SEVENTH EDITION

PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS

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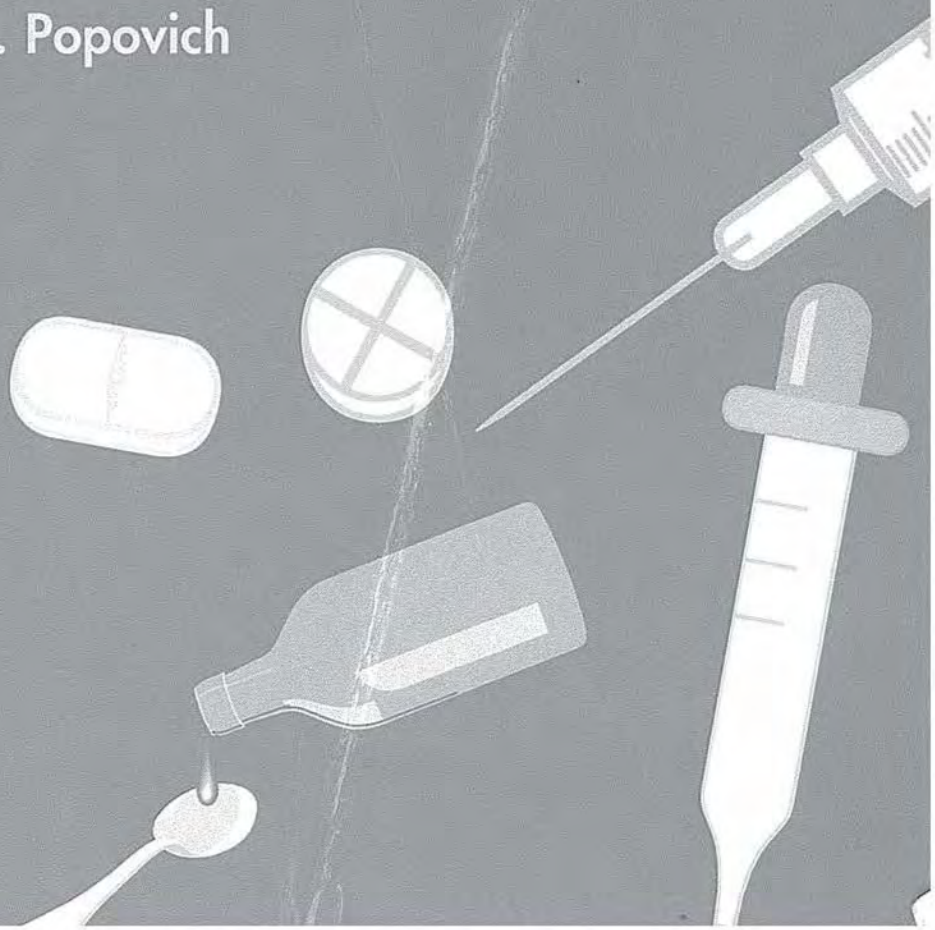

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Chapter at a Glance

CONSIDERED IN this chapter are important pharmaceutical dosage forms that have the common characteristic of being prepared to be sterile; that is, free from contaminating microorganisms. Among these sterile dosage forms are the various small- and large-volume injectable preparations, irrigation fluids intended to bathe body wounds or surgical openings, and dialysis solutions. Biological preparations as vaccines, toxoids, and antitoxins are also among this group and discussed in Chapter 15. Sterility in these preparations is of utmost importance because they are placed in direct contact with

the internal body fluids or tissues where infection can easily arise. Ophthalmic preparations, which are also prepared to be sterile, will be discussed separately in Chapter 16.

Injections

Injections are sterile, pyrogen-free preparations intended to be administered parenterally. The term *parenteral* refers to the injectable routes of administration. The term has its derivation from the Greek words *para* and *enteron*, meaning outside of the intestine, and denotes routes of administration other than the oral route. *Pyrogens* are fever-producing organic substances arising from microbial contamination and are responsible for many of the febrile reactions which occur in patients following intravenous injection. Pyrogens and the determination of their presence in parenteral preparations will be discussed later in this chapter. In general, the parenteral routes of administration are undertaken when rapid drug action is desired, as in emergency situations, when the patient is uncooperative, unconscious, or unable to accept or tolerate medication by the oral route, or when the drug itself is ineffective by other routes. With the exception of insulin injections, which are commonly *self*-administered by diabetic patients, most injections are administered by the physician, his/her assistant, or nurse in the course of medical treatment. Thus injections are employed mostly in the hospital, extended care facility, and clinic and less frequently in the home. An exception would be in *home health care* programs in which health professionals pay scheduled visits to patients in their homes, providing needed treatment, including intravenous medications. These programs enable patients who do not require or are unable to pay for more expensive hospitalization to remain in the familiar surroundings of their homes while receiving appropriate medical care. The pharmacist supplies injectable preparations to the physician and nurse, as required for their use in the institutional setting, clinic, office, or home health care program.

Perhaps the earliest injectable drug to receive official recognition was the hypodermic morphine solution, which appeared first in the 1874 addendum to the 1867 British Pharmacopeia, and later, in 1888 in the first edition of the National Formulary of the United States. Today, there are literally hundreds of drugs and drug products available for parenteral administration.

