

## A REVIEW ON ASHP GUIDELINES OF QUALITY ASSURANCE FOR PHARMACY-PREPARED STERILE PRODUCTS

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Patient morbidity and mortality have resulted from incorrectly prepared or contaminated pharmacy-prepared products.<sup>1-7</sup> Pharmacists seldom know that inaccurate or contaminated products are dispensed when pharmacy quality monitors are inadequate.<sup>8-10</sup> In contemporary health care organizations, more patients are receiving compounded sterile products that are stored for extended periods before use (allowing the growth of a pathological bioload of microorganisms<sup>11</sup>), more patients are seriously ill, and more patients are immunocompromised than ever before.

These ASHP guidelines are intended to help pharmacists and pharmacy technicians prepare sterile products of high quality. The pharmacist is responsible for compounding and dispensing sterile products of correct ingredient identity, purity (freedom from physical contaminants, such as precipitates,<sup>12</sup> and chemical contaminants), strength (including stability<sup>13</sup> and compatibility), and sterility and for dispensing them in appropriate containers, labeled accurately and appropriately for the end user. Other professional organizations have published useful guidelines on compounding and dispensing sterile products. The United States Pharmacopeia (USP) publishes the official compendium *The United States Pharmacopeia and The National Formulary (USP)* and its supplements, all of which may have legal implications for pharmacists.<sup>14,15</sup> The reader would especially benefit from studying the USP general information chapter on sterile drug products for home use,<sup>13</sup> which is referred to often in this ASHP guideline. The National Association of Boards of Pharmacy (NABP) has published less detailed model regulations for use by state boards of

pharmacy.<sup>16,17</sup> The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) recently published a special report on safe practices for parenteral nutrition formulations.<sup>18</sup> Other governmental and accreditation sources are more general. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) publishes at least four sets of standards that mention pharmacy compounding. The hospital accreditation standards simply state that the organization adheres to laws, professional licensure, and practice standards governing the safe operation of pharmaceutical services.<sup>19</sup> The JCAHO home care standards require that medications be safely prepared, including "using appropriate techniques for preparing sterile and nonsterile medications and products." For example, the home care standards state that "appropriate quality-control techniques are used to check for preparation accuracy and absence of microbial contamination. Techniques for preparing sterile products follow guidelines established by the American Society of Health-System Pharmacists."<sup>20</sup> The JCAHO standards for long-term-care pharmacies list important conditions for product preparation, such as separate areas for sterile product preparation, use of a laminar-airflow workbench or class 100 cleanroom, and quality control systems to ensure the accuracy and sterility of final products.<sup>21</sup> The JCAHO standard for ambulatory care infusion centers states, among other things, several facility-related standards, for example the use of biological safety cabinets to protect personnel preparing cytotoxic or hazardous medications; work surfaces free of equipment, supplies, records, and labels unrelated to the medication being prepared; and a separate area for preparing

sterile products that is constructed to minimize opportunities for particulate and microbial contamination.<sup>22</sup>

The Food and Drug Administration (FDA) publishes regulations on current good manufacturing practices that apply to sterile products made by pharmaceutical manufacturers for shipment in interstate commerce. Pursuant to the FDA Modernization Act of 1997 (FDAMA), Section 503A of the Food, Drug, and Cosmetic Act states that pharmacy compounding must comply with an applicable *USP* monograph, if one exists, and the *USP* chapter on pharmacy compounding<sup>14</sup> or be a component of an FDA-approved drug product; or, if neither of these apply to the ingredient being compounded, the substance must appear on a list of bulk drug substances developed by FDA and must be accompanied by a valid certificate of analysis and be manufactured in an FDA-registered establishment.<sup>23</sup> Inactive ingredients compounded by licensed pharmacies must comply with applicable *USP* monographs, if they exist, and the *USP* chapter on pharmacy compounding.<sup>14</sup> FDAMA prohibits pharmacists from compounding drug products that appear on a list of products that have been withdrawn or removed from the market because they have been found unsafe or ineffective. FDAMA also says that pharmacists may not compound, regularly or in inordinate amounts, drug products that are essentially copies of commercially available drug products; nor may they compound drug products identified by regulation as presenting demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on safety or effectiveness. The Centers for Disease Control and Prevention (CDC) has published guidelines for hand washing, prevention of intravascular infections, and hospital environmental control.<sup>24,25</sup> The ASHP Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products are applicable to pharmaceutical services in various practice settings, including, but not limited to, hospitals, community pharmacies, nursing homes, ambulatory care infusion centers, and home care organizations. ASHP has also published practice standards on handling cytotoxic and hazardous drugs<sup>26</sup> and on pharmacy-prepared ophthalmic products.<sup>27</sup> These ASHP guidelines *do not* apply to the *manufacture* of sterile pharmaceuticals as defined in state and federal laws and regulations, *nor* do they apply to the preparation of medications by pharmacists, nurses, or physicians in emergency situations for *immediate* administration to patients (e.g.,

cardiopulmonary resuscitation). All guidelines may not be applicable to the preparation of radiopharmaceuticals. These guidelines are referenced with supporting scientific data when such data exist. In the absence of published supporting data, guidelines are based on expert opinion or generally accepted pharmacy procedures. Pharmacists are urged to use professional judgment in interpreting these guidelines and applying them in practice. It is recognized that, in certain emergency situations, a pharmacist may be requested to compound products under conditions that do not meet these guidelines. In such situations, it is incumbent upon the pharmacist to employ professional judgment in Drug Distribution and Control: Preparation and Handling—*Guidelines*<sup>55</sup> weighing the potential patient risks and benefits associated with the compounding procedure in question.

### Objectives

The objectives of these guidelines are to provide

1. Information on quality assurance and quality control activities that should be applied to the preparation of sterile products in pharmacies and
  2. A method to match quality assurance and quality control activities with the potential risks to patients posed by various types of products.
- Multidisciplinary Input** Pharmacists are urged to participate in the quality or performance improvement, risk management, and infection control programs of their health care organizations, including developing optimal sterile product procedures.

### Definitions

Definitions of selected terms, as used in this document, are provided in Appendix A. For brevity in this document, the term *quality assurance* will be used to refer to both quality assurance and quality control (as defined in Appendix A), as befits the circumstances. Risk-Level Classification In this document, sterile products are grouped into three levels of risk to the patient, increasing from least (level 1) to greatest (level 3) potential risk based on the danger of exposing multiple patients to inaccurate ingredients or pathogens and based on microbial growth factors influenced by product storage time, temperature and product ability to support microbial growth, surface and time exposure of critical sites, and microbial bioload in the environment. When circumstances make risk-level assignment unclear, guidelines for the higher risk level should prevail. Consideration should be given to factors that increase

potential risk to the patient such as high-risk administration sites and immunocompromised status of the patient. A comparison of risk-level attributes appears in Appendix B.

**Risk Level 1.** Risk level 1 applies to compounded sterile products that exhibit characteristics 1, 2, and 3, stated below. All risk level 1 products should be prepared with sterile equipment (e.g., syringes and vials), sterile ingredients and solutions, and sterile contact surfaces for the final product. Risk level 1 includes the following:

**1.** Products **a.** Stored at room temperature (see Appendix A for temperature definitions) and completely administered within 28 hours after preparation or **b.** Stored under refrigeration for 7 days or less before complete administration to a patient over a period not to exceed 24 hours (Table 1) or **c.** Frozen for 30 days or less before complete administration to a patient over a period not to exceed 24 hours. **2.** Unpreserved sterile products prepared for administration to one patient or batch-prepared products containing suitable preservatives prepared for administration to more than one patient. **3.** Products prepared by closed-system aseptic transfer of sterile, nonpyrogenic, finished pharmaceuticals (e.g., from vials or ampuls) obtained from licensed manufacturers into sterile final containers (e.g., syringes, minibags, elastomeric containers, portable infusion-device cassettes) obtained from licensed manufacturers. Examples of risk level 1 processes include transferring a sterile drug product from a vial into a commercially produced i.v. bag; compounding total parenteral nutrient (TPN) solutions by combining dextrose injection and amino acids injection via gravity transfer into a sterile empty container, with or without the subsequent addition of sterile drug products to the final container with a sterile needle and syringe; and transferring a sterile, preserved drug product into sterile syringes with the aid of a mechanical pump and appropriate sterile transfer tubing device.

**Risk Level 2.** Risk level 2 sterile products exhibit characteristic 1, 2, or 3, stated below. All risk level 2 products should be prepared with sterile equipment, sterile ingredients and solutions, and sterile contact surfaces for the final product and with closed-system transfer methods. Risk level 2 includes the following: **1.** Products stored beyond 7 days under refrigeration, stored beyond 30 days frozen, or administered beyond 28 hours after preparation and storage at room temperature (Table 1). **2.** Batch-prepared

products *without preservatives* (e.g., epidural products) that are intended for use by more than one patient. (Note: Batch-prepared products without preservatives that will be administered to multiple patients carry a greater risk to the patients than products prepared for a single patient because of the potential effect of inaccurate ingredients or product contamination on the health and well-being of a larger patient group.) **3.** Products compounded by complex or numerous manipulations of sterile ingredients obtained from licensed manufacturers in a sterile container or reservoir obtained from a licensed manufacturer by using closed-system aseptic transfer; for example, TPN solutions prepared with an automated compounder. (Note: So many risks have been associated with automated compounding of TPN solutions that its complexity requires risk level 2 procedures.<sup>18</sup>) Examples of risk level 2 processes include preparing portable-pump reservoirs for multiday (i.e., ambient temperature) administration; subdividing the contents of a bulk, sterile injectable (without preservatives) into singledose syringes; and compounding TPN solutions with an automated compounding device involving repeated attachment of fluid containers to proximal openings of the compounder tubing set and of empty final containers to the distal opening, the process concluding with the transfer of additives into the filled final container from individual drug product containers or from a pooled additive solution.

