDA et al., at 1 (Jan. 5, 2007). *See* also: FDA Acting Director, Steven Galston testimony before the Senate Committee on Health, Education, Labor and Pensions hearing on the "Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients. October 23, 2003.

[22] Testimony of FDA Commissioner Margaret Hamburg before the House Subcommittee on Oversight and Investigations Committee On Energy and Commerce hearing on "The Fungal Meningitis Outbreak: Could it Have Been Prevented?" November 14, 2012.

Regulation of Compounding Pharmacies-State Role

State governments, typically through the state boards of pharmacy, have traditionally been the primary entities responsible for all pharmacy practices. It is the duty of the boards to enforce all the laws of the state that pertain to the practice of pharmacy and distribution of drugs. The state boards of pharmacy are also typically the entities responsible for establishing quality assurance and best practices for pharmacies and for examining, licensing, regulating and disciplining pharmacy practitioners. Typically boards are comprised of anywhere from 5-20 members appointed by the state's governor for a specified renewable term. Many boards set aside one or two seats designated for a public member with no pharmacy affiliation who represents the interests of consumers and patients.

Conducting inspections is typically the method that state boards of pharmacy utilize to determine whether pharmacies and pharmacists are in compliance with state regulations for the practice of pharmacy. The methods states use to employ inspections as a compliance tool varies widely. While some states perform routine surprise in-person inspections, other states rely on scheduled announced inspections, while still others primarily rely in whole or in part on pharmacy self-inspections. In a self-inspection, a pharmacy submits responses to a questionnaire on its compliance with laws and regulations. In some states, inspections are driven primarily by the receipt of complaints that warrant an investigation into pharmacy activities.

Historically, any federal regulatory role for the compounding pharmacy sector has been resisted by the industry. In 2007, when draft legislation was circulated to clarify the FDA's role in overseeing the safety of compounding pharmacies, it was immediately denounced by trade associations representing the sector.[23] The trade associations argued that "state boards of pharmacy have done a great job to write compounding standards…There's no way that the FDA will be equipped to handle this."[24] Compounding pharmacy trade organizations have in the past fought vehemently to ensure that pharmacy compounding remained the sole authority of the states, and even issued emails instructing its members what to say to deny FDA authorities access to facilities or samples from facilities that were compounding drugs.[25]

Post-NECC: Massachusetts and other State Actions

Following the NECC tragedy, Massachusetts Governor Deval Patrick put in place aggressive emergency regulations that required all sterile compounding pharmacies in Massachusetts to immediately and on bi-annual basis report the volume of prescriptions dispensed, states to which prescriptions were distributed and a certification that pharmacies were operating in compliance with all laws and regulations for sterile compounding. The Governor also appointed a special compounding oversight

[23] See: http://drugtopics.modernmedicine.com/drugtopics/Community+Pharmacy/New-bill-on-pharmacy-compoundingstirs-concern/ArticleStandard/Article/detail/414436
[24] See: http://drugtopics.modernmedicine.com/news/new-bill-pharmacy-compounding-stirs-concern
[25] Walt Bogdanich and Sabrina Tavernise. "U.S. Concern Over Compounders Predates Outbreak of Meningitis." *The New York Times* 23 October 23 2012 A1.

commission that proposed twenty-five additional compounding pharmacy safety measures, many of which were then filed as a legislative package.[26] The legislative package would require a special license for sterile compounding and out-of-state pharmacies, a reorganization of the board members and new authorization for the board to issue fines against pharmacies that violate state laws and regulations. The Governor also immediately hired temporary inspection staff and put in place an enhanced pharmacy inspection schedule that required unannounced inspections of all sterile compounding pharmacies.

Even before the recent fungal meningitis outbreak, in the state of Massachusetts any retail pharmacy that wished to specifically compound sterile injectable drugs[27] had to meet specific regulatory requirements with respect to its clean room facilities and were further expected, but not required, to obtain board of pharmacy approval. In Massachusetts there existed 26 such pharmacies that were known by the state to be producing sterile injectable drugs, including NECC and its sister company Ameridose. However, following the NECC incident, the state requested that pharmacies attest under penalty of law to the scope of its practice. In response to this request, 39 pharmacies,[28] out of a total of 1,179, self-identified as conducting sterile compounding. The Massachusetts Department of Public Health subsequently performed unannounced inspections of these pharmacies to see if they would identify similar issues to those discovered at NECC. These inspections revealed that only 4 were in full compliance with safety standards and required the state to issue 11 immediate full or partial cease and desist orders and 21 deficiency notices to sterile compounding pharmacies.[29]

Since other states have not undertaken such efforts publicly, it is unknown to what extent this rampant disregard for sterile compounding requirements holds true in other states. However, there are several states that have taken steps to increase enforcement activities relating to compounding pharmacies. For example, Iowa has initiated an effort in conjunction with the National Association of Boards of Pharmacy to inspect 600 out-of state pharmacies that ship medications into Iowa. The state of Mississippi adopted an accreditation process in November 2012 for certain sterile compounding pharmacies located in and out of the state.[30]Additionally, Arizona announced plans to establish a task force to determine any regulatory changes that need to be made. The state laws documented in this report are the laws and regulations in place as of November 2012 when states were sent the survey. In the wake of the NECC tragedy, several states, including Maryland, Massachusetts, California, Minnesota, New Hampshire, New Jersey,

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[26] See: http://www.mass.gov/governor/pressoffice/pressreleases/2013/0104-compounding-industry-legislation.html

[27] Note that this represents a subset of all sterile compounders in Massachusetts

[28] Two of these 39 pharmacies attested to either closing their operations or ceasing the practice of sterile compounding, leaving 37 self-identified as conducting sterile compounding. This number does not include NECC, Ameridose or Alaunus.

[29] Kay Lazar and Chelsea Conaboy. "Just 4 of 37 Massachusetts Compounding Pharmacies Passed Surprise Health Inspections" *The Boston Globe* 6 February 2013 online.

[30] In Mississippi, accreditation for sterile pharmacies excludes hospitals preparing sterile injectable drugs for use within 24 hours and pharmacies compounding these drugs for administration to institutional patients within 72 hours. Mississippi also put in place an accreditation requirement for non-sterile compounding pharmacies that compound more than 25 % of their total prescription volume.

Oklahoma, South Carolina, Utah, and Virginia have either introduced or passed new legislation or implemented new regulations placing additional restrictions on compounding pharmacies. These post-November 2012 announcements are not reflected in this analysis as most do not represent final enacted and implemented legislation and/or administrative changes.

Additionally, several states, including California, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, Oklahoma, South Carolina, Utah, and Virginia have introduced legislation to put stronger controls in place for compounding pharmacies, though to date, none of these legislative solutions have been adopted. It is also expected that additional states will be announcing changes in the coming months.[31]

Among many issues, the NECC tragedy highlighted the inability of states to oversee or manage compounding pharmacies that are located in another state, but that are shipping and selling drugs across state boundaries. In December 2012, the FDA convened a meeting of all 50 state boards of pharmacy to discuss the roles of state and federal entities in the oversight of compounding activities. At this meeting, the states discussed the fact that each state is dependant on other states to regulate pharmacies that are present in their state and this can be a "potential issue, if in fact, there are states that don't have sufficient funding (or) don't have the resources necessary to regulate facilities in their state" because this "can have an impact on every state."[32] A group of state boards present at the meeting expressed their opinion that for "facilities like NECC, there is a role for the FDA to be involved," while pharmacies that are conducting traditional compounding pursuant to a prescription sold only within state borders could be left to most states to adequately oversee. The National Association Boards of Pharmacy (NABP) shared this sentiment, stating that "there's a big disparity among the states in terms of the resources and expertise to regulate compounding" and that "the definition of compounding is that it's patient specific" and once you lose that patient specificity, "It's not a state regulatory issue. It's an FDA issue."[33]

> *"It's not a state regulatory issue. It's an FDA Issue."*
> *-National Association of Boards of Pharmacy*

A previous report issued by Rep. Markey's staff examined media reports, FDA's database of enforcement actions and state board of pharmacy websites and found that state pharmacy boards generally focus enforcement efforts on the types of activities typically associated with traditional pharmacy licensing, such as billing violations, failing to register with the state, failing to have a licensed pharmacist on site, and violations

[31] This report notes some of these pending state changes, but is not an exhaustive discussion. In many instances the policy positions are not final, and in others, states may have initiated such efforts but not reported them to Congressional requesters.
[32] FDA Framework for Pharmacy Compounding: State and Federal Roles. December 19, 2012.Transcript.
[33] February 1, 2013: NPR Diane Rehm Show: Safety Concerns at Compounding Pharmacies, Statement by Carmen Catizone, Executive Director of the National Association of Boards of Pharmacy.

related to the use and distribution of controlled substances.[34] The state boards' of pharmacy efforts are not typically focused on undertaking enforcement actions that relate to the safety or scope of compounding pharmacy practices. Furthermore, state enforcement records are typically not publically available, and when they are available the databases do not allow for keyword searches, preventing the public from easily locating enforcement records or infractions associated with particular pharmacies or medications. When states do keep this information in a public format, the details of the circumstances necessitating the enforcement action is typically lacking, making the information generally useless to a member of the public.

This report summarizes a more extensive investigation into the state oversight of compounding pharmacies, launched to get a better understanding of the information that is maintained internally by state boards of pharmacy, the oversight of pharmacy practices and the actions that states have taken historically to ensure the safety of compounding pharmacies and the products they sell.

[34] October 29, 2012 Compounding Pharmacies, Compounding Risk. See: http://markey.house.gov/press-release/new-markey-report-reveals-current-outbreak-least-23-deaths-86-serious-illnesses

INVESTIGATION AND METHODOLOGY

To better understand the role that state boards of pharmacy play in managing the oversight of compounding pharmacies and protecting against another NECC-like tragedy, on November 20, 2012, Reps. Markey, Waxman, Dingell, Pallone and DeGette sent a letter to the boards of pharmacy in all states, territories, and Washington, DC requesting answers to six questions that asked for historical information about compounding pharmacies, pharmacy licensing, inspections of pharmacies, and pharmacy board budgets, as well as information about the structure and policy governing the board (See Appendix C). The questions were designed to examine the degree to which individual states are capable of overseeing the safety of compounding pharmacy practices and enforcing against the type of safety related matters raised by the New England Compounding Center.

With the exception of Rhode Island, Guam, Puerto Rico and the U.S. Virgin Islands, we received a response from all of the state boards of pharmacy queried. When particular responses were incomplete, staff followed up with the board of pharmacy to obtain this information. While a number of states do not have the capacity or system requirements to keep or review historical data, or in some cases simply do not track this information, the states attempted to respond to all questions, providing estimations or projections in areas where hard data was not available or retrievable. Presented below is a summary and analysis of the information provided by the state boards of pharmacy. Additional analysis and findings can be found in Appendix A. Appendix B contains a table that summarizes all state boards of pharmacy responses.

FINDINGS

1. **State boards of pharmacy generally do not know which pharmacies engage in compounding, do not know whether pharmacies ship compounded drugs across state lines, and do not know which pharmacies manufacture large quantities of compounded drugs. In many cases, states are incapable of even providing accurate information regarding the numbers of registered pharmacies in their states.**

To gauge the ability of states to track compounding activities, the state boards were asked to provide information about the number of licensed compounding pharmacies, pharmacies licensed for sterile compounding and pharmacies that sell high volumes of compounded drugs, or sell across state lines.

Key Findings:

- *No state boards require disclosure of volumes of compounded drugs or whether compounded drugs are sold across state lines*
- *Only two states (MO and MS) routinely track the number of compounding pharmacies in their state*
- *Only 32 states were able to provide historical data on the number of licensed pharmacies in their states*

The vast majority of states allow any pharmacy to compound without a specific compounding license or permit. Forty-seven states and the District of Columbia were unable to provide an exact number of pharmacies that are authorized to compound in the state (See Table 1). Only Missouri and Mississippi require a license or permit for basic drug compounding.

In Mississippi, over the last decade, 102 pharmacies have received specific permits designating them as compounding pharmacies by the Mississippi board of pharmacy. This number does not, however, take into account pharmacies that are no longer in operation, or that simply choose to no longer offer compounding services. Furthermore, because Mississippi does not issue specific permits for facilities engaged in sterile compounding, it's impossible to discern how many of the 102 compounding pharmacies may also be compounding complex and risky sterile drug products.

Missouri's board of pharmacy employs a fairly sophisticated licensing system, which provides different permits for different classes of licensed pharmacies (i.e. internet, veterinary, renal dialysis, etc). In Missouri, all 1,570 pharmacies authorized to dispense medication may perform traditional pharmacy compounding without additional licensure, however the state requires a specific non-sterile compounding permit for pharmacies performing batch compounding from bulk ingredients. Additionally, a sterile compounding permit is required for facilities wishing to engage in sterile compounding activities. In the state of Missouri, 442 pharmacies, approximately one-third of all in-state pharmacies, hold specific permits for compounding both non-sterile drugs from bulk ingredients and for sterile drugs—however, any pharmacy could perform simple compounding services without notifying the state.

None of the states indicated that they track whether pharmacies are selling compounded drugs across state lines, or the volume of compounded drugs that are being produced by a facility.

TABLE 1: STATES THAT PROVIDED INFORMATION ON THE NUMBER OF COMPOUNDING PHARMACIES

STATE	# licensed in-state pharmacies in most recent year provided	# compounding in-state pharmacies	# in-state sterile compounding pharmacies
AR	755	21*	State does not track
ME	335	3*	State does not track
MO	1,570	442	Did not provide separate number of sterile compounding pharmacies.
MS	1,678 permits issued in the past 10 years	102	State does not track
OR	728	81*	State does not routinely track, but based on inspection records is aware of 11 pharmacies that do sterile compounding and also hold non-resident licenses

*Estimated based on disclosure on initial license application and/or annual renewal. Additional pharmacies may compound without notice.

While Mississippi and Missouri were the only states that indicated the requirement for a specific permit or license to track certain compounding activities, three additional states (Arkansas, Maine, and Oregon) ask that pharmacies indicate on their initial license application whether they intend to engage in compounding activities (See Table 1). Using this information, Maine was able to identify 3 pharmacies and Arkansas 21 pharmacies that provided such an indication. In addition, Oregon, which asks pharmacies to indicate whether they engage in compounding both on the initial license application and on annual renewals, identified 81 compounding pharmacies. It is important to note, however, that in all of these states any pharmacy is authorized to engage in compounding regardless of whether it indicated this intent on their license applications. One additional state, Minnesota, indicated that recent regulatory changes require pharmacies to notify the board and receive approval before they engage in compounding sterile or non-sterile products of any type. However, the state did not indicate how many such pharmacies have self-identified as compounders since this change in state law was implemented.

Several states noted that pharmacies engaging in high-volumes of compounding would trigger the requirement for a manufacturer's registration, as this would be beyond the scope of a state-licensed compounding pharmacy and would instead fall under FDA's jurisdiction. However, it is unclear how any state would know whether this requirement was triggered, as no state indicated that they routinely request information from pharmacies about quantities of compounded drugs or whether such drugs are shipped across state lines as a part of their license or registration.

