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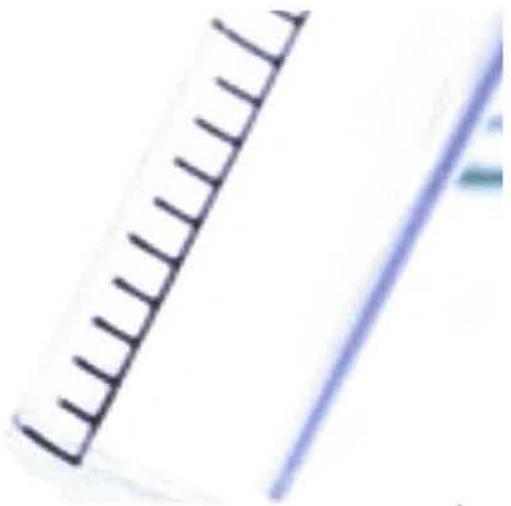
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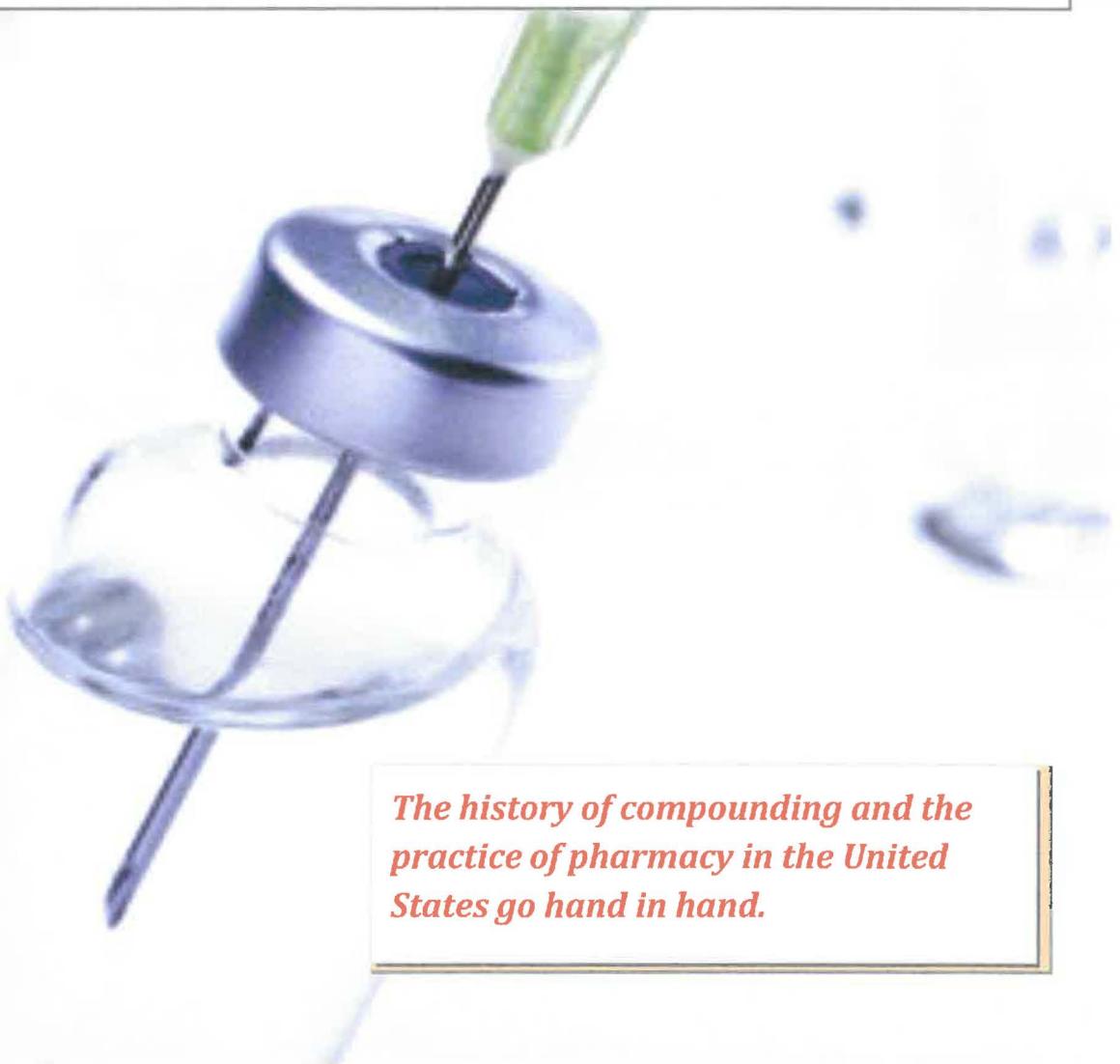
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## Sterile Compounding: Regulations Addressed After the Meningitis Outbreak of 2012

