

Compounding Parenteral Nutrition: Options and Updates

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
Abstract

The compounding of “sterile” products has made headlines in the news in the United States over the last several years, due the lack of sterile conditions in a compounding pharmacy causing an outbreak of fungal meningitis. Although USP Chapter <797> was released in 2008 and outlines in detail procedures needed to keep pharmacies sterile, these lapses in sterility still occurred. However, the state governments were primary responsible for enforcing these procedures until recently. In 2013, the United States Congress broadened laws by passing the Drug Quality and Security Act of 2013, which gave the federal government the power to enforce USP Chapter <797> for compounding pharmacies. In addition, USP Chapter <797> is undergoing updates, and all practitioners in the field should be aware of the changes that are coming in the future. The field of parenteral nutrition has changed over the last few years as well, giving options such as premixed bags with multiple chambers.

Keywords: Drug quality; Parenteral nutrition; Microbial contamination; Sterile products

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Introduction

The compounding of “sterile” products has made headlines in the news in the United States over the last several years, due the lack of sterile conditions in a compounding pharmacy causing an outbreak of fungal meningitis [1]. Although USP Chapter <797> was released in 2008 and outlines in detail procedures needed to keep pharmacies sterile, these lapses in sterility still occurred [2]. However, the state governments were primary responsible for enforcing these procedures until recently [1]. In 2013, the United States Congress broadened laws by passing the Drug Quality and Security Act of 2013, which gave the federal government the power to enforce USP Chapter <797> for compounding pharmacies. In addition, USP Chapter <797> is undergoing updates, and all practitioners in the field should be aware of the changes that are coming in the future [3]. The field of parenteral nutrition has changed over the last few years as well, giving options such as premixed bags with multiple chambers.

A recent outbreak of fungal meningitis in the United States left many health care professionals questioning the standards and enforcement currently in place regarding the safety of compounding pharmacies [1]. Although USP Chapter <797> was published in 2008, the laws surrounding the way it was enforced were arguably ambiguous. Regardless, the intent of the chapter was to standardize conditions for compounding sterile products.

This article will examine the chapter’s current enforceability, specific procedures associated with parenteral nutrition, and updates that are coming to the Chapter in the near future.

Standards and Oversight

USP Chapter <797> was published on January 1, 2008, and was the first enforceable document outlining safe conditions regarding the compounding of sterile products [4]. There seems to be some controversy regarding the “enforceability” of this document, which takes place over a period of several decades. In 1938, the Food, Drug, and Cosmetic Act (FD & C Act) recognized the USP/NF as the official compendia of drug standards. This means the FDA is responsible for enforcing the standards outlined in the USP/NF. However, regarding the practice of pharmacy, the FDA defers to the states to dictate and enforce law. Sadly, many states did not even refer to USP Chapter <797> as a standard to be enforced [1]. In order to give the FDA more latitude, Congress passed the Compliance Policy Guide of 1992 and then the Food and Drug Administration Modernization Act (FDAMA) of 1997. Unfortunately, the FDAMA contained a clause in section 503A regarding the “advertising” of drugs that was later deemed unconstitutional by the Supreme Court, thus invalidating the entire section regarding drug compounding. Finally, in 2013,

Congress passed the Drug Quality and Security Act [5]. Although this legislation continues to give state Boards of Pharmacy the responsibility for enforcing standards over compounding pharmacies, it gives the pharmacies the option to register with the FDA. If so registered, the FDA would be responsible for monitoring these pharmacies and enforcing USP/NF standards. Also, the pharmacies would be able to legally compound and distribute bulk substances, if the substances are on the approved FDA list.

Compounding Procedures: Risks Specific to Parenteral Nutrition

Per the definition of USP Chapter <797>, parenteral nutrition (PN) falls under the category of a “compounded sterile preparation [2].” As such, as a finished product, it must adhere to the standards outlined in the chapter to “prevent harm, including death, to patients that could result from (1) microbial contamination (nonsterility), (2) excessive bacterial endotoxins, (3) variability in the intended strength of correct ingredients that exceeds either monograph limits for official articles ... (4) unintended chemical and physical contaminants and 5) ingredients of inappropriate quality in compounded sterile preparations.” These standards require maintenance of air quality, surface disinfection, personnel garbing and gloving, personnel training and competency, compounding procedures, and equipment maintenance.

Institutions now have many options for parenteral nutrition, including two-chamber premixed PN, three-chamber premixed PN, two-in-one compounded PN, and three-in-one compounded PN [6]. Smaller institutions using a few bags of PN per month may opt for premixed PN. Two-chamber PN is prepared by the manufacturer, with or without electrolytes, having amino acids in one chamber and dextrose (plus or minus electrolytes) solution in the other chamber. The chamber seal is broken prior to administration, which allows for mixing of the two chambers. Patients receiving two-chamber PN bags will also require a separate infusion of intravenous fat emulsion (IVFE). Three-chamber premixed PN bags follow the same concept as the two-chamber bags, except that the third chamber contains IVFE.