2. <u>Only thirteen state boards of pharmacy know which pharmacies are providing sterile compounding services and only five of these states have inspectors that are trained to identify problems with sterile compounding.</u>

While most states allow any pharmacy to compound without requiring a specific compounding permit or license, a few states have specific requirements for pharmacies that intend to compound sterile drugs. Sterile drugs are more difficult to produce than other drugs and pose significant health threats if improperly produced.

Including Massachusetts, which even prior to NECC had a clean-room approval process in place for pharmacies that were producing sterile injectable drugs, there were a total of only 13 states (26% of respondents) that were able to provide some estimate as to the number of currently operating sterile compounding pharmacies. Only 5 out these 13 states (ID, NJ, NV,OK and TX) specifically track all pharmacies that perform sterile compounding activities (See Table 2).

Key Findings:

- *37 state boards of pharmacy (74% of respondents) do not routinely track which pharmacies are providing risky sterile compounding services*
- *Only 19 state boards of pharmacy provide their inspectors with special training to identify problems with sterile compounding*

- Oklahoma requires in-state retail pharmacies that perform sterile compounding to receive a specific permit and currently has 88 pharmacies permitted to provide these services.
- Alabama requires pharmacies that are compounding preparations for parenteral or intravenous (IV) administration to have a separate certification. Currently there are 103 institutional hospitals and 67 chain and community pharmacies that have parenteral certification. This does not include pharmacies that compound other sterile products whose administration is not through injection.
- Connecticut currently has records of 17 sterile pharmacies, but this doesn't include any hospital pharmacies, which are assumed to be undertaking some sterile compounding.
- As of March 2012, Idaho requires any pharmacy that is engaging in sterile drug preparation to obtain a registration for aseptic environmental control devices, such as laminar flow hoods. Currently, Idaho has provided 77 such registrations, each of which requires an onsite inspection by the board of pharmacy prior to producing sterile drugs.
- While New Jersey doesn't require specific permits or licenses for compounding activities, it does have regulations that require pharmacies to notify the board in advance of compounding sterile preparations. Once notified, the New Jersey board inspects the facility to ensure compliance with regulations related to sterile compounding and then grants approval for the pharmacy to engage in such operations. New Jersey estimated that they have 41 sterile compounding pharmacies.
- California has the second highest number of registered in-state pharmacies (6,761 pharmacies), 266 of which are board-licensed for sterile compounding. However,

this number is likely to be a significant underestimate, as pharmacies that are accredited by outside agencies are allowed to perform sterile compounding without additional licensure with the California board of pharmacy.

- The remainder of the 37 states that responded do not systematically track which pharmacies are providing sterile compounding services. The lack of information makes it impossible for pharmacy boards to target enforcement and inspection efforts towards the highest-risk pharmacy operations and appropriately oversee their safe operation.

TABLE 2: ONLY THIRTEEN STATES ARE ABLE TO DETERMINE THE NUMBER OF PHARMACIES THAT PERFORM STERILE COMPOUNDING

STATE	# licensed in-state pharmacies in most recent year provided	# in-state sterile compounding pharmacies
AL	State does not track	103 institutional hospitals and 67 chain and community pharmacies with parenteral certification
CA	6,761	266 board licensed sterile pharmacies*
CT	670	17 sterile compounding retail pharmacies, not including hospitals
DE	157	State does not track but knows of one sterile facility other than hospitals
IA	1,510	51** sterile compounding retail pharmacies, not including hospitals
ID	445	77
MA	1,179	39^
NJ	2,835	41
NV	709	22**
OK	910	88
TX	6,509	652
VA	1,762	159**
WA	1,425	State does not license, but based on inspections there are 19 pharmacies focusing on parenteral products

*Additional accredited sterile compounders exist, but do not require licensure with the board.
**Any pharmacy could provide sterile compounding services; sterile compounding pharmacies are estimated based on inspection or other information.
^ Represents all sterile compounding pharmacies that self-identified following the fungal meningitis outbreak. Only 4 were found to be in full compliance of safety standards following unannounced inspections.

A previous analysis of state inspection and enforcement records issued by Rep. Edward J. Markey[35] found that state boards of pharmacy do not, as a general rule, undertake enforcement actions that relate to the safety or scope of compounding pharmacy practices. Instead the boards tend to focus efforts on compliance with traditional pharmacy licensing and use of controlled substances. As a result most enforcement actions taken by boards appear to deal with issues such as whether technicians have completed appropriate training hours, appropriate intern supervision by licensed pharmacists, valid and updated registration and licensing documentation and valid distribution of controlled substances.

The survey results indicated that only 19 states (38% of respondents) provide some or all of their inspectors with special training in sterile compounding activities and regulations (See Table 3). An additional 9 states (CA, IA, IL, KS, MN, MT, NE, UT, and WY) indicated that while there is no special inspector training in compounding or sterile operations, some or all of the inspectors employed by the state are licensed pharmacists and therefore are expected to have basic knowledge of sterile and non-sterile compounding operations.

TABLE 3: STATES WITH INSPECTORS TRAINED IN STERILE COMPOUNDING

STATE	# Inspectors Trained in Sterile Compounding Operations in Most Recent Year Reported
AR	3 inspectors and 2 directors involved in investigations and inspections
CO	3
FL	18
GA	14
IN	6
KY	5
LA	5
MD	6.5 full-time pharmacists and 4 technicians split between 2 agencies
MI	5
MO	8
NC	9
ND	2
NJ	7 + 2 part-time inspectors
NM	5
NV	5*
OK	5
TX	7
VA	4
WV	5

*Only a portion of the inspectors receive training

[35] Compounding Pharmacies, Compounding Risk; issued October 29, 2012. See: http://markey.house.gov/press-release/new-markey-report-reveals-current-outbreak-least-23-deaths-86-I serious-illnesses

A few states indicated that after learning about the NECC tragedy, the boards have or are in the process of reevaluating their inspection procedures and developing training specific to sterile compounding for inspectors. For example, Alabama indicated that it is contracting with a consultant to establish particular inspection protocols and training. Additionally, Nebraska and Virginia indicated that it has required inspectors to complete online training in compounding and will provide additional on site training. Mississippi also noted that while state inspectors have limited training in inspecting sterile compounding procedures, they will perform in depth inspections with assistance of inspectors from FDA or the Drug Enforcement Administration (DEA).

3. States typically do not maintain pharmacy inspection records that enable them to identify systemic or repeated compounding pharmacy safety problems that originate either in-state or out-of-state.

States were asked to indicate whether they have over the last decade, during the course of an inspection or other oversight activity, identified the kinds of problems that were found at NECC, namely issues with contamination, cleanliness, drug potency, drug safety, bulk manufacturing or other similar concerns. Many states (22 states or 44% of respondents) either do not keep historical records of inspections, or do not track problems relating to compounding. Other states used a combination of inspection records, public complaints and "staff recollections" and were able to indicate a sample of noted problems or disciplinary actions taken against in-state compounding pharmacies due to safety related problems similar to those identified at NECC.

Key Finding:

- *22 state boards of pharmacies do not keep any historical inspection records for compounding pharmacies*

States reported a total of 2,682 disciplinary actions taken or concerns raised against compounding pharmacies in all 49 states and DC over the last decade. These 2,682 compounding concerns or actions pertained to issues of unsafe storage, compounding copies of commercially available drugs, compounding without a prescription, issues with potency, problems with sterility, use of improper ingredients, and manufacturing large quantities of drugs outside the scope of a pharmacy license It is unclear how many of these compounding-related concerns were evaluated by the boards or rose to the level of formal disciplinary action, as states do not routinely track this information.

Furthermore, because many states do not keep inspection histories, have limited access to details of inspection records, keep them only in an unsearchable paper format, or for a limited timeframe the number of compounding issues reported by the states is likely severely underestimated. These record-keeping practices would make it difficult to determine whether there are particular pharmacies that have a history of violating the law.

As previously indicated, enforcement actions taken against compounding pharmacies are not always publically available on state websites, and when available do

not always contain sufficient information for the public to understand the nature of the violation in question, making it impossible for consumers to determine whether a particular facility has had prior safety issues with compounding drugs.[36] When comparing the actions that are disclosed on state websites, and that were analyzed in a previous report,[37] to those disclosed by the states in response to this survey, none of the states reported in their response all of the actions that were listed on their own websites or in media reports. This calls into question the completeness of the states' online databases and their internal record-keeping systems.

4. <u>States are unable to effectively police compounding pharmacy activities in other states.</u> <u>Moreover, when issues arise with out-of-state pharmacies, states do not consistently inform the origination state or the FDA.</u>

Problems with compounded drugs originating from out-of-state pharmacies are common. Nineteen states (38% of respondents) identified 224 issues arising from compounding pharmacies located in other states in the past 10 years. These issues ranged from consumer complaints about potency or safety to discoveries that pharmacies were selling copies of commercially available drugs or distributing samples to medical facilities within the state. In many cases, pharmacies located out-of-state were reprimanded for selling drugs in a different state without the appropriate license or registration. Since three states do not have a requirement for out-of-state pharmacies to be licensed to sell drugs within their state, these states would have no way of even knowing that these sales were occurring.[38] Many state boards indicated frustration with the lack of control they have over pharmacies located in another state and the absence of a formal mechanism for boards to know about safety related or other issues that arise with out-of-state pharmacies. Please see Table 4, but what follows are highlights from these findings:

Key Finding:

- *There is no formal mechanism for state boards to know about issues with out-of-state pharmacies*

- The majority (144 out of the 223 or 65 %) of the concerns about out-of-state pharmacies were reported by Iowa, of which just 20 rose to the level of formal disciplinary action.
- North Carolina reported 37 concerns with out-of-state pharmacies. These North Carolina concerns included drugs being linked to several meningitis cases, compounding pharmacies sending samples of drugs directly to medical professionals, pharmacies compounding commercially available drugs and drugs

[36] Compounding Pharmacies, Compounding Risk; issued October 29, 2012. See: http://markey.house.gov/press-release/new-markey-report-reveals-current-outbreak-least-23-deaths-86-serious-illnesses

[37] Ibid.

[38] Three states (Massachusetts, Georgia and Pennsylvania) do not require out-of-state pharmacies to hold a license within their state. Following the NECC linked fungal meningitis outbreak, the Governor of Massachusetts filed legislation to make several reforms, including a requirement that all non-resident pharmacies be licensed and subject to the regulations of the board of pharmacy.

that are not approved for human use and out-of-state pharmacies dispensing drugs in the state of North Carolina without a non-resident pharmacy permit.

- The state of Missouri, which has taken 3 public disciplinary actions against known compounding pharmacies in the last decade issued a cease and desist order to NECC in 2002, but did not indicate the reason for this disciplinary action.
- The state of Colorado also issued a cease and desist order to NECC in 2011, when it was discovered that NECC was manufacturing drugs and shipping them to a hospital pharmacy in violation of Colorado law. At the time, this action was reported to the National Association of Boards of Pharmacy (NABP), the Drug Enforcement Agency (DEA) and FDA, but apparently not directly to the Massachusetts board of pharmacy. When in 2012 the same problem was discovered, Colorado's board of pharmacy notified both the FDA and the Massachusetts board of pharmacy. This second notification occurred approximately two months before the first patient who contracted meningitis from NECC was discovered.

The remaining 31 responsive states indicated that prior to NECC, they were never made aware of a problem with an out-of-state pharmacy or simply did not track this type of information. Even in cases where there was an identified problem related to an out-of-state pharmacy the direct communication between state boards is limited, as most states never notify other state boards about problems discovered within their borders, even if the pharmacy in question is located in another state. As a result, a state may discover a serious problem with the drugs produced by a pharmacy located in another state, take an action to stop that pharmacy from shipping drugs into its state, but never notify the home state or any other state about the drug safety problem identified. Instead states typically report issues with pharmacies to NABP, and typically this reporting only occurs when the problem is investigated and rises to the level of a formal public disciplinary action. A few states mentioned that they do not report to NABP because they do not share their enforcement activity with non-government entities. Therefore, even NABP would not be a comprehensive source for problems identified at compounding pharmacies

States also tend to report formal disciplinary actions against pharmacies to the National Practitioner Data Bank (NPDB) and the Healthcare Integrity and Protection Data Bank (HIPDB), the two federal data banks that have been created to serve as repositories of information about health care providers in the United States. Federal law requires that adverse actions taken against a health care professional's license be reported to these data banks. Once reported to these various entities, however, there does not appear to be any systematic manner in which other states are notified of these issues so that they can take proactive action to protect state residents from being harmed. Moreover, these data banks only make individual reports available to the state boards upon request and for a fee.[39] Based on survey results, the only time states seem to routinely inform the FDA about problems with out-of-state pharmacies is when the pharmacy has produced a drug which has caused the death of one or more people.

[39] Informal communication with Massachusetts Department of Public Health.

TABLE 4: STATES WITH INFORMATION ABOUT COMPOUNDING CONCERNS ORIGINATING OUT-OF-STATE IN THE LAST DECADE

STATE	# Out-of-state Compounding Concerns or Actions	Nature of Concern	Who was Informed
OR	1	Texas Pharmacy sent drugs that were 10 times as potent as indicated on the label, resulting in 3 deaths. The pharmacy was not licensed in Oregon as an out-of-state pharmacy	This particular out-of-state case was investigated by the FDA and Texas BOP
NH	1	Accepted a voluntary license surrender from Infusion Resource located in Massachusetts, based on action taken by FDA and Massachusetts BOP on November 16, 2012	No one
NJ	1	An out-of-state pharmacy notified the NJ Board that they were subject to a disciplinary action as a result of a compounding error in the pharmacy's home state	No one
ID	1	Mail order of invalid prescription drug orders	State of Utah where pharmacy was located
OK	1*	Pharmacy violated state rules by sending sterile drugs to physician's office for patient pick up	NABP
KS	1	Pharmacy operating without out-of-state registration	The state where the pharmacy was located
GA	1	Selling drugs to an unlicensed facility without prescriptions	Alabama, where pharmacy was located
NY	1**	Pharmacy dispensed contaminated products. Under investigation so details not provided	Unknown
FL	1	Not indicated	No one
NV	2	Compounding a controlled substance without proper in-state registration and selling adulterated drugs	1 case, the State of pharmacy origin was notified. The other case was under CDC and FDA investigation
MN	3	2 unlicensed out-of-state pharmacies and another where an unregistered pharmacy was selling whole sale	The states of origin
LA	3	1 expired in-state permit, 2 pharmacies with histories of adverse events in other states.	NABP as notified in 2 instances
TN	3	1 pharmacy was investigated, but revealed no violation and was dismissed. 2 pharmacies were engaging in manufacturing or wholesaling without licensure	HIPDB and NPDB

TABLE 4: STATES WITH INFORMATION ABOUT COMPOUNDING CONCERNS ORIGINATING OUT-OF-STATE IN THE LAST DECADE (CONTINUED)

STATE	# Out-of-state Compounding Concerns or Actions	Nature of Concern	Who was Informed
MO	3	Not indicated	NABP, NPDB and HIPDB. The board may also provide FDA or state notification when appropriate
WY	6	1 pharmacy was compounding a commercially available drug. 2 pharmacies were operating without a WY license. 1 pharmacy didn't label compounded product for delivery in cold weather. 1 pharmacy had a compounding error. 1 pharmacy was selling a compounded product to a pharmacy for resale.	In 2 of these cases FDA was made aware. In the other cases no was notified
CO	5	1 pharmacy was shipping into the state without a nonresident pharmacy license. 2 pharmacies (one of which was NECC, which was cited twice) were selling manufactured drugs to a hospital pharmacy.	In each case different entities were notified (NABP, HIPDB, state of origin, FDA and DEA)
CA	9	Only one was investigated based on information from another agency. This one example involved Franck's pharmacy which was dispensing contaminated drugs.	N/A
NC	37*	25 pharmacies were shipping without an in-state license, 1 pharmacy had compounded drugs leading to several cases of meningitis, 1 pharmacy was issuing samples, 2 pharmacies were providing drugs for resale by pharmacies, 2 pharmacies were improperly distributing hormone products, 1 pharmacy was dispensing without prescriptions, 3 pharmacies improperly compounded drugs, 1 pharmacy mislabeled drugs, 1 pharmacy compounded a copy of a commercially available drug	In some cases the home state where the pharmacy was located was notified
IA	144	Nature of the issues was not provided, 20 disciplinary actions were taken and several are still pending.	disciplinary actions are typically reported to NABP and HIPDB

*Information was provided for a more limited 6 year period.
**State did not provide historic information, just one pending action.

