Microbiology & Compounding Pharmacies

What the 483s tell us

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A PATIENT AT VANDERBILT UNIVERSITY Hospital was readmitted with what physicians originally misdiagnosed as bacterial meningitis. This time around, Dr. April Pettit, an astute infectious disease specialist, ordered additional tests for fungi and tuberculosis to be performed on the patient's spinal fluid. The next day a surprising result came back from the lab — *Aspergillus* species . Fungal meningitis is very rare. Within a few days, the Tennessee Department of Health and the CDC were able to trace the infection back to an epidural injection the patient had our weeks earlier to treat back pain. Meanwhile, more cases of fungal meningitis were being reported around the country.

The CDC and FDA reacted quickly. The outbreak was linked to three lots of preservative-free methylprednisolone acetate (MPA) distributed by the New England Compounding Center (NECC) in Waltham, MA. The US FDA and the Massachusetts Department of Health inspected the site and found unsanitary conditions and poor manufacturing practices. Product was recalled and the plant has been shut down since October 2012.

But the damage was done. The CDC continues to update the status of its investigation each month, and the casualty count continues to climb, one year later. As of August 5, 2013, 749 people have been sickened by the contaminated drug in 20 different states and 63 people have died.

How did this happen? Americans have grown accustomed to news of drug manufacturing disasters in other countries. The last few years has brought news of Asian and African patients dying from medicines contaminated with diethylene glycol, melamine, or adulterated heparin. But how could such large-scale microbial adulteration happen in North America?

NECC was registered with the FDA as a compounding pharmacy, this is an important point. As a compounding pharmacy, it was not held to the same cGMP standards that drug manufacturers are. Compounding pharmacies formulate drugs for patients with special needs, patients with allergies to certain excipients in the marketed product, for example, or who may not be able to swallow the solid oral dosage form of a commonly available drug substance. Compounding pharmacies step in to produce small batch formulations for these individuals. They provide a valuable service.

But NECC was no longer making individualized medicines. Before closing its doors in October 2012 it had logged $32,000,000 in annual revenue and its products reached patients as far from New England as Idaho, Texas and Florida. In addition, the contaminated product was not a specialty formulated medicine. Methylprednisone acetate is a well-estab-

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lished drug manufactured by generic giants Sandoz and Teva. NECC essentially crossed the line from specialty compounder to large-scale drug manufacturer. Presumably, a large-scale drug manufacturer would have conducted cogent hazard analysis and recognized that aseptically packaging a non-preserved immunosuppressing drug for injection *directly into a patient's spinal cavity* is an extremely high risk proposition and requires strict manufacturing control.

Aseptic processing of any parenteral drug is inherently difficult and risky. As the FDA says in its guidance document on aseptic processing, "Aseptic processing involves more variables than terminal sterilization. Before the aseptic assembly into a final product, the individual parts of the final product are generally subjected to various sterilization processes. Each of these manufacturing processes requires validation and control. Each process could introduce an error that ultimately could lead to the distribution of a contaminated product. Any manual or mechanical manipulation of the sterilized drug, components, containers or closures prior to or during aseptic assembly poses the risk of contamination and thus necessitates careful control. Sterile drug manufacturers should have a keen awareness of the public health implications of distributing a nonsterile product. Poor cGMP conditions at a manufacturing facility can ultimately pose a life-threatening health risk to a patient"

As a compounding pharmacy, NECC was not accountable to FDA cGMP regulations, but rather was under the inspection authority of the Massachusetts Department of Health. Current law requires compounders to register with the FDA but limits the agency's enforcement; guidance and inspection is up to states' Departments of Health. This difference was allowed to afford compounding pharmacies the flexibility they need to formulate small batches of specialty product.

It is counterintuitive in this era of harmonization and consolidation to consider so many different state agencies legislating separate inspection codes and equally inspecting so many compounding pharmacies. USP stepped in to help standardize manufacturing quality expectations for these compounders. USP <797> Pharmaceutical Compounding – Sterile Preparations is a comprehensive chapter, offering significant detail on environmental monitoring, gowning, validation, and storing compounded sterile preparations. It is in the mandatory section of the USP. Twenty-three states now require compounding pharmacies to comply with USP <797>, but as useful as this chapter is, we must stress that it was written for true compounding pharmacies — pharmacists who mix small-scale specialty formulations for immediate use.

The question at this point is, how wide-spread is the manufacturing risk? Are other compounding pharmacies distributing large batches of product nationally and how safe are their manufacturing practices? During the 12 months following the NECC disaster, the FDA has conducted audits of many compounding pharmacies. As of this writing, more than 50 US 483s have been issued for these companies, and each is posted on the FDA's website at 1.usa.gov/13DqpIS. These reports not only give us a peak into current compounding pharmacy practices, they also provide valuable insight into current FDA expectations. What follows is a summary of observations related to the major microbiological control points of aseptic processing: environmental monitoring, personnel gowning, process validation and product testing.

Environmental Monitoring

Of the 52 483s reviewed, 47 listed deficiencies in the environmental monitoring program of the host company. Almost no company monitored viable organisms during manufacturing; most only monitored twice a year while there was no activity in the plant. Environmental control is a dynamic situation, and the quality of an ISO 5 room will change as people and items enter it. HVAC performance, seasonal fluctuations, and process variety will all impact the ability of an ISO 5 room or device to do its job. To test only twice a year and not during actual manufacturing does not give a clear assessment of the microbial control. Other FDA observations concerning environmental monitoring included:

- Specific locations where samples were taken were not mapped
- No neutralizers were added to the media in the contact plates.
- Surfaces were only sampled after sanitization, and not during or after processing.
- Samples of gloves were only taken after glove sanitization.
- Cart wheels which were rolled from ISO 7 to ISO 5 areas were not sampled.
- Media used to support growth of fungi (such as Malt Extract Agar) were not used to sample in high risk areas
- Contact plates were not incubated upside down, with agar side up, allowing condensation to form on agar surface and possibly causing bacterial colony swarming.

