

Introduction to Parenteral Preparations

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Chapter Objectives

1. Define a parenteral preparation.
2. List various routes of parenteral administration.
3. Describe advantages and disadvantages of the parenteral route of administration.
4. Discuss the role of safety, accuracy, and attitude in risk prevention associated with parenteral preparation.
5. Discuss United States Pharmacopeia chapters applicable to pharmaceutical compounding of sterile preparations.

Key Terminology

Hazardous agent

Pyrogen

Sterility

Particulate matter

Isotonicity

Normal saline

United States Pharmacopeia

Compounded sterile preparations

Automated compounding devices

Radiopharmaceutical

Parenteral nutrition

Accreditation Council for Pharmacy Education (ACPE)

Precipitate

Overview

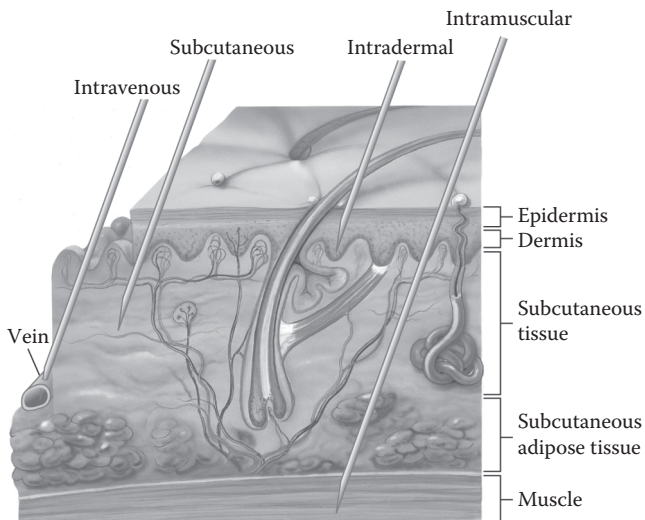
Compounded sterile preparations (CSPs) are often prepared for parenteral administration from manufactured sterile products. Patients frequently require administration of parenteral preparations as a means of drug delivery. This mode of delivery provides both benefits and risks compared to other forms of drug delivery. Pharmacists and pharmacy technicians assume various roles in the preparation and verification of parenteral preparations. Understanding the basics of parenteral preparation is the beginning of building the knowledge and skills needed as part of required personnel training. Patient and personnel safety related to the preparation and administration of parenteral preparations depends on many factors, including accuracy, safety, and the attitude of those involved in the compounding process.

Parenteral Administration

Medications can be delivered into the body through a variety of routes. Drug delivery characteristics and pharmacodynamic properties vary depending on the route of administration chosen for the drug. Parenteral preparations circumvent the intestinal tract and, therefore, are not subject to pharmacodynamic properties associated with oral or other formulations. While many routes of parenteral administration are available, all of which bypass the intestinal tract, the intravenous, intramuscular, and subcutaneous routes of administration are the most commonly used. **Table 1-1** lists various routes and locations of delivery of parenteral administration. **Figure 1-1** illustrates the locations utilized in intravenous, intradermal, intramuscular, and subcutaneous parenteral

Table 1-1 Parenteral Routes

Route	Injection Site
Intravenous (IV)	Vein
Intramuscular (IM)	Muscle tissue
Intradermal (ID)	Dermis of the skin
Subcutaneous (subcut; SQ)	Subcutaneous tissue of the skin
Intrathecal (IT)	Subarachnoid space of the spinal cord
Epidural	Epidural space of the spinal cord
Intra-arterial	Artery
Intra-articular	Joint space
Intracardiac	Heart
Intraocular	Eye
Intraperitoneal	Peritoneal cavity

**Figure 1-1** Routes of Parenteral Administration

administration. Intrathecal and epidural administration of medications offer additional routes of administration within the spinal cord; **Figure 1-2** depicts the location of drug delivery with these routes of administration. Because medications administered parenterally bypass the intestinal tract, the pharmacodynamic properties of such medications will differ depending on the site