5. <u>Despite general increases in state board of pharmacy budgets, the number of pharmacy inspectors has remained consistently low. Furthermore, states usually do not distinguish between inspections of traditional and compounding pharmacies.</u>

State boards of pharmacy were queried on their historical operating budgets. Forty-six percent of the respondents (23 out of 50 boards) were either unable to provide any information on budgets or were only able to provide data for a more limited time frame than the ten year interval that was requested, citing lack of easy access to historical information. Nine of these states[40] (18% of respondents) were unable to provide any indication of their operating budget, because the board of pharmacy does not manage its own budget; rather it falls under an umbrella agency that consolidates the budget for all medical and professional boards and manages the expenditures for each board in the state.

Even when factoring in the increase in licensed pharmacies over the last decade, budgets for state boards have generally increased. However, the budgetary constraints vary widely between states. For example, Nevada currently has a pharmacy board operating budget that provides for approximately $3260 per pharmacy for which the board is responsible for inspecting, while Indiana's board of pharmacy has an operating budget that provides for approximately $173 per pharmacy.

Key Findings:

- *On average states employ just 5 inspectors with responsibility to inspect all pharmacies.*
- *Only 5 state boards of pharmacy were able to provide an estimation of the number of inspections occurring at compounding pharmacies.*

While state pharmacy budgets have modestly grown over the last decade, several recent comments made by state boards of pharmacy representatives[41] and industry indicated that wide-spread budgetary constraints limit board oversight activities.[42] The difficulty of many states to access data needed to respond to this survey in a timely manner and the inability of many states to track compounding activities in their state does call into question whether state budgets are allowing for the type of oversight that is necessary to ensure the safety of these drugs and the protection of public health.

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[40] States with boards of pharmacy that fall under a consolidated umbrella agency: Connecticut, Delaware, Georgia, Hawaii, Michigan, New York, Utah, Vermont, Virginia. Wisconsin also falls under an umbrella agency, but was able to provide an estimate of its budget.

[41] For example, informal communications between some state board of pharmacy contacts and Rep. Markey's staff indicated that states with consolidated professional boards and those who rely on annual state appropriations for their budgets have a difficult time with securing the resources needed to adequately oversee the full range of licensed entities, while independent boards funded directly via pharmacy licensing fees typically have more budget stability

[42] See: December 19, 2012: FDA Framework for Pharmacy Compounding: State and Federal Roles. Statement by Dr. Cody Wiberg, Minnesota Board of Pharmacy. February 1, 2013: NPR Diane Rehm Show: Safety Concerns at Compounding Pharmacies, Statement by Dr. David Miller of the International Academy of Compounding Pharmacists.

Even with increasing numbers of pharmacies and general increases in board of pharmacy budgets, on average states employ just 5 inspectors per state, with the most inspectors being utilized in California-30, Ohio-22, Florida-18 and Georgia-14 and the fewest being utilized in Alaska-1, Vermont-1, Hawaii-1, and Wyoming-1.5. These inspectors are responsible for inspecting all pharmacy activities, and based on survey results, the average number of 5 inspectors has stayed fairly consistent over the last decade. In several cases these inspectors are also split between the board of pharmacy and other professional licensed boards and are responsible for inspecting and investigating all such facilities (for example, dental and medical facilities or other drug distribution facilities including wholesalers) that fall under their purview. For example, the state of New York indicated that it has 58 inspectors that are responsible for oversight of 50 different professions ranging from elementary educational institutions to pharmacy practice. Many states increasingly rely on pharmacies to conduct and submit self-inspections. While some states have policies that require all pharmacies to be inspected once a year or every other year, other states only inspect when they receive a complaint about a particular pharmacy or when a pharmacy first receives its license or permit.

States do not typically track inspections of compounding pharmacies, implying that inspections of entities that engage in riskier compounding behavior such as NECC would not be more likely to be inspected than a traditional pharmacy. There were only 5 states (California, Maryland, Nevada, New Jersey and New Mexico) that were able to provide some indication of the number of inspections that occurred at compounding pharmacies (a total of 404 compounding pharmacies or 7 percent of the total number of inspections) (See Table 5). However, in all of these states any pharmacy can engage in compounding, so the data provided are not considered to be fully inclusive of compounding activities. Since the problems were identified at NECC, Massachusetts enhanced the frequency of its inspection schedule, conducting unannounced inspections of all 37 sterile compounding pharmacies[43] in the state between November 2012 and the end of January 2013.

TABLE 5: STATES THAT PROVIDED DATA ON THE NUMBER OF INSPECTED COMPOUNDING PHARMACIES

STATE	# full-time inspectors	# licensed pharmacies in most recent year provided	#inspections in most recent year provided	# compounding inspections in most recent year provided
CA	30	6,761	2,248	231
MD	10.5	1,819	1,676	106
NJ	7 + 2 part time	2,835	1,026	38
NM	5	283	158	7**
NV	5	709	587	22

* 6.5 pharmacists and 4 technicians split between the Maryland Board of Pharmacy and Division of Drug Control
**indicated that compounding areas within retail pharmacies would be evaluated as a part of routine inspections.

[43] There were 39 sterile compounding pharmacies in Massachusetts, but 2 of these ceased operating as sterile compounders, leaving 37 subject to inspections.

APPENDIX A

ADDITIONAL FINDINGS

1. **Over the last decade, forty-seven state boards of pharmacy have seen an increase in the number of licensed pharmacies, but the lack of historical records makes it difficult for most states to accurately track the sector's growth**.

As a part of the survey, the state boards of pharmacy were asked to provide historical data on the number of licensed pharmacies each year for the last decade. Because of limitations in the way several states maintain records or collect data, there were only 32 states (64% of states) that could provide this information in full. Five states were able to pull responsive records that dated back a more limited timeframe (4-9 years). The remaining 13 states (26% of states) either did not maintain information on the number of licensed pharmacies or could not access this information without a significant time and resource commitment that the state was unable to expend.

According to the survey results, the number of pharmacies in any given state typically increased over the last decade, with the greatest increase happening in the state of Florida where 2,144 new pharmacies opened over the last decade. Florida was followed in rate of growth by Texas, which opened 1,045 new pharmacies. Florida is also the state which currently has the most licensed operating pharmacies (8,868 pharmacies) followed by California (6,761 pharmacies) and Texas (6,509 pharmacies). In contrast, the states with the fewest licensed pharmacies were New Mexico (34 pharmacies), Vermont (146 pharmacies) and Washington, DC (150 pharmacies). There existed only 3 states (Nebraska, Louisiana, and Oregon) where the number of licensed pharmacies decreased over the last decade, with Oregon losing the most pharmacy operations (149 pharmacies), from 877 in 2003 to 728 pharmacies in 2012.

In total there were approximately 68,000 licensed pharmacy facilities disclosed by the states. However, given poor records kept by states, the fact that some states do not differentiate in their records between in-state and out-of-state pharmacies, and the fact that some states track pharmacies alongside other facilities that dispense drugs, such as distributers and wholesalers, it is impossible to know how accurate this figure is of operating retail and hospital pharmacies in the U.S. Typical estimates made by other industry trade associations place the number of community based retail pharmacies in the U.S at about 56,000.[44]

[44] http://www.iacprx.org/displaycommon.cfm?an=1&subarticlenbr=277

2. Regional inconsistencies caused by different case law rulings on the applicability of the 1997 federal pharmacy compounding law have had no apparent impact on the state boards of pharmacy or on the oversight of compounding pharmacies in the Fifth or Ninth Circuits.

In 1997, Congress enacted the FDA Modernization Act of 1997 (FDAMA) that added a section to FDA law, which exempted compounded drugs from various "new drug" requirements, as long as the compounded drugs met a variety of restrictions. One of the restrictions was that drug providers were prohibited from soliciting or advertising particular compounded drugs. These speech restrictions were challenged on First Amendment grounds and were struck down by the Supreme Court.

Following this decision, there was controversy over the current status of compounded drugs under the FDA law and whether the remaining provisions that set up standards for compounded drugs remained in affect. The two circuits that addressed this issue took different positions. While the Ninth Circuit determined that the section of law that governed compounding was struck down in its entirety, the Fifth Circuit found that the provisions that didn't deal with speech restrictions are still in effect. Accordingly, these cases have created an interesting scenario of non-uniform federal law throughout the U.S. In the Fifth Circuit, compounded drugs are specifically exempted from having to apply as a new drug, complying with good manufacturing practices, and certain labeling requirements, as long as certain criteria are met; while in the Ninth Circuit, compounded drugs are subject to all of these requirements that apply to manufactured drugs, but the FDA may exercise discretion in taking action against an entity that violates these provisions.

We compared the states that fall within the Fifth circuit Court's jurisdiction (Texas, Louisiana, and Mississippi) to some of the Western states that fall under the Ninth Circuit Court's jurisdiction and found that there were no significant differences in the composition of the boards, the maintenance of historical records, the number or presence of trained inspectors, or the systematic tracking and oversight of compounding pharmacies (See Appendix Table 1).

APPENDIX TABLE 1: COMPARISON OF RESPONSES FOR STATES IN THE FIFTH CIRCUIT COURT JURISDICTION (TX, LA, MS) TO THOSE IN THE NINTH CIRCUIT COURT JURISDICTION (OR, NV, CA)

STATE	# Compounding pharmacies in most recent year	# Sterile compounding pharmacies in most recent year	Specific rules for sterile compounding pharmacies	Inspector training in sterile compounding	# Inspectors in most recent year reported	# Licensed in- state pharmacies (# pharmacies inspected)	# Licensed pharmacies increased or decreased over last decade (by this #)	Reported operating budget	# Board members
TX	State does not track	652	Yes	Yes	7	6,509 (2,140)	Increased (1,045)	$3,717,335 (2003) $6,202,645 (2012)	9 (3 public members)
LA	State does not track	State does not track	Yes	Yes	5	1,758 (793)	Decreased (60)	$1,170,252 (2003) $2,645,000 (2012)	17 (1 public member)
MS	102	State does not track	No*	No	6	Not indicated (1,559)	Provided only number of 1,638 new permits issued in past decade	$1,191,615 (2004) $2,026,913 (2013)	7 (0 public members)
OR	81**	State does not track	Yes	No	5	728 (728)	Decreased (149)	$2,358,405 (2001-2003) $6,130,811 (2013-2015)	7 (2 public members)
NV	State does not track	22 (based on inspection records)	Yes	Some inspectors	5	766 (587)	Increased (310)	$1,400,000 (2003) $2,500,000 (2012)	7 (1 public member)
CA	State does not track	266	Pharmacies that compound sterile injections require licensure or accreditation from an approved agency	No	30	6,761 (2,248)	Increased (623)	$7,390,000 (2003) $14,200,000 (2012)	13 (6 public members)

*Post-NECC the board adopted a new policy requiring accreditation of sterile compounders.
**Any pharmacy is permitted to compound, numbers estimated based on information provided in application and renewal forms.

3. <u>All state boards of pharmacy have similar structures and methods to deal with potential conflicts of interest, such as when there is a financial relationship between a pharmacy that is up for disciplinary action and a board of pharmacy member.</u>

The states were surveyed to get a better understanding of the structure of the state boards of pharmacy. The number of board members varies from 5-17 members, with an average of 8 board members that are typically appointed by the governor, either directly or with input provided by nominations, for a renewable term limit.[45] All boards are composed of licensed pharmacists, with some states requiring that the pharmacists represent various sectors of the industry, such as chain pharmacies or hospital pharmacies, and additionally may require that some board members are pharmacy technicians or other medical professionals. With the exception of Mississippi, every state has a requirement that board members include at least one public member who is intended to represent the consumer perspective. This public member is typically required to have no past or present affiliation with or financial interest in the practice of pharmacy.

In Mississippi and California the boards are comprised of 11 and 13 members, respectively, and include just one more pharmacist than public members, making these the states with the most public representation. In California, two of the public members are appointed by the Senate Rules and Speaker of Assembly, and the remaining members of the board are appointed by the Governor. Additionally, three states (Arkansas, Florida and Tennessee) require that a member of the board be elderly, usually defined as over the age of 60, and in Arkansas and Tennessee, the laws require that board members include one racial minority member. In Arkansas, this racial minority member must be a licensed pharmacist.

With the exception of Alabama, all states have some policy to deal with conflicts of interest that arise within the board. Typically this policy involves recusal that is either voted on by the board, decided upon by the state Attorney General or other legal counsel, or occurs automatically upon member disclosing an actual or perceived conflict. Several states also require the board members to provide a financial disclosure that is evaluated by legal counsel to proactively identify conflicts of interest. In many cases the financial disclosure and perceived conflict policies extend to a board member's spouse and immediate family.

While many of the conflict of interest policies require forthrightness of the board members, Washington State has a unique method to proactively avoid conflicts of interest impacting board member decisions. In Washington, any complaints that are handled in a prosecution case are de-identified and only one member of the board knows the identity of the entity that is being prosecuted, leaving board members to decide based purely on the merits and facts of the case. Additionally, any potential conflicts are screened by the Attorney General's office and state executive ethics board and until a decision is made about the conflict, the member in question is barred from participation in that matter.

[45] New York Regents Board appoints the Board of Pharmacy members, New Hampshire State Board of Health appoints its Board members.

Additionally, in Utah, conflicts are proactively investigated prior to appointment to the board, and if any conflicts arise during service, they constitute grounds for removal from the board.