Parenteral Routes of Administration

Drugs may be injected into almost any organ or area of the body, including the joints *(intra-articular)*, a joint-fluid area *(intrasynovial)*, the spinal column *(intraspinal)*, into spinal fluid *(intrathecal)*, arteries *(intra-arterial)*, and in an emergency, even into the heart *(intracardiac)*. However, most commonly injections are performed into a vein *(intravenous, IV)*, into a muscle *(intramuscular, IM)*, into the skin *(Intradermal, ID, intracutaneous)*, or under the skin *(subcutaneous, SC, Sub-Q, SQ, hypodermic, Hypo)* (Fig. 14.1).

Intravenous Route

The intravenous injection of drugs had its scientific origin in 1656 in the experiments of Sir Christopher Wren, architect of St. Paul's Cathedral and amateur physiologist. Using a bladder and quill for a syringe and needle, he injected wine, ale, opium, and other substances into the veins of dogs and studied their effects. Intravenous medication was first given to humans by Johann Daniel Major of Kiel in 1662, but was abandoned for a period because of the occurrence of thrombosis and embolism in the patients so treated. The invention of the hypodermic syringe toward the middle of the 19th century created a new interest in intravenous techniques and toward the turn of the century, intravenous administration of solutions of sodium chloride and glucose became popular. Today, the intravenous administration of drugs is a routine occurrence in the hospital, although there are still recognized dangers associated with the practice. Thrombus and embolus formation may be induced by intravenous needles and catheters, and the possibility of particulate matter in parenteral solutions poses concern for those involved in the development, administration, and use of intravenous solutions.

Intravenously administered drugs provide rapid action compared with other routes of administration and because drug absorption is not a factor, optimum blood levels may be achieved with the accuracy and immediacy not possible by other routes. In emergency situations, the intravenous administration of a drug may be a life-saving procedure because of the placement of the drug directly into the circulation and the prompt action which ensues. On the negative side, once a drug is administered intravenously, it cannot be retrieved. In the case of an adverse reaction to the drug, for instance, the drug cannot be easily removed from the circulation as it could, for example, by the induction of vomiting after the oral administration of the same drug.

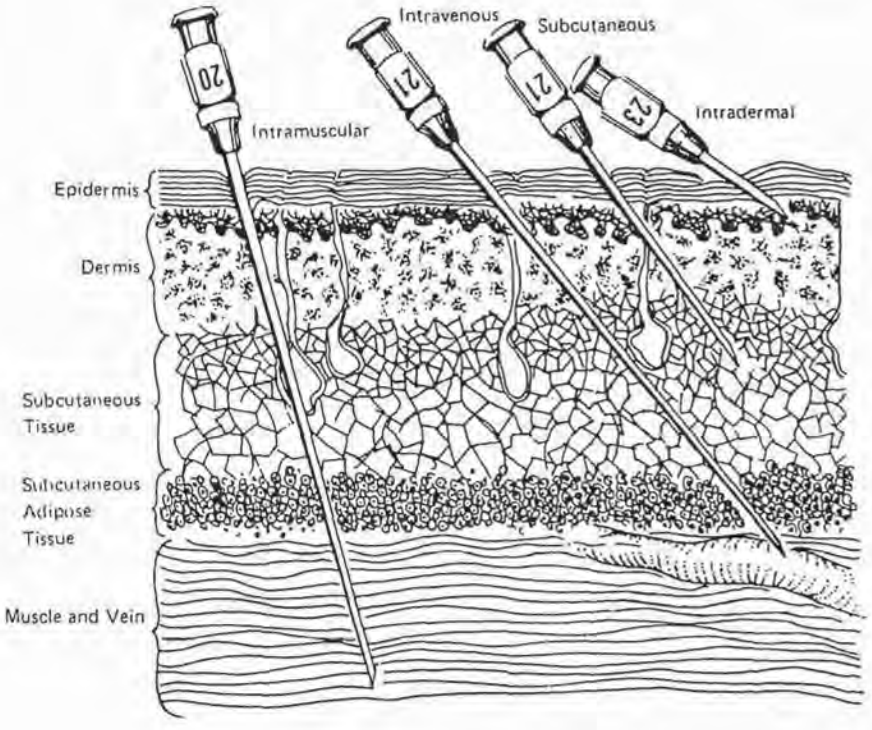

Fig. 14.1 *Routes of parenteral administration. Numbers on needles indicate size or gauge of needle based on outside diameter of needle shaft. (Reprinted with permission from Turco S, King RE. Sterile Dosage Forms: Their Preparation and Clinical Applications. 3rd Ed. Lea & Febiger, 1987.)*

Although most superficial veins are suitable for venipuncture, the veins of the antecubital area (situated in front of the elbow) are usually selected for direct intravenous injection. The veins in this location are large, superficial, and easy to see and enter. Most clinicians insert the needle with the bevel facing upward, at the most acute angle possible with the vein, to ensure that the direction of flow of the injectable is that of the flow of the blood. Strict aseptic precautions must be taken at all times to avoid risk of infection. Not only are the injectable solutions sterile, the syringes and needles used must also be sterilized and the point of entrance must be disinfected to reduce the chance of carrying bacteria from the skin into the blood via the needle. Before injection, administration personnel must withdraw the plunger of the syringe or squeeze a special bulb found on most IV sets to ensure that the needle has been properly located. In both instances, a "flashback" of blood into the administration set or the syringe indicates proper placement of the needle within the vein.