Larger institutions with high acuity may use automated compounding devices (ACDs) to compound PN. These devices are used to customize a PN prescription for each patient. Some institutions use ACDs to compound two-in-one PN bags that contain amino acids, dextrose and other additives in one bag, or three-in-one PN bags that contain amino acids, dextrose, additives, and fat all in one bag. Some institutions compound both types, and will infuse IVFE as a separate infusion with two-in-one PNs. This strategy is often used for pediatric patients. Many institutions with pediatric patients will consider repackaging fat emulsion into smaller doses. Although this is not the “mixing of ingredients,” it still falls under the category of “compounding,” by USP Chapter <797> because it is the “packaging” of a drug based on a prescription [2]. The most recent guidelines published by the American Society for Parenteral and Enteral Nutrition recommend against the repackaging of fat emulsion [6]. Reiter examined repackaging of fat into syringes in two separate studies and found 3.3% and 2.7% contamination rates in his 2002 and

2004 studies, respectively [7,8]. Crill in 2010 studied fat emulsions repackaged into syringes and also found a contamination rate of 3.3% [9]. Ybarra used an ACD to repackage fat emulsion and found an even higher rate of contamination at 7.9% [10]. Indeed, the only methods that did not show contamination were those tested by Crill which were either hanging the fat emulsion from the manufacturer at the bedside or using a “draw-down” technique [9]. The draw-down technique consists of puncturing the fat emulsion bag from the manufacturer, drawing out the excess volume and discarding it. The fat emulsion bag from the manufacturer can then be hung at the bedside in its original container with the correct volume for the patient.

Updates to the Chapter

A proposed draft of updates to USP Chapter <797> was posted on the website [3] for commentary. This draft updates nearly the entirety of the chapter, from competencies for gloving and garbing to “how-to” guides for standard operating procedures. This article will outline the updates, although describing each update in detail is beyond the scope of this article.

First, the chapter changes the previous three categories of compounds (low-, medium-, and high-risk compounds) to only two categories: Category 1 and Category 2 compounds. Category 1 compounds are “assigned a beyond-use date of 12 hours or less at controlled room temperature or 24 hours or less refrigerated.” Category 2 compounds are “assigned a beyond-use date of greater than 12 hours at controlled room temperature or greater than 24 hours refrigerated that is compounded...with all applicable standards for Category 2 compounded sterile products (CSPs)..”. The chapter continues to describe the standards that apply to Category 2 CSPs, including facility requirements, garbing requirements, and sterility testing requirements (if applicable). Next, the chapter describes competencies required by all personnel staffed in compounding areas, including new “core” competencies including the following: hand hygiene, cleaning and disinfection, measuring and mixing, proper cleanroom behavior, methods of sterilization and de-pyrogenation, use of equipment, understanding the direction of the HEPA-filtered unidirectional airflow within ISO Class 5, documentation of the compounding process, proper use of PECs, and impact of moving materials in and out of the compounding area. Initial and quarterly re-evaluation of the following skills is required: visual observation, glove-tip sampling, media fill testing, as well as cleaning and disinfecting. Annual core competencies are required of all personnel.

A section titled “Facility Design and Environmental Controls” describes the compounding area and areas needed for garbing and gloving, etc. Updates include requirements for not only particle control, but also temperature and humidity control. Other updates include suggestions regarding airlocks and interlocking doors, as well as requirements for maintaining pressure differentials. Certification and recertification of facilities are required, including airflow testing, HEPA filter integrity, particle count testing, and smoke studies. There are also updates describing requirements for facilities that compound hazardous drugs.

A nice addition to the chapter which pertains to PN includes a section on ACDs that describes suggestions for maintenance. A section that follows this is titled, "Component Selection," and is particularly relevant, given the recent and ongoing shortages of drugs in the United States. This section urges facilities to use qualified vendors and USP- or NF-validated ingredients. If these ingredients are not available, the chapter outlines procedures to ensure the acquisition of chemically pure, safely prepared ingredients.

The chapter continues to urge facilities to create Standard Operating Procedures, including procedures for master formulation records, compounding records, release testing, sterility testing, bacterial endotoxin testing, and labeling. A new section describes the difference between "beyond-use date" and "in-use time." "Beyond-use date" is the same definition as in the previous USP Chapter <797>, "the time after which a CSP cannot be used and must be discarded." "In-use time" is the "time before which a conventionally manufactured product or CSP must be used after it has been opened or needle punctured (e.g., after a container closure of a vial has been penetrated)." Other

updated sections include: Quality Assurance and Quality Control, Handling of Hazardous Drugs, Adverse Event Documentation, and Documentation.

An entire section dedicated to radiopharmaceuticals is new. Although this section is short, it describes the equipment needed to compound radiopharmaceuticals, as well as the conditions under which they must be compounded. It also describes the personal protective equipment required for staff. This section is helpful for any facility involved with compounding these products.

Summary

Regulations concerning sterile compounding have evolved over the last few decades. Each new set of regulations strives to protect the public and make sterile compounding as safe as possible. Compounding parenteral nutrition can still be a complex process, depending on which type of parenteral nutrition is chosen. The updates to USP Chapter <797> are many. The proposed chapter is very detailed and this makes it easy to read and easy to use. The updates will no doubt help to improve the future of sterile compounding.

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