APPENDIX B

Table Summarizing the Responses Received from All State Boards of Pharmacy

APPENDIX B:

STATE	# Licensed in-state pharmacies in most recent year *estimation	# Compounding in-state pharmacies *additional pharmacies can compound	Sterile compounding: Pharmacy registration for sterile injectables— Inspector training — Ability to readily search historical inspection records for problems	# Full-time inspectors	# Pharmacy inspections in most recent year reported (if tracked— # inspections of compounding pharmacies) *estimation ^ includes facilities other than pharmacies	Total # concerns related to in-state compounding pharmacies in time period reported *only a sample reported, not representative of all concerns	# Disciplinary actions for all in-state pharmacies for any reason in the last decade *limited time frame	# Concerns with out-of-state compounding pharmacies	Budget change from first reported year to most recent reported year *provided data for less than decade requested	# non-pharmacist public board members/ total # board members
AK	128	State does not track	No-No-No	1	24	State does not track	101	State does not track	Increased	2/7
AL	1,896*	State does not track	Yes-No-No	6	1,889	1*	102 (includes out of state pharmacies)	State does not track	data not provided	0/5
AR	755	21*	No-Yes-No	5	667	14*	250	Unaware of any	Increased*	2/8
AZ	1,681	State does not track	No-No-Yes	4	894	26	644	Unaware of any	Increased	2/9
CA	6,761	State does not track	Yes-No-Limited	30	2,248 (231)	2,357	82*	9	Increased	6/13
CO	959	State does not track	No-Yes-No	3	1,415^	13*	163	5	Increased	2/7
CT	670	State does not track	No-No-No	7	84	State does not track	State does not track	Unaware of any	data not provided	2/6
DC	150	State does not track	No-No-Yes	6	200^	64	498*	Unaware of any	Increased	2/7
DE	157	State does not track	No-No-Yes	2	88	State does not track	2	Unaware of any	data not provided	3/9
FL	8,868	State does not track	No-Yes-No	18	4,908	State does not track	324	1	Increased	2/9
GA	2,750	State does not track	No-Yes-No	14	2,500	9*	464	1	data not provided	1/8
HI	2,918	State does not track	No-No-No	1	State does not track	State does not track	State does not track	Unaware of any	data not provided	2/7
IA	1,510	State does not track	No-No-Yes	7	212	36*	611	144	Increased*	2/7
ID	445	State does not track	Yes-No-No	3	360	2	239	1	Increased	1/5
IL	3,299	State does not track	No-No-No	3-6	300*	State does not track	158	State does not track	Increased*	2/9

APPENDIX B:

STATE	# Licensed in-state pharmacies in most recent year *estimation	# Compounding in-state pharmacies *additional pharmacies can compound	Sterile compounding: Pharmacy registration for sterile injectables— Inspector training — Ability to readily search historical inspection records for problems	# Full-time inspectors	# Pharmacy inspections in most recent year reported (if tracked— # inspections of compounding pharmacies) *estimation ^ includes facilities other than pharmacies	Total # concerns related to in-state compounding pharmacies in time period reported *only a sample reported, not representative of all concerns	# Disciplinary actions for all in-state pharmacies for any reason in the last decade *limited time frame	# Concerns with out-of-state compounding pharmacies	Budget change from first reported year to most recent reported year *provided data for less than decade requested	# non-pharmacist public board members/ total # board members
IN	1,413	State does not track	No-Yes-Limited	6	685	State does not track	26*	State does not track	Decreased	1/7
KS	893	State does not track	No-No-No	4	864	State does not track	180*	1	Increased*	1/7
KY	2,143	State does not track	No-Yes-Yes	5	2,143*	4	473	Unaware of any	Increased	1/6
LA	1,758	State does not track	No-Yes-Yes	5	793	10	311	3	Increased	1/17
MA	1,179	State does not track	Yes-No-Yes	5	121	8	67	Unaware of any	Increased	2/11
MD	1,819	State does not track	No-Yes-Limited	10.5 split between 2 agencies	1,676 (106)	8	334*	Unaware of any	Increased	2/12
ME	335	3*	No-No-No	2	154	0	732	Unaware of any	Increased	2/7
MI	3,257	State does not track	No-Yes-No	5	1,379	State does not track	100*	State does not track	data not provided	5/11
MN	1,278	State does not track	No-No-Limited	6	352	11	State does not track	3	Increased	2/7
MO	1,570	442	Yes-Yes-No	8	1,242^	State does not track	137*	3	Decreased	1/7
MS	Current year not provided, 1,678 new permits issued in the past 10 years	102	No-No-Yes	6	1,559	5	430	Unaware of any	Increased	0/7
MT	370	State does not track	No-No-No	2	326	State does not track	160*	Unaware of any	Increased	2/7
NC	2,740	State does not track	No-Yes-Limited	9	289	33	516*	37	Increased	1/6

APPENDIX B:

STATE	# Licensed in-state pharmacies in most recent year *estimation	# Compounding in-state pharmacies *additional pharmacies can compound	Sterile compounding: Pharmacy registration for sterile injectables— Inspector training — Ability to readily search historical inspection records for problems	# Full-time inspectors	# Pharmacy inspections in most recent year reported (if tracked— # inspections of compounding pharmacies) *estimation ^ includes facilities other than pharmacies	Total # concerns related to in-state compounding pharmacies in time period reported *only a sample reported, not representative of all concerns	# Disciplinary actions for all in-state pharmacies for any reason in the last decade *limited time frame	# Concerns with out-of-state compounding pharmacies	Budget change from first reported year to most recent reported year *provided data for less than decade requested	# non-pharmacist public board members/ total # board members
ND	249	State does not track	No-Yes-No	2	Not indicated	2	49	Unaware of any	data not provided	1/7
NE	524	State does not track	No-No-No	2	133	State does not track	1	Unaware of any	Increased*	1/5
NH	300*	State does not track	No-No-Limited	2	269	2	138*	1	Increased	1/7
NJ	2,835	State does not track	No-Yes-Limited	7 full-time and 2 part-time	1,026 (38)	225	2,424*	1	Increased	2/11
NM	283	State does not track	No-Yes-Yes	5	158 (7)	0	8	Unaware of any	Increased	3/9
NV	766	State does not track	No-Partial-Yes	5	587 (22)	34	161	2	Increased	1/7
NY	5,244	State does not track	No-No-No	58 responsible for 50 professions	Not indicated	State does not track	Did not respond	1	data not provided	2/14
OH	2,700*	State does not track	No-No-No	22	1,100*	State does not track	State does not track	State does not track	data not provided	1/9
OK	910 (548 suppliers)	State does not track	Yes-Yes-Limited	5	639	5	284*	1	Increased*	1/6
OR	728	81*	No-No-No	5	728	State does not track	314	1	Increased	2/7
PA	3,200	State does not track	No-No-No	6	1,995	State does not track	400	Unaware of any	Increased*	2/9
SC	2,591	State does not track	No-No-No	4	1,618	State does not track	39*	State does not track	Increased	1/8
SD	295	State does not track	No-No-No	2	Not indicated	0	8*	Unaware of any	data not provided	1/5

APPENDIX B:

STATE	# Licensed in-state pharmacies in most recent year *estimation	# Compounding in-state pharmacies *additional pharmacies can compound	Sterile compounding: Pharmacy registration for sterile injectables— Inspector training — Ability to readily search historical inspection records for problems	# Full-time inspectors	# Pharmacy inspections in most recent year reported (if tracked— # inspections of compounding pharmacies) *estimation ^ includes facilities other than pharmacies	Total # concerns related to in-state compounding pharmacies in time period reported *only a sample reported, not representative of all concerns	# Disciplinary actions for all in-state pharmacies for any reason in the last decade *limited time frame	# Concerns with out-of-state compounding pharmacies	Budget change from first reported year to most recent reported year *provided data for less than decade requested	# non-pharmacist public board members/ total # board members
TN	2,319 (in-state and out-of-state)	State does not track	No-No-No	5	469	State does not track	262*	3	Increased	1/7
TX	6,509	State does not track	Yes-Yes-Yes	7	2,140	18*	684	Unaware of any	Increased	3/9
UT	1,331	State does not track	No-No-No	4	142	State does not track	365	State does not track	data not provided	1/7
VA	1,754	State does not track	No-Yes-No	4	647	State does not track	412	State does not track	data not provided	2/10
VT	146	State does not track	No-No-No	1	Not indicated	State does not track	Did not respond	Unaware of any	data not provided	2/7
WA	1,425	State does not track	No-No-Limited	11	1,198	36	29	Unaware of any	Increased	2/7
WI	1,220	State does not track	No-No-No	9	67	State does not track	14	Unaware of any	Increased (estimate)	2/7
WV	636	State does not track	No-Yes-No	5	Not indicated	State does not track	Did not respond	Unaware of any	Increased*	2/7
WY	174	State does not track	No-No-No	1.5	174-200*	15	29	4	Increased*	1/8

APPENDIX C

Letter to State Boards of Pharmacy sent by Reps. Edward J. Markey (D-Mass.), Henry A. Waxman (D-Calif.), John Dingell (D-Mich.), Frank Pallone (D-N.J.) and Diana DeGette (D-Colo.)

FRED UPTON, MICHIGAN
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ONE HUNDRED TWELFTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON ENERGY AND COMMERCE

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November 20, 2012

Mitzi Ellenburg
Interim Director
Alabama State Board of Pharmacy
PO Box 381988
Birmingham, AL 35238-1988

Dear Ms. Ellenburg:

The recent deadly outbreak of fungal meningitis linked to spinal injections of a pain-reliving steroid produced by the New England Compounding Center in Framingham, Massachusetts, has raised serious questions about the oversight of compounding pharmacies and the appropriate role for federal and state regulators in this sector.

Traditional compounding pharmacies that produce specialized drug formulations in response to an individual prescription play an important role in our healthcare system. However, we learned at our November 14 hearing that there have been a growing number of large compounding pharmacies engaging in mass production of drugs to be sold in bulk, often over state lines, in a manner much more akin to drug manufacturers. While drug manufacturers are required to meet stringent standards enforced by the Food and Drug Administration (FDA), compounding pharmacies, like all pharmacies, are licensed and overseen primarily by the states, allowing some of these facilities to evade federal safety requirements, putting public health and safety at risk.

With state budgets stretched thin, we are concerned that many state boards of pharmacies lack adequate resources and may have an insufficient number of inspectors trained in overseeing and inspecting large compounding pharmacies that engage in highly complex sterile processes as part of their operation as *de facto* manufacturers. To better understand how state boards of pharmacies manage the oversight of compounding pharmacies, we respectfully request that you respond to the following questions:

1. Please describe the role played by your pharmacy oversight board, the number of members of your pharmacy oversight board, the process for appointing such members and the qualifications required of such

members, and the process for managing conflicts of interest on your pharmacy oversight board.

2. For each of the past ten years, please indicate how many pharmacies in your state were a) licensed; b) licensed as compounding pharmacies; c) licensed to conduct sterile compounding; and d) licensed to sell high volumes of compounded drugs or sell compounded drugs across state lines (if your state does not require a specific license for sterile compounding activities, or for high volumes of compounded drugs, or for compounding pharmacies more generally, please also indicate this in your response).

3. Does your state require special licensing, safety requirements or certification for sterile compounding pharmacies or for compounding pharmacies that sell high volumes of compounded drugs or sell compounded drugs across state lines? If so, please provide a copy of or citation to these requirements. Are inspectors with responsibility for inspecting pharmacies in your state trained or certified in such sterile or high volume compounding procedures?

4. For each of the past ten years, please list a) the operating budget of the state board, b) the number of inspectors with responsibility for inspecting pharmacies, c) the number of pharmacy inspections conducted in your state, and d) the number of inspections of compounding pharmacies that took place in your state.

5. For each of the past ten years, please list a) the number of times an inspection or other oversight function of the state board identified concerns (e.g., contamination, cleanliness, drug potency, drug safety, bulk manufacturing or other similar problems) during an inspection of a compounding pharmacy, b) what the nature and outcome of the concern was, including the type of pharmacy, type of concern, involved medication, and any disciplinary actions taken, c) whether and how the state board informed the FDA, the National Association of Boards of Pharmacy, other state Boards of Pharmacy, or other regulatory authorities regarding the investigation or disciplinary action taken, and d) the total number of disciplinary actions taken against any type of pharmacy for any reason by your board in each year.

6. With the exception of the most recent issues with the New England Compounding Center, in each of the past ten years, how many times has the board identified concerns with the activities of a compounding pharmacy located in another state that shipped drugs into your state? For each such occurrence, please describe the nature and outcome of the concern, including whether your board notified the FDA, the National Association of Boards of Pharmacy, or the board of pharmacy of the state in which the compounding pharmacy was located. Please additionally provide a copy of all documents (including emails, letters, telephone logs

or faxes) in possession of your board related to such notification, including any response the board may have received.

Thank you for your assistance and timely response. Please provide your response no later than Friday December 7, 2012. Should you have any questions about this request please contact Dr. Avenel Joseph or Dr. Michal Freedhoff of Rep. Markey's staff at 202-225-2836.

Sincerely,

Edward J. Markey
Member of Congress

Henry A. Waxman
Ranking Member
Energy and Commerce Committee

John D. Dingell
Chairman Emeritus
Energy and Commerce Committee

Frank Pallone, Jr.
Ranking Member
Subcommittee on Health

Diana DeGette
Ranking Member
Subcommittee on Oversight and Investigations

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EXECUTIVE SUMMARY AND RESULTS IN BRIEF

An outbreak of fungal meningitis that has thus far claimed the lives of 53 people and sickened 733 brought national attention to compounding pharmacies, the drugs they produce, and the potential risks from these drugs. At the center of this outbreak was the Massachusetts-based New England Compounding Center (NECC) that produced the preservative-free injectable steroid drug that caused the deadly outbreak. This drug, found later to be contaminated with mold, was shipped to 23 states and injected into more than 14,000 patients, resulting in the worst pharmaceutical-related public health crisis in U.S. history. The NECC tragedy was not the first incident of compounding pharmacies causing fatalities or illnesses. Over the last decade, compounding pharmacies have been responsible for at least 23 additional deaths and 86 serious illnesses across the nation.

Unlike drug manufacturers, which are subjected to rigorous Food and Drug Administration (FDA) oversight, there is no requirement for compounding pharmacies to register with the FDA or to follow any FDA-specified procedures to ensure that the drugs they produce are safe and effective. In fact, the oversight of all pharmacies typically falls under the purview of individual states. Attempts by the FDA and by Congress to address safety concerns by ensuring uniform federal standards for compounding pharmacies have led to numerous lawsuits and conflicting judicial rulings and according to the FDA, created "ambiguity associated with FDA's authority over compounding pharmacies." The agency has called on Congress to take action to prevent another such outbreak, stating that if FDA's authority remains unchanged, "this type of incident will happen again. It's a matter of when, not if."

> *"This type of incident will happen again. It's a matter of when, not if."*
> *-Food and Drug Administration*

In November 2012, Reps. Edward J. Markey (D-Mass.), Henry A. Waxman (D-Calif.), John Dingell (D-Mich.), Frank Pallone (D-N.J.) and Diana DeGette (D-Colo.) launched an investigation to examine how state boards of pharmacies oversee compounding pharmacies, requesting detailed information from all boards on their regulatory and information collection processes.[1] This report analyzes the information provided in response to this request. A summary of all state board responses can be found in Appendix B.

The results of this investigation reveal that most states are incapable of assuring the safety of compounded drugs that are prepared using even the riskiest sterile processes or that are shipped into their state from an out-of-state pharmacy. The investigation also found that poor record-keeping practices by the states make it difficult, if not impossible, for the states to identify compounding pharmacies with systemic, repetitive compounding safety problems. Instead of being able to proactively address safety problems, many states rely on public complaints made after a compounded drug is implicated in an injury or death before they can initiate an investigation and take steps to prevent harm to more

[1] Appendix C includes a copy of this request.

patients. Moreover, when problems are identified with compounded drugs from pharmacies located in another state, there is no uniform method by which the states notify the FDA or the state in which the problematic pharmacy is located. As a result, these unsafe pharmacies often continue to operate, potentially shipping dangerous or even deadly products across the nation, without increased oversight or penalties.

