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Parenteral Preparations

Michael J Akers, PhD

CHAPTER 41



Parenteral (Gk, *para enteron*, beside the intestine) dosage forms differ from all other drug dosage forms because they are injected directly into body tissue through the primary protective system of the human body, the skin, and mucous membranes. They must be exceptionally pure and free from physical, chemical, and biological contaminants. These requirements place a heavy responsibility on the pharmaceutical industry to practice current good manufacturing practices (cGMPs) in the manufacture of parenteral dosage forms and upon pharmacists and other health care professionals to practice good aseptic practices (GAPs) in dispensing them for administration to patients.

Certain pharmaceutical agents, particularly peptides, proteins, and many chemotherapeutic agents, can only be given parenterally because they are inactivated in the gastrointestinal tract when given by mouth. Parenterally administered drugs are relatively unstable and generally high potent drugs that require strict control of their administration to the patient. Because of the advent of biotechnology, parenteral products have grown in number and usage around the world.

This chapter will focus on the unique characteristics of parenteral dosage forms and the basic principles for formulating, packaging, manufacturing, and controlling the quality of these unique products. The references and bibliography at the end of this chapter contain the most up-to-date texts, book chapters, and review papers on parenteral product formulation, manufacture, and quality control.

OVERVIEW OF UNIQUE CHARACTERISTICS OF PARENTERAL DOSAGE FORMS

Parenteral products are unique from any other type of pharmaceutical dosage form for the following reasons:

- All products must be sterile.
- All products must be free from pyrogenic (endotoxin) contamination.
- Injectable solutions must be free from visible particulate matter. This includes reconstituted sterile powders.
- Products should be isotonic although strictness of isotonicity depends on the route of administration. Products to be administered into the cerebrospinal fluid must be isotonic. Ophthalmic products, while not parenteral, also must be isotonic. Products to be administered by bolus injection by routes other than intravenous (IV) essentially should be isotonic or at least very close to isotonicity. IV infusions must be isotonic.

The author recognizes the long time contributions of Dr. Kenneth Avis. Dr. Avis died in January 1999. Dr. Avis authored this chapter in Remington since 1965. To honor his memory, the author has maintained most of his organization of this chapter with new material and revised information added where appropriate.

- All products must be stable (not only chemically and physically like all other dosage forms, but also "stable" microbiologically, i.e., sterility, freedom from pyrogenic and visible particulate contamination must be maintained throughout the shelflife of the product).
- Products must be compatible (if applicable) with IV diluents, delivery systems, and other drug products co-administered.

FORMULATION PRINCIPLES

Parenteral drugs are formulated as solutions, suspensions, emulsions, liposomes, microspheres, nanosystems, and powders to be reconstituted as solutions. This section will describe the components that are commonly used in parenteral formulations focusing on solutions and freeze-dried products. General guidance also will be provided on appropriate selection of the finished sterile dosage form and initial approaches used to develop the optimal parenteral formulation.

VEHICLES

WATER—Since most liquid injections are quite dilute, the component present in the highest proportion is the vehicle. The vehicle of greatest importance for parenteral products is water. Water of suitable quality for compounding and rinsing product contact surfaces may be prepared either by distillation or by reverse osmosis, to meet United States Pharmacopeia (USP) specifications for Water for Injection (WFI). Only by these two methods is it possible to separate adequately various liquid, gas, and solid contaminating substances from water. These two methods for preparation of WFI and specifications for WFI are discussed later in this chapter. With the possible exception of freeze-drying, there is no unit operation more important and none more costly to install and operate than the one for the preparation of WFI.

WATER-MISCIBLE VEHICLES—A number of solvents that are miscible with water have been used as a portion of the vehicle in the formulation of parenterals. These solvents are used primarily to solubilize certain drugs in an aqueous vehicle and to reduce hydrolysis. The most important solvents in this group are ethyl alcohol, liquid polyethylene glycol, and propylene glycol. Ethyl alcohol is used particularly in the preparation of solutions of cardiac glycosides and the glycols in solutions of barbiturates, certain alkaloids, and certain antibiotics. Such preparations usually are given intramuscularly. There are limitations with the amount of these co-solvents that can be administered because of toxicity concerns, greater potential for hemolysis, and potential for drug precipitation at the site of injection.¹ Formulation scientists needing to use one or more of these solvents must consult the literature (eg, reference ²) and toxicologists to ascertain the maximum amount of co-solvents

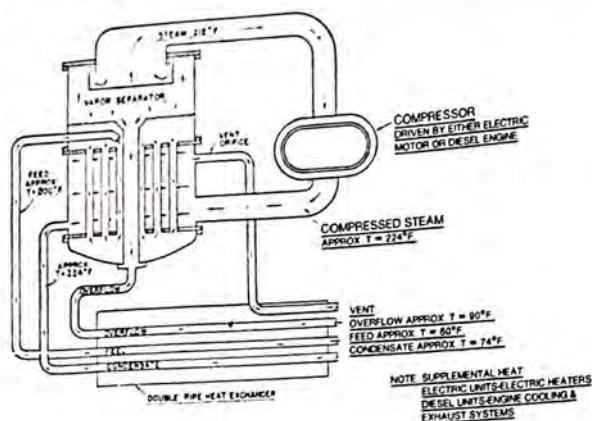


Figure 41-2. Vapor compressor still.

