Quality Assurance *for* Sterile Products

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The focus on developing, implementing, and using quality systems during the preparation of pharmacy-prepared sterile products has never been more important than it is today. On November 17, 1998, former President William Jefferson Clinton signed into law the US Food and Drug Administration Modernization Act (FDAMA) of 1997. Section 503A of the FDAMA, which is titled "Pharmacy Compounding," defined the limits of legitimate compounding. By limiting the scope of pharmacy compounding, the law is designed to protect patients from the unnecessary use of compounded drugs. Commercially manufactured drugs are scientifically tested, approved by the Food and Drug Administration (FDA), and manufactured under controlled conditions that meet current good manufacturing practices (cGMPs).[1]

By virtue of the FDAMA, the FDA is empowered to identify certain drug products that are difficult to compound and for which compounding can adversely affect safety or effectiveness. The Pharmacy Compounding Advisory Committee of the FDA agreed that sterile products prepared by means of procedures other than those described in <Chapter 1206> ("Sterile Drug Products for Home Use") of the *United States Pharmacopeia* (*USP*) met the requirements for being difficult to compound.[2]

Although Section 503A was ruled unconstitutional by the 9th Circuit Court of Appeals on February 6, 2001,[3] pharmacists must realize that the FDA has taken a great interest in pharmacy compounding. That interest and the issues surrounding Section 503A may not go away. *USP* Chapter <1206>, which is constantly undergoing revision, can be used as the standard for the compounding of sterile preparations.

Over the past two decades, news articles have reported patient injuries and deaths caused by pharmacy compounding errors.[4-9] Many of those errors resulted from inadequate quality control measures. In 1996, the American Society of Health-System Pharmacists (ASHP) conducted a national survey of quality assurance for pharmacy-prepared sterile products. That survey indicated that few pharmacies were equipped with adequately controlled compounding environments, which are essential in producing a sterile product. The survey also indicated that many pharmacists were not performing critical quality assurance checks by means of environmental monitoring, end-product testing, and process validation.[10]

The focus of this article is twofold. The first is to emphasize that the operating standards described in the ASHP *Guidelines on Quality Assurance for Pharmacy-Prepared Products*[11] and/or *USP* Chapter <1206>[13] should be reviewed and followed by responsible pharmacy personnel (pharmacists or technicians) who prepare sterile products such as compounds for intravenous or intramuscular administration, ophthalmic use, or inhalation. The second focus is that of identifying operating metrics that can used to design a quality system for the preparation of sterile products in a pharmacy.

ASHP Quality Assurance Guidelines and *USP* Chapter <1206>

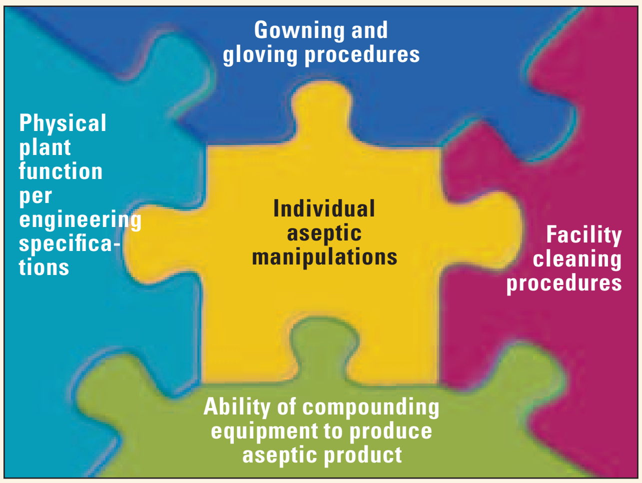
The ASHP quality assurance guidelines define activities that should be used in the preparation of sterile products in the pharmacy. In those guidelines, a variety of different operating parameters such as physical plant, types of products used, and length of product storage are described. The guidelines are also intended to "help pharmacists and pharmacy technicians prepare sterile products of the highest quality."[11] They were developed for use in a variety of practice settings that include hospitals, community retail pharmacies, long-term care facilities, and home care organizations.