**Risk Level 3.** Risk level 3 products exhibit either characteristic 1 or 2: **1.** Products compounded from nonsterile ingredients or compounded with nonsterile components, containers, or equipment before terminal sterilization. <sup>56</sup> Drug Distribution and Control: Preparation and Handling—*Guidelines* **2.** Products prepared by combining multiple ingredients—sterile or nonsterile—by using an open-system transfer or open reservoir before terminal sterilization. Examples of risk level 3 products are calcium levulinate injection, estradiol in oil injection, and morphine sulfate 50-mg/mL injection.<sup>32</sup> Quality Assurance for Risk Level 1

#### **RL 1.1: Policies and Procedures.**<sup>33</sup>

Up-to-date policies and procedures for compounding sterile products should be written and available to all personnel involved in these activities. When policies and procedures are changed they should be updated, as necessary, to reflect current standards of practice and quality. Additions,

revisions, and deletions should be communicated to all personnel involved in sterile compounding and related activities. These policies and procedures should address personnel education and training requirements, competency evaluation, product acquisition, storage and handling of products and supplies, storage and delivery of final products, use and maintenance of facilities and equipment,<sup>34</sup> appropriate garb and conduct for personnel working in the controlled area, process validation, preparation technique,<sup>35</sup> labeling, documentation, and quality control.<sup>36</sup> Further, written policies and procedures should address personnel access and movement of materials into and near the controlled area. Policies and procedures for monitoring environmental conditions in the controlled area should take into consideration the amount of exposure of the product to the environment during compounding and the environmental control devices used to create the critical area. Sources of information include vendor-supplied inservice programs and multimedia training programs, such as videotapes and Internet-site information. Before compounding sterile products, all personnel involved should read the policies and procedures. Written policies and procedures are required for all environmental control devices used to create the critical area for manipulation of sterile products. Examples of such devices are laminar-airflow work stations, biological safety cabinets, class 100 cleanrooms, and barrier isolator workstations (see Appendix A).c

#### **RL 1.2: Personnel Education, Training, and Evaluation**

Training is the most important factor in ensuring the quality of sterile products. Pharmacy personnel preparing or dispensing sterile products must receive suitable didactic and experiential training and competency evaluation through demonstration, testing (written or practical), or both. Some aspects that should be included in training programs include aseptic technique; critical-area contamination factors; environmental monitoring; facilities, equipment, and supplies; sterile product calculations and terminology; sterile product compounding documentation; quality assurance procedures; aseptic preparation procedures; proper gowning and gloving technique; and general conduct in the controlled area. In addition to knowledge of chemical, pharmaceutical, and clinical properties of drugs, pharmacists should be knowledgeable about the principles of pharmacy compounding.<sup>14</sup> Videotapes<sup>37, 38</sup> and

additional information on the essential components of a training, orientation, and evaluation program are described elsewhere.<sup>39,40</sup> All pharmacy and nonpharmacy personnel (e.g., environmental services staff) who work in the controlled area should receive documented training on cleaning, sanitizing, and maintaining equipment used in the controlled area. Training should be specific to the environmental control device and equipment present in the controlled area and should be based on current procedures. The aseptic technique of each person preparing sterile products should be observed and evaluated as satisfactory during orientation and training and at least annually thereafter.<sup>41</sup> In addition to observation, methods of evaluating the knowledge of personnel include written or practical tests and process validation.<sup>42,43</sup>

#### **RL 1.3 Storage and Handling within the Pharmacy<sup>44</sup>**

Solutions, drugs, supplies, and equipment used to prepare or administer sterile products should be stored in accordance with manufacturer or *USP* requirements. Temperatures in refrigerators and freezers used to store ingredients and finished sterile preparations should be monitored and documented daily to ensure that compendial storage requirements are met. Warehouse and other pharmacy storage areas where ingredients are stored should be monitored to ensure that temperature, light, moisture, and ventilation remain within manufacturer and compendial requirements. To permit adequate floor cleaning, drugs, supplies, and compounding equipment should be stored on shelving, cabinets, and carts above the floor. Products that have exceeded their expiration dates should be removed from active storage areas. Before use, each drug, ingredient, and container should be visually inspected for damage, defects, and expiration date.<sup>45</sup> Unnecessary personnel traffic in the controlled area should be minimized. Particle-generating activities, such as removal of intravenous solutions, drugs, and supplies from cardboard boxes, should not be performed in the controlled area. Products and supplies used in preparing sterile products should be removed from shipping containers outside the controlled area before aseptic processing is begun. Packaging materials and items generating unacceptable amounts of particles (e.g., cardboard boxes, paper towels [unless lint-free], reference books) should not be

permitted in the controlled area or critical area. The removal of immediate packaging designed to retain the sterility or stability of a product (e.g., syringe packaging, light-resistant pouches) is an exception; obviously, this type of packaging should not be removed outside the controlled area. Disposal of packaging materials, used syringes, containers, and needles should be performed Table 1.

**Assignment of Products to Risk Level 1 or 2 according to Time and Temperature before Completion of Administration No. Days Storage Risk Level Room Temperature (15–30 °C) Refrigerator (2–8 °C) Freezer (–20 to –10°C)**

1 Completely administered within 28 hr Storage and administration exceed 28 hr >7 >30 Drug Distribution and Control: Preparation and Handling—*Guidelines* 57

at least daily, and more often if needed, to enhance sanitation and avoid accumulation in the controlled area. Trash cans should be below the level of the laminar-airflow workbench and should be removed from the controlled area before being emptied. Sharps containers should be safely placed into the waste stream, according to policies developed by the institution to comply with regulations of the Occupational Safety and Health Administration (OSHA). In the event of a product recall, there should be a mechanism for tracking and retrieving affected products from specific patients to whom the products were dispensed.

**RL 1.4: Facilities<sup>46</sup> and Equipment.<sup>47</sup>** The controlled area should be a limited-access area sufficiently separated from other pharmacy operations to minimize the potential for contamination that could result from the unnecessary flow of materials and personnel into and out of the area. The controlled area is a buffer from outside air that is needed because strong air currents from briefly opened doors, personnel walking past the laminar-airflow workbench, or the air stream from the heating, ventilating, and air conditioning system can easily exceed the velocity of air from the laminar-airflow workbench. Also, operators introducing supplies into the laminar-airflow workbench or reaching in with their arms can drag contaminants from the environment surrounding the workbench.<sup>15</sup> Cleanliness of the controlled area can be enhanced by (1) limiting access to those personnel assigned to work in the controlled area, (2) having those personnel wear the appropriate garb, (3) donning and removing garb outside the

controlled area, (4) keeping doors to the controlled area closed, (5) limiting storage in the controlled area to items in constant use, (6) using low-particulate shelving, counters, and carts (e.g., stainless steel) in the controlled area, (7) not allowing cardboard and other particle-generating materials in the controlled area, (8) controlling the temperature and humidity inside the room, and (9) implementing a regular cleaning (e.g., nightly floor disinfection) and maintenance schedule.<sup>48</sup> Barrier isolator workstations are closed systems and are not as sensitive to their external environment as laminar-airflow equipment. It is good practice to (1) place barrier isolator workstations in limited-access areas, (2) control the temperature and humidity of the surrounding area, and (3) clean and sanitize the surrounding area on a routine basis.<sup>49</sup> Special precautions should be taken to clean equipment and compounding areas meticulously after preparing products that contain allergenic ingredients (e.g., sulfonamides and penicillins). Equipment should be of appropriate design and size for compounding and suitable for the intended uses. Equipment and accessories used in compounding should be inspected, maintained, and cleaned at appropriate intervals to ensure the accuracy and reliability of their performance.<sup>14</sup> Computer entry, order processing, label generation, and record keeping should be performed outside the critical area.

