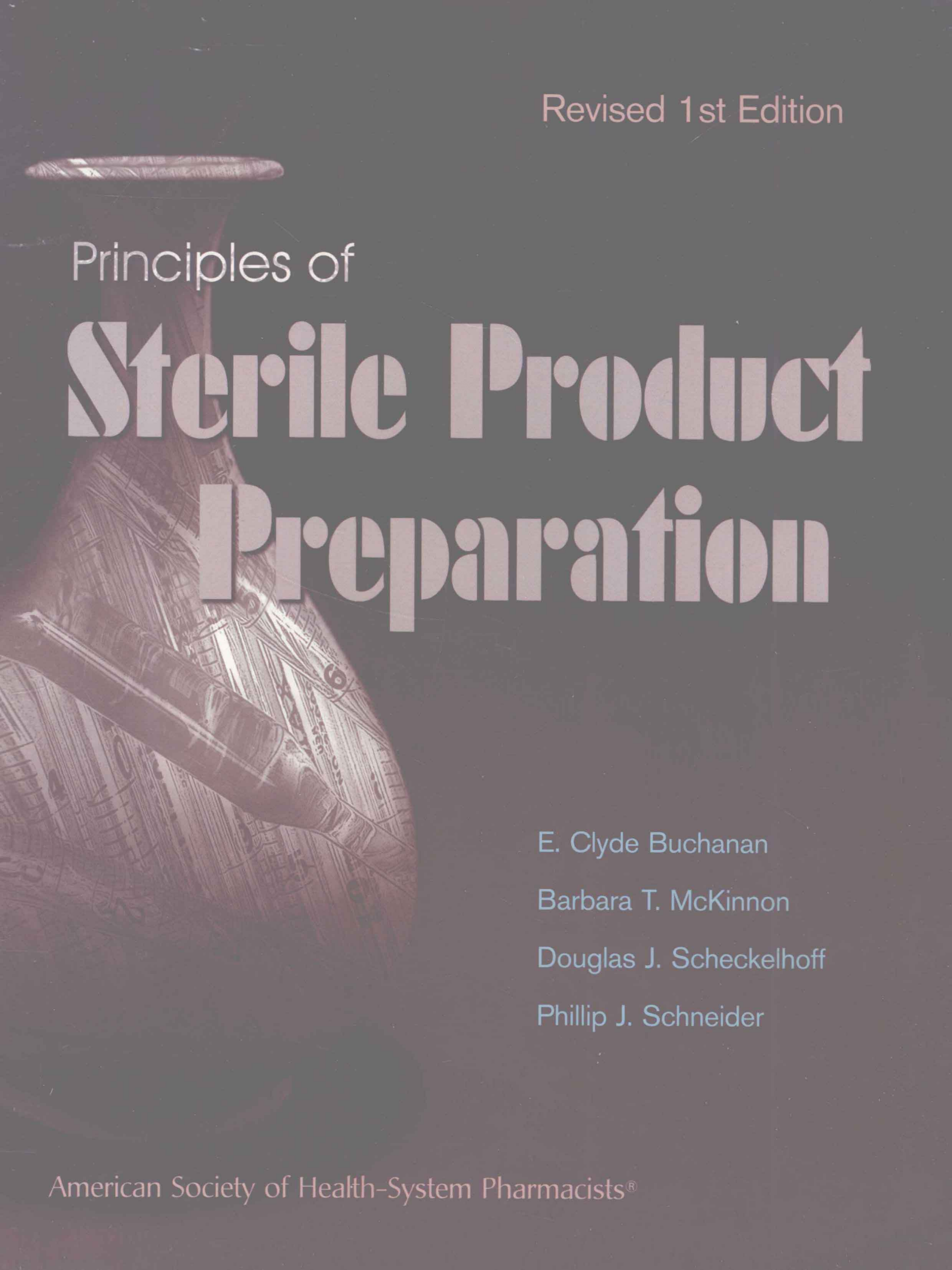




Revised 1st Edition

Principles of

Sterile Product Preparation

E. Clyde Buchanan

Barbara T. McKinnon

Douglas J. Scheckelhoff

Phillip J. Schneider

American Society of Health-System Pharmacists®

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藏书章

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Introduction

Principles of Sterile Product Preparation is a textbook of fundamentals. Nevertheless, the basic information supplied in this book has been lost to many in the profession of pharmacy. While our profession has gained much expertise in providing patient-oriented services during the past two decades, we may have lost ground in the skill of compounding sterile products.