Both small and large volumes of drug solutions may be administered intravenously. The use of 1000-mL containers of solutions for intravenous infusion is commonplace in the hospital. These solutions containing such agents as nutrients, blood extenders, electrolytes, amino acids, and other therapeutic agents are administered through an indwelling needle or catheter by continuous infusion. The infusion or flow rates may be adjusted by the clinician according to the needs of the patient. Generally, flow rates for intravenous fluids are expressed in mL/hour, and range from 42 to 150 mL/hour. Lower rates are used for "keep open" lines. For intravenous infusion, the needle or catheter is placed in the prominent veins of the forearm or leg and taped firmly to the patient so that it will not slip from place during infusion. The main hazard of intravenous infusion is the possibility of thrombus formation induced by the touching of the wall of the vein by the catheter or needle. Thrombi are more likely to occur when the infusion solution is of an irritating nature to the biologic tissues. A *thrombus* is a blood clot formed within the blood vessel (or heart) due usually to a slowing of the circulation or to an alteration of the blood or vessel wall. Once such a clot circulates, it becomes an *embolus*, carried by the blood stream until it lodges in a blood vessel, obstructing it, and resulting in a

blockage or occlusion referred to as an *embolism.* Such an obstruction may be a critical hazard to the patient, depending upon the site and severity of the obstruction.

Intravenously administered drugs ordinarily must be in aqueous solution; they must mix with the circulating blood and not precipitate from solution. Such an event could lead to pulmonary microcapillary occlusion and the subsequent blockage of blood passage. Intravenously delivered fat emulsions (e.g., Intralipid, 10%;20% [Clintec], Liposyn II, 10%;20% [Abbott], Liposyn III, 10%;20% [Abbott]) have gained acceptance for use as a source of calories and essential fatty acids for patients requiring parenteral nutrition for extended periods of time (usually for more than 5 days). The product contains up to 20% soybean oil emulsified with egg yolk phospholipids, in a vehicle of glycerin in water for injection. The emulsion is administered via a peripheral vein or by central venous infusion.

Naturally, the intravenous route is used in the administration of blood transfusions and it also serves as the point of exit in the removal of blood from patients for diagnostic work and for obtaining blood from donors.

In the late 1980s, automated intravenous delivery systems became commercially available for intermittent, self-administration of analgesics. Patient-controlled analgesia (PCA) has been used to control the pain associated with postoperative pain from a variety of surgical procedures, labor, sickle cell crisis, and chronic pain associated with cancer. For patients with chronic malignant pain, PCA allows a greater degree of ambulation and independence (1).

The typical PCA device includes a syringe or chamber that contains the analgesic drug and a programmable electomechanical unit. The unit, which might be compact enough to be worn on a belt or carried in a pocket (e.g., WalkMed™ PCA-Medex, Inc.), controls the delivery of drug by advancing a piston when the patient presses a button. The drug can be loaded into the device by a health care professional or dispensed from preloaded cartridges available through the manufacturer. The devices take advantage of intravenous bolus injections to produce rapid analgesia, along with slower infusion to produce steady-state opiate concentrations for sustained pain control.

The advantage of the PCA is its ability to provide constant and uniform analgesia. The typical intramuscular injection of an opioid into a depot muscular site may result in variable absorption, leading to unpredictable blood concentrations. Further, these injections are usually given when needed and are often inadequate to treat the pain. The PCA can prevent pharmacokinetic and pharmacodynamic differences between patients from interfering with the effectiveness of analgesia. Because opioid kinetics differ greatly among patients, the rates of infusion must be tailored (2).

The PCA also permits patients to medicate themselves when there is breakthrough pain. It eliminates the delay between the time of the patient's perception of pain and receiving the analgesic medication. Further, it saves nursing time. Otherwise, the nurse must check analgesic orders given by the physician, sign out the pain reliever from a controlled, locked location, and then administer the medication to the patient.

The PCA also provides better pain control with less side effects by minimizing the variations between suboptimal pain relief and overuse of narcotics. When the side effect profile of PCA patients is compared to patients maintained on IM narcotics, nausea, sedation, and respiratory depression occur less often in the PCA group. Lastly, patients accept the PCA as a favorable mode of relief, perhaps due to the sense of being in control and taking an active part in their pain relief.

Fig. 14.2 *PCA Plus II (LifeCare 4100)-Patient-controlled analgesic infuser. (Courtesy of Abbott Hospital Products Division.)*

PCA devices can be used for intravenous, subcutaneous, or epidural administration. Usually, these devices are either *demand dosing* (i.e., a fixed dose of drug is injected intermittently) or *constant-rate infusion plus demand dosing* (2). Regardless of type utilized, the physician or nurse establishes the loading dose, the rate of background infusion, dose per demand, lockout interval (i.e., minimum time between demand doses), and maximum dosage over a specified time interval. Figure 14.2 demonstrates the PCA Plus II (Lifecare 4100) infuser. With this device, the patient pushes a button on a pendant to deliver a prescribed quantity of the analgesic.

Intramuscular Route

Intramuscular injections of drugs provide drug effects that are less rapid, but generally of greater duration than those obtained from intravenous administration (3). Aqueous or oleaginous solutions or suspensions of drug substances may be administered intramuscularly. Depending on the type of preparation employed, the absorption rates may vary widely. It would be expected that drugs in solution would be more rapidly absorbed than those in suspension and that drugs in aqueous preparations would be more rapidly absorbed than when in oleaginous preparations. The physical type of preparation employed is based on the properties of the drug itself and on the therapeutic goals desired.