In *USP* Chapter <1206>, key requirements that are essential in the production of quality products are defined. Several of those requirements are described below.[12]

- Personnel must be capable and qualified to perform their assigned duties.
- Ingredients used in compounding must have their expected identity, quality, and purity.
- Critical processes must be validated to ensure that procedures used consistently result in the expected quality of the finished product.
- The production environment must be suitable for its intended

Figure 1. Types of Activities Validated by Process Simulation Testing.

Process Simulation Testing Validates . . .



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purposes with respect to environmental cleanliness, control, monitoring, and the determination of environmental microbial action limits.

- Appropriate release checks or testing procedures must be performed to ensure that finished products have their expected potency, purity, quality, and characteristics at the time of release.
- Appropriate stability evaluation must be performed to establish reliable beyond-use dates to ensure that finished products have their expected potency, purity, quality, and characteristics, at least until the respective beyond-use date.
- Processes must always be carried out as intended or specified and must be under control.
- Preparation conditions and procedures must be designed to prevent mix-ups.
- Effective procedures for investigating and correcting failures or problems in the preparation or testing of a product (or in the product itself) must be followed and recorded.
- Quality control functions and decisions must be adequately separated from those of production.

Those sets of guidelines, however, do not provide pharmacists and technicians with specific actions that facilitate environmental monitoring, cleaning, and facility maintenance or the assessment of quality assurance activities in daily sterile-product preparation.[13] How do pharmacists and technicians decide which actions to implement? Usually, professional organizations or regulatory agencies do not dictate specific actions that have to be followed but instead publish general guidelines for creating a quality product. The FDA does not dictate how drug or medical-device manufacturers should meet the standards of cGMPs or quality system requirements (QSRs). It is the responsibility of each sterile-product manufacturer to use the guidelines described to develop, implement, validate, and monitor critical phases of sterile-product preparation.

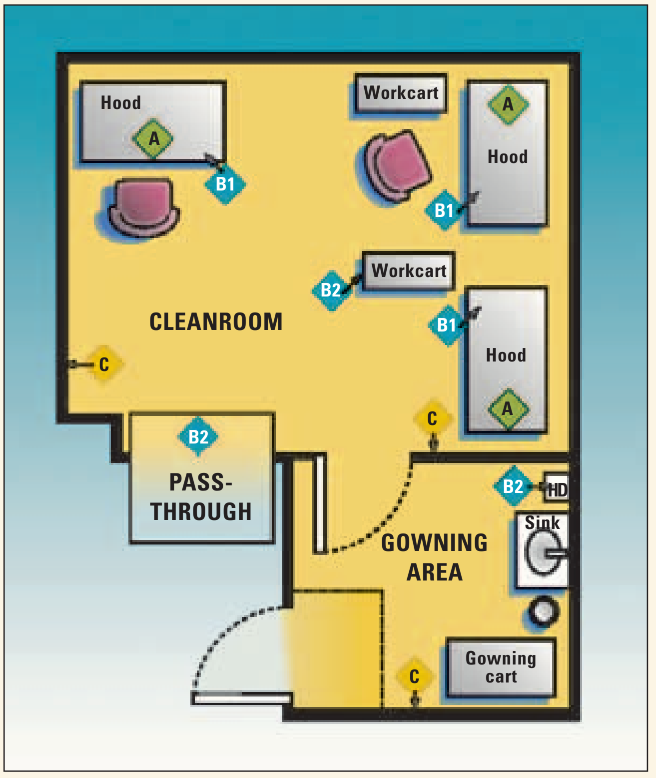
Quality is the consistent production of products or services that meet or exceed customer expectations. It does not occur by accident or by chance. The quality of sterile products depends on the control of factors that can destroy chemical stability and sterility. To ensure quality, those who prepare such products must monitor the following factors:

- The controlled work area microbial bioburden
- Routine cleaning procedures
- Initial and ongoing aseptic technique testing and/or process validation
- The compounding setup, solution verification processes, and final product inspection

Process Simulation Testing

Process simulation testing (Figure 1) is used to validate sterile-product preparation during all phases of production.

