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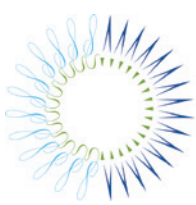
Pharmacy Sterile Compounding Summit

Summary of a Stakeholder Meeting



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Pharmacy Sterile Compounding Summit

Introduction

The Pharmacy Sterile Compounding Summit was jointly convened by The Pew Charitable Trusts, the American Society of Health-System Pharmacists (ASHP), and the American Hospital Association (AHA) on February 6, 2013, in Washington, D.C. The goals of the summit were to:

- Characterize the spectrum of activities from traditional pharmacy sterile compounding to manufacturing.
- Identify the drivers of outsourced sterile compounding.
- Identify current gaps in regulatory oversight and recommend strategies to ensure the quality and safety of compounded sterile preparations.

Summit participants included representatives from health professional organizations, large and small health systems, companies providing compounded sterile preparations (CSPs), experts in compounding and manufacturing quality, group purchasing organizations and other collaboratives representing health systems, and the U.S. Centers for Disease Control and Prevention.

Representatives from the U.S. Food and Drug Administration (FDA), a state board of pharmacy, and an organization representing member state boards of pharmacy also participated in portions of the meeting.

A complete list of attendees is found in Appendix A.

Introductory comments were made by Kasey K. Thompson, PharmD, MS, Vice President, Policy, Planning, and Communications, ASHP; Roslyne Schulman, MHA, MBA, Director, Policy Development, AHA; and Allan Coukell, BScPharm, Director of Drugs and Medical Devices, Pew. Gary Kerr, PharmD, MBA, President, Massachusetts Society of Health-System Pharmacists, provided the opening keynote address.

An overview of the scope and level of risk associated with sterile compounding was provided by Angela W. Yaniv, PharmD, BS, Assistant Director of Pharmacy – Sterile Products, Cleveland Clinic Health System; Eric Morgan, PharmD, Director of Pharmacy, Prattville Baptist Hospital, and Richard J. Kruzynski, MBA, BS Pharm, President, PharMEDium Services, LLC.

Sterile product quality standards were discussed by Eric S. Kastango, MBA, BS Pharm, FASHP, President and

Chief Executive Officer, Clinical IQ, LLC; Matthew Weinberg, MS, Chief Executive Officer, The Weinberg Group; and Stephen R. Byrn, PhD, Professor of Medicinal Chemistry, Department of Industrial and Physical Pharmacy, Purdue University.

The roles of state and federal government in compounding pharmacy oversight were discussed by Jane A. Axelrad, JD, Associate Director for Policy, Center for Drug Evaluation and Research, FDA; Cody C. Wiberg, PharmD, MS, BS Pharm, Executive Director, Minnesota Board of Pharmacy; and Elizabeth "Scotti" Russell, BS Pharm, Government Affairs Manager, National Association of Boards of Pharmacy.

Areas of Consensus

Outcomes of the Pharmacy Sterile Compounding Summit included the development of initial recommendations and participant agreement to continue collaborating to address safety concerns associated with sterile compounding. Informed by these discussions, Pew, ASHP and AHA offer the following recommendations:

- Clarify the role of federal and state bodies with oversight of sterile compounding, with an emphasis on developing clear and consistent processes that will ensure the safety of CSPs regardless of origin.
- Strengthen federal oversight of activities that are not currently overseen as traditional pharmacy compounding by states and that represent a higher degree of patient safety risk based on factors such as product volume, risk category of CSPs, whether a patient-specific prescription is received, and breadth of distribution.
- Better define and standardize licensing categories for patient care sites, companies, and other entities involved in sterile compounding activities.
- Explore development of a set of standards that combine key precepts or concepts from two distinct quality specifications—the *United States Pharmacopeial Convention Chapter <797>*[1] *Pharmaceutical Compounding: Sterile Preparations* (USP <797>) and current Good Manufacturing Practices (cGMPs)[2]—that could be used to facilitate oversight of large-scale sterile compounding activities while also recognizing that these standards were intended for separate purposes.
- Standardize training of pharmacy inspectors, survey processes, and assessment tools.

Other areas that the stakeholders noted for further investigation and potential action are:

- Describing the universe of compounding pharmacies, including quantifying the market.
- Providing education and other resources to improve the training and competence of personnel involved in sterile compounding activities.
- Fostering the development and uptake of robust beyond-use dating, including evidence-based studies that provide extended stability and sterility information. In addition, expanding the use and quality of laboratory testing, when appropriate.
- Increasing collaboration among professional associations representing health care providers, with the goal of providing education and other information that will result in decreased demand for CSPs by reducing variation among prescriber-requested medications and increasing the standardization of medication orders, when appropriate.

1 The United States Pharmacopeial Convention is a nongovernmental standards-setting authority for medicines manufactured or sold in the United States. USP <797> is a quality standard for sterile compounding by pharmacies.