Intramuscular injections are performed deep into the skeletal muscles. The point of injection should be as far as possible from major nerves and blood vessels. Injuries to patients from intramuscular injection usually are related to the point at which the needle entered and where the medication was deposited. Such injuries include paralysis resulting from neural damage, abscesses, cysts, embolism, hematoma, sloughing of the skin, and scar formation.

In adults, the upper outer quadrant of the gluteus maximus is the most frequently used site for intramuscular injection. In infants, the gluteal area is small and composed primarily of fat, not muscle. What muscle there is is poorly developed. An injection in this area might be presented dangerously close to the sciatic nerve, especially if the child is resisting the injection and squirming or fighting. Thus, in infants and young children, the deltoid muscles of the upper arm or the midlateral muscles of the thigh are preferred. An injection given in the upper or lower portion of the deltoid would be well away from the radial nerve. The deltoid may also be used in adults, but the pain is more noticeable here than in the gluteal area. If a series of injections are to be given, the injection site is usually varied. To be certain that a blood vessel has not been entered, the clinician may aspirate slightly on the syringe following insertion of the needle to observe if blood enters the syringe. Usually, the volume of medication which may be conveniently administered by the intramuscular route is limited; generally a maximum of 5 mL is administered intramuscularly in the gluteal region and 2 mL in the deltoid of the arm.

The Z-Track Injection technique is useful for intramuscular injections of medications that stain upper tissue, e.g., iron dextran injection, or those that irritate tissue, e.g., Valium, by sealing these medications in the lower muscle. Because of its staining qualities, iron dextran injection, for example, must be injected only into the muscle mass of the upper outer quadrant of the buttock. The skin is displaced laterally prior to injection, then the needle is inserted and syringe aspirated, and the injection performed slowly and smoothly. The needle is then withdrawn and the skin released. This creates a "Z" pattern that blocks infiltration of medication into the subcutaneous tissue. The injection is 2 to 3 inches deep, and a 20 to 22 gauge needle is utilized. To further prevent any staining of upper tissue, usually one needle is used to withdraw the iron dextran from its ampul, and then replaced with another for the purposes of the injection.

Subcutaneous Route

The subcutaneous route may be utilized for the injection of small amounts of medication. The injection of a drug beneath the surface of the skin is usually made in the loose interstitial tissues of the outer surface of the upper arm, the anterior surface of the thigh, and the lower portion of the abdomen. The site of injection is usually rotated when injections are frequently given, e.g., daily insulin injections. Prior to injection, the skin at the injection site should be thoroughly cleansed. The maximum amount of medication that can be comfortably injected subcutaneously is about 1.3 mL and amounts greater than 2 mL will most likely cause painful pressure. Syringes with up to 3 mL capacities and utilizing needles with 24 to 26 gauges are used for subcutaneous injections. These needles will have cannula lengths that vary between 3/8 inch to 1 inch. Most typically, subcutaneous insulin needles are between 25 to 30 gauge with needle length between 5/16 to 5/8 inch. Upon insertion, if blood appears in the syringe, a new site should be selected.

Drugs that are irritating or those that are present in thick suspension form may produce induration, sloughing, or abscess formation and may be painful

to the patient. Such preparations should be considered not suitable for subcutaneous injection.

Intradermal Route

A number of substances may be effectively injected into the corium, the more vascular layer of the skin just beneath the epidermis. These substances include various agents for diagnostic determinations, desensitization, or immunization. The usual site for intradermal injection is the anterior surface of the forearm. A short (3/8 in.) and narrow gauge (23- to 26-gauge) needle is usually employed. The needle is inserted horizontally into the skin with the bevel facing upward. The injection is made when the bevel just disappears into the corium. Usually only about 0.1 mL volumes may be administered in this manner.

Specialized Access

In those instances where it is necessary to administer repeated injections over a period of time, it might be more prudent to employ devices that provide continued access and help eliminate patient pain associated with administration. Thus, it is important to list a few at this juncture.

Several types of central venous catheters are used in institutions and on an outpatient basis. These are used for a variety of parenteral medications (e.g., cancer chemotherapy, long-term antibiotic therapy, total parenteral nutrition solutions), and their placement can remain for a few days to several months. When not in use, these require heparinization to maintain patency of the catheter lumen.

The use of plastic, indwelling catheters helps eliminate the need for multiple punctures during IV therapy. Composed of polyvinyl chloride, Teflon, and polyethylene, these should be radiopaque to ensure that they demonstrate visibility on x-ray films. Usually, these must be removed within 48 hours after insertion. The choice of catheter depends upon several factors (e.g., length of time of the infusion, purpose of the infusion, the condition/availability of the veins). Three types of catheters are available: plain plastic, catheter-over-needle or catheter-outside-needle, and catheter-inside-needle.

Implantable devices provide long-term venous access in various diseases. Broviac and Hickman catheters are notable examples. These do carry a risk of morbidity, including fracture of the catheters, entrance site infection, and catheter sepsis. These have been developed to overcome catheter complications and are designed to provide repeated access to the infusion site. The delivery catheter can be placed in a vein, cavity, artery, or CNS system. A Huber point needle allows system access through the skin into a self-sealing silicone plug positioned in the center of the portal.

Official Types of Injections

According to the USP, injections are separated into five general types, all of which are suitable for, and intended for, parenteral administration. These may contain buffers, preservatives, and other added substances.

