Scope of Meningitis Outbreak Widens

by David Bronstein

Health officials now say that 121 patients have contracted fungal meningitis after being injected with a contaminated steroid solution prepared by the New England Compounding Center (NECC). Twelve of the patients who were given the spinal injections for back pain have died in the outbreak, with cases occurring in 11 states, according to newly released figures from state health departments and the Centers for Disease Control and Prevention (CDC), in Atlanta.

As concern over the outbreak deepens, several government officials are calling for stronger regulatory oversight of compounding pharmacies, which they say operate in a grey area that does not require routine batch testing and other types of rigorous safety checks that the FDA mandates be done by the major drug makers.

U.S. Rep. Edward J. Markey said he would introduce legislation to strengthen the FDA’s oversight of pharmacy compounding, which he called “a regulatory black hole.” It is “shocking,” he said, that a company such as NECC could ship 17,000 doses of a medication across various state lines without FDA regulation. “That’s impossible for an individual state to regulate.”

Despite that lack of oversight, many health systems continue to outsource selected drug therapies to pharmacy compounders. At South Jersey Healthcare Regional Medical Center, in Vineland, N.J., for example, 124 patients at two hospitals were given injections of potentially tainted methylprednisolone acetate that the hospital purchased from NECC, according to The Wall Street Journal. As of Wednesday, one of those patients was hospitalized with fungal meningitis, the New Jersey Department of Health reported.

A History of Safety Issues

The current outbreak comes on the heels of several well-publicized cases of illness and death in recent years caused by tainted drugs from compounding pharmacies. Why, then, would a hospital pharmacy continue to purchase products from outside compounders? One pharmacy director who continues to occasionally outsource selected products said the answer is pretty straightforward: ongoing drug shortages.
Tom Van Hassel, RPh, MPA, director of pharmacy at Yuma Regional Medical Center, in Yuma, Ariz., noted that in the case of the implicated methylprednisolone solutions shipped by NECC, "at times they were the only company that could consistently provide this product in the strengths needed by pain clinics and some hospitals."

In an ideal world, Mr. Van Hassel noted, "of course" it is always preferable to purchase drug products from established manufacturers because those products "are regulated for quality control by the FDA, as opposed to compounders, where no one regulatory body fully embraces that responsibility. But when only the compounders reliably have a short-supply medication, we really have no other recourse."

Mr. Van Hassel stressed that the majority of compounders are large, well-run operations that produce millions of doses each year and follow strict quality-control processes and procedures. "But if their error rate is 0.1%—that is, 99.9% accuracy—it means that hundreds if not thousands of potentially contaminated or otherwise unsafe doses are still getting into the supply chain."

That lack of fail-safe quality control “is really scary,” added Mr. Van Hassel. “This is what keeps pharmacy directors up at night.”

Virginia Ghafoor, PharmD, a clinical pharmacy specialist for pain management at the University of Minnesota Medical Center, in Minneapolis, has a suggestion for pharmacy directors who are losing sleep over the safety of methylprednisolone purchased from outside compounding pharmacies:

Stop buying from those companies unless you have a deep knowledge of how the product is prepared.

Dr. Ghafoor explained that because the steroid used for epidural injection is a suspension, it is difficult to adequately remove pyrogens and other bacterial contaminants via the usual method—using a 0.2 micron filter—due to clogging and product integrity issues. Additionally, heat sterilization, another method for ensuring sterility, "will not necessarily remove pyrogens and fungal contaminants," she said.

Given those production and safety challenges, "our pharmacy compounding experts ... decided that compounding injectable steroid suspensions was risky. So when methylprednisolone is in short supply, our policy now is to always use alternative agents such as triamcinolone or betamethasone, if available. And we get those medications from one of the larger manufacturers who are regulated by the FDA and who therefore you know are far more likely to follow Good Manufacturing Practices."

More Homegrown Solutions, Please

As for the proper level of increased regulatory scrutiny that needs to be applied to compounding pharmacies, Dr. Ghafoor warned against overreacting to the current outbreak.
Being in a state where more than 800 patients have been injected with the contaminated product from NECC, she noted, "I am acutely aware of the need for tighter safety controls. But I don't think heavy-handed governmental oversight is the right answer; I would prefer that our national pharmacy organizations and State Boards of Pharmacy come up with some viable solutions, since we have lots of talented people who have a deep understanding of the safety and quality issues we all face in sterile compounding."

That approach, Dr. Ghafoor noted, will ensure that patients continue to have access to pain therapy, "which is something that I feel very passionate about, especially for individuals with chronic pain, who often have difficulty getting adequate symptom relief," she said.

Mr. Van Hassel, who currently serves as vice president of the Arizona Board of Pharmacy, cautioned that homegrown solutions also have some flaws. In 2004, for example, the United States Pharmacopeia (USP) issued safe-practice guidelines for compounding pharmacies. "My understanding is that less than 20 states have adopted those guidelines," he said. "I appreciate the other states' hesitation."

The USP guidelines, he explained, are "very complex, very prescriptive and very hard to comply with." As a result, he noted, "in Arizona, we actually chose to develop our own rules for pharmacy compounders that frankly are more targeted and raise far fewer compliance issues."

Voluntary accreditation of compounding pharmacies is another quality-control tool that has some adherents. The Pharmacy Compounding Accreditation Board (PCAB), a joint effort by eight leading pharmacy organizations including the USP, the National Association of Boards of Pharmacy and the International Academy of Compounding Pharmacists, offers such testing. To date, however, only 162 out of about 3,000 compounding pharmacies have elected to undergo accreditation, according to Joe Cabaleiro, executive director of the PCAB.

Why the slow uptake? "When the market demands that pharmacies be accredited, it will happen [on a more widespread basis]," Mr. Cabaleiro said. The meningitis outbreak, he noted, "might help people see the value of some type of accreditation. We certainly have been trying to get the message out in as many ways as possible to patients, prescribers and payers that if you need compounded medications, you should consider using a PCAB-accredited pharmacy."

Mr. Van Hassel said that accreditation is a laudable goal. "But only some of those 162 [PCAB-accredited] companies do sterile compounding; many others only do topicals and other items that won't relieve the chronic shortages we are struggling with. So we are nowhere near a critical mass for accreditation to make a real difference."

More Developments

As health officials continue their investigations into the meningitis outbreak, new details about the deadly infection are being released. Initial reports, for example, attributed the infections only to spinal injections contaminated with Aspergillus fumigatus, one of the most common
Aspergillus species to cause disease in individuals with compromised immune function. But on Tuesday, health officials in Tennessee announced that they had identified a second fungus called Exserohilum as the primary cause of the meningitis cases in the state. At a news briefing, a state health official said that the organism is "a fungus so rare that most physicians never see it in a lifetime of practicing medicine."

Additionally, CDC officials are now stressing that although NECC has recalled all of its products from the market and the period of exposure to tainted products is over, the number of meningitis cases might continue to rise. That’s the case, they say, because of the variable incubation period of the potentially deadly infection—anywhere from a few days to six weeks. To stem any future outbreaks, the CDC said that health professionals should not use any products made by NECC.

Health officials also are urging clinicians who manage patients given the implicated spinal steroid injection to heed the warning signs of a meningitis infection. Those include flu-like symptoms, such as fever or headache, and neurologic problems, such as numbness and confusion. Additionally, a person who has developed an infection of a normally sterile site (e.g., blood, cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, surgical aspirate, bone, joint fluid, etc.) following use of a product labeled as sterile prepared by the NECC should also be seen as a having contracted a “suspect case” of fungal meningitis, the CDC reported.