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. In June 2015, the FDA advisory group met to consider adding four more drugs to the list: aprotinin, ondansetron, bromocriptine, and acetaminophen. The compounder would be prohibited from any form of compounding that includes one of the banned active ingredients.[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 creates also 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 and validation of procedures used. Presterilized sealed containers should be used when feasible. Final containers must be sterile and capable of maintaining product integrity through the beyond-use date (BUD). The sterilization method must be based on the preparation's properties. Whatever method of sterilization is used, a sterility test is still required to ensure safety of the contents. The sterility test must be validated to determine if a contamination could be isolated if one were present as well as to determine the sensitivity of the assay (USP Chapter <71> Sterility Test). See **Table 4-1** for a review of the different types of terminal sterilization, their advantages, and their disadvantages. See reference 9 for a review of the FDA perspective on terminal sterilization.[9]

USP Chapter <797> specifies that nonsterile active ingredients and added substances, or excipients, for compounded sterile preparations (CSPs) should preferably be official *USP–NF* articles.[1] When unofficial ingredients are used, they must be accompanied by certificates of analysis from their suppliers to aid compounding personnel in judging the identify, quality, and purity in relation to the intended use in a particular CSP.[10] Bulk or unformulated drug substances and added substances, or excipients, must be stored in tightly closed containers under temperature, humidity, and lighting conditions, which are either indicated by official monographs or approved by suppliers. Also, the date of receipt in the compounding facility must be clearly and indelibly marked on each package of ingredient. Careful consideration and evaluation of nonsterile ingredient sources is especially warranted when the CSP will be administered into the vascular, central nervous system, and eyes. Upon receipt of each lot of the bulk drug substance or excipient, the individual compounding the preparation performs a visual inspection of the lot for evidence of deterioration, other types of unacceptable quality and mislabeling, as described in a written protocol.

Table 4-1.
Terminal Sterilization[a]

Sterilization Method	Specifications	Advantages	Disadvantages
Dry heat	180 °C for 30 min or 170 °C for 1 hr 160 °C for 2 hr	Destroys pyrogens	Heat sensitivity
Moist eat Autoclave, gravity sterilizer	Pressure: 15 lb/sq inch Temperature: 121 °C Time: 15 min	Uses biological indicator to verify sufficient heat/pressure	Heat/moisture sensitivity
Filtration	0.2 µm Numerous fiber/size and load specifications	Filter integrity test, verifies filter did not rupture	Filter must be certified for volume and filtrate load
Gamma irradiation	~25 kGy; requires very high radiation to be effective	Containers and packaging may remain intact	Not good for some heat sensitive
Ethylene oxide/nitrous oxide, hydrogen peroxide fog	Depending on gas used different saturation and permeation	Less invasive, good for heat sensitive but has compatibility issues	Requires tight wrap to avoid leaks, contaminates adjacent areas

[a]See Chapter 17 for a more detailed review.

Written Procedures

The compounder of sterile preparations should develop and comply with the following written procedures (Chapters 16, 22, and 31):

- There must be a specifically designated and adequate area for the orderly placement of equipment and materials to be used in compounding. CSPs should be prepared in a separate and distinct area from nonsterile compounding.[1]
- USP Chapter <797> requires that presterilization procedures for high-risk level CSPs, such as weighing and mixing, be completed in at least an International Organization for Standardization Class 8 environment.
- For hazardous material, the storage should be in an environment of negative pressure to ensure safety of the compounder according to National Institute for Occupational Safety and Health and USP Chapter <800> Hazardous Drugs—Handling in Healthcare Settings (will become official July, 2018).[11] This new chapter supersedes the section on Hazardous Drug handling outlined in USP Chapter <797> earlier.
- Special attention should be made to handling bulk agents, which would be expected when formulating a sterile compound that contains a hazardous material.
- Careful selection of respiratory and personal protective wear is crucial as is appropriate engineering controls to ensure safety of staff.
- Liquid preparations are especially hazardous as the vapor easily will pass through filtration-based transfer systems, rendering them ineffective for exposure control.[12]
- Biological-based pharmaceuticals should be handled in accordance with the Biosafety Level designation as outlined by the Centers for Disease Control and Prevention (CDC): The CDC operates an excellent "Quick Learn Lesson," which outlines the appropriate precautions and identifications of biological risks level.[13]
- When *USP–NF* compendial monographs are not available, another high-quality ingredient source may be acceptable (e.g., certified analytical reagent) certified by the American Chemical Society or Food Chemicals Codex grade.

The pharmacist ensures that the sterile components under their supervision meet acceptable criteria of stability and sterility by the following[14]:

- Observing expiration dates and dispensing the oldest stock first. The expiration date of a compounded preparation's ingredients should exceed the expiration date set for the final product. Not all chemicals used in pharmaceuticals have been assigned an expiration date. The pharmacist should use good judgment to ensure the purity of any additive. A shelf-life of no longer than 3 years after the container has been opened is considered a good maximum.
- Storing components under the environmental conditions stated in the individual monographs and labeling.
- Visual observation is an ineffective measure of instability. Most chemical changes fail to demonstrate a visible change. A certified laboratory must compile a stability indicating analysis that will ensure safety through use of validated procedures to identify degradants.[15] If a component has undergone a physical change not explained in the labeling, such an ingredient should never to be dispensed. Visual checks are of limited value in this setting as the best observations will detect 20–50 μm diameters. Although a microscope will enhance the size of the particles, the volume needed to be tested is quite large according to USP Chapter <788> Particulate Matter in Injections.[16] Light obscuration particle sizer is the ideal as it can detect fine precipitates that may occlude small blood vessels (4–9 μm in diameter)
- Testing sterility using validated procedures as outlined in USP Chapter <71>. Sufficient numbers of test samples are required for adequate strength of the analysis. Sterility test by membrane filtration is the ideal methodology, but viscous liquids cannot pass the 0.4–μm filters used. For those samples that cannot be filtered, an inoculation test may be used, but it has a much lower capacity to catch microbial contamination.[17] Visual observations are not an effective measure of sterility. Evidence that the integrity of the seal has been violated should make the component suspect of microbial contamination.
- Properly handling and labeling preparations that are repackaged, diluted, or mixed with other products.