Figure 2. Pharmacy Cleanroom Environmental Sampling Locations.



A sites = surface sampling
B sites = air sampling
C sites = surface (wall) sampling
HD = hand dryer

Table 1. Baseline, Alert, and Action-limit Values for Pharmacy Cleanroom Environmental Sampling.

Room	Description	Location*	Baseline (Ideal)	Alert Limit	Action Limit
Cleanroom	Air sampling	A	0	0	3
		B1	0	0	3
		B2	≤ 5	> 5	8
	Surface sampling	A	0	> 0	3
		C	≤ 10	> 10	15
Gowning area and pass-through (if applicable)	Air sampling	B2	≤ 10	> 10	15
	Surface sampling	C	≤ 20	> 20	30

*Letter corresponds to the legend and locations from the previous diagram.

Developing a Dynamic Environmental Monitoring Program

The ability to achieve and maintain the integrity of the controlled work areas and the sterility of pharmacy-prepared products depends on factors such as:

- The ingredients of the compounded product (sterile versus nonsterile)
- The compounding equipment and processes used (closed systems versus open systems)
- Hand washing, garbing, and gloving procedures
- Aseptic technique used for compounding
- Facility and environmental conditions under which products are prepared

Both the ASHP and the USP publish recommendations about the type and frequency of environmental monitoring according to the risk involved in the compounding process. Most pharmacy operations batch-prepare and store antibiotics for more than 28 hours and prepare parenteral nutrition solutions (TPNs) by means of an automated compounding device. Those operations should be conducted according to ASHP risk level II procedures, which are closely related to the USP high-risk category I.

It is important to monitor the microbial bioburden of controlled work areas by monitoring air and surface samples. The total amount of airborne particles (viable and nonviable) under static conditions should be determined twice a year during routine hood and cleanroom certification. This is referred to as a "room particle count." Routine ongoing environmental monitoring involves establishing baseline data for the microbial bioburden of the controlled work areas. Air and surface sampling involve collecting environmental "snapshots" on tryptic soy broth (TSB)/agar (TSA) plates that support the growth of many types of microorganisms. Air sampling is accomplished by placing air-settling plates at various locations throughout the controlled environment according to the types of activities performed or the number of personnel and extent of product movement in the area. In Figure 2, various locations that can be used for environmental sampling are illustrated.

Each location is assigned three values: baseline (ideal), alert, and action limit (Table 1). Before the baseline is determined, the controlled work area should be thoroughly cleaned with a disinfecting detergent. After the cleaned areas are dry, locations from which samples are obtained should be tested. In class 100 environments (hoods or clean zones), the ideal baseline should be zero. The integrity of class 100 environments is closely correlated with the sterility of pharmacy-prepared sterile products.

Settling plates are TSA agar plates that are 100 mm in diameter. They should be exposed to cleanroom air for a period of 1 hour but not more than 3 hours. Exposure of longer than 3 hours causes the agar to dry out. Air sampling is a cost-effective way of obtaining quantitative data relative to the viable microbial particles expected to settle from the air at each sampling site. Other volume-of-air samplers such as the slit-to-agar (STA) sampler and the Reuter Centrifugal Air Sampler (RCS) (Biotest Hycon Corporation, Denville, New Jersey) can also be used to collect air samples. Those methods, which require the purchase of expensive collection devices, also provide quantitative sampling data.[12]

Surface sampling is performed with raised TSA plates that are 60 mm in diameter (RODAC plates). The TSA in RODAC plates is mixed with polysorbate 80 and lecithin, which inactivate many residual disinfectants. Polysorbate 80 neutralizes phenols, hexachlorophene, and formalin, and lecithin inactivates quaternary ammonium compounds. During sampling, a RODAC plate is pressed onto the area to be tested. Any microorganisms on the surface of the area tested (which should ideally be flat) are transferred onto the RODAC plate. After the sample has been obtained, the area tested should be wiped down with isopropyl alcohol to remove any residue left by the RODAC plate. While the sample is being obtained, operating conditions should be rotated between production (dynamic) and nonproduction (static) times. Testing under dynamic conditions is useful in monitoring the effectiveness of hand washing, garbing, and gloving by personnel. It also records the microbial condition of the controlled work area when staff are present. Testing under static conditions provides information about the functioning of high-efficiency particulate air (HEPA) filters and controls for pressure differentials, air exchanges, temperature, and humidity and about the effectiveness of cleaning and sanitizing procedures.

