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Quality Assurance and <797> Compliance:

Fact Versus Fiction

Which are your environmental monitoring and sterility testing programs based on?

THREE YEARS AFTER THE RELEASE OF USP CHAPTER <797>, PHARMACISTS and technicians are still struggling to identify reliable products and sources of information to help them comply with the standard's environmental monitoring, sterility testing, and facility/engineering control requirements. Like all good free-market economies, vendors and consultants alike offer tools and services to assist those in need. However, customers should be cautious and make well-researched choices. This is especially true for items that are not covered under a strict warranty. Wouldn't it be interesting to ask vendors to guarantee that their products – if used according to directions – would comply with <797> requirements?

Pharmacists also need to stop creating their own quality assurance (QA) procedures without first ensuring that the methods are based on the correct rationale. Recently, on a professional pharmacy message board (listserv), a pharmacist complained about "home-grown" methods for compliance that have developed due to the lack of formal training for the compounding of sterile preparations and the lack of information on how to comply with USP-accepted methods.

This article will discuss the science-based QA procedures required to comply with <797> and ensure that your compounded sterile preparations (CSPs) are safe and effective for your patients, while arming you with the information you need to "trust, but verify" the representations of vendors and consultants.

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Environmental Monitoring

Assessing and verifying the performance of your aseptic compounding environment are critical quality assurance (QA) procedures. Environmental monitoring programs are designed to promptly identify potential sources of contamination, allowing for the implementation of corrective actions to minimize the possibility of CSP contamination. An environmental monitoring program provides information that demonstrates that your engineering controls, disinfecting procedures, and employee work practices create a compounding environment that consistently maintains acceptably low microbial levels. The compounding area includes the ISO Class 5 primary engineering controls, the ISO Class 7 cleanroom, and the ISO Class 8 anteroom or ante-area. The value of an environmental monitoring program lies in the consistent, quantitative assessment of environmental conditions in these areas over time.

When performing environmental monitoring functions, there are a few critical points that need to be considered to ensure the validity of your test results (growth of environmental bioburden).

The bullets below are not just for settling plates; air sampling and surface sampling should use the same medium base – tryptic soy casein with polysorbate 80 and lecithin agar or broth. These offer a good buffering effect and keep the organisms separated so that they do not clump into aggregates, thereby making your counts more reliable. Temperature and incubation are the same for air and surface sampling, as well.

- Settling plates used for air sampling should be 60 mm to 100 mm in diameter and contain sufficient and appropriate media to detect organisms of concern.
- Settling plates should be exposed to air for four hours.
- Surface or contact plate areas vary from 24 to 30 cm^2. When swabs are used in sampling, the area covered should be greater than or equal to 24 cm^2, but no larger than 30 cm^2.
- Surface or contact plates should contain polysorbate 80 and lecithin, which inactivate many residual disinfectants. Polysorbate 80 neutralizes phenols, hexachlorophene, and formalin, and lecithin inactivates quaternary ammonium compounds.
- The aerobic bacterial count can be obtained by incubating the tryptic soy broth settling plates at 30° C to 35° C for 48 to 72 hours.

There is evidence to suggest that settling plates are not as effective as an electronic or impaction-type air sampler. USP Chapter <1116> states that settling plates should "not be used for quantitative estimations of the microbial contamination levels of critical environments."

The following are among the limiting factors associated with the use of settling plates for air sampling:

- Gravity or depositional sampling is a non-quantitative collection method in which an agar medium is exposed to the environment and airborne organisms are collected primarily by gravity.
- The collection of airborne microorganisms by settling plates is affected by the size and shape of the particles and by the motion of the surrounding air (turbulence within ISO Class 5 engineering controls).
- Large particles are more likely to be deposited on the collection surface, which can lead to misrepresentation of the prevalence of airborne microorganisms and the exclusion of smaller particles from collection.
- Airborne concentration of the microorganisms cannot be determined by gravity sampling, because the volume of air from which the particles originate is unknown.
- Gravity sampling has been compared with various methods that pass a known volume of air to the collection medium. The results show that the airborne concentrations derived from gravity sampling are not qualitatively or quantitatively accurate and do not compare favorably with those obtained by other sampling methods.

Sterility Testing

To extend the beyond-use dating of compounded sterile preparations, you must perform a sterility test. Pharmacists struggle with this QA method, since historically, we only considered chemical stability, with little or no regard for microbial sterility. There are currently only two USP-approved methods of sterility testing for aseptic compounded preparations – direct inoculation and membrane filtration – and they are described in USP 29/NF 24, Chapter <71>, Sterility Tests.

Photos courtesy of AnazaoHealth

The assessment of your aseptic compouding environment's performance is a critical QA procedure.