2 Current Good Manufacturing Practices are regulations for drug manufacturers that describe the methods, equipment, facilities, and controls required for producing safe products.

Opening Keynote

Gary Kerr from the Massachusetts Society of Health-System Pharmacists opened the meeting with his perspectives on the aftermath of the sterile compounding tragedy that resulted in the death of more than 50 patients from fungal meningitis caused by a tainted corticosteroid injection prepared by the New England Compounding Center (NECC) in Massachusetts. The incident also affected hundreds of other patients and led to product recalls and plant closures.

In response to this incident, Massachusetts Governor Deval Patrick appointed the Special Commission on Compounding Pharmacies, which was charged with developing recommendations for preventing similar occurrences. The final report of this commission contained more than two dozen recommendations.

Key recommendations include directing the Massachusetts Board of Pharmacy to actively and continuously monitor the practice of compounding to minimize patient risk and allow for a rapid response to problems that arise. It also recommends that the board of pharmacy be granted the authority for oversight of free-standing pharmacies, hospital-based pharmacies, and physician offices, and the authority to establish content-specific expert advisory groups to address specialized areas of pharmacy practice.

Other recommendations include creating specific licensing categories, establishing minimum requirements for pharmacy inspector training and education, and enhancing pharmacy inspection schedules. The report also recommends creation of a list of drugs that may not be compounded without prior approval from the board of pharmacy.

Further, the state was encouraged to strengthen the definitions, regulations, and continuing education requirements to ensure compliance to USP quality standards for compounding in all settings, including *USP Chapter <795> Pharmaceutical Compounding: Nonsterile Preparations* (USP <795>) and USP <797>. The need to establish formal mechanisms to communicate with the FDA about ongoing investigations and clearly delineate between state and FDA responsibilities was also identified.

Kerr concluded by sharing the concerns of other directors of pharmacy within Massachusetts, which include whether it is still advisable to use external compounding pharmacies to prepare CSPs and whether they, as directors of pharmacy, have the appropriate expertise and resources to assess these vendors. He also raised questions about the role of organizations that accredit compounding pharmacies and vendors engaged in end-product testing and related services, such as environmental testing and media fills. As the most urgent need, he encouraged immediate development of an evidence-based and standardized assessment process or audit tool that could be used by state pharmacy inspectors and others across the country.

SESSION 1

Scope and Risk Factors for Pharmacy Sterile Compounding

Summary of Presentations

The first panel of experts included pharmacy staff from both a large and small health system and the president of a company that provides outsourced sterile compounding services.

Angela Yaniv from Cleveland Clinic Health System (CCHS) provided an overview of the scope of sterile compounding services at CCHS, a large health system comprised of 10 hospitals and 15 outpatient pharmacies. Sterile compounding activities occur at each hospital, but the majority of CSPs are prepared by the pharmacy at the main campus facility, which serves approximately 1,300 beds.

In 2012, approximately 870,000 doses were compounded, with 56 percent of doses prepared in response to patient-specific orders and 44 percent of doses prepared in anticipation of patient need based on historical data. A wide range of patient-specific CSPs are produced, including anti-infectives, pain management therapies, chemotherapy drugs, replacement fluids and electrolytes, and ophthalmic preparations. Anticipatory compounding includes preparation of syringes used in the operating room, epidurals, narcotic infusions, diluted and concentrated medications that are not commercially available, and medications that are unavailable due to drug shortages.

Yaniv described compounding activities at CCHS based on the three levels of risk defined in USP <797>. All hospitals within the health system perform low- and medium-risk compounding, with most CSPs falling into these categories. High-risk CSPs are prepared at the main campus, generally using end-product filtration as the sterilization method. Other hospitals within CCHS outsource the few high-risk CSPs that they need, such as pain pump refills. CCHS, including the main campus pharmacy, outsources parenteral nutrition compounding and some cardioplegia solutions. To ensure the quality of outsourced CSPs, CCHS requires the vendor to comply with all of the state board of pharmacy's rules and regulations, performs site visits, and requires quality assurance reporting.

Yaniv described several areas of risk inherent in patient-specific sterile compounding. A key area is establishing an appropriate beyond-use date in accordance with USP <797> limits, including ensuring that appropriate storage conditions are maintained once

the CSP leaves the pharmacy. Availability and proper maintenance of the facilities in which CSPs are compounded, such as a USP <797> – compliant clean room or laminar flow cabinet in a satellite pharmacy, are also a concern. Staff knowledge, competency, and compliance with established procedures are additional areas of focus.

Limiting preparation to one CSP at a time, standardizing concentrations, minimizing interruptions, and use of checking mechanisms, including syringe pull back, visual verification, or technology, are important processes to ensure the quality of CSPs.