- Dispensing in the proper container with the proper closure.
- Using sterile compounding equipment that is appropriate in design, size, and composition so that surfaces contacting components are not reactive, additive, or absorptive. These surfaces should not alter the required safety, identity, strength, quality, and purity of the components.[1] Prescription balances and volume-measurement devices should meet USP specifications.[18]
- Inspecting and approving or rejecting all formulas, calculations, substances, containers, closures, and in-process materials. There should be a written standard operating procedure in the event of nonconformance of bulk chemicals or compounded preparations to quality assurance tests.[19]

Pharmacists who compound batches of parenteral preparations must follow a master formula sheet to reproduce preparations that consistently meet all purported norms. For more information about this, readers are referred to USP Chapter <1163> Quality Assurance in Pharmaceutical Compounding.[20]

Components

Components are any ingredients used in compounding, whether or not they appear in the final preparation (i.e., intermediate ingredients). Commercially sterile components should be used whenever available. These ingredients should be made in an FDA-approved facility and meet official compendial requirements.[10] If these requirements cannot be met, pharmacists should determine if alternative substances should be procured.[19]

Vehicles

Vehicles for most liquid sterile preparations should have no therapeutic activity or toxicity. Rather, they serve as solvents or mediums for the administration of therapeutically active ingredients. For parenteral preparations, the most common vehicle is water. Vehicles must meet USP requirements for the pyrogen or bacterial endotoxin tests.[21,22]

Water for Injection

Water for injection is purified by distillation or reverse osmosis and is free of pyrogens. Water for injection USP is sterilized and packaged in single-dose containers. Bacteriostatic water for injection is sterilized and contains one or more bacteriostatic agents.

Sterile water for inhalation is sterilized and packaged in single-dose containers that are labeled with the full name. As implied, this component cannot be used to prepare parenterals. Sterile water for irrigation is sterilized and packaged in single-dose containers with no added substances.

Sterile water for injection is not intended for direct injection. The low tonicity will cause hemolysis of the cells and may be fatal. Purified water may be used for enteral medication compounding but cannot be used for compounding sterile preparations. See a detailed review of water for pharmaceutical purposes in USP.[23]

Aqueous Isotonic Vehicles

Aqueous isotonic vehicles are often used in sterile preparations. A common vehicle is sodium chloride injection, a 0.9% solution (also known as normal saline) that is sterilized and packaged in single-dose containers no larger than 1,000 mL. Bacteriostatic sodium chloride injection is a 0.9% sodium chloride injection that contains one or more bacteriostatic agents in a container no larger than 30 mL. Sodium chloride irrigation also is a 0.9% solution. It has no preservatives and may be packaged in a container larger than 1,000 mL. Other isotonic vehicles include Ringer's injection, dextrose injection 5%, and lactated Ringer's injection. None of these components is available in containers larger than 1,000 mL.

Water-Miscible Solvents

Several water-miscible solvents are used as a portion of the vehicle in sterile preparations (i.e., as cosolvents). These solvents (e.g., ethyl alcohol, liquid polyethylene glycol, propylene glycol) dissolve drugs with low water solubility. Preparations compounded with these components are usually administered intramuscularly or require significant dilution for parenteral administration.[24] Examples of drugs in cosolvent formulations include some vitamins, antihistamines, and cardiac glycosides. When the solvent has toxic properties or produces toxic

decomposition preparations (e.g., Cremophor), the formulation requires extra caution (e.g., limiting the final cosolvent concentrations). Administration of these viscous liquids as an undiluted intravenous (IV) injection has resulted in complications.[25]

Nonaqueous Vehicles

Nonaqueous vehicles such as fixed oils can be used to formulate parenteral preparations. USP specifies that fixed oils must be vegetable (metabolizable) in origin and odorless (or nearly so) and also have no rancid odor or taste.[26] Examples include peanut, cottonseed, corn, and sesame oils. Some vitamins and hormones can only be solubilized in these oils. Moreover, oil-based parenterals can only be given intramuscularly. However, emulsified oils (e.g., soybean and safflower) prepared as liposomes, mimic the natural chylomicrons which circulate in the bloodstream. Liposomes may be used as vehicles for lipid-based drugs such as propofol and amphotericin, or as a source of essential fatty acids in nutrition support.

Sterile compounding of total parenteral nutrition (TPN) often includes lipids along with the amino acids and dextrose. These combined products are called 3-in-1 or total nutrient admixtures. Special handling is necessary for these formulations as they are easily contaminated (Chapter 5). Special limitations on compatibility are also required as the destabilized emulsions can lead to pulmonary and immunological consequences. Review USP Chapter <729> Globule Size in Lipid Emulsions for a detailed method to evaluate stability of IV lipid emulsions.[27]

Solutes

Solute chemicals dissolved in vehicles should be USP grade or better because their contaminants, especially metals such as aluminum can alter solubility and compatibility of other solutes, cause catalytic chemical reactions, or cause toxicity to patients.

Added substances can increase stability or usefulness. Some additives are used although they have limited effectiveness or have a narrow range of usefulness before producing complications. Solubilizers prepared from castor oil have been used for many injectables despite a high incidence of side effects and compatibility issues. Cyclodextrins are linked sugars that enhance water solubility but can cause nephrotoxicity at higher concentrations.[28] A pharmacist must consider the total formulation of active ingredients and added substances; moreover, no coloring agent should be added to a sterile preparation solely to color it.

Antimicrobial Preservatives

Antimicrobial preservatives may be added up to a concentration that is considered bacteriostatic or fungistatic. Some preservatives, however, have innate toxicity within these concentrations (e.g., phenylmercuric nitrate 0.01%, benzalkonium chloride 0.01%, and phenol 0.5%). Because of their toxicity, these preservatives are used mostly in ophthalmics and with multidose injectables intended for intramuscular or subcutaneous injections

Benzyl alcohol (usually 0.9%) and the parabens (methyl 0.18% combined with propyl 0.02%) are commonly used in injectables. In oleaginous preparations, no antimicrobial is highly effective. However, hexylresorcinol 0.5% and phenylmercuric benzoate 0.1% are reported to be moderately bacteriocidal.[29] Mercurial-based preservatives have fallen into disfavor as they are associated with mercury contaminants such as those found in some fish. Although there is no such relationship, many manufacturers have avoided their use.