Direct Inoculation

With direct inoculation, a small solution aliquot is withdrawn from a compounded solution bag (either a small-volume parenteral minibag or a large-volume parenteral bag) and is then added to a small volume (3 to 10 mL) of tryptic soy broth and incubated. Turbidity in the growth medium would indicate contamination. In order to observe turbidity in tryptic soy broth solutions, the number of microorganisms needs to approach 1 million organisms per mL. There are several limitations with this method of testing.

If the tested solution is a milky or turbid product such as triple-mix TPN solution, the medium will immediately appear turbid, making the visual detection of microorganism growth very difficult. Using this method to test an antibiotic solution will also be problematic, unless the antibiotic has been neutralized.

Most solutions will not be grossly contaminated and as such, direct inoculation is not necessarily sensitive enough to accurately reflect the condition of the batch. For example, if a 1-mL aliquot sample is withdrawn from a 1000-mL bag, direct inoculation will only detect a contamination level of over one microorganism per mL. If the compounded preparation is only contaminated with 10 microorganisms, the direct inoculation method will have a minimal chance of detecting the contamination.

USP requires that the quantity of the aliquot comply with the parameters established in Tables 1 and 2. Following these guidelines ensures that the volume of the tested compounded solution aliquot is not more than 10% of the volume of the medium.

This method is routinely employed by pharmacists and technicians as both a method of verifying a compounding employee's aseptic technique and as a "valid" sterility test to extend the beyond-use dating of compounded sterile preparations within USP Chapter <797>. Because of the inherent flaw in this method, the risk of having a false negative is extremely high, creating a false security that the compounded sterile preparation is sterile or that the employee has good aseptic technique. Personnel aseptic technique needs to be tested through the manipulation of tryptic soy broth under simulated compounding conditions and methods routinely employed by staff when preparing compounded sterile preparations.

Membrane Filtration

Membrane filtration is preferred over direct inoculation for several reasons. The method does not depend on preparation type, container volume, or con-

Table 1:
Minimum Quantity to Be Used for Each Medium

Quantity Per Container	Minimum Quantity to Be Used (unless otherwise justified and authorized)
Liquids (other than antibiotics)	
Less than 1 mL	The whole contents of each container
1 to 40 mL	Half the contents of each container, but not less than 1 mL
Greater than 40 mL, but not greater than 100 mL	20 mL
Greater than 100 mL	10% of the contents of the container, but not less than 20 mL
Antibiotic liquids	1 mL
Other preparations soluble in water or in isopropyl myristate	The whole contents of each container to provide not less than 200 mg
Insoluble preparations, creams, and ointments to be suspended or emulsified	The contents of each container to provide not less than 200 mg

Table 2:
Minimum Number of Articles to Be Tested Per Batch

Number of items in the batch	Minimum number of items recommended to be tested
Injectable preparations	
No more than 100 containers/articles	10% or four items, whichever is greater
More than 100 but less than 500 containers	10 containers
More than 500 containers	2% or 20 containers, whichever is less
Large-volume parenterals (LVPs)	2% or 10 containers, whichever is less
Ophthalmic and other non-injectable preparations	
No more than 200 containers	5% or two containers, whichever is greater
More than 200 containers	10 containers
Bulk solids	
Less than four containers	Each container
Between four and 50 containers	20% or four containers, whichever is greater
More than 50 containers	2% or 10 containers, whichever is greater

Ensuring the Sterility and Stability of Outsourced CSPs

If you choose to buy compounded sterile preparations from an outsourcer, be sure to verify that the company is following QA procedures that are supported by science. For instance, if the outsourcer claims their product has a beyond-use date that exceeds <797>'s limits, request a copy of the stability data that verifies that dating. Those beyond-use dates should be supported by a reliable study. If the outsourcer supports their claims with an internal study, you should have access to it. The rule is: Trust, but verify. You should also request a copy of the outsourcer's product release checks and tests documentation. To ensure the safety of your patients, ask for evidence that they have done the sterility testing.

centration of microorganisms to provide a statistically valid sample. With membrane filtration, the entire CSP volume is filtered using either a 0.45- or 0.22-micron filter, which will capture all the microorganisms present and remove product components that could cause the growth medium to appear turbid. There are special considerations that must be employed when testing antibiotic solutions. USP Chapter <71> has very specific requirements for handling antibiotics. The nature of the membrane-filter method reduces operator handling, thereby decreasing the likelihood of accidental contamination. The USP makes specific membrane filtration recommendations in <71>. The bubble-point of the filter must also be robust enough to withstand the pressure of the solution transfer. If the filter breaks or raptures, it could cause a false negative. It is important to carefully read USP Chapter <71> for more information. Also remember that both direct inoculation and membrane filtration are aseptic procedures that could lead to contamination and, hence, cause a false positive.

Summary

Pharmacists need to stop "inventing" methods to "test" the sterility of CSPs. To put into practice the QA methods necessary to ensure the sterility of your CSPs, you need knowledgeable and properly trained personnel using validated methods. Quality and sterility can be achieved when properly trained and garbed personnel work in controlled environments that are maintained through routine procedures. ■

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