Using medium-fill simulation to establish a benchmark microbiological contamination rate for low-risk-level compounding

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Abstract: A benchmark contamination rate for prefilled syringe compounding was determined by using a medium-fill-simulation method.

One thousand thirty-five 1-mL tuberculin syringes were aseptically filled with 0.9 mL of sterile soybean-casein digest medium and capped. These syringes were placed into clear nonsterile plastic bags and incubated at 35 °C for seven days, then inspected for cloudiness or colony formation indicative of bacterial growth. The operation was performed by two certified pharmacy technicians in an ISO Class 5 vertical-airflow biological safety cabinet in a typical inpatient pharmacy compounding area over two days. The technicians wore protective garments and gloves and followed standard procedures of preparing sterile injections. The adequacy of the methodology was verified by using four syringes that contained deliberately contaminated medium and incubating them along with 15 aseptically prepared syringes at 35 °C for seven days.

Colony formation in the four syringes containing contaminated medium was directly observed and differentiated from the control syringes, which confirms the validity of the method. No bacterial growth was detected in any of the 1035 medium-filled syringes studied. Therefore, the contamination rate for aseptic compounding operation was less than 0.1%.

Medium-fill-simulation testing of 1035 prefilled tuberculin syringes yielded no contamination. A contamination rate of less than 0.1% should be achievable and expected for this type of low-risk pharmacy preparation after pharmacies validate their own compounding operation.

Index terms: Benchmarking; Compounding; Contamination; Control, quality; Methodology; Sterile products; Storage; Syringes
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Recent cases of injury and death due to improperly prepared and contaminated injections compounded by pharmacists have once again raised questions about pharmacists' ability to prepare sterile products safely.[1-3] The same questions were asked a dozen years ago with respect to sterile products prepared in both hospital and community pharmacy settings. Those concerns led to the publication of guidelines on preparing sterile products by the American Society of Health-System Pharmacists (ASHP)[4] and the United States Pharmacopeia (USP).[5] The recent incidents show that failure to implement the recommendations can lead to tragedy and point to the need for stricter regulation and control of such compounding. Many state boards of pharmacy are considering changes to the regulations governing pharmacy compounding. USP is issuing a new chapter on compounding sterile preparations providing a quality assurance framework that can be enforced by state boards.[6] The Food and Drug Administration is considering new legislation. Clearly, pharmacy needs to embrace a culture of quality in compounding—particularly sterile-product compounding—and adopt the necessary quality assurance steps.

Reiter[7] recently reported a study of contamination associated with prefilled syringes of fat emulsion for neonatal use. The author noted, "It is imperative that the repackaging not compromise sterility and thus place the immunocompromised neonate at increased risk of infection." However, the study found an overall contamination rate of 3.3% for these

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prefilled syringes when results for both newly prepared syringes (1 of 66 syringes contaminated) and syringes returned from patient areas after use (2 of 33) were pooled. Some readers believed that the reported contamination rate was unacceptably high for this simple compounding operation, particularly for the intended patient population, and could lead to harm or even death.[8,9]

Aseptic prefilling of syringes qualifies as low-risk-level compounding according to USP[5,6] and ASHP.[4] Arguably, syringe prefilling is the least challenging kind of sterile preparation encountered in pharmacy practice. It entails only a single stopper penetration and needle removal, followed by capping of the syringe tip, with each step handled aseptically in a suitable clean-air environment. Both USP and ASHP call for a combination of environmental engineering controls, barriers against contamination by personnel, and adequate training in aseptic preparation to minimize the risk of inadvertent contamination.

The purpose of this study was to determine a benchmark contamination rate for prefilled-syringe compounding by using a growth medium-fill-simulation method as specified in both the USP and ASHP guidelines.[4-6]

Methods

To simulate prefilled-syringe compounding, 1-mL tuberculin syringes[a] were fitted with 20-gauge 1.5-inch short-bevel needles,[a] aseptically filled with 0.9 mL of sterile soybean–casein digest medium,[b] and capped with syringe-tip caps.[c] The syringe-filling manipulations were performed by two certified pharmacy technicians working in one certified and properly operating Class 5 vertical-airflow biological safety cabinet[d] located in a room closed off from the outside corridor by a conventional door and having uncontrolled air supplied. This room is routinely used for training purposes, and trainees and trainers were present elsewhere in the room during part of the syringe-prefilling operation. This arrangement was intended to represent the typical operating conditions found in many hospital and community pharmacies. Higher-quality facilities are more appropriate for products actually intended for human use and provide a greater degree of quality assurance.[4,6]

In a preliminary experiment to verify the adequacy of the test methodology, 15 syringes were filled with 0.9 mL of sterile growth medium and capped. Separately, about 5 mL of growth medium was deliberately contaminated with a small amount of microorganisms collected from an oral swab. Four additional syringes were filled with the contaminated medium, capped, and incubated at 35 °C for seven days in accordance with the instructions provided by the growth medium manufacturer.