Highly publicized incidents involving patient injury and death caused by pharmacy-compounded sterile products have prompted professional pharmacy organizations to refocus their attention on this area. After all, pharmaceutical compounding is still the unique right and responsibility of pharmacists and pharmacy technicians among health care professionals.

OBJECTIVES OF THIS BOOK

The objectives of *Principles of Sterile Product Preparation* are to

- ❑ Enable pharmacists, pharmacy technicians, and pharmacy students to understand the new, stricter, sterile compounding guidelines adopted by the pharmacy profession.
- ❑ Supplement other educational materials on pharmacy-prepared sterile products published by the American Society of Health-System Pharmacists (ASHP).
- ❑ Provide pharmacy personnel with a reliable reference for compounding and dispensing safe and effective sterile products.

This text is suitable as both a teaching guide and a reference for pharmacists, pharmacy technicians, and students. Although it is a comprehensive review of the fundamentals of preparing sterile products, it also indicates other sources of information on stability and incompatibility. Moreover, this book applies to sterile product preparation regardless of the pharmacy setting—hospital, home care, or community.

ORGANIZATION OF THIS BOOK

Principles of Sterile Product Preparation is composed of two main sections, chapters and appendices. There is also a glossary of sterile product terms.

The chapters cover topics essential to the pharmacy professional's understanding of why and how to prepare safe and effective sterile products. Each chapter begins with an outline that facilitates locating information within it.

Chapters 1 and 2 present background on pharmacy compounding of sterile products and the extent to which pharmacists and technicians are required to learn this skill. Chapters 3–11 develop the compounding process—from formulation through facilities and equipment, garb, aseptic technique, and batch production.

Chapters 12–15 describe the dispensing process, including expiration dating, labeling, storing, and handling of products. Then Chapters 16–19 cover quality-assurance methods of process validation and end-product evaluation, as well as documentation of preparation and procedures.

The eight appendices reproduce the most recent professional standards for sterile product preparation published by the Food and Drug Administration, the National Association of Boards of Pharmacy, ASHP, and the American Society for Parenteral and Enteral Nutrition.

ACKNOWLEDGMENTS

On behalf of the authors, I express sincere appreciation to the Special Publishing staff of ASHP. This group helped us organize some good ideas into a text that should inspire the profession of pharmacy to revisit its roots in compounding. We also hope that this book will guide pharmacists and technicians in producing the quality and variety of sterile products needed by their patients.

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July 5, 2001

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Chapter 1

Concepts and Guidelines in Preparing Sterile Products

E. Clyde Buchanan
Philip J. Schneider

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The Institute of Medicine recently recommended “have the central pharmacy supply high-risk intravenous medications” to reduce medical errors.¹ The preparation of sterile products is an integral part of any health-system setting. However, pharmacy preparation procedures vary widely across the country.^{2,3} This lack of uniformity, combined with changing technology in sterile product preparation and delivery, has led to serious medication errors and, therefore, recommendations for a variety of practice guidelines. Professional organizations have focused on improving pharmacy sterile product preparation practice for more than 10 years; still, few pharmacists are performing environmental sampling, end-product testing, or process validation, and the preparation of sterile products in uncontrolled environments outside pharmacies continues to be common.⁴

ADVERSE DRUG EVENTS

Over the past 20 years, pharmacists have been publicly cited many times for harming patients through a variety of errors in preparing sterile products.⁵ Errors can be categorized as incorrect ingredients⁶ (identity or purity of ingredients), incorrect strengths of ingredients (inaccurate measurements, instabilities or incompatibilities),⁷ and contamination with pathogenic microorganisms.⁸ In five U.S. hospital pharmacies, Flynn et al. observed a 9% error rate in the compounding of IV admixtures.⁹