An antimicrobial agent may be effective in one formula of ingredients but not in another. For example, large molecule components such as polysorbate 80, polyvinylpyrrolidone, and polyethylene glycol form complexes that inactivate the parabens. To select a preservative, an appropriate reference should be consulted and its effectiveness should be verified.[30] USP provides a test for the efficacy of antimicrobial preservatives.[31] Antimicrobial effectiveness is limited to 28 days (USP Chapter <797 >).

Allergen extracts for multidose sterile injectables require antimicrobial preservatives like phenol or glycerin (Chapter 9). Compoundingtoday.com has a database of commonly used preservatives and antioxidants.[32] Note that simply adding a preservative to a CSP does not automatically extend the BUD unless the compounder has a robust sterility testing program in place.

Preservatives should be avoided with preparations for neonates and premature infants. Surfactant-based preservatives are toxic to neurological tissue and must be avoided in injectable for intrathecal administration.

pH buffers

Buffering agents stabilize an aqueous solution of a chemical against degradation. Limit the use of sodium bicarbonate to neutralize acid in an injection as it can form gas as a reactant and precipitate salts.

Buffer systems are formulated at the lowest concentration needed for stability so that the body's physiologic pH is not disturbed. Acid salts such as citrates, acetates, and phosphates are commonly used as buffers. For an in-depth review of parenteral buffering systems, readers should consult reference 33. Cysteine is added in pediatric and neonatal parenteral nutrition compounding solutions. It acts to reduce pH and enhances solubility of the calcium and phosphate, which would normally form a precipitate (Chapter 5). Tables are available to predict the limits of calcium and phosphate in solutions of varying amino acid concentrations. It must be noted that these are probability tables that do not consider other additives that may contribute to precipitate formation (e.g., dextrose). The consequences of a lack of understanding of this phenomenon have resulted in patient complications.[34] Despite the use of solubilization enhancers, a filter should always be used with parenteral nutrition solutions as the potential for precipitation can be significantly reduced, but it cannot be eliminated.

Antioxidants

Antioxidants help to prevent oxidation of the active drug. The most common antioxidants are the sodium and potassium salts of metabisulfite and sulfite ions.[35] However, the choice of salt depends on the pH of the system to be stabilized. Metabisulfite is used for low pH values, bisulfite for intermediate pH values, and sulfite for high pH ranges. The administration of large amounts (500 mg/L) of sodium bisulfite in peritoneal dialysis fluids causes toxicity with large volumes (10–40 L/day). Allergic reactions have been noted with the use of this preservative. Other antioxidants include acetone metabisulfite, ascorbic acid, and cysteine hydrochloride.

Chelating Agents

Chelating agents enhance the effectiveness of antioxidants. They form complexes with trace amounts of heavy metals, thereby eliminating the catalytic activity of metals during oxidation. The most commonly used chelating agent is edetate disodium.

Tonicity Agents

Some injectable preparation monographs require that the osmolar concentration appear on the preparation's label. Ideally, parenteral preparations are formulated to be isotonic by use of an isotonic vehicle (e.g., normal saline). When the desired concentration of the active ingredient is hypertonic, the drug must be administered by slowing the rate of injection or by infusion into a large vein (e.g., administration of TPN into subclavian vein).[24] In peripheral parenteral nutrition (PPN), the solution is administered through one of the smaller veins. PPN requires that the overall osmolarity of the combined ingredients below 900 mOsm/L to maintain the integrity of the vein (Chapter 5).

Solubilizers

Pharmacists must know the solubility characteristics of new drug substances (especially in aqueous systems) because they must possess some aqueous solubility to elicit a therapeutic response. To maintain some drugs in solution, pharmacists may have to include either a miscible cosolvent or a chemical solubilizer (**Table 4-2**). Polyethylene glycols 300 and 400, propylene glycol, glycerin, and ethyl alcohol frequently are used. However, toxic levels of these solvents must be avoided as well as amounts that make the preparation too viscous for parenteral use.

Emulsifiers

Some drugs are minimally soluble in water. Emulsifiers are used to suspend tiny oil globules in water to create an emulsion that contains a uniform concentration of the active drug through-

Table 4-2.
Modalities to Improve Solubility of Parenteral Formulations

Intervention	Issues	Advantages
Lyophilization	Requires a sugar to structure crystal formation	Has stability against hydrolysis
		Enhances speed of dissolution of reconstituted powders
Cyclodextrin	B-cyclodextrins is associated with nephrotoxicity	α, β,and γ types contain 6, 7, and 8 glucopyranose units
Surfactants	Castor oil-based has higher incidence side effects	Allows lipophilic drugs to have aqueous solubility
Liposomal (emulsions)	Limits on droplet size, USP <729>	Can target droplets for immune clearance: amphotericin
	PFAT5	Or can be designed for "stealth" mode and avoid immune clearance: doxorubicin

PFAT5 = percentage of fat residing in globules larger than 5 μm.

out the volume of the liquid. Emulsions may serve as a caloric source in parenteral nutrition. One example is soybean oil and water emulsion manufactured with egg yolk phospholipids 1.2% and glycerol 1.7% as emulsifiers. An example of an active drug is propofol that is dissolved in soybean oil which is emulsified at a concentration of 100 mg/mL in water with glycerol (22.5 mg/mL) and egg lecithin (12 mg/mL) as emulsifiers. Lipids are also used to encapsulate the active pharmaceutical.

Containers

Containers are defined as "that which holds the article and is or may be in direct contact with the article. The closure is part of the container."[36] All containers for sterile preparations must be sterile and free of both particulate matter and pyrogens. These containers should not interact physically or chemically with formulations to alter their required strength, quality, or purity. Containers also must permit inspection of their contents.[26]

Container volumes are specified by USP standards. Each container of an injection is filled with liquid, slightly in excess of the labeled size or volume that is to be withdrawn. USP provides a guide showing recommended excess volumes for both mobile and viscous liquids.[26]

Single or Multiple Dose

Sterile, single-dose containers are intended for parenteral, inhalation, irrigation, otic, and ophthalmic administration. Examples are prefilled syringes, cartridges, ampuls, and vials (when labeled as single-use).

