

Using a medium-fill simulation to evaluate the microbial contamination rate for USP medium-risk-level compounding

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For at least a dozen years, pharmacists who compound sterile preparations have had guidance from national organizations on quality assurance for the safe compounding of these preparations. The American Society of Health-System Pharmacists (ASHP) and the United States Pharmacopeia (USP) provide a framework for quality assurance and assessment that offers minimum standards that patients have a right to expect of those who prepare their sterile medications.^{1,2} USP recently issued a new standard on the compounding of sterile preparations, chapter 797,³ that was developed from the previous chapter (1206) and is enforceable by regulatory entities.

Recent injuries and deaths due to improperly prepared and contaminated injections compounded by pharmacists continue to call into question the ability of pharmacists to prepare these products safely and the adequacy of the training and guidance they receive.⁴⁻⁶ Quality assurance failures continue to haunt the profession and to injure and kill patients. Many state boards of pharmacy across the nation are considering

Purpose. The estimated microbial contamination rate for complex, multiple-step, medium-risk-level compounding was studied.

Methods. The results of evaluations of the aseptic technique of pharmacists and technicians in compounding complex USP medium-risk-level sterile preparations were compiled to estimate the microbial contamination rate. The testing took place in 2002 and 2003 at a single institution and involved reconstitution of sterile dry growth medium and a series of complicated transfers of the medium from vials and ampuls to intravenous bags. The bags were incubated at 25–35 °C for 14 days and observed for microbial growth.

Results. Of 539 evaluations, 28 (5.2%) resulted in preparations that yielded micro-

al growth. Pharmacists' compounding resulted in a slightly lower contamination rate (4.4%) than that of technicians (6.2%). Inadvertent touch contamination may have been the principal source of the contamination.

Conclusion. A two-year series of 539 evaluations of the aseptic technique of pharmacists and technicians conducted with sterile growth medium and designed to simulate the compounding of USP medium-risk-level sterile preparations yielded an overall contamination rate of 5.2%.

Index terms: Compounding; Contamination; Drugs; Injections; Methodology; Personnel, pharmacy; Pharmacists; Stability; Sterile products; Storage

Am J Health-Syst Pharm. 2005; 62:285-8

regulatory changes for pharmacy compounding, and the Food and Drug Administration is considering new initiatives to protect public safety. The recent tragedies demonstrate that pharmacy needs to embrace a culture of quality in sterile compounding and adopt the necessary quality assurance steps.

Previously, we reported the use of medium-fill simulation to establish a

benchmark microbiological contamination rate for a USP chapter 797 low-risk-level aseptic compounding operation, prefilling of syringes.⁷ No contamination occurred among 1035 syringes filled with sterile growth medium. This result was consistent with those of previous studies.^{8,9} However, we suspected that the low contamination rate (less than 0.1%) was unlikely to extend to more

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The assistance of David W. Newton, Ph.D., is acknowledged.

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complicated aseptic compounding, such as that of medium- or high-risk-level preparation. While low-risk-level compounding constitutes over 90% of the sterile preparations at our institution, medium-risk-level sterile preparations are compounded when needed.

We used the results of evaluations of the aseptic technique of pharmacists and technicians for a two-year period to estimate the microbial contamination rate for complex, multiple-step, medium-risk-level compounding. A medium-fill simulation was used, as specified by both USP and ASHP.¹⁻³

Background

As a matter of policy and routine, the division of pharmacy at our institution provides training in sterile product preparation to employees, including a 20-hour didactic course for all pharmacists and a 40-hour course for technicians who may be involved in sterile product preparation. In addition to the didactic courses, a practical evaluation is performed that involves a complex series of aseptic transfers to ensure that each individual is competent in aseptic technique. Both the didactic training and the practical evaluation must be completed before an individual may prepare a sterile medication for administration.