Other health professionals have also caused harm through poor aseptic technique. Anesthesia personnel in seven hospitals accidentally contaminated propofol, a lipid-based anesthetic, with a variety of pathogens leading to infectious complications in dozens of patients.¹⁰ Dialysis personnel caused *Serratia* infections in at least 12 patients through multiple punctures of single-use vials and pooling of preservative-free epoetin alfa.¹¹ Pharmacists are obligated to train other personnel in handling sterile products even if pharmacists are not available to carry out aseptic manipulations themselves.

MORE CHALLENGES AHEAD

These adverse events are but a few examples of the dangers inherent in preparing sterile products. While many institutions have developed practices to prevent these dangers, new technologies and procedures are challenging pharmacists' abilities to compound, package, and label appropriately.¹²⁻¹⁴

New Technologies

New technologies, such as syringe pump infusion systems and patient-controlled analgesia (PCA) pumps, require pharmacists to repackage injectables into syringes, increasing the chance of errors.¹⁵ Infusion pumps that allow a pharmacist to place multiple intermittent doses into a single IV bag also increase the risks of incorrect preparation, packaging, and labeling. Portable pumps and indwelling medication reservoirs permit longer infusion periods and higher product temperatures, possibly leading to mistakes in expiration dating.^{16,17} Elastomeric infusion devices, which are simple to use but require special storage conditions, may lead to dosing errors.¹⁸

New Procedures

The use of high-risk routes of administration (e.g., intrathecal) also increases the danger level. Additionally, the use of more toxic sterile products—highly concentrated injections of potassium chloride, dextrose, lidocaine, and doxorubicin—has led to fatal medication errors. The preparation of sterile drugs from nonsterile ingredients also increases the level of risk. Common examples include concentrated morphine injection for epidural analgesia and reservoirs, alum for bladder irrigation,¹⁹ and caffeine for neonatal respiratory distress.

Another technical, and possibly legal, issue for pharmacists is the use of automated compounders:

- ❑ How do such large devices affect laminar-air-flow in a hood?
- ❑ How does a pharmacist ensure that the right additives are hung on individual stations?²⁰
- ❑ How does a pharmacist ensure that the pump is measuring ingredients accurately?^{21,22}

Other complexities arise because pharmacy-prepared sterile products are now used in numerous settings, including patients' homes, physicians' offices, and long-term care facilities. In these settings, pharmacists must ensure the efficacy and safety of any product they compound or check.

FDA AUTHORITY AND ACTIONS

The technological and procedural issues described here

have led to action by the Food and Drug Administration (FDA), which has the authority to regulate the quality of drug products prepared in pharmacies. Since 1990, the FDA has sent warning letters to retail pharmacies that may manufacture, distribute, and promote unapproved drugs for human use outside the bounds of licensed pharmacy practice. The FDA's position was stated in a 1980 compliance guide (see Appendix 1). After recognizing some serious pharmacy errors in batch compounding, in 1990 the FDA formally reminded pharmacists that they are responsible for adhering to good manufacturing practices and safe packaging.²³

Under its authority to regulate "new" drugs, the FDA allows physicians to prescribe "an unusual preparation that requires compounding by a pharmacist from drugs readily available for other uses and which is not generally regarded as safe and effective for the intended use"²⁴ (see Appendix 2). However, processing and repackaging of approved drugs by pharmacists for resale to hospitals, other pharmacies, etc., are subject to premarket approval by the FDA as new drug products. The FDA's regulatory authority over extemporaneous and batch compounding is interpreted by its inspectors, who generally do not examine state-licensed pharmacies.