1. [Drug] *Injection*—Liquid preparations that are drug substances or solutions thereof. (Ex: Insulin Injection, USP)
2. [Drug] *for Injection*—Dry solids that, upon the addition of suitable vehicles, yield solutions conforming in all respects to the requirements for Injections. (Ex: Cefamandole Sodium for Injection)
3. [Drug] *Injectable Emulsion*—Liquid preparations of drug substances dissolved or dispersed in a suitable emulsion medium. (Ex: Propofol)
4. [Drug] *Injectable Suspension*—Liquid preparations of solids suspended in a suitable liquid medium. (Ex: Methylprednisolone Acetate Suspension)
5. [Drug] for *Injectable Suspension*—Dry solids that, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for *Injectable Suspensions*. (Ex: Imipenem)

The form in which a given drug is prepared for parenteral use by the manufacturer depends upon the nature of the drug itself, with respect to its physical and chemical characteristics, and also upon certain therapeutic considerations. Generally, if a drug is unstable in solution, it may be prepared as a dry powder intended for reconstitution with the proper solvent at the time of its administration, or it may be prepared as a suspension of the drug particles in a vehicle in which the drug is insoluble. If the drug is unstable in the presence of water, that solvent may be replaced in part or totally by a solvent in which the drug is insoluble. If the drug is insoluble in water, an injection may be prepared as an aqueous suspension or as a solution of the drug in a suitable nonaqueous solvent, such as a vegetable oil. If an aqueous solution is desired, a water-soluble salt form of the insoluble drug is frequently prepared to satisfy the required solubility characteristics. Aqueous or blood-miscible solutions may be injected directly into the blood stream. Blood-immiscible liquids, e.g., oleaginous injections and sus-

pensions, can interrupt the normal flow of blood within the circulatory system, and their use is generally restricted to other than intravenous administration. The onset and duration of action of a drug may be somewhat controlled by the chemical form of the drug used, the physical state of the injection (solution or suspension), and the vehicle employed. Drugs that are very soluble in body fluids generally have the most rapid absorption and onset of action. Thus, drugs in aqueous solution have a more rapid onset of action than do drugs in oleaginous solution. Drugs in aqueous suspension are also more rapid acting than drugs in oleaginous suspension due to the greater miscibility of the aqueous preparation with the body fluids after injection and the subsequent more rapid contact of the drug particles with the body fluids. Oftentimes more prolonged drug action is desired to reduce the necessity of frequently repeated injections. These long-acting types of injections are commonly referred to as repository or "depot" types of preparations.

The solutions and suspensions of drugs intended for injection are prepared in the same general manner as was discussed previously in this text for solutions (Chapter 12) and disperse systems (Chapter 13), with the following differences:

1. Solvents or vehicles used must meet special purity and other standards assuring their safety by injection.
2. The use of added substances, as buffers, stabilizers, and antimicrobial preservatives, fall under specific guidelines of use and are restricted in certain parenteral products. The use of coloring agents is strictly prohibited.
3. Parenteral products are always sterilized and meet sterility standards and must be pyrogen-free.
4. Parenteral solutions must meet compendial standards for particulate matter.
5. Parenteral products must be prepared in environmentally controlled areas, under strict sanitation standards, and by personnel specially trained and clothed to maintain the sanitation standards.
6. Parenteral products are packaged in special hermetic containers of specific and high quality. Special quality control procedures are utilized to ensure their hermetic seal and sterile condition.
7. Each container of an injection is filled to a volume in slight excess of the labeled "size" or volume to be withdrawn. This overfill permits the ease of withdrawal and administration of the labeled volumes.
8. There are restrictions over the volume of injection permitted in multiple-dose containers and also a limitation over the types of containers (single-dose or multiple-dose) which may be used for certain injections.
9. Specific labeling regulations apply to injections.
10. Sterile powders intended for solution or suspension immediately prior to injection are frequently packaged as *lyophilized* or freeze-dried powders to permit ease of solution or suspension upon the addition of the solvent or vehicle.

Solvents and Vehicles for Injections

The most frequently used solvent in the large-scale manufacturer of injections is *Water for Injection, USP.* This water is purified by distillation or by reverse osmosis and meets the same standards for the presence of total solids as does *Purified Water, USP,* not more than 1 mg per 100 mL Water for Injection, USP and may not contain added substances. Although water for injection is not required to be sterile, it must be pyrogen-free. The water is intended to be used in the manufacture of injectable products which are to be sterilized after their preparation. Water for injection should be stored in tight containers at temperatures below or above the range in which microbial growth occurs. Water for injection is intended to be used within 24 hours following its collection. Naturally, the water should be collected in sterile and pyrogen-free containers. The containers are usually glass or glass-lined.

Sterile Water for Injection, USP is water for injection which has been sterilized and packaged in single-dose containers of not greater than 1-liter size. As water for injection, it must be pyrogen-free and may not contain an antimicrobial agent or other added substance. This water may contain a slightly greater amount of total solids than water for injection due to the leaching of solids from the glass-lined tanks during the sterilization process. This water is intended to be used as a solvent, vehicle or diluent for already-sterilized and packaged injectable medications. The one-liter bottles cannot be administered intravenously because they have no tonicity. Thus, they are used for reconstitution of multiple antibiotics. In use, the water is aseptically added to the vial of medication to prepare the desired injection. For instance, a suitable injection may be prepared from the dry powder, Sterile Ampicillin Sodium, USP, by the aseptic addition of sterile water for injection.