The controlled area should be well organized<sup>50</sup> and lighted<sup>51</sup> and of sufficient size to support sterile compounding activities. For hand washing, a sink with hot and cold running water should be in close proximity to but outside the controlled area. Refrigeration, freezing, ventilation, and room temperature control capabilities appropriate for storage of ingredients, supplies, and pharmacy-prepared sterile products in accordance with manufacturer, USP, and state or federal requirements should exist. The controlled area should be cleaned and disinfected at regular intervals with appropriate agents, according to written policies and procedures.<sup>52</sup> Disinfectants should be alternated periodically to prevent development of resistant microorganisms. The floors of the controlled area should be nonporous and washable to enable regular disinfection. Active work surfaces in the controlled area (e.g., carts, compounding devices, counter surfaces) should be disinfected, in accordance with written procedures. Refrigerators, freezers, shelves, and other areas where pharmacy-prepared sterile



products are stored should be kept clean. Sterile products must be prepared in a class 100 environment (i.e., the critical area).<sup>29</sup> Such an environment exists inside a certified horizontal- or vertical-laminar-airflow workbench, a class 100 clean room, or a barrier isolator.<sup>53</sup> Cytotoxic and other hazardous products should be prepared in a vented class II biological safety cabinet or a barrier isolator of appropriate design to meet the personnel exposure limits described in product material safety data sheets (MSDS).<sup>54</sup> Barrier isolators are gaining favor as clean environments, especially for cytotoxic drug compounding.<sup>55–57</sup> Properly maintained barrier isolators provide suitable environments for the preparation of risk level 1, 2, and 3 sterile products.<sup>58</sup> Laminar-airflow workbenches are designed to be operated continuously. If a laminar-airflow workbench is turned off between aseptic processes, it should be operated long enough to allow complete purging of room air from the critical area (e.g., at least 30 minutes), then disinfected before use. Barrier isolators, because of their closed nature, require less start-up time. If the barrier isolator has been turned off for less than 24 hours, a two-minute start-up time is sufficient. For periods greater than 24 hours, the chamber should be sanitized and the isolator should not be used for a minimum of 10 minutes after application of the sanitizing agent. The critical-area work surface and all accessible interior surfaces of the workbench should be disinfected with an appropriate agent before work begins and periodically thereafter, in accordance with written policies and procedures.<sup>52</sup> The exterior surfaces of the laminar-airflow workbench should be cleaned periodically with a mild detergent or suitable disinfectant; 70% isopropyl alcohol may damage the workbench's clear plastic surfaces. The laminar-airflow workbench should be certified by a qualified contractor<sup>59</sup> every six months<sup>53</sup> or when it is relocated to ensure operational efficiency and integrity. Prefilters in the laminar-airflow workbench should be changed (or cleaned, if they are washable) periodically (e.g., monthly), in accordance with written policies and procedures.

A method should be established for calibrating and verifying the accuracy of automated compounding devices used in aseptic processing (e.g., routine reconstitution of bulk or individual vials, transferring of doses from a bulk container to a minibag, syringe, or other single-dose container).

#### **RL 1.5: Garb**<sup>60</sup>

Procedures should require that personnel wear clean gowns or coveralls that generate few particles in the controlled area.<sup>53</sup> Scrub attire by itself is not acceptable (but can, like street clothes, be covered by a gown or coverall). Hand, finger, and wrist jewelry should be minimized or eliminated. Fingernails should be kept clean and trimmed. Head and facial hair should be covered. Masks are recommended because most personnel talk<sup>61</sup> or may cough or sneeze. Gloves are recommended. Personnel who have demonstrated sensitivity to latex should use either powder-free, low-latex protein gloves or, in the case of severe allergy, latex-free (synthetic) gloves.<sup>62,63</sup> <sup>58</sup> Drug Distribution and Control: Preparation and Handling—*Guidelines*.

#### **RL 1.6: Aseptic Technique**<sup>64,65</sup> **and Product Preparation**<sup>66</sup>

Sterile products must be prepared with aseptic technique in a class 100 environment. Personnel should scrub their hands and forearms for an appropriate length of time with a suitable antimicrobial skin cleanser at the beginning of each aseptic compounding process and when reentering the controlled area, in accordance with written procedures. Personnel should wear appropriate attire (see RL 1.5: Garb). Eating, drinking, and smoking are prohibited in the controlled area. Talking should be minimized in the critical area during aseptic preparation (even when masks are worn).

Ingredients used to compound sterile products should be determined to be stable, compatible, and appropriate for the product to be prepared, according to manufacturer or USP guidelines or appropriate scientific references. The ingredients of the preparation should be predetermined to result in a final product that meets physiological norms for solution osmolality and pH, as appropriate for the intended route of administration. Each ingredient and container should be inspected for defects, expiration date, and product integrity before use. Expired, inappropriately stored, or defective products must not be used in preparing sterile products. Defective products should be promptly reported to the FDA MedWatch Program.<sup>67</sup> Only materials essential for preparing the sterile product should be placed in the laminar-airflow workbench or barrier isolator. The surfaces of ampuls, vials, and container closures (e.g., vial stoppers) should be disinfected by swabbing or spraying with an appropriate disinfectant solution (e.g., 70% isopropyl alcohol or 70% ethanol) before placement in the workbench. Materials used in aseptic preparation should

be arranged in the critical area (within the laminar-airflow workbench or barrier isolator) in a manner that prevents interruption of the unidirectional airflow between the high-efficiency particulate air (HEPA) filter and critical sites of needles, vials, ampuls, containers, and transfer sets. All aseptic procedures should be performed at least 6 inches inside the front edge of the laminar-airflow workbench, in a clear path of unidirectional airflow between the HEPA filter and work materials (e.g., needles, closures). The number of personnel preparing sterile products in the workbench at one time should be minimized. Overcrowding of the critical work area may interfere with unidirectional airflow and increase the potential for compounding errors. Likewise, the number of units being prepared in the workbench at one time should allow unobstructed airflow over critical areas. Automated compounding devices and other equipment placed in or adjacent to the critical area should be cleaned, disinfected, and placed to avoid contamination or disruption of the unidirectional airflow between the HEPA filter and sterile surfaces. Closed systems like barrier isolators require less stringent placement of sterile units and equipment because the critical area encompasses the entire work surface. Hand and arm movements are not critical because the walls of the barrier isolator provide protection from the outside environment.<sup>50</sup> Aseptic technique should be used to avoid touch contamination of sterile needles, syringe parts (e.g., plunger, syringe tip), and other critical sites. Solutions from ampuls should be properly filtered to remove particles. Solutions of reconstituted powders should be mixed carefully, ensuring complete dissolution of the drug with the appropriate diluent. Needle entry into vials should be performed in such a manner as to avoid coring of the vial closure. Some patients may require a latex-free admixture to avoid severe allergic reactions.<sup>68</sup> Latex-related policies and procedures should be developed by each institution, given the paucity of evidence that latex closures and syringe plungers are implicated in patient reactions to latex.<sup>69,70</sup> Before, during, and after the preparation of sterile products, the pharmacist should carefully check the identity and verify the amounts and sequence of the additives in sterile preparations against the original prescription, medication order, or other appropriate documentation (e.g., computerized patient profile, label generated from a pharmacist-verified order) before the product is released or dispensed.

**RL 1.7: Process Validation**<sup>71</sup> Validation of aseptic processing procedures provides a mechanism for ensuring that processes consistently result in sterile products of acceptable quality.<sup>10</sup> In risk level 1, process validation (or process simulation) of compounding procedures is actually a method of assessing the adequacy of an operator's aseptic technique. Each individual involved in the preparation of sterile products should successfully complete a validation process on technique before being allowed to prepare sterile products. The validation process should follow written procedures.<sup>42,43,45</sup> Commercial kits are available for process validation; however, their ability to support microbial growth should be tested by challenging the intended kit with an indicator organism (e.g., *Bacillus stearothermophilus*) that can be purchased in known concentrations, is known not to be pathogenic, and grows only at relatively high temperatures. Process simulation allows for the evaluation of opportunities for microbial contamination during all steps of sterile product preparation. The sterility of the final product is a cumulative function of all processes involved in its preparation and is ultimately determined by the processing step providing the lowest probability of sterility.<sup>31</sup> Process simulation testing is carried out in the same manner as normal production, except that an appropriate microbiological growth medium is used in place of the actual product used during sterile preparation. The same personnel, procedures, equipment, and materials are involved. Completed medium samples are incubated. If no microbial growth is detected, this provides evidence that adequate aseptic technique was used. If growth is detected, the entire sterile preparation process must be evaluated, corrective action taken, and the process simulation test performed again. No products intended for patient use should be prepared by an individual until the process simulation test indicates that the individual can competently perform aseptic procedures. It is recommended that personnel competency be revalidated at least annually, whenever the quality assurance program yields an unacceptable result, and whenever unacceptable techniques are observed; this revalidation should be documented.

**RL 1.8: Expiration Dating.**<sup>72</sup>

All pharmacy-prepared sterile products should bear an appropriate expiration date. The expiration date assigned should be based on currently available drug stability information and sterility considerations. Sources of drug

stability information include references (e.g., *AHFS Drug Information*,<sup>73</sup> *Extended Stability for Parenteral Drugs*,<sup>74</sup> *Handbook on Injectable Drugs*,<sup>75</sup> *King Guide to Parenteral Admixtures*<sup>76</sup>), manufacturer recommendations, and reliable, published research. When interpreting published drug stability information, the pharmacist should consider all aspects of the final sterile product being prepared (e.g., drug reservoir, drug concentration, storage conditions). Methods used for establishing expiration dates should be documented. Drug Distribution and Control: Preparation and Handling—*Guidelines* 59 Appropriate inhouse (or contract service) stability testing may be used to determine expiration dates when drug stability data are not readily available. Home care pharmacies are often required to assign extended beyond-use dates to sterile products, so ASHP has published guidelines for home care pharmacies that address beyond-use dating.<sup>74,77</sup>

#### **RL 1.9: Labeling**<sup>78</sup>

Sterile products should be labeled with at least the following information:

1. For patient-specific products: the patient's name and any other appropriate patient identification (e.g., location, identification number); for batch-prepared products: control or lot number,
2. All solution and ingredient names, amounts, strengths, and concentrations (when applicable),
3. Expiration date and time, when applicable,
4. Prescribed administration regimen, when appropriate (including rate and route of administration),
5. Appropriate auxiliary labeling (including precautions),
6. Storage requirements,
7. Identification (e.g., initials) of the responsible pharmacist (and technician),
8. Device-specific instructions (when appropriate), and
9. Any additional information, in accordance with state or federal requirements; for example, a prescription number for products dispensed to ambulatory care, long-term-care, and home care patients. The label should be legible and affixed to the final
10. container in a manner enabling it to be read while the sterile product is being administered (when possible). Written policies and procedures should address proper placement of labels on containers.<sup>79</sup>