While most states do not separately track compounding pharmacy activities and the problems associated with them, some states also do a poor job of tracking and overseeing even traditional pharmacy activities. For example, in addition to failing to keep and track records of compounding pharmacy concerns, states including South Dakota, Illinois, Hawaii, New York, Ohio and Vermont, also generally do not routinely track the number of regular pharmacy inspections that are performed. New York, Ohio, Minnesota and Connecticut do not keep searchable records on the number of disciplinary actions that are taken against pharmacies for any reason. The inability of these states to maintain basic records on general pharmacy operations calls into question the capability of these states to oversee more complex and more risky compounding pharmacy activities.

Some states have initiated administrative or legislative improvements to their compounding safety efforts. Despite these efforts, however, deficiencies associated with state record-keeping, communication, resources, and specialized expertise combined with the inability of any single state to monitor the adequacy of compounding pharmacy safety in 49 other states appear to be systemic barriers to relying solely on the states to assure the safety of compounded drug products. The FDA needs clear, unambiguous authority that would enable it to set and enforce safety standards for the riskiest and largest compounding pharmacies, as well as those that sell compounded drugs across state lines.

FINDING 1: State boards of pharmacy generally do not know which pharmacies engage in compounding, do not know whether pharmacies ship compounded drugs across state lines, and do not know which pharmacies manufacture large quantities of compounded drugs. In many cases, states are incapable of even providing accurate information regarding the numbers of registered pharmacies in their states.

- Only two states, Mississippi and Missouri, routinely track the number of compounding pharmacies in their state.
- Only thirty-two states were able to provide historical data on the number of licensed pharmacies in their states.
- None of the state boards have requirements for pharmacies to disclose the volumes of compounded drugs they produce or whether compounded drugs are being sold across state lines.

FINDING 2: Only thirteen state boards of pharmacy know which pharmacies are providing sterile compounding services and only five of these states have inspectors that are trained to identify problems with sterile compounding.

- Thirty-seven state boards of pharmacy (74% of respondents) do not routinely track which pharmacies are providing risky sterile compounding services

- Only 19 state boards of pharmacy provide their inspectors with special training to identify problems with sterile compounding.

FINDING 3: States typically do not maintain pharmacy inspection records that enable them to identify systemic and repeated compounding pharmacy safety problems that originate either in-state or out-of-state.

- Twenty-two state boards of pharmacies do not keep any historical inspection records for compounding pharmacies.

FINDING 4: States are unable to effectively police compounding pharmacy activities in other states. Moreover, when issues arise with out-of-state pharmacies, states do not consistently inform the origination state or the FDA.

FINDING 5: Despite general increases in state board of pharmacy budgets, the number of pharmacy inspectors has remained consistently low. Furthermore, states usually do not distinguish between inspections of traditional and compounding pharmacies.

- On average, states employ just 5 inspectors (a range of 1-30 inspectors was reported) with responsibility to inspect all pharmacies.
- Only 5 state boards of pharmacy were able to provide an estimation of the number of inspections occurring at compounding pharmacies.

BACKGROUND

NECC and the Outbreak of Fungal Meningitis

On September 21, 2012 the Centers for Disease Control and Prevention (CDC) was notified by the Tennessee Department of Health (TDH) of a patient who had developed a rare type of fungal meningitis 19 days after receiving an epidural steroid injection at an ambulatory surgical center in Nashville. Less than a week later, the CDC and TDH had discovered several other infected patients and linked the outbreak to the same preservative-free injectable steroid produced by the New England Compounding Center (NECC) in Framingham, Massachusetts.

Once identified as the likely culprit of the infections, NECC initiated a voluntary recall of the suspected lots, identifying more than 17,000 doses shipped to customers in 23 states. By the time the voluntary recall was initiated, more than 14,000 patients had already received a potentially contaminated injection. To date, these tainted drugs have been responsible for 53 deaths and 733 serious illnesses across 20 states.

Following the identification of NECC as the source of the fungal meningitis outbreak, the Massachusetts Department of Public Health and the Food and Drug Administration (FDA) inspected the NECC facility and identified significant problems with cleanliness and sterilization processes at the facility.[2] These problems included observing mold and other foreign material on surfaces of areas in the facility that should have been kept sterile.[3] FDA also found that NECC's own monitoring systems had identified unsafe levels of bacteria and mold, but the company had taken no action.[4]

In addition to the contamination, investigators also found evidence that the NECC had not been compounding drugs for patient-specific prescriptions, as is required of licensed pharmacies under both state and federal regulation. Instead, the NECC accepted patient lists generated by out-patient medical centers, clinics, hospitals, and pain management facilities and provided to NECC for the purpose of obtaining its products. Despite NECC selling contaminated drugs in this manner to at least 23 states, only Colorado had identified NECC as being involved in producing drugs in the absence of a patient-specific prescription two months before the outbreak occurred.[5] At the time of the discovery, the Colorado board notified the Massachusetts board of pharmacy director, who was subsequently fired for never acting on this information.

While this most recent public health nightmare has garnered wide public attention, it isn't the first time that a compounding pharmacy has been at the center of a

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[2] Food and Drug Administration, *Form 483 Issued to Barry Cadden* (Oct. 26, 2012) and Massachusetts Department of Public Health, Board of Registration in Pharmacy Report, *New England Compounding Center: Preliminary Investigation Findings* (Oct. 23, 2012).
[3] The Committee on Energy and Commerce Hearing on "The Fungal Meningitis Outbreak: Could it Have Been Prevented?" Majority Memorandum. November 12, 2012.
[4] Food and Drug Administration, *Form 483 Issued to Barry Cadden* (Oct. 26, 2012)
[5] Colorado Board of Pharmacy also discovered NECC engaging in illegal distribution of compounded drugs to hospitals in April 2011, but did not notify the Massachusetts Board of Pharmacy at this time.

contamination crisis. On October 29, 2012, Rep. Markey released a report entitled "Compounding Pharmacies, Compounding Risk"[6] that documented more than a decade of violations and problems at compounding pharmacies throughout the country. This report revealed that even before the current meningitis outbreak, compounding pharmacies were responsible for at least 23 deaths and 86 serious illnesses in at least 34 states. Many of the violations at these compounding pharmacies mirrored the issues revealed at NECC, including selling drugs without a valid prescription, manufacturing large quantities of drugs, and preparing sterile drugs in facilities that were visibly dirty leading to contaminated drug products.

Regulation of Compounding Pharmacies-Federal Role

The 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, to produce a medication tailored to that patient's special medical needs.[7] In its simplest form, the practice has been used to provide a patient with a medication that is not commercially available, such as adding flavor to a child's dose or removing a dye or preservative for a patient who has specific allergies.

Unlike drug manufacturers, which are required to register with the FDA to make, distribute and sell drugs, there is no requirement for compounding pharmacies to register with the FDA. Furthermore, drug manufacturers are subject to FDA inspections and are required to follow specified safety procedures known as good manufacturing practices (GMPs), as well as report to the FDA any adverse events that are associated with use of their drug products. Compounding pharmacies do not have to follow these same requirements, and like all pharmacies, the oversight of the practice of pharmacy compounding has largely been left to the states.

However, over the last several decades the practice of compounding has expanded and evolved. Today, compounding pharmacies produce injectable medications and other sterile drug products that require the utmost sterility and sophisticated processes and equipment. Internet pharmacies provide mail-order medications to patients in different states whom they will never examine or counsel. Hospitals have moved from in-house to outsourcing pharmacy services for drugs used throughout the hospital. Pharmacies have also expanded their operations to produce thousands of identical drug products, sometimes in advance of prescriptions for easy distribution to medical facilities across the country. In many ways, the activities of these types of pharmacies are more akin to drug manufacturers or distributors, even though the regulatory framework that governs them requires far less regulatory oversight and far less rigorous safety practices.

[6] October 29, 2012 Compounding Pharmacies, Compounding Risk. See: http://markey.house.gov/press-release/new-markey-report-reveals-current-outbreak-least-23-deaths-86-serious-illnesses

[7] November 12, 2012. Statement of Dr. Margaret Hamburg, Commissioner of Food and Drugs before the Subcommittee on Oversight and Investigations Committee on Energy and Commerce.

A Historic View of the Federal Regulation of Compounding Pharmacies

In the early 1990's, after receiving reports of several adverse events associated with compounded medication, the FDA issued a Compliance Policy Guide (CPG) to clarify what constituted appropriate and legitimate pharmacy compounding. The CPG made clear that the agency would use its authority to regulate new drugs in commerce to stop the operation of pharmacies whose activities raise the kinds of concerns normally associated with a drug manufacturer.

In 1997, in order to "clarify the status of pharmacy compounding under federal law,"[8] Congress included provisions to regulate the practice of pharmacy compounding in the Food and Drug Administration Modernization Act (FDAMA).[9] Section 503(A) of the law exempted compounded drugs from the other requirements of the Federal Food, Drug, and Cosmetic Act (FFDCA), most notably the requirements to apply for a new drug approval and follow good manufacturing practices, as long as the pharmacy was licensed in a state, made the drug pursuant to a valid prescription for an individual patient, made the drug using approved ingredients and endorsed standard compounding processes, did not compound inordinate amounts or copies of commercially available drugs, and did not engage in advertising or promotion.[10] Additionally, the exemption from requirements of FFDCA would only hold in states that had entered into a memorandum of understanding (MOU) with the FDA addressing the manner in which the state regulators would investigate and address complaints about compounding pharmacies that were distributing outside the state. In states that did not enter into such an MOU, the exemptions from the provisions of FDAMA only applied if the compounding pharmacy limited its distribution of drugs outside of the state to no more than five percent of its sales.

Before the law took effect, compounding pharmacies challenged the advertising and promotion restrictions of Section 503(A) in federal court.[11] The Ninth Circuit Court found that the Section 503(A) ban on advertising and promotion was an unconstitutional limit on free speech. It also found that the unconstitutional provisions could not be severed from the remainder of Section 503(A), rendering the entire section of law void.[12] Subsequently, the Supreme Court affirmed the lower court rulings that the speech restrictions were unconstitutional, but did not rule on the Ninth Circuit ruling that the unconstitutional provisions could not be severed from the remainder of Section 503(A).

In 2002, FDA issued a new Compliance Policy Guide (CPG), which in large part was very similar to the 1992 CPG and outlined how the agency intended to use its enforcement discretion. FDA stated in its CPG that it would rely heavily on state oversight of compounders and focus its enforcement on compounding pharmacies that were producing large quantities of drugs without valid prescriptions, producing commercially available products, selling drugs wholesale or to third parties for resale, or otherwise violating the new drug, adulteration, or misbranding provisions of the FFDCA.

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[8] Conference Report H.Rept. 105-399 at 94. November 9, 1997.
[9] Pub.L. No.105-115, (1997)
[10] Pub.L. No.105-115, §503(A) (1997).
[11] *Western States Medical Center, et al. v. Shalala*, 69 F. Supp. 2d 1288 (D. Nev. 1999).
[12] *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002).

In 2003, amid rising concerns about compounded drug products, the FDA issued a report entitled "Limited FDA Survey of Compounded Drug Products,"[13] which examined 12 compounding pharmacies that allowed Internet orders. The FDA found that ten of the 29 products it sampled failed one or more standard safety or efficacy tests that were performed on them. A second similar FDA report was issued in 2006.[14] This time the FDA analyzed 36 samples, of which 12 (33%) failed analytical testing using "rigorously defensible testing methodology." The report also mentioned that in the 15 years between 1990 and 2005, "the FDA learned of at least 240 serious illnesses and deaths associated with improperly compounded products."[15]

In 2004, 10 compounding pharmacies brought suit against FDA, challenging more broadly FDA's authority to regulate compounded drugs.[16] The companies charged that compounded drugs were not "new drugs" and were therefore exempt from all of FDA's authority governing new drugs under the FFDCA. In 2008, the Fifth Circuit Court of Appeals found that compounded drugs were in fact "new drugs" and were subject to the FDA's drug approval, adulteration, and misbranding requirements. The Court went further and disagreed with the Ninth Circuit's view on the severability of Section 503(A), effectively reinstating Section 503(A) within the Fifth Circuit's jurisdiction - Texas, Louisiana, and Mississippi.

Throughout the rest of the country not covered by the Fifth or Ninth Circuit decisions, it remains unclear whether the remaining provisions of Section 503(A), that were not ruled unconstitutional, remain in force. FDA has therefore continued to exercise its authority under the FFDCA in accordance with its 2002 Compliance Policy Guide.

However, FDA's 2002 Compliance Policy Guide cannot set binding legal standards. As noted in a recent report by the nonpartisan Congressional Research Service:[17]

> "In contrast to agency rules, which have the force and effect of law, guidance documents are merely considered to be a general statement of policy. Congress has passed requirements specific to FDA guidance documents, which state that such documents 'shall not create or confer any rights for or on any person, although they present the views of the Secretary on matters under the jurisdiction of the Food and Drug Administration.' Under regulations prescribing FDA good guidance practices, it is stated that 'guidance documents do not establish legally enforceable rights or responsibilities' and 'do not legally bind the public or the FDA.'"

[13] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm155725.htm
[14] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm204237.htm
[15] Ibid.
[16] Med. Ctr. Pharmacy v. Mukasey, 536 F.3d 383 (5th Cir. 2008).
[17] FDA's Authority to Regulate Drug Compounding: A Legal Analysis. Jennifer Staman, October 17, 2012.

Ambiguity of Agency Authority and Industry Litigation has led to Regulatory Confusion

As a result of this ambiguity in law and the non-binding nature of FDA's CPG, when the agency has attempted to utilize its enforcement discretion on a compounding pharmacy, its authority to do so has often been challenged in court. A prime example of this occurred in 2003 when FDA attempted to inspect Wedgewood Village Pharmacy after complaints alleged the pharmacy was making large quantities of drugs without prescriptions.[18] Wedgewood took the agency to court alleging that since they were a licensed compounding pharmacy, FDA had no authority to inspect the facility. Although the court ultimately disagreed with Wedgewood, it took more than a year for the judgment to be issued, and in the meantime the FDA could not collect the evidence necessary to take enforcement action against this pharmacy. On several other occasions when the FDA has been concerned about large quantities of drugs in interstate commerce, it has attempted to inspect the compounding pharmacies in question and has been challenged by the pharmacy and forced to obtain a court-ordered warrant, delaying the agency's ability to address a potential public health crisis.[19]

The FDA has also attempted to rein in the activities of compounding pharmacies through the issuance of dozens of warning letters since 2001 sent to pharmacies believed to have violated federal law governing the production of drugs .[20] While several pharmacies that received these letters ceased problematic activities, some instead challenged FDA's authority to oversee any activities that occur in pharmacies.[21]

The FDA has stated that the multiple court challenges "have produced conflicting case law and amplified the perceived gaps and ambiguity associated with FDA's authority over compounding pharmacies."[22] The agency has called on Congress to take action to prevent another fungal meningitis outbreak and compounded drug tragedy, stating that in the absence of legislation that provides clear authority to the FDA, "this type of incident will happen again, it's a matter of when, not if."