ciple, it is simply a series of single-effect stills or columns running at differing pressures where phase changes of water take place. A series of up to seven effects may be used, with the first effect operated at the highest pressure and the last effect at atmospheric pressure. See a schematic drawing of a multiple-effect still in Figure 41-3. Steam from an external source is used in the first effect to generate steam under pressure from feed water; it is used as the power source to drive the second effect. The steam used to drive the second effect condenses as it gives up its heat of vaporization and forms a distillate. This process continues until the last effect, when the steam is at atmospheric pressure and must be condensed in a heat exchanger.

The capacity of a multiple-effect still can be increased by adding effects. The quantity of the distillate also will be affected by the inlet steam pressure; thus, a 600-gal/hr unit designed to operate at 115 psig steam pressure could be run at approximately 55 psig and would deliver about 400 gal/hr. These stills have no moving parts and operate quietly. They are available in capacities from about 50 to 7000 gal/hr (*AMSCO, Barnstead, Finn-Aqua, Kuhlman, Vaponics*).

REVERSE OSMOSIS (RO)—As the name suggests, the natural process of selective permeation of molecules through a semipermeable membrane separating two aqueous solutions of different concentrations is reversed. Pressure, usually between 200 and 400 psig, is applied to overcome osmotic pressure and force pure water to permeate through the membrane. Membranes, usually composed of cellulose esters or polyamides, are

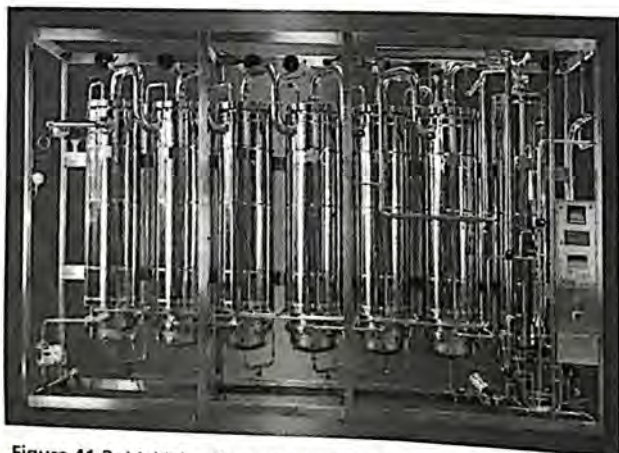


Figure 41-3. Multiple effect still (courtesy, Getinge). See Color Plate 6.

selected to provide an efficient rejection of contaminant molecules in raw water. The molecules most difficult to remove are small inorganic ones such as sodium chloride. Passage through two membranes in series is sometimes used to increase the efficiency of removal of these small molecules and to decrease the risk of structural failure of a membrane to remove other contaminants, such as bacteria and pyrogens.

Several WFI installations utilize both RO and distillation systems for generation of the highest quality water. Since feed water to distillation units can be heavily contaminated, and thus, affect the operation of the still, water is first run through RO units to eliminate contaminants. For additional information, see Collentro.¹⁵

Reverse osmosis systems are available in a range of production sizes (*AMSCO, Aqua-Chem, Finn-Aqua, Meco, Millipore*, etc).

Whichever system is used for the preparation of WFI, validation is required to be sure that the system, consistently and reliably, will produce the chemical, physical, and microbiological quality of water required. Such validation should start with the determined characteristics of the source water and include the pretreatment, production, storage, and distribution systems. All of these systems together, including their proper operation and maintenance, determine the ultimate quality of the WFI.

STORAGE AND DISTRIBUTION—The rate of production of WFI usually is not sufficient to meet processing demands; therefore, it is collected in a holding tank for subsequent use. In large operations, the holding tanks may have a capacity of several thousand gallons and be a part of a continuously operating system. In such instances the USP requires that the WFI be held at a temperature too high for microbial growth. Normally, this temperature is a constant 80°C.

The USP also permits the WFI to be stored at room temperature but for a maximum of 24 hours. Under such conditions, the WFI usually is collected as a batch for a particular use with any unused water being discarded within 24 hours. Such a system requires frequent sanitization to minimize the risk of viable microorganisms being present. The stainless-steel storage tanks in such systems usually are connected to a welded stainless-steel distribution loop supplying the various use sites with a continuously circulating water supply. The tank is provided with a hydrophobic membrane vent filter capable of excluding bacteria and nonviable particulate matter. Such a vent filter is necessary to permit changes in pressure during filling and emptying. The construction material for the tank and connecting lines usually is electropolished 316L stainless steel with welded pipe. The tanks also may be lined with glass or a coating of pure tin. Such systems are very carefully designed and constructed and often constitute the most costly installation within the plant.

