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The Science and Practice of Pharmacy

23rd Edition

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Chapter 29

Parenteral preparations

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29.1 Introduction

Parenteral is derived from the word *para enteron* meaning "beside the intestine" indicates delivery of drug that does not utilize gastrointestinal tract to enter into body tissues. The US Pharmacopeia (USP) defines parenteral products as products that are injected through the skin or external boundary tissue, or implanted within the body to allow the direct administration of the active drug into blood vessels, organs, tissues, or lesions. Because they are directly injected in the body, they must stringently comply with specifications of purity. They must also comply strictly with requirements of sterility and apyrogenicity (free of endotoxin). Solutions and powders reconstituted as solution should be free from visible particulate matter. Isotonicity is preferred, although requirement of isotonicity depends on the route of administration. Further, like other dosage forms, they should be physically, chemically, and microbiologically stable. In certain cases where the injection is required to be diluted or coadministered with other delivery systems, compatibility with IV diluents and other coadministered drug products needs to be evaluated.

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 on pharmacists and other health-care professionals to practice good aseptic practices in dispensing parenteral dosage forms for administration to patients. Due to the advent of biotechnology, formulation technology, and techniques for administration, parenteral products have grown in number and usage around the world. Table 29.1 provides information about some parenteral products recently approved by US-FDA.

This chapter focuses 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 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 (QC).

29.2 Advantages of parenteral route and formulations

- Parenteral route, more specifically intravenous injection, serves as the best route for immediate physiological action. Pharmacokinetics and pharmacological response to the drug administered can be reliably predicted.
- Products that degrade in gastrointestinal tract (GIT) and which are relatively unstable and highly potent, for example, peptides, chemotherapeutic agents can preferably be administered by parenteral route.
- Modified release/controlled release can be achieved by selecting an appropriate site of injection.
- Since the drug is administered by a professionally trained person, dose is accurately administered.
- This route is advantageous in case of unconscious or uncooperative state of the patient when drug cannot be administered orally.
- The route is also preferred in case of diseases wherein absorption in the intestinal tract is impaired.

29.3 Concerns with parenteral route and formulations

- The dosage form requires aseptic practices to be followed during the administration to avoid contamination. The product, therefore, should be administered by a professionally trained person or in a hospital setting.
- Certain products in vials must be withdrawn into a syringe prior to injection and often combined with other products in infusion solutions prior to administration. Incompatibilities can occur and cause inactivation of

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TABLE 29.1 List of few recently approved parenteral formulations (US-FDA, 2019; Zhong et al., 2018).

Brand name	Active ingredient	Company	Approval year	Route	Formulation
Emgality	Galcanezumab-gnlm	Eli-Lilly	2018	Subcutaneous	Solution
Lumoxiti	Moxetumomab pasudotox-tdfk	Astra-Zeneca	2018	Intravenous infusion	Lyophilized powder for reconstitution
Polivy	Polatuzumab vedotin-piiq	Genentech	2019	Intravenous	Powder for reconstitution
Vyleesi (autoinjector)	Bremelanotide acetate	Amag Pharms, Inc.	2019	Subcutaneous	Solution
Omegaven	Fish oil triglycerides	Fresenius Kabi USA	2019	Intravenous	Emulsion
Jeuveau	Prabotulinumtoxina-Xvfs	Evolus, Inc.	2019	Intramuscular	Powder for reconstitution

one or more ingredients or other undesired reactions. In some instances, incompatibilities are visible as precipitation or color change, but, in other instances, there may be no visible effect.

- There is a risk of tissue toxicity from local irritation.
- Patient compliance is low due to real or psychological pain factor.
- Any error in dosage cannot be corrected once the injection is administered.
- However, the advent of home healthcare as an alternative to extended institutional care and availability of new medications from biotechnology to treat chronic diseases have mandated the development of programs for training lay persons to administer these dosage forms.

29.4 Considerations for formulation development of parenterals

Injections may be available in variety of dosage forms such as solutions, dry products to be combined with a diluent prior to use, suspensions, emulsions, and concentrates ready for dilution prior to administration. Injections may be administered by various routes such as intravenous, subcutaneous, intradermal, intramuscular, intraarticular, intralesional, and intrathecal. The type of dosage form (solution, suspension, etc.) determines the particular route of administration employed. Conversely, the desired route of administration places requirements on the formulation. Table 29.2 provides details about considerations regarding various parenteral routes of administration.

29.5 Formulation components

Parenteral drugs products are formulated as conventional dosage forms such as solutions, suspensions, emulsions, as well as more specialized systems such as microspheres, liposomes, nanosystems, in situ gels, implants, and powders to be reconstituted as solutions. This section describes the components commonly used in parenteral formulations, focusing on solutions. Table 29.3 outlines the steps involved in the formulation development of a new parenteral drug product.

29.5.1 Vehicles

The solubility of the drug would be influenced by the physiochemical properties of the drug which would govern the vehicle to be selected. If the drug is insufficiently soluble in water at the required dosage, then a cosolvent or a solubilizer that sufficiently increases the solubility of the drug in the vehicle must be added. If relatively simple formulation additives do not result in a solution, then a dispersed system must be developed. Solubility also dictates the concentration of drug in the dosage form.

29.5.1.1 Water

The component present in the highest proportion in most parenteral preparations is the vehicle. Water is the most commonly used vehicle in parenteral products. USP describes monographs and specifications for water to be used for parenterals under the title of *Water for Injection* (WFI). WFI is water purified by distillation or a purification process that is equivalent to distillation in the removal of chemicals and microorganisms. WFI should be prepared and stored in a manner that ensures purity and freedom from endotoxins. USP and EP (European Pharmacopeia) monographs provide the official standards of purity for WFI and sterile WFI (SWFI).

There are specifications on total organic carbon (TOC), with a limit of 500 ppb mg/L, and conductivity, with a limit of 1.3 μS/cm at 25°C or 1.1 μS/cm at 20°C. The former is an instrumental method capable of detecting all

TABLE 29.2 Considerations regarding parenteral routes of administrations.

Route—site of injection	Volume	Needle used	Formulation aspects	Application
Intradermal—into the skin between epidermis and dermis	0.05–0.2 mL	25–26 ga; 3/8–3/4 inch.	Solution formulation, isotonicity preferred	For diagnostic tests
Subcutaneous—under the skin, into subcutaneous tissue	Less than 1 mL, not exceeding 2 mL	23 ga; 1/4–5/8 inch.	Solution, dispersion, isotonicity preferred	For administration of peptides, microspheres, as a depot
Intramuscular—into striated muscle fibers beneath subcutaneous layer, for example, muscle in lateral thighs, upper arm, buttocks	Usually less than 2 mL, not exceeding 4 mL	22 ga; 1–2 inch.	Solutions aqueous and oily, aqueous and oily suspensions. Isotonicity is desirable	For quick onset of action of medicament, For sustained release of agents such as steroids, peptides, and proteins
Intravenous—into vein, most commonly median basilica vein	Varies for less than 1 mL to in excess of 500 mL in case of infusion	20–22 ga; 1–2 inch.	Solutions, O/W emulsions, liposomal dispersions. Isotonicity is desirable	Rapid onset of action
Intrathecal/intraspinal—around spinal cord in the cerebrospinal fluid	Usually1–4 mL Less than 20 mL	24–28 ga; 5/8 to 1/4 inch	Aqueous solutions, isotonicity is essential	For delivery of agents to treat chronic spasticity due to injury, multiple sclerosis and cerebral palsy, management of cancer, neuropathic pain
Intraocular—into the internal tissue of the eye	Less than 1 mL	≥ 27 ga; 1/2–5/8 inch.	Aqueous solutions, isotonicity is essential	For delivery of anti- Vascular endothelial growth factor (VEGF) drugs, Antibiotics, antiviral and antifungal, treatment of AMD, diabetic retinopathy and retinal vein occlusion
Intraarticular/intrabursal—directly into the joint	2–20 mL	18–22 ga; 1.5 – 1 inch	Aqueous solutions and suspensions, Isotonicity is essential	For delivery of corticosteroids, hyaluronic acid to treat osteoarthritis

AMD, Age-related macular degeneration.

TABLE 29.3 General considerations for development of parenteral products.

Property/activity	Parameters to be taken into consideration	Remarks
Physical properties of API	Structure, molecular weight, solubility; effect of pH on solubility and isoelectric point, hygroscopicity, aggregation potential for protein or peptide	Solubilization approaches such as cosolvency for improving solubility. Appropriate buffers for stability.
Chemical properties of API	Must have a "validatable" analytical method for potency and purity, pH stability profiling, forced degradation studies, study of sensitivity to oxygen and light	Major routes of degradation and degradation products must be ascertained.
Initial formulation approaches	Excipient compatibility studies, Shelf life goals, combination with other products, diluents, single dose, or multiple dose	Selection of excipients, decide upon whether preservative agent be part of drug solution/powder or part of diluent in case of multidose preparations.
Packaging	Primary container and closure	Compatibility with formulation should be assessed. Use of silicone can induce protein aggregation. If concentration must be low, due to stability and/or solubility limitations, then the size of primary container must be larger, and this might preclude the use of syringes, cartridges, and/or smaller vial sizes.
Manufacturing	Design and implementation of an initial manufacturing method of the product	Influenced by API properties, dosage form.
Stability of final formulation	Storage conditions	If a product must be refrigerated, container cannot be too large. Formulation components must be soluble and stable at colder conditions.
Sterilization process	Terminal sterilization, aseptic processing or filtration	Stability of API and components largely dictate selection of process.

API, Active pharmaceutical ingredient.

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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. The TOC and conductivity specifications are now considered adequate minimal predictors of the chemical/physical purity of WFI. However, the wet chemistry tests are still used when WFI is packaged for commercial distribution and for SWFI.

Biological requirements continue to be, for WFI, not more than 10 CFU/100 mL and less than 0.25 USP endotoxin units (EU)/mL. The SWFI requirements differ in that it must pass the USP sterility test. SWFI also should pass the limit for particulate matter.

Bacteriostatic WFI 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 would probably 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. The unit operation for WFI preparation is costly to install and operate.

29.5.1.2 Water-miscible vehicles

Cosolvents in some proportion are incorporated to enhance solubility of certain drugs in an aqueous vehicle. The most important solvents in this group are ethyl alcohol, liquid polyethylene glycol, and propylene glycol. Ethyl alcohol is used in the preparation of solutions of cardiac glycosides and the glycols in solutions of barbiturates, certain alkaloids, and certain antibiotics. Recently solvents such as dimethyl acetamide, *N*-methylpyrrolidone, and benzyl alcohol have also been incorporated as cosolvents for parenteral administration (Kalepu and Nekkanti, 2015). There are limitations with the amount of these cosolvents that can be administered, due to toxicity concerns, greater potential for hemolysis, and potential for drug precipitation at the site of injection (Yalkowsky et al., 1998). Several references provide information on concentrations of cosolvents used in approved commercial parenteral products (Mottu et al., 2000; Rayaprolu et al., 2018; Nema et al., 1997; Powell et al., 1998; Strickley, 1999, 2000a, 2000b; Rowe et al., 2009).

29.5.1.3 Nonaqueous vehicles

Fixed oils are the major group of nonaqueous vehicles, for example, corn oil, cottonseed oil, peanut oil, and sesame oil. The USP provides specifications regarding the source of fixed oils (vegetable origin), their physical characteristics, and their stability (being prone to rancidity) to be used in parenteral preparations. The USP also specifies limits for the free fatty acid content, iodine value, and saponification value. Fixed oils are used as vehicles for certain hormone (e.g., progesterone, testosterone, deoxycorticosterone) and vitamin (e.g., Vitamins K and E) preparations. These injections are administered intramuscularly and should never be given by IV route. The label must state the name of the vehicle, so the user may beware in case of known sensitivity or other reactions to it.

29.5.2 Active pharmaceutical ingredient

Active pharmaceutical ingredient (API) and excipients used for formulations must be pure, have a low microbial level, and be nonpyrogenic. GMP requires establishing microbial and endotoxin limits on APIs and most excipients. Therefore manufacturers should use the best grade of chemicals obtainable and use its analytical profile to determine that each lot of chemical used in the formulation meets the required specifications. Properties of API influencing formulation of parenterals are detailed in Table 29.3.