Multiple-dose containers permit withdrawal of successive portions of their contents without changing the strength, quality, or purity of the remaining portion. Sterile, multiple-dose containers are available for preserved parenterals, ophthalmics, and otics.[37]

Glass

Glass is the most popular material for sterile preparation containers. USP classifies glass as Type I (borosilicate glass), Type II (soda-lime-treated glass), Type III (soda-lime glass), or NP (soda-lime glass unsuitable for parenteral containers).[38] Different glass types vary in their resistance to attack by water and chemicals. For pharmaceutical containers, glass must meet the USP test for chemical resistance.[39] Because most pharmacists do not have the time or facilities to perform glass chemical interaction studies, they should use only Type I glass to minimize sterile preparation incompatibilities.[40]

Syringes

Polypropylene syringes are not considered a approved long-term storage for compounded medications.[41] Although the concept of packaging the medication in a syringe enhances the ready-to-use concept to improve patients care, packaging in a syringe is only for short-term use. The syringe allows air exposure, higher contamination risks, and, in some cases, reactions have been noted with the rubber plunger leading to reduced drug effectiveness. Two-part syringes are available (without lubricant and rubber plunger) but do not resolve sterility issues.

Plastic

Plastic polymers can be used as sterile preparation containers but present three problems:

1. Permeation of vapors and other molecules in either direction through the container
2. Leaching of constituents from the plastic into the preparation
3. Adsorption of drug molecules onto the plastic

Plastics must meet USP specifications for biological reactivity and physicochemicals.[26] Most plastic containers do not permit ready inspection of their contents because they are not clear. Most plastics also melt under heat sterilization.[24] Rice and Markel reviewed parenteral medications that require selected containers because of adsorption to or leaching of plasticizers from polyvinyl chloride (PVC) plastic bags.[42] Lipophilic drugs can leach the plasticizer from the container into the patient. Avoid lipids and lipophilic drugs when using PVC containers. PVC containers also allow for evaporation of fluid over time and should not be stored outside protective overwrap for extended periods.

Closures

Rubber closures must be rendered sterile and free from pyrogens and surface particles. To meet these specifications, multiple washings and autoclavings are required. Closures are made of natural, neoprene, or butyl rubber. In addition, rubber contains the following[43]:

- Sulfur as a vulcanizing agent
- Guanidines or sulfide compounds as accelerators
- Zinc oxide or stearic acid as an activator
- Carbon, kaolin, or barium sulfate as a filler
- Dibutyl phthalate or stearic acid as a plasticizer
- Aromatic amines as antioxidants

Latex closures have been implicated as a risk factor for patients with latex allergies (Chapter 29). Removal of the stopper does not alter the latex exposure. Despite the prevalence of latex allergies, there has not been a single documented case of anaphylaxis due to exposure of a latex sensitive patient to a drug prepared from a container with latex stopper

Thus, the rubber sealing of a vial or the plug in a syringe is a complex material that can interact with the ingredients of a formula. Rubber closures also are subject to coring. Therefore, pharmacists should consult compendial or literature standards when selecting a rubber closure for sterile preparations.

Parenteral Preparations

Parenteral preparations are classified into six general categories[24]:

1. Solutions ready for injection
2. Dry, soluble preparations ready to be combined with a solvent before use
3. Suspensions ready for injection
4. Dry, insoluble preparations ready to be combined with a vehicle before use
5. Emulsions
6. Liquid concentrates ready for dilution prior to administration

Most CSPs are aqueous solutions (first category). Other categories usually require the equipment and expertise of a licensed pharmaceutical manufacturer. In addition to using the appropriate vehicle, solvent, and container, the pharmacist must ensure that the final aqueous solution maintains the appropriate physiologic and physical norms.

Physiologic Norms

When injectable solutions are formulated, every effort should be made to mimic the body's normal serum values for pH and tonicity and to create a pyrogen-free preparation.

pH

Normal human serum pH, a logarithmic measure of the hydronium ion concentration in solution, is 7.4. Drugs that are acids or bases or their salts sometimes must be buffered to a pH near normal (e.g., 3–8) to prevent pain or tissue damage. As mentioned previously, acid salts are commonly used as buffers. Stranz and Kastango have provided a good review of pH considerations in parenteral products.[44]

Tonicity

Any chemical dissolved in water exerts a certain osmotic pressure (i.e., a solute concentration related to the number of dissolved particles—un-ionized molecules, ions, macromolecules, and aggregates per unit volume).[45] Blood has an osmotic pressure corresponding to sodium chloride 0.9%; thus, its common name is normal saline. Normal saline is said to be iso-osmotic with blood and other physiologic fluids.

In the medical setting, the term *isotonic* is used synonymously with *iso-osmotic*. A solution is isotonic with a living cell if no net gain or loss of water is experienced by the cell and no other change is present when the cell contacts that solution. Very hypotonic IV preparations can cause hemolysis of red blood cells. Very hypertonic injections can damage tissue and cause pain on injection or crenation of red blood cells. Parenteral solutions usually exert an osmotic pressure of 150–900 mOsm/kg compared to a physiologic norm of 282–288 mOsm/kg for blood. The greater the volume of solution to be injected, the closer the parenteral preparation should be to isotonicity.

Pyrogenicity

Pyrogens are fever-producing endotoxins from bacterial metabolism. They are contaminants that are unacceptable in final CSPs. As large proteins, pyrogens are not removed by normal sterilization procedures and can exist for years in aqueous solution or dried form.