Bacteriostatic Water for Injection, USP is sterile water for injection containing one or more suitable

antimicrobial agents. It is packaged in pre-filled syringes or in vials containing not more than 30 mL of the water. The container label must state the name and proportion of the antimicrobial agent(s) present. The water is employed as a sterile vehicle in the preparation of small volumes of injectable preparations. Theoretically, presence of the bacteriostatic agent gives the flexibility for multiple-dose vials. If the first person to withdraw medication inadvertently contaminates the vial contents, the preservative will destroy the microorganism. Although, historically, there has been debate on how much protection the antimicrobial agent can provide in a multiple-dose vial (4). Because of the presence of antimicrobial agents the water must only be used in parenterals that are administered in small volumes. Its use in parenterals administered in large volume is restricted due to the excessive and perhaps toxic amounts of the antimicrobial agents which would be injected along with the medication. Generally, if volumes of greater than 5 mL of solvent are required, sterile water for injection rather than bacteriostatic water for injection is preferred. In using bacteriostatic water for injection, due regard must also be given to the chemical compatibility of the bacteriostatic agent(s) present with the particular medicinal agent being dissolved or suspended.

USP labeling requirements demand that the label state, "Not for Use in Newborns." This labeling statement was the result of problems encountered with neonates and the toxicity of the bacteriostat, i.e., benzyl alcohol. This toxicity results from the high cumulative amounts (mg/kg) of benzyl alcohol and the limited detoxification capacity of the neonate liver. This solution has not been reported to cause problems in older infants, children, or adults.

Benzyl alcohol poisoning is recognized as the "gasping syndrome." In one study, ten premature infants developed this clinical syndrome characterized by the development of multi-organ failure and eventually died (5). The typical clinical course included metabolic acidosis, respiratory distress requiring mechanical ventilation, central nervous system dysfunction, hyperactivity, hypotonia, depression of the sensorium, apnea, seizure, coma, intraventricular hemorrhage, hepatic and renal failure, and eventual cardiovascular collapse and death. In the study, the amount of benzyl alcohol received ranged from 99–234 mg/kg/day. Based on the concentration of 0.9% benzyl alcohol in the Bacteriostatic Water for Injection and Sodium Chloride Injection death resulted from as little as 11 mL/kg/day.

Following toxicity reports and the deaths of infants in the early 1980s, the FDA issued a very strong recommendation to stop the use of fluids preserved with benzyl alcohol for use in neonates as a flush solution or to reconstitute medications.

Sodium Chloride Injection, USP is a sterile isotonic solution of sodium chloride in Water for Injection. It contains no antimicrobial agents. The sodium and chloride ion contents of the injection are approximately 154 mEq of each per liter. The solution may be used as a sterile vehicle in preparing solutions or suspensions of drugs for parenteral administration.

Besides its use to reconstitute medications for injection, Sodium Chloride Injection is frequently used as a catheter or IV line flush to maintain patency. Catheters or IV lines are constantly used to infuse fluids and intravenous medications and draw blood for laboratory analysis, among others. Usually 2 mL is used to flush the line after each use or every 8 hours if the line is not used.

Bacteriostatic Sodium Chloride Injection, USP is a sterile isotonic solution of sodium chloride in Water for Injection. It contains one or more suitable antimicrobial agents which must be specified on the labeling. Sodium chloride is present at 0.9% concentration to render the solution isotonic. For the reasons noted previously for bacteriostatic water for injection, this solution may not be packaged in containers greater than 30 mL in size. When this solution is used as a vehicle, care must be exercised to assure the compatibility of the added medicinal agent with the preservative(s) present as well as with the sodium chloride.

Bacteriostatic Sodium Chloride Injection is also used to flush a catheter or IV line to maintain its patency. When used in only small quantities for flushing lines and reconstituting medications, the amount of benzyl alcohol is negligible and safe. But, in neonates, especially premature infants with very low birth weights, accumulation of benzoic acid and unmetabolized benzyl alcohol may occur due to the aforementioned liver immaturity. Because of their low physical weight, their need for more medications due to acute illness, and the frequent use of the umbilical catheter for various purposes, these patients may receive many more flush solutions relative to their body weight compared to adults. Thus, Bacteriostatic Sodium Chloride Injection also carries the warning, "Not for Use in Newborns."

Suffice to say, that benzyl alcohol may also be present in other parenteral medications and the pharmacist must be vigilant for its inappropriate use in neonates. Generally speaking, however, the

amount of benzyl alcohol received through this means is negligible compared to the amount received from flush solutions. Preferably, the medication is available in a preservative-free formulation (i.e., single-use dose) and that should be utilized. However, if such a formulation is not available and there is no alternative, a medication preserved with benzyl alcohol might still be used based on the physician's clinical judgment and the risk-to-benefit ratio.

Ringer's Injection, USP is a sterile solution of sodium chloride, potassium chloride, and calcium chloride in water for injection. The three agents are present in concentrations similar to that found in physiologic fluids. The solution is employed as a vehicle for other drugs, or alone as an electrolyte replenisher and fluid extender. *Lactated Ringer's Injection, USP* has different quantities of the same three salts in Ringer's Injection and contains sodium lactate. This injection is a fluid and electrolyte replenisher and a systemic alkalizer.

Nonaqueous Vehicles

Although an aqueous vehicle is generally preferred for an injection, its use may be precluded in a formulation due to the limited water solubility of a medicinal substance or its susceptibility to hydrolysis. When such physical or chemical factors limit the use of a wholly aqueous vehicle, the pharmaceutical formulator must turn to one or more nonaqueous vehicles.