29.5.3 Excipients

- Complexing agents and surfactants: The most commonly used complexing agents are the cyclodextrins, (sulfobutyl ether of beta-cyclodextrin and hydroxypropyl beta-cyclodextrins). Polyoxyethylene sorbitan monolaurate (Tween 20) and polyoxyethylene sorbitan monooleate (Tween 80). Cremophor EL and lecithin are some surfactants that have been explored. They help to improve drug solubility.
- Buffers and stabilizers: Buffers are used to control pH and prevent pH-induced instability, that is, chemical degradation of drugs and aggregation/precipitation of proteins. Buffer systems should have as low a buffering capacity as feasible, so as not to significantly disturb the body's buffering systems when injected. The acid salts most frequently employed as buffers are citrates, acetates, and phosphates. Amino acid buffers, especially histidine, have become buffer systems of choice for controlling solution pH of monoclonal antibody solutions.
- Antioxidants: They are frequently required to prevent oxidative degradation. Sodium bisulfite, ascorbic acid, and sodium salt of ethylenediaminetetraacetic acid (EDTA) are commonly used. EDTA chelates metallic ions that would otherwise catalyze the oxidation reaction. Displacing the air (oxygen) dissolved in the solution and also from the headspace, by purging with an inert gas, such as nitrogen, would be the first line of action to control oxidation of a sensitive drug. Isolator technology, where the entire atmosphere can be recirculating nitrogen or another nonoxygen gas, can be used to completely eliminate oxygen from product.

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- Isotonicity imparting agents: These agents provide patient comfort by reducing pain and tissue irritation, as do substances added to make a solution isotonic or near physiological pH. Common tonicity adjusters are sodium chloride, dextrose, and glycerin. Certain formulations require dilution of the injection with isotonic vehicles to be administered as an infusion to reduce discomfort. Isotonic vehicles include sodium chloride injection, ringer's injection, dextrose injection, dextrose and sodium chloride injection, and lactated ringer's injection.
- Cryoprotectants and lyoprotectants are additives that serve to protect biopharmaceuticals from adverse effects, due to freezing and/or drying of the product during freeze-dry processing. Excipients that are preferentially excluded from the surface of the protein are the best cryoprotectants, and excipients that remain amorphous during and after freeze-drying serve best as lyoprotectants. Common protectants include sugars, such as sucrose and trehalose, and amino acids, such as glycine.
- Preservatives: Preservatives retard or prevent the chemical, physical, or biological degradation of a preparation and prevent microbial growth. The USP states that antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to preparations contained in multiple-dose containers. The EP requires multiple-dose products to be bactericidal and fungicidal. They must be present in adequate concentration at the time of use to counter any contamination. The USP provides a test for antimicrobial preservative effectiveness to determine that an antimicrobial substance or combination adequately inhibits the growth of microorganisms in a parenteral product (Sutton and Porter, 2002). USP prescribes maximum volume and concentration limits for commonly used preservatives in parenteral products due to toxicity concerns (e.g., phenylmercuric nitrate and thimerosal 0.01%, benzethonium chloride and benzalkonium chloride 0.01%, phenol or cresol 0.5%, and chlorobutanol 0.5%). Phenylmercuric nitrate is the most frequently employed at a concentration of 0.002%. Methyl *p*-hydroxybenzoate 0.18% and propyl *p*-hydroxybenzoate 0.02%, in combination, and benzyl alcohol 2% are also used frequently. Hexylresorcinol 0.5% and phenylmercuric benzoate 0.1% are moderately bactericidal in oily preparations. Antimicrobial agents must be studied with respect to compatibility with all other components of the formula. It has been reported that macromolecules such as proteins and surfactants, that is, Tween 80 binds to esters of *p*-hydroxybenzoic acid and inactivates them. Phenol and benzyl alcohol are the two most common antimicrobial preservatives used in peptide and protein products. Phenoxyethanol is the most frequently used preservative in vaccine products. Reaction and adsorption by rubber closures are another cause for inactivation of antimicrobial preservatives. Phenylmercuric nitrate reacts with sulfide residues in rubber closures. The International Conference for Harmonization/Committee for Proprietary Medicinal Products (ICH/CPMP) guidelines require that products without preservatives be used immediately. Special care must be exercised in storing products without preservatives after the containers have been opened to prepare an admixture, particularly those that support the growth of microorganisms, such as total parenteral nutrition solutions and emulsions. It should be noted that, although refrigeration slows the growth of most microorganisms, it does not prevent their growth.

Suspending agents, emulsifiers, precipitation inhibitors, release retardants are some other added substances in injectables. Competitive binders, such as albumin, and surface-active agents which minimize protein interaction with inert surfaces, such as glass and rubber and plastic, are also included.

Excipients and certain drugs can form insoluble complexes. Impurities in excipients can cause drug degradation reactions. Peroxide impurities in polymers may catalyze oxidative degradation reactions with drugs, including proteins, which are oxygen sensitive. Compatibility studies of drugs and products with diluents and IV fluids must be undertaken from the physical, chemical, and therapeutic aspects.

Ultimately, a thorough study should be undertaken of each therapeutic agent in combination with other drugs and IV fluids, not only of generic, but also of commercial preparations, from the physical, chemical, and therapeutic aspects.

29.6 Containers and closures

Ideally, containers for injectables should be made up of material which is inert, impermeable to air and water vapors, has low coefficient of thermal expansion, is amenable to modification to provide light protection if required, can be designed easily in required form of containers which can withstand shock and impacts during transport and handling; are clear and transparent to facilitate inspection; with proper closure maintain integrity of contained product; and are relatively inexpensive. A comparative assessment of properties of various packaging materials is depicted in Table 29.4.

29.6.1 Glass

Glass is material of choice for containers of most small-volume injectables. It is a product of fusion that has cooled to a rigid state without crystallization. It is composed of silicon dioxide as major constituent in tetrahedron structure, with varying amounts of oxides, such as sodium, potassium, calcium, magnesium, aluminum, boron, and iron. Boric oxide enters into the structure, but most of the other oxides are relatively free to migrate. These oxides may be leached into a solution in contact with the glass, during stress conditions such as autoclaving due to accelerated reactivity. The hydrolysis of dissolved oxides may raise the pH

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TABLE 29.4 Comparison of properties of packaging materials.

	Leaching	Potential leachables	Water vapor permeation extent	Gas permeation	Adsorption (selective)
Borosilicate glass	Low	Oxides of sodium, potassium, magnesium, and calcium	None	None	Low
Soda lime glass	High	Oxides of sodium, barium, and calcium	None	None	Low
Polyethylene low density	Low	Low amount of plasticizers, antioxidants	High	Low	Low
Polyethylene high density	Low	Low amount of antioxidants	Low	Low	Low
PVC	Low	HCl, especially plasticizers, antioxidants, other stabilizers	High	Low	Low
Polyolefins	Low	Antioxidants	Low	Low	Low
Polypropylene	Low	Antioxidants, lubricants	Moderate	Low	Low
natural and related synthetic rubber	High	Heavy metal salts, lubricants, reducing agents	Moderate	Moderate	High
Butyl rubber	Moderate	Heavy metal salts, lubricants, reducing agents	Low	Moderate	Moderate
Silicone	Moderate	Insignificant	Very high	Very high	Low

of the solution and catalyze or initiate reactions. In addition, attack by solutions may dislodge flakes from glass into the solution.

29.6.1.1 Types of glass

The USP provides a classification of glass: Type I, a borosilicate glass; Type II, a soda lime-treated glass; Type III, a soda—lime glass; and NP, a soda—lime glass not suitable for containers for parenterals.

Type I glass is composed, principally, of silicon dioxide and boric oxide, with low levels of the migratory oxides, such as sodium and aluminum oxides. It is a chemically resistant glass (low leachability), also having a low thermal coefficient (CoE) of expansion as compared to soda—lime glass. The lower the thermal CoE, the more dimensionally stable the glass against thermal expansion stress that can result in cracking.

Types II and III glass are composed of relatively high proportions of sodium oxide and calcium oxide. This reduces the chemical resistance of glass. Types II and III glass melt at a lower temperature, are easier to mold into various shapes, and have a higher thermal coefficient of expansion. Type II glass 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. Although it remains intact, this surface neutralization increases substantially the chemical resistance of the glass. However, repeated exposures to sterilization and alkaline detergents break down this dealkalized surface and expose the underlying soda—lime compound.

The glass types are determined from the results of three USP tests. The glass grains test distinguishes Type I glass from Types II and III. The surface glass test classifies Types I and II to have high hydrolytic resistance and Type III to be moderately resistant. The surface glass test is used only for Type II glass and is performed on the whole container, due to the dealkalized surface; the glass grain test is performed on powdered glass, which exposes internal surfaces of the glass compound. The results are based on 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 glass grains test challenges the leaching potential of the interior structure of the glass, whereas the surface glass test challenges only the intact surface of the container. There is an additional surface etching test which to distinguish between Types I and II glass and determines whether high hydrolytic resistance is due to inner surface or chemical composition of glass containers. The test includes pretreatment of containers with mixture of 1:9 hydrofluoric acid and hydrochloric acid followed by surface glass test procedure.

Glass can be the source/cause of leachables/extractables, particulates due to glass lamellae formation, adsorption of formulation components especially proteins and cracks/scratches.

Leaching of ions from the glass container particularly at high pH may result in chemical instability, formation

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of particulate, or change in pH of solution. Sodium and silicon constitute major *extractable*. Potassium, barium, calcium, and aluminum leach in small amounts, while iron, magnesium, and zinc are trace extractable. The presence of a metal chelating agents, such as EDTA and citrate, in the formulation is of special concern.

Delamination, or glass particulate formation, is caused by chemical attack on the glass matrix by the formulation, resulting in weakening of the glass structure and dislodgement of flakes from the glass surface (Iacocca et al., 2010). These fragments can be difficult to detect due to subvisible size. Higher pH values >8, high sodium chloride content or specific buffer components, known to attack or partially solubilize of the glass component may enhance delamination. Careful control of process parameters such as lower heat levels during the conversion process of glass formation may be critical. Ammonium sulfate–treated glass containers are also known to be more susceptible to delamination.

Adsorption of drug solution and consequent loss of potency of drug product is a primary concern of container/solution compatibility and must be rigorously and formally evaluated during solution/container evaluation and stability studies. Small-volume products, products formulated at low concentration of therapeutic proteins carry a higher risk for loss of potency due to adsorption and should be carefully evaluated for drug loss (Hoehne et al., 2011). *Cracks* and *scratches* on glass containers can best be minimized by strict controls and high-quality 100% inspection practices by both glass and final product manufacturers.

Schott has developed a technology, which coats the inner surface of Type I glass vials with an ultrathin film of silicon dioxide (Walther et al., 2002). Such treated glass is especially useful for preventing interaction with drug products having high pH values or formulations with complexing agents.

29.6.1.2 Physical characteristics of glass containers

Commercially available containers vary in size from 0.5 to 1000 mL. Sizes up to 100 mL may be obtained as syringes, cartridges, ampoules, and vials. Bottles are used for intravenous and irrigating solutions. 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 optically clearer and have a thinner wall than molded containers (Fig. 29.1). Compared to molded glass, tubing glass also has better wall and finish dimensional consistency and no seams, is easier to label, weighs less, facilitates inspection, and has lower tooling costs. Tubing glass is preferable to molded glass for freeze-dried products, due to more efficient heat transfer from the shelf into the product. Molded containers are uniform in external dimensions, stronger, and heavier. Also, molded glass is not as susceptible to leachables and delamination, because the glass formation temperatures to vaporize and condense the alkali components of the glass are not as high as for tubing container manufacture (Swift, 2016). Scoring or applying a ceramic paint at the neck with a different coefficient of thermal expansion facilitates easy

FIGURE 29.1 Various types of glass containers for packaging of parenterals.

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opening of ampoules. Modifications of design such as double-chambered vial, or wide-mouth ampoules with flat or rounded bottoms are available to meet a particular need like for freeze-dried product or filling with dry materials or suspensions, respectively.