Gowning

Forty-three of the 52 483 observations listed a deficiency in gowning. The human element in an aseptic process is the dirtiest variable, with each person carrying 100 trillion organisms along into the clean room. A typical person will shed 100,000 particles per minute. A simple nod will shed 50,000 particles. To avoid introducing potential contaminants, any technician in a critical processing area is expected to be completely covered by sterile gown, gloves, boot, hood, mask and goggles. Yet the majority of compounders had personnel in critical areas with exposed skin. And the coverings that many were wearing were not received as sterile. Many re-used their gowns.

In addition, it is important to verify at the end of the process that the technician is still clean. Typically contact plates are placed on fingertips, sleeves and other body components. Most compounding pharmacies only tested fingertips. And when counts were found on the fingertips, often investigations were not conducted to assess what the impact was on the product.

The significance of gowning is amplified when a process is not optimized and human intervention in the process occurs. There were several incidences of technicians grabbing pens from outside the controlled area and bringing them inside with the product. Consider this observation: "Technician was observed picking up the stoppers with her gloved hand and placing them onto filled vials. At this time, the operator's glove

was observed to be torn. In addition, exposed skin was observed at the wrist, due to the glove not being pulled up over the sleeve. Technician observed passing her hand and arms over the top of open vials in the hood that were in the process of being filled."

Other observations of note included:

- No written procedure for gowning
- In-ear headphones outside gowning touching edge of ISO 5 BSC and equipment.
- Coveralls touching ground while gowning.

Disinfection

There were many observations of improper disinfection. Most compounders were sanitizing equipment in the ISO 5 critical region with 70% isopropanol (IPA). Often this IPA was not sterile. IPA is germicidal but will not render the equipment sterile. It is ineffective against bacillus spores. There were many observations of no sporicide use in critical areas.

There were several observations that the disinfectants which were used were not validated. This is an observation that the FDA has also been making of large-scale manufacturers. USP <1072> Disinfectants and Antiseptics outlines validation expectations. Disinfectants are registered by the US EPA to be effective against a few select ATTC strains when placed on very well defined hard surface carriers. The concern is that the EPA registration process does not adequately address the variety of wild strains that might be present in a manufacturing plant, nor does it address the ability of these antimicrobials to be effective on the variety of surfaces. The expectation is that manufacturers will show efficacy against environmental isolates on coupons made of typical manufacturing surfaces, such as stainless steel, fiberglass walls, and hypalon gloves.

Other observations regarding disinfection included:

- No rotation of disinfecting agents
- Sponge mop used, not a non-particle-shedding device.
- Cleaning not conducted properly with overlapping wipes from front to back.

Validation

In an aseptic process, individual components are sterilized through heat or filtration, and are brought together in an aseptic environment. The individual sterilization steps and the final processing step must be validated. The final aseptic processing step is validated with a media fill where microbiological growth media is processed in place of the drug substance. If personnel, environment, or processes are lacking, contaminants will enter the final container closure, and subsequent incubation would allow proliferation and visible failure. In most cases, the FDA noted that compounders were not validating worst-case situations.

In many cases the method to sterilize incoming product or ingredients were not validated. Filter efficacy was not always verified with *B. dimunita* tests to verify product could be cleared of contaminants prior to aseptic packaging. Autoclave and deyprogenation cycles were not validated to show they could remove contaminants or endotoxin prior to compounding.

Testing

Final product testing to confirm that the process was in control becomes even more important when critical points within the process are not in fact stringently controlled. Yet most of the companies did not routinely test finished product, and several did not test at all. Several released product early, before the results were in. In the case of NECC, the contract laboratory offered a preliminary report showing samples initiated on 5/22/2012 were passing on 5/25/2012. USP <71> sterility tests require 14 days of incubation, so a three-day incubation is meaningless.

Other observations regarding testing included:

- No growth promotion testing performed on medium used for sterility test
- Lack of culture standardization for growth promotion: one growth promotion test consisted of technician spitting saliva into specimen cup, diluting and using aliquot for growth promotion
- Incubation of plates at ambient temperature, without an incubator
- Insufficient sample size
- No Fluid Thyoglycollate Medium used for anaerobe detection in the sterility test
- No Antimicrobial Effectiveness Testing performed on preserved product at end of shelf life
- Insufficient sample quantity tested
- No investigation after failed results; tests were simply re-run

The defense of at least one compounder to such observations was that it was following USP <797> as required by its state Department of Health. That is, it was following the letter of the law. And perhaps that's true, but meanwhile, each month brings more bad news. In June *Bacillus species* and *Penicllium species* were isolated by the FDA from vials of methylprednisone acetate made by Main Street Pharmacy. In July the FDA requested a recall of all NuVision Pharmacy's sterile products, noting multiple manufacturing problems and a failed sterility test. August marks the twelfth month since the NECC disaster was uncovered, and the casualty count continues to rise. Good manufacturing practices are based on good science, and good science seems to be the missing component in most of the pharmacies' 483 observations. ■

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