Straight from the Headlines: What Is Going On in Compounding Pharmacies, and How Can Clinical Microbiologists Help?

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In late 2004, I was the outgoing Chair of the American Society for Microbiology's (ASM's) Committee on Professional Affairs in Microbiology. The U.S. Pharmacopeial Convention sent a letter to ASM asking us to comment on their newly minted chapter <797>, regarding compounded sterile preparations (CSPs) in pharmacies. In 2005, I was appointed the ASM delegate to the USP for a 5-year term; that term was renewed in 2010.

During the 9 years that I have been involved in working with sterile-compound pharmacists, I have learned a lot about their profession. I would like to be able to say that they learned a lot about what we do as clinical microbiologists, but unfortunately, they did not feel that they had much to learn from us. In fact, over the years, I found that anyone with one semester of microbiology thought that he or she was a clinical microbiologist. The disaster at the New England Compounding Center (NECC) promises to change that.

The contamination of a CSP, preservative-free methylprednisolone acetate, prepared by NECC and administered intrathecally for management of back pain has so far affected 730 patients and caused 51 deaths (1); the CDC website <http://www.cdc.gov/hai/outbreaks/meningitis-map.html> is updated every Monday. There is a bill before the Senate introduced by Senator Harkin of Iowa that will improve oversight of compounding pharmacies (2). It reminds me of the legislation that resulted in the Clinical Laboratory Improvement Act of 1967 (CLIA-67) (3) following problems with "sink testing" in clinical laboratories in the 1960s. There are a number of similarities in calls for personnel competency assessment, a robust quality assurance program, and testing for the sterility of supposedly sterile products. We have a lot to teach our pharmacy colleagues about compliance programs, which likely will become mandatory and will be enforced. There are also five parts of their quality assurance program with which clinical microbiologists can help. These are discussed later in this paper. Working with the pharmacy in this regard is actually an extension of our infection prevention duties and our participation in hospital antibiotic stewardship programs. Simply put, how could so many patients get fungal meningitis from a CSP?

WHAT IS STERILE i.v. COMPOUNDING?

There are two ways that drugs are prepared for administration to the patient. One is preparation in bulk, which is done by pharmaceutical manufacturers under strict supervision of the Food and Drug Administration (FDA). The second way is compounding, in which a medicine is prepared following receipt of a prescription for a specific patient (4). Sterile intravenous (i.v.) compounding is performed in hospital pharmacies, in free-standing facilities, and in nursing homes, as well as in physician offices. Chapter <797> is, therefore, site neutral, as is CLIA-88 (4a). Anesthesiologists who mix their own drugs in the operating room are compounders, as are nurses who mix drugs in the emergency room. When phar-

macies compound and distribute large quantities of CSPs without prescriptions for individual patients, they should be considered manufacturers and should have to follow good manufacturing practices (GMP) (5).

THE PAST AS PRELUDE

Role of the FDA. In 1906, the U.S. Congress passed the Food and Drugs Act and the U.S. Pharmacopeial Convention's reference standards became the official standards for drugs in the United States. The Food and Drugs Act was revised in 1938, when Congress passed the Food, Drug, and Cosmetic Act. The revision recognized the *U.S. Pharmacopeia-National Formulary* (USP-NF) (6) as the official compendia of drug standards. The FDA was the agency charged with enforcement of the Food, Drug, and Cosmetic Act for pharmaceutical manufacturers. In 1997, the U.S. Food and Drug Administration Modernization Act (FDAMA) (7) was signed into law by President Clinton. Section 503A of the FDAMA, entitled "Pharmacy Compounding," defined the limits of legitimate compounding (8). Two days before the law was to take effect, seven compounding pharmacies sued to block it. In addition to handling other issues affecting compounding pharmacies, section 503A(c) banned advertising by compounding pharmacies. In 2002, in a 5-to-4 decision, the U.S. Supreme Court ruled that compounders have a constitutional right to advertise (9). By striking down section 503A, the Supreme Court inadvertently wound up also negating the FDA's ability to regulate compounding pharmacies. Since then, states have had the primary responsibility of overseeing the practice of pharmacy.

Had section 503A of the FDAMA not been declared unconstitutional, it would have provided a test for distinguishing between compounding and manufacturing. In fact, section 503A would have limited interstate shipments to no more than 5% of the compounder's business unless the home state had entered into a memorandum of understanding with the FDA, creating a federal-state partnership. Of interest, the State of Colorado had alerted the State of Massachusetts that NECC was shipping batch preparations of drugs to their state in violation of compounding regulations. No one knows why compounding pharmacies started to perform as manufacturers to the detriment of patients. However, from examining the history of CLIA-67, it is clear that if profes-

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sionals cannot police themselves, Congress will step in and do it for them.

Role of the states. One of the most demoralizing aspects of the deaths and injuries of patients receiving contaminated CSPs is the failure of the majority of states to adopt and enforce chapter <797>. In fact, only 18 states have adopted most of the requirements outlined in chapter <797> (10). Most state boards have insufficient funding to send experienced and well-trained inspectors to inspect pharmacies in their state. The National Association of Boards of Pharmacy (NABP) is an association of state boards of pharmacy similar to the Association of Public Health Laboratories (APHL), which represents state public health laboratories. The NABP has incorporated the requirements outlined in chapter <797> into its Model State Pharmacy Act and Model Rules (11). However, the NABP has no enforcement authority. Each state gives its own board of pharmacy (BOP) or health department the authority to inspect and apply chapter <797> as it sees fit.