Preparations that are light-sensitive should be in amber glass containers or by employing opaque cartons labeled to remain on the container. The amber color is imparted to the glass by the incorporation of heavy metals, mostly iron and manganese, leaching of these ions can catalyze oxidative degradation reactions. Silicone coatings are sometimes 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 restricted in size to limit the number of withdrawal of doses and the risk of contamination of the contents. 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 and it cannot be reused.

Due to concerns for user safety and glass particulate matter generated while breaking of glass, glass sealed ampoules are no longer glass containers of choice for new small-volume injections in the United States.

29.6.2 Plastic

Large-volume parenterals, ophthalmic solutions, small-volume parenterals are nowadays being packed in containers made of thermoplastic. Plastic is also being used in packaging of novel injectables like implants. Plastic is nonbreakable and has less weight than glass. The flexible bags of polyvinyl chloride or select polyolefins (Lohse, 2000), currently in use for large-volume intravenous fluids, have the added advantage that the wall simply collapses as the solution flows out of the bag.

Permeation of vapors and other molecules such as oxygen from air through container walls, leaching of constituents of plastic into the product, and sorption of ingredients from formulation on to the plastic material are principal concerns while using plastic. Overwraps could be used for large volume solutions in PVC bags to prevent loss of water during storage. Plastics used for parenteral packaging are preferred to have as few additives as possible to reduce leaching. Insulin and other proteins, vitamin A acetate, and warfarin sodium have been shown to be adsorbed on PVC bags and tubing, when these drugs were administered as IV admixtures. Proper compatibility evaluation is therefore necessary before choosing the appropriate plastic material for packaging. Most plastic materials have the disadvantage of not being as clear as glass, and, therefore, inspection of the contents is impeded. However, recent technologies evidenced by plastic resins, such as CZ (polycyclopentane, Daikyo Seiko) and Topas COC (cyclic olefin copolymer, Ticona) have overcome this limitation.

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. 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.

29.6.3 Rubber closures

Rubber closures are used as primary closures for the vial and sealed by an aluminum cap that holds closure in place (Fig. 29.2). The closure assembly allows introduction of a needle from a hypodermic syringe into a multiple-dose vial and facilitates resealing as soon as the needle is withdrawn. This principle is also 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.

The desirable properties of rubber closure include elasticity, hardness, low tendency to fragment, and low permeability to vapor transfer. The elasticity is important in establishing snug fit with the lip and neck of a vial or other opening and in resealing by springing back to

FIGURE 29.2 Aluminium seals for stoppering vials and rubber closures (Courtesy Janssen Pharmaceutica, Belgium).

original state after withdrawal of a hypodermic needle. The hardness should provide firmness but not excessive resistance to the insertion of a needle through the closure, and minimal fragmentation of pieces of rubber should occur as the needle penetrates through the closure. Although vapor transfer cannot be completely prevented, it is possible to control the degree of permeability through appropriate selection of the type of closures. Maintaining its properties after exposure to oxygen, heat, light, moisture, solvents are desirable in view of pharmaceutical applications of rubber closures.

Rubber closures are composed of mix of ingredients (Table 29.5) such as elastomer, vulcanizing agent, accelerator, activator, antioxidant, plasticizer, and fillers. The elastomer primarily used is synthetic butyl or halobutyl rubber. Natural rubber is also used, but, if it is natural rubber latex, then the product label must include a warning statement, as latex exposure may result in allergic reactions.

The mix of ingredients is plasticized at an elevated temperature on milling machines. The plasticized mixture is placed in molds and vulcanized (cured) under high temperature and pressure. During vulcanization 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. Table 29.5 provides examples of rubber-closure ingredients.

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 (Table 29.5) may leach into the product solution, resulting in incompatibilities that must be evaluated. Further, some ingredients like accelerators must be evaluated for potential toxicity.

To reduce the problem of leachables, special polymer coating or laminates have been applied to the product contact surfaces of closures, the most successful being Teflon (polytetrafluoroethylene) and Flurotec (copolymer of tetrafluoroethylene and ethylene) (Sacha et al., 2010). Although rubber coatings do reduce the potential for extractables/leachables, they may have disadvantages of not flowing as easily during high-speed filling operations and may not have the same container-closure integrity as uncoated stoppers with vial openings.

The physical shape of some typical closures may be seen in Fig. 29.3. 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 underneath 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 are usually designed for pouring.

Rubber closures must move easily with minimal friction through a closure hopper and other stainless steel passages in a filling and sealing machine, until they are fitted onto the filled vials. Traditionally, rubber materials are "siliconized" to produce such lubrication. However, advances in rubber-closure technologies

TABLE 29.5 Additives in rubber closures.

Ingredient	Examples
Elastomer	Natural rubber, butyl rubber, halobutyl rubber, silicone rubber, neoprene
Curing or vulcanizing agent	Sulfur, peroxides
Accelerator	Dithiocarbamate, amine, thiazole, thiuram
Activator	Zinc oxide, stearic acid
Antioxidant	Dilauryl thiodipropionate
Plasticizer/lubricant	Paraffinic oil, silicone oil, phthalates, organic phosphates
Fillers	Carbon black, aluminum silicate, magnesium silicate, barium sulfate
Pigments	Inorganic oxides, carbon black, organic dyes

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FIGURE 29.3 Rubber closures for vials.

have introduced special polymer coating that eliminates the need for siliconization.

29.6.4 Needles

Needles are hollow devices composed of stainless steel or plastic. Needle lengths range from 0.25 to 6 in. Needle size is referred to as its gauge (G), or the outside diameter (OD) of the needle shaft. Needle shape includes regular, short bevel, intradermal, and winged. Needle shape is defined by one end of a needle enlarged to form a hub with a delivery device, such as a syringe, or other administration devices. The other end of the needle is beveled, meaning 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 dictates the length and size of the needle used. 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 (e.g., radiology, anesthesia, biopsy, cardiovascular, ophthalmic, transfusions, tracheotomy) have their own peculiar types of needle preferences.

29.7 Pyrogens (endotoxins) and depyrogenation

The most potent pyrogenic substances (endotoxins) are constituents of the cell wall of Gram-negative bacteria (e.g., *Pseudomonas* sp., *Salmonella* sp., *Escherichia coli*). Gram-positive bacteria produce peptidoglycans, whereas fungi product β-glucans, both of which can cause nonendotoxin pyrogenic responses. Endotoxins are LPS that exist in high molecular weight aggregate forms. However, the monomer unit of LPS is less than 10,000 Da, enabling endotoxin to easily pass through sterilizing 0.2 μm filters. The lipid portion of the molecule is responsible for the biological activity. LPS targets circulating mononuclear cells (monocytes and macrophages) that produce proinflammatory cytokines, such as interleukin 2, interleukin 6, and tissue necrosis factor. Exotoxin A, peptidoglycan, and muramuyl peptides also mimic the activity of LPS and induce cytokine release. Pyrogens, when present in parenteral drug products and injected into patients, can cause fever, chills, pain in the back and legs, and malaise. They can cause serious discomfort and, in the seriously ill patient, shock-like symptoms that can be fatal. Intrathecal administration is most hazardous if contaminated with pyrogens followed by intravenous, intramuscular, and subcutaneous.

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. Therefore WFI should be used for compounding the product or rinsing product contact surfaces, such as tubing, mixing vessels, and rubber closures. Rinsed equipment and supplies are left wet and improperly exposed to the environment, there is a high risk they will become pyrogenic. WFI 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

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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 reduces contamination, and subsequent dry-heat treatment can render contaminated equipment suitable for use. Aseptic processing guidelines require validation of the depyrogenation process by demonstrating at least 3-log reduction in an applied endotoxin challenge. Solutes may also be a source of pyrogens. 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.

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 minutes. Exposure of 650°C for 1 minute or 180°C for 4 hours, likewise, will destroy pyrogens. The usual autoclaving cycle will not do so. Heating with strong alkali or oxidizing solutions destroys 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 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 remove pyrogens from water. Also, although reverse osmosis (RO) membranes will eliminate them, the most reliable method for their elimination from water is distillation. 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. Although ultrafiltration now makes pyrogen separation on a molecular-weight basis possible and the process of tangential flow is making large-scale processing more practical, use of this technology is limited, except in biotechnological processing.

Through understanding the means by which pyrogens may contaminate parenteral products, their control becomes more achievable. 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. Preferably, no more products should be prepared than can be processed completely within one working day, including sterilization.

29.8 General considerations—production facilities

Production of a sterile product of high quality requires integrated effort of different departments and facility in which the activities are undertaken is of paramount importance. The production facility must be designed, constructed, and operated properly for the manufacture of a high-quality sterile product. Production facility of a quality product includes functional areas in which following activities are undertaken: (1) warehousing or procurement; (2) compounding/formulation; (3) Cleaning and sterilization of containers, closures, equipment preparation; (4) filtration and sterile receiving; (5) aseptic filling, stoppering, lyophilization (if warranted); and (6) packaging, labeling, and quarantine.

Although the aseptic area must be adjacent to support areas, to ensure efficient flow of components, barriers must be provided to minimize ingress of contaminants. Such barriers may consist of sealed walls, manual or automatic doors, air-lock pass-throughs, ports of various types, or plastic curtains.

29.8.1 Flow plan

General activity flowchart could be as shown in Fig. 29.4. Depending on the product, either terminal sterilization in its final container or aseptic filling may be adopted followed by freeze-drying if necessary. After review of the batch records, and the product found to comply with its release specifications, it is moved to the finishing area for final release.

29.8.2 Classification of clean areas

Due to high-quality requirements of parenteral products, in order to minimize risks of microbiological contamination, and of particulate and pyrogen, area in which these products are manufactured should meet standards of cleanliness. Table 29.6 compares US and European classifications and clean-room designations assigned by the International Society of Pharmaceutical Engineers. Table 29.7 prescribes specifications for the environments (clean rooms) in which these products are manufactured. The table provides the International Standards Organization (ISO) 14644 Classification of Cleanroom Particle Limits (more specifically) for class 5−8 adhered to by the parenteral manufacturing industry. Table 29.7 also gives the maximum allowed number of airborne particles/ft^3 or particles/m^3 of 0.5 μm or larger size and, for

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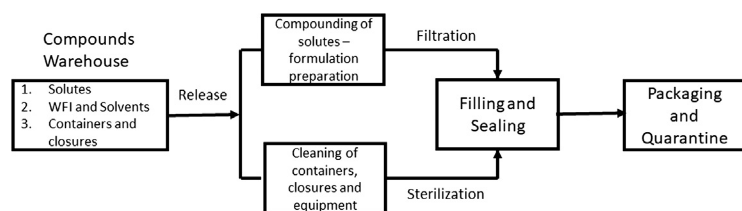

FIGURE 29.4 General flow of operations in parenteral manufacturing.

TABLE 29.6 ISO 14644 classification of cleanroom particle limits (ISO, 2015).

ISO classification	Maximum concentration limits (particles per cubic meter of air) for particles ≥ the sizes per each column				
	0.1 μm	0.3 μm	0.5 μm	1 μm	5 μm
5	100,000	10,200	3520	832	–
6	1,000,000	102,000	35,200	8320	293
7	–	–	352,000	83,200	2930
8	–	–	3,520,000	832,000	29,300
9	–	–	35,200,000	8,320,000	293,000

ISO, International Standards Organization.

TABLE 29.7 Clean room Classifications (US-FDA Guidance for industry, 2004; EU Guidelines to Good Manufacturing Practice, 2008).

European grade	US classification	Maximum no. of particles per m^3 ≥ 0.5 μm	Maximum no. of particles per m^3 ≥ 5 μm	Air sample (CFU/m^3) (During operation)	Microbiological settling plates action levels (diameter 90 mm; CFU/4 h) (During operation)
A	100	3520	20	<1	<1
B	100	3520	29	10	5
C	10,000	352,000	2900	100	50
D	100,000	3,520,000	29,000	200	100

Europe, 5.0 μm or larger size. The classifications used in pharmaceutical practice normally range from Class 100,000 (Grade D) to Class 100 (Grade A).