When the water cannot be used at 80°C, heat exchangers must be installed to reduce the temperature at the point of use. Bacterial retentive filters should not be installed in such systems because of the risk of bacterial buildup on the filters and the consequent release of pyrogenic substances.

PURITY—While certain purity requirements have been included to above, the USP and EP monographs provide the official standards of purity for WFI and Sterile Water for Injection (SWFI).

The chemical and physical standards for WFI have changed in the past few years. The only physical/chemical tests remaining are the new *total organic carbon* (TOC), with a limit of 500 ppb (0.5 mg/L), and *conductivity*, with a limit of 1.3 μ S/cm at 25°C or 1.1 μ S/cm at 20°C. The former is an instrumental method capable of detecting all organic carbon present, and the latter is a three-tiered instrumental test measuring the conductivity contributed by ionized particles (in microSiemens or micromhos) relative to pH. Since conductivity is integrally related to pH, the pH requirement of 5 to 7 in previous revisions has been eliminated. The TOC and conductivity specifications are now considered to be adequate minimal predictors of the

chemical/physical purity of WFI. However, the *wet chemistry* tests still are used when WFI is packaged for commercial distribution and for SWFI.

Biological requirements continue to be, for WFI, not more than 10 colony-forming units (CFUs)/100 mL and 0.25 USP endotoxin units/mL. The SWFI requirements differ in that since it is a final product, it must pass the USP Sterility Test.

WFI and SWFI may not contain added substances. Bacteriostatic Water for Injection (BWFI) may contain one or more

suitable antimicrobial agents in containers of 30 mL or less. This restriction is designed to prevent the administration of a large quantity of a bacteriostatic agent that probably would be toxic in the accumulated amount of a large volume of solution, even though the concentration was low.

The USP also provides monographs giving the specifications for Sterile Water for Inhalation and Sterile Water for Irrigation. The USP should be consulted for the minor differences between these specifications and those for SWFI.

CONTAINERS AND CLOSURES

Injectable formulations are packaged into containers made of glass or plastic. Container systems include ampoules, vials, syringes, cartridges, bottles, and bags (Fig 41-4).

Ampoules are all glass while bags are all plastic. The other containers can be composed of glass or plastic and must include rubber materials such as rubber stoppers for vials and bottles and rubber plungers and rubber seals for syringes and cartridges. Irrigation solutions are packaged in glass bottles with aluminum screw caps.

Table 41-2 provides a generalized comparison of the three compatibility properties—leaching, permeation, and adsorption—of container materials most likely to be involved in the formulation of aqueous parenterals. Further, the integrity of the container/closure system depends upon several characteristics, including container opening finish, closure modulus, durometer and compression set, and aluminum seal application force. Container-closure integrity testing will be discussed in the Quality Assurance and Control section.

CONTAINER TYPES

Glass

Glass is employed as the container material of choice for most SVIs. It is composed principally of silicon dioxide, with varying amounts of other oxides such as sodium, potassium, calcium, magnesium, aluminum, boron, and iron. The basic structural network of glass is formed by the silicon oxide tetrahedron.

Boric oxide will enter into this structure, but most of the other oxides do not. The latter are only loosely bound, are present in the network interstices, and are relatively free to migrate. These migratory oxides may be leached into a solution in contact with the glass, particularly during the increased reactivity of thermal sterilization. The oxides thus dissolved may hydrolyze to raise the pH of the solution and catalyze or enter into reactions. Additionally, some glass compounds will be attacked by solutions and, in time, dislodge glass flakes into the solution. Such occurrences can be minimized by the proper selection of the glass composition.

TYPES—The USP has aided in this selection by providing a classification of glass:

Type I, a borosilicate glass

Type II, a soda-lime treated glass

Type III, a soda-lime glass

NP, a soda-lime glass not suitable for containers for parenterals

Type I glass is composed principally of silicon dioxide (~81%) and boric oxide (~13%), with low levels of the non-network-forming oxides (eg, sodium and aluminum oxides). It is a chemically resistant glass (low leachability) also having a low thermal coefficient of expansion (68×10^{-7} cm/cm-°C).

Types II and III glass compounds are composed of relatively high proportions of sodium oxide (~14%) and calcium oxide (~8%). This makes the glass chemically less resistant. Both types melt at a lower temperature, are easier to mold into various shapes, and have a higher thermal coefficient of expansion than Type I (eg, 90×10^{-7} cm/cm-°C for Type III). While there is no one standard formulation for glass among manufacturers