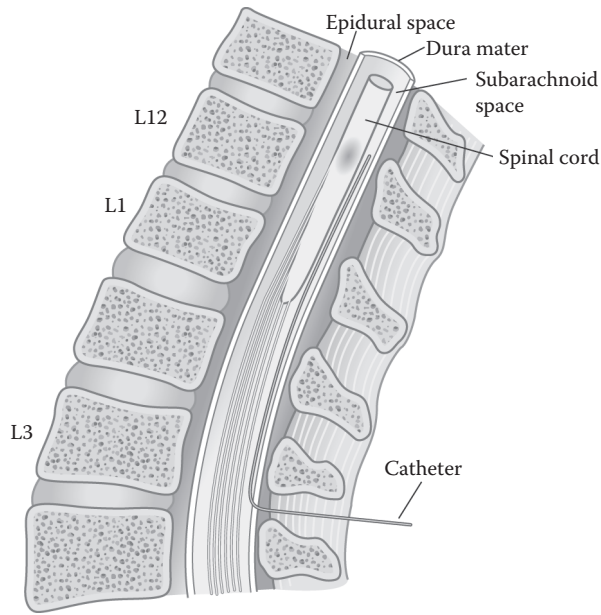


Figure 1-2 Epidural administration

of administration. This can result in advantages—and sometimes disadvantages—that are unique to the parenteral formulation.

The United States Pharmacopeia (USP) defines five main types of preparations intended for parenteral administration:

- Injection: liquid preparations that are drug substances or solutions thereof
- For injection: dry solids that, upon addition of suitable vehicles, yield solutions conforming in all respects to the requirements for injections
- Injectable emulsion: liquid preparations of drug substances dissolved or dispersed in a suitable emulsion medium
- Injectable suspension: liquid preparations of solids suspended in a suitable liquid medium
- For injectable suspension: dry solids that, upon addition of suitable vehicles, yield preparations conforming in all respects to the requirements of injectable suspensions

Advantages and Disadvantages of Parenteral Administration

While many drugs are available only for parenteral administration, the parenteral route is often chosen as the preferred method of administration in certain circumstances. It provides advantages in circumstances in which multiple medications need to be administered simultaneously, in emergent situations, and for specialized dosing regimens. Often, patient-specific dosing is needed to achieve optimal drug levels, as with medications needing monitoring for narrow therapeutic windows. Additionally, continuous infusions and unique titrations can be achieved conveniently with parenteral administration of certain medications.

Patients who are unable to tolerate oral medications or are unconscious may be limited to receiving medications parenterally. Examples include patients who do not have a functioning gastrointestinal tract, who have restricted oral intake, and who may be experiencing nausea or vomiting. For these patients, parenteral preparations can be a means of effective drug delivery.

Further, bypassing the gastrointestinal tract can provide an immediate physiological response and complete systemic circulation of a drug, resulting in increased serum concentration of the drug. For example, many antibiotics achieve higher serum peak concentrations with IV delivery compared to the oral route, due to the limited bioavailability of some oral antibiotics. In addition, parenteral CSPs offer benefits to patients such as quick onset of action, providing rapid availability of the drug to the body. Pain medications and emergent situations are examples of situations in which the quick onset of action provided by parenteral preparations represents a key advantage over oral or other formulations. Parenteral CSPs also offer the advantage of localized delivery of drugs, as with intra-articular administration of corticosteroids in patients with rheumatoid arthritis.

Finally, the potential for an extended duration of effect is a key consideration when choosing drug formulations. For example, depot injection of certain drugs, such as contraceptives, can provide an extended effect with a single injection.

While the benefits of parenteral administration of drugs are many, use of this route also poses some potentially significant risks

to the patient. Disadvantages of parenteral preparations to the patient include lack of drug reversal, risk of infection and emboli, risk of hypersensitivity reactions, and cost. In particular, because parenteral drugs may be introduced into the systemic circulation of the body, as with the IV route, drugs administered parenterally may not be able to be readily removed or their effects easily reversed. This is an important point of consideration, and it explains why any drug delivered parenterally must be prepared and verified in such a manner to ensure complete accuracy and sterility. Proper preparation and verification of CSPs can prevent misadventures in dosing and potential risks, including death, to the patient.

If contamination of the preparation occurs, such as with bacteria, fungi, or viruses, the contaminants will be directly administered to the patient—an outcome that will likely result in infection or even potentially death of the patient. Physical contamination of a parenteral preparation, such as with microscopic shards of glass or precipitates, can cause an embolus if administered into the vein or artery.