The following are sources of pyrogens in sterile preparations:

- Aqueous vehicles
- Equipment
- Containers and closures
- Chemicals used as solutes
- Human touch

If sterile water for injection USP is the vehicle, the risk of pyrogens in water is eliminated. Equipment, containers, and closures can be decontaminated by dry heat or by washing or soaking with acids or bases. Dry heat depyrogenation must be used to render glassware or containers such as vials free from pyrogens as well as viable microbes. USP Chapter <797> requires that the description of the dry heat depyrogenation cycle and duration for specific load items shall be included in written documentation in the compounding facility. The effectiveness of the dry heat depyrogenation cycle must be verified using endotoxin challenge vials (ECVs).[21,22] The bacterial endotoxin test should be performed on the ECVs to verify that the cycle is capable of achieving a 3-log reduction in endotoxin.

Bulk supplies of chemicals may be specified as pyrogen free, although they usually are not. Therefore, sterile preparations made from bulk chemicals must undergo a USP pyrogen test.[21] Touch contamination is most easily prevented with proper aseptic technique. The maximum limit of endotoxin in a drug product labeled for intrathecal use is set at 0.2 USP endotoxin units/kg/hr. Thus, to prepare high-risk intrathecal dosage forms, the compounding pharmacist must be much more critical during the procedural protocol than during that for IV administered preparations.[22]

Physical Norms

Particulates

Parenteral solutions must be free of particulate matter—mobile, undissolved solids not intended for sterile preparations. Examples include lint, cellulose and cotton fibers, glass, rubber, metals, plastics, undissolved chemicals, rust, diatoms, and dandruff. To determine levels of particulates, USP sets limits and provides tests.[16]

However, a careful choice of components, containers, and closures can minimize particulate contamination. Moreover, filtration can remove particles and bacteria from sterile preparations.[46]

The USP Chapter <788> states that visual checks for particles are unreliable method of evaluation only capable of reliably noting particles 150-µm in diameter. It is possible to detect smaller with enhanced techniques but nothing smaller than 20 µm. The USP sets limits on the number of allowable 10- and 25-µm particles that can be detected using a microscope or a light obscuration device. The automated device has the higher reliability. Pulmonary blood vessels have a 4–9-µm diameter and will occlude if the only quality assurance for undissolved particles is a visual check.[34]

Stability

Stability of parenteral preparations must be ensured so that patients receive the intended dose. Hydrolytic and oxidative drug degradations are the most common forms of instability but rarely show as cloudiness, precipitates, or color changes. The rate of hydrolysis may be affected by storage temperature or pH of the solution. Oxidation is affected by temperature, pH, exposure to light, oxygen concentration of the solution, impurities (e.g., heavy metals), and concentration of the oxidizable drug. Other types of degradation (e.g., racemization, polymerization, isomerization, and deamination) also can occur in solution.

The method chosen for stability should have the capacity to view the breakdown products as well as the original entity. Attempts should be made to force degradation and determine the changes to the original entity. To determine stability, it must be known what instability looks like.[47]

Because many factors affect the stability of drug molecules, pharmacists who compound parenterals from bulk chemicals should use a short BUD or know from the literature that longer stability exists. Antioxidant and chelation additive systems should be reserved for formulas that are verified in the literature as stable for a given period. The choice of packaging also is important for parenteral drug stability. ASHP publishes the following guides that include information about sterile preparation stability and compatibility:

- Bing CD, Nowabilski-Vasilios A. *Extended stability for parenteral drugs*. 5th ed. Bethesda, MD: ASHP; 2013.
- ASHP. *Handbook on injectable drugs*. 19th ed. Bethesda, MD: ASHP; 2016.

Impurities

FDA requires that large volume parenterals used in TPN limit the aluminum content to 25 µg/L.[48] Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.[49] The FDA requires that small volume parenterals used to compound TPN show on the product container the maximum concentration of aluminum at expiry or state that the product contains no more than 25 µg/L of aluminum. Renal-impaired patients who receive parenteral aluminum at >5 µg/kg/day may accumulate aluminum at levels associated with central nervous system and bone toxicity.[49] When formulating TPN, pharmacists should measure and calculate the soluble aluminum load that a patient will receive and notify the patient's physician if the FDA limit will be exceeded.[48] The physician is responsible for making a clinical decision as to patient risk for aluminum exposure versus the risk of a reduced or different treatment.

Heavy metals (e.g., lead and mercury) are also to be minimized in sterile preparations. Heavy metals can be toxic and can catalyze the degradation of active ingredients and preservatives. Introduction of these impurities is most likely when nonsterile, raw materials are used in compounding. This is why the pedigree of a chemical source is necessary either by meeting *USP–NF* standards or by written manufacturer certification of analysis and purity.

Of particular concern for formulators of TPN are the relative concentrations of calcium salts and phosphate salts. If either is too high, an insoluble calcium phosphate precipitate results and has led to deaths.[50] Although some pharmacists rely on a "magic sum" of calcium and phosphorus to prevent calcium phosphate precipitates, this practice is unsafe because many variables affect the likelihood of precipitation, such as the type of calcium salt (chloride or gluconate) or amount of proteins (as amino acids). A widely used guide to resolving the calcium–phosphate problem is available.[51]

Parenteral Formulas

The American Pharmacists Association (APhA) has published a collection of 168 formulas, some of which are parenteral, organized by therapeutic category, including analgesics, antiemetics, anti-infective agents, and anti-inflammatory agents.[52] The *International Journal of Pharmaceutical Compounding* (*IJPC*) maintains a website (www.ijpc.com) that lists formulas for many parenteral products, including some products that have been discontinued by pharmaceutical manufacturers.[53] The *IJPC* website lists files for purchase that contain articles and formulations from back issues of the journal, including sterile product compounding, stability, and compatibility studies.

Ophthalmic Formulations

Ophthalmic preparations share many of the same properties as parenteral preparations but present additional concerns. For example, ophthalmic formulations may use different added substances (e.g., buffers, antimicrobial preservatives, tonicity-adjusting chemicals, and thickening agents). Furthermore, ophthalmic preparations include solutions (eye drops or washes), suspensions, and ointments. Because pharmacists rarely compound sterile suspensions or ointments, this discussion is limited to solutions.