#### **RL 1.10: End-Product Evaluation.**

The final product should be inspected when preparation is completed and again when the product is dispensed. This inspection includes an evaluation for container leaks, container integrity, solution cloudiness or phase separation, particulates in the solution, appropriate solution color, and solution volume. The responsible pharmacist should verify that the product was compounded accurately with the correct ingredients, quantities of each ingredient, containers, and reservoirs; different methods may be used for end-product verification (e.g., observation, calculation checks, documented records). Refractive index measurement may also be used to verify the addition of dextrose, for example in parenteral nutrient solutions.<sup>81</sup>

#### **RL 1.11: Handling of Sterile Products Outside the Pharmacy**<sup>82</sup>

Pharmacists should participate in developing procedures for the safe use (e.g., stability, sterility) of sterile products once they are distributed outside the pharmacy. How the product is transported from the pharmacy, how it is stored outside the pharmacy, and methods for return, recycling, and disposal should be addressed in written policies and procedures.<sup>15,83</sup> Sterile products should be transported so as to be protected from extremes of temperature outside their range of stability and from light if they are photosensitive. Storage containers and packaging verified as suitable for protection during transport should be specified. Transit time and conditions should also be specified and controlled. Delivery personnel should be instructed on special handling procedures. Once delivered to the end user, sterile products should be appropriately stored before use. Pharmacists should ascertain that the user has appropriate locations and equipment for storage (e.g., a refrigerator with a suitable thermometer). Special instructions for storage should be a part of the label or a separate information sheet (e.g., instructions for cleanliness, proper storage, interpretation of the expiration date and how to look for signs of product deterioration). The pharmacist should be notified if storage conditions do not remain suitable so that the pharmacist can give advice as to the disposition of the sterile products and remedies for storage problems. Pharmacists should participate in training end users on the proper care and storage of sterile products, either directly or through written instructional materials.

#### **RL 1.12: Documentation**<sup>84</sup>

The following should be documented and maintained on file for an adequate period of



time, according to organizational policies and state regulatory requirements: (1) the training and competency evaluation of employees in sterile product procedures, (2) refrigerator and freezer temperatures, (3) certification of laminar-airflow workbenches, and (4) other facility quality control logs specific to the pharmacy's policies and procedures (e.g., cleaning logs for facilities and equipment). Pharmacists should also maintain appropriate dispensing records for sterile products, in accordance with state regulatory requirements. Quality Assurance for Risk Level 2 Because the risks of inaccurate products are associated with more complex procedures and because instability and contamination are more likely with long-term storage and administration, more stringent requirements are appropriate for risk level 2 preparations. These requirements may be viewed as more important in circumstances where the medical need is *routine*. In circumstances where the medical need for a product is immediate (and there is not a suitable alternative) or when the preparation of such a product is rare, professional judgment should be applied to the extent to which some guidelines (e.g., cleanroom design and final product testing before product dispensing) must be applied.

#### **RL 2.1: Policies and Procedures**

In addition to all guidelines for risk level 1, a written quality assurance program should define and identify necessary environmental monitoring devices and techniques to be used to ensure an adequate environment for risk level 2 sterile product preparation. Examples include the use of airborne particle counters, air velocity and temperature meters, viable particle samplers (e.g., slit samplers), agar plates, and swab sampling of surfaces and potential contamination sites. All aspects of risk level 2 sterile product preparation, storage, and distribution, including such details as the choice of cleaning materials and disinfectants and the monitoring of equipment accuracy, should be addressed in written policies and procedures. Limits of acceptability (threshold or action levels) for environmental monitoring and process validation and actions to be implemented when thresholds are exceeded should be defined in written policies. For sterile batch compounding, written policies and procedures should be established for the use of master formulas and work sheets and for appropriate documentation. Policies and procedures should also address personnel attire in the controlled area, lot number determination and documentation, and any

other quality assurance procedures unique to compounding risk level 2 sterile products.<sup>60</sup> Drug Distribution and Control: Preparation and Handling—*Guidelines*.

#### **RL 2.2: Personnel Education, Training, and Evaluation**

All guidelines for risk level 1 should be met. In addition to guidelines for risk level 1, assessment of the competency of personnel preparing risk level 2 sterile products should include appropriate process validation (as described in RL 1.7: Process validation). However, process simulation procedures for assessing the preparation of risk level 2 sterile products should be representative of all types of manipulations, products, and batch sizes personnel preparing risk level 2 products are likely to encounter.<sup>15</sup> Personnel should also be taught which products are to undergo end-product quantitative analysis (see RL 2.10).

#### **RL 2.3: Storage and Handling**

All storage and handling guidelines for risk level 1 should be met.

#### **RL 2.4: Facilities and Equipment**

In addition to all guidelines for risk level 1, the following guidelines should be followed for risk level 2 sterile product preparation:

1. The controlled area should meet the standards of a class **10,000** cleanroom, e as defined by Federal Standard 209E.<sup>85, f</sup> A positive air pressure relative to adjacent pharmacy areas is required, as are an appropriate number of air exchanges per hour and appropriate humidity and temperature levels.<sup>86</sup> For open-architecture cleanrooms, it is appropriate to measure the volume of air entering the cleanroom versus the volume of air entering adjacent rooms, so as to ensure a positive pressure gradient for the cleanroom. To allow proper cleaning and disinfection, walls, floors, and ceilings in the controlled area should be nonporous. To help reduce the number of **particles** in the controlled area, an adjacent support area (e.g., anteroom) should be provided. A properly maintained barrier isolator also provides an acceptable environment.<sup>57</sup> A barrier isolator provides a class 100 environment for product preparation; therefore, the isolator itself can be in a separate area of the pharmacy but need not actually be in a cleanroom.
2. Cleaning materials (e.g., mops, sponges, and germicidal disinfectants) for use in the cleanroom should be carefully selected. They should be made of materials that generate a low amount of

particles. If reused, cleaning materials should be cleaned and disinfected between uses.

3. The critical-area work surfaces (e.g., interior of the laminar-airflow workbench) should be disinfected frequently and before and after each batch-preparation process with an appropriate agent, according to written policies and procedures. Floors should be disinfected at least daily. Carpet or porous floors, porous walls, and porous ceiling tiles are not suitable in the controlled area because these surfaces cannot be properly cleaned and disinfected. Exterior workbench surfaces and other hard surfaces in the controlled area, such as shelves, carts, tables, and stools, should be disinfected weekly and after any unanticipated event that could increase the risk of contamination. Walls should be cleaned at least monthly.
4. To ensure that an appropriate environment is maintained for risk level 2 sterile product preparation, an effective written environmental monitoring program is recommended.<sup>87</sup> Sampling of air and surfaces according to a written plan and schedule is recommended.<sup>31</sup> The plan and frequency should be adequate to document that the controlled area is suitable and that the laminar-airflow workbench or biological safety cabinet meets class 100 requirements. Limits of acceptability (thresholds or action levels) and appropriate actions to be taken in the event thresholds are exceeded should be specified. *USP* presents examples of environmental monitoring.<sup>15</sup> Settle plates or wipe samples can provide a simple but effective means of routinely monitoring airborne microbial contamination in controlled and critical areas.<sup>45,88,89</sup>
5. To help reduce the number of particles in the **controlled** area, an adjacent support area (e.g., anteroom) of high cleanliness, separated from the controlled area by a barrier (e.g., plastic curtain, partition, wall), is recommended. Appropriate activities for the support area include, but are not limited to, hand washing, gowning and gloving, removal of packaging and cardboard items, and cleaning and disinfecting hard-surface containers and supplies before placing these items into the controlled area.
6. Methods should be established for calibrating and verifying the accuracy and sterility of automated compounding methods used in aseptic processing.<sup>90-96</sup>

### RL 2.5: Garb

All guidelines for risk level 1 should be met. Gloves, gowns, and masks are required for the preparation of all risk level 2 sterile products. Even when sterile gloves are used, they do not remain sterile during aseptic compounding; however, they do assist in containing bacteria, skin, and other particles that may be shed even from scrubbed hands. Clean gowns, coveralls, or closed jackets with sleeves having elastic binding at the cuff are recommended; these garments should be made of low-shedding materials. Shoe covers may be helpful in maintaining the cleanliness of the controlled area. Barrier isolators do not require the same level of gowning as laminar-airflow workstations as long as they operate as closed systems with HEPA filtration of air entering and leaving the barrier isolator and a separate area for entrance, such as an air lock for product transfers. During sterile product preparation, gloves should be rinsed frequently with a suitable agent (e.g., 70% isopropyl alcohol) and changed when their integrity is compromised (i.e., when they are punctured or torn). Personnel should discard gloves upon leaving the cleanroom and don new gloves upon reentering the cleanroom.