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## **Background**

With the news of the fungal infection outbreak among patients receiving tainted preparations of methylprednisolone acetate injections, compounding pharmacies have found themselves thrust into the spotlight. Prepared by the New England Compounding Center (NECC) in Framingham, Massachusetts, the contaminated injections have spurred the largest health care associated fungal outbreak in the United States.<sup>1</sup> This tragedy has caused many to focus their attention on pharmacy practice, the safety of pharmaceuticals and the current regulations in place to protect the public.

The history of compounding and the practice of pharmacy in the United States go hand in hand. Since the eighteenth century, 'druggists' were responsible for both the preparation and the dispensing of medications.<sup>2</sup> During this time the preparation of medication remained largely unregulated by the federal government with inconsistencies in the compounded medication and techniques.<sup>2</sup> With the end of World War II, a growth in the drug manufacturing companies took place, and medications prepared by traditional compounding pharmacies declined.<sup>3</sup> However, in recent years, a resurgence of compounding specialized medications of drugs has occurred due to an increased use of compounded sterile preparations (CSP) by home infusion services and drug shortages from commercial manufacturers.<sup>1,3</sup> The appeal of specialized medications, whether specially flavored or formulated for patients, has also increased. Throughout this rise of compounded preparations, there has been a need for regulations. Therefore, different pharmaceutical organizations including the United States Pharmacopeia (USP) and the American Society of Health-System Pharmacists (ASHP) have formulated guidelines for the preparation of CSPs.<sup>3</sup> The USP, which was first published in 1820, was created to provide pharmacists with a guide to the preparation of compounded products and was primarily a listing of recipes.<sup>2</sup> Since that time it has evolved to be the nationally recognized standard-setting compendium.

The USP differentiates compounding from manufacturing based on "the existence of specific practitioner-patient-compounder relationship, the quantity of medication prepared in anticipation of receiving a prescription or a prescription order, and the conditions of sale, which are limited to specific prescription orders."<sup>4</sup> The finished preparation must be dispensed in accordance and compliance with boards of pharmacy and other regulatory agency requirements.

The USP defines compounding as either nonsterile or sterile. The difference between sterile and nonsterile compounding is the fact sterile compounding requires the use of sterile ingredients and protocol set by the International Standards Organization (ISO) when preparing the product, while nonsterile compounding does not.<sup>3</sup> This standard of practice is important for sterile products as there is an increased risk level associated with these products. The USP discusses three different risk levels for CSPs (low, medium and high) which are determined by the potential for microbial, chemical and physical contamination.<sup>5,6</sup>

As mentioned above, the use of CSP began increasing in the 1980s and early 1990s. Additionally, adverse events and medication errors associated with these products have also been on the rise.<sup>3</sup> In January 2004, the publication of USP General Chapter <797> Pharmaceutical Compounding—Sterile Preparations (USP <797>) became the first official publication to describe the conditions and requirements for the compounding of sterile products.<sup>3</sup> A revision to this publication was published in 2007, and the U.S. Food and Drug Administration (FDA) gave compounding specialists until 2008 to comply with the regulations. Compliance is enforced through the FDA, state boards of pharmacy and pharmacy accrediting agencies.<sup>3</sup>

The topic of sterile compounding is a relevant topic in the practice of pharmacy, and events like the contaminated injections at the NECC only solidify the need for proper protocols, oversight and regulations.