With strong support from pharmacy organizations, the U.S. Congress passed the Food and Drug Administration Modernization Act of 1997 (FDAMA).²⁵ Section 127 of this Act, which codified pharmacy compounding, states that pharmacy compounding must comply with an applicable *United States Pharmacopeia–National Formulary* (USP–NF) monograph, if one exists, and the USP–NF chapter on pharmacy compounding or the compounded substance must 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.

In February 2001, the Federal Ninth Circuit Court of Appeals declared pharmacy compounding provisions in the FDAMA entirely invalid.²⁶ This court agreed with the federal district court, which had found that the advertising restrictions contained in Section (c) of the law were unconstitutional because they abrogated the constitutional right to free speech. However, the court of appeals went further, stating that the advertising section could not be severed from the rest of the law because Congress would not have passed the law without the advertising prohibition. Although the Ninth Circuit covers only the western states, the FDA has suspended actions to complete regulations supporting FDAMA. The effect has been to leave pharmacy compounding primarily under state pharmacy laws but with no safe haven from federal inspections of compounding pharmacies.

NABP ACTIONS AND GUIDELINES

The National Association of Boards of Pharmacy (NABP) hold that prescription compounding is a pharmacist's responsibility and should be regulated by state boards of pharmacy.²⁷ To distinguish between compounding and manufacturing, NABP defined these terms in its Model State Pharmacy Practice Act:²⁸

*Compounding—means the preparation, mixing, assembling, packaging, or labeling of a drug or device (i) as the result of a practitioner's prescription drug order or initiative based on the practitioner/patient/pharmacist relationship in the course of professional practice, or (ii) for the purpose of, or as an incident to, research, teaching, or chemical analysis and not for sale or dispensing. Compounding also includes the preparation of drugs or devices in anticipation of prescription drug orders based on routine, regularly observed prescribing patterns.*²⁹

*Manufacturing—means the production, preparation, propagation, conversion, or processing of a drug or device, either directly or indirectly, by extraction from substances of natural origin or independently by means of chemical or biological synthesis, and includes any packaging or repackaging of the substance(s) or labeling or relabeling of its container, and the promotion and marketing of such drugs or devices. Manufacturing also includes the preparation and promotion of commercially available products from bulk compounds for resale by pharmacies, practitioners, or other persons.*²⁹

NABP published "Good Compounding Practices Applicable to State Licensed Pharmacies" (see Appendix 3), a general compounding document for state boards of pharmacy prepared at the request of the FDA. The other pertinent NABP model regulation is "Model Rules for Sterile Pharmaceuticals" (see Appendix 4). NABP model regulations do not have the force of law. They merely serve as a basis for individual state boards to develop rules and regulations. Many state boards circulate NABP model regulations in their newsletters.

Appendixes 3 and 4 should be studied to gain a thorough understanding of the model regulations. Neither guideline distinguishes levels of product risk to patients (see discussion of risk levels, below).

ASHP ACTIONS AND GUIDELINES

ASHP has continually promoted appropriate pharmacy compounding in the institutional setting. In 1990, ASHP developed a multistep action plan to encourage and teach pharmacists to compound safe and effective sterile products.

Letter and Survey

The first step of this plan was to send a letter to pharmacy directors, assistant directors, and IV supervisors across the nation, urging them to review and revise their sterile product techniques.³⁰ In the second step, ASHP sent a survey to a representative sample of hospital pharmacy directors to assess the quality of sterile product procedures.³¹ Some key findings were:¹

- ❑ Nearly 96% of hospital pharmacies extemporaneously compounded sterile products; 61% also batch-prepared such products.
- ❑ Almost all pharmacists (99.4%) who prepared sterile products used a laminar-airflow hood.
- ❑ About 75% of respondents used laminar-airflow hoods in limited-access areas.
- ❑ About 50% of respondents said that their hoods were certified every 6 months and that prefilters were changed monthly.
- ❑ Less than 33% of respondents reported sampling the environment in and around the hood for microbial contamination.
- ❑ About 33% of pharmacists used final filtration to sterilize some products prepared extemporaneously, and 16% of pharmacists filtered products in batch compounding.