### RL 2.6: Aseptic Technique and Product Preparation<sup>97-99</sup>

All guidelines for risk level 1 sterile product preparation should be met. Relative to batch-prepared products, a master work sheet should be developed for a batch of each discrete identity and concentration of sterile product to be prepared. The master work sheet should consist of the formula, components, compounding directions or procedures, a sample label, and evaluation and testing requirements. Once the original master work sheet is approved by the designated pharmacist, a verified duplicate (e.g., a photocopy) of the master work sheet should be used as the preparation work sheet from which each batch is prepared and on which all documentation for each batch occurs. (For small-formula, frequently prepared batches, it may be more efficient to have multiple lines on the preparation work sheet for documenting more than one batch.) The preparation work sheet should be used to document the following:

1. Identity of all solutions and ingredients and their corresponding amounts, concentrations, or volumes, Drug Distribution and Control: Preparation and Handling—*Guidelines* 61

2. Manufacturer lot number and expiration date for each component,
3. Component manufacturer or suitable manufacturer identification number,
4. Container specifications (e.g., syringe, pump cassette),
5. Lot or control number assigned to batch,
6. Expiration date of batch-prepared products,
7. Date of preparation,
8. Identity (e.g., initials, codes, signatures) of personnel involved in preparation,
9. End-product evaluation and testing specifications and results,
10. Storage requirements,
11. Specific equipment used during aseptic preparation (e.g., a specific automated compounding device), and
12. Comparison of actual yield with anticipated yield, when appropriate.

However documentation is done, a procedure should exist for easy retrieval of all records pertaining to a particular batch. Each batch of sterile products should bear a unique lot number. Identical lot numbers must never be assigned to different products or different batches of the same product. Lot numbers may be alphabetic, numeric, or alphanumeric. The process of combining multiple sterile ingredients into a single sterile reservoir for subdivision into multiple units for dispensing may necessitate additional quality control procedures. A second pharmacist should verify calculations associated with this process, when possible; this verification should be documented. Because this process often involves making multiple entries into the intermediate sterile reservoir, the likelihood of contamination may be greater than that associated with the preparation of other risk level 2 sterile products. For preparation involving automated compounding devices, a pharmacist should verify data entered into the compounding device before compounding begins. End-product checks should be performed to verify accuracy of ingredient delivery. These checks may include weighing and visually verifying the final product. For example, the expected weight (in grams) of the final product, based on the specific gravities of the ingredients and their respective volumes, can be documented on the compounding formula sheet, dated, and initialed by the responsible pharmacist. Once compounding is completed, each final product can be weighed and its weight compared with the expected weight. The product's actual weight should fall within a preestablished threshold for variance. Visual verification may be aided by marking the

beginning level of each bulk container before starting the automated mixing process and checking each container after completing the mixing process to determine whether the final levels appear reasonable in comparison with expected volumes. The operator should also periodically observe the device during the mixing process to ensure that the device is operating properly (e.g., check to see that all stations are operating). If there are doubts whether a product or component has been properly prepared or stored, the product should not be used.

#### **RL 2.7: Process Validation**

Each individual involved in the preparation of risk level 2 sterile products should successfully complete a validation process, as recommended for risk level 1. Process simulation for compounding risk level 2 sterile products should be representative of all types of manipulations, products, and batch sizes that personnel preparing risk level 2 sterile products are likely to encounter.

#### **RL 2.8: Expiration Dating**

All guidelines for risk level 1 should be met.

#### **RL 2.9: Labeling**

All guidelines for risk level 1 should be met.

#### **RL 2.10: End-Product Evaluation**

All guidelines for risk level 1 should be met. For complex or toxic products, it is appropriate, when possible, to obtain quantitative testing of the accuracy of sterile additives, for example, the dextrose concentration in pediatric parenteral nutrient solutions or the potassium concentration in cardioplegia solutions.g

#### **RL 2.11: Handling of Sterile Products Outside the Pharmacy**

All guidelines for risk level 1 should be met.

#### **RL 2.12: Documentation**

All guidelines for risk level 1 should be met. Additionally, documentation of end-product sampling and batch-preparation records should be maintained for an adequate period, in accordance with organizational policies and procedures and state regulatory requirements. 100 Documentation for sterile batch-prepared products should include the

1. Master work sheet,
2. Preparation work sheet, and
3. End-product evaluation and testing results. Quality Assurance for Risk Level 3 Risk level 3 addresses the preparation of products that

pose the greatest potential risk to patients. The quality assurance activities described in this section are clearly more demanding—in terms of processes, facilities, and final product assessment— than for risk levels 1 and 2. Ideally, the activities described for risk level 3 would be used for all high-risk products. However, the activities may be viewed as most important in circumstances where the medical need for such high-risk products is *routine*. In circumstances where the medical need for such a product is immediate (and there is not a suitable alternative) or when the preparation of such a product is rare, professional judgment must be applied as to the extent to which some activities (e.g., strict facility design, quarantine, and final product testing before product dispensing) should be applied.

### RL 3.1: Policies and Procedures

There should be written policies and procedures related to every aspect of preparation of risk level 3 sterile products. These policies and procedures should be detailed enough to ensure that all products have the identity, strength, quality, and purity purported for the product.<sup>14,101</sup> All policies and procedures should be reviewed and approved by the designated pharmacist. There should be a mechanism designed to ensure that policies and procedures are communicated, understood, and adhered to by personnel cleaning or working in the controlled area or support area. Written policies and procedures should define and identify the environmental monitoring activities necessary to ensure an adequate environment for risk level 3 sterile product preparation.

In addition to the policies and procedures required for risk levels 1 and 2, there should be written policies and procedures for the following: 62 Drug Distribution and Control: Preparation and Handling—*Guidelines*

1. Component selection, handling, and storage,
2. Any additional personnel qualifications commensurate with the preparation of risk level 3 sterile products,
3. Personnel responsibilities in the controlled area (e.g., sterilization, cleaning, maintenance, access to controlled area),
4. Equipment use, maintenance, calibration, and testing, Sterilization and expiration dating,
5. Master formula and master work sheet development and use,
6. End-product evaluation and testing,
7. Appropriate documentation for preparation of risk level 3 sterile products,

8. Use, control, and monitoring of environmentally controlled areas and calibration of monitoring equipment,
9. Process simulation for each risk level 3 sterile product,
10. Quarantine of products and release from quarantine, if applicable,
11. A mechanism for recalling products from patients in the event that end-product testing procedures yield unacceptable results, and
12. Any other quality control procedures unique to the preparation of risk level 3 sterile products.

### RL 3.2: Personnel Education, Training, and Evaluation

Persons preparing sterile products at risk level 3 must have specific education, training, and experience to perform all functions required for the preparation of risk level 3 sterile products. However, final responsibility should lie with the pharmacist, who should be knowledgeable in pharmacy compounding practice<sup>14</sup> and proficient in quality assurance requirements, equipment used in the preparation of risk level 3 sterile products, and other aspects of sterile product preparation. The pharmacist should have sufficient education, training, experience, and demonstrated competency to ensure that all sterile products prepared from sterile or nonsterile components have the identity, strength, quality, and purity purported for the products.<sup>101</sup> In addition to the body of knowledge required for risk levels 1 and 2, the pharmacist should possess sufficient knowledge in the following areas:

1. Aseptic processing,
2. Quality control and quality assurance as related to environmental, component, and end-product testing,
3. Sterilization techniques,<sup>98</sup> and
4. Container, equipment, and closure system selection. All pharmacy personnel involved in the cleaning and maintenance of the controlled area should be specially trained and thoroughly knowledgeable in the special requirements of class 100 critical-area technology and design. There should be documented, ongoing training for all employees to enable retention of expertise.

### RL 3.3: Storage and Handling

In addition to guidelines for risk levels 1 and 2, risk level 3 policies and procedures for storage and handling should include procurement,

identification, storage, handling, testing, and recall of nonsterile components.<sup>14,101</sup> Components and finished products ready to undergo end-product testing should be stored in a manner that prevents their use before release by a pharmacist, minimizes the risk of contamination, and enables identification. There should be identified storage areas that can be used to quarantine products, if necessary, before they are released.<sup>15.</sup>

#### **RL 3.4: Facilities and Equipment**

Preparation of risk level 3 sterile products should occur in a class 100 horizontal- or vertical-laminar-airflow workbench that is properly situated in a class 10,000 cleanroom or in a properly maintained and monitored class 100 cleanroom (without the workbench).<sup>102</sup> The cleanroom area should have a positive pressure differential relative to adjacent, less clean areas of at least 0.05 inch of water. A properly designed and maintained barrier isolator provides an aseptic environment for risk level 3 products.

To allow proper cleaning and disinfection, walls, floors, and ceilings in the controlled area should be nonporous. To help reduce the number of particles in the controlled area, an adjacent support area (e.g., anteroom) should be provided.