Physiologic Norms

Buffers and pH

Lacrimal fluid has a pH of approximately 7.4 and limited buffering capacity. Ophthalmic solutions of weak bases (e.g., alkaloids), for which therapeutic efficacy depends on the bioavailability of the alkaloid base, are buffered to acidity but as near pH 7.4 as possible while keeping the alkaloid in solution after instillation.[54] The buffer system (e.g., phosphate or acetate) should maintain pH within the drug's solubility range for the duration of expiration dating.[47] A moderately acidic solution does not cause discomfort on instillation unless the buffer system overcomes the buffer capacity of lacrimal fluid. Nonisotonic ophthalmic solutions below pH 6.6 or above pH 9.0 have been associated with irritation, reflex tears, and blinking.[55]

Tonicity

Lacrimal fluid has an osmotic pressure or tonicity similar to aqueous sodium chloride 0.9% solution. Eye tissue can tolerate tonicities of 0.5–1.8% sodium chloride without much discomfort.[56] However, the tonicity of eyewashes is more important than drops because a larger volume of solution contacts the eye. The tonicity of intraocular solutions also should be as close as possible to physiologic.

When formulating ophthalmic solutions, pharmacists should adjust the tonicity to approximate lacrimal fluid by adding a substance such as sodium chloride. Several methods can be used to calculate the amount of sodium chloride needed. The following example uses the colligative property, freezing-point depression. Lacrimal fluid lowers the freezing point of water by 0.52 °C. To make a boric acid 1% solution isotonic, sodium chloride crystals are added. Boric acid 1% lowers the freezing point by 0.29 °C; therefore, sodium chloride must be added to lower the freezing point further by 0.23 °C.

To use a proportion:

$$\frac{0.52\ ^\circ C}{0.9\%} = \frac{0.23\ ^\circ C}{X}$$

Therefore, X = 0.4%. Thus, sodium chloride is added to a boric acid 1% solution to make it a sodium chloride 0.4% solution.[57]

Another easy method of calculation is to add the sodium chloride equivalent. See Chapter 31, Appendix A, of Remington's *The Science and Practice of Pharmacy* for the sodium chloride equivalents, freezing-point depressions, and hemolytic effects of nearly 400 medicinal chemicals.[58]

Viscosity

Viscosity is important in ophthalmic preparations. Viscosity sometimes is increased to extend contact between the solution and eye. Moreover, water-dispersible polymers (e.g., methylcellulose, carboxymethylcellulose, hydroxypropyl cellulose, and polyvinyl alcohol) are used as thickening agents. A good review of viscosity agents, including their maximum concentrations, may be found in *IJPC*.[59]

Although USP discusses use of cellulose derivatives, precautions are necessary. Cellulose derivative solutions cannot be filtered. When autoclaved, the derivative precipitates from solution because of decreased water solubility at high temperatures but redissolves at room temperature.[60]

When a heat-labile drug is formulated with a cellulose derivative, all components must be sterilized separately and then recombined aseptically. The drug in solution is sterilized by filtration, and the cellulose derivative is sterilized by autoclaving.[60] Viscosity of 25–50 centipoises improves contact time with the eye, whereas higher viscosity offers no contact advantage but usually leaves a residue on eyelid margins.[59]

Sterility

To ensure sterility of ophthalmic solutions, pharmacists must prepare them in a sterile environment in single-dose containers or use antimicrobial preservatives in multiple-dose containers. The microbe that causes great concern is *Pseudomonas aeruginosa;* however, no preservative is 100% effective against all strains of it.

The most common preservative is benzalkonium chloride (0.004–0.02%), but high concentrations of it irritate the eye. This preservative is incompatible with large anions (e.g., soaps) as well as with nitrates and salicylates. Other preservatives include phenylmercuric acetate and nitrate (0.001–0.01%), phenyl-ethanol (0.5%), parabens (0.1%), and chlorobutanol (0.5%). Because chlorobutanol is stable only near pH 5–6, it is used only with solutions within this pH range.

Remington's Chapter 43 discusses different ophthalmic preservatives.[54] The properties of various ophthalmic preservatives have been discussed above. Some ophthalmologists prefer nonpreserved solutions because of allergic reactions to common preservatives. This is particularly true for ophthalmic solutions injected during cataract surgery.[61]

Physical Norms

Required physical characteristics of ophthalmics include clarity, stability, and compatibility. Ophthalmics are made clear or particle free by filtration; therefore, nonshedding filters, containers, and closures must be used.

Stability depends on the chemical nature of the drug, preparation pH, preparation method (especially temperature), solution additives, and packaging. If oxidation is a problem, sodium bisulfite (up to 0.3%), ascorbic acid, or acetylcysteine can be added. Surfactants are used in low concentrations to achieve solution or suspension of active ingredients.

Ophthalmic Formulas

APhA has published a handbook that contains some ophthalmic formulas along with their stability information.[59] *IJPC* has published an issue containing formulas for 15 ophthalmic preparations[60]:

1. Acetylcysteine 15% ophthalmic solution
2. Amphotericin B 2 mg/mL ophthalmic solution
3. Ascorbic acid 10% ophthalmic solution
4. Calcium gluconate 1% ophthalmic irrigation solution
5. Cyclosporin 2% ophthalmic solution
6. Dexamethasone sodium phosphate 0.05% ophthalmic ointment
7. Fluconazole 0.2% ophthalmic solution
8. Fortified gentamicin ophthalmic solution
9. Glucose 40% ophthalmic ointment
10. Idoxuridine 0.5% ophthalmic ointment
11. Idoxuridine 0.1% ophthalmic solution
12. Lissamine Green 0.5% ophthalmic solution
13. Ophthalmic lubricant
14. Rose Bengal 1% ophthalmic solution
15. Vancomycin 25 mg/mL ophthalmic solution

These formulas are accompanied by the method of preparation, packaging, labeling, stability, discussion, and references.

ASHP has published extemporaneous formulations from The Children's Hospital of Philadelphia for ophthalmics, including the following[56]:

- Bacitracin ophthalmic solution 10,000 units/mL
- Cefazolin ophthalmic solution 33 mg/mL

- Cidofovir intravitreous solution 0.2 mg/mL
- Gentamicin ophthalmic solution 13.6 mg/mL (fortified)
- LET (lidocaine 4%/epinephrine 0.1%/tetracaine 0.5%) gel
- Tobramycin ophthalmic solution 13.6 mg/mL (fortified)
- Tobramycin ophthalmic solution 15 mg/mL
- Vancomycin ophthalmic solution 31 mg/mL

Summary

In many cases, no commercial preparation is available for a final sterile preparation. Legally, pharmacists may compound these preparations under the FDCA regulations. However, various sterile components (e.g., vehicles, buffers, and solubilizers) are required. It is the pharmacist's responsibility to ensure that they meet the appropriate compendial requirements.