European standards differ from US standards, as European standards:

1. use Grades A, B, C, and D classifications, rather than Class 100, 1000, etc.;
2. use particle and microbial limits per cubic meter, rather than per cubic foot;
3. require particle measurements at 5 μm in addition to 0.5 μm in Grade A and B areas; and
4. differentiate area cleanliness in operation and "at rest."

For the sake of convenience, hereafter the chapter uses Class 100, /1000, /10,000, /100,000 designations, although it is recognized that the use of grades or ISO numbers is more contemporary.

29.8.3 Laminar-flow systems

The required level of air quality in aseptic areas has been made possible by the use of laminar airflow at a uniform velocity, 100 ft./min ± 20%, in parallel lines, employing a

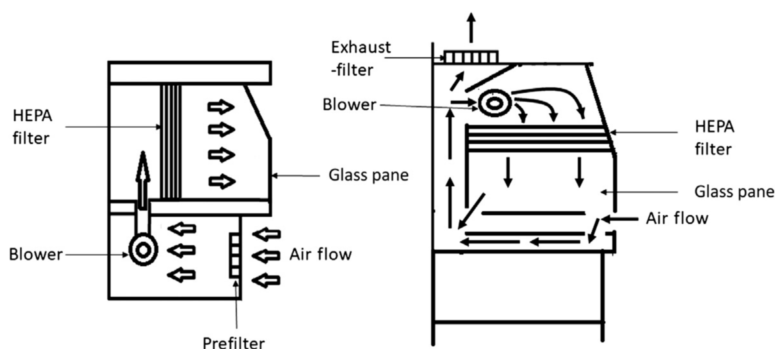

FIGURE 29.5 Horizontal and vertical laminar air flow system.

high-efficiency particulate air (HEPA) filter, in such a way that the orientation for the direction of airflow can be horizontal or vertical (Fig. 29.5) and may involve a limited area, such as a workbench, or an entire room.

Critical activities, wherein the product or product contact surfaces may be exposed to the environment, even for a brief period of time, must be carried out in area that meets Class 100 clean-room standards. Vertical flow has advantage over the horizontal one as any contamination introduced upstream will be blown downstream and not toward working site or operator. For most large-scale operations, a vertical system is much more desirable. Checks of the air stream should be performed initially and usually every 6 months, to ensure no leaks through or around the HEPA filters.

Materials support area is usually a Class 100,000 clean room. The ceiling, walls, and floor should be constructed of impervious materials like vinyl or epoxy-sealing coat that provides a continuous surface free from all holes or crevices. All such surfaces can be washed at regular intervals for thorough cleaning. These areas should be provided with exhaust facility for the comfort of personnel. Precautions must be taken to prevent the accumulation of dirt and the growth of microorganisms due to the high humidity and heat. In this area, preparation for the filling operation, such as cleaning and assembling equipment, is undertaken. Adequate sink and counter space must be provided. This area must be cleanable, and the microbial load must be monitored and controlled. Precautions must also be taken to prevent deposition of particles or other contaminants on clean containers and equipment, until they have been properly wrapped/covered preparatory to sterilization and depyrogenation.

The formula is compounded in the compounding area. Control of microorganisms and particulates should be more stringent than in the materials support area. Dust generated from weighing and compounding operations should be controlled. Cabinets and counters, preferably, of stainless steel should fit snugly to walls. Other furniture, and the ceiling, walls, and floor should be similar to those for the materials support area.

It is preferable to have an area classified from Class 1000 to 10,000 in a buffer area between a Class 100 and Class 100,000 area. The design differential pressure as measured between different classified rooms should be a minimum 10−15 Pa (0.04−0.06 in. water gauge, w.g.), with all doors in their normal closed positions. Air change rate is another important clean-room design parameter. For Class 100,000 (ISO 8) supporting rooms, airflow sufficient to achieve at least 20 air changes per hour is typically acceptable. Significantly higher air change rates are normally needed for Class 10,000 and Class 100 areas.

Aseptic area is designed to provide an environment where a sterile product may be exposed to the environment for a brief period during filling and sealing, without becoming contaminated. The aseptic area requires maximum microbial and particulate control. To achieve Class 100 conditions, HEPA filters are required with the filtered air provided at a uniform velocity, 100 ft./min ± 20%, in parallel lines, that is, laminar airflow. The ceiling, walls, and floor must be sealed to facilitate washing and sanitization with a disinfectant. All counters should be constructed of stainless steel and hung from the wall, to prevent accumulation of dirt. All light fixtures, utility service lines, and ventilation fixtures should be recessed in the walls or ceiling to eliminate ledges, joints, and other locations for the accumulation of dust and dirt. The product should be received into the area through hose lines usually following filtration. Large mechanical equipment located in the aseptic area should be housed as completely as possible within a stainless steel cabinet, to seal the operating parts with particulate producing tendencies from the aseptic environment. Further, all such equipment parts should be located below the filling line. Mechanical parts that will contact the parenteral product should be demountable, so they can be cleaned and sterilized. The area must be adjacent to support areas and to minimize ingress of contaminants; barriers are required in the form of sealed walls, doors, air-lock pass-throughs, ports, or plastic curtains.

Personnel entering the aseptic area should enter only through an airlock. They should be attired in sterile coveralls with sterile hats, masks, goggles, foot covers, and double gloves. Movement within the room should be minimal, and in-and-out movement restricted during a filling procedure. The requirements for room preparation and the personnel may be comparatively relaxed, if the product is to be sterilized terminally in a sealed container.

29.8.4 Air handling and heating, ventilating, and air conditioning systems

Air is drawn into clean rooms by the heating, ventilating, and air conditioning systems by a series of treatments.

In one of the systems, air from the outside, first, is passed through a prefilter, usually of glass wool, cloth, or shredded plastic, to remove large particles and subsequently through an electrostatic precipitator to remove charged particles by attraction to oppositely charged plates. The air then passes through the most efficient cleaning device, a HEPA filter. HEPA filters are defined as 99.99% or more efficient in removing 0.3 μm particles, from the air. Air conditioning and humidity control are incorporated into the system for personnel comfort. The clean, aseptic air is introduced into the Class 100 area at the highest speed to maintain positive pressure, which prevents outside air from rushing into the aseptic area through cracks, temporarily open doors, or other openings for return air and pressure differential. The pressure is reduced successively so that the airflows from Class 100 area to less critical areas for return to air handling system. At the intake end of the system, usually 25% fresh air is continually introduced for comfort and needs of the personnel.

29.8.5 Isolation/barrier technology

Isolator or barrier technology used in the pharmaceutical industry ranges from simple screens to restricted access barriers (RABs) to full isolation systems. The objective of these designs is to isolate aseptic operations from personnel and the surrounding environment. Sterility tests are now almost exclusively conducted within isolators. Isolation technology in various formats has been adapted to automated, large-scale, aseptic filling operations (Lysfjord, 2009). An example of an isolator used in aseptic operation is shown in Fig. 29.6.

Use of isolation technology has been very promising by providing significantly enhanced control of the aseptic processing environment. Isolators are enclosed, usually positively pressurized units with HEPA filters, supplying ISO 5 airflow in a unidirectional manner to the interior. Air recirculates by returning it to the air handlers through sealed ductwork. Cleaning can be manual or automated (clean-in-place). Access to an isolator is through glove ports and sterile transfer systems. Isolators can be located in an ISO 8 or better environment. The operations are performed within windowed, sealed walls, with operators working through glove ports.

Conversion from conventional filling of existing production lines to filling within an isolator is time and cost prohibitive. Modifications of isolation systems, RABs, have been applied. RABs offer a combined physical (e.g., plexiglas partitions) and aerodynamic barrier, ideally controlled by positive pressure with clean-air filtration, providing air exchanges and particulate clean-up for an ISO 5 critical process zone. RABs come in two types—"passive," where there is no in-process open-door access; and "active," where, under certain validated system configurations and control conditions, access may be included. The area outside the RAB can be maintained at a slightly

FIGURE 29.6 Isolator used in aseptic operation (Courtesy Janssen Pharmaceutica, Belgium)

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lower level of cleanliness than that inside, perhaps Class 10,000 down to Class 1000.

Concern over the level of sterility assurance in aseptic processing, incidences of product recall, safety considerations for cytotoxic compounds, heat sensitive products from biotechnology, and requirements of smaller batch production for many biopharmaceutical drugs have together contributed to increased importance and utilization of barrier isolator technology. Isolators not only protect the product from potential human contamination but also protect the human from potential toxic effects of exposure to the drug product, like cytotoxic drug products.

29.8.6 Cleaning and sanitation

Materials of construction for sterile product production facilities must be smooth, cleanable, and impervious to moisture and other damage. Frequency of cleaning, ranging from daily to monthly, should be decided depending on the location and its relation to the most critical Class 100 areas. Tools used should be designed for clean-room use, reserved for the area, should not generate particles and preferably, sterilizable.

Liquid disinfectants (sanitizing agents) should be selected carefully based on their reliable activity against inherent environmental microorganisms. They should never be considered as substitutes but recognized as support to good housekeeping. They should be rotated with sufficient frequency to avoid the development of resistance by microorganisms. The sanitizing solution should be sterilized prior to use.

Ultraviolet light rays of 237.5 nm wavelength, as radiated by germicidal lamps, are an effective surface disinfectant. However, it must also be noted that they are only effective, if they contact the target microorganisms at a sufficient intensity for adequate time. The limitations of their use and the toxic effect on epithelium of human eyes should be recognized. It is stated that an irradiation intensity of 20 μw/cm^2 is required for effective antibacterial activity.

29.9 Personnel

A well-designed, maintained, and operated aseptic process minimizes personnel intervention. To ensure maintenance of product sterility, it is critical for personnel involved in aseptic activities to use aseptic technique at all times. Personnel working must be neat, orderly, and reliable. They should be in good health. If personnel show symptoms of a head cold, allergies, dermatological conditions, or similar illness, they should not be permitted in the aseptic area, until complete recovery. Healthy personnel present in clean rooms also shed particles; effective training and proper gowning must be undertaken to reduce particle shedding (Howorth, 1988). Formal training in the principles and techniques of aseptic processing must be imparted and periodically evaluated (Groves and Murty, 1995). Retraining should be performed on a regular schedule to enhance the maintenance of the required level of expertise. Supervisors should make aware of the personnel the unique requirements of aseptic procedures and their role in achieving quality of the product.

Uniforms should consist of coveralls for both men and women, hoods to cover the hair completely, face masks, and Dacron or plastic boots. Sterile rubber or latex-free gloves are also required for aseptic operations, preceded by thorough scrubbing of the hands with a disinfectant soap. In addition, goggles are required for complete body coverage. For use in the aseptic area, fresh, sterile uniforms should be used after every break period. Gowning and degowning rooms should be provided separately. Dacron or Tyvek uniforms are effective barriers to discharged body particles (viable and nonviable), are essentially lint-free, and are reasonably comfortable. Air showers are sometimes directed on personnel entering the processing area to blow loose lint from the uniforms.

29.10 Environmental control evaluation

The tests for environmental control evaluation consist of counting viable and nonviable particles suspended in the air or settled on surfaces in the workspace. A baseline count is determined when the facility is operating under controlled conditions to establish the optimal test results expected. To measure the total particle content in an air sample, electronic particle counters are available, operating on the principle of the measurement of light scattered from particles as they pass through the cell of the optical system. These instruments cannot differentiate between viable (e.g., bacterial and fungal) and nonviable particles. Viable particles are fewer in number than nonviable particles and are detectable as colony-forming units (CFUs) after a suitable incubation period at, for example, 30°C−35°C for up to 48 hours.

A widely used method for microbiological sampling consists of the exposure of nutrient agar culture plates to the settling of microorganisms from the air. This method is very simple and inexpensive to perform, but will detect only those organisms that have settled on the plate; therefore it does not measure the number of microorganisms in a measured volume of air (a nonquantitative test). Locations for sampling should be planned to reveal potential contamination levels that may be critical in the control of the environment. Examples include the filling room, gowning room, high-traffic sites in and out of the filling area, the penetration of conveyor lines through walls, and sites near the inlet and exit of the air system.