During the preparation of risk level 3 sterile products, access to the controlled area or cleanroom should be limited to those individuals who are required to be in the area and are properly attired. The environment of the main access areas directly adjacent to the controlled area (e.g., anteroom) should meet at least Federal Standard 209E class 100,000 requirements. To help maintain a class 100 critical-area environment during compounding, the adjacent support area (e.g., anteroom) should be separated from the controlled area by a barrier (e.g., plastic curtain, partition, wall). Written policies and procedures for monitoring the environment of the controlled area and adjacent areas should be developed. No sterile products should be prepared in the controlled area if it fails to meet established criteria specified in the policies and procedures. A calibrated particle counter capable of measuring air particles 0.5  $\mu\text{m}$  and larger should be used to monitor airborne particulate matter.<sup>103</sup> Before product preparation begins, the positive-pressure air status should meet or exceed the requirements. Air samples should be taken at several places in the controlled area with the appropriate environmental monitoring devices (e.g., nutrient agar plates). Surfaces on which

work actually occurs, including laminar-airflow workbench surfaces and tabletops, should be monitored by using surface contact plates, the swab-rinse technique, or other appropriate methods.<sup>104</sup> Test results should be reviewed and criteria be pre established to determine the point at which the preparation of risk level 3 sterile products will be disallowed until corrective measures are taken. When the environment does not meet the criteria specified in the policies and procedures, sterile product processing should immediately cease and corrective action should be taken. In the event that this occurs, written policies and procedures should delineate alternative methods of sterile product preparation to enable timely fulfillment of prescription orders. Equipment should be adequate to prevent microbiological contamination. Methods should be established for the cleaning, preparation, sterilization, calibration, and documented use of all equipment. Critical-area work surfaces should be disinfected with an appropriate agent before the preparation of each product. Floors in the controlled area should be disinfected at least daily. Exterior workbench surfaces and other hard surfaces in the controlled area, such as shelves, tables, and stools, should be disinfected weekly and after any unanticipated event that could increase the risk of contamination. Walls and ceilings in the controlled area or cleanroom should be disinfected at least weekly. Large pieces of equipment, such as tanks, carts, and tables, used in the controlled area or cleanroom should be made of a material that can be easily cleaned and disinfected; stainless steel is recommended. Stools and chairs should be cleanroom Drug Distribution and Control: Preparation and Handling—*Guidelines* 63 quality. Equipment that does not come in direct contact with the finished product should be properly cleaned, rinsed, and disinfected before being placed in the controlled area. All nonsterile equipment that will come in contact with the sterilized final product should be properly sterilized before introduction into the controlled area; this precaution includes such items as tubing, filters, containers, and other processing equipment. The sterilization process should be monitored and documented.<sup>101</sup>

#### **RL 3.5: Garb**

All guidelines for risk levels 1 and 2 should be met. Additionally, cleanroom garb should be worn inside the controlled area at all times during the preparation of risk level 3 sterile products. Attire should consist of a lowshedding



coverall, head cover, face mask, and shoe covers. These garments may be either disposable or reusable. Head and facial hair should be covered. Before donning these garments over street clothes, personnel should thoroughly wash their hands and forearms with a suitable antimicrobial skin cleanser.<sup>25</sup> Sterile disposable gloves should be worn and rinsed frequently with an appropriate agent (e.g., 70% isopropyl alcohol) during processing. The gloves should be changed if their integrity is compromised. If persons leave the controlled area or support area during processing, they should regown with clean garments before reentering.

### **RL 3.6: Aseptic Technique and Product Preparation**

All guidelines for risk levels 1 and 2 should be met. Methods should ensure that components and containers remain free from contamination and are easily identified as to the product, lot number, and expiration date. If components are not finished sterile pharmaceuticals obtained from licensed manufacturers, pharmacists should ensure that these components meet USP and FDA standards. Products prepared from nonsterile ingredients should be tested to ensure that they do not exceed specified endotoxin limits, unless the ingredient will denature all proteins (e.g., concentrated hydrochloric acid).<sup>105</sup> As each new lot of components and containers is received, the components should be quarantined until properly identified, tested, or verified by a pharmacist.<sup>101</sup> The methods for preparing sterile products and using process controls should be designed to ensure that finished products have the identity, strength, quality, and purity they are intended to have. Any deviations from established methods should be documented and appropriately justified. A master work sheet should be developed for the preparation of each risk level 3 sterile product. Once the pharmacist approves the master work sheet, a verified duplicate of the master work sheet should be used as the controlling document from which each sterile end product or batch of prepared products is compounded and on which all documentation for that product or batch occurs. The preparation work sheet should document all the requirements for risk level 2 plus the following:

1. Comparison of actual with anticipated yield,
2. Sterilization methods,<sup>106,107</sup>
3. Pyrogen testing,<sup>108</sup> and
4. Quarantine specifications.

The preparation work sheet should serve as the batch record for each time a risk level 3 sterile product is prepared. Each batch of pharmacy-prepared sterile products should bear a unique lot number, as described in risk level 2. There should be documentation on the preparation work sheet of all additions of individual components plus the signatures or initials of those individuals involved in the measuring or weighing and addition of these components. The selection of the final packaging system (including container and closure) for the sterile product is crucial to maintaining product integrity.<sup>109</sup> To the extent possible, presterilized containers obtained from licensed manufacturers should be used. If an aseptic filling operation is used, the container should be sterile at the time of the filling operation. If nonsterile containers are used, methods for sterilizing these containers should be established. Final containers selected should be capable of maintaining product integrity (i.e., identity, strength, quality, and purity) throughout the shelf life of the product.<sup>110</sup> For products requiring sterilization, selection of an appropriate method of sterilization is of prime importance. Methods of product sterilization include sterile filtration, autoclaving, dry heat sterilization, chemical sterilization, and irradiation.

<sup>111,112</sup> The pharmacist must ensure that the sterilization method used is appropriate for the product components and does not alter the pharmaceutical properties of the final product. A method of sterilization often used by pharmacists is sterile filtration.<sup>113</sup> In sterile filtration, the filter should be chosen to fit the chemical nature of the product, and the product should be filtered into presterilized containers under aseptic conditions. Sterilizing filters of 0.22- $\mu\text{m}$  or smaller porosity should be used in this process. Colloidal or viscous products may require a 0.45- $\mu\text{m}$  filter; however, extreme caution should be exercised in these circumstances, and more stringent end product sterility testing is essential.<sup>114</sup> To ensure that a bacteria-retentive filter did not rupture during filtration of a product, an integrity test should be performed on all filters immediately after filtration. This test may be accomplished by performing a bubble point test, in which pressurized gas (e.g., air in a syringe attached to the used filter) is applied to the upstream side of the filter with the downstream outlet immersed in water and the pressure at which a steady stream of bubbles begins to appear is noted.<sup>98</sup> The observed pressure is then compared with the manufacturer's specification for the filter. To

compare the used filter with the manufacturer's specifications, which would be based on the filtration of water through the filter, it is necessary to first rinse the filter with sterile water for injection. An observed value lower than the manufacturer's specification indicates that the filter was defective or ruptured during the sterilization process. Methods should be established for handling, testing, and re-sterilizing any product processed with a filter that fails the integrity test.

#### **RL 3.7: Process Validation**

In addition to risk level 1 and 2 guidelines, written policies and procedures should be established to validate all processes involved in the preparation of risk level 3 sterile products (including all procedures, equipment, and techniques) from sterile or nonsterile components. In addition to evaluating personnel technique, process validation provides a mechanism for determining whether a particular process will, when performed by qualified personnel, consistently produce the intended results.<sup>115</sup>

#### **RL 3.8: Expiration Dating**

In addition to risk level 2 guidelines, there should be reliable methods for establishing all expiration dates, including laboratory testing of products for sterility, nonpyrogenicity, and chemical content, when 64 Drug Distribution and Control: Preparation and Handling—*Guidelines* necessary. These tests should be conducted in a manner based on appropriate statistical criteria, and the results documented.

#### **RL 3.9: Labeling**

All guidelines for risk levels 1 and 2 should be met.

#### **RL 3.10: End-Product Evaluation**

For each preparation of a sterile product or a batch of sterile products, there should be appropriate laboratory determination of conformity (i.e., purity, accuracy, sterility, and nonpyrogenicity) to established written specifications and policies. Any reprocessed material should undergo complete final product testing. Additionally, process validation should be supplemented with a program of end-product sterility testing, according to a formal sampling plan.<sup>116–127</sup> Written policies and procedures should specify measurements and methods of testing. Policies and procedures should include a statistically valid sampling plan and acceptance criteria for the sampling and testing. The criteria should be statistically adequate to reasonably ensure that the entire batch meets all specifications.

Products not meeting all specifications should be rejected and discarded. There should be a mechanism for recalling all products of a specific batch if end-product-testing procedures yield unacceptable results. On completion of final testing, products should be stored in a manner that ensures their identity, strength, quality, and purity.

It is advisable to quarantine sterile products compounded from nonsterile components, pending the results of end-product testing. If products prepared from nonsterile components must be dispensed before satisfactory completion of end-product testing, there must be a procedure to allow for immediate recall of the products from patients to whom they were dispensed.

#### **RL 3.11: Handling of Sterile Products Outside the Pharmacy**

All guidelines for risk levels 1 and 2 should be met.

#### **RL 3.12: Documentation**

In addition to the guidelines for risk levels 1 and 2, documentation for risk level 3 sterile products should include

1. Preparation work sheet,
2. Sterilization records of final products (if applicable),
3. Quarantine records (if applicable), and
4. End-product evaluation and testing results.

#### **Aseptic Preparation or Aseptic Processing**

The technique involving procedures designed to preclude contamination (of drugs, packaging, equipment, or supplies) by microorganisms during processing.

#### **Batch Preparation**

Compounding of multiple sterile product units, in a single discrete process, by the same individuals, carried out during one limited time period.

#### **Cleanroom**

A room (1) in which the concentration of airborne particles is controlled, (2) that is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room, and (3) in which other relevant variables (e.g., temperature, humidity, and pressure) are controlled as necessary.<sup>28</sup>

For example, the air particle count in a class 100 cleanroom cannot exceed a total of 100 particles 0.5 µm or larger per cubic foot of air.<sup>29</sup>

#### **Clean Zone**

Dedicated space (1) in which the concentration of airborne particles is controlled, (2) that is constructed

and used in a manner that minimizes the introduction, generation, and retention of particles inside the zone, and (3) in which other relevant variables (e.g., temperature, humidity, and pressure) are controlled as necessary.