Anticipatory compounding presents additional challenges, including ensuring that the CSP remains sterile and stable. For CSPs assigned beyond-use dating longer than those indicated by USP <797> standards, the CCHS pharmacy conducts its own sterility testing based on sample size requirements defined in *USP Chapter <71> Sterility Tests* using commercially available media. These CSPs are quarantined for 14 days while awaiting test results. If a test result is positive, the sample is sent to the microbiology laboratory for identification.

For stability, CCHS refers to information available in published resources. Yaniv noted that it is important that CSP activities mirror what is described in the reference, such as the same concentration and same container. Testing for stability is done periodically using external vendors. Process controls for anticipatory compounding include those previously described, plus standard operating procedures, limited batch sizes, in-process checks and labeling, product sterilization, and quality assurance activities.

Eric Morgan from Prattville Baptist Hospital provided a community hospital's perspective on sterile compounding, specifically highlighting the difficulties that smaller, rural hospitals face. Prattville is part of Baptist Health, a three-hospital network in Alabama that includes two large cancer centers and one outpatient pharmacy. Prattville's 85-bed facility focuses on adult patient care and has a large volume of outpatient surgeries, a dialysis center, and pulmonology and neurology services. These services often require specialty intravenous products that are not commercially available.

Morgan, who also serves as President of the Alabama Society of Health-System Pharmacists, stated that most small, community hospitals in his state and elsewhere reduce the need for sterile compounding by using ready-to-administer products that are commercially available, whenever possible. According to Morgan, community hospitals typically avoid compounding high-risk CSPs, focusing instead on low- and medium-risk CSPs. The CSPs that community hospitals typically make are large-volume parenterals, such as continuous intravenous infusions, and small-volume intermittent infusions, including IV piggy-backs of antibiotics and other therapies.

The advantages of obtaining CSPs from an external source include assurance of product sterility and quality, standardization of IV medication concentrations, and the immediate availability of critical medications. Morgan noted that his facility, like many small rural hospitals, does not have pharmacy services available 24 hours a day, seven days a week. Purchasing CSPs also decreases pharmacy workload and reduces waste that can result from limited beyond-use dating for in-house CSPs. The reduced availability of ready-to-use products, primarily due to the unreliability of the supply chain, has led to an increased need for CSPs.

Several other emerging trends were noted in sterile compounding:

- The development of multisite health systems, which may allow for the creation of a hub-and-spoke model of management that increases the buying power of smaller hospitals, as well as their access to quality-control personnel and equipment.
- Use of complex drug therapy regimens that are dosed based on the patient's weight instead of standardized dosing.
- Limited product presentations available from manufacturers.

- Drug shortages that can require health systems to repackage injectable drugs to conserve supplies or that create a need to compound high-risk preparations to replace the drug in short supply.

Morgan echoed the characteristics associated with level of risk noted by Yaniv.

The first expert panel concluded with an overview of services provided by an external compounding company by Richard Kruzynski from PharMEDium Services, LLC. PharMEDium's model, which mirrors that of other compounding companies, focuses on serving over 2,300 hospital pharmacy clients. These clients purchase CSPs that range from patient-specific preparations and physician- and surgery-specific small batches to CSPs made in anticipation of patient need. Compounding methods include admixture, reconstitution, and repackaging of FDA-approved sterile ingredients.

In other compounding models that serve the retail or community pharmacy market, there is greater focus on extemporaneous CSPs for physician office or clinic use. Kruzynski believes that hospital models are more likely to start with sterile ingredients, and less likely to start with active pharmaceutical ingredients, or powders that are commonly referred to as API. The inverse is true of retail-focused compounding companies. He noted that the licenses and registrations PharMEDium is required to hold vary from state to state, such as wholesaler/distributor, pharmacy, manufacturer, or a combination of these categories. The duration and types of inspections that PharMEDium is subject to also vary.

Kruzynski described the distinct roles of a company providing compounding services and the hospitals using these CSPs; these roles are described in written legal agreements. He noted that a compounding company assumes responsibility for drug storage, sterile preparation (e.g., stability, sterility, and labeling), and distribution, but is dependent on the hospital to ensure appropriate prescribing and other clinical functions related to use of CSPs.

Compounding companies must ensure that the CSP contains the correct drug at the correct dose and that it is free of chemical and microbial contamination. Kruzynski noted that there are certain procedures and processes that compounding companies use to meet these requirements, including cleaning procedures; validation of the facility and equipment; sterilization of contact surfaces and utensils; environmental monitoring; depyrogenation of glass vials and rubber stoppers when using API; end-product testing; and qualification, training, and testing of personnel.

Kruzynski identified four factors that contribute to or mitigate the risk of sterile product compounding: the starting drug type (sterile or nonsterile ingredients); volume generators, such as geographic coverage or sales force; expertise and self-policing, including training programs, environmental controls, and audits of suppliers; and third-party oversight, including licensing requirements, inspections, and accreditation. He highlighted that the largest compounding risks within each of those categories are: unreliable drug product source, such as those obtained from the gray market; lack of compounding expertise; offering CSPs that are beyond a company's capabilities; and inconsistent or inadequate inspections of the compounding company's facilities and slow response when the quality of CSPs appears to be compromised, respectively.