The selected vehicle must be nonirritating, nontoxic in the amounts administered, and nonsensitizing. Like water, it must not exert a pharmacologic activity of its own, nor may it adversely affect the activity of the medicinal agent. In addition, the physical and chemical properties of the solvent or vehicle must be considered, evaluated, and determined to be suitable for the task at hand before it may be employed. Among the many considerations are the solvent's physical and chemical stability at various pH levels, its viscosity, which must be such as to allow ease of injection (syringeability), its fluidity, which must be maintained over a fairly wide temperature range, its boiling point, which should be sufficiently high to permit heat sterilization, its miscibility with body fluids, its low vapor pressure to avoid problems during heat sterilization, and its constant purity or ease of purification and standardization. There is no single solvent that is free of limitations, and thus the cross-consideration and the assessment of each solvent's advantages and disadvantages help the formulator determine the most appropriate solvent for use in a given preparation. Among the nonaqueous solvents presently employed in parenteral products are fixed vegetable oils, glycerin, polyethylene glycols, propylene glycol, alcohol, and a number of lesser used agents as ethyl oleate, isopropyl myristate, and dimethylacetamide. These and other nonaqueous vehicles may be used provided they are safe in the amounts administered and do not interfere with the therapeutic efficacy of the preparation or with its response to prescribed assays and tests.

The USP specifies restrictions on the fixed vegetable oils which may be employed in parenteral products. For one thing, they must remain clear when cooled to 10°C to ensure the stability and clarity of the injectable product upon storage under refrigeration. The oils must not contain mineral oil or paraffin, as these materials are not absorbed by body tissues. The fluidity of a vegetable oil generally depends upon the proportion of unsaturated fatty acids, such as oleic acid, to saturated acids, such as stearic acid. Oils to be employed in injections must meet officially stated requirements of iodine number and saponification number.

Although the toxicities of vegetable oils are generally considered to be relatively low, some patients exhibit allergic reactions to specific oils. Thus, when vegetable oils are employed in parenteral products, the label must state the specific oil present. The most commonly used fixed oils in injections are corn oil, cottonseed oil, peanut oil, and sesame oil. Castor oil and olive oil have been used on occasion.

By the selective employment of solvent or vehicle, a pharmacist can prepare injectable preparations as solutions or suspensions of a medicinal substance in either an aqueous or nonaqueous vehicle. For the most part, oleaginous injections are administered intramuscularly. They must not be administered intravenously as the oil globules will occlude the pulmonary microcirculation. Some examples of official injections employing oil as the vehicle are presented in Table 14.1.

Added Substances

The USP permits the addition of suitable substances to the official preparations intended for injection for the purpose of increasing their stability or usefulness, provided the substances are not interdicted in the individual monographs and are harmless in the amounts administered and do not interfere with the therapeutic efficacy of the preparation or with specified assays and tests. Many of these added substances are antibacterial preservatives, buffers, solubilizers, antioxidants, and other

Table 14.1. Examples of Some Injections in Oil

Injection	*Oil*	*Category*
Dimercaprol Injection	Peanut	Antidote to arsenic, gold and mercury poisoning
Estradiol Cypionate Injection	Cottonseed	Estrogen
Estradiol Valerate Injection	Sesame or Castor	Estrogen
Fluphenazine Decanoate Injection	Sesame	Antipsychotic
Fluphenazine Enanthate Injection	Sesame	Antipsychotic
Hydroxyprogesterone Caproate Injection	Castor	Progestin
Progesterone in Oil Injection	Sesame or Peanut	Progestin
Testosterone Cypionate Injection	Cottonseed	Androgen
Testosterone Cypionate and Estradiol Cypionate Injection	Cottonseed	Androgen and Estrogen
Testosterone Enanthate Injection	Sesame	Androgen
Testosterone Enanthate and Estradiol Valerate Injection	Sesame	Androgen and Estrogen

pharmaceutical adjuncts. Agents employed solely for their coloring effect are strictly prohibited in parenteral products.

The USP requires that one or more suitable substances be added to parenteral products that are packaged in multiple-dose containers, to prevent the growth of microorganisms regardless of the method of sterilization employed, unless otherwise directed in the individual monograph or unless the injection's active ingredients are themselves bacteriostatic. Such substances are used in concentrations that prevent the growth of or kill microorganisms in the preparations. Because many of the usual preservative agents are toxic when given in excessive amounts or irritating when parenterally administered, special care must be exercised in the selection of the appropriate preservative agents. For the following preservatives, the indicated maximum limits prevail for use in a parenteral product unless otherwise directed: for agents containing mercury and the cationic, surface-active compounds, 0.01%; for agents like chlorobutanol, cresol, and phenol, 0.5%; for sulfur dioxide as an antioxidant, or for an equivalent amount of the sulfite, bisulfite, or metabisulfite of potassium or sodium, 0.2%.

In addition to the stabilizing effect of the additives, the air within an injectable product is frequently replaced with an inert gas, such as nitrogen, to enhance the stability of the product by preventing chemical reaction between the oxygen in the air and the drug.

Methods of Sterilization

The term *sterilization,* as applied to pharmaceutical preparations, means the complete destruction of all living organisms and their spores or their complete removal from the preparation. Five general methods are used for the sterilization of pharmaceutical products:

1. Steam sterilization
2. Dry-heat sterilization
3. Sterilization by filtration
4. Gas sterilization
5. Sterilization by ionizing radiation

The method used in attaining sterility in a pharmaceutical preparation is determined largely by the nature of the preparation and its ingredients. However, regardless of the method used, the resulting product must pass a test for sterility as proof of the effectiveness of the method and the performance of the equipment and the personnel.