The sampling plates are incubated for 48 hours at 86°F to 95°F. Any discrete colonies, which are known as colony forming units (CFUs), that grow on the plates are counted at the completion of the incubation period and are noted on a collection form. Ideally, the plates with CFUs should be sent for analysis so that the species of the microorganisms can be identified.

Environmental monitoring should be performed daily at all sampling locations for 1 week to establish a microbial baseline and then once weekly to monitor overall bioburden trends over time. After a baseline has been established, action limits can be identified for each area and routine monitoring is required less frequently. A sample environmental monitoring schedule is shown in Figure 3.

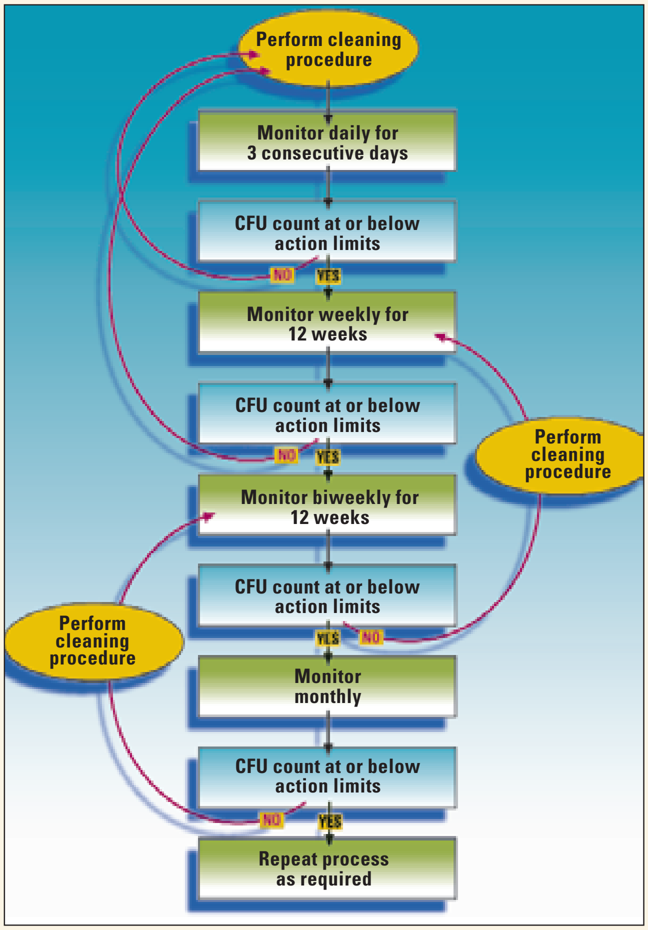
Observing the trends in the microbial bioburden over time is the key to having an effective environmental monitoring program. Any sudden increase in established action limits or trended increases in bioburden over time is a signal that an investigation should occur and that possible intervention may be necessary. Potential interventions include:

- Retesting sampling areas if alert limits are breached
- Reassessing cleaning procedures, which may include a review of cleaning documentation and the training of personnel
- Examining recent production activities for changes, such as the arrival of new compounding equipment in the controlled work area or irregularities that may have contributed to an increased bioburden
- Performing a three-time cleaning of the controlled work area
- Using a different cleaning agent
- Reviewing other validation outcomes to see whether they indicate an increase in the bioburden
- Retraining cleaning and compounding staff members

Routine Cleaning and Sanitizing Procedures

Staff who work in controlled work areas are the greatest source of viable and nonviable contamination.[14] All controlled work areas in which the staging, compounding, and storage of pharmacy-prepared sterile products are performed should undergo routine cleaning and sanitizing to maintain facility and environmental controls.