Each pharmacist and pharmacy technician must also demonstrate competency annually by performing a multiple-step aseptic transfer of growth medium successfully, that is, with no subsequent growth of microorganisms (Appendix). The aseptic transfers are designed to simulate manual compounding of the most complicated medium-risk-level preparations anticipated, as is specified in USP chapter 797.

Methods

The sterile growth medium and process used in the evaluations was the Valiteq Aseptic Technique Vali-

ation System.^a The process involved multiple discrete manipulations, including reconstitution of dry growth medium; withdrawals of growth medium from vials and ampuls with syringes, needles, a dispensing pin, and a filter straw; and transfers of the growth medium to an empty plastic intravenous bag. Each of these manipulations was routinely required of personnel performing aseptic compounding. The complexity of the preparation steps made the process a simulation of USP chapter 797 medium-risk-level compounding. All the materials and devices were sterile upon purchase. Each individual being tested had to perform all the steps without contaminating the sterile growth medium. An observer was present to remind the individual of the steps to be performed and to evaluate the appropriateness of the technique.

The test procedure for each individual resulted in 100 mL of growth medium packaged in a plastic bag. The bags were stored according to the manufacturer's recommendation and observed for growth of organisms. If growth occurred, it appeared as cloudy turbidity or discrete colonies and sedimentation. The test was judged to have been completed successfully if the growth medium in the plastic bag remained a uniform, clear, light-amber solution. If growth occurred, the pharmacist or technician had to repeat the test until a satisfactory result was achieved.

Before a test, each individual removed any finger, hand, or wrist jewelry and wristwatch; donned shoe covers^b and a hair cover^b; thoroughly cleaned the hands, nail areas, and arms with antimicrobial detergent and water; and donned gowns.^c Gloves were optional during 2002 and became mandatory in 2003. When used, gloves^d were latex-free, powder-free, nonsterile chemotherapy protective gloves that were sanitized with 70% isopropyl alcohol prior to the start of the test. The gloves

were considered to be, and were handled as, nonsterile containment devices to prevent contamination from shedding of skin organisms in the compounding area. Test takers were reminded to avoid touch contamination throughout the testing.

No facemasks were used, because the vertical-laminar-airflow biological-safety cabinets (BSCs)^e were equipped with transparent face shields. The BSCs had all been certified to meet International Organization for Standardization class 5 (class 100) air-quality standards on a routine twice-yearly schedule. The BSCs, whose blowers ran for at least 60 minutes before the test began, were located in a cleanroom and in a satellite pharmacy separate from the general environment and were cleaned thoroughly on all surfaces with 70% isopropyl alcohol before each evaluation.

Results and discussion

In 2002, a total of 267 personnel underwent the competency evaluation. In 2003, the number increased to 272. Most of these individuals had extensive experience in sterile preparation and had participated in the testing for a number of years.

Twenty-eight of the 539 tests of aseptic technique resulted in solutions with visually apparent growth of microorganisms. The overall contamination rate was therefore 5.2%. Personnel who failed the test were required to repeat it. No individual who underwent repeat testing prepared a sample that resulted in visible growth upon retesting. Furthermore, only one individual failed the evaluation in both years.

Pharmacists failed 15 of 343 tests, or 4.4%. Pharmacists who worked directly and regularly in the sterile product preparation area had a worse record, with a contamination rate of 6.3%. The contamination rate for pharmacists who did not work regularly on sterile product preparation was 3.9%. Whether this coun-

terintuitive outcome was a result of the familiarity of those individuals with aseptic compounding, leading to less rigorous aseptic practices, or was simply an anomaly is not known. Technicians who routinely prepared sterile products generated contaminated solutions in 12 (6.2%) of 193 tests. Three technicians who did not routinely prepare sterile products were evaluated as well; all three generated contaminated solutions.

Traditionally, pharmacy has considered microbial contamination during evaluations of aseptic technique to be a personal failing of the individual's knowledge and skill. The failure then necessitates corrective action, such as reeducation and training in aseptic technique, before the individual retakes the test—one hopes with a better outcome. This approach certainly seems reasonable, since most growth probably stems from inadvertent touch contamination. There may also be a certain element of chance involved.

