Chapter 4

Sterile Preparation Formulation

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Introduction

This chapter will provide insight into the issues of formulation when applied to compounding sterile preparations. The majority of options discussed in this chapter will involve *high-risk compounding* as defined by USP Chapter <797> Pharmaceutical Compounding—Sterile Preparations.[1] Also, sterile compounding that requires specialized formulations may be designated *difficult to compound* by the newly created U.S. Food and Drug Administration (FDA) Task Force. This group examines specialized formulations and the resources available to pharmacists to safely conduct such procedures. This group then decides which modality or therapy is outside the scope of compounding. The Pharmacy Compounding Advisory Committee has met several times to evaluate what drug products are exempt from compounding under both Sections 503A and 503B of the Federal Food, Drug and Cosmetic Act. The compounder will be prohibited from using these ingredients, in some cases at specific quantities outlined in the document.[2]

Please refer to Chapter 21 for the stability and incompatibility of drugs, Chapter 15 for labeling compounded preparations, Chapter 16 for documentation, Chapter 17 for sterilization methods, and Chapter 18 for finished preparation release checks and tests.

Federal Regulations

New Compounding Drug Regulations

The following is an excerpt of an FDA release pertinent to compounding sterile preparations:

> On November 27, 2013, President Obama signed the Drug Quality and Security Act (DQSA), legislation that contains important provisions relating to the oversight of compounding of human drugs.

Note: The author acknowledges E. Clyde Buchanan who authored this chapter in the previous edition.

Title I of this new law, the Compounding Quality Act, removes certain provisions from section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA) that were found to be unconstitutional by the U.S. Supreme Court in 2002. Section 503A describes the conditions under which certain compounded human drug products are exempt from three sections of the FDCA requiring:

- Compliance with current good manufacturing practices (CGMPs) (section 501(a)(2)(B));
- Labeling with adequate directions for use (section 502(f)(1)); and
- FDA approval prior to marketing (section 505).

The new law also creates a new section 503B in the FDCA. Under section 503B, a compounder can become an *outsourcing facility*. An outsourcing facility will be able to qualify for exemptions from the FDA approval requirements and the requirement to label products with adequate directions for use, but not the exemption from CGMP requirements. Outsourcing facilities:

- Must comply with CGMP requirements,
- Will be inspected by FDA according to a risk-based schedule, and
- Must meet certain other conditions, such as reporting adverse events and providing FDA with certain information about the products they compound.[3]

When formulating and compounding sterile preparations, pharmacists must follow both state laws and FDA regulations. State pharmacy practice acts and board of pharmacy regulations cover these activities. The FDA also regulates formulation and compounding under adulteration, misbranding, and new drug provisions of the FDA.[4]

Since 1980, in their Field Regulatory Guidance, *"Hospital Pharmacies Status as Drug Manufacturer,"* FDA Guide 7132.06 states that "a physician may 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."[5] If the pharmacy fills each prescription as received, clearance under the "new drug" provisions is not required.[5]

Compounding Phase 1 investigational drugs does not require full compliance with CGMPs because of the low volume of patients.[6] Compounding medications for Phase II and III trials requires complete adherence to CGMPs, and products prepared for Phase I cannot be used for the subsequent phases if not prepared under full CGMPs.

If a pharmacist compounds finished drugs from bulk active ingredients that are not obtained from an FDA-approved facility or are not compliant with compendial standards (i.e., *The United States Pharmacopeia* and *The National Formulary* [*USP–NF*]), these finished preparations must be covered by a new drug application.[7] In other words, bulk compounded preparations must conform to USP Chapter <795> Pharmaceutical Compounding—Nonsterile Preparations and USP Chapter <797>; otherwise, FDA requires that a new drug application be filed and accepted for the bulk compounded preparation.[1]

If a pharmacist changes the strength, dosage form, or components of a commercially available preparation in a compounded prescription, good compounding procedures should be used.[7] Pharmacists are responsible for compounding and dispensing finished preparations pursuant to prescribed therapy, and for compounding and preparing those preparations in compliance with established boards of pharmacy and other regulatory agencies. These requirements vary from state to state.

Professional Standards

Formulating, compounding, and sterilizing a pharmaceutical from nonsterile ingredients or in nonsterile containers is the most difficult and is considered a high-risk procedure.[1] The chemical purity and content strength of ingredients must meet their original or compendial specifications in unopened or in opened packages of bulk ingredients in compliance with the Ingredient Section of USP Chapter <795>.[8] Batch master worksheets should include comparisons of actual with anticipated yields, sterilization methods, and quality control