When formulating either parenteral or ophthalmic preparations, a pharmacist should use components so that the final sterile preparation achieves both physiologic and physical norms.

References

1. U.S. Pharmacopeial Convention. USP chapter <797> pharmaceutical compounding—sterile preparations. In: *USP 37–NF 32*. Rockville, MD: U.S. Pharmacopeial Convention; 2014.
2. U.S. Food and Drug Administration, Science Board to the Food and Drug Administration. Advisory Committee; Notice of Meeting. Doc No. 80 FR 67766. www.federalregister.gov/a/2015-27957 (accessed 2017 May 8).
3. U.S. Food and Drug Administration. Compounding Quality Act Title I of the Drug Quality and Security Act of 2013. www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/default.htm (accessed 2016 Mar 15).
4. U.S. Food and Drug Administration (FDA), Office of Enforcement, Division of Compliance Policy. Manufacture, distribution, and promotion of adulterated, misbranded, or unapproved new drugs for human use by state-licensed pharmacies. FDA Guide 7132.16. Washington, DC: FDA; 2016 Mar.
5. U.S. Food and Drug Administration. FDA CPG sec. 460.100 hospital pharmacies—status as drug manufacturer. www.fda.gov/iceci/compliancemanuals/compliancepolicyguidancemanual/ucm074397.htm (accessed 2017 May 8).
6. U.S. Food and Drug Administration (FDA), Center for Drug Evaluation and Research. Guidance for industry, CGMP for phase 1 investigational drugs. Washington, DC: FDA; 2008 Jul.
7. National Association of Boards of Pharmacy. Appendix J: good compounding practices applicable to state licensed pharmacies. In: *Model state pharmacy act and model rules of the National Association of Boards of Pharmacy*. Mount Prospect, IL: National Association of Boards of Pharmacy; 2012 Aug.
8. U.S. Pharmacopeial Convention. USP chapter <795> pharmaceutical compounding—sterile preparations. In: *USP 39–NF 34*. Rockville, MD: U.S. Pharmacopeial Convention; 2016.
9. U.S. Food and Drug Administration (FDA). FDA guidance: guidance for industry and FDA staff; submission and review of sterility information in premarket notification (510(k)) submissions for devices labeled as sterile. Washington, DC: FDA; 2008.
10. Anon. Standard operating procedure: certificates of analysis of materials used for pharmaceutical compounding. *Internat J Pharma Compound*. 2001; 5:147.
11. U.S. Pharmacopeial Convention. USP chapter <800> hazardous drugs—handling in healthcare settings. In: *USP 39–NF 34*. Rockville, MD: U.S. Pharmacopeial Convention; 2016.
12. Centers for Disease Control and Prevention (CDC). NIOSH A vapor containment performance protocol for closed system transfer devices used during pharmacy compounding and administration of hazardous drugs (NIOSH docket number 288, CDC-2015-0075). Atlanta, GA: CDC; 2015.
13. Centers for Disease Control and Prevention. Quick learn lesson. www.cdc.gov/training/QuickLearns/biosafety/ (accessed 2016 Mar 15).
14. U.S. Pharmacopeial Convention. USP chapter <1191> stability considerations in dispensing practice. In: *USP 39–NF 34*. Rockville, MD: U.S. Pharmacopeial Convention; 2016.
15. Tamizi E, Jouyban A. Forced degradation studies of biopharmaceuticals: selection of stress conditions. *Eur J Pharm Biopharm*. 2016; 98:26-46.
16. U.S. Pharmacopeial Convention. USP chapter <788> particulate matter in injections. In: *USP 39–NF 34*. Rockville, MD: U.S. Pharmacopeial Convention; 2016.
17. U.S. Pharmacopeial Convention. USP chapter <71> sterility test. In: *USP 39–NF 34*. Rockville, MD: U.S. Pharmacopeial Convention; 2016.