## **Meningitis Outbreak 2012**

Beginning on May 21, 2012, NECC prepared and shipped three lots of the steroid methylprednisolone acetate to health care providers in 23 different states. Over a four month period, this steroid would be administered to over 14,000 patients as a spinal or peripheral joint injection.<sup>7</sup> The product was made to be a suspension and therefore lacked the ability to be filtered, which would have removed bacteria and fungi. Also, due to the majority of the injections being administered into the spine, they were unable to be made with preservatives which could have inhibited microbial growth.<sup>8</sup> In regard to compounding practices, NECC's records have revealed that over the past year (spanning the 2012 calendar year) their cleanrooms have repeatedly tested positive for bacteria/mold levels that should have warranted remedial measures, yet no corrective action was taken.<sup>7</sup> The Massachusetts Health Department's report stated that there were visible black particulate matter in the vials, soiled floor mats and a leaky boiler, all which could have played a role in the growth of microbial organisms. This compounding pharmacy also failed to properly sterilize equipment to ensure that drugs they produced were safe. On numerous occasions, NECC shipped drugs before they received results back from the lab ensuring their sterility, which included two of three lots implicated in the meningitis outbreak.<sup>7</sup> Failure to comply with strict compounding practices led to an unknown number of the steroid doses becoming contaminated with Exserohilum rostratum, among other pathogens, that were confirmed by the Centers for Disease Control (CDC). The FDA also stated that the raw ingredients were not the source of the contamination, but rather the breakdown came from the actual compounding process, testing for sterility, or perhaps both. In total, as of May 2013, 730 cases have been reported tallying 55 deaths in 20 different states.<sup>9</sup> Since fungus grows slowly and screening tests are not always sensitive to all pathogens, this strain was difficult to detect.

Additionally, *Exserohilum rostratum*, was not known to previously cause meningitis. It is also worthy to note that the patients receiving methylprednisolone injections from NECC were vulnerable to infection and had complicated treatment regimens. To complicate matters further, steroids have an immunosuppressant effect which may have suppressed patient immunity. Due to this particular outbreak affecting such a large number of people in many different geographical locations, it is imperative that federal and state laws be put into place to ensure patient safety.

#### Current Sterile Compounding Guidelines

Pharmaceutical preparations are required to be compounded in a designated environment that meets sterility standards, which is meant to protect both patients and pharmacy staff members. Since 2004, the USP <797> has set the standard for pharmacies to practice proper sterile compounding. The USP <797> outlines specific regulations surrounding the procedures and environmental specifications that are to be followed by compounding pharmacies. As defined by USP <797>:

***Pharmaceutical preparations are required to be compounded in a designated environment that meets sterility standards, which is meant to protect both patients and pharmacy staff members.***

The objective of this chapter is to describe conditions and practices to prevent harm, including death, to patients that could result from (1) microbial contamination (nonsterility), (2) excessive bacterial endotoxins, (3) variability in the intended strength of correct ingredients... (4) unintended chemical and physical contaminants, and (5) ingredients of inappropriate quality in CSPs.<sup>5</sup>

Deviating from these criteria may increase the chance of compounding a contaminated product. The standards of USP <797> are enforced by the FDA, state boards of pharmacy and accrediting agencies such as the Joint Commission and the Pharmacy Compounding Accreditation Board.<sup>10</sup> The USP <797> standards apply to all persons who prepare CSPs and all places where CSPs are prepared, stored and transported.<sup>5</sup>

In the case of the contaminated methylprednisolone acetate made by the NECC, sterility procedures and/or sterility testing were not properly executed or corrected, resulting in the preventable outbreak.<sup>7</sup> The NECC was compounding “high risk” level CSP medications, the most susceptible type of compound to becoming contaminated. According to USP <797>, CSPs compounded under any of the following conditions are either contaminated or at a high risk to become contaminated:

1. Nonsterile ingredients, including manufactured products not intended for sterile routes of administration (e.g. oral) are incorporated or a nonsterile device is employed before terminal sterilization.
2. Any of the following are exposed to air quality worse than ISO (International Organization for Standardization) Class 5 for more than one hour: sterile contents of commercially manufactured products, CSPs that lack effective antimicrobial preservatives, and sterile surfaces of devices and containers for the preparation, transfer, sterilization and packaging of CSPs.
3. Compounding personnel are improperly garbed and gloved.
4. Nonsterile water-containing preparations are stored for more than six hours before being sterilized.
5. It is assumed, and not verified by examination of labeling and documentation from suppliers or by direct determination, that the chemical purity and content strength of ingredients meet their original or compendial specifications in unopened or in opened packages of bulk ingredients.<sup>5</sup>

Therefore, if any of these specific USP <797> regulations on high risk level CSPs were violated, this could have resulted in the compromised products. Specifically for the NECC, documented records revealed a contaminated cleanroom deemed unfit to compound sterile products.<sup>7</sup> The raw ingredients used by the NECC and various other regulations of the pharmacy were evaluated against USP <797> specifications.