In addition, compared to other formulations, administering drugs parenterally may increase the risk of hypersensitivity reactions. While other routes of administration also pose the risk of hypersensitivity reactions, the parenteral route is believed to be the most immunogenic.^{1,2}

Finally, the overall cost of parenteral administration can often exceed the cost of other formulations. This cost is not limited to the drug alone, which is typically more expensive than medications delivered via other routes.³ Increased costs incurred with parenteral administration of medications may include the cost of supplies and preparation, such as tubing and syringes, and the cost of personnel time to prepare the CSP. Additionally, parenteral medications may require dedicated (and costly) equipment and personnel—only personnel with specialized training can administer parenteral preparations. Because of the increased potential for adverse effects associated with parenteral administration of medications, mitigation of such adverse effects can add even more costs.

Table 1-2 lists various advantages and disadvantages of administering drugs parenterally.

Table 1-2 Advantages and Disadvantages of Parenteral Products

Advantages	Disadvantages
Provides drug and nutritional options for patients unable to tolerate oral therapy	Difficulty/impossibility of drug removal/reversal
Circumvents absorption limitations of gastrointestinal tract	Risk of infection
Quick onset of action	Risk of emboli
Localized delivery	Risk of hypersensitivity reactions
Prolonged duration of effect	Higher costs

Safety, Accuracy, and Attitude

Safety is an important consideration when preparing parenteral medications, both for the patient and for the personnel involved in compounding. Because of the significant risks that this route of administration may pose to the patient, such as emboli and infection, patient safety must be a primary focus during the preparation process. Quality measures and preparation practices utilized on a consistent basis will provide aseptic preparations that are safe for patient administration. Risks also exist to the personnel involved in compounding. Exposure to certain types of hazardous agents and injuries resulting from needle sticks are examples of these risks. In addition to measures that ensure patient safety, measures should be incorporated into each preparation process that lead to increased personnel safety.

Due to the nature of the delivery method, parenteral medications must be prepared in a manner so as to ensure their accuracy. Owing to the inability to reverse the effects and quick onset of action with many medications when administered parenterally, there is no leniency regarding accuracy of the preparation. Accuracy is important for selection of products, calculations, and preparation technique. For example, an error of one decimal point when calculating the amount of product to use may result in serious harm or death, depending on the medication being administered. Thus verification processes must be integrated into the preparation process and consistently utilized to ensure accuracy. Importantly, personnel involved in compounding must accept

responsibility for ensuring accuracy and systematic measures must be in place to support personnel with such responsibility.

Developing and maintaining an attitude of safety and accuracy is the core of parenteral preparation and administration. The level of attentiveness by each individual in the preparation, verification, and administration of parenteral medications is an important component of ensuring patient and personnel safety. It must be emphasized that the ultimate responsibility for care of the patient and prevention of risks related to parenteral preparations is directly in the hands of those personnel involved in compounding and administering the CSP. At all points in time, techniques to ensure safety and accuracy must be utilized. As discussed earlier in the chapter, parenteral administration does not allow for easy removal of the drug and poses multiple risks to the patient. Thus safety and accuracy are of utmost importance.

While certain risks may inevitably be associated with parenteral administration, processes and techniques can be employed to mitigate those risks:

- Proper training of all personnel involved in compounding and administering parenteral preparations
- Maintaining a proper environment for compounding sterile preparations
- Using aseptic techniques and manipulations while compounding
- Implementing systems to ensure accuracy and quality of the preparation prior to patient administration

It is the responsibility of all persons involved in the preparation and verification processes to ensure that methods to prevent risks to patients are utilized with each preparation. Ensuring that such risk prevention strategies are utilized can prevent harm to both the patient and the personnel compounding parenteral preparations.

Because of the potentially significant risks to the patient in the event of error or contamination, stringent parameters must exist regarding the quality of the final preparation. Preparations not only need to meet standards for accuracy, potency, and stability,

but also need to meet standards for microbial (pyrogens and sterility), physical (particulate matter), and chemical (isotonicity) parameters.⁵

United States Pharmacopeia Chapters

The USP is an independent organization that provides definitions, descriptions, and requirements for multiple pharmaceutical settings. In particular, this organization publishes standards for identity, quality, strength, purity, packaging, and labeling. Standards provided by the USP provide guidance as to processes and conditions for sterile compounding.