The slit-to-agar sampler draws, by vacuum, a measured volume of air through an engineered slit, causing

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the air to impact the surface of a slowly rotating nutrient agar plate. Microorganisms adhere to the surface of the agar and grow into visible colonies counted as CFUs, since it is not known whether the colonies arise from a single microorganism or a cluster.

If the results exceed selected alert or action levels, a plan of action must be put into operation to determine if or what corrective and follow-up measures are required.

29.11 Process simulation testing by media fill

An aseptic processing operation should be validated using a microbiological growth medium in place of the product. This process simulation, also known as a media fill, includes preparation and sterilization of trypticase soya broth and filling sterile containers with this broth, to closely simulate the same exposure that the product itself will undergo in a filling process. The important consideration is that the studies should simulate all factors that occur during the normal production of a lot (Food and Drug Administration, 2004).

Media fills are conducted when a new filling line or new product container is introduced. For initial qualification of a line or product, three consecutive, separate, and successful media fill runs must take place. The FDA stresses that three is a minimum number of runs. Today, the term "successful" means there is no growth in any of the units filled with sterile broth. A generally acceptable starting point for run size is in the range of 5000−10,000 U. Typically, for each filling line and process, the filling operation is validated for the smallest and largest container size that will be used.

After initial qualification, media fills are then conducted on a periodic basis, semiannually on the same filling line, to ensure that conditions that existed during the initial qualification have been maintained. The culture media used for each media fill exercise must be tested to ensure it will support the growth of microorganisms. Inspection of media filled units, before and after incubation, is conducted by individuals trained as qualified inspectors and certified by the QC unit. Most media fills are a minimum of 3 hours; some may be as long as 24 hours.

29.12 Manufacturing of parenteral product

The preparation of a parenteral product begins with procurement of materials. Procurement encompasses selecting and testing the raw-material ingredients confirming to specifications and the containers and closures for the primary and secondary packages. Processing includes cleaning containers and equipment to validated specifications, compounding the solution (or other dosage form), filtering the solution, sanitizing or sterilizing the containers and equipment, filling measured quantities of product into the sterile containers, stoppering (either completely or partially for products to be freeze-dried), freeze-drying, terminal sterilization (if possible), and final sealing of the final primary container. Packaging normally consists of the labeling and cartoning of filled and sealed primary containers. Each step of the process involves checks and tests to ensure that the required specifications at the respective step are being met. The QC unit is responsible for reviewing the batch history and performing the release testing required to clear the product for shipment to users.

Each step in the *production process* must be controlled very carefully, so the product has its required quality. Each process should be validated to ensure it is accomplishing what it is intended to do. The validation of processes requires extensive and intensive effort to be successful and is an integral part of cGMP requirements.

29.12.1 Manufacturing of water for injection

Water is the most commonly used excipient in parenteral products. Water is the most widely used substance, raw material, or starting material in the production, processing, and formulation of pharmaceutical products. Control of the quality of water, including microbiological and chemical quality, throughout the production, storage, and distribution processes, is a major concern. Pharmaceutical water production, storage, and distribution systems should be designed, installed, commissioned, qualified, and maintained to ensure the reliable production of water of an appropriate quality.

USP prescribes stringent specifications to be met for water to be used in manufacturing. WFI can be prepared using two technologies—distillation and RO/ultrafiltration. The processes encompass means of removing solid chemicals and microorganisms and pryogens from water. Distillation is a process of converting water from a liquid to its gaseous form (steam). Since steam is pure gaseous water, all other contaminants in the feedwater are removed. The unit consists of a boiler (evaporator), containing feedwater (distilland); a source of heat to vaporize the water in the evaporator; a headspace above the level of distilland, with condensing surfaces for refluxing the vapor, thereby returning nonvolatile impurities to the distilland; a means for eliminating volatile impurities (demister/separation device) before the hot water vapor is condensed; and a condenser for removing the heat of vaporization, thereby converting the water vapor to a liquid distillate. The source water must be pretreated using processes such as chemical softening and filtration. The baffles (condensing surfaces) determine the effectiveness of refluxing. They should be designed for efficient

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removal of the entrainment at optimal vapor velocity, collecting and returning the heavier droplets contaminated with the distilland.

There are two basic types of WFI distillation units—the vapor-compression still and the multiple-effect still.

29.12.1.1 Compression distillation

These units are available in large capacities and operate at low energy consumption. Source water in evaporator is heated to boiling externally. The vapor produced in the tubes is separated from the entrained distilland in the separator and conveyed to a compressor that compresses the vapor and raises its temperature to approximately 107°C. It then flows to the steam chest, where it condenses on the outer surfaces of the tubes containing the distilland; the vapor is, thus, condensed and drawn off as a distillate, while giving up its heat to bring the distilland in the tubes to the boiling point.

29.12.1.2 Multiple-effect stills

The multiple-effect still is also designed to conserve energy and water usage. In principle, 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. Steam from an external source is used in the first effect to generate steam under pressure from feedwater; 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 will also be affected by the inlet steam pressure. These stills have no moving parts and operate quietly.

29.12.1.3 Reverse osmosis

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. The pores of the membrane allow movement of water but restrict the movement of hydrated chemical ions, organic molecules, and microorganisms. Membranes, usually composed of cellulose esters or polyamides, are selected to provide an efficient rejection of contaminant molecules in raw water. The molecules most difficult to remove are small inorganic molecules, such as sodium chloride.

Whichever system is used for the preparation of WFI, validation is required to ensure that the system, consistently and reliably, produces the chemical, physical, and microbiological quality of water required.

29.12.2 Storage and distribution of water for injection

In large operations, WFI is stored in a holding tank of 316 SS/lined with glass or pure tin having a capacity of several thousand gallons. USP requires that the WFI be held at a temperature too high for microbial growth, normally a constant 80°C. The USP also permits the WFI to be stored at room temperature but for a maximum of 24 hours. Such a system requires frequent sanitization to minimize the risk of viable microorganisms being present. 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.

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, due to the risk of bacterial buildup on the filters and the consequent release of pyrogenic substances.

29.12.3 Cleaning of containers

New containers and equipment are contaminated with dust, fibers, and other materials from atmosphere, cartons, manufacturing process, and human hands and therefore must be cleaned meticulously. In case of equipment, residues from previous use must be removed before reuse. Equipment should be reserved exclusively for parenteral preparations preferably for specific products to reduce the risk of contamination.

Machines available for cleaning new containers for parenteral products vary in from a small, hand loaded, rotary rinsers to large, automatic washers. Validation of cleaning procedures includes drawing either swab samples or rinse samples obtained surfaces most difficult to clean and analyzing for residual API.

The cycle of treatments to be employed varies with the condition of the containers to be cleaned. In general, loose debris can be removed by vigorous rinsing with water. The containers are inverted on spindles and carried through a series of rinses by introduction of the jet stream in one rotation. Sometimes, only an air rinse is used for new containers, if only loose debris is present. Detergent treatment is rarely used due to the risk of leaving detergent residues. However, alternating hot and cold water treatment in the cycle is usually employed to aid, by expansion and contraction, loosening of debris that may be adhering to the

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container wall. Ultraclean air or WFI is used for final rinses so that no particulate residues are left.

Wet, rinsed containers must be protected from dust or other particulate either by a laminar flow of clean air until covered, within a stainless steel box, or within a sterilizing tunnel. Wet, clean containers should be dry-heat sterilized, as soon as possible after washing to reduce microbial contamination. In continuous, automated line processing, the clean, wet containers are protected by filtered, laminar-flow air from the rinser, through the tunnel, and until they are delivered to the filling line.

29.12.4 Cleaning of closures

The rough and convoluted surface of rubber closures renders them difficult to clean. Gentle agitation in a hot solution of a mild water softener or detergent is usually employed. The closures are removed from the solution and rinsed thoroughly with filtered WFI for effective removal of loosened debris. The objective is to remove debris accumulated on the surface and leachable constituents. The wet closures are carefully protected from environmental contamination, sterilized, usually by steam sterilization, and stored in closed containers, until ready for use. It is the cleaning and final, thorough rinsing with WFI that must remove pyrogens. If the closures must be dry for use, they may be subjected to vacuum drying at a temperature in the vicinity of 100°C. Some freeze-dried products require extremely dry closures to avoid desorption of moisture from the closure into the moisture-sensitive powder during storage. This may require long drying times, following steam sterilization.

The equipment used for washing large numbers of closures is usually an agitator or horizontal basket-type automatic washing machine. Vigorous action of these machines is associated with the risk of particulate generation. Gental agitation with air bubbles, basket rotation with spray rinsing, or heating the closures in kettles in detergent solution, followed by prolonged flush rinsing may also be employed as mild cleaning. The final rinse should always be with low-particulate WFI.

29.12.5 Cleaning of equipment

All equipment should be disassembled and surfaces should be scrubbed thoroughly using an effective detergent. Particular attention should be paid to joints, crevices, screw threads, and other debris collecting structures. Exposure to a stream of clean steam aids in loosening residues from the walls of stationary tanks, spigots, pipes, and similar structures. Thorough rinsing with distilled water should follow the cleaning steps.

Due to the inherent variation in manual cleaning and the difficult accessibility of large stationary tank, clean-in-place systems, have been developed. Such an approach involves designing the system, normally of stainless steel, with smooth, rounded internal surfaces and without crevices. Cleaning is accomplished with high-pressure spray balls or nozzles delivering hot detergent solution from tanks captive to the system, followed by thorough rinsing with WFI. The system is often extended to allow sterilizing-in-place, to accomplish sanitizing or sterilizing as well.

Rubber tubing, rubber gaskets, and other rubber parts may be washed in a manner as described for rubber closures. However, due to the relatively porous nature of rubber compounds and the difficulty in removing all traces of chemicals from previous use, reuse of rubber or polymeric tubing is not recommended. Rubber tubing must be left wet when preparing for sterilization by autoclaving.

29.12.6 Product preparation/compounding

Each batch formula sheet should be prepared from the master formula and confirmed for accuracy. All measurements of quantities should be made as accurately as possible and checked by a second qualified person.

Care must be taken that equipment is not wet to avoid dilution of the product significantly or a physical incompatibility in the case of anhydrous products. The order of mixing of ingredients, homogeneity of the product, particularly those of large volume, where attaining homogeneity requires considerable mixing time, the adjustment of pH by the addition of an acidifier or alkalizer may affect the quality of product significantly. Compounding problems may vary with batch scale and it should be recognized that small multiple errors may be additive.

Parenteral dispersions, including colloids, emulsions, and suspensions, provide particular problems. In addition to the problems of achieving reduction in particle size under aseptic conditions, the uniformity of suspension is required to be maintained during preparation, transfer, and subdividing operations.

Biopharmaceuticals are usually extremely sensitive to temperature, mixing time and speed, order of addition of formulation components, pH adjustment and control, and contact time with various surfaces, such as filters and tubing. Development studies must include evaluation of manufacturing conditions to minimize adverse effects of the process on the activity of the protein.

Protein aggregation can result from nucleation on foreign particles, originating from the manufacturing process [i.e., mixing tanks, process tubing, filter systems, filling machines (Tyagi et al., 2009) or any other stainless steel, rubber, glass, or plastic surface (Sharma, 2007)] and from the container/closure system (Tyagi et al., 2009). It is well known that silicone oil, used as a lubricant for rubber

closures, on vials, on rubber plungers, in prefilled syringes, and to coat the inner surface of glass syringes and cartridges can also induce protein aggregation (Thirumangalathu et al., 2009; Esfandiary et al., 2008). Further, since thermal sterilization increases the possibility of chemical reactions and degradation, formulation of a stable product is of paramount importance.

29.12.7 Filtration

The primary objective of filtration is to clarify a solution removing particulate matter down to 0.2 μm in size, thus eliminating microorganisms and thereby accomplish cold sterilization. A solution with a high degree of clarity conveys the impression of high quality and purity, desirable characteristics for a parenteral solution.