Role of the USP. Besides being the repository for monographs of the *National Formulary*, the U.S. Pharmacopeial Convention is responsible for maintaining several thousand chapters defining the practice of pharmacy and pharmaceutical manufacturing. Each general chapter is assigned a number, which appears in angle brackets along with the chapter name. General chapters <1> to <999> are considered official standards, whereas chapters <1000> to <1999> are considered best-practice recommendations or informational chapters; chapters above <2000> apply to nutritional supplements.

USP chapter <797>, entitled “Pharmaceutical Compounding: Sterile Preparations,” became effective 1 January 2004 (12) (published in USP 27-NF 22) and was revised in June 2008 (13, 14). From the beginning, compounders rose up against the requirements of the chapter as too costly and unduly burdensome. Ultimately, many sterile compounders simply refused to follow what the chapter prescribed; picture yourself, as a clinical microbiologist, refusing to follow CLIA. However, chapter <797> is still considered a requirement, and pharmacies may be subject to inspections against these standards by state BOPs, the FDA (which exercises “enforcement discretion”), and private accreditation organizations, such as The Joint Commission (TJC) and the Pharmacy Compounding Accreditation Board (PCAB). Unfortunately, only about 10% of free-standing pharmacies are accredited by PCAB, and TJC views the chapter as a best practice but often does not send “trained” individuals to hospital pharmacies to inspect for compliance.

ARE PROBLEMS SYSTEMIC IN COMPOUNDING PHARMACIES?

The professional organization for hospital compounding pharmacists is the American Society of Health-System Pharmacists (ASHP). In 1995, ASHP conducted a national survey of quality assurance of U.S. pharmacies (15). They found that many pharmacists were not performing critical quality assurance checks, such as environmental monitoring, end preparation testing, and process validation. Seven years later (2002), they conducted a second survey, and unfortunately, the results were the same (16).

What can be done? If you look at the history of problems in compounding pharmacies, you can see that history repeats itself (17). For example, in 2002, there were cases of fungal meningitis caused by *Exophiala* (*Wangiella*) *dermatitis* in North Carolina fol-

lowing intrathecal injection of preservative-free methylprednisolone acetate (18), the same medication that caused the problems in the NECC case 10 years later. The only difference this time is that the fungi are *Exserohilum rostratum* and *Aspergillus fumigatus* (one case) (19–21). More disturbing is the fact that some of the problems in each incident were the same, e.g., an autoclave that was not working properly and a boiler that was leaking. NECC was a free-standing compounding pharmacy, and many others have also been involved in incidents (22–29). Hospital compounding pharmacies have also distributed contaminated CSPs (30–34). Several of these involve neonates who have become sick from contaminated heparin syringes used to flush their i.v. lines. PCAB remains a voluntary accrediting body; only approximately 10% of free-standing compounding pharmacies participate with this board, and NECC was not one of them. The Joint Commission has yet to begin surveying hospital pharmacies against the chapter <797> standards as discussed in a 2006 ASHP Newsletter (35). Again, only 18 states have specifically adopted USP chapter <797> in its entirety, although a number of them, e.g., California, have passed their own legislation, which meets or exceeds those of the chapter.

HOW CLINICAL MICROBIOLOGISTS CAN HELP

There are five microbial components that are a part of a compounding pharmacy’s quality assurance program, i.e., (i) environmental monitoring of the air in the pharmacy and under various hoods, (ii) environmental monitoring of pharmacy surfaces, (iii) gloved-fingertip testing, (iv) sterility testing of CSPs, and (v) assessment of the competency of pharmacists and pharmacy techs to compound sterily by performance of media fill testing (36).

The first component involves the incubation and reading of fungal and bacterial plates that have been used for air sampling of the laminar-flow workbenches, biological safety cabinets, i.v.-drug-compounding areas, and anterooms where donning of personal protective equipment takes place. The microorganisms on these plates are counted, and pathogens are identified. The second component is surface sampling using contact plates containing tryptic soy agar with polysorbate and lecithin (TSAPL), which neutralizes or buffers residual chemical compounds left from cleaning. Compounding surfaces are sampled, and plates are incubated and microorganisms counted to determine whether cleaning has been performed properly. The third component is gloved-fingertip testing. At the end of a compounder’s shift, he or she places the five fingers of each hand in separate TSAPL plates before removing his or her gloves.

These first three components have action limits which, when exceeded, result in recleaning and retraining of personnel. However, areas will always fail if a pathogen is present in any number. Clinical microbiologists are in the unique position of being able not only to identify microorganisms but also to assess their potential pathogenicity and virulence.

The fourth component is sterility testing of sterile end preparations. This testing is performed by direct inoculation or membrane filtration of a sterile compounded preparation into thioglycolate and tryptic soy broth for 14 days according to USP chapter <71> (37). Unfortunately, the USP does not currently recognize the inoculation of CSPs into blood culture systems (blood culture systems are a faster and much more sensitive method than direct inoculation and membrane filtration) as an acceptable method of testing sterility. Finally, the

fifth component is the incubation of media fill vials for competency testing of compounding pharmacists and pharmacy techs. Media fill testing is performed based upon the highest risk level of products that the pharmacy compounds. For example, the preparation of a total parenteral nutrition (TPN) solution is medium risk, while the preparation of a steroid from a nonsterile powder is considered high risk. Tryptic soy broth is used as a surrogate in both of these cases, and the laboratory incubates and reads the vials or i.v. bags for turbidity (36).

Clinical microbiologists are in a unique position to help pharmacies with their quality control program and prevent the kind of incident that occurred at NECC. The Federal Government is certain to pass legislation requiring compliance with USP chapter <797>. More states may as well. Four other Massachusetts pharmacies have been closed down by its state BOP since the NECC incident, and the governor of Massachusetts is proposing stricter enforcement and oversight of the USP chapter <797> quality program (38). Budget constraints only reinforce the need for conscientious, cost-effective, and concise reforms that positively affect patient outcomes.

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