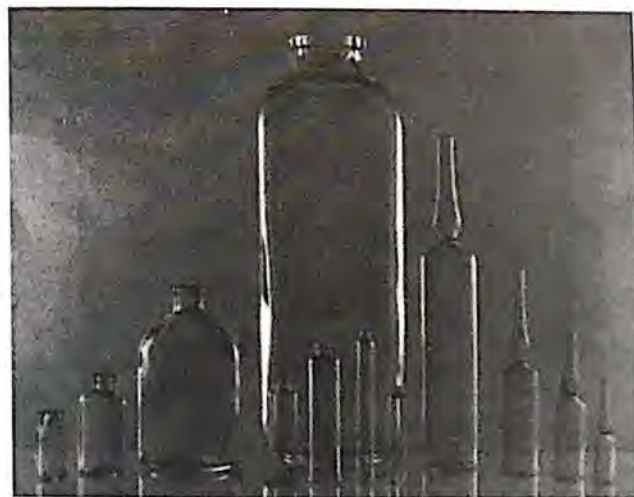


Figure 41-4. Various types of packaging for parenterals (courtesy, Kimble, Baxter).

Table 41-2. Comparative Compatibility Properties of Container Materials

	LEACHING		PERMEATION		ADSORPTION (SELECTIVE) EXTENT*
	EXTENT*	POTENTIAL LEACHABLES	EXTENT*	POTENTIAL AGENTS	
Glass					
Borosilicate	1	Alkaline earth and heavy metal oxides	0	N/A	2
Soda-lime	5	Alkaline earth and heavy metal oxides	0	N/A	2
Plastic polymers					
Polyethylene	2	Plasticizers, antioxidants	5	Gases, water vapor, other molecules	2
Low density	1	Antioxidants	3	Gases, water vapor, other molecules	2
High density	1	Antioxidants	3	Gases, especially water vapor and other molecules	2
PVC	4	HCl, especially plasticizers, antioxidants, other stabilizers	5	Gases, water vapor, other molecules	2
Polyolefins	2	Antioxidants	2	Gases, water vapor	2
Polypropylene	2	Antioxidants, lubricants	4	Gases, water vapor	1
Rubber polymers					
Natural and related synthetic	5	Heavy metal salts, lubricants, reducing agents	3	Gases, water vapor	3
Butyl	3	Heavy metal salts, lubricants, reducing agents	1	Gases, water vapor	2
Silicone	2	Minimal	5	Gases, water vapor	1

* Approximate scale of 1 to 5, with 1 as the lowest.

of these USP type categories, Type II glass usually has a lower concentration of the migratory oxides than Type III. In addition, Type II has been treated under controlled temperature and humidity conditions with sulfur dioxide or other dealkalizers to neutralize the interior surface of the container. While it remains intact, this surface will increase substantially the chemical resistance of the glass. However, repeated exposures to sterilization and alkaline detergents will break down this dealcalized surface and expose the underlying soda-lime compound.

The glass types are determined from the results of two USP tests: the Powdered Glass Test and the Water Attack Test. The latter is used only for Type II glass and is performed on the whole container, because of the dealcalized surface; the former is performed on powdered glass, which exposes internal surfaces of the glass compound. The results are based upon the amount of alkali titrated by 0.02 *N* sulfuric acid after an autoclaving cycle with the glass sample in contact with a high-purity distilled water. Thus, the Powdered Glass Test challenges the leaching potential of the interior structure of the glass while the Water Attack Test challenges only the intact surface of the container.

Selecting the appropriate glass composition is a critical facet of determining the overall specifications for each parenteral formulation.

In general, the following rules apply with respect to glass leachables:

- Relatively low levels of leachables at pH 4–8
- Relatively high levels of leachables at pH > 9
- Major extractables are silicon and sodium
- Minor extractables include potassium, barium, calcium, and aluminum.
- Trace extractables include iron, magnesium and zinc.
- Treated glass gives less extractables if pH < 8

Type I glass will be suitable for all products, although sulfur dioxide treatment sometimes is used for even greater resistance to glass leachables. Because cost must be considered, one of the other, less-expensive types may be acceptable. Type II glass may be suitable, for example, for a solution that is buffered, has a pH below 7, or is not reactive with the glass. Type III glass usually will be suitable principally for anhydrous liquids or dry substances. However, some manufacturer-to-

manufacturer variation in glass composition should be anticipated within each glass type. Therefore, for highly chemically sensitive parenteral formulations it may be necessary to specify both USP Type and a specific manufacturer.

Schott has developed a technology called Plasma Impulse Chemical Vapor Deposition (PICVD) that coats the inner surface of Type I glass vials with an ultrathin film of silicon dioxide.¹⁶ This film forms a highly efficient diffusion barrier that practically eliminates glass leachables. Such treated glass is especially useful for drug products having high pH values, formulations with complexing agents, or products showing high sensitivity to pH shifts.

PHYSICAL CHARACTERISTICS—Commercially available containers vary in size from 0.5 to 1000 mL. Sizes up to 100 mL may be obtained as ampoules and vials, and larger sizes as bottles. The latter are used mostly for intravenous and irrigating solutions. Smaller sizes also are available as syringes and cartridges. Ampoules, syringes, and cartridges are drawn from glass tubing. The smaller vials may be made by molding or from tubing. Larger vials and bottles are made only by molding. Containers made by drawing tubing are generally optically clearer and have a thinner wall than molded containers (see Fig 41-4). Compared to molded glass, tubing glass also has better wall and finish dimensional consistency, no seams, easier to label, weighs less, facilitates inspection, and has lower tooling costs. Tubing glass is preferable to molded glass for freeze-dried products because of more efficient heat transfer from the shelf into the product. Molded containers are uniform in external dimensions, stronger, and heavier.