USP standards are organized into chapter numbers. Chapters numbered from <1> to <999> are considered enforceable, whereas chapters numbered from <1000> to <1999> are not enforceable. USP Chapter <797> provides procedures and requirements for all persons who transport, store, and prepare CSPs, as well as all places where CSPs are prepared. Locations where CSPs may be prepared include hospitals, pharmacies, treatment clinics, and physicians' offices. Personnel who may transport, store, and prepare CSPs include pharmacists, pharmacy technicians, nurses, and physicians. The objective of the <797> chapter is to prevent harm to patients by preventing exposure to microorganisms or bacterial endotoxins as well as to provide patients with sterile, stable, and accurate CSPs.^{5,6}

The USP Chapter <797> was first introduced on January 1, 2004. The original version underwent extensive revision following considerable feedback from the public. The revised standard was released in December 2007 and became official on June 1, 2008. The chapter is enforceable by the Food and Drug Administration (FDA), although the enforcement is typically deferred to state boards of pharmacy.⁵

State boards of pharmacy are empowered by the individual state legislatures to promulgate rules designed to ensure the health and safety of the citizens residing within their specific states. Therefore, state boards of pharmacy can deviate somewhat

from the standards set forth in USP chapter <797>. For instance, a given state board of pharmacy may require training for personnel who are compounding sterile preparations that is more stringent than the training requirements provided in chapter <797>. Through the rules-making process, a board of pharmacy may require proof of completion of an Accreditation Council for Pharmacy Education (ACPE)–certified course providing a specified number of didactic and experiential hours in compounding sterile preparations. In addition, a state board of pharmacy may require more training, provided by the individual pharmacy in which the pharmacist or pharmacy technician works, before that person is allowed to compound a CSP intended for administration to a patient. Moreover, a state board of pharmacy may require proof of sterile compounding competencies and demonstration of aseptic technique for all pharmacy compounding personnel. This assurance could be provided through written and/or practical examinations and completion of media-fill testing, followed by a waiting period for sterility results, before allowing the individual compounder to prepare patient-specific CSPs.

State boards of pharmacy may also require stricter environmental controls, quality assurance, and quality control procedures than those required in USP Chapter <797>. Likewise, a state may develop specific requirements for recall procedures, if it is discovered that a compounded sterile preparation or a batch of compounded sterile preparations has been identified as exhibiting the potential for, or confirmed, harm to a patient or patients. Thus it is incumbent upon all personnel involved in any aspect of the compounding of sterile preparations to be familiar with the contents of <797>, as well as the rules pertaining to sterile compounding set forth by the state’s board of pharmacy.

Essential USP Chapter <797> procedures and requirements have been incorporated throughout this text to provide a general understanding of safe transport, storage, and preparation of CSPs, but the information presented here is not intended to serve as an alternative to the actual USP Chapter <797> publication. All personnel who prepare CSPs should at a minimum read the full USP Chapter <797> to fully understand the fundamental practices discussed in this text; they should also familiarize themselves with

local state board of pharmacy rules. In addition to USP Chapter <797>, other USP chapters provide specific content that may be relevant to those involved in specific types of compounding, such as high-risk compounding. Other USP chapters that may serve helpful include: USP Chapter <71> on sterility tests, USP Chapter <85> on bacterial endotoxin tests, USP Chapter <788> on particular matter in injections, USP Chapter <1075> on good compounding practices, USP Chapter <1116> on microbiological evaluation of cleanrooms and other controlled environments, and USP Chapter <1191> on stability considerations. USP Chapter <823> provides useful information for those involved in compounding radiopharmaceuticals. The following outline describes the major sections of the USP Chapter <797>.⁶

- Definitions
- Responsibility of Compounding Personnel
- CSP Microbial Contamination Risk Levels
- Personnel Training and Evaluation in Aseptic Manipulation Skills
- Immediate-Use CSPs
- Single-Dose and Multiple-Dose Containers
- Hazardous Drugs and CSPs
- Radiopharmaceuticals and CSPs
- Allergen Extracts and CSPs
- Verification of Compounding Accuracy and Sterility
- Environmental Quality and Control
- Suggested Standard Operating Procedures
- Elements of Quality Control
- Verification of Automated Compounding Devices for Parenteral Nutrition Compounding
- Finished Preparation Release Checks and Tests
- Storage and Beyond-Use Dating
- Maintaining Sterility, Purity, and Stability of Dispensed and Distributed CSPs
- Patient or Caregiver Training
- Patient Monitoring and Adverse Events Reporting
- Quality Assurance Program
- Abbreviations and Acronyms

Responsibilities of Compounding Personnel

Throughout this text, the responsibility of compounding personnel will be discussed. It is important to understand the role and accountability that each individual has in compounding a sterile preparation that is sterile, accurate and safe for patients. USP Chapter <797> defines the responsibility that all personnel involved in compounding share, as listed here. These responsibilities will be expanded upon and discussed further in the textbook.

