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# Understanding the Microbiology Behind USP <797>

If you are reading this article, you probably realize that USP is about to finalize its 2006 revisions to Chapter <797> on sterile compounding. The tentative changes were published in May 2006, with the public comment period opened through August 15, 2006. Soon the USP Sterile Compounding Expert Committee will review each comment and the final document should be published in January 2007.

Probably the most controversial parts of Chapter <797> are the sections on establishing an on-going program for environmental monitoring in the pharmacy, as well as the media-fill competency testing of personnel and sterility testing of CSPs (compounded sterile products). Some pharmacists have objected to these particular standards as too prescriptive and ridiculous; some do not think that they will increase patient safety and claim patients have not been harmed. However, the fact is that patients have been harmed by contaminated CSPs.

Literature has been published referencing investigations by the Centers for Disease Control and Prevention and the Food and Drug Administration into instances of patient morbidity and mortality from improperly compounded, supposedly sterile drugs. (See "References" for more information.) Moreover, in August 2006, *USA Today* published a lead article on the case of families suing a free-standing compounding pharmacy for the deaths of their loved ones caused by nosocomial infections from improperly compounded, nonsterile solutions used during cardiac surgery.

Photo courtesy of Q.I. Medical

**Personnel glove fingertip sampling was added as a requirement in the proposed changes to <797>.**

Photo courtesy of Biotest

The best way to sample the air is to use electronic air samplers in a process known as **volumetric air sampling**.

A well-thought-out microbial program should not break the institutional bank, nor should it inevitably require expensive or extensive renovations. This article will review each of the areas requiring microbial monitoring and will suggest a best-practice scenario for each. Endotoxin testing of high-risk products, although required by USP Chapter <797> and supported by these authors, is not covered here. (*See article on page 12 for more information on endotoxin testing.*)

## Air Sampling

Probably the most confusing part of the 2006 revisions is the section on air sampling. The original 2004 chapter monograph allowed the use of settling plates; this practice was also known as gravimetric sampling, and sometimes incorrectly referred to as "passive" sampling, because organisms present in the air would settle onto the surface of an agar plate by gravity. Unfortunately, this technique is not suitable for three reasons:

1) Most hospital and/or free standing compounding pharmacies do not have laminar flow rooms where gravimetric sampling can be used more successfully than volumetric sampling.

2) Small microorganisms (≤10 microns) are affected by turbulence and air flow rate and do not settle onto the agar surface. These small organisms are very important agents of morbidity and mortality and are the ones most commonly found in the hospital environments, especially in heating, ventilation, and air conditioning systems. Their absence in cultures of settling plates would be a critical underestimation of any contaminants in the air.

3) Stainless steel and other nonporous surfaces have been studied for decades in health care facilities and are not conducive to microbial growth or amplification. Furthermore, settling plates must be exposed to the air for four hours and should be in the stream of unidirectional flow. This dries out the agar medium, which, in turn, inhibits the growth of any potentially viable microorganisms.

The best way to sample the air is to use electronic air samplers in a process known as volumetric air sampling. Volumetric air sampling may be either active or passive. The 2006 updates to USP Chapter <797> require active air sampling, and mandate that compounding (occupant activity) take place during sampling. The 2006 revisions also call for a volume of 1000 L of air to be collected at each sampling point. There are two specified media, one for bacteria (TSAp/l or tryptic soy agar with polysorbate 80 and lecithin) and one for fungi (MEA or malt extract agar). A sampling plan must be written prior to beginning the ongoing environmental program and an air sampler must be selected.