However, there is another view that does not blame fallible humans but instead focuses on the aseptic manipulations and processes used for compounding medium-risk-level preparations. The contamination rate for the 539 tests may be representative of the contamination rate for our system that produces complex, multiple-step, medium-risk-level preparations and not just deficiencies in the techniques of specific individuals. All the personnel tested had received specialized training and were considered competent at compounding sterile preparations. Since this kind of sterile compounding was routinely conducted by many of the same individuals over the same two-year period to produce drug preparations for actual human use, the contamination rate for such medium-risk-level preparations may have been 5% or greater in the practice setting. In fact, contamination might actually have occurred more frequently during actual practice,

since the individuals tested may have been even more careful than usual during testing.

The vast majority of the sterile product preparation in our institution and most other institutional pharmacies consists of single aseptic transfers of sterile products, which would be categorized as USP chapter 797 low-risk-level compounding. Such simple compounding appears to be associated with a relatively small chance of inadvertent contamination.⁷ The complexity of multiple-step medium-risk-level compounding may greatly increase the risk of contamination. Our evaluations of these individuals' aseptic technique over two years were performed in compounding environments that are better than those in many pharmacies and that meet most of the standards of ASHP and USP. Every individual tested had received extensive aseptic training, and most were highly skilled and experienced. Even so, the chance of touch contamination during complex manual aseptic manipulations appears to be much higher than that for compounding low-risk-level preparations. We believe that a contamination rate of over 5% is unacceptable for this institution or any other sterile compounding practice.

Our institution had implemented most of the requirements of USP chapter 797 before the chapter existed, and the personnel tested were highly skilled and experienced in aseptic technique. Yet a contamination rate of over 5% occurred with complex, multiple-step, medium-risk-level compounding. This may indicate that, even under the best possible conditions, complicated manual aseptic preparation still leaves much room for systemwide quality improvement. It may also indicate that such compounding is an unrecognized source of morbidity and possibly mortality due to infection.

Personnel who perform sterile compounding typically consider ev-

ery unit they produce to be sterile. Too little consideration is given to the fact that inadvertent contamination of compounded units is occurring at some rate on a regular basis. The contamination rate is a result of all the contamination risk factors, including the nature and complexity of the compounding operation, the quality of the preparation environment, and the skill of the preparer. Even with the best environmental controls and the most highly skilled staff, the possibility of contamination should be considered and evaluated for its patient safety implications. Each pharmacy is obligated to determine the rate of contamination for its operations, particularly for more complex sterile compounding, to ensure that an inordinately high contamination rate is not creating an unacceptable risk.

The likeliest source of the contamination we identified was probably the personnel compounding the preparations. The reality is that there are abundant opportunities for human beings to inadvertently contaminate products during complex manipulations.

No obvious changes in practices, procedures, or other options seem to exist that will absolutely prevent inadvertent contamination of complicated medium-risk-level preparations. In light of this, pharmacists should limit complex, multi-component, medium-risk-level sterile preparations to those that are essential for patient care. Considering the risks to the patient, it would be unacceptable to undertake such compounding for any other reason. Furthermore, on occasions when it is essential for patient care, medium-risk-level compounding should be conducted just before administration, and the products should not be stored prior to use.

Another possible preventive approach may be to employ sterilizing techniques, such as filtration, before or at least during administration in

recognition of the 5.2% rate of contamination we observed. In effect, this would be treating medium-risk-level preparations as high-risk-level preparations, which must be terminally sterilized. USP high-risk-level preparations are those prepared from nonsterile components or that contact nonsterile materials or devices.³ Inadvertent touch contamination should be included in this latter group, and such preparations should be sterilized before they are administered.