Easy-opening ampoules that permit the user to break off the tip at the neck constriction without the use of a file are weakened at the neck by scoring or applying a ceramic paint with a different coefficient of thermal expansion. An example of a modification of container design to meet a particular need is the double-chambered vial (eg, Univial, RediVial, Lyo-ject, Inter-VialPLUS, Clip'nJect,) designed to contain a freeze-dried product in the lower, and solvent in the upper, chamber. Other examples are wide-mouth ampoules with flat or rounded bottoms to facilitate filling with dry materials or suspensions, and various modifications of the cartridge for use with disposable dosage units.

Glass containers must be strong enough to withstand the physical shocks of handling and shipping and the pressure differentials that develop, particularly during the autoclave sterilization cycle. They must be able to withstand the thermal shock resulting from large temperature changes during processing, for example, when the hot bottle and contents are exposed to room air at the end of the sterilization cycle. Therefore, a glass with a low coefficient of thermal expansion is necessary. The container also must be transparent to permit inspection of the contents.

Preparations that are light-sensitive must be protected by placing them in amber glass containers or by enclosing flint glass containers in opaque cartons labeled to remain on the container during the period of use. It should be noted that the amber color of the glass is imparted by the incorporation of potentially leachable heavy metals, mostly iron and manganese, which may act as catalysts for oxidative degradation reactions. Silicone coatings sometimes are applied to containers to produce a hydrophobic surface, for example, as a means of reducing the friction of a rubber-tip of a syringe plunger.

The size of single-dose containers is limited to 1000 mL by the USP and multiple-dose containers to 30 mL, unless stated otherwise in a particular monograph. Multiple-dose vials are limited in size to reduce the number of punctures for withdrawing doses and the accompanying risk of contamination of the contents. As the name implies, single-dose containers are opened or penetrated with aseptic care, and the contents used at one time. These may range in size from 1000-mL bottles to 1-mL or less ampoules, vials, or syringes. The integrity of the container is destroyed when opened, so that the container cannot be closed and reused.

A multiple-dose container is designed so that more than one dose can be withdrawn at different times, the container maintaining a seal between uses. It should be evident that with full aseptic precautions, including sterile syringe and needle for withdrawing the dose and disinfection of the exposed surface of the closure, there is still a substantial risk of introducing contaminating microorganisms and viruses into the contents of the vial. Because of this risk, the USP requires that all multiple-dose vials must contain an antimicrobial agent or be inherently antimicrobial, as determined by the USP *Antimicrobial Preservatives-Effectiveness* tests. There are no comparable antiviral effectiveness tests, nor are antiviral agents available for such use. In spite of the advantageous flexibility of dosage provided by multiple-dose vials, single-dose, disposable container units provide the clear advantage of greater sterility assurance and patient safety.

Because of concerns for user safety and glass particulate matter occurring when glass is broken, glass sealed ampoules are no longer glass containers of choice for new SVIs in the United States.

RUBBER CLOSURES

To permit introduction of a needle from a hypodermic syringe into a multiple-dose vial and provide for resealing as soon as the needle is withdrawn, each vial is sealed with a rubber closure held in place by an aluminum cap. Figure 41-5 illustrates how this is done. This principle also is followed for single-dose containers of the cartridge type, except that there is only a single introduction of the needle to make possible the withdrawal or expulsion of the contents.

Rubber closures are composed of multiple ingredients that are plasticized and mixed together at an elevated temperature on milling machines. The elastomer primarily used in rubber closures, plungers, and other rubber items used in parenteral packaging and delivery systems is synthetic butyl or halobutyl rubber. Natural rubber also is used, but if it is natural rubber latex, then the product label must include a warning statement due to the potential for allergic reactions from latex exposure.

The plasticized mixture is placed in molds and vulcanized (cured) under high temperature and pressure. During vulcan-



Figure 41-5. Extended view of sealing components for a multiple-dose vial (courtesy, West).

ization the polymer strands are cross-linked by the vulcanizing agent, assisted by the accelerator and activator, so that motion is restricted and the molded closure acquires the elastic, resilient character required for its use. Ingredients not involved in the cross-linking reactions remain dispersed within the compound and, along with the degree of curing, affect the properties of the finished closure. Examples of rubber-closure ingredients are given in Table 41-3.