After reviewing NECC’s records, the cleanrooms of the pharmacy recurrently tested positive for bacteria and mold over 2011 to 2012, yet no corrective measures were taken.<sup>7</sup> Maintaining compliance to the guidelines set forth by the ISO 5 specification air quality and disinfecting compounding areas are important qualities of a proper cleanroom. International Organization for Standardization 5 is the classification for particulate matter in room air, a strict sterility regulation for cleanrooms in which high risk compounds are made. In order for a cleanroom to be classified as ISO 5, no more than 3,520 particulates greater than or equal to  $0.5 \mu\text{m}/\text{m}^3$  are to be measured in the air.<sup>5</sup> Moreover, a cleanroom that is classified as ISO 5 should be cleaned at a minimum frequency: ISO 5 rooms are to be disinfected at the beginning of each shift, not longer than 30 minutes following each ongoing compounding activity and immediately after a contamination is suspected or known. Counters and floors are to be cleaned daily, while

walls, ceilings and storage shelving are cleaned monthly.<sup>5</sup> Another important condition under high-risk level CSPs is the use of non-sterile ingredients that are not intended for use as a sterile route of administration.<sup>5</sup> However, the FDA confirmed that raw ingredients used by NECC were pure and thereby not the source of contamination.<sup>7</sup>

### Regulatory Issues

State boards of pharmacy are currently defending their abilities in regulating all compounding pharmacies in their respective state. However, federal authorities argue that the FDA should play a role in regulating larger compounding pharmacies like the NECC in addition to manufacturing companies, which the FDA already oversees.

#### State

All pharmacies that compound sterile and nonsterile preparations are subject to oversight by federal and state authorities.<sup>8</sup> State boards of pharmacy are the traditional regulators of compounding pharmacies, where pharmacists are expected to follow suitable procedures for the various compounded products.<sup>8</sup>

In response to the unfortunate meningitis outbreak, state pharmacy boards are currently assessing their ability to properly manage compounding pharmacies in their state. Paul Kiritsy, PharmD, M.S., an associate professor at the Massachusetts College of Pharmacy and Health Sciences in Boston, believes that current compounding practices are sufficient to protect the public: "Pharmacists have been making parenteral medications for decades. The vast majority of patients have not been adversely affected, but rather, received safe products."<sup>11</sup> Ernest Boyd, PharmD, executive director of the Ohio Pharmacists Association (OPA) shares his thoughts on Ohio's current regulations over their pharmacies:

The OPA is pleased that the Ohio State Board of Pharmacy has maintained strict oversight of our pharmacies, including those who engage in sterile compounding. The board is insistent that the products be compounded for particular patients, labeled as such. Therefore, we haven't had, and don't anticipate having, the type of large-volume manufacturing that the problem pharmacies seemed to be engaged in. Our pharmacists are aware of the [USP] 797 regulations, and use good technique and equipment to perform these functions in both community and hospital practice ... we strongly believe that we have all the regulation and oversight we need through the Ohio State Board of Pharmacy. (Email from Ernest Boyd on April 3, 2013; unreferenced, see Notes section.)

Moreover, state boards of pharmacy are accustomed to regulating pharmacies that are "traditional" compounders. Traditional pharmacy compounding is defined as "the combining or altering of ingredients by a pharmacist, in response to a licensed practitioner's prescription, to produce a drug tailored to an individual patient's special medical needs. Compounded drugs are not for resale by the patient or prescriber."<sup>8,12</sup> Though many state boards still feel confident in their ability to regulate pharmacies within their state, the NECC in Framingham, Massachusetts, was a "nontraditional" exception. Nontraditional compounding steps beyond the boundaries of traditional compounding and approaches the processes of a drug manufacturer. The NECC was compounding drugs that closely resembled a manufacturing company, mass producing drug products that have been approved by the FDA and reselling these products to pharmacies and other health care providers.<sup>8</sup> The current conflict of debate asks whether or not the FDA should be involved in both traditional and nontraditional compounding pharmacies. Cody Wiberg, PharmD, M.S., executive director of the Minnesota Board of Pharmacy, stated that fewer states have the resources to regulate pharmacies that engage in large-scale drug production.<sup>13</sup> Wiberg also mentioned, "... for the facilities like NECC, there is a role for the FDA to be involved." Underlying the issue regarding lack of oversight of the NECC, Wiberg said, "there is a lack of clarity on differences between compounding and manufacturing." In broader terms, compounding pharmacies are less controlled than manufacturers, creating a regulation problem when compounding pharmacies produce and distribute large quantities of product.