18. U.S. Pharmacopeial Convention. USP chapter <1176> prescription balances and volumetric apparatus. In: *USP 39–NF 34*. Rockville, MD: U.S. Pharmacopeial Convention; 2016.
19. Anon. Standard operating procedure: procedures in the event of nonconformance of bulk chemicals or compounded preparations. *Internat J Pharma Compound*. 2006; 10:381.
20. U.S. Pharmacopeial Convention. USP chapter <1163> quality assurance in pharmaceutical compounding. In: *USP 39–NF 34*. Rockville, MD: U.S. Pharmacopeial Convention; 2016.
21. U.S. Pharmacopeial Convention. USP chapter <151> pyrogen test. In: *USP 39–NF 34*. Rockville, MD: U.S. Pharmacopeial Convention; 2016.
22. U.S. Pharmacopeial Convention. USP chapter <85> bacterial endotoxins. In: *USP 39–NF 34*. Rockville, MD: U.S. Pharmacopeial Convention; 2016.
23. U.S. Pharmacopeial Convention. USP chapter <1231> water for pharmaceutical purposes. In: *USP 39–NF 34*. Rockville, MD: U.S. Pharmacopeial Convention; 2016.
24. Akers MJ. Parenteral preparations. In: Allen LV, ed. *Remington: the science and practice of pharmacy*. 22nd ed. London and Philadelphia: Pharmaceutical Press; 2013:861-98.
25. Lim TY, Poole RL, Pageler NM. Propylene glycol toxicity in children. *J Pediatr Pharmacol Ther*. 2014; 19:277-82.
26. U.S. Pharmacopeial Convention. USP chapter <1> injections. In: *USP 37–NF 32*. Rockville, MD: U.S. Pharmacopeial Convention; 2014.
27. U.S. Pharmacopeial Convention. USP chapter <729> globule size in lipid emulsions. In: *USP 37–NF 32*. Rockville, MD: U.S. Pharmacopeial Convention; 2014.
28. Gidwani B, Vyas A. A comprehensive review on cyclodextrin-based carriers for delivery of chemotherapeutic cytotoxic anticancer drugs. *Biomed Res Int*. 2015; 2015:198268.
29. Akers MJ. Considerations in selecting antimicrobial preservative agents for parenteral product development. *Pharm Technol*. 1984; 8:36.
30. Ando HY, Radebaugh GW. Property-based drug design and preformulation. In: Troy DB, ed. *Remington: the science and practice of pharmacy*. 21st ed. Baltimore: Lippincott Williams & Wilkins; 2005:720–44.
31. U.S. Pharmacopeial Convention. USP chapter <51> antimicrobial effectiveness testing. In: *USP 37–NF 32*. Rockville, MD: U.S. Pharmacopeial Convention; 2014.
32. Anon. Preservatives and antioxidants [database]. www.compoundingtoday.com (accessed 2016 Feb 15).
33. Wang YJ, Kowal RR. Review of excipients and pHs for parenteral products used in the United States. *J Parenter Drug Assoc*. 1980; 34:452-62.
34. Knowles JB, Cusson G, Smith M et al. Pulmonary deposition of calcium phosphate crystals as a complication of home total parenteral nutrition. *JPEN J Parenter Enteral Nutr*. 1989; 13:209-13.
35. Akers MJ. Preformulation screening of antioxidant efficacy in parenteral products. *J Parenter Drug Assoc*. 1979; 33:346-56.
36. U.S. Pharmacopeial Convention. General notices and requirements. In: *United States pharmacopeia, 39th rev./national formulary, 34th ed*. Rockville, MD: U.S. Pharmacopeial Convention; 2016.
37. Turco SJ. Characteristics. In: Turco SJ, ed. *Sterile dosage forms, their preparation, and clinical application*. 4th ed. Philadelphia: Lea & Febiger; 1994:28-38.
38. U.S. Pharmacopeial Convention. USP chapter <661> containers. In: *USP 39–NF 34*. Rockville, MD: U.S. Pharmacopeial Convention; 2016.
39. Turco SJ. Extemporaneous preparation. In: Turco SJ, ed. *Sterile dosage forms, their preparation, and clinical application*. 4th ed. Philadelphia: Lea & Febiger; 1994:57-78.
40. U.S. Pharmacopeial Convention. USP chapter <87> biological reactivity tests, in vitro. In: *USP 39–NF 34*. Rockville, MD: U.S. Pharmacopeial Convention; 2016.
41. Anon. ISMP comments on BD syringe potency issue (2015 Aug 27). www.ismp.org/newsletters/acutecare/showarticle.aspx?id=117 (accessed May 8, 2017).
42. Rice SP, Markel JA. A review of parenteral admixtures requiring select containers and administration sets. *Internat J Pharma Compound*. 2002; 6:120-2.
43. Turco SJ. Large-scale preparation. In: Turco SJ, ed. *Sterile dosage forms, their preparation, and clinical application*. 4th ed. Philadelphia: Lea & Febiger; 1994:39-56.
44. Stranz M, Kastango ES. A review of pH and osmolarity. Internat *J Pharma Compound*. 2002: 6:216-20.
45. U.S. Pharmacopeial Convention. USP chapter <785> osmolarity. In: *USP 39–NF 34*. Rockville, MD: U.S. Pharmacopeial Convention; 2016.
46. McKinnon BT, Avis KE. Membrane filtration of pharmaceutical solutions. *Am J Hosp Pharm*. 1993; 50:1921-36.
47. Tamizi E, Jouyban A. Forced degradation studies of biopharmaceuticals: selection of stress conditions. *Eur J Pharm Biopharm*. 2016; 98:26-46.
48. U.S. Food and Drug Administration. Aluminum in large and small volume parenterals used in total parenteral nutrition: delay of effective date. *Fed Reg*. 2003; 68:32979-81.

49. Smith BS, Kothari H, Hayes BD et al. Effect of additive selection on calculated aluminum content of parenteral nutrient solutions. *Am J Health-Syst Pharm*. 2007; 64:730-9.
50. U.S. Food and Drug Administration. Safety alert: hazards of precipitation associated with parenteral nutrition. *Am J Hosp Pharm*. 1994; 51:1427-8.
51. Trissel LA. *Trissel's calcium and phosphate compatibility in parenteral nutrition*. Bethesda, MD: ASHP; 2001.
52. Allen LV. *Allen's compounded formulations: complete collection*. Washington, DC: American Pharmacists Association; 2003.
53. International Journal of Pharmaceutical Compounding [website]. www.ijpc.com (accessed 2016 Feb 20).
54. Chowhan M, Lang JC, Missel P. Ophthalmic preparations. In: Allen LV, ed. *Remington: the science and practice of pharmacy*. 22nd ed. London and Philadelphia: Pharmaceutical Press; 2013:907-29.
55. Leiter CW. Buffer solutions for ophthalmic preparations. *Internat J Pharma Compound*. 1998; 2:190-91.
56. Mobley C. Anatomical and physiological considerations for pharmacy compounding. *Drug Topics*. 2003; 147:64-72.
57. Turco SJ. Ophthalmic preparations. In: Turco SJ, ed. *Sterile dosage forms, their preparation and clinical application*. 4th ed. Philadelphia: Lea & Febiger; 1994:344-54.
58. Ingham A, Poon CY. Tonicity, osmoticity, osmolality and osmolarity. In: Allen LV, ed. *Remington: the science and practice of pharmacy*. 22nd ed. London & Philadelphia: Pharmaceutical Press; 2013:641-64.
59. Anon. Compounding ophthalmic preparations. *Internat J Pharma Compound*. 1998; 2:184-8.
60. Anon. Preservation, sterilization and sterility testing of ophthalmic preparations. *Internat J Pharma Compound*. 1998; 2:192-5.
61. Anderson NJ, Edelhauser HF. Ophthalmic solutions in cataract surgery. *Internat J Pharma Compound*. 1998; 2:196-202.