Figure 3. Sample Environmental Monitoring Schedule.



CFU, Colony forming unit

Sanitizing eliminates many or all pathogenic microorganisms on inanimate objects. Disinfectants, which do not kill endospores and are not sterile, are used in the pharmaceutical industry to kill vegetative bacteria and fungi. A sanitizing agent should reduce the non–spore-forming microbial population by 3 logs or should cause a 99.999% reduction in the number of microorganisms within 30 seconds of contact time.[15]

Effective cleaning and sanitizing agents are from one of four chemical families. They include:

- Phenolic compounds
- Quaternary ammonium compounds (QUATs)
- Chlorine compounds
- Alcohol compounds

Table 2 provides detailed information about each chemical family.

After the initial construction of a controlled work area or at the conclusion of a controlled work area certification process, a special three-time cleaning of all surfaces (ceiling, walls, floor, hoods, carts, etc) must be performed with appropriate agents. Two cycles of a sanitizing detergent like Vesphene LpH (Calgon Vestal, St.

Table 2. Characteristics of Cleaning and Sanitizing Agents.

Class	Recommended Use	Advantages	Disadvantages	Comments and Hazards	Examples
Phenolic compounds	Excellent bactericide Excellent fungicide Excellent tuberculocide Excellent viricide	Nonspecific concerning bactericidal and fungicidal action If boiling water causes rusting, the presence of phenolic substances produces an antirusting effect	Unpleasant odor Some areas have disposal restrictions Effectiveness reduced by alkaline pH, natural soap, or organic material Not sporicidal	Skin and eye irritant Sensitizer Corrosive Toxic	Hil-Phene LpH Metar Vesphene brand
70% Isopropyl alcohol solution	Cleaning some instruments Cleaning skin	Fairly inexpensive	< 50% Solution not very effective Not active when organic matter is present Not active against certain types of viruses Evaporates quickly Contact time not sufficient for killing microbes	Flammable Eye irritant Toxic	–
Chlorine compounds	Spills of human body fluids Good bactericide Good fungicide Good sporicide at >1000 ppm sodium hypochlorite	Kills hardy viruses (eg, hepatitis) Kills a wide range of organisms Inexpensive Penetrates well Relatively quick microbial kill May be used on food prep surfaces	Corrodes metals such as stainless steel and aluminum Organics may reduce activity Increases alkalinity Decreases bactericidal properties Unpleasant taste and odor Tuberculocidal with extended contact time	Follow spill procedure and dilution instructions Make fresh solutions before use Eye, skin, and respiratory irritant Corrosive Toxic	Bleach solutions (sodium hypochlorite) Clorox Cyosan Purex
Quaternary ammonium compounds (QUATS)	Ordinary housekeeping (eg, for floors, furniture, walls) Excellent bactericide Good fungicide Good viricide (not as effective as phenols)	Contains a detergent to help loosen soil Rapid action Colorless, odorless Nontoxic, less corrosive Highly stable May be used on food prep surfaces	Does not eliminate spores, tuberculosis bacteria, some viruses Effectiveness influenced by hard water Layer of soap interferes with action	Select from EPA list of hospital disinfectants Skin and eye irritant Toxic	Quatsyl Coverage 258 End-Bac Hi Tor

Source: Barbara Fox Nellis

EPA, Environmental Protection Agency

Louis, Missouri) followed by one cleaning cycle of sodium hypochlorite (bleach) should be performed. This type of cleaning removes viable and nonviable contaminants from certification personnel, certification equipment and tools, and compounds such as poly (alpha-olefin) (Emery 3004) (Cognis Corporation, Cincinnati, Ohio) that are used to test the HEPA filters and other parts of the heating, venting, and air-conditioning (HVAC) system. This establishes a baseline cleanliness level that can be used to determine the baseline bioburden.