Filters are thought to function by one or, usually, a combination of (1) sieving or screening, (2) entrapment or impaction, and (3) electrostatic attraction. When a filter retains particles by sieving, they are retained on the surface of the filter. Entrapment occurs when a particle smaller than the dimensions of the passageway (pore) becomes lodged in a turn or impacted on the surface of the passageway. Electrostatic attraction causes particles opposite in charge to that of the surface of the filter pore to be held or adsorbed to the surface. It should be noted that increasing, prolonging, or varying the force behind the solution may tend to sweep particles initially held by entrapment or electrostatic charge through the pores and into the filtrate.

Membrane filters are used exclusively for parenteral solutions, due to their particle-retention effectiveness, nonshedding property, nonreactivity, and disposable characteristics. The most common membranes are composed of cellulose esters, nylon, polysulfone, polycarbonate, polyvinylidine difluoride (PVDF), or polytetrafluoroethylene (Teflon). Nonreactivity does not apply in all cases, more specifically polypeptide products may show considerable adsorption through some membrane filters, but polysulfone and PVDF membranes are majorly nonadsorptive for these products.

Filters are available as flat membranes or pleated into cylinders to increase surface area and, thus, flow rate. Each filter in its holder should be tested for integrity before and after use, particularly if it is being used to eliminate microorganisms. This integrity test is performed either as the "bubble-point test" or as the "diffusion or forward flow" test. The bubble-point test is commonly used on smaller filters. As the surface area of filters becomes large, diffusion of air through the water-filled pores tends to obscure the bubble point. Therefore the diffusion test has been developed as an integrity test for filters with large surface areas. A "pressure hold test" can also be applied to large surface area filters. The filter manufacturer will recommend the best integrity test for the filter system in question.

Although membrane filters are disposable and discarded after use, the holders must be cleaned thoroughly between uses or commercially available disposable assemblies for small, as well as large, volumes of solutions may be used.

29.12.8 Filling

If the product has been sterilized by filtration and will not be sterilized in the final container, the most stringent requirements need to be exercised to prevent contamination, during step of filling in final containers. The process is called an "aseptic fill" and is validated with media fills. During the filling operation, the product is transferred from a bulk container or tank and subdivided into final containers. This operation exposes the sterile product to the environment, equipment, and manipulative technique of the operators, until it can be sealed in the final container. Therefore this operation is carried out with a minimum exposure time, even though maximum protection is provided by filling under HEPA-filtered laminar-flow air within the aseptic area.

Most frequently, the compounded product is in the form of a solution. However, products are also compounded as dispersed systems, for example, suspensions and emulsions and as powders. A liquid is more readily subdivided uniformly and introduced into a container having a narrow mouth than is a solid. Mobile liquids are easier to transfer and subdivide than viscous, sticky liquids, which require heavy-duty machinery for rapid production filling.

Devices are available for filling containers with liquids that have certain common features. Measured volume of the liquid is forced through the orifice of a delivery tube introduced into the container. The size of delivery tube required is influenced by the physical characteristics of the liquid, the desired delivery speed, and the inside diameter of the neck of the container. The tube must enter the neck and deliver the liquid well into the neck to eliminate spillage, allowing sufficient clearance to allow air to leave the container as the liquid enters. The delivery tube should be as large in diameter as possible to reduce resistance and decrease velocity of flow of the liquid and foaming. For smaller volumes of liquids, delivery usually is obtained from the stroke of the plunger of a syringe, forcing the liquid through a two-way valve, providing for alternate filling of the syringe and delivery of mobile liquids. For heavy, viscous liquids, a sliding piston valve, the turn of an auger in the neck of a funnel, or the oscillation of a rubber diaphragm may be used. Also, stainless steel syringes are required with viscous liquids, because

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glass syringes are not strong enough to withstand the high pressures developed during delivery. For large volumes the quantity delivered is measured in the container by the level of fill in the container, the force required to transfer the liquid being provided by gravity, a pressure pump, or a vacuum pump.

The narrow neck of an ampoule limits the clearance possible between the delivery tube and the inside of the neck. Since a drop of liquid normally hangs at the tip of the delivery tube after a delivery, the neck of an ampoule will be wet as the delivery tube is withdrawn, unless the drop is retracted. Therefore filling machines should have a mechanism by which this drop can be drawn back into the lumen of the tube. Since the liquid will be in intimate contact with the parts of the machine through which it flows, these must be constructed of nonreactive materials, such as borosilicate glass or stainless steel. In addition, they should easily be demountable for cleaning and sterilization.

29.12.8.1 Filling of liquids

Volumetric filling, time/pressure dosing, and net weight filling are the three main methods for filling liquids into containers. Volumetric filling machines, employing pistons or peristaltic pumps, are most commonly used.

When high-speed filling rates are desired with accuracy and precision, multiple filling units are often joined in an electronically coordinated machine. When the product is sensitive to metals, a peristaltic-pump filler may be used, because the product comes in contact only with silicone rubber tubing but with comparatively lower filling accuracy.

Time-pressure (or time-gravity) filling machines are gaining popularity in filling sterile liquids. A product tank is connected to the filling system equipped with a pressure sensor. The sensor continuously measures pressure and transmits values to the PLC system controlling the flow of product from tank to filling manifold. Product flow occurs when tubing is mechanically unpinched and stops when tubing is mechanically pinched. The main advantage of time/pressure filling operations is that these filling apparatuses do not contain mechanical moving parts in the product stream. The product is driven by pressure (usually nitrogen) with no pumping mechanism involved. Thus, especially for proteins that are quite sensitive to shear forces, time/pressure filling is preferable.

Most high-speed fillers for large-volume solutions use the bottle as the measuring device, transferring the liquid either by vacuum or by positive pressure from the bulk reservoir to the individual unit containers. Therefore a high accuracy of fill is not achievable.

The USP requires that each container be filled with a sufficient volume in excess of the labeled volume to ensure withdrawal of the labeled volume and provides a table of suggested fill volumes.

The filling of a small number of containers may be accomplished with a hypodermic syringe and needle, the liquid drawn into the syringe, and forced through the needle into the container. An example of such a device that provides greater speed of filling is the Cornwall Pipet (Becton Dickinson). The device has a two-way valve between the syringe and the needle and a means for setting the stroke of the syringe, so the same volume is delivered each time. Clean, sterile, disposable assemblies operating on the same principle have particular usefulness in hospital pharmacy or experimental operations.

29.12.8.2 Filling of solids

Sterile solids, such as antibiotics, are more difficult to subdivide evenly into containers than are liquids. The flow of solid material is relatively poor and often irregular. Even though a container with a larger diameter opening is used to facilitate filling, it is difficult to introduce the solid particles, and the risk of spillage is ever-present. The accuracy of the quantity delivered cannot be controlled, as well as with liquids. Due to these factors, the tolerances permitted for the content of such containers must be relatively large.

Some sterile solids are subdivided into containers by individual weighing. A scoop is usually provided to aid in approximating the quantity required, but the quantity filled into the container is finally weighed on a balance. This is a slow process. When the solid is obtainable in a granular form, so it will flow more freely, other methods of filling may be employed. In general, these involve the measurement and delivery of a volume of the granular material that has been calibrated in terms of the weight desired.

29.12.9 Sealing of filled containers

Filled containers should be sealed as soon as possible, to prevent the contents from being contaminated by the environment. An incompletely sealed ampoule is called a "leaker."

Ampoules are sealed by melting a portion of the glass neck. Two types of seals are employed normally: tip-seals (bead-seals) or pull-seals. Tip-seals are made by melting enough glass rapidly in a high-temperature gas-oxygen flame at the tip of the neck of an ampoule to form a bead and close the opening. The ampoule neck must be heated evenly on all sides to produce a uniform bead. Care must be taken to properly adjust the flame temperature and the duration of heating to completely close the opening with a bead of glass. Excessive heating results in the expansion of the gases within the ampoule against the soft bead seal, which causes a bubble to form. The wall of the bubble will be thin and fragile and if the bubble bursts, the

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ampoule is no longer sealed. Insufficient heating will leave an open capillary through the center of the bead.

Pull-seals are made by heating the neck of the ampoule below the tip to make possible for grasping with forceps or other mechanical devices. The ampoule is rotated in the flame and when the glass has softened, the tip is grasped firmly and pulled quickly away from the body of the ampoule, to twist close the small capillary tube formed. Pull-sealing though slower provides more secure seals than tip-sealing.

Ampoules having a wide opening must be sealed by pull-sealing. Fracture of the neck of ampoules during sealing may occur, if wetting of the necks occurs at the time of filling. Also, wet necks increase the frequency of bubble formation and unsightly and contaminating deposits.

For product susceptible to oxidative degradation the air in the headspace may be replaced with an inert gas, by introducing a stream of the gas, such as nitrogen or carbon dioxide, during or after filling with the product. Immediately thereafter, the ampoule is sealed, before the gas can diffuse to the outside.

Glass or plastic vials and bottles should be closed with a rubber closure (stopper) as rapidly as possible after filling and with reasoned care, preferably under HEPA-filtered laminar airflow to prevent contamination of the contents.

The closure must fit the mouth of the container snugly enough and with its elasticity provide a good seal. Closures are inserted mechanically, using an automated process, especially with high-speed processing. Halogenated closure surfaces or treatment with silicone helps to reduce friction, so the closure may slide more easily through a chute and into the container opening. When the closure is positioned at the insertion site, it is pushed mechanically into the container opening. When small lots are encountered, manual stoppering with orceps may be used, but such a process poses a greater risk of introducing contamination than automated processes. Container-closure integrity tests are covered in pharmacopeia.

Aluminum caps are used to hold rubber closures in place and are crimped under the lip of the vial or bottle. The closure cannot be removed without destroying the aluminum cap; therefore an intact aluminum cap is a proof that the closure has not been removed intentionally or unintentionally. Such confirmation is necessary to ensure the integrity of the contents, as to sterility and other aspects of quality.

The aluminum caps are designed so the outer layer of double-layered caps, or the center of single-layered caps, can be removed to expose the center of the rubber closure, without disturbing the band that holds the closure in the container. Rubber closures for use with intravenous administration sets often have a permanent hole through the closure. In such cases a thin rubber disk, overlayed with a solid aluminum disk, is placed between an inner and outer aluminum cap, thereby providing a seal of the hole through the closure.

29.12.10 Sterilization of parenteral product

Whenever possible, the parenteral product should be sterilized within as short a time as possible after being sealed in its final container (terminal sterilization). Since this usually involves a thermal process, due consideration must be given to the effect of the elevated temperature on the stability of the product. Many products, both pharmaceutical and biological, are affected adversely by temperatures required for thermal sterilization. Therefore heat-labile products should be sterilized by a nonthermal method, usually by filtration through bacteria-retaining filters. Subsequently, all operations must be carried out in an aseptic manner, so that contamination is not introduced into the filtrate. Colloids, oleaginous solutions, suspensions, and emulsions that are thermolabile may require a process in which each component is sterilized separately and the product is formulated and processed under aseptic conditions.

The aseptic processing of a product is challenging, but technical advances in aseptic processing, including improved automation, use of isolator systems, formulations to include antimicrobial effects, and combinations of limited sterilization with aseptic processing, have decreased the risk of contamination.

Radiation sterilization is gaining momentum as an alternative terminal sterilization method. There has been limited understanding of the molecular transformations that may occur in drug molecules and excipients under exposure to the high-energy gamma radiation levels of the process. However, lower energy beta-particle (electron beam) radiation has seen some success. Significant research must still be accomplished before radiation sterilization is used as a terminal sterilization process. The use of radiation for the sterilization of materials, such as plastic medical devices, is well established.

Dry-heat sterilization may be employed for a few dry solids not affected adversely by the high temperatures and for the relatively long heating period required. This method is applied most effectively to the sterilization of glassware and metalware. After sterilization, the equipment will be sterile, dry, and, if the sterilization period is long enough, pyrogen-free.

Saturated steam under pressure (autoclaving) is the most commonly used and the most effective method for the sterilization of aqueous liquids or substances that can be reached or penetrated by steam. A survival probability of at least 10^{-6} is readily achievable with terminal autoclaving of a thermally stable product.