PERSONNEL RESPONSIBILITIES⁶

- Perform antiseptic hand washing and maintain good hand hygiene
- Disinfection of critical areas, such as non-sterile compounding surfaces
- Proper selection and donning of personal protective equipment
- Maintenance or achievement of sterility of CSPs in appropriate compounding devices
- Protect personnel and compounding environments from contamination by radioactive, cytotoxic, and chemotoxic drugs
- Accurately identify, weigh, and measure ingredients
- Manipulate sterile products aseptically
- Sterilize high-risk level CSPs, while maintaining integrity and strength of active ingredients
- Label and quality inspect CSPs

The Role of the Pharmacist

State boards of pharmacy are often asked why an individual pharmacist who only “checks” the final preparation should receive the same training in sterile compounding as the pharmacists or pharmacy technicians who actually compound the preparations. As has already been stated, the most important consideration in compounding of sterile preparations is the safety of the patient

for whom the preparation is intended. The pharmacist who provides the final verification of a compounded sterile preparation is usually the last person with pharmacy expertise who sees the preparation prior to its administration to the patient. Thus this person must be fully familiar with all aspects of the compounding of sterile preparations, including drug–diluent incompatibilities, physical characteristics of the finished preparation, proper dosing and calculations associated with the preparation, methods for determining whether precipitants exist in the preparation, and so on. For example, certain chemotherapeutic preparations are very highly colored. If a sterile doxorubicin preparation is being verified, the pharmacist verifying the preparation should expect to see a final preparation that is a shade of red and not dark blue, which could indicate that mitomycin was added to the diluent by mistake.

In particular, the pharmacist should verify the following items before releasing the CSP to leave the pharmacy:

- Incompatibilities and/or particulate matter is not present in the CSP.
- All calculations involved in preparation of the CSP were performed correctly.
- The right drug was used.
- The right volume of drug was used.
- The right diluent was used.
- The right volume of diluent was used.
- The expiration date of drug(s) used is in-date.
- The expiration date of diluent(s) used is in-date.
- Labeling accurately reflects contents.
- Auxiliary labels are included and are appropriate.
- Instructions for administration are correct.

Pharmacists involved in the preparation and distribution of CSPs should consider the preceding list to be the minimum components that should be verified. Verification methods will vary by organization as well as by the type of preparation. For example, some organizations may utilize procedures that involve weighing the final preparation to verify the volume of contents added

Table 1-3 The Five Rights of Medication Administration

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1. The right medication
 2. The right dose
 3. The right time
 4. The right route
 5. The right patient
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to the CSP. Other preparations may require that two pharmacists are involved in the verification process.

Once the CSP has been distributed, those involved in administration of that CSP should utilize the “Five Rights” of medication administration—a patient safety measure that is completed prior to administering a medication to a patient (**Table 1-3**).

Conclusion

CSPs are an important mode of drug delivery for patients who may benefit from advantages that parenteral preparations provide. While risks are associated with administration of CSPs, it is the responsibility of all persons involved in the preparation and administration of CSPs to ensure that such risks are mitigated to the greatest extent possible by using proper techniques and having systems in place to ensure accuracy and sterility of the preparation. Personnel involved in the preparation process must unfailingly consider the patient who will be receiving the preparation and attitudes of patient safety must consistently and uniformly be employed.

Review Questions

1. List advantages and disadvantages of parenteral administration.
2. List circumstances in which parenteral administration may be preferred.

3. What is the role of attitude in parenteral product preparation?
4. Which methods can be utilized to increase safety and accuracy of parenteral preparation and administration?
5. Which USP chapters provide recommendations regarding the transport, storage, and preparation of compounded sterile preparations?

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