Nearly half the survey respondents never tested the chemical purity, drug concentration, sterility, or pyrogenicity of sterile products. Less than a third of the pharmacies tested their pharmacists or technicians, either by written exam or process validation, on aseptic technique. In other words, the majority of hospital pharmacists did not determine whether they were compounding safe and effective sterile products. ASHP concluded that certain quality-assurance procedures for sterile products needed significant improvement.

Conference

The third step in ASHP's plan was to invite key persons to participate in a conference³² to list apparent problems with pharmacy-prepared sterile products and to identify possible solutions. Attendees included representatives from the FDA, United States Pharmacopeial Convention, American Hospital Association (AHA), NABP, Intravenous Nurses Society, Association for Practitioners of Infection Control, American College of Apothecaries, Joint Commission on the Accreditation of Healthcare Organizations (JCAHO), AACP, Parenteral Drug Association, Pharmaceutical Manufacturers Association, American Biological Safety Association, Canadian Society of Hospital Pharmacists, American Nurses Association, and some members and staff of ASHP.

Conference participants listed 12 problems with pharmacy sterile compounding practices. These problems may be categorized into four groups:

1. A lack of appropriate policies and procedures.
2. A lack of personnel training and education materials.
3. A lack of consistent regulatory definitions, standards, and enforcement by professional and governing groups.
4. A lack of commercially available sterile products.

Twenty-six ideas were suggested for resolving the problems.

Educational Programs and Publications

ASHP began the fourth step of its plan with educational programs and publications to teach pharmacy personnel how to prepare safe and effective sterile products. Several articles and editorials also have been published in the *American Journal of Health-System Pharmacy* (formerly the *American Journal of Hospital Pharmacy*) that explain the need for professional guidelines for preparing sterile products.^{5, 33-36}

As a final step, ASHP developed a practice standard for the quality assurance of pharmacy-prepared sterile products. First published in 1993 as a technical assistance bulletin, this standard was updated and republished in 2000 (Appendix 5).³⁷ ASHP has also published a technical assistance bulletin on preparing ophthalmic products³⁸ and guidelines on the safe use of automated compounding devices for preparation of parenteral nutrition admixtures (Appendix 8).³⁹

Risk levels

The ASHP *Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products* designates three levels of risk to patients, increasing from the least (Risk Level 1) to the greatest (Risk Level 3) potential for harm. Risk levels are defined, and examples of sterile products in each level are given. Quality-assurance practices for patient safety and product effectiveness are also listed for each level. This categorization by risk levels allows pharmacists to match sterile compounding procedures to the products they prepare. When compounding a product under conditions that do not meet risk-level requirements, pharmacists are required to use their best judgment regarding the risk-to-benefit relationship for the patient.

Cleanrooms

A controversial part of these guidelines pertains to the suitable environment (or controlled area) for sterile compounding. While Risk Level 1 products require a sepa-

rate, clean space of sufficient size, Risk Levels 2 and 3 require "cleanrooms." A cleanroom is a separate room that houses the laminar-airflow hood; the room receives air filtered to a standard level of cleanliness (expressed in airborne particles per cubic foot). Airborne particles are the main vectors for microbes that contaminate products during processing. A properly maintained barrier isolator also provides an acceptable environment.⁴⁰ 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.

The special environment requirement is controversial because of its cost-benefit ratio. The key to ensuring the best possible compounding environment is to ensure that airborne microbes do not enter the laminar-airflow hood workspace. One study showed that simple changes in operating procedures can produce a cleanroom environment without costly architectural changes.⁴¹ Finally, a laminar-airflow hood suited to the compounded products is the most important equipment, but it must be properly used and maintained to prevent contamination.

Garb

A discussion on garb (clothing, masks, gloves, and shoe covers) is also an integral part of the quality assurance guidelines. Operators should wear garb that sheds low levels of particulates, wash their hands frequently, and use proper hygiene. Sterile gloves are recommended in Risk Level 1 and are required in Risk Levels 2 and 3.