Roundtable Discussion

During the open discussion, summit participants acknowledged the difficulty in characterizing the spectrum of sterile compounding activities, including defining the distinction between compounding pharmacies and commercial manufacturers. The number of compounding pharmacies in operation and how many of these are shipping CSPs across state lines is unknown. Participants debated where compounding ends and conventional manufacturing begins, but considerations included the risk level of the CSP, number of units produced, and whether a patient-specific prescription is

received. The use of nonsterile ingredients in CSPs was identified as an especially high-risk activity.

Factors complicating clear categorization include practice patterns and the ability to meet the needs of special patient populations. For example, there are instances when a pharmacist must use nonsterile ingredients to make CSPs that are not commercially available but that are essential to meet the clinical needs of an individual patient, such as using a standardized recipe, or protocol, to compound a high-concentration hydromorphine preparation for an end-of-life hospice patient.

In addition to patient-specific needs, a number of other factors drive the need for CSPs. Prescriber requests for medications in dosages that are not commercially available are increasing, making it necessary for pharmacists to either compound the medications themselves or purchase them from a compounding pharmacy. Hospitals also compound in anticipation of patient need to increase efficiency and provide timely care.

It was noted that small and rural hospitals are more likely to outsource sterile compounding as they often cannot prepare CSPs onsite because they may not have the appropriate sterile compounding facilities, staff expertise, or hours of operation. Typically, community hospitals that engage in compounding activities do so for low- and medium-risk CSPs, leaving high-risk compounding to compounding pharmacies, unless the need for the product is urgent. Participants noted that there is a need for consistency among regulations and in the enforcement of regulations so that hospitals can ensure that when a supplier of outsourced CSPs is selected, it meets the requirements established for their state.

Participants echoed speaker statements that a useful and emerging trend among health systems is the development of a hub-and-spoke model. Under this model, smaller hospitals within a health system have increased their access to quality-control personnel and equipment, as well as minimized costs, by centralizing compounding services at larger hospitals within the same health system. Centralized or regional compounding centers offer economies of scale, more effectively produce CSPs, and enhance the opportunity for process standardization.

Participants stated that there is a need for better data on the stability and sterility of CSPs to determine how long they can be safely used. End-product stability assays are expensive, and it was noted that results of some testing companies are not accepted by all regulatory entities. Health systems that don't complete stability assays use published studies and drug information references to assign expiration dates to CSPs. However, participants reaffirmed that compounding must exactly match study conditions to ensure stability and sterility until the anticipated beyond-use date, and a concern was raised that this level of rigor is not always present.

Summit participants emphasized that drug shortages cause increased reliance on CSPs to replace commercial drugs that are temporarily or permanently unavailable. Finally, it was noted that products procured for, or compounded in, physician offices are a distinct area of compounding practice that is outside the scope of the summit, but warrants further attention.

SESSION 2

Quality Standards for Sterile Product Production

Summary of Presentations

The second panel of experts provided insights on quality standards for sterile compounding activities and manufacturing.

Eric Kastango from Clinical IQ, LLC, noted that sterile compounding is an integral part of pharmacy practice and necessary to meet the clinical needs of patients. All states license pharmacists to compound as part of the practice of pharmacy. However, he noted that state compounding regulations and oversight are inconsistent, which he believes provides an opportunity for some compounding pharmacies to operate as manufacturers without FDA oversight.

In fact, seven years after USP <797> was first released, fewer than 20 states require full compliance with it. *The USP Chapter <797> Compliance Study,* which was conducted in 2011 and repeated in 2012, found that pharmacies in states that required adherence to at least some aspect of the standards were likely to be more compliant than pharmacies in states that did not require compliance with USP <797>. The Joint Commission also does not specifically survey pharmacies for USP <797> compliance. Further, the *ASHP Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products* have not been fully embraced by the profession.

Training in sterile compounding technique is also a significant area of concern. Kastango stated that schools of pharmacy are challenged in training pharmacy students to practice in this area, with only 1 in 6 graduates adequately prepared for sterile compounding work.

Kastango described USP <797>, which was initially released in 2004, revised in 2008, and is now in the process of further revision. The chapter is a consistent, enforceable compounding standard that applies to all pharmacy practice settings in which CSPs are prepared and stored. It is intended to prevent harm and fatality caused by microbial contamination, excessive endotoxins, and large errors of strength or ingredients. He described the three risk levels (low, medium, and high) and noted that most sterile compounding is low or medium risk. He noted that while USP <797> is intended to be scalable and flexible, some practice sites have decided to outsource sterile compounding services to minimize risk and ensure quality.