This zone may be open or enclosed and may or may not be located within a cleanroom.<sup>28</sup> For example, an open-architecture controlled area should be a clean zone.

#### **Closed-System Transfer**

The movement of sterile products from one container to another in which the containers–closure system and transfer devices remain intact throughout the entire transfer process, compromised only by the penetration of a sterile, pyrogen-free needle or cannula through a designated closure or port to effect transfer, withdrawal, or delivery. Withdrawal of a sterile solution from an ampul through a particulate filter in a class 100 environment would generally be considered acceptable; however, the use of a flexible closure vial, when available, would be preferable.

#### **Compounding**

For purposes of these guidelines, compounding simply means the mixing of ingredients to prepare a medication for patient use. This activity would include dilution, admixture, repackaging, reconstitution, and other manipulations of sterile products.

#### **Controlled Area**

For purposes of these guidelines, a controlled area is the area designated for preparing sterile products. This is referred to as the buffer zone (i.e., the cleanroom in which the laminar-airflow workbench is located) by USP.<sup>15</sup>

#### **Corrective Action**

Action to be taken when the results of monitoring indicate a loss of control or when action levels are exceeded.

**Critical Area:** Any area in the controlled area where products or containers are exposed to the environment.

#### **Critical Site**

An opening providing a direct pathway between a sterile product and the environment or any surface coming into contact with the product or environment.

**Critical Surface:** Any surface that comes into contact with previously sterilized products or containers.

#### **Designated Pharmacist**

The pharmacist chosen by experience and training to be in charge of a sterile product preparation area or unit in a licensed pharmacy.

#### **Expiration Date**

The date (and time, when applicable) beyond which a product should not be used (i.e., the product should be discarded beyond this date and time). Expiration date and time should be assigned on the basis of both stability and risk level, whichever is the shorter period. **Note:** Circumstances may occur in which the expiration date and time arrive while an infusion is in progress. When this occurs, judgment should be applied in determining whether it is appropriate to discontinue that infusion and replace the product. Organizational policies on this should be clear.<sup>15</sup>

#### **High-Efficiency Particulate Air (HEPA) Filter**

A filter composed of pleats of filter medium separated by rigid sheets of corrugated paper or aluminum foil that direct the flow of air forced through the filter in a uniform parallel flow. HEPA filters remove 99.97% of all air particles 0.3  $\mu\text{m}$  or larger. When HEPA filters are used as a component of a horizontal- or vertical-laminar-airflow workbench, an environment can be created consistent with standards for a class 100 clean room.

#### **Isolator (or Barrier Isolator)**

A closed system made up of four solid walls, an air-handling system, and transfer and interaction devices. The walls are constructed so as to provide surfaces that are cleanable with coving between wall junctures. The air-handling system provides HEPA filtration of both inlet and exhaust air. Transfer of materials is accomplished through air locks, glove rings, or ports. Transfers are designed to minimize the entry of contamination. Manipulations can take place through either glove ports or half-suits.

#### **Media Fill**

See process validation or simulation.

#### **Preservatives**

For purposes of these guidelines, preservatives refer to any additive intended to extend the content, stability, or sterility of active ingredients (e.g., antioxidants, emulsifiers, bacteriocides).

**Process Validation or Simulation**

Microbiological simulation of an aseptic process with growth medium processed in a manner similar to the processing of the product and with the same container or closure system.<sup>30</sup> Process simulation tests are synonymous with medium fills, simulated product fills, broth trials, and broth fills.

**Quality Assurance**

For purposes of these guidelines, quality assurance is the set of activities used to ensure that the processes used in the preparation of sterile drug products lead to products that meet predetermined standards of quality.

**Quality Control**

For purposes of these guidelines, quality control is the set of testing activities used to determine that the ingredients, components (e.g., containers), and final sterile products prepared meet predetermined requirements with respect to identity, purity, nonpyrogenicity, and sterility.

**Repackaging**

The subdivision or transfer of a compounded product from one container or device to a different container or device, such as a syringe or an ophthalmic container.

**Sterilization**

A validated process used to render a product free of viable organisms.

**Sterilizing Filter**

A filter that, when challenged with a solution containing the microorganism *Pseudomonas diminuta* at a minimum concentration of 10<sup>12</sup> organisms per square centimeter of filter surface, will produce a sterile effluent.

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**Temperatures (USP)**

Frozen means temperatures between –20 and –10 °C (–4 and 14 °F). Refrigerated means temperatures between 2 and 8 °C (36 and 46 °F). Room temperature means temperatures between 15 and 30 °C (59 and 86 °F).

**Validation**

Documented evidence providing a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

**Worst Case**

A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, that pose the greatest chance of process or product failure when compared with ideal conditions. Such conditions do not necessarily induce product or process failure.<sup>31</sup> Appendix B—Comparison of Risk-Level Attributes

This appendix does not show all details of the guidelines, nor does it tell whether an aspect of the sterile compounding process is “required” (must be) or “advisable” (should be). Regardless of the examples given, each compounding pharmacist must decide, according to the circumstances at the time, what conditions are appropriate for compounding a sterile product. In an emergency, it may be of more benefit to a patient to receive a sterile drug prepared under lower risk-level conditions. For the immunocompromised patient, even simple, single-patient admixtures may need to be compounded under higher risk-level conditions.

**Definition of Products by Risk Level**

**Risk Level 1 Risk Level 2 Risk Level 3**  
Products that are (1) stored at room temperature and completely administered within 28 hours from preparation, (2) unpreserved and sterile and prepared for administration to one patient, or batch prepared for administration to more than one patient and contain suitable preservatives, and (3) prepared by closed-system aseptic transfer of sterile, nonpyrogenic, finished pharmaceuticals obtained from licensed manufacturers into sterile final containers obtained from licensed manufacturers.

Products that are (1) administered beyond 28 hours after preparation and storage at room temperature, (2) batch prepared without preservatives and intended for use by more than one patient, or (3) compounded by complex or numerous manipulations of sterile ingredients obtained from licensed manufacturers in a sterile container obtained from a licensed manufacturer by using closed-system, aseptic transfer. Products that are (1) compounded from nonsterile ingredients or with nonsterile components, containers, or equipment before terminal sterilization or (2) prepared by combining multiple ingredients (sterile or nonsterile) by using an open-system transfer or open reservoir before terminal sterilization.

### Examples of Sterile Products by Risk Level

**Risk Level 1 Risk Level 2 Risk Level 3**  
 Single-patient admixture Single-patient ophthalmic, preserved Single-patient syringes without preservatives used in 28 hours  
 Batch-prefilled syringes with preservatives  
 Total parenteral nutrient (TPN) solution made by gravity transfer of carbohydrate and amino acids into an empty container with the addition of sterile additives with a syringe and needle  
 Injections for use in portable pump or reservoir over multiple days  
 Batch-reconstituted antibiotics without preservatives  
 Batch-prefilled syringes without preservatives  
 TPN solutions mixed with an automatic compounding device  
 Alum bladder irrigation  
 Morphine injection made from powder or tablets  
 TPN solutions made from dry amino acids, TPN solutions sterilized by final filtration  
 Autoclaved i.v. solutions.

### Policies and Procedures Risk Level 1 Risk Level 2 Risk Level 3

Up-to-date policies and procedures for compounding sterile products should be available to all involved personnel. When policies are changed, they should be updated. Procedures should address personnel education and training, competency evaluation, product acquisition, storage and handling of products and supplies, storage and delivery of final products, use and maintenance of facilities and equipment, appropriate garb and conduct of personnel working in the controlled area, process validation, preparation technique, labeling, documentation, quality control, and material movement. In addition to risk level 1 guidelines, procedures describe environmental monitoring devices and techniques, cleaning materials and disinfectants, equipment accuracy monitoring, limits of acceptability and corrective actions for environmental monitoring and process validation, master formula and work sheets, personnel garb, lot numbers, and other quality control methods. Procedures cover every aspect of preparation of level 3 sterile products, so that all products have the identity, strength, quality, and purity purported for the product. Thirteen general policies and procedures, in addition to those in levels 1 and 2, are required. 70 Drug Distribution and Control: Preparation and Handling—*Guidelines*.

### Personnel Education, Training, and Evaluation Risk Level 1 Risk Level 2 Risk Level 3

All pharmacy personnel preparing sterile products should receive suitable didactic and experiential training and competency

evaluation through demonstration or testing (written or practical). In addition to the policies and procedures listed above, education includes chemical, pharmaceutical, and clinical properties of drugs and current good compounding practices. In addition guidelines in risk level 1, training includes assessment of competency in all types of risk level 2 procedures via process simulation. Personnel show competency in endproduct testing as well. Operators have specific education, training, and experience to prepare risk level 3 products. Pharmacist knows principles of good compounding practice for risk Level 3 products, including aseptic processing; quality assurance of environmental, component, and end-product testing; sterilization; and selection and use of containers, equipment, and closures.

### Storage and Handling in the Pharmacy Risk Level 1 Risk Level 2 Risk Level 3

Solutions, drugs, supplies, and equipment must be stored according to manufacturer or USP requirements. Refrigerator and freezer temperatures should be documented daily. Other storage areas should be inspected regularly to ensure that temperature, light, moisture, and ventilation meet requirements. Drugs and supplies should be shelved above the floor. Expired products must be removed from active product storage areas. Personnel traffic in storage areas should be minimized. Removal of products from boxes should be done outside controlled areas. Disposal of used supplies should be done at least daily. Product-recall procedures must permit retrieving affected products from specific involved patients. All guidelines for risk level 1 apply. In addition to risk level 1 guidelines, procedures include procurement, identification, storage, handling, testing, and recall of components and finished products. Finished but untested products must be quarantined under minimal risk for contamination or loss of identity in an identified quarantine area.