Process validation and key points

The guidelines also describe the need for process validation to determine whether an operator, working under the most challenging situation, can consistently produce a sterile product. Growth media are substituted for normal ingredients in the compounding process to validate the environment, equipment, supplies, and aseptic technique. Process validation (sometimes referred to as "media fills") is better than end-product sterility sampling, which can lead to accidental contamination, delayed results, and higher costs. The guidelines stipulate process validation for individual operators in Risk Level 1, for each compounding process in Risk Level 2, and for each product in Risk Level 3.

Other key points in the guidelines include:

- ❑ Development and maintenance of up-to-date procedures.
- ❑ Training and competency testing of personnel.
- ❑ Storage and handling of closures, containers, and supplies.
- ❑ Product stability (compatibility and physical and chemical stability) at the time of use.
- ❑ Expiration dating of compounded products.
- ❑ Labeling requirements.

- ❑ Final product inspection (sterility, nonpyrogenicity, accurate drug concentration, and stability).
- ❑ Documentation of all sterile compounding processes.
- ❑ Documentation of employee testing and validation, refrigerator temperatures, hood certification, batch control testing, and quarantine records.

USP ACTIONS AND GUIDELINES

Well before pharmacy compounding errors came into public attention, USP decided that preparation of sterile IV products for home use involved special concerns (e.g., extended product storage and patient manipulations prior to use). Therefore, they established a Home Health Care Advisory Panel in 1989 to draft a monograph or guideline on compounding sterile products for home use. The first draft of this monograph was published in March 1992.⁴² The official chapter appeared in the 1995 USP–NF⁴³ and was revised in the 2000 USP–NF⁴⁴ (Appendix 6). *At the time of this book's publication in September 2001, this document was under revision and, therefore, was not available for inclusion. Please consult the USP–NF for the current version of this document.*

COMPARISON OF ASHP AND USP GUIDELINES

Like ASHP, USP defines three risk levels to patients, a low-risk and two high-risk categories. However, USP risk levels are defined somewhat differently from the ASHP guidelines; therefore, some product types do not match ASHP's corresponding risk levels. Table 1-1 presents examples of which products fit into corresponding risk levels of the ASHP and USP documents.

Recently, FDA had proposed requiring that pharmacists prepare sterile products only according to the USP monograph, before the FDAMA was ruled unconstitutional.⁴⁵ This ruling is notable because the ASHP and USP guidelines each have their advantages.

Advantages of ASHP Guidelines

1. Risk level sections and topics are organized and clear.
2. A single, extensive glossary defines all terms.
3. Exhaustive references, 127 in number, cite original literature.
4. Effects of storage time and temperature on sterility before product use are addressed.
5. Use of barrier isolators in the preparation of sterile products is considered.

6. Emphasis is placed on educating pharmacy personnel on sterile preparation technique.
7. Laminar-airflow workbenches recertification is specified for at least every 6 months, instead of every year.
8. Environmental cleaning standards and intervals are listed.
9. Calibration of automated compounder and pumps is specified. (ASHP also published a separate guideline on the use of automated compounding devices for the preparation of parenteral nutrition admixtures; see Appendix 8.)

Advantages of USP Monograph

1. Covers "redispensing" of sterile products that have been rerouted from one patient who no longer needs the product to another patient who does need the product, in two sections: Storage and Beyond-use Dating and Sterile Preparations for Institutional Use.
2. Extensively treats environmental control and monitoring.
3. Recommends a Class 100,000 cleanroom environment for low-risk and Class 10,000 environment for both high-risk categories as well as an anteroom for both high-risk categories.
4. Recommends nonshedding coats or coveralls for all risk level categories.
5. Recommends that each operator perform medial fills quarterly for low-risk operations plus gives a more thorough discussion of validation.
6. Provides a better discussion of sterilization by filtration and heat.
7. Provides a more thorough discussion on maintaining product quality and control after the sterile product leaves the pharmacy.
8. Covers responsibilities of off-site compounding pharmacies and corresponding receiving pharmacies.
9. Specifies responsibilities for pharmacies dispensing to patients in the home, including a patient monitoring and complaint system.