## Electronic Air Samplers

There are at least three air samplers that meet the criteria outlined in the proposed changes to <797>. The first is the Andersen N-6 (available from ThermoElectron Corporation), the second is the SKC Quick 30 (available from SKC, Inc.), and the third is the SAS (available from Bioscience International). Each of these can be calibrated the day of use, so that the exact volume of air specified is collected. A two-headed version of the SAS sampler allows both the TSAp/l and MEA plates to be collected at the same time and accomodates contact plates as well as petri dishes. Since the SAS can be set to collect 500 L to 1000 L in each head within approximately two to five minutes, it is the most time-efficient of all the samplers men-

tioned above and requires the least calculations. The Andersen N-6 and SKC sampler are usually set to collect ≥ 28.3 liters per minute (lpm) and 30 lpm, respectively. Thus, it would take between 30 and 35 minutes to collect 1000 L of air using either of these instruments. Other samplers can be connected for use in tandem. These manufacturers suggest 10 minutes of sampling for sterile sites; however, this will only represent approximately 300 L in a hood or a room where the positive airflow may compete with the lower negative flow rate (vacuum) of the equipment. The representative sample collected would be small compared to the volume under the hood or in the room during compounding activities.

## Developing a Sampling Plan

The sampling plan should be developed based upon the size of the compounding area and the number of hoods. In order to trend the number and type of organisms on a weekly (high-risk) or monthly (low- or medium-risk) basis, it is necessary to sample with the same equipment and by the same method at the same general area each time. Areas to be sampled should be indicated on a floor plan of the pharmacy, including the LAFWs (laminar airflow workbenches), BSCs (biological safety cabinets), CAIs (compounding aseptic isolators), the cleanroom or buffer zone, and the gowning and/or anteroom areas.

## Incubation

USP Chapter <797> states that the media must be incubated at specific temperatures requiring two separate incubators; the TSAp/l is incubated at 35°C +/- 2°C and the MEA at 28°C +/- 2°C. It is in the best interests of the pharmacy to partner with a microbiology laboratory for this procedure, as well as for the in-house quality control check of the media prior to use, and for the identification of any organisms that grow. Although the media comes from the manufacturer with a certificate of conformance, they must be retested for sterility and growth promotion prior to use. This testing allows the user to verify that there were no adverse conditions (e.g., extreme heat, extreme cold, or excessive drying) during shipping. It is not prudent for a pharmacy to keep stock cultures of molds and bacteria for purposes of quality control, as these are likely to contaminate the air in the pharmacy. In fact, the pharmacy or the microbiology lab must be a

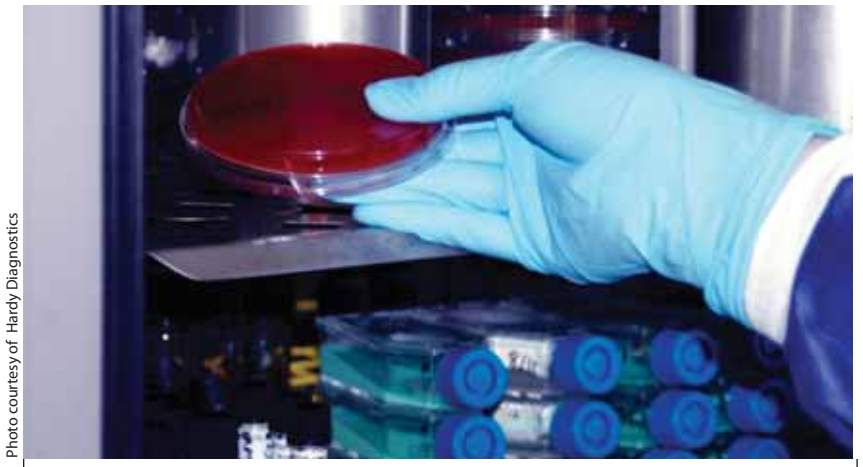

Photo courtesy of Hardy Diagnostics

**Media used in your environmental monitoring program must be incubated at the specified temperatures.**

BSL2 (Biological Safety Level 2) facility in order to handle positive fungus cultures and certain bacteria. A BSL2 lab/facility must be under negative pressure similar to the chemotherapy preparation room. Most importantly, it is necessary to track the organisms from week-to-week or month-to-month, and this involves partial or full identification of bacteria or fungi. The federal government regulates microbial identification as a high-complexity microbiology test.