We plan to perform the next annual set of evaluations of aseptic technique with mandatory use of sterile latex gloves and frequent decontamination during compounding to see if these measures will reduce the contamination rate. The nonsterile chemotherapy protective gloves that were used during the tests reported here are bulky and thick, which greatly decreases tactile sensitivity and increases the chance of undetected touch contamination. Sterile latex gloves, although not remaining sterile with use, are much tighter fitting and thinner.

We suspect that the contamination rate for the simple low-risk-level compounding of one- or two-component admixtures that represent the bulk of sterile compounded doses in most institutions is much lower than the contamination rate we reported for more complex preparations. We plan to test this hypothesis in a later study.

The essence of quality assurance in sterile compounding is delivering what the pharmacy purports to be delivering: a sterile preparation. The burden of responsibility is on each compounding facility to document its contamination rates for sterile preparations with the various USP risk levels and to work to reduce those contamination rates as much as possible.

Conclusion

A two-year series of 539 evaluations of the aseptic technique of pharmacists and technicians conducted with sterile growth medium and designed to simulate the compounding of USP medium-risk-level sterile preparations yielded an overall contamination rate of 5.2%. Pharmacists should question the advisability of such complex manual compounding unless it is absolutely essential for patient care, and sterile filtration of medium-risk-level preparations should be considered.

^aLab Safety Corporation, Des Plaines, IL 60016.

^bAlliance, McGaw Park, IL 60085.

^cChemo Safety, The Ludlow Company, LP, Chicopee, MA 01022.

^dSafeskin Purple Nitrile Exam Gloves, Kimberly-Clark, Roswell, GA 30076.

^enuAire, Inc., Plymouth, MN 55447.

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Appendix—Procedure for testing medium-risk-level aseptic technique

1. Using a 30-mL syringe and an 18-gauge needle, reconstitute a vial of dry sterile Trypticase soy growth medium (vial 1) with 20 mL of sterile water for injection.
2. Using a 60-mL syringe and an 18-gauge needle, transfer 50 mL of sterile water for injection from a 50-mL vial into a sterile empty 150-mL Viaflex bag.
3. Insert a dispensing pin into a 30-mL vial of sterile liquid Trypticase soy growth medium (vial 2). Using a 10-mL syringe, withdraw 5 mL of growth medium through the dispensing pin. Attach an 18-gauge needle to the syringe, and transfer the growth medium into the Viaflex bag.
4. Using a 10-mL syringe and an 18-gauge needle, withdraw 5 mL of sterile growth medium from the reconstituted vial 1, and transfer it into the Viaflex bag.
5. Using a 20-mL syringe and an 18-gauge needle, withdraw 10 mL of sterile growth medium from a 10-mL vial (vial 3), and transfer it into the Viaflex bag.
6. Using a 10-mL syringe, make a second withdrawal of 5 mL of sterile Trypticase soy growth medium from vial 2 through the dispensing pin. Attach an 18-gauge needle to the syringe, and transfer the growth medium into the Viaflex bag.
7. Using a 10-mL syringe and an 18-gauge needle, make a second withdrawal of 5 mL from the reconstituted vial 1, and transfer it into the Viaflex bag.
8. Carefully open a 10-mL ampul of sterile Trypticase soy growth medium. Using a 20-mL syringe and a 5- μ m filter straw, withdraw 10 mL of sterile Trypticase soy growth medium from the ampul. Remove the filter straw, and replace it with an 18-gauge needle. Transfer the growth medium into the Viaflex bag.
9. Using a 10-mL syringe, make a third withdrawal of 5 mL of sterile Trypticase soy agar from vial 2 through the dispensing pin. Attach an 18-gauge needle to the syringe, and transfer the growth medium into the Viaflex bag.
10. Using a 10-mL syringe and an 18-gauge needle, make a third withdrawal of 5 mL from the reconstituted vial 1, and transfer it into the Viaflex bag.
11. Label the bag, incubate it at 25–35 °C for 14 days, and observe the content for cloudy turbidity or discrete colonies that indicate microbial growth.