Kastango then provided his perspective on the differences between compounding and manufacturing, which

he described in the context of whether a relationship between the pharmacist, physician, and patient exists. According to Kastango, a CSP is created in small batches and made for individual patients, is regulated by the state boards of pharmacy, undergoes little or no end-product quality testing or environmental monitoring, and matches the drug to the patient.

A manufactured sterile product is created in larger quantities for distribution to wholesalers and pharmacies; is regulated by the FDA; is required to undergo pre-, in-, and post-process quality testing and environmental monitoring; and matches the patient to the drug. Kastango described cGMP as minimum practice guidelines for manufacturing, processing, packing, or holding of drug products that are intended to prevent sub- or super-potency, contamination, unpredictable safety or effectiveness, and misbranding. Quality control is expected to increase as the manufacturing processes become more complex, and practices established by a manufacturer to meet cGMP can evolve to improve manufacturing processes. A quality-control program must be independent, continuous, and integrated into all aspects of the product lifecycle. Consistency and documentation are key elements of cGMP processes.

According to Kastango, under current oversight systems, sterile compounding companies or any pharmacy providing non-patient-specific CSPs should register with the FDA, unless the pharmacy or company is located in a state that recognizes a central-fill model. Some, but not all, state boards of pharmacy have developed regulations to provide oversight of health-system pharmacies that use a central-fill model.

Kastango noted that compounding pharmacies that register with the FDA may follow some, but not all portions of cGMP. These companies are not equivalent to commercial drug manufacturers, are not inspected by the FDA on a regular basis, and do not sell FDA-approved drugs. He identified this registration as an area where additional clarity is needed.

In addition, he proposed that several other areas require FDA oversight, including regulation and inspection of companies that offer testing, supplies, or other services that are intended to improve or demonstrate compliance with USP <797> standards; compounding for office use that exceeds 5 percent of total prescription volume; nonsterile-to-sterile batch compounding; sterile compounding companies who provide CSPs but do not have a direct relationship to the patient; and drugs that should not be compounded due to difficulties or uncertainties in ensuring safety or effectiveness, including metered dose inhalers, sustained release dosage formulations, and suspensions.

Matthew Weinberg of The Weinberg Group provided detail about the similarities and differences between cGMP and USP <797>. He noted that these standards served two distinct purposes and that they are not interchangeable. While both are applicable to sterile production of medicines, cGMPs are process-directed and require a system of specific standard operating procedures (SOPs) that ensure compliance throughout the drug manufacturing process, from acquisition of raw materials to storage of the final product. The FDA expects adherence to the established processes and for manufacturers' quality-control systems to continuously monitor and measure consistency in complying with the SOPs. Quality is judged by how well the process is followed, not necessarily by the drug itself. Changes in SOPs require FDA approval.

In contrast, USP <797> was described as a group of broadly defined procedures that describe how CSPs are made in small batches (e.g., less than five doses). Weinberg stated that USP <797> is not intended to be used as a procedure for manufacturing and that it is not a substitute for cGMPs. Under USP <797>, there are a limited number of definitions of processes, controls, and quality measurements. It also has no minimal requirements for recordkeeping and does not recognize deviations. Weinberg reiterated that cGMPs are not needed in circumstances in which CSPs are made in small quanti-

ties, but suggested that large-scale sterile compounding activities demanded cGMP precepts, such as use of more detailed SOPs and quality-assurance activities. He believed that implementing these types of activities would assist these compounders in working with the FDA.

Stephen Byrn from Purdue University also provided his perspective on how USP <797> differs from cGMP based on a side-by-side comparison of the two standards. Quality systems, including SOPs, are a significant area where there are differences. USP <797> does not require batch, method and equipment validation, or production records, which are used by manufacturers to ensure product consistency. Microbial testing and specifications that can be measured to ensure CSP consistency and stability are also not provided by USP <797>.

He noted, however, that the reason this and other process validations are not addressed is because these standards are intended to apply to single CSPs, which can't be tested because the preparation is essentially "destroyed" when it is administered to the patient. He also noted that some of these aspects are covered in other USP standards. USP standards do not require testing of API or other components before use, but rather relies on the certificate of analysis.

Both sets of standards address facilities, but cGMP includes more stringent requirements for controlling activities, such as separate production facilities to prevent cross-contamination from penicillin. To improve sterile compounding under USP <797>, he recommended that professional associations consider creating a template for SOPs and that state boards of pharmacy evaluate the potential for a state-run laboratory for CSP testing.

Roundtable Discussion

During the open discussion, summit participants reiterated that the quality of CSPs depends on the ingredients used to make them, the procedures and equipment in the facilities where they are created, and the training and competence of the pharmacists and pharmacy technicians who prepare them. There was concern that education and training for compounding personnel as well as the state board of pharmacy inspectors surveying compounding practices vary by state. In health systems, staff training, competency assessment, accreditation standards, and the pharmacy and therapeutics (P&T) committee play a role in ensuring the quality of CSPs. However, there is room for improvement.