Since the temperature employed in an autoclave is lower than that for dry-heat sterilization, equipment made

of materials, such as rubber and polypropylene, may be sterilized if the time and temperature are carefully controlled. As mentioned previously, some injections are affected adversely by the elevated temperature required for autoclaving. For some products, such as Dextrose Injection, a shortened cycle, using an autoclave designed to permit a rapid temperature rise and rapid cooling with water spray or other cooling methods, makes it possible to use this method. It is ineffective in anhydrous conditions, such as within a sealed ampoule containing a dry solid or an anhydrous oil. Other products that will not withstand autoclaving temperatures may withstand marginal thermal methods, such as tyndallization or pasteurization (e.g., 10−12 hours at 60°C). These methods may be rendered more effective for some injections, by the inclusion of a bacteriostatic agent in the product.

Articles to be sterilized must be properly wrapped or placed in suitable containers to permit penetration of sterilants and provide protection from contamination after sterilization. Sheets or bags made of special steam-penetrating paper or polymeric materials are available for this purpose. Further, containers or bags impervious to steam can be equipped with a microbe-excluding vent filter to permit adequate steam penetration and air exit. Multiple wrapping permits sequential removal of outer layers, as articles are transferred from zones of lower to higher environmental quality. The openings of equipment subjected to dry-heat sterilization are often covered with metal or glass covers. Laboratories often used silver−aluminum foil for covering glassware used for endotoxin testing. The effectiveness of any sterilization technique must be proved (validated), before it is employed in practice. During validation of a sterilization process, biological indicator (BI) of known resistance and numbers are used in association with physical-parameter indicators, such as recording thermocouples. Once the lethality of the process is established in association with the physical measurements, the physical measurements can be used for subsequent monitoring of in-use processes without the BIs.

In addition to the data printout from thermocouples, sometimes other physical indicators are used, such as color change and melting indicators, to give visual indication that a package or truckload has been subjected to a sterilization process. Such evidence can become a part of the batch record to confirm that sterilization was accomplished.

29.12.11 Freeze-drying (lyophilization)

Proteins and peptides that are unstable in solution must be converted to a solid form for clinical and commercial use. Several technologies are available to produce sterile dry powder drug products such as freeze-drying, sterile crystallization, or spray-drying and powder filling. However, freeze-drying is the most common unit process for manufacturing drug products which are unstable as solutions. The term "lyophilization" describes a process to produce a product that "loves the dry state." Equipment used to freeze-dry products are called freeze-dryers or lyophilizers (Fig. 29.7). Table 29.8 lists the advantages, features, and disadvantages of freeze-drying.

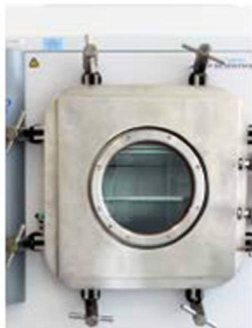

FIGURE 29.7 Front view of freeze direr (Courtesy Janssen Pharmaceutica, Belgium).

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TABLE 29.8 Advantages and disadvantages of freeze-drying along with desired characteristics of final product.

Advantages	Disadvantages
• Dried product with enhanced stability is obtained	• Process-related stability concerns of API
• Good for oxygen sensitive/thermolabile drugs	• Volatile compounds may be removed due to vacuum
• Rapid reconstitution time due to homogenous dispersion	• Single most expensive operation
• Sterility can be achieved and maintained	• Sterility of dryer chamber and aseptic loading of vials can be problematic
Desired characteristics of freeze-dried products: Intact cake, sufficient strength, uniform color, dry and porous cake, sterile, free of pyrogens and particulates, and chemically stable	

API, Active pharmaceutical ingredient.

Freeze-drying, essentially, involves freezing the product solution at a temperature below its eutectic (crystalline) or glass transition temperature. This is followed by primary drying which involves removal of solvent (ice) from the product, by reducing pressure, usually below 0.1 Torr (100 μmHg). The temperature of the product must remain slightly below its critical temperature, called "collapse temperature" which is similar to the eutectic or glass transition temperature of the product. The ice sublimes and condenses on to a cold surface at a temperature below that of the product. This step is followed by secondary drying stage in which the bound water from solute(s) is reduced to a level that assures long-term stability of the product (usually 1% or less moisture, except for some proteins that require a minimum amount of water for conformational stability) by application of heat under controlled conditions. For small molecules the highest secondary drying temperature used is 40°C, whereas for proteins, it is no more than 30°C to avoid chemical degradation. The end product is a dry sponge-like matrix of the solids.

The containers must remain open during the drying process to allow water vapor to escape; therefore they must be protected from contamination during transfer from the filling area to the freeze-drying chamber, while in the freeze-drying chamber and at the end of the drying process until sealed. Freeze-dryers are equipped with hydraulic or pneumatic internal-stoppering devices designed to push slotted rubber closures into the vials to be sealed while the chamber is still evacuated, the closures having been partially inserted immediately after filling, so the slots were open to the outside. If internal stoppering is not available or containers, such as ampoules, are used, filtered dry air or nitrogen should be introduced into the chamber at the end of the process to establish atmospheric pressure. The direction of heat and mass transfer causes the top of the product to dry first with drying proceeding downward to the bottom of the vial. Therefore, as drying proceeds, there exists a three-component or layer system in each vial—the upper dry product, the middle sublimation front, and the lower frozen liquid product. As the dried layer increases, it offers greater resistance to the transfer of mass out of the vials. Thus, if large volumes of solution are processed, the surface area relative to the depth may increase, utilizing larger vials or by using such devices as freezing the container in a slanted position to increase the surface area.

The actual driving force for the process is the vapor pressure differential between the vapor at the surface where drying of the product is occurring (the drying boundary) and at the surface of the ice on the condenser. The latter is determined by the temperature of the condenser, as modified by the insulating effect of the accumulated ice. The vapor pressure at the drying boundary is governed by the rate of heat conduction through the container and the frozen material to the drying boundary, the impeding effect of the increasing depth of dried, porous product above the drying boundary and the temperature and heat capacity of the shelf itself.

The passageways between the product surface and the condenser surface must be wide open and direct for effective operation. The amount of solids in the product, the ice crystal size, and their thermal conductance affect the rate of drying. The more solids present, the more impediment will be provided to the escape of the water vapor. The degree of supercooling (i.e., how much lower the product temperature goes below its equilibrium freezing point before ice crystals first form) and the rate of ice crystallization define the freezing process and efficiency of primary drying. The larger the size of ice crystals formed, usually as a result of slow freezing, the larger the pore sizes are when the ice sublimes and, consequently, the faster the rate of drying. A high degree of supercooling produces a large number of small ice crystals, a small pore size when the ice sublimes in the dried layer, and a greater resistance to water vapor transport during primary drying. The poorer the thermal

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conducting properties of the solids in the product, the slower the rate of heat transfer through the frozen material to the drying boundary.

The rate of drying is slow, most often requiring 24 hours or longer for completion. The actual time required, the rate of heat input, and the product temperatures used must be determined for each product and then reproduced carefully with successive processes.

The active constituent of many pharmaceutical products is present in such a small quantity that, if freeze-dried alone, its presence would be hard to detect visually. In fact, the solids content of the original product, ideally, should be between 5% and 30%. Therefore excipients are often added to increase the amount of solids. Such excipients are called "bulking agents"; the most commonly used bulking agent in freeze-dried formulations is mannitol. However, most freeze-dried formulations must contain other excipients, due to the need to buffer the product and/or to protect the active ingredient from the adverse effects of freezing and/or drying. Thus buffering agents, such as sodium or potassium phosphate, sodium acetate, and sodium citrate, are commonly used in freeze-dried formulations. Sucrose, trehalose, dextran, and amino acids, such as glycine, are commonly used lyoprotectants. Each of these substances contributes to the appearance characteristics of the plug, such as whether dull and spongy or sparkling and crystalline, firm or friable, expanded or shrunken, and uniform or striated. Therefore the formulation of a product to be freeze-dried must include consideration not only of the nature and stability characteristics required during the liquid state, both freshly prepared and when reconstituted before use, but also the characteristics desired in the dried plug.

29.12.12 Packaging and labeling

The USP includes certain requirements for the packaging and storage of injections. The volume of injection in single-dose containers is defined as that which is specified for parenteral administration at one time and is limited to a volume of 1 L. Parenterals intended for intraspinal, intracisternal, or peridural administration are packaged only in single-dose containers. Unless an individual monograph specifies otherwise, no multiple-dose container shall contain a volume of injection more than sufficient to permit the withdrawal and administration of 30 mL. Containers for injections packaged for use as hemofiltration or irrigation solutions may be designed to empty rapidly and may contain a volume in excess of 1 L.

The labeling of an injection must provide all information needed to ensure the safe and proper use of the product. The label upon primary container states the name of the preparation, the percentage content of drug of a liquid preparation, the amount of active ingredient of a dry preparation, the volume of liquid to be added to prepare an injection or suspension from a dry preparation, the route of administration, a statement of storage conditions, and an expiration date. The label must state the name of the vehicle and the proportions of each constituent, if it is a mixture, and the names and proportions of all substances added to increase stability or usefulness. Preparations labeled for use as dialysis, hemofiltration, or irrigation solutions must meet the requirements for injections, other than those relating to volume, and must also bear on the label statements that they are not intended for intravenous injection. Injections intended for veterinary use are so labeled. Also, the label must indicate the name of manufacturer/distributor and lot number.

29.13 Quality assurance and control

Every component and step of the manufacturing process must be subjected to intense scrutiny to ensure that quality is attained in the finished product. The responsibility for achieving this quality is divided appropriately in concept and practice into quality assurance and QC. The principles for achieving quality are basically the same for the manufacture of any pharmaceutical. Certain selected tests that are characteristically required before a finished parenteral product is released are discussed next.

29.13.1 Sterility test

The USP test is performed by means of filtration. Products are filtered and the membrane is washed appropriately to remove inhibitors. Filters are then incubated in soyabean casein digest medium and fluid thioglycollate medium for 14 days and observed for microbial growth. USP requires that all lots of culture media be tested for their growth-promotion capabilities. In the event of a sterility-test failure the USP does not permit a retest, unless specific evidence is discovered to suggest contamination occurred during the test. It should be noted that a "lot," with respect to sterility testing, is that group of product containers that has been subjected to the same sterilization procedure. For containers of a product that have been sterilized by autoclaving, for example, a lot would constitute those processed in a particular sterilizer cycle. For an aseptic filling operation, a lot would constitute all of those product containers filled during a period in which there was no change in the filling assembly or equipment and which is no longer than one working day or shift. Samples taken for sterility testing should be representative of the whole of the batch but should, in particular, include samples taken from parts of the batch considered to be most at risk of contamination.

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29.13.2 Pyrogen test

The USP evaluates the presence of pyrogens in parenteral preparations by the pyrogen test (Section ⟨151⟩), and the bacterial endotoxins test (BET) (Section ⟨85⟩). The test described in Section ⟨151⟩, involved injecting small amount of test material in rabbits bloodstream and monitoring increases in temperature. USP prescribes the minimum pyrogenic dose as dose required to produce a 0.6°C rise in temperature. If the medicinal agent may have the ability to mask any fever response, this test should not be employed for pyrogen quantification.

The BET is an in vitro test based on the formation of a gel or the development of color in the presence of bacterial endotoxins and the lysate of the amebocytes of the horseshoe crab (*Limulus polyphemus*). The limulus amebocyte lysate test detects pyrogens of Gram-negative bacteria in simpler, more rapid manner with greater sensitivity than the rabbit test. This test has enabled endotoxin limits to be established for finished products and bulk drug substances and excipients. To provide standardization for the test, the USP has established a reference standard endotoxin against which lots of the lysate is standardized. Thus the sensitivity of the lysate is given in terms of EU.

Monocyte activation test is another test can detect pyrogenic and nonpyrogenic material that induces release of cytokines that cause fever and a potential cascade of adverse physiological effects (Gaines Das et al., 2004).