### Facilities and Equipment Risk Level 1 Risk Level 2 Risk Level 3

The controlled area should be separated from other operations to minimize unnecessary flow of materials and personnel through the area. The controlled area must be clean, well lighted, and of sufficient size for sterile compounding. A sink with hot and cold water should be near, but not in, the controlled area. The controlled area and inside equipment must be cleaned and disinfected regularly. Sterile products must be prepared in a class 100 environment (the critical area),



such as within a horizontal- or vertical-laminar-airflow workbench or barrier isolator. Computer entry, order processing, label generation, and record keeping should be performed outside the critical area. The critical area must be disinfected periodically. A workbench should be recertified every six months or when it is moved; prefilters should be changed periodically. Pumps should be recalibrated according to procedure. In addition to risk level 1 guidelines, the following are recommended for risk level 2 products: controlled area must meet class 10,000 cleanroom standards; cleaning supplies should be selected to meet cleanroom standards; critical-area work surface must be cleaned between batches; floors should be disinfected daily, equipment surfaces weekly, and walls monthly; and there should be environmental monitoring of air and surfaces. An anteroom of high cleanliness is desirable. Automated compounding devices must be calibrated and verified as to accuracy, according to procedure. Products must be prepared in a class 100 workbench in a class 10,000 cleanroom, in a class 100 cleanroom, or in a suitable barrier isolator. Access to the cleanroom must be limited to those preparing the products who are in appropriate garb. Methods are needed for cleaning, preparing, sterilizing, calibrating, and documenting the use of all equipment. Walls and ceilings should be disinfected weekly. All nonsterile equipment that is to come in contact with the sterilized final product should be sterilized before introduction into the cleanroom. An anteroom of high cleanliness (i.e., class 100,000) should be provided. Appropriate cleaning and disinfection of the environment and equipment are required. Drug Distribution and Control: Preparation and Handling—*Guidelines*.

### 71 Garb Risk Level 1 Risk Level 2 Risk Level 3

In the controlled area, personnel wear lowparticulate, clean clothing covers such as clean gowns or coverall with sleeves having elastic cuffs. Hand, finger, and wrist jewelry is minimized or eliminated. Nails are clean and trimmed. Gloves are recommended; those allergic to latex rubber must wear gloves made of a suitable alternative. Head and facial hair is covered. Masks are recommended during aseptic preparation. Personnel preparing sterile products scrub their hands and arms with an appropriate antimicrobial skin cleanser. In addition to risk level 1 guidelines, gloves, gowns, and masks are required. During sterile preparation, gloves should be rinsed frequently with a suitable agent (e.g., 70% isopropyl alcohol) and

changed when their integrity is compromised. Shoe covers are helpful in maintaining the cleanliness of the controlled area. In addition to risk level 1 and 2 guidelines, cleanroom garb must be worn inside the controlled area at all times during the preparation of risk level 3 sterile products. Attire consists of a low-shedding coverall, head cover, face mask, and shoe covers. Before donning this garb, personnel must thoroughly wash their hands and arms. Upon return to the controlled area or support area during processing, personnel should regown with clean garb.

### Aseptic Technique and Product Preparation Risk Level 1 Risk Level 2 Risk Level 3

Sterile products must be prepared in a class 100 environment. Personnel scrub their hands and forearms for an appropriate period at the beginning of each aseptic compounding process. Eating, drinking, and smoking are prohibited in the controlled area. Talking is minimized to reduce airborne particles. Ingredients are determined to be stable, compatible, and appropriate for the product to be prepared, according to manufacturer, USP, or scientific references. Ingredients result in final products that meet physiological norms as to osmolality and pH for the intended route of administration. Ingredients and containers are inspected for defects, expiration, and integrity before use. Only materials essential for aseptic compounding are placed in the workbench. Surfaces

of ampuls and vials are disinfected before placement in the workbench. Sterile components are arranged in the workbench to allow uninterrupted laminar airflow over critical surfaces of needles, vials, ampuls, etc. Usually only one person and one preparation are in the workbench at a time. Automated devices and equipment are cleaned, disinfected, and placed in the workbench

to enable laminar airflow. Aseptic technique is used to avoid touch contamination of critical sites of containers and ingredients. Sterile powders are completely reconstituted. Particles are filtered from solutions. Needle cores are avoided. The pharmacist checks before, during, and after preparation to verify the identity and amount of ingredients before release. In addition to risk

level 1 guidelines, a masterwork sheet containing formula, components, procedures, sample label, final evaluation, and testing is made for each product batch. A separate work sheet and lot number are used for each batch. When combining multiple sterile

ingredients, a second pharmacist should verify calculations. The pharmacist should verify data entered into an automatic compounder before processing and check the end product for accuracy. In addition to risk level 1 and 2 guidelines, nonsterile

components must meet USP standards for identity, purity, and endotoxin levels, as verified by a pharmacist. Batch master work sheets should also include comparisons of actual with anticipated yields, sterilization methods, and quarantine specifications. Presterilized containers should be used if feasible. Final containers must be sterile and capable of maintaining product integrity throughout shelf life. Sterilization method is based on properties of the product. Final filtration methods require attention to many elements of product, filter, and filter integrity.

#### **Process Validation Risk Level 1 Risk Level 2 Risk Level 3**

All persons who prepare sterile products should pass a process validation of their aseptic technique before they prepare sterile products for patient use. Personnel competency should be reevaluated by process validation at least annually, whenever the quality assurance program yields an unacceptable result, and whenever unacceptable techniques are observed. If microbial growth is detected, the entire sterile process must be evaluated, corrective action taken, and the process simulation test performed again.

All risk level 1 guidelines apply, and process-simulation procedures should cover all types of manipulations, products, and batch sizes that are encountered in risk level 2. In addition to risk level 1 and 2 guidelines, written policies should be made to validate all processes (including all procedures, components, equipment, and techniques) for each risk level 3 product.

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#### **Handling Sterile Products Outside the Pharmacy Risk Level 1 Risk Level 2 Risk Level 3**

Sterile products are transported so as to be protected from excesses of temperatures and light. Transit time and condition should be specified. Delivery personnel should be trained as appropriate. Pharmacists ascertain that the end user knows how to properly store products. End users notify pharmacists when storage conditions are exceeded or when products

met. All guidelines for risk level 1 should be met.

#### **Documentation Risk Level 1 Risk Level 2 Risk Level 3**

The following must be documented according to policy, laws, and regulations

(1) training and competency evaluation of employees,

(2) refrigerator and freezer temperature logs,

(3) certification of workbenches, and (4) other facility quality control logs as appropriate. Pharmacists maintain appropriate records for the compounding and dispensing of sterile products. In addition to the guidelines in risk level 1, documentation of end-product testing and batch-preparation records must be maintained according to policies, laws, and regulations. In addition to the guidelines in risk levels 1 and 2, documentation for risk level 3 products must include

(1) preparation work sheet,

(2) sterilization records if applicable,

(3) quarantine records if applicable,

(4) end-product evaluation and testing records.

#### **Expiration Dating Risk Level 1 Risk Level 2 Risk Level 3**

All sterile products must bear an appropriate expiration date. Expiration dates are assigned based on current drug stability information and sterility considerations. The pharmacist considers all aspects of the final product, including drug reservoir, drug concentration, and storage conditions. All guidelines for risk level 1 should be met. In addition to risk level 1 and 2 guidelines, there must be a reliable method for establishing all expiration dates, including laboratory testing of product stability, pyrogenicity, and chemical content when necessary.

#### **Labeling Risk Level 1 Risk Level 2 Risk Level 3**

Sterile products should be labeled with at least the following information: (1) for patient-specific product's, the patient's name and other appropriate patient identification; for batch-prepared products, control or lot numbers, (2) all solution and ingredient names, amounts, strengths, and concentrations, (3) expiration date (and time when applicable), (4) prescribed administration regimen, (5) appropriate auxiliary labeling, (6) storage requirements, (7) identification of the responsible pharmacist, (8) any device-specific instructions, and (9) any additional information, in accordance with state and federal regulations. A reference number for the

prescription or order may also be helpful. The label should be legible and affixed to the product so that it can be read while being administered. All guidelines for risk level 1 must be met. All guidelines for risk levels 1 and 2 must be met.

#### **End-Product Evaluation Risk Level 1 Risk Level 2 Risk Level 3**

The final product must be inspected for container leaks, integrity, solution cloudiness or phase separation, particulates in solution, appropriate solution color, and solution volume. The pharmacist must verify that the product was compounded accurately as to ingredients, quantities, containers, and reservoirs. In addition to risk level 1 guidelines, toxic products, like concentrated glucose and potassium chloride, should be tested for accuracy of concentration. In addition to risk level 1 and 2 guidelines, the medium-fill procedure should be supplemented with a program of end-product sterility testing according to a formal sampling plan. Samples should be statistically adequate to reasonably ensure that batches are sterile. A method for recalling batch products should be established if end-product testing yields unacceptable results. Each sterile preparation or batch must be laboratory tested for conformity to written specifications (e.g., concentration, pyrogenicity). It is advisable to quarantine sterile products compounded from nonsterile components pending the results of end-product testing

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