Before starting the experimental filling operation, the technicians, who were clad in scrubs and shoes worn in from outside the building, donned shoe covers[e] and hair covers[e]; thoroughly cleaned their hands, fingernails, and arms with antimicrobial detergent and water; donned gowns[f]; and put on gloves.[g] No bare skin was left exposed on hands and arms that would be in the compounding area inside the hood. The gloves were latex-free, powder-free nonsterile gloves that were sanitized with 70% isopropyl alcohol before the start of syringe filling. No facemasks were used because the biological safety cabinet was equipped with a transparent face shield. The biological safety cabinet, which had been left running for 24 hours, was cleaned thoroughly on all surfaces with 70% isopropyl alcohol before each session of syringe filling.

Syringe filling was performed during two afternoon sessions of approximately four hours each by the technicians, who had successfully completed their annual verification of proper aseptic technique. A total of 535 syringes were prepared in the first session and 500 in the second session. The time of day and length of the session were selected to ensure that the technicians would be relatively tired and bored. Periodically, the filled syringes and debris were removed from the hood and new syringes and caps in intact packaging were placed inside. Each time a technician's hands left the hood, the gloves were changed and the new gloves were sanitized with 70% isopropyl alcohol. The gloves were considered to be and were used as nonsterile containment devices to prevent contamination from entering the critical compounding area. Efforts to avoid touch contamination were employed throughout the filling.

The syringes were filled individually, as occurs commonly in compounding pharmacies in both hospital and community settings. The syringe was fitted with a needle, which was used to penetrate the vial stopper, and 0.9 mL of growth medium was drawn into the syringe. The needle was withdrawn and removed from the syringe. A syringe-tip cap was then attached. The filled and capped syringes were placed into clear nonsterile plastic bags, which could accommodate about 125 syringes each. The capped syringes in the bags were incubated at 35 °C for seven days in accordance with the instructions provided by the growth medium manufacturer and then inspected for cloudiness or colony formation resulting from microbial contamination.

Results

In the preliminary experiment done to verify the adequacy of the methodology, the contaminated syringes could be readily detected by visual inspection after incubation at 35 °C for seven days. A small number of colonies had formed in each syringe containing the contaminated growth medium. These syringes were easily differentiated from the other

syringes filled with sterile growth medium that showed no visible growth, demonstrating the validity of the syringe-inspection procedure.

No growth was detected in any of the 1035 growth medium-filled syringes in the experiment. A contamination rate could not be established because no contamination had occurred. However, the expected benchmark contamination rate for this aseptic compounding operation in this facility can be classified as less than 0.1%, or less than 1 in 1000 syringes.

Discussion

USP requires and ASHP suggests that each pharmacy compounding sterile products regularly establish its own contamination rates by using medium-fill simulations for the various types of sterile dosage forms it prepares.[4,6] The contamination rates will be unique to each facility and its cadre of compounding personnel. Rates may vary not only from pharmacy to pharmacy but from location to location within pharmacies.

Personnel who compound sterile products typically consider every unit they produce to be sterile. Too often, little consideration is given to the reality that contamination of compounded units is occurring at some rate. 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 preparers. Even with the best environmental controls and the most skilled personnel, inadvertent contamination is an ever-present possibility that should be considered and evaluated. Each pharmacy is obligated to determine the contamination rate for its sterile-product-compounding operations, particularly for more complex compounding, to ensure that an inordinately high contamination rate is not creating an unacceptable risk for patients.

The preferred method for evaluating the overall process used in sterile compounding is a simulation using growth medium.[4-6] In our study, we found no contamination among 1035 syringes. Earlier studies in which this method was used to test 250 syringes[10] and 150 syringes[11] also found no contamination.

The essence of quality assurance in sterile compounding is proving that the pharmacy is delivering what it purports to be delivering: a sterile preparation. The burden of proof is on the pharmacy to document that the contamination rates for the various risk levels are acceptably low. For prefilling syringes—the least difficult type of sterile-product preparation in the USP low-risk-level category—we found that a contamination rate of less than 0.1% is readily achievable with appropriate precautions. No pharmacy or its patients should be expected to accept a substantially higher contamination rate for this type of compounding. This is a benchmark that can be used for comparison. However, it is up to each pharmacy to prove that an adequately low contamination rate is achieved for its own operation.

For more complex manipulations, preliminary unpublished evidence exists that a higher rate of contamination may occur. If so, then measures must be taken to reduce the underlying contamination rate as much as possible. A quality assurance process that includes medium-fill simulation must be established in each pharmacy that compounds sterile products to ensure that the contamination rate remains acceptably low and under control. It is incumbent on the profession of pharmacy to ensure that a culture of safety exists to forestall a culture of microbes.

Conclusion

Medium-fill-simulation testing of 1035 prefilled tuberculin syringes identified no contamination. The underlying rate of contamination under the conditions tested was therefore less than 0.1%, a rate that may serve as a benchmark in pharmacies after validating their own compounding operation.

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[a]Becton Dickinson and Company, Franklin Lakes, NJ 07417.

[b]GroMed TSB Medium, Q.I. Medical, Inc., Nevada City, CA 95959.

[c]Red Cap, B. Braun Medical, Inc., Bethlehem, PA 07417.

[d]NuAire, Inc., Plymouth, MN 55447.

[e]Allegiance, McGaw Park, IL 60085.

[f]Chemo Safety, The Ludlow Company LP, Chicopee, MA 01022.

[g]Safeskin Purple Nitrile examination gloves, Kimberly-Clark, Roswell, GA 30076.

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