The physical properties to be considered in the selection of a particular formulation include elasticity, hardness, tendency to fragment, and permeability to vapor transfer. The elasticity is critical in establishing a seal with the lip and neck of a vial or other opening and in resealing after withdrawal of a hypodermic needle from a vial closure. The hardness should provide firmness but not excessive resistance to the insertion of a needle through the closure, while minimal fragmentation of pieces of rubber should occur as the hollow shaft of the needle is pushed through the closure. While vapor transfer occurs to some degree with all rubber formulations, appropriate selection of ingredients makes it possible to control the degree of permeability. Physicochemical and toxicological tests for evaluating rubber closures are described in section <381> in the USP.

The ingredients dispersed throughout the rubber compound may be subject to leaching into the product contacting the closure. These ingredients, examples of which are given in Table 41-2, pose potential compatibility interactions with product ingredients if leached into the product solution, and these effects must be evaluated. Further, some ingredients must be evaluated for potential toxicity. To reduce the problem of leachables, coatings have been applied to the product contact surfaces of

Table 41-3. Examples of Ingredients Found in Rubber Closures

INGREDIENT	EXAMPLES
Elastomer	Natural rubber (latex) Butyl rubber Neoprene
Vulcanizing (curing) agent	Sulfur Peroxides
Accelerator	Zinc dibutyldithiocarbamate
Activator	Zinc oxide Stearic acid
Antioxidant	Dilauryl thiopropionate
Plasticizer/lubricant	Paraffinic oil Silicone oil
Fillers	Carbon black Clay
Pigments	Barium sulfate Inorganic oxides Carbon black

closures, with various polymers, the most successful being Teflon. Recently, polymeric coatings have been developed that are claimed to have more integral binding with the rubber matrix, but details of their function are trade secrets.

The physical shape of some typical closures may be seen in Figure 41-5. Most of them have a lip and a protruding flange that extends into the neck of the vial or bottle. Many disk closures are being used now, particularly in the high-speed packaging of antibiotics. Slotted closures are used on freeze-dried products to permit the escape of water vapor, since they are inserted only partway into the neck of the vial until completion of the drying phase of the cycle. Also, the top design of the freeze-dry closure is important to minimize sticking of the closure to the underneath of the dryer shelf after stoppering the vial. Stoppers normally have a small protruding circle at the center of the top of the stopper. Gaps provided within the protruding circle minimize the tendency of the stopper to stick to the freeze-dryer shelf.

The plunger type of rubber is used to seal one end of a syringe or cartridge. At the time of use, the plunger expels the product by a needle inserted through the closure at the distal end of the package. Intravenous solution closures often have permanent holes for adapters of administration sets; irrigating solution closures usually are designed for pouring.

As will be discussed later, rubber closures must be "slippery" in order to move easily through a rubber closure hopper and other stainless steel passages until they are fitted onto the filled vials. Traditionally, rubber materials are "siliconized" (silicone oil or emulsion applied onto the rubber) in order to produce such lubrication. However, advances in rubber closure technologies have introduced closures that do not require siliconization because of a special polymer coating applied to the outer surface of the closure. Examples are the *Daichyo*/West closures (Flurotec) and the *Helvoet* (Omniflex) closures. The *Daichyo* Flurotec coating is a copolymer of tetrafluoroethylene and ethylene.

Plastic

Thermoplastic polymers have been established as packaging materials for sterile preparations such as large-volume parenterals, ophthalmic solutions, and, increasingly, small-volume parenterals. For such use to be acceptable, a thorough understanding of the characteristics, potential problems, and advantages for use must be developed. Three principal problem areas exist in using these materials:

1. Permeation of vapors and other molecules in either direction through the wall of the plastic container
2. Leaching of constituents from the plastic into the product
3. Sorption (absorption and/or adsorption) of drug molecules or ions on the plastic material

Permeation, the most extensive problem, may be troublesome by permitting volatile constituents, water, or specific drug molecules to migrate through the wall of the container to the outside and thereby be lost. This problem has been resolved, for example, by the use of an overwrap in the packaging of IV solutions in PVC bags to prevent the loss of water during storage. Reverse permeation also may occur in which oxygen or other molecules may penetrate to the inside of the container and cause oxidative or other degradation of susceptible constituents. **Leaching** may be a problem when certain constituents in the plastic formulation, such as plasticizers or antioxidants, migrate into the product. Thus, plastic polymer formulations should have as few additives as possible, an objective characteristically achievable for most plastics being used for parenteral packaging. **Sorption** is a problem on a selective basis, that is, sorption of a few drug molecules occurs on specific polymers. For example, sorption of insulin and other proteins, vitamin A acetate, and warfarin sodium has been shown to occur on PVC bags and tubing when these drugs were present as additives in IV admixtures. A brief summary of some of these compatibility relationships is given in Table 41-2.

One of the principle advantages of using plastic packaging materials is that they are not breakable as is glass; also, there is a substantial weight reduction. The flexible bags of polyvinyl chloride or select polyolefins, currently in use for large-volume intravenous fluids, have the added advantage that no air interchange is required; the flexible wall simply collapses as the solution flows out of the bag.