Several participants stated that physician-specific preferences are one of many factors that drive the need for sterile compounding. While there is general acceptance of variability in prescribing, in many instances there is little or no evidence supporting the need for many highly customized CSPs. Some questioned whether all clinicians had a full understanding of the increased risk associated with sterile compounding and suggested that education might assist in driving standardization.

Summit participants described cGMP and USP <797> as two standards with distinctly different approaches to quality. cGMP was described as a quality control system that sets expectations for procedures in a manufacturing plant through the use of SOPs, but allows the manufacturer to define those procedures, while USP <797> provides detailed recommendations for sterile compounding. Important differences were noted, including process validation, testing, expiration and beyond-use dating, and processes to authenticate API.

Participants suggested that USP <797> was not a sufficient standard for large-scale compounding activities and called for a new set of standards that would incorporate key precepts or concepts from cGMP, which would be suitable for use in large-scale compounding. Participants considered whether concepts from cGMP should be applied to all instances of large-scale compounding or only in cases where a pharmacist is using nonsterile ingredients to make CSPs, the highest risk category. It was noted that the majority of compounding incidents causing patient harm identified by Pew involved high-risk compounding (Appendix B).

SESSION 3

Federal and State Roles in Sterile Compounding Oversight

Summary of Presentation

The final panel of experts included representatives from the FDA, a state board of pharmacy, and an organization representing member state boards of pharmacy.

Jane Axelrad from the FDA discussed the complexity of compounding oversight, the impact of court decisions on compounding, and the FDA's initial recommendations to improve regulation of compounding activities. She stated that the current line between sterile compounding and conventional manufacturing is not always clear.

Axelrad noted that the legal framework for oversight of compounding activities varies by geographic region because of court decisions in the United States Courts of Appeals in the Fifth and Ninth Circuit that have determined whether a region operates under Section 503A of the Federal Food, Drug, and Cosmetic Act (FFDCA) or an FDA Compliance Policy Guide issued in 2002. In other areas of the country, the legal framework remains undetermined by the courts. Section 503A, which was enacted in 1997, attempted to draw a line between compounding and conventional manufacturing.

Compounding that meets the requirements of Section 503A is exempt from FDA requirements for new drug approvals, cGMPs, and adequate directions for use. Compounding that does not meet requirements of Section 503A is considered manufacturing that is subject to all relevant requirements. Exemptions under Section 503A require receipt of a patient-specific prescription.

The statute also contains specific requirements for bulk drug substances and excipients. It prevents compounding of drugs that have been removed from the United States market for reasons of safety or efficacy and those that are difficult to compound, as defined by the FDA, and places limits on compounding of drug products that are essentially copies of commercially available products. Axelrad acknowledged that several of these provisions are vague and challenging for the FDA to implement. However, she noted that the FDA had made some progress in implementing Section 503A prior to the Supreme Court decision in May 2002 that held parts of Section 503A unconstitutional based on the Ninth Circuit decision mentioned previously.

In 2002, after the Supreme Court ruling, the FDA issued a Compliance Policy Guide that does not explicitly exempt

compounding from the requirements for new drugs, cGMPs, or adequate directions for use because it cannot do so as a legal matter.

The guidance, however, provides a list of factors that the FDA considers when deciding whether to take an enforcement action. She noted that the language used to describe anticipatory compounding, copying commercially available products, and other areas differs between the Compliance Policy Guide and Section 503A. Layered over this framework are compounding laws at the state level, which are inconsistent in substance and enforcement across the country.

Axelrad then described the FDA's initial recommendations for improving oversight of compounding activities that were developed following meetings with multiple stakeholders. These recommendations included an initial framework for FDA oversight of practices and CSPs that pose the highest degree of risk. This would include making CSPs in anticipation of, or without, a prescription and shipping them out of the state in which they were produced.

Among the issues considered in developing these recommendations were whether this new category should be limited to CSPs; whether large-volume, nonsterile anticipatory compounding should be regulated the same as traditional compounding; and what could serve as an appropriate mechanism for distinguishing compounders from conventional manufacturers.

Axelrad also discussed development of a list of drugs that could not be compounded, including copies of FDA-approved drugs, those removed from market for reasons of safety or efficacy, and those that are difficult to compound. She noted that several models for FDA and state boards of pharmacy collaboration in regulating compounding were also discussed and stressed that states should continue to play the primary role in regulating traditional compounding.

Cody Wiberg from the Minnesota Board of Pharmacy discussed the state's existing compounding requirements, which he believes are among the strictest in the country. The state has adopted both USP <795> and USP <797>. Current Minnesota law does not allow a prescription to be written for office use, meaning that all prescriptions must be written for a specific patient.