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[18] In the Matter of Establishment Inspection of Wedgewood Pharmacy, 421 F.3d 263 (3rd Cir. 2005) See: http://www.fda.gov/downloads/iceci/enforcementactions/enforcementstory/enforcementstoryarchive/ucm091066.pdf

[19] See for example In the Matter of Establishment Inspection of Wedgewood Pharmacy, 421 F.3d 263 (3rd Cir. 2005).

[20] See FDA's database on warning letters: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm

[21] *See*: Warning Letter (NEW-06-07W) from Gail T. Costello, Dist. Dir., New England Dist. Office, FDA, to Barry J. Cadden, Dir. of Pharmacy, New England Compounding Center (Dec. 4, 2006) and Letter from Barry J. Cadden, Dir. of Pharmacy, New England Compounding Center, to Compliance Officer, New England Dist. Office, FDA et al., at 1 (Jan. 5, 2007). *See* also: FDA Acting Director, Steven Galston testimony before the Senate Committee on Health, Education, Labor and Pensions hearing on the "Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients. October 23, 2003.

[22] Testimony of FDA Commissioner Margaret Hamburg before the House Subcommittee on Oversight and Investigations Committee On Energy and Commerce hearing on "The Fungal Meningitis Outbreak: Could it Have Been Prevented?" November 14, 2012.

Regulation of Compounding Pharmacies-State Role

State governments, typically through the state boards of pharmacy, have traditionally been the primary entities responsible for all pharmacy practices. It is the duty of the boards to enforce all the laws of the state that pertain to the practice of pharmacy and distribution of drugs. The state boards of pharmacy are also typically the entities responsible for establishing quality assurance and best practices for pharmacies and for examining, licensing, regulating and disciplining pharmacy practitioners. Typically boards are comprised of anywhere from 5-20 members appointed by the state's governor for a specified renewable term. Many boards set aside one or two seats designated for a public member with no pharmacy affiliation who represents the interests of consumers and patients.

Conducting inspections is typically the method that state boards of pharmacy utilize to determine whether pharmacies and pharmacists are in compliance with state regulations for the practice of pharmacy. The methods states use to employ inspections as a compliance tool varies widely. While some states perform routine surprise in-person inspections, other states rely on scheduled announced inspections, while still others primarily rely in whole or in part on pharmacy self-inspections. In a self-inspection, a pharmacy submits responses to a questionnaire on its compliance with laws and regulations. In some states, inspections are driven primarily by the receipt of complaints that warrant an investigation into pharmacy activities.

Historically, any federal regulatory role for the compounding pharmacy sector has been resisted by the industry. In 2007, when draft legislation was circulated to clarify the FDA's role in overseeing the safety of compounding pharmacies, it was immediately denounced by trade associations representing the sector.[23] The trade associations argued that "state boards of pharmacy have done a great job to write compounding standards…There's no way that the FDA will be equipped to handle this."[24] Compounding pharmacy trade organizations have in the past fought vehemently to ensure that pharmacy compounding remained the sole authority of the states, and even issued emails instructing its members what to say to deny FDA authorities access to facilities or samples from facilities that were compounding drugs.[25]

Post-NECC: Massachusetts and other State Actions

Following the NECC tragedy, Massachusetts Governor Deval Patrick put in place aggressive emergency regulations that required all sterile compounding pharmacies in Massachusetts to immediately and on bi-annual basis report the volume of prescriptions dispensed, states to which prescriptions were distributed and a certification that pharmacies were operating in compliance with all laws and regulations for sterile compounding. The Governor also appointed a special compounding oversight

[23] See: http://drugtopics.modernmedicine.com/drugtopics/Community+Pharmacy/New-bill-on-pharmacy-compoundingstirs-concern/ArticleStandard/Article/detail/414436
[24] See: http://drugtopics.modernmedicine.com/news/new-bill-pharmacy-compounding-stirs-concern
[25] Walt Bogdanich and Sabrina Tavernise. "U.S. Concern Over Compounders Predates Outbreak of Meningitis." *The New York Times* 23 October 23 2012 A1.

commission that proposed twenty-five additional compounding pharmacy safety measures, many of which were then filed as a legislative package.[26] The legislative package would require a special license for sterile compounding and out-of-state pharmacies, a reorganization of the board members and new authorization for the board to issue fines against pharmacies that violate state laws and regulations. The Governor also immediately hired temporary inspection staff and put in place an enhanced pharmacy inspection schedule that required unannounced inspections of all sterile compounding pharmacies.

Even before the recent fungal meningitis outbreak, in the state of Massachusetts any retail pharmacy that wished to specifically compound sterile injectable drugs[27] had to meet specific regulatory requirements with respect to its clean room facilities and were further expected, but not required, to obtain board of pharmacy approval. In Massachusetts there existed 26 such pharmacies that were known by the state to be producing sterile injectable drugs, including NECC and its sister company Ameridose. However, following the NECC incident, the state requested that pharmacies attest under penalty of law to the scope of its practice. In response to this request, 39 pharmacies,[28] out of a total of 1,179, self-identified as conducting sterile compounding. The Massachusetts Department of Public Health subsequently performed unannounced inspections of these pharmacies to see if they would identify similar issues to those discovered at NECC. These inspections revealed that only 4 were in full compliance with safety standards and required the state to issue 11 immediate full or partial cease and desist orders and 21 deficiency notices to sterile compounding pharmacies.[29]

Since other states have not undertaken such efforts publicly, it is unknown to what extent this rampant disregard for sterile compounding requirements holds true in other states. However, there are several states that have taken steps to increase enforcement activities relating to compounding pharmacies. For example, Iowa has initiated an effort in conjunction with the National Association of Boards of Pharmacy to inspect 600 out-of state pharmacies that ship medications into Iowa. The state of Mississippi adopted an accreditation process in November 2012 for certain sterile compounding pharmacies located in and out of the state.[30]Additionally, Arizona announced plans to establish a task force to determine any regulatory changes that need to be made. The state laws documented in this report are the laws and regulations in place as of November 2012 when states were sent the survey. In the wake of the NECC tragedy, several states, including Maryland, Massachusetts, California, Minnesota, New Hampshire, New Jersey,

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[26] See: http://www.mass.gov/governor/pressoffice/pressreleases/2013/0104-compounding-industry-legislation.html

[27] Note that this represents a subset of all sterile compounders in Massachusetts

[28] Two of these 39 pharmacies attested to either closing their operations or ceasing the practice of sterile compounding, leaving 37 self-identified as conducting sterile compounding. This number does not include NECC, Ameridose or Alaunus.

[29] Kay Lazar and Chelsea Conaboy. "Just 4 of 37 Massachusetts Compounding Pharmacies Passed Surprise Health Inspections" *The Boston Globe* 6 February 2013 online.

[30] In Mississippi, accreditation for sterile pharmacies excludes hospitals preparing sterile injectable drugs for use within 24 hours and pharmacies compounding these drugs for administration to institutional patients within 72 hours. Mississippi also put in place an accreditation requirement for non-sterile compounding pharmacies that compound more than 25 % of their total prescription volume.

Oklahoma, South Carolina, Utah, and Virginia have either introduced or passed new legislation or implemented new regulations placing additional restrictions on compounding pharmacies. These post-November 2012 announcements are not reflected in this analysis as most do not represent final enacted and implemented legislation and/or administrative changes.

Additionally, several states, including California, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, Oklahoma, South Carolina, Utah, and Virginia have introduced legislation to put stronger controls in place for compounding pharmacies, though to date, none of these legislative solutions have been adopted. It is also expected that additional states will be announcing changes in the coming months.[31]

Among many issues, the NECC tragedy highlighted the inability of states to oversee or manage compounding pharmacies that are located in another state, but that are shipping and selling drugs across state boundaries. In December 2012, the FDA convened a meeting of all 50 state boards of pharmacy to discuss the roles of state and federal entities in the oversight of compounding activities. At this meeting, the states discussed the fact that each state is dependant on other states to regulate pharmacies that are present in their state and this can be a "potential issue, if in fact, there are states that don't have sufficient funding (or) don't have the resources necessary to regulate facilities in their state" because this "can have an impact on every state."[32] A group of state boards present at the meeting expressed their opinion that for "facilities like NECC, there is a role for the FDA to be involved," while pharmacies that are conducting traditional compounding pursuant to a prescription sold only within state borders could be left to most states to adequately oversee. The National Association Boards of Pharmacy (NABP) shared this sentiment, stating that "there's a big disparity among the states in terms of the resources and expertise to regulate compounding" and that "the definition of compounding is that it's patient specific" and once you lose that patient specificity, "It's not a state regulatory issue. It's an FDA issue."[33]

> *"It's not a state regulatory issue. It's an FDA Issue."*
> *-National Association of Boards of Pharmacy*

A previous report issued by Rep. Markey's staff examined media reports, FDA's database of enforcement actions and state board of pharmacy websites and found that state pharmacy boards generally focus enforcement efforts on the types of activities typically associated with traditional pharmacy licensing, such as billing violations, failing to register with the state, failing to have a licensed pharmacist on site, and violations

[31] This report notes some of these pending state changes, but is not an exhaustive discussion. In many instances the policy positions are not final, and in others, states may have initiated such efforts but not reported them to Congressional requesters.
[32] FDA Framework for Pharmacy Compounding: State and Federal Roles. December 19, 2012.Transcript.
[33] February 1, 2013: NPR Diane Rehm Show: Safety Concerns at Compounding Pharmacies, Statement by Carmen Catizone, Executive Director of the National Association of Boards of Pharmacy.

related to the use and distribution of controlled substances.[34] The state boards' of pharmacy efforts are not typically focused on undertaking enforcement actions that relate to the safety or scope of compounding pharmacy practices. Furthermore, state enforcement records are typically not publically available, and when they are available the databases do not allow for keyword searches, preventing the public from easily locating enforcement records or infractions associated with particular pharmacies or medications. When states do keep this information in a public format, the details of the circumstances necessitating the enforcement action is typically lacking, making the information generally useless to a member of the public.

This report summarizes a more extensive investigation into the state oversight of compounding pharmacies, launched to get a better understanding of the information that is maintained internally by state boards of pharmacy, the oversight of pharmacy practices and the actions that states have taken historically to ensure the safety of compounding pharmacies and the products they sell.

[34] October 29, 2012 Compounding Pharmacies, Compounding Risk. See: http://markey.house.gov/press-release/new-markey-report-reveals-current-outbreak-least-23-deaths-86-serious-illnesses

INVESTIGATION AND METHODOLOGY

To better understand the role that state boards of pharmacy play in managing the oversight of compounding pharmacies and protecting against another NECC-like tragedy, on November 20, 2012, Reps. Markey, Waxman, Dingell, Pallone and DeGette sent a letter to the boards of pharmacy in all states, territories, and Washington, DC requesting answers to six questions that asked for historical information about compounding pharmacies, pharmacy licensing, inspections of pharmacies, and pharmacy board budgets, as well as information about the structure and policy governing the board (See Appendix C). The questions were designed to examine the degree to which individual states are capable of overseeing the safety of compounding pharmacy practices and enforcing against the type of safety related matters raised by the New England Compounding Center.

With the exception of Rhode Island, Guam, Puerto Rico and the U.S. Virgin Islands, we received a response from all of the state boards of pharmacy queried. When particular responses were incomplete, staff followed up with the board of pharmacy to obtain this information. While a number of states do not have the capacity or system requirements to keep or review historical data, or in some cases simply do not track this information, the states attempted to respond to all questions, providing estimations or projections in areas where hard data was not available or retrievable. Presented below is a summary and analysis of the information provided by the state boards of pharmacy. Additional analysis and findings can be found in Appendix A. Appendix B contains a table that summarizes all state boards of pharmacy responses.

FINDINGS

1. **State boards of pharmacy generally do not know which pharmacies engage in compounding, do not know whether pharmacies ship compounded drugs across state lines, and do not know which pharmacies manufacture large quantities of compounded drugs. In many cases, states are incapable of even providing accurate information regarding the numbers of registered pharmacies in their states.**

To gauge the ability of states to track compounding activities, the state boards were asked to provide information about the number of licensed compounding pharmacies, pharmacies licensed for sterile compounding and pharmacies that sell high volumes of compounded drugs, or sell across state lines.

Key Findings:

- *No state boards require disclosure of volumes of compounded drugs or whether compounded drugs are sold across state lines*
- *Only two states (MO and MS) routinely track the number of compounding pharmacies in their state*
- *Only 32 states were able to provide historical data on the number of licensed pharmacies in their states*

The vast majority of states allow any pharmacy to compound without a specific compounding license or permit. Forty-seven states and the District of Columbia were unable to provide an exact number of pharmacies that are authorized to compound in the state (See Table 1). Only Missouri and Mississippi require a license or permit for basic drug compounding.

In Mississippi, over the last decade, 102 pharmacies have received specific permits designating them as compounding pharmacies by the Mississippi board of pharmacy. This number does not, however, take into account pharmacies that are no longer in operation, or that simply choose to no longer offer compounding services. Furthermore, because Mississippi does not issue specific permits for facilities engaged in sterile compounding, it's impossible to discern how many of the 102 compounding pharmacies may also be compounding complex and risky sterile drug products.

Missouri's board of pharmacy employs a fairly sophisticated licensing system, which provides different permits for different classes of licensed pharmacies (i.e. internet, veterinary, renal dialysis, etc). In Missouri, all 1,570 pharmacies authorized to dispense medication may perform traditional pharmacy compounding without additional licensure, however the state requires a specific non-sterile compounding permit for pharmacies performing batch compounding from bulk ingredients. Additionally, a sterile compounding permit is required for facilities wishing to engage in sterile compounding activities. In the state of Missouri, 442 pharmacies, approximately one-third of all in-state pharmacies, hold specific permits for compounding both non-sterile drugs from bulk ingredients and for sterile drugs—however, any pharmacy could perform simple compounding services without notifying the state.

None of the states indicated that they track whether pharmacies are selling compounded drugs across state lines, or the volume of compounded drugs that are being produced by a facility.

TABLE 1: STATES THAT PROVIDED INFORMATION ON THE NUMBER OF COMPOUNDING PHARMACIES

STATE	# licensed in-state pharmacies in most recent year provided	# compounding in-state pharmacies	# in-state sterile compounding pharmacies
AR	755	21*	State does not track
ME	335	3*	State does not track
MO	1,570	442	Did not provide separate number of sterile compounding pharmacies.
MS	1,678 permits issued in the past 10 years	102	State does not track
OR	728	81*	State does not routinely track, but based on inspection records is aware of 11 pharmacies that do sterile compounding and also hold non-resident licenses

*Estimated based on disclosure on initial license application and/or annual renewal. Additional pharmacies may compound without notice.

While Mississippi and Missouri were the only states that indicated the requirement for a specific permit or license to track certain compounding activities, three additional states (Arkansas, Maine, and Oregon) ask that pharmacies indicate on their initial license application whether they intend to engage in compounding activities (See Table 1). Using this information, Maine was able to identify 3 pharmacies and Arkansas 21 pharmacies that provided such an indication. In addition, Oregon, which asks pharmacies to indicate whether they engage in compounding both on the initial license application and on annual renewals, identified 81 compounding pharmacies. It is important to note, however, that in all of these states any pharmacy is authorized to engage in compounding regardless of whether it indicated this intent on their license applications. One additional state, Minnesota, indicated that recent regulatory changes require pharmacies to notify the board and receive approval before they engage in compounding sterile or non-sterile products of any type. However, the state did not indicate how many such pharmacies have self-identified as compounders since this change in state law was implemented.