A.S.P.E.N. GUIDELINES FOR PARENTERAL NUTRITION

Recognizing the importance of safe practices associated with these products, the National Advisory Group on Standards and Practice Guidelines for Parenteral Nutrition was formed, consisting of five pharmacists who were members of the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). Their report, "Safe practices for parenteral nutrition formulations" was published in 1998 (Appendix 7).⁴⁶

Table 1-1. *Examples of Sterile Products by Risk-Level Category*

ASHP Guidelines	USP Monograph
Risk Level 1 Single-patient admixture Single-patient ophthalmic, preserved Single-patient syringes without preservatives used within 28 hours Batch-prefilled syringes with preservatives Total parenteral nutrient (TPN) solution made by gravity transfer of carbohydrates and amino acids into an empty container with the addition of sterile additives with a syringe and needle	Low-Risk Category Transferring sterile drug products from vials or ampuls into sterile final containers using a sterile needle and syringe Transferring sterile drug products into sterile elastomeric infusion containers with the aid of a mechanical pump and an appropriate sterile transfer tubing device, with or without the subsequent addition of sterile drug products to the infusion container with a sterile needle and syringe Compounding sterile nutritional solutions by combining dextrose injection and amino acids injection via gravity transfer into sterile empty containers, with or without the subsequent addition of sterile drug products to the final container with a sterile needle and syringe
Risk Level 2 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	High-Risk Category 1 Compounding sterile nutritional solutions using an automated compounding device involving repeated attachment of fluid containers to proximal opening of the compounder tubing set and of empty final containers to the distal opening. The process concludes with the transfer of additives into the filled final container from individual drug product containers or from a pooled additive solution Preparing ambulatory pump reservoirs by adding more than one drug product with the evacuation of air from the reservoir prior to dispensing Preparing ambulatory pump reservoirs for multi-day (i.e., ambient temperature) administration
Risk Level 3 Alum bladder irrigation Morphine injection made from powder or tablets TPN solutions made from dry amino acids TPN solutions sterilized by final filtration Autoclaved IV solutions	High-Risk Category 2 Compounding injectable morphine solutions from nonsterile morphine substance and suitable vehicles Compounding sterile nutritional solutions from nonsterile ingredients with initial mixing in a nonsealed or nonsterile reservoir

The A.S.P.E.N. guidelines are organized into six sections, each of which includes evidence to support the need for a practice guideline, specific practice guidelines based on a consensus of the National Advisory Group, a summary of areas requiring further study, and a list of references. The six sections include:

- ☐ Introduction
- ☐ Labeling parenteral nutrition formulations
- ☐ Standard nutrient ranges and sample parenteral

nutrition formulations

- ☐ Extemporaneous compounding of parenteral nutrition formulations
- ☐ Stability and compatibility of parenteral nutrition formulations
- ☐ In-line filtration of parenteral nutrient admixtures

Compliance with these guidelines was recently assessed by O'Neal et al.⁴⁷ They found compliance ranging from

15.4% to 86.9%, suggesting a need to improve practices in the preparation of parenteral nutrition formulations. Areas of high compliance included use of filters, verification of stability and compatibility by a pharmacist or computer, evaluating aseptic technique of staff, clarification of doses out of range, and use of standard order forms. Areas of low compliance included use of dosing weight on the label, including daily ingredient amounts on the label, having pharmacist-to-pharmacist communication during patient transfer, end-product sterility testing, and use of 2-in-1 formulations in neonatal and infant patients.

SUMMARY

Pharmacists who are responsible for compounding sterile products face many issues unknown 10–15 years ago. With current publicity, governmental scrutiny, and technological changes, pharmacists are greatly challenged to meet this responsibility.

To compound sterile products appropriately, pharmacists must understand the guidelines of NABP, ASHP, USP, and A.S.P.E.N. Each guideline has a unique perspective and offers information not covered in the others. However, professional judgment is required in applying these guidelines to individual practice settings.



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