Most plastic materials have the disadvantage that they are not as clear as glass and, therefore, inspection of the contents is impeded. However, recent technologies have overcome this limitation, evidenced by plastic resins such as CZ (polycyclopentane, *Daichyo Seiko*) and Topas COC (cyclic olefin copolymer, *Ticona*). In addition, many of these materials will soften or melt under the conditions of thermal sterilization. However, careful selection of the plastic used and control of the autoclave cycle has made thermal sterilization of some products possible, large-volume parenterals in particular. Ethylene oxide or radiation sterilization may be employed for the empty container with subsequent aseptic filling. However, careful evaluation of the residues from ethylene oxide or its degradation products and their potential toxic effect must be undertaken. Investigation is required concerning potential interactions and other problems that may be encountered when a parenteral product is packaged in plastic. For further details see Chapter 54 (*Plastic Packaging Materials*) and the review article by Jenke.¹⁷

NEEDLES

Historically, stainless steel needles have been used to penetrate the skin and introduce a parenteral product inside the body. The advent of needleless injection systems (eg, Bioject, AdvantaJet, Medi-ject, Medi-Jector Vision) has obviated the need for the use of needles for some injections (eg, vaccines) and are gaining in popularity over the conventional syringe and needle system. However, needleless injections are generally more expensive, can still produce pain on injection, are potentially a greater source of contamination (and cross-contamination from incontinent use), and may not be as efficient in dose delivery.

Needles are hollow devices composed of stainless steel or plastic. Needles are available in a wide variety of lengths, sizes, and shapes. **Needle lengths** range from 1/4 inch to 6 inches. **Needle size** is referred to as its gauge (G), or the outside diameter (OD) of the needle shaft. Gauge ranges are 11 to 32 gauge with the largest gauge for injection usually being no greater than 16 G. 16 G needles have an OD of 0.065 inches (1.65 mm) whereas 32 G have an OD of 0.009 inches (0.20 mm). **Needle shape** includes regular, short bevel, intradermal, and winged. Needle shape typically is defined by one end of a needle enlarged to form a hub with a delivery device such as a syringe or other administration device. The other end of the needle is beveled, meaning that it forms a sharp tip to maximize ease of insertion.

The route of administration, type of therapy, and whether the patient is a child or adult dictate the length and size of needle used.¹⁸ Intravenous injections typically use 1–2 inch 15 to 25 G needles. Intramuscular injections use 1–2 inch 19–22 G needles. Subcutaneous injections use 1/4 to 5/8 inch 24 to 25 G needles. Needle gauge for children rarely is larger than 22 G, usually 25–27 G. Winged needles are used for intermittent heparin therapy. Many different types of therapies, (eg, radiology, anesthesia, biopsy, cardiovascular, ophthalmic, transfusions, tracheotomy) have their own peculiar types of needle preferences.

Needles are purchased either alone (eg, Luer-Lok) to be attached to syringes, cartridge, and other delivery systems, or, for syringes, can be part of the syringe set (stake needle).

PYROGENS (ENDOTOXINS)

Since water and packaging materials are the greatest sources of pyrogenic contamination, this subject will now be covered.

Pyrogens are products of metabolism of microorganisms. The most potent pyrogenic substances (endotoxins) are con-

stituents (lipopolysaccharides, LPS) of the cell wall of gram-negative bacteria (eg, *Pseudomonas* sp, *Salmonella* sp, *Escherichia coli*). Gram-positive bacteria and fungi also produce pyrogens but of lower potency and of different chemical nature. Gram-positive bacteria produce peptidoglycans whereas fungi produce β -glucans, both of which can cause non-endotoxin pyrogenic responses. Endotoxins are lipopolysaccharides that typically exist in high molecular weight aggregate forms. However, the monomer unit of LPS is less than 10,000 daltons, enabling endotoxin easily to pass through sterilizing 0.2 micron filters. Studies have shown that the lipid portion of the molecule is responsible for the biological activity. Since endotoxins are the most potent pyrogens and gram-negative bacteria are ubiquitous in the environment, especially water, this discussion focuses on endotoxins and the risk of their presence as contaminants in sterile products.

Pyrogens, when present in parenteral drug products and injected into patients, can cause fever, chills, pain in the back and legs, and malaise. Although pyrogenic reactions are rarely fatal, they can cause serious discomfort and, in the seriously ill patient, shock-like symptoms that can be fatal. The intensity of the pyrogenic response and its degree of hazard will be affected by the medical condition of the patient, the potency of the pyrogen, the amount of the pyrogen, and the route of administration (intrathecal is most hazardous followed by intravenous, intramuscular, and subcutaneous). When bacterial (exogenous) pyrogens are introduced into the body, LPS targets circulating mononuclear cells (monocytes and macrophages) that, in turn, produce pro-inflammatory cytokines such as interleukin-2, interleukin-6, and tissue necrosis factor. Besides LPS, gram-negative bacteria also release many peptides (eg, exotoxin A, peptidoglycan, and muramyl peptides) that can mimic the activity of LPS and induce cytokine release. The Limulus Amebocyte Lysate (LAL) test, discussed later, can only detect the presence of LPS. It has been suggested that a new test, called Monocyte Activation Test, replace LAL as the official pyrogen test because of its greater sensitivity to all agents that induce the release of cytokines that cause fever and a potential cascade of other adverse physiological effects.¹⁹

CONTROL OF PYROGENS—In general, it is impractical, if not impossible, to remove pyrogens once present without adversely affecting the drug product. Therefore, the emphasis should be on preventing the introduction or development of pyrogens in all aspects of the compounding and processing of the product.