Several states noted that pharmacies engaging in high-volumes of compounding would trigger the requirement for a manufacturer's registration, as this would be beyond the scope of a state-licensed compounding pharmacy and would instead fall under FDA's jurisdiction. However, it is unclear how any state would know whether this requirement was triggered, as no state indicated that they routinely request information from pharmacies about quantities of compounded drugs or whether such drugs are shipped across state lines as a part of their license or registration.

2. <u>Only thirteen state boards of pharmacy know which pharmacies are providing sterile compounding services and only five of these states have inspectors that are trained to identify problems with sterile compounding.</u>

While most states allow any pharmacy to compound without requiring a specific compounding permit or license, a few states have specific requirements for pharmacies that intend to compound sterile drugs. Sterile drugs are more difficult to produce than other drugs and pose significant health threats if improperly produced.

Including Massachusetts, which even prior to NECC had a clean-room approval process in place for pharmacies that were producing sterile injectable drugs, there were a total of only 13 states (26% of respondents) that were able to provide some estimate as to the number of currently operating sterile compounding pharmacies. Only 5 out these 13 states (ID, NJ, NV,OK and TX) specifically track all pharmacies that perform sterile compounding activities (See Table 2).

Key Findings:

- *37 state boards of pharmacy (74% of respondents) do not routinely track which pharmacies are providing risky sterile compounding services*
- *Only 19 state boards of pharmacy provide their inspectors with special training to identify problems with sterile compounding*

- Oklahoma requires in-state retail pharmacies that perform sterile compounding to receive a specific permit and currently has 88 pharmacies permitted to provide these services.
- Alabama requires pharmacies that are compounding preparations for parenteral or intravenous (IV) administration to have a separate certification. Currently there are 103 institutional hospitals and 67 chain and community pharmacies that have parenteral certification. This does not include pharmacies that compound other sterile products whose administration is not through injection.
- Connecticut currently has records of 17 sterile pharmacies, but this doesn't include any hospital pharmacies, which are assumed to be undertaking some sterile compounding.
- As of March 2012, Idaho requires any pharmacy that is engaging in sterile drug preparation to obtain a registration for aseptic environmental control devices, such as laminar flow hoods. Currently, Idaho has provided 77 such registrations, each of which requires an onsite inspection by the board of pharmacy prior to producing sterile drugs.
- While New Jersey doesn't require specific permits or licenses for compounding activities, it does have regulations that require pharmacies to notify the board in advance of compounding sterile preparations. Once notified, the New Jersey board inspects the facility to ensure compliance with regulations related to sterile compounding and then grants approval for the pharmacy to engage in such operations. New Jersey estimated that they have 41 sterile compounding pharmacies.
- California has the second highest number of registered in-state pharmacies (6,761 pharmacies), 266 of which are board-licensed for sterile compounding. However,

this number is likely to be a significant underestimate, as pharmacies that are accredited by outside agencies are allowed to perform sterile compounding without additional licensure with the California board of pharmacy.

- The remainder of the 37 states that responded do not systematically track which pharmacies are providing sterile compounding services. The lack of information makes it impossible for pharmacy boards to target enforcement and inspection efforts towards the highest-risk pharmacy operations and appropriately oversee their safe operation.

TABLE 2: ONLY THIRTEEN STATES ARE ABLE TO DETERMINE THE NUMBER OF PHARMACIES THAT PERFORM STERILE COMPOUNDING

STATE	# licensed in-state pharmacies in most recent year provided	# in-state sterile compounding pharmacies
AL	State does not track	103 institutional hospitals and 67 chain and community pharmacies with parenteral certification
CA	6,761	266 board licensed sterile pharmacies*
CT	670	17 sterile compounding retail pharmacies, not including hospitals
DE	157	State does not track but knows of one sterile facility other than hospitals
IA	1,510	51** sterile compounding retail pharmacies, not including hospitals
ID	445	77
MA	1,179	39^
NJ	2,835	41
NV	709	22**
OK	910	88
TX	6,509	652
VA	1,762	159**
WA	1,425	State does not license, but based on inspections there are 19 pharmacies focusing on parenteral products

*Additional accredited sterile compounders exist, but do not require licensure with the board.
**Any pharmacy could provide sterile compounding services; sterile compounding pharmacies are estimated based on inspection or other information.
^ Represents all sterile compounding pharmacies that self-identified following the fungal meningitis outbreak. Only 4 were found to be in full compliance of safety standards following unannounced inspections.

A previous analysis of state inspection and enforcement records issued by Rep. Edward J. Markey[35] found that state boards of pharmacy do not, as a general rule, undertake enforcement actions that relate to the safety or scope of compounding pharmacy practices. Instead the boards tend to focus efforts on compliance with traditional pharmacy licensing and use of controlled substances. As a result most enforcement actions taken by boards appear to deal with issues such as whether technicians have completed appropriate training hours, appropriate intern supervision by licensed pharmacists, valid and updated registration and licensing documentation and valid distribution of controlled substances.

The survey results indicated that only 19 states (38% of respondents) provide some or all of their inspectors with special training in sterile compounding activities and regulations (See Table 3). An additional 9 states (CA, IA, IL, KS, MN, MT, NE, UT, and WY) indicated that while there is no special inspector training in compounding or sterile operations, some or all of the inspectors employed by the state are licensed pharmacists and therefore are expected to have basic knowledge of sterile and non-sterile compounding operations.

TABLE 3: STATES WITH INSPECTORS TRAINED IN STERILE COMPOUNDING

STATE	# Inspectors Trained in Sterile Compounding Operations in Most Recent Year Reported
AR	3 inspectors and 2 directors involved in investigations and inspections
CO	3
FL	18
GA	14
IN	6
KY	5
LA	5
MD	6.5 full-time pharmacists and 4 technicians split between 2 agencies
MI	5
MO	8
NC	9
ND	2
NJ	7 + 2 part-time inspectors
NM	5
NV	5*
OK	5
TX	7
VA	4
WV	5

*Only a portion of the inspectors receive training

[35] Compounding Pharmacies, Compounding Risk; issued October 29, 2012. See: http://markey.house.gov/press-release/new-markey-report-reveals-current-outbreak-least-23-deaths-86-I serious-illnesses

A few states indicated that after learning about the NECC tragedy, the boards have or are in the process of reevaluating their inspection procedures and developing training specific to sterile compounding for inspectors. For example, Alabama indicated that it is contracting with a consultant to establish particular inspection protocols and training. Additionally, Nebraska and Virginia indicated that it has required inspectors to complete online training in compounding and will provide additional on site training. Mississippi also noted that while state inspectors have limited training in inspecting sterile compounding procedures, they will perform in depth inspections with assistance of inspectors from FDA or the Drug Enforcement Administration (DEA).

3. States typically do not maintain pharmacy inspection records that enable them to identify systemic or repeated compounding pharmacy safety problems that originate either in-state or out-of-state.

States were asked to indicate whether they have over the last decade, during the course of an inspection or other oversight activity, identified the kinds of problems that were found at NECC, namely issues with contamination, cleanliness, drug potency, drug safety, bulk manufacturing or other similar concerns. Many states (22 states or 44% of respondents) either do not keep historical records of inspections, or do not track problems relating to compounding. Other states used a combination of inspection records, public complaints and "staff recollections" and were able to indicate a sample of noted problems or disciplinary actions taken against in-state compounding pharmacies due to safety related problems similar to those identified at NECC.

Key Finding:

- *22 state boards of pharmacies do not keep any historical inspection records for compounding pharmacies*

States reported a total of 2,682 disciplinary actions taken or concerns raised against compounding pharmacies in all 49 states and DC over the last decade. These 2,682 compounding concerns or actions pertained to issues of unsafe storage, compounding copies of commercially available drugs, compounding without a prescription, issues with potency, problems with sterility, use of improper ingredients, and manufacturing large quantities of drugs outside the scope of a pharmacy license It is unclear how many of these compounding-related concerns were evaluated by the boards or rose to the level of formal disciplinary action, as states do not routinely track this information.

Furthermore, because many states do not keep inspection histories, have limited access to details of inspection records, keep them only in an unsearchable paper format, or for a limited timeframe the number of compounding issues reported by the states is likely severely underestimated. These record-keeping practices would make it difficult to determine whether there are particular pharmacies that have a history of violating the law.

As previously indicated, enforcement actions taken against compounding pharmacies are not always publically available on state websites, and when available do

not always contain sufficient information for the public to understand the nature of the violation in question, making it impossible for consumers to determine whether a particular facility has had prior safety issues with compounding drugs.[36] When comparing the actions that are disclosed on state websites, and that were analyzed in a previous report,[37] to those disclosed by the states in response to this survey, none of the states reported in their response all of the actions that were listed on their own websites or in media reports. This calls into question the completeness of the states' online databases and their internal record-keeping systems.

4. <u>States are unable to effectively police compounding pharmacy activities in other states.</u> <u>Moreover, when issues arise with out-of-state pharmacies, states do not consistently inform the origination state or the FDA.</u>

Problems with compounded drugs originating from out-of-state pharmacies are common. Nineteen states (38% of respondents) identified 224 issues arising from compounding pharmacies located in other states in the past 10 years. These issues ranged from consumer complaints about potency or safety to discoveries that pharmacies were selling copies of commercially available drugs or distributing samples to medical facilities within the state. In many cases, pharmacies located out-of-state were reprimanded for selling drugs in a different state without the appropriate license or registration. Since three states do not have a requirement for out-of-state pharmacies to be licensed to sell drugs within their state, these states would have no way of even knowing that these sales were occurring.[38] Many state boards indicated frustration with the lack of control they have over pharmacies located in another state and the absence of a formal mechanism for boards to know about safety related or other issues that arise with out-of-state pharmacies. Please see Table 4, but what follows are highlights from these findings:

Key Finding:

- *There is no formal mechanism for state boards to know about issues with out-of-state pharmacies*

- The majority (144 out of the 223 or 65 %) of the concerns about out-of-state pharmacies were reported by Iowa, of which just 20 rose to the level of formal disciplinary action.
- North Carolina reported 37 concerns with out-of-state pharmacies. These North Carolina concerns included drugs being linked to several meningitis cases, compounding pharmacies sending samples of drugs directly to medical professionals, pharmacies compounding commercially available drugs and drugs

[36] Compounding Pharmacies, Compounding Risk; issued October 29, 2012. See: http://markey.house.gov/press-release/new-markey-report-reveals-current-outbreak-least-23-deaths-86-serious-illnesses

[37] Ibid.

[38] Three states (Massachusetts, Georgia and Pennsylvania) do not require out-of-state pharmacies to hold a license within their state. Following the NECC linked fungal meningitis outbreak, the Governor of Massachusetts filed legislation to make several reforms, including a requirement that all non-resident pharmacies be licensed and subject to the regulations of the board of pharmacy.

that are not approved for human use and out-of-state pharmacies dispensing drugs in the state of North Carolina without a non-resident pharmacy permit.

- The state of Missouri, which has taken 3 public disciplinary actions against known compounding pharmacies in the last decade issued a cease and desist order to NECC in 2002, but did not indicate the reason for this disciplinary action.
- The state of Colorado also issued a cease and desist order to NECC in 2011, when it was discovered that NECC was manufacturing drugs and shipping them to a hospital pharmacy in violation of Colorado law. At the time, this action was reported to the National Association of Boards of Pharmacy (NABP), the Drug Enforcement Agency (DEA) and FDA, but apparently not directly to the Massachusetts board of pharmacy. When in 2012 the same problem was discovered, Colorado's board of pharmacy notified both the FDA and the Massachusetts board of pharmacy. This second notification occurred approximately two months before the first patient who contracted meningitis from NECC was discovered.

The remaining 31 responsive states indicated that prior to NECC, they were never made aware of a problem with an out-of-state pharmacy or simply did not track this type of information. Even in cases where there was an identified problem related to an out-of-state pharmacy the direct communication between state boards is limited, as most states never notify other state boards about problems discovered within their borders, even if the pharmacy in question is located in another state. As a result, a state may discover a serious problem with the drugs produced by a pharmacy located in another state, take an action to stop that pharmacy from shipping drugs into its state, but never notify the home state or any other state about the drug safety problem identified. Instead states typically report issues with pharmacies to NABP, and typically this reporting only occurs when the problem is investigated and rises to the level of a formal public disciplinary action. A few states mentioned that they do not report to NABP because they do not share their enforcement activity with non-government entities. Therefore, even NABP would not be a comprehensive source for problems identified at compounding pharmacies

States also tend to report formal disciplinary actions against pharmacies to the National Practitioner Data Bank (NPDB) and the Healthcare Integrity and Protection Data Bank (HIPDB), the two federal data banks that have been created to serve as repositories of information about health care providers in the United States. Federal law requires that adverse actions taken against a health care professional's license be reported to these data banks. Once reported to these various entities, however, there does not appear to be any systematic manner in which other states are notified of these issues so that they can take proactive action to protect state residents from being harmed. Moreover, these data banks only make individual reports available to the state boards upon request and for a fee.[39] Based on survey results, the only time states seem to routinely inform the FDA about problems with out-of-state pharmacies is when the pharmacy has produced a drug which has caused the death of one or more people.

[39] Informal communication with Massachusetts Department of Public Health.