A phenol-based cleaning agent such as Vesphene LpH (Calgon Vestal) should be alternated with sodium hypochlorite to prevent the development of microbicide-resistant bacteria. Cleaning agents should be alternated weekly and should be rotated with another cleaning agent like Quatsyl-256 (Sterling Drug, Montvale, New Jersey) at least every 3 months. A sample cleaning plan is outlined in Table 3.

Buckets and other cleaning tools should be dedicated to each area of use. Buckets used to clean floors should never be used to clean hoods or walls. To prevent inadvertent contamination, the cleaning implements used in the cleanroom or controlled work areas should be dedicated to those areas and should not be used in the anteroom or preparation area. To prevent soiled wipes from contaminating the cleaning solutions, low-lint wipes should be used only once to wipe down equipment, after which they should be discarded.

Table 3. Sample Cleaning Plan for Controlled Work Areas.

Area	Monday	Tuesday	Wednesday	Thursday	Friday
Agent	**Vesphene LpH**	**Bleach**	**Vesphene LpH**	**Vesphene LpH**	**Vesphene LpH**
Class 100 Aseptic processing area Hoods	Wipe down equipment Mop floor	Wipe down equipment Mop floor	Wipe down equipment Mop floor	Wipe down equipment Mop floor	Wipe down equipment Mop floor Mop walls Mop ceilings*
Class 10,000 Anteroom Gowning room	Wipe down equipment Mop floor	Wipe down equipment Mop floor	Wipe down equipment Mop floor	Wipe down equipment Mop floor	Wipe down equipment Mop floor Mop walls Mop ceilings*
Class 100,000 Pass-through Prep area	Mop floor	Mop floor	Mop floor	Mop floor	Wipe down counter tops Mop floor Wipe down bins*

*Performed monthly.
Equipment: Interior surfaces of hoods, chairs, workstations, pumps, wire storage (Metro) carts, garbage cans, and benches.

It is critical that all activities associated with cleaning, such as the preparation of cleaning solutions, be properly documented in logs or notebooks. Special three-time cleanings as well as routine daily, weekly, and monthly cleaning procedures must be performed and documented consistently. The training of personnel who perform cleaning procedures but are not pharmacy staff must be documented to ensure proper monitoring as well as compliance with policies on sterile compounding. Routine, consistent cleaning minimizes the overall bioburden of the controlled work area.

Aseptic Technique Validation

Proper aseptic technique is an acquired skill. Pharmacists and technicians who compound must complete aseptic technique validation before they are allowed to produce products for patient use. Aseptic technique validation is accomplished by means of media fills, in which actual compounding conditions and aseptic processes are simulated to demonstrate that microorganisms are not introduced during process-related activities. The activities performed by the operator of the media fill should mimic actual compounding activities, because the greatest risk of contamination occurs during normal production runs.

The amount and frequency of media-fill runs are controversial topics. At a minimum, the initial media-fill validation should occur daily for 3 days. This will allow the operator's technique to be tested for consistency and reproducibility and will eliminate results skewed by chance. It may be reasonable to consider quarterly media-fill runs, if that frequency is sufficient to satisfy minimum competency requirements. The frequency, number, and results of media-fill units (MFUs) must be documented. Media fills should not be performed during normal production, but rather immediately after daily production activity under worst-case conditions when microbial burden is at the highest level. TSB should not be used while sterile products are being prepared because of the potential for cross-contamination and dispensing errors (such as cases in which media-fill units are accidentally labeled and sent to patients for infusion).

Several aseptic technique validation kits are currently available. Some are limited to the use of only ampules, vials, and syringes. Although those kits produce a valid representation of aseptic technique for ampule and vial transfer activities, many do not include aseptic manipulations performed in most pharmacy operations. Other methods may be required to mimic the range of activities performed in pharmacies that compound parenteral solutions. Ideally, a media-fill procedure should incorporate multiple manipulations with syringes, ampules, vials, media-fill bags, transfer tubing, and empty bags for the administration of intravenous medication.