Other aspects of the state's laws and regulations prohibit pharmacies from providing office CSPs to practitioners, clinics, and other health care providers or facilities. Compounding pharmacies that provide these services are required to be licensed as both a manufacturer and wholesaler. These entities must also register as a manufacturer with the FDA, or obtain a letter of exemption from the FDA. Entities that may be exempt from FDA registration include health systems that compound centrally and distribute CSPs to facilities within their own health system. These health systems are, however, required to register with the state as a manufacturer and a wholesaler.

Legislation proposed in Minnesota would define compounding as preparing a CSP for an identified patient as a result of a practitioner's prescription or drug order based on a prescriber-patient-pharmacist relationship. The proposed legislation would prohibit compounding for wholesale distribution and compounding of drugs that are essentially copies of commercially available products. It would also amend the definition of manufacturing to exclude repackaging, extemporaneous compounding, and anticipatory compounding of a drug within a licensed pharmacy for later dispensing pursuant to a prescription.

Further, the proposed legislation would require out-of-state wholesalers and manufacturers to be licensed or registered in the state in which they are located, and require out-of-state facilities to supply a current inspection report to the Minnesota Board of Pharmacy or agree to be inspected by an authorized agent. Licenses to distribute CSPs in Minnesota could be suspended if correction of a deficiency is not documented in submitted follow-up inspection reports. Wiberg noted that some of these requirements already exist in Minnesota

State Board of Pharmacy regulations, but that these elements would be consolidated in statute under the draft proposal.

Wiberg spoke in support of amending Section 503A as a mechanism to improve oversight of compounding activities. He also recommended that Congress provide the FDA with the resources to inspect compounding pharmacies and take necessary regulatory action, or contract with states to inspect those facilities according to federal standards. In turn, states should develop more consistent compounding statutes, rules, and standards; improve their inspection and regulation of compounding pharmacies; and better coordinate the regulation of compounding pharmacies.

Scotti Russell from the National Association of Boards of Pharmacy (NABP) discussed steps that NABP is taking to assist its member boards of pharmacy in the aftermath of the NECC tragedy. State boards of pharmacy were inundated with requests for information on compounding pharmacies from state and federal legislators, members of the media, and the public. NABP began assisting its member boards in collecting and collating requested information and responding to these inquiries and began building an information-sharing network for the states.

Predominantly due to the downturn in the national economy several years ago, state boards of pharmacy have been dealing with budget cuts and resulting dwindling resources, including reductions, or furloughs, of staff, lack of funds for education and training, and cuts in programs and services such as inspection programs. As a result of the NECC situation, state boards have shown a strong commitment to identifying system failures, correcting them, and implementing solutions to prevent further tragedies.

With input from the state boards of pharmacy, NABP developed a four-step action plan to respond to this crisis and help prevent future crises. The first step was to collect data from the states and other sources on the number, identity, and scope of operations of compounding pharmacies and use this information to populate a system of electronic profiles of compounding pharmacies that will be used to efficiently communicate information to and between state boards of pharmacy.

The second step, to inspect identified pharmacies, is being conducted through a contract with the Iowa Board of Pharmacy through which NABP will inspect more than 600 pharmacies regulated by the Iowa Board of Pharmacy that do not reside within that state. NABP is coordinating these inspections with the state boards of pharmacy where each pharmacy is located and encouraging those state inspectors to participate in these assessments. This work is scheduled to be completed by the end of 2013.

For step three of the action plan, Russell indicated that NABP will continue its collaboration with the FDA and state and federal legislators to address the regulatory difficulties that occur when compounding crosses into manufacturing.

For step four, in recognition of the significant need for training in how to inspect sterile compounding pharmacies, NABP has endorsed a training program in sterile compounding requirements for board of pharmacy inspectors and compliance officers that will be provided by Clinical IQ. This web-based program called State Board Assist is being offered at no charge to the state boards of pharmacy. In addition, Clinical IQ and Critical Point, an online education portal, have a live training program that is being offered at a reduced rate for state board inspectors.

Russell noted that many state boards of pharmacy have already initiated steps to increase oversight of sterile compounding, including completing immediate inspections of those pharmacies known to be engaging in sterile compounding and taking action for violations of compounding standards, requiring recent approved inspections from pharmacies located outside of the state and taking action against those pharmacies as result of an action by another state, and conducting surveys to collect data on the scope of compounding activities for these pharmacies.

There is also a movement to require USP <797> in states that do not already do so, to address the office-use exemption in states where it is currently allowed, and to set standards for sterile compounding in physician offices.

Roundtable Discussion

During the open discussion, participants expressed concern that states' laws and regulations governing compounding pharmacies are variable. Concerns included that fewer than half of state pharmacy practice acts require USP <797> compliance and that not all states inspect every pharmacy on a regular basis due to a lack of resources. The education, training, and experience of state inspectors also may be inadequate in some cases.

As a result of these factors, compounding pharmacies can have different inspection results depending on which board of pharmacy the inspector represents and the expertise of the inspector. Hospitals rely on state boards of pharmacy to inspect compounding pharmacies to ensure they are following the necessary procedures to produce safe CSPs. This reliance is necessary because hospitals often lack resources or expertise to inspect compounding pharmacies themselves.