TABLE 4: STATES WITH INFORMATION ABOUT COMPOUNDING CONCERNS ORIGINATING OUT-OF-STATE IN THE LAST DECADE

STATE	# Out-of-state Compounding Concerns or Actions	Nature of Concern	Who was Informed
OR	1	Texas Pharmacy sent drugs that were 10 times as potent as indicated on the label, resulting in 3 deaths. The pharmacy was not licensed in Oregon as an out-of-state pharmacy	This particular out-of-state case was investigated by the FDA and Texas BOP
NH	1	Accepted a voluntary license surrender from Infusion Resource located in Massachusetts, based on action taken by FDA and Massachusetts BOP on November 16, 2012	No one
NJ	1	An out-of-state pharmacy notified the NJ Board that they were subject to a disciplinary action as a result of a compounding error in the pharmacy's home state	No one
ID	1	Mail order of invalid prescription drug orders	State of Utah where pharmacy was located
OK	1*	Pharmacy violated state rules by sending sterile drugs to physician's office for patient pick up	NABP
KS	1	Pharmacy operating without out-of-state registration	The state where the pharmacy was located
GA	1	Selling drugs to an unlicensed facility without prescriptions	Alabama, where pharmacy was located
NY	1**	Pharmacy dispensed contaminated products. Under investigation so details not provided	Unknown
FL	1	Not indicated	No one
NV	2	Compounding a controlled substance without proper in-state registration and selling adulterated drugs	1 case, the State of pharmacy origin was notified. The other case was under CDC and FDA investigation
MN	3	2 unlicensed out-of-state pharmacies and another where an unregistered pharmacy was selling whole sale	The states of origin
LA	3	1 expired in-state permit, 2 pharmacies with histories of adverse events in other states.	NABP as notified in 2 instances
TN	3	1 pharmacy was investigated, but revealed no violation and was dismissed. 2 pharmacies were engaging in manufacturing or wholesaling without licensure	HIPDB and NPDB

TABLE 4: STATES WITH INFORMATION ABOUT COMPOUNDING CONCERNS ORIGINATING OUT-OF-STATE IN THE LAST DECADE (CONTINUED)

STATE	# Out-of-state Compounding Concerns or Actions	Nature of Concern	Who was Informed
MO	3	Not indicated	NABP, NPDB and HIPDB. The board may also provide FDA or state notification when appropriate
WY	6	1 pharmacy was compounding a commercially available drug. 2 pharmacies were operating without a WY license. 1 pharmacy didn't label compounded product for delivery in cold weather. 1 pharmacy had a compounding error. 1 pharmacy was selling a compounded product to a pharmacy for resale.	In 2 of these cases FDA was made aware. In the other cases no was notified
CO	5	1 pharmacy was shipping into the state without a nonresident pharmacy license. 2 pharmacies (one of which was NECC, which was cited twice) were selling manufactured drugs to a hospital pharmacy.	In each case different entities were notified (NABP, HIPDB, state of origin, FDA and DEA)
CA	9	Only one was investigated based on information from another agency. This one example involved Franck's pharmacy which was dispensing contaminated drugs.	N/A
NC	37*	25 pharmacies were shipping without an in-state license, 1 pharmacy had compounded drugs leading to several cases of meningitis, 1 pharmacy was issuing samples, 2 pharmacies were providing drugs for resale by pharmacies, 2 pharmacies were improperly distributing hormone products, 1 pharmacy was dispensing without prescriptions, 3 pharmacies improperly compounded drugs, 1 pharmacy mislabeled drugs, 1 pharmacy compounded a copy of a commercially available drug	In some cases the home state where the pharmacy was located was notified
IA	144	Nature of the issues was not provided, 20 disciplinary actions were taken and several are still pending.	disciplinary actions are typically reported to NABP and HIPDB

*Information was provided for a more limited 6 year period.
**State did not provide historic information, just one pending action.

5. <u>Despite general increases in state board of pharmacy budgets, the number of pharmacy inspectors has remained consistently low. Furthermore, states usually do not distinguish between inspections of traditional and compounding pharmacies.</u>

State boards of pharmacy were queried on their historical operating budgets. Forty-six percent of the respondents (23 out of 50 boards) were either unable to provide any information on budgets or were only able to provide data for a more limited time frame than the ten year interval that was requested, citing lack of easy access to historical information. Nine of these states[40] (18% of respondents) were unable to provide any indication of their operating budget, because the board of pharmacy does not manage its own budget; rather it falls under an umbrella agency that consolidates the budget for all medical and professional boards and manages the expenditures for each board in the state.

Even when factoring in the increase in licensed pharmacies over the last decade, budgets for state boards have generally increased. However, the budgetary constraints vary widely between states. For example, Nevada currently has a pharmacy board operating budget that provides for approximately $3260 per pharmacy for which the board is responsible for inspecting, while Indiana's board of pharmacy has an operating budget that provides for approximately $173 per pharmacy.

Key Findings:

- *On average states employ just 5 inspectors with responsibility to inspect all pharmacies.*
- *Only 5 state boards of pharmacy were able to provide an estimation of the number of inspections occurring at compounding pharmacies.*

While state pharmacy budgets have modestly grown over the last decade, several recent comments made by state boards of pharmacy representatives[41] and industry indicated that wide-spread budgetary constraints limit board oversight activities.[42] The difficulty of many states to access data needed to respond to this survey in a timely manner and the inability of many states to track compounding activities in their state does call into question whether state budgets are allowing for the type of oversight that is necessary to ensure the safety of these drugs and the protection of public health.

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[40] States with boards of pharmacy that fall under a consolidated umbrella agency: Connecticut, Delaware, Georgia, Hawaii, Michigan, New York, Utah, Vermont, Virginia. Wisconsin also falls under an umbrella agency, but was able to provide an estimate of its budget.

[41] For example, informal communications between some state board of pharmacy contacts and Rep. Markey's staff indicated that states with consolidated professional boards and those who rely on annual state appropriations for their budgets have a difficult time with securing the resources needed to adequately oversee the full range of licensed entities, while independent boards funded directly via pharmacy licensing fees typically have more budget stability

[42] See: December 19, 2012: FDA Framework for Pharmacy Compounding: State and Federal Roles. Statement by Dr. Cody Wiberg, Minnesota Board of Pharmacy. February 1, 2013: NPR Diane Rehm Show: Safety Concerns at Compounding Pharmacies, Statement by Dr. David Miller of the International Academy of Compounding Pharmacists.

Even with increasing numbers of pharmacies and general increases in board of pharmacy budgets, on average states employ just 5 inspectors per state, with the most inspectors being utilized in California-30, Ohio-22, Florida-18 and Georgia-14 and the fewest being utilized in Alaska-1, Vermont-1, Hawaii-1, and Wyoming-1.5. These inspectors are responsible for inspecting all pharmacy activities, and based on survey results, the average number of 5 inspectors has stayed fairly consistent over the last decade. In several cases these inspectors are also split between the board of pharmacy and other professional licensed boards and are responsible for inspecting and investigating all such facilities (for example, dental and medical facilities or other drug distribution facilities including wholesalers) that fall under their purview. For example, the state of New York indicated that it has 58 inspectors that are responsible for oversight of 50 different professions ranging from elementary educational institutions to pharmacy practice. Many states increasingly rely on pharmacies to conduct and submit self-inspections. While some states have policies that require all pharmacies to be inspected once a year or every other year, other states only inspect when they receive a complaint about a particular pharmacy or when a pharmacy first receives its license or permit.

States do not typically track inspections of compounding pharmacies, implying that inspections of entities that engage in riskier compounding behavior such as NECC would not be more likely to be inspected than a traditional pharmacy. There were only 5 states (California, Maryland, Nevada, New Jersey and New Mexico) that were able to provide some indication of the number of inspections that occurred at compounding pharmacies (a total of 404 compounding pharmacies or 7 percent of the total number of inspections) (See Table 5). However, in all of these states any pharmacy can engage in compounding, so the data provided are not considered to be fully inclusive of compounding activities. Since the problems were identified at NECC, Massachusetts enhanced the frequency of its inspection schedule, conducting unannounced inspections of all 37 sterile compounding pharmacies[43] in the state between November 2012 and the end of January 2013.

TABLE 5: STATES THAT PROVIDED DATA ON THE NUMBER OF INSPECTED COMPOUNDING PHARMACIES

STATE	# full-time inspectors	# licensed pharmacies in most recent year provided	#inspections in most recent year provided	# compounding inspections in most recent year provided
CA	30	6,761	2,248	231
MD	10.5	1,819	1,676	106
NJ	7 + 2 part time	2,835	1,026	38
NM	5	283	158	7**
NV	5	709	587	22

* 6.5 pharmacists and 4 technicians split between the Maryland Board of Pharmacy and Division of Drug Control
**indicated that compounding areas within retail pharmacies would be evaluated as a part of routine inspections.

[43] There were 39 sterile compounding pharmacies in Massachusetts, but 2 of these ceased operating as sterile compounders, leaving 37 subject to inspections.

APPENDIX A

ADDITIONAL FINDINGS

1. **Over the last decade, forty-seven state boards of pharmacy have seen an increase in the number of licensed pharmacies, but the lack of historical records makes it difficult for most states to accurately track the sector's growth**.

As a part of the survey, the state boards of pharmacy were asked to provide historical data on the number of licensed pharmacies each year for the last decade. Because of limitations in the way several states maintain records or collect data, there were only 32 states (64% of states) that could provide this information in full. Five states were able to pull responsive records that dated back a more limited timeframe (4-9 years). The remaining 13 states (26% of states) either did not maintain information on the number of licensed pharmacies or could not access this information without a significant time and resource commitment that the state was unable to expend.

According to the survey results, the number of pharmacies in any given state typically increased over the last decade, with the greatest increase happening in the state of Florida where 2,144 new pharmacies opened over the last decade. Florida was followed in rate of growth by Texas, which opened 1,045 new pharmacies. Florida is also the state which currently has the most licensed operating pharmacies (8,868 pharmacies) followed by California (6,761 pharmacies) and Texas (6,509 pharmacies). In contrast, the states with the fewest licensed pharmacies were New Mexico (34 pharmacies), Vermont (146 pharmacies) and Washington, DC (150 pharmacies). There existed only 3 states (Nebraska, Louisiana, and Oregon) where the number of licensed pharmacies decreased over the last decade, with Oregon losing the most pharmacy operations (149 pharmacies), from 877 in 2003 to 728 pharmacies in 2012.

In total there were approximately 68,000 licensed pharmacy facilities disclosed by the states. However, given poor records kept by states, the fact that some states do not differentiate in their records between in-state and out-of-state pharmacies, and the fact that some states track pharmacies alongside other facilities that dispense drugs, such as distributers and wholesalers, it is impossible to know how accurate this figure is of operating retail and hospital pharmacies in the U.S. Typical estimates made by other industry trade associations place the number of community based retail pharmacies in the U.S at about 56,000.[44]

[44] http://www.iacprx.org/displaycommon.cfm?an=1&subarticlenbr=277

2. Regional inconsistencies caused by different case law rulings on the applicability of the 1997 federal pharmacy compounding law have had no apparent impact on the state boards of pharmacy or on the oversight of compounding pharmacies in the Fifth or Ninth Circuits.

In 1997, Congress enacted the FDA Modernization Act of 1997 (FDAMA) that added a section to FDA law, which exempted compounded drugs from various "new drug" requirements, as long as the compounded drugs met a variety of restrictions. One of the restrictions was that drug providers were prohibited from soliciting or advertising particular compounded drugs. These speech restrictions were challenged on First Amendment grounds and were struck down by the Supreme Court.

Following this decision, there was controversy over the current status of compounded drugs under the FDA law and whether the remaining provisions that set up standards for compounded drugs remained in affect. The two circuits that addressed this issue took different positions. While the Ninth Circuit determined that the section of law that governed compounding was struck down in its entirety, the Fifth Circuit found that the provisions that didn't deal with speech restrictions are still in effect. Accordingly, these cases have created an interesting scenario of non-uniform federal law throughout the U.S. In the Fifth Circuit, compounded drugs are specifically exempted from having to apply as a new drug, complying with good manufacturing practices, and certain labeling requirements, as long as certain criteria are met; while in the Ninth Circuit, compounded drugs are subject to all of these requirements that apply to manufactured drugs, but the FDA may exercise discretion in taking action against an entity that violates these provisions.

We compared the states that fall within the Fifth circuit Court's jurisdiction (Texas, Louisiana, and Mississippi) to some of the Western states that fall under the Ninth Circuit Court's jurisdiction and found that there were no significant differences in the composition of the boards, the maintenance of historical records, the number or presence of trained inspectors, or the systematic tracking and oversight of compounding pharmacies (See Appendix Table 1).

APPENDIX TABLE 1: COMPARISON OF RESPONSES FOR STATES IN THE FIFTH CIRCUIT COURT JURISDICTION (TX, LA, MS) TO THOSE IN THE NINTH CIRCUIT COURT JURISDICTION (OR, NV, CA)

STATE	# Compounding pharmacies in most recent year	# Sterile compounding pharmacies in most recent year	Specific rules for sterile compounding pharmacies	Inspector training in sterile compounding	# Inspectors in most recent year reported	# Licensed in- state pharmacies (# pharmacies inspected)	# Licensed pharmacies increased or decreased over last decade (by this #)	Reported operating budget	# Board members
TX	State does not track	652	Yes	Yes	7	6,509 (2,140)	Increased (1,045)	$3,717,335 (2003) $6,202,645 (2012)	9 (3 public members)
LA	State does not track	State does not track	Yes	Yes	5	1,758 (793)	Decreased (60)	$1,170,252 (2003) $2,645,000 (2012)	17 (1 public member)
MS	102	State does not track	No*	No	6	Not indicated (1,559)	Provided only number of 1,638 new permits issued in past decade	$1,191,615 (2004) $2,026,913 (2013)	7 (0 public members)
OR	81**	State does not track	Yes	No	5	728 (728)	Decreased (149)	$2,358,405 (2001-2003) $6,130,811 (2013-2015)	7 (2 public members)
NV	State does not track	22 (based on inspection records)	Yes	Some inspectors	5	766 (587)	Increased (310)	$1,400,000 (2003) $2,500,000 (2012)	7 (1 public member)
CA	State does not track	266	Pharmacies that compound sterile injections require licensure or accreditation from an approved agency	No	30	6,761 (2,248)	Increased (623)	$7,390,000 (2003) $14,200,000 (2012)	13 (6 public members)

*Post-NECC the board adopted a new policy requiring accreditation of sterile compounders.
**Any pharmacy is permitted to compound, numbers estimated based on information provided in application and renewal forms.

3. <u>All state boards of pharmacy have similar structures and methods to deal with potential conflicts of interest, such as when there is a financial relationship between a pharmacy that is up for disciplinary action and a board of pharmacy member.</u>

The states were surveyed to get a better understanding of the structure of the state boards of pharmacy. The number of board members varies from 5-17 members, with an average of 8 board members that are typically appointed by the governor, either directly or with input provided by nominations, for a renewable term limit.[45] All boards are composed of licensed pharmacists, with some states requiring that the pharmacists represent various sectors of the industry, such as chain pharmacies or hospital pharmacies, and additionally may require that some board members are pharmacy technicians or other medical professionals. With the exception of Mississippi, every state has a requirement that board members include at least one public member who is intended to represent the consumer perspective. This public member is typically required to have no past or present affiliation with or financial interest in the practice of pharmacy.

In Mississippi and California the boards are comprised of 11 and 13 members, respectively, and include just one more pharmacist than public members, making these the states with the most public representation. In California, two of the public members are appointed by the Senate Rules and Speaker of Assembly, and the remaining members of the board are appointed by the Governor. Additionally, three states (Arkansas, Florida and Tennessee) require that a member of the board be elderly, usually defined as over the age of 60, and in Arkansas and Tennessee, the laws require that board members include one racial minority member. In Arkansas, this racial minority member must be a licensed pharmacist.

With the exception of Alabama, all states have some policy to deal with conflicts of interest that arise within the board. Typically this policy involves recusal that is either voted on by the board, decided upon by the state Attorney General or other legal counsel, or occurs automatically upon member disclosing an actual or perceived conflict. Several states also require the board members to provide a financial disclosure that is evaluated by legal counsel to proactively identify conflicts of interest. In many cases the financial disclosure and perceived conflict policies extend to a board member's spouse and immediate family.

While many of the conflict of interest policies require forthrightness of the board members, Washington State has a unique method to proactively avoid conflicts of interest impacting board member decisions. In Washington, any complaints that are handled in a prosecution case are de-identified and only one member of the board knows the identity of the entity that is being prosecuted, leaving board members to decide based purely on the merits and facts of the case. Additionally, any potential conflicts are screened by the Attorney General's office and state executive ethics board and until a decision is made about the conflict, the member in question is barred from participation in that matter.

[45] New York Regents Board appoints the Board of Pharmacy members, New Hampshire State Board of Health appoints its Board members.

Additionally, in Utah, conflicts are proactively investigated prior to appointment to the board, and if any conflicts arise during service, they constitute grounds for removal from the board.