Sample Media-Fill Procedure

One MFU can be produced by the following method:

- Use a straight needle (not a filter needle) to withdraw 1 mL of sterile, preservative-free water from a glass ampule and inject the water into each of two TSB bags.
- Make five additional 1-mL withdrawals from the vial of sterile, preservative-free water and inject the water into each TSB bag.
- Transfer the content of both TSB bags via a Y-type transfer set into an empty bag used for the administration of intravenous medications.
- Clamp the tubing of the transfer set, crimp the tubing to seal it, cut the tubing, and incubate the bag for 7 days at room temperature and then for 7 days in an incubator at a temperature between 30°C and 35°C.

The instructions of the manufacturers of media-fill test kits must be carefully followed. The MFU should be incubated according to

Sample Validation Plan.

Validation Type	Requirement
Initial validation of operator aseptic technique	
Must be successfully completed before the product is mixed for use by patients	3 consecutive daily media-fill runs[a]
Revalidation after failure of media fill	
Must be completed if operator has one media-positive bag during the initial validation or two media-positive bags during ongoing revalidation	3 consecutive daily media-fill runs[a]
Ongoing revalidation of operator aseptic technique	
Must be completed quarterly	1 media-fill run[a]

[a] A media-fill run is defined as 10 media-fill units per day.

the following guidelines from the *USP*: seven days at room temperature followed by 7 days at a temperature between 30°C and 35°C or 14 days at room temperature (15°C to 30°C).

Ideally, MFUs should be read daily, but they must be read on days 7 (the last day of room temperature incubation) and 14 (the last day of incubator incubation). Cloudiness or turbidity indicates a media-positive (contaminated) bag. No one should be permitted to compound a product for use by patients until he or she can successfully prepare MFUs that demonstrate no microbial growth. Policies on the type and frequency of validation of aseptic technique required for compounding staff must also be in place.

Validation of Compounding Equipment

Manufacturers validate the capability of their equipment to measure components from source containers and to produce an accurate (but not sterile) product. Validating the ability of each type of equipment used to compound sterile products according to written policy is strongly recommended. After the initial validation, equipment does not need to be revalidated unless it is moved or physically modified. If for example, a syringe-filler or TPN automated compounder is relocated to a different type or size of hood (eg, from an 8-foot hood to a 6-foot hood), revalidation is required. Environmental factors can adversely affect the aseptic operation of compounding equipment. As a result, revalidation is required when environmental changes in the sterile-compounding environment occur.

The initial validation procedure for all pieces of equipment should be consistent. TSB should be used as the source solution during equipment validation, during which the entire compounding process must be mimicked. Ten units of TSB should be prepared and incubated for 7 days at room temperature followed by 7 days in the incubator. Evidence of no growth is usually sufficient to validate equipment. After successful validation, an automated compounder can be used to produce patient products. This process validates only the capability of the automated compounder to produce sterile products and does not replace the need for its daily calibration, which is necessary to ensure the accuracy of the products produced.

End-product Testing

Sterility Assurance

The requirement for end-product testing is controversial. The ASHP and the USP differ in their recommendations for sterility testing. Ideally, a compounding process should be built on the integration of systematic process controls (SPCs) rather than on a greater reliance on end-product testing. "Systematic process control" is defined as validated policies, procedures, and processes that are used to consistently produce products of the highest quality. Demonstrating control of the production process, the performance of personnel, and the quality of the product over time by means of complete, consistent collection of data is an essential component of SPC.[14]

SPC is designed to eliminate variations caused by the performance of staff by breaking down processes into individual steps and identifying each of the critical tasks necessary to achieve a product of consistent yield and quality. SPC also enables the inclusion of critical indicators generated by end-product testing such as random product sterility checks. Those indications are the source of crucial data used to ensure optimal product quality demonstrated by properly prepared sterile products.