29.13.3 Particulate matter evaluation

Presence of particulate matter such as visible dirt in parenterals is unacceptable and would indicate inferior quality. Particles of lint, rubber, insoluble chemicals, and other foreign matter can produce emboli in the vital organs of animals and man when injected intravenously. Infusion phlebitis may be related to the presence of particulate matter in intravenous fluids. Since erythrocytes have a diameter of approximately 4.5 μm, limiting particles of more than 5 μm should be the basis for evaluation of particulates. cGMP requires inspection of each final container of an injection. Containers with visible particulates should be discarded. All units from a production line should be inspected by human inspectors, under a good light, baffled against reflection into the eye, and against a black and white background. This inspection is subject to the limitation of the size of particles that can be seen, the interpersonal variation of visual acuity, their emotional state, eye strain, fatigue along with other factors. Automated inspection machines are increasingly being used today.

The assessment of the level of particulate matter below the visible size of about 50 μm has become an increasingly used QC indicator of process cleanliness in the manufacture of injections. The tests used, however, are destructive of container units, besides these methods require stringent, ultraclean procedures to prevent inadvertent contamination of product during sample preparation or testing procedure. The USP has identified two test methods in ⟨788⟩, particulate matter in injections. All large volume injectables (LVIs) for single-dose infusion and those small volume injectables (SVIs) for which the monograph specifies a limit (primarily those commonly added to infusion solutions). The first test used is the light obscuration test, which uses an electronic instrument designed to count and measure the size of particles by means of a shadow cast by the particle as it passes through a high-intensity light beam. If the injection formulation is not a clear, colorless solution (e.g., an emulsion) or it exceeds the limits specified for the light obscuration test, it is to be subjected to the microscopic count test. The latter method consists of filtering a measured sample of solution through a membrane filter under ultraclean conditions and then counting the particles on the surface of the filter, using a microscope and oblique light at 100 × magnification. The latter test requires a very long time. These standards are readily met in the United States today by the manufacturers of LVIs and the specified SVIs.

The administration sets and the techniques used for preparing and administering intravenous infusion fluids may introduce substantial amounts of particulate matter into an otherwise clean solution. Therefore the pharmaceutical manufacturer, the administration set manufacturer, the pharmacist, the nurse, and the physician must share responsibility for making sure the patient receives a clean intravenous injection.

29.13.4 Container/closure integrity test

USP classifies tests for testing integrity of containers and closures as deterministic tests and probabilistic tests. Deterministic test is typically nondestructive and include electrical conductivity measurement, laser-based gas headspace analysis, mass extraction, pressure decay, tracer gas detection, vacuum mode, and vacuum decay. Probabilistic tests are destructive tests and are preferred when the product–package system proves incompatible with deterministic methods, or when method outcome requirements demand a particular probabilistic testing approach. These methods include bubble emission, microbial challenge, immersion exposure, tracer gas detection, and tracer liquid test. Ampoules that have been sealed by fusion must be subjected to a test to determine if there are any leakers that may spoil the package or introduce microorganisms or other contaminants into the product. Ampoules are submerged entirely in a 1% methylene blue solution. Application of vacuum (27 in. Hg or more) forces the dye to enter an incompletely sealed ampoule

indicating a leaker. Typical dye ingress test has limitation like loss of color intensity, of not able to detect capillaries less than 15 μm. USP now describes the tracer liquid test method which is destructive approach for detecting leaks in nonporous rigid or flexible packages. The test procedure described for ingress of dye can also use radionuclides or metallic ions as tracers. The presence of leakage can be determined qualitatively by visual inspection and quantitatively by other analytical techniques. Additional test options include use of positive pressure or multiple cycles of differential pressure conditions. Vials and bottles are not subjected to such a leaker test since the sealing material (rubber stopper) is not rigid. However, container-closure sealing integrity should be ensured, by developing specifications for the fit of the closure in the neck of the container, the physical characteristics of the closure, the need for lubrication of the closure, and the capping pressure.

29.13.5 Safety test

The National Institutes of Health requires routine safety testing of biologicals in animals. Most pharmaceutical preparations are now required to be tested for safety under law. A parenteral product may comply with the in vitro pyrogen test, sterility test, and chemical analyses and still cause unfavorable reactions, a safety test in animals is essential, to ascertain the absence of unexpected toxicity.

References

Esfandiary, R., Joshi, S.B., Vilivalam, V., Middaugh, C.R., 2008. Characterization of protein aggregation and adsorption on prefillable syringe surfaces. In: AAPS National Biotechnology Conference, Toronto, US-FDA Guidance for industry, 2004; EU Guidelines to Good Manufacturing Practice, 2015, p. 22−25.

Food and Drug Administration, 2004. Guidance for Industry—Sterile Drug Products Produced by Aseptic Processing. Current Good Manufacturing Practice. FDA, Silver Spring, MD.

Gaines Das, R.E., Brugger, P., Patel, M., Mistry, Y., Poole, S., 2004. Monocyte activation test for pro-inflammatory and pyrogenic contaminants of parenteral drugs: test design and data analysis. J. Immunol. Methods 288, 165−177.

Groves, M.J., Murty, R., 1995. Aseptic Pharmaceutical Manufacturing II: Applications for the 1990s. CRC Press.

Hoehne, M., Samuel, F., Dong, A., Wurth, C., Mahler, H.C., Carpenter, J.F., et al., 2011. Adsorption of monoclonal antibodies to glass microparticles. J. Pharm. Sci. 100, 123−132.

Howorth, H., 1988. Movement of airflow, peripheral entrainment, and dispersion of contaminants. J. Parenter. Sci. Technol. 42, 14−19.

Iacocca, R.G., Toltl, N., Allgeier, M., Bustard, B., Dong, X., Foubert, M., et al., 2010. Factors affecting the chemical durability of glass used in the pharmaceutical industry. AAPS PharmSciTech 11, 1340−1349.

ISO-14644-1, 2015. Cleanrooms and associated controlled environments. (accessed October 2019.).

Kalepu, S., Nekkanti, V., 2015. Insoluble drug delivery strategies: review of recent advances and business prospects. Acta Pharm. Sin. B 5, 442−453.

Lohse, D.J., 2000. Polyolefins. Applied Polymer Science: 21st Century. Elsevier.

Lysfjord, J., 2009. Practical Aseptic Processing: Fill and Finish. PDA.

Mottu, F., Laurent, A., Rufenacht, D.A., Doelker, E., 2000. Organic solvents for pharmaceutical parenterals and embolic liquids: a review of toxicity data. PDA J. Pharm. Sci. Technol. 54, 456−469.

Nema, S., Washkuhn, R., Brendel, R., 1997. Excipients and their use in injectable products. PDA J. Pharm. Sci. Technol. 51, 166−171.

Powell, M.F., Nguyen, T., Baloian, L., 1998. Compendium of excipients for parenteral formulations. PDA J. Pharm. Sci. Technol. 52, 238−311.

Rayaprolu, B.M., Strawser, J.J., Anyarambhatla, G., 2018. Excipients in parenteral formulations: selection considerations and effective utilization with small molecules and biologics. Drug Dev. Ind. Pharm. 44, 1565−1571.

Rowe, R.C., Sheskey, P., Quinn, M., 2009. Handbook of Pharmaceutical Excipients. Libros Digitales-Pharmaceutical Press.

Sacha, G.A., Saffell-Clemmer, W., Abram, K., Akers, M.J., 2010. Practical fundamentals of glass, rubber, and plastic sterile packaging systems. Pharm. Dev. Technol. 15, 6−34.

Sharma, B., 2007. Immunogenicity of therapeutic proteins. Part 2: Impact of container closures. Biotechnol. Adv. 25, 318−324.

Strickley, R.G., 1999. Parenteral formulations of small molecules therapeutics marketed in the United States (1999)—Part I. PDA J. Pharm. Sci. Technol. 53, 324−349.

Strickley, R.G., 2000a. Parenteral formulations of small molecules therapeutics marketed in the United States (1999)—Part II. PDA J. Pharm. Sci. Technol. 54, 69−96.

Strickley, R.G., 2000b. Parenteral formulations of small molecules therapeutics marketed in the United States (1999). Part III. PDA J. Pharm. Sci. Technol. 54, 152−169.

Sutton, S.V., Porter, D., 2002. Development of the antimicrobial effectiveness test as USP chapter ⟨51⟩. PDA J. Pharm. Sci. Technol. 56, 300−311.

Swift, R., 2016. Glass containers for parenteral products. Pharmaceutical Dosage Forms—Parenteral Medications. CRC Press.

Thirumangalathu, R., Krishnan, S., Ricci, M.S., Brems, D.N., Randolph, T.W., Carpenter, J.F., 2009. Silicone oil-and agitation-induced aggregation of a monoclonal antibody in aqueous solution. J. Pharm. Sci. 98, 3167−3181.

Tyagi, A.K., Randolph, T.W., Dong, A., Maloney, K.M., Hitscherich JR, C., Carpenter, J.F., 2009. IgG particle formation during filling pump operation: a case study of heterogeneous nucleation on stainless steel nanoparticles. J. Pharm. Sci. 98, 94−104.

US Department of Health and Human Services, 2004. Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice: Guidance for Industry. US Department of Health and Human Services, Food and Drug Administration.

US-FDA, 2019. Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice. [Online]. <https://www.accessdata.fda.gov/scripts/cder/daf/> (accessed September 2019).

Walther, M., Rupertus, V., Seemann, C., Brecht, J., Hormes, R., Swift, R.W., 2002. Pharmaceutical vials with extremely high chemical inertness. PDA J. Pharm. Sci. Technol. 56, 124−129.

Par Health Inc. Ex. 1006-0040

Yalkowsky, S.H., Krzyzaniak, J.F., Ward, G.H., 1998. Formulation-related problems associated with intravenous drug delivery. J. Pharm. Sci. 87, 787–796.

Zhong, H., Chan, G., Hu, Y., Hu, H., Ouyang, D., 2018. A comprehensive map of FDA-approved pharmaceutical products. Pharmaceutics 10.

Further reading

Akers, M.J., 2010. Sterile Drug Products—Formulation, Packaging, Manufacturing, and Quality. Informa Healthcare, London.

Avis K.E. et al., (Eds.), 1992–1993. Pharmaceutical Dosage Forms: Parenteral Medications, vols. 1–3. second ed. Dekker, New York.

Avis, K.E., et al., (Eds.), 1998. Biotechnology: Quality Assurance and Validation Drug Manufacturing Technology Series, vol. 4. CRC Press, Boca Raton, FL.

Akers, M.J., et al., 2002. Parenteral Quality Control, third ed. Dekker, New York.

Carleton, F.J., Agalloco, J.P. (Eds.), 1998. Validation of Aseptic Pharmaceutical Processes. second ed. Dekker, New York.

Carpenter, J.F., Manning, M.C. (Eds.), 2002. Rational Design of Stable Protein Formulations. Kluwer Academic/Plenum, New York.

Jennings, T., 1999. Lyophilization: Introduction and Basic Principles. CRC Press, Boca Raton, FL.

Kuhlman, H., Coleman, D., 1995. Engineering aspects of WFI systems design. In: Avis, K.E. (Ed.), Sterile Pharmaceutical Products: Process Engineering Applications. Interpharm Press (now CRC Press), Buffalo Grove, IL, pp. 221–268.

Manufacture of Sterile Medicinal Products, Annexure 4, EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, 2008.

Meltzer, T.H., Jornitz, M.W. (Eds.), 1998. Filtration in the Biopharmaceutical Industry. Dekker, New York.

Nail, S.L., Akers, M.J. (Eds.), 2002. Development and Manufacture of Protein Pharmaceuticals. Kluwers Academic/Plenum, New York.

third ed. Nema, S., Ludwig, J. (Eds.), 2010. Pharmaceutical Dosage Forms: Parenteral Medications, 3 vols. Informa Healthcare, London.

Phillips, G.B., Miller, W.S. (Eds.), 1973. Industrial Sterilization. Duke University Press, Durham, NC.

Swarbrick, J., Boylan, J.C. (Eds.), 2002. Encyclopedia of Pharmaceutical Technology. second ed. Dekker, New York.

Turco, S., King, R.E., 1987. Sterile Dosage Forms, third ed. Lea & Febiger, Philadelphia, PA.

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