Participants also described a regulatory gap between state and federal oversight. For example, an external supplier of CSPs can be seen as a manufacturer by a state, and be required to register with the FDA. However, practitioners mistakenly perceive that registration ensures a high level of FDA oversight, which is not the case.

There was general support for a new category of FDA oversight of some compounding pharmacies, specifically non-health-system entities producing CSPs in anticipation of, or without, a prescription and those engaging in interstate commerce. Some concern was expressed that this approach would leave some providers of large-volume compounding and high-risk nonsterile-to-sterile compounding under state oversight. Participants supported a partnership between the state boards of pharmacy and the FDA to eliminate gaps in the enforcement of compounding laws and regulations.

There was also general support for a list of do-not-compound products that the FDA would update on a continual basis, and a recommendation to increase the availability of USP compounding monographs.

APPENDIX A

Pharmacy Sterile Compounding Summit Participants

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U.S. Illnesses and Deaths Associated With Compounded Medications (2001-Present)

APPENDIX B

The Pew Charitable Trusts has identified 20 pharmacy compounding errors associated with 1022 adverse events, including 75 deaths, since 2001. Contamination of sterile products was the most common compounding error, though some incidents were the result of pharmacists' and technicians' miscalculations and mistakes in filling prescriptions.

Year	States	Reported cases	Reported deaths	Adverse events	Compounding error	Product
2012	FL, GA, ID, IL, IN, MD, MI, MN, NC, NH, NJ, NY, OH, PA, RI, SC, TN, TX, VA	733	53	Fungal meningitis and other infections	Contamination[1]	Spinal injections: preservative-free sterile methylprednisolone acetate
2012	CA and six other states	33		Fungal eye infection; 23 cases of partial to severe vision loss	Contamination[2]	Eye injections: Brilliant Blue-G (BBG) retinal dye and triamcinalone
2011	FL, TN	21		Bacterial eye infection; one case of meningitis and encephalitis; four cases of loss of eyesight; three patients had eye removals	Contamination[3]	Eye injections: intravitreal bevacizumab (Avastin) injections
2011	CA	5		Blindness	Unintended presence of another medication[4]	Eye injections: intravitreal bevacizumab (Avastin) injections
2011	AL	19	9	Bacterial bloodstream infection	Contamination[5]	Parenteral nutrition solution
2010	IL	1	1	Fatal overdose	Dose of sodium 60 times stronger than ordered[6]	IV solution: sodium chloride
2007	WA, OR	3	3	Fatal overdose	Dose of colchicine eight times stronger than labeled concentration[7]	IV solution: colchicine
2007	MD, CA	8		Bacterial bloodstream infection	Contamination[8]	IV solution: fentanyl

Year	States	Reported cases	Reported deaths	Adverse events	Compounding error	Product
2004-2006	MI, MO, NY, SD, TX, WY	80		Bacterial bloodstream infection	Contamination[9]	IV flush syringes: heparinized saline
2006	OH	1	1	Fatal overdose	Dose of sodium chloride stronger than ordered[10]	Chemotherapy infusion
2006	NV	1	1	Fatal overdose	Dose of zinc 1,000 times stronger than ordered[11]	Neonatal parenteral nutrition solution
2005		2		Bacterial bloodstream infection	Contamination[12]	IV flush vials: preservative-free heparinized saline
2005	MN and 1 other state	6		Bacterial eye infection; all cases had partial or complete loss of vision; two patients had eye removals	Contamination[13]	Eye solution: trypan blue
2005	VA	5	3	Systemic inflammatory response syndrome	Contamination[14]	Heart infusion: cardioplegia
2005	CA, NJ, NC, NY, MA	18		Bacterial bloodstream infection	Contamination[15]	IV solution: magnesium sulfate
2004	CT	2		Bacterial bloodstream infection	Contamination[16]	IV flush syringes: heparin-vancomycin
2004	MO, NY, TX, MI, SD	64		Bacterial bloodstream infection	Contamination[17]	IV flush syringes: heparinized saline
2002	NC	5	1	Fungal meningitis and sacroiliitis	Contamination[18]	Spinal injections: methylprednisolone acetate
2001	CA	11	3	Five cases of bacterial meningitis; five cases of epidural abscess; one patient had an infected hip joint	Contamination[19]	Spinal or joint injections: betamethasone
2001		4		Bacterial bloodstream infection	Contamination[20]	IV infusion: ranitidine
TOTAL		**982**	**67**			

Pew's Drug Safety Project works to ensure a safe, reliable pharmaceutical manufacturing and distribution system. For more information, visit www.pewhealth.org/drugsafety.

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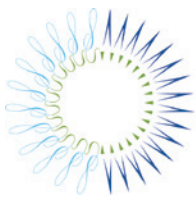

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