The ASHP risk level II recommendations for end-product testing are as follows:

- End products should be inspected to detect leaks, irregularities in the appearance of solutions (cloudiness, particulates, unexpected color), and final volume by a pharmacist and by technicians.
- Pharmacists should verify the accuracy of the amounts and types of the compounded product components by means of direct observation throughout the process, a review of documentation, and rechecking of calculations.
- A formal sampling plan should be followed during sterility testing. That plan should be specified in writing as a policy and procedure of the organization; it must set standards for sampling and outcomes and must identify methods of recalling batches that demonstrate bacterial growth. If sterility is examined via culturing processes, then daily inspection of media must be performed.

Unlike the ASHP, in *USP* Chapter <1206>, sterility testing for only category II high-risk operations is recommended. According to the *USP*, in a category II high-risk facility, sterile products are produced from non-sterile powder or open solution transfer methods are used. The classification "category II, high risk" is analogous to the ASHP risk level III. Most hospitals, community retail pharmacies, long-term care facilities, and home care organizations do not use processes that require risk level III quality assurance procedures.

Other issues about sterility testing also merit discussion. Unless sterility testing is accomplished via a filter-integrity method, which produces an immediate pass-or-fail result, products are released before sample cultures from those products have been sufficiently incubated. This is especially true in a hospital or regionalized mixing facility in which sterile products are prepared and used on a daily basis. In those instances, even when mechanisms that ensure daily reading of media cultures are available, patients receive products before the final sample culture reading has occurred, and sterility testing is of little practical value. Sterility testing is also performed on randomly selected products. Because not all products can be examined, end-product testing provides only one data point, which may not be statistically significant and therefore not representative of all the products prepared.

Effective process validation controls can also be used to monitor the efficacy of the compounding process. Those controls can be used to validate all manipulations made during routine compounding (withdrawals from vials and ampules, connections to bags, transfer through tubing and compounding equipment, and needle manipulations). It may be preferable to perform routine sterility checks of compounded products by obtaining random samples of production units. Determining the appropriate methods of sample collection and sample sizes is then necessary.

Quantitative Testing

Quantitative end-product testing involves verifying that the components of the solutions are of the correct type and amount. Various methods, such as refractive index and flame spectrophotometry, can be used to test the accuracy of end products. If systematic process controls are used, however, the reliance on costly end-product testing can be minimized or eliminated.

Complex parenteral solutions should be prepared by means of an automated compounder that interfaces with computer software. By linking the prescription order entry process to the compounder, the additional step of inputting (keying in) critical compounding data (nutrient volumes and specific gravities) into the compounder is eliminated, thus decreasing a significant potential for error. Automated compounders must be calibrated daily before use. Without proper calibration, the equipment cannot accurately validate the delivery volumes of components. Other systematic process controls include:

- Double-checking source containers before the compounder is started and after every source container change
- Observing out-of-limit warnings, concentration alerts, and other fault alarms tripped by automated compounding devices
- Observing and double-checking components added manually

Consideration should be given to the addition of quantitative end-product testing if complex solutions such as TPN and cardioplegia are compounded without the aid of automated compounders. Although systematic process controls can be integrated into a manual process, they may not ensure product accuracy because of the variability of human performance. Organizations must assess their own processes as well as the types of products they routinely prepare. All processes used individually and collectively to ensure product integrity must be documented in policy and procedure; the need for this documentation cannot be overemphasized.

Such procedures may appear overwhelming, expensive, and unattainable, but by slowly implementing one process at a time, these quality systems can be established. After the systems have been implemented, maintaining them requires vigilance and follow up. Some initial costs are associated with establishing these systems, but the time, energy, and cost required to maintain them is far less than that of retrospective or manual systems of collecting, reviewing, and collating quality assurance data on a monthly basis. Complaints about the quality of the end products will be reduced; physicians, nurses, and patients will receive a higher quality product and service; product wastage will be reduced; redelivery costs will be unnecessary; and additional business can be garnered because the pharmacy will acquire a reputation for producing quality products.

By embracing these types of quality systems, we as pharmacists will demonstrate to the FDA our concern with preparing sterile products of the highest quality and integrity. Pharmacy compounding is a privilege and not a right. We must control the destiny of the profession, and we must not allow others to control what pharmacists and technicians can and cannot do. If we do not take this action, others will.

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