Pyrogens may enter a preparation through any means that will introduce living or dead microorganisms. However, current technology generally permits the control of such contamination, and the presence of pyrogens in a finished product indicates processing under inadequately controlled conditions. It also should be noted that time for microbial growth to occur increases the risk for elevated levels of pyrogens. Therefore, compounding and manufacturing processes should be carried out as expeditiously as possible, preferably planning completion of the process, including sterilization, within the maximum allowed time according to process validation studies. Aseptic processing guidelines require establishment of time limitations throughout processing for the primary purpose of preventing the increase of endotoxin (and microbial) contamination that subsequently cannot be destroyed or removed.

Pyrogens can be destroyed by heating at high temperatures. A typical procedure for depyrogenation of glassware and equipment is maintaining a dry heat temperature of 250°C for 45 min. Exposure for 650°C for 1 min or 180°C for 4 hr likewise will destroy pyrogens. The usual autoclaving cycle will not do so. Heating with strong alkali or oxidizing solutions will destroy pyrogens. It has been claimed that thorough washing with detergent will render glassware pyrogen-free if subsequently rinsed thoroughly with pyrogen-free water. Rubber stoppers cannot withstand pyrogen-destructive temperatures, so reliance must be placed on an

effective sequence of washing, thorough rinsing with WFI, prompt sterilization, and protective storage to ensure adequate pyrogen control. Similarly, plastic containers and devices must be protected from pyrogenic contamination during manufacture and storage, since known ways of destroying pyrogens affect the plastic adversely. It has been reported that anion-exchange resins and positively charged membrane filters will remove pyrogens from water. Also, although reverse osmosis membranes will eliminate them, the most reliable method for their elimination from water is distillation.

A method that has been used for the removal of pyrogens from solutions is adsorption on adsorptive agents. However, since the adsorption phenomenon also may cause selective removal of chemical substances from the solution, this method has limited application. Other in-process methods for their destruction or elimination include selective extraction procedures and careful heating with dilute alkali, dilute acid, or mild oxidizing agents. In each instance, the method must be studied thoroughly to be sure it will not have an adverse effect on the constituents of the product. Although ultrafiltration now makes possible pyrogen separation on a molecular-weight basis and the process of tangential flow is making large-scale processing more practical, use of this technology is limited, except in biotechnological processing.

SOURCES OF PYROGENS—Through understanding the means by which pyrogens may contaminate parenteral products, their control becomes more achievable. Therefore, it is important to know that water is probably the greatest potential source of pyrogenic contamination, since water is essential for the growth of microorganisms and frequently contaminated with gram-negative organisms. When microorganisms metabolize, pyrogens will be produced. Therefore, raw water can be expected to be pyrogenic and only when it is appropriately treated to render it free from pyrogens, such as WFI, should it be used for compounding the product or rinsing product contact surfaces such as tubing, mixing vessels, and rubber closures. Even when such rinsed equipment and supplies are left wet and improperly exposed to the environment, there is a high risk that they will become pyrogenic. Although proper distillation will provide pyrogen-free water, storage conditions must be such that microorganisms are not introduced and subsequent growth is prevented.

Other potential sources of contamination are containers and equipment. Pyrogenic materials adhere strongly to glass and other surfaces, especially rubber closures. Residues of solutions in used equipment often become bacterial cultures, with subsequent pyrogenic contamination. Since drying does not destroy pyrogens, they may remain in equipment for long periods. Adequate washing will reduce contamination and subsequent dry-heat treatment can render contaminated equipment suitable for use. However, all such processes must be validated to ensure their effectiveness. Aseptic processing guidelines require validation of the depyrogenation process by demonstrating at least 3-log reduction in an applied endotoxin challenge.

Solutes may be a source of pyrogens. For example, the manufacturing of bulk chemicals may involve the use of pyrogenic water for process steps such as crystallization, precipitation, or washing. Bulk drug substances derived from cell culture fermentation will almost certainly be heavily pyrogenic. Therefore, all lots of solutes used to prepare parenteral products should be tested to ensure that they will not contribute unacceptable quantities of endotoxin to the finished product. It is standard practice today to establish valid endotoxin limits on active pharmaceutical ingredients and most solute additives.

The manufacturing process must be carried out with great care and as rapidly as possible, to minimize the risk of microbial contamination. Preferably, no more product should be prepared than can be processed completely within one working day, including sterilization.