## Federal

Conflict still exists between state and federal authorities in determining the safest and most efficacious manner to oversee and regulate compounding pharmacies. The FDA has been aggressive in fighting for a larger role in regulating compounding pharmacies that act as nontraditional mass producers. However, legislation has blocked the FDA from gaining this power. The Supreme Court denied a federal law enacted in 1997, that would have allowed the FDA to regulate pharmacy compounding practices.<sup>11</sup> Moreover, the drafted Safe Drug Compounding Act of 2007 would have extended the FDA's regulatory reach into pharmacies, but was never passed.<sup>11</sup> Interestingly, the International Academy of Compounding Pharmacists (IACP) reportedly spent \$1.1 million on lobbying to defeat such proposed bills that would have strengthened the FDA's authority on regulating compounding pharmacies.<sup>7</sup>

The House Energy and Commerce Subcommittee on Oversight and Investigations held its second hearing on the fungal meningitis outbreak on April 16, 2013, where the FDA sought more authority.<sup>14</sup> FDA Commissioner Margaret A. Hamburg, M.D., "repeatedly argued for new legislative authority over the highest-risk compounding pharmacies."<sup>14</sup> However, no agreement or new legislation was established, as new legislation "take[s] a lot of time, especially given the current political environment," said subcommittee vice chair, Michael C. Burgess, M.D.<sup>14</sup> Hamburg insisted on refocusing by stating, "Patients and public health have to be our first priority. If you give us [FDA] additional authority that we feel we need to do the best possible job for the American people, we will use it."<sup>14</sup> However, compounding pharmacies are continuing to fight against additional federal oversight in order to maintain independence and integrity.

## **Proactive Measures From the Pharmacy Profession**

Current pharmacies that practice compounding can be proactive to ensure consumers that their practice is legitimately adherent to national standards. The Pharmacy Compounding Accreditation Board (PCAB) is a nonregulatory agency that was formed to provide quality standards for compounding pharmacies. The PCAB upholds national standards to which accredited pharmacies must adhere. As of April 2, 2013, 172 compounding pharmacies have been certified by PCAB.<sup>15</sup> The accreditation process is voluntary, but is a strong statement that contributes a sense of validity to the pharmacies that participate in the program. The PCAB stresses that by pursuing accreditation, "patients, prescribers and payers" know that the compound they are receiving is of high quality.<sup>15</sup> Upon receiving accreditation, the pharmacy is granted the PCAB Seal of Accreditation, providing "evidence of adherence to quality standards and to principles of the profession of pharmacy compounding."<sup>15</sup> While the establishment of PCAB is an impressive preemptive measure, all compounding pharmacies may not have the resources or script volume to justify its need. Ernest Boyd (OPA) states that PCAB may not be suitable for every pharmacy:

PCAB certification is a good thing for those pharmacies doing enough volume to justify its cost. However, we don't believe it should be mandated. It is very expensive, requires a lot of paperwork, and does not ensure that each and every prescription is correct. The primary safety factor for patients is knowledgeable, ethical pharmacists supervising well-trained technicians in preparation. (Email from Ernest Boyd on April 3, 2013; unreferenced, see Notes section.)

## **Conclusion**

The recent meningitis outbreak spurred from contaminated methylprednisolone acetate injections compounded by the NECC has caused many to focus their attention on the safety of pharmaceutical compounding and the current regulations in place to protect the public. The regulation of compounding pharmacies is under much debate due to the apparent lack of oversight of mass-producing pharmacies such as the NECC. The majority of state boards of pharmacy are confident in their ability to regulate their compounding pharmacies, but the FDA is adamant in placing further supervision on "nontraditional" pharmacies with large volumes of distribution. In the meantime, patients are entitled to the confidence that their prescription products are safely compounded. Pharmacists have firsthand authority in ensuring appropriate USP <797> procedures are followed and quality end products are distributed. While accreditation programs for pharmacies such as the PCAB are available that certify quality, pharmacists are ultimately held ethically and legally responsible to ensure appropriate, safe and well-compounded products leave their pharmacy.

## **Notes**

Permission given to use information from personal communication with Ernest Boyd.

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