## Equipment and Personnel Certification

It is important to remember that your microbial environmental program supplements, but does not replace, the routine recertification of the hoods and the certification of each room and hood to ISO Class 8, 7, or 5 standards, depending on the particle counts. USP Chapter <797> also places a lot of emphasis on certifying that compounding personnel can competently prepare sterile products. This process is known as media-fill competency testing and is specific for each risk level. Depending upon the complexity of compounding in the pharmacy, different numbers of manipulations are performed with TSB (tryptic soy broth). The broth in the completed test vials or IV bags is then incubated for 14 days to see if they promote microbial growth. Growth is indicated by the observation of turbidity or cloudiness. Every member of the compounding staff, including individuals compounding products for immediate use (like emergency room nurses) should be tested at least annually; high-risk compounding personnel should be tested every six months.

An additional way to see if individual personnel are compounding aseptically is to set-up a program in which CSPs that would be discarded (e.g., medications prescribed to a patient who has been discharged prior to use, a compound nearing its expiration date, or medications prepared with the wrong concentrations) can be sent to the microbiology laboratory for sterility testing. This is a good way to measure your compounding staff's aseptic technique on an on-going basis. However, three rules should be kept in mind when determining whether any product is sterile. The first is that the direct inoculation of TSB and thioglycollate broth is permissible only if the volume of the prepared product is small. For larger volumes, the product must be membrane filtered, and the membrane must be aseptically cut in half, with one-half being placed in TSB and the other in thioglycollate broth. Finally, beta-lactam antibiotics must be neutralized with their respective penicillinase or cephalosporinase prior to testing. All of these "rules" are part of USP Chapter <71>, which, like USP Chapter <797>, is enforceable.

## Light at the End of the Tunnel

The current upheaval surrounding <797> in the pharmacy is similar to that which occurred in the clinical laboratory when the federal government legislated the Clinical Laboratory Improvement Act in 1967. If it is any comfort, laboratories have grown accustomed to what seemed to be a heavy-handed set of regulations at the time. Pharmacists and pharmacy technicians will likewise grow more comfortable with USP Chapter <797> as they see the improvement in the quality of the CSPs leaving the pharmacy. ■

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**WHERE TO FIND IT: SUPPLIES AND EQUIPEMENT**

| Vendor | Reader Service | Website |
|---|---|---|
| **Air Samplers** | | |
| Biotest | 24 | www.biotestusa.com |
| Millipore | 26 | www.millipore.com |
| Thermo Electron Corporation | 27 | www.thermo.com |
| SKC, Inc. | 28 | www.skcinc.com |
| Bioscience International | 33 | www.biosci-intl.com |
| **Media** | | |
| Remel | 34 | www.remel.com |
| Hardy Diagnostics | 36 | www.hardydiagnostics.com |
| Becton-Dickinson | 63 | www.bd.com |
| **Media-Fill Competency Kits** | | |
| Hardy Diagnostics | 64 | www.hardydiagnostics.com |
| Q.I. Medical | 66 | www.qimedical.com |
| Valiteq | 67 | www.valiteq.com |

## REFERENCES:

1. Centers for Disease Control and Prevention. 2002. Exophiala infection from contaminated injectable steroids prepared by a compounding pharmacy – United States, July – November 2002. *MMWR* 51:1109-1112.
2. Centers for Disease Control and Prevention. 2005. Pseudomonas bloodstream infections associated with a heparin/saline flush – Missouri, New York, Texas, and Michigan, 2004 – 2005. *MMWR* 54: 269-272.
3. Perz JF , Craig AS, Stratton CW, Bodner SJ, Phillips, Jr. WE, and Schaffner W. Pseudomonas putida septicemia in a special care nursery due to contaminated flush solutions prepared in a hospital pharmacy. *J. Clin. Microbiol.* 2005: 43; 5316-18.