Steam Sterilization

Steam sterilization is conducted in an autoclave and employs steam under pressure. It is recognized as the method of choice in most cases where the product is capable of withstanding such treatment (Fig. 14.3).

Most pharmaceutical products are adversely affected by heat and cannot be heated safely to the temperature required for dry-heat sterilization (about 170°C). When moisture is present, bacteria are coagulated and destroyed at a considerably lower temperature than when a moisture is absent. In fact, bacterial cells with a large percentage of water are generally killed rather easily. Spores, which contain a relatively low percentage of water, are comparatively difficult to destroy. The mechanism of microbial destruction in moist heat is thought to

Fig. 14.3 *Autoclaving of intravenous electrolyte solutions. (Courtesy of Abbott Laboratories.)*

be by denaturation and coagulation of some of the organism's essential protein. It is the presence of the hot moisture within the microbial cell that permits destruction at relatively low temperature. Death by dry heat is thought to be by the dehydration of the microbial cell followed by a slow burning or oxidative process. Because it is not possible to raise the temperature of steam above 100°C under atmospheric conditions, pressure is employed to achieve higher temperatures. It should be recognized that the temperature, not the pressure, is destructive to the microorganisms and that the application of pressure is solely for the purpose of increasing the temperature of the system. Time is another important factor in the destruction of microorganisms by heat. Most modern autoclaves have gauges to indicate to the operator the internal conditions of temperature and pressure and a timing device to permit the desired exposure time for the load. The usual steam pressures, the temperatures obtainable under these pressures, and the approximate length of time required for sterilization after the system reaches the indicated temperatures are as follows:

10 pounds pressure (115.5°C), for 30 minutes
15 pounds pressure (121.5°C), for 20 minutes
20 pounds pressure (126.5°C), for 15 minutes.

As can be seen, the greater the pressure applied, the higher the temperature obtainable and the less the time required for sterilization.

The temperature at which most autoclaves are routinely operated is usually 121°C, as measured at the steam discharge line running from the autoclave. It should be understood that the temperature attained in the chamber of the autoclave must also be reached by the interior of the load being sterilized, and this temperature must be maintained for an adequate time. The penetration time of the moist heat into the load may vary with the nature of the load, and the exposure time must be adjusted to account for this latent period. For example, a solution packaged in a thin-walled 50-mL ampul may reach a temperature of 121°C in from 6 to 8 minutes after that temperature is registered in the steam discharge line, whereas 20 minutes or longer may be required to reach that temperature within a solution packaged in a completely filled thick-walled 1000-mL glass bottle. An estimate of these latent periods must be added to the total time in order to ensure adequate exposure times. Because this sterilization process depends upon the presence of moisture and an elevated temperature, air is removed from the chamber as the sterilization process is begun, because a combination of air and steam yields a lower temperature than does steam alone under the same condition of pressure. For instance, at 15 pounds pressure the temperature of saturated steam is 121.5°C, but a mixture of equal parts of air and steam will reach only about 112°C.

In general, this method of sterilization is applicable to pharmaceutical preparations and materials that can withstand the required temperatures and are penetrated by, but not adversely affected by, moisture. In sterilizing aqueous solutions by this method, the moisture is already present, and all that is required is the elevation of the temperature of the solution for the prescribed period of time. Thus solutions packaged in sealed containers, as ampuls, are readily sterilized by this method. The method is also applicable to bulk solutions, glassware, surgical dressings, and instruments. It is not useful in the sterilization of oils, fats, oleaginous preparations, and other preparations not penetrated by the moisture or the sterilization of exposed powders that may be damaged by the condensed moisture.

Dry-Heat Sterilization

Dry-heat sterilization is usually carried out in sterilizing ovens specifically designed for this purpose. The ovens may be heated either by gas or electricity and are generally thermostatically controlled.

Because dry heat is less effective in killing microorganisms than is moist heat, higher temperatures and longer periods of exposure are required. These must be determined individually for each

product with consideration to the size and type of product and the container and its heat distribution characteristics. In general, individual units to be sterilized should be as small as possible, and the sterilizer should be loaded in such a manner as to permit free circulation of heated air throughout the chamber. Dry-heat sterilization is usually conducted at temperatures of 160° to 170°C for periods of not less than 2 hours. Higher temperatures permit shorter exposure times for a given article; conversely, lower temperatures require longer exposure times. For example, if a particular chemical agent melts or decomposes at 170°C, but is unaffected at 140°C, the lower temperature would be employed in its sterilization, and the exposure time would be increased over that required to sterilize another chemical that may be safely heated to 170°C.

Dry-heat sterilization is generally employed for substances that are not effectively sterilized by moist heat. Such substances include fixed oils, glycerin, various petroleum products such as petrolatum, liquid petrolatum (mineral oil), and paraffin and various heat-stable powders such as zinc oxide. Dry-heat sterilization is also an effective method for the sterilization of glassware and surgical instruments. Dry-heat sterilization is the method of choice when dry apparatus or dry containers are required, as in the handling of packaging of dry chemicals or nonaqueous solutions.

Sterilization by Filtration

Sterilization by filtration, which depends upon the physical removal of microorganisms by adsorption on the filter medium or by a sieving mechanism, is used for the sterilization of heat-sensitive solutions. Medicinal preparations sterilized by this method are required to undergo severe validation and monitoring since the effectiveness of the filtered product can be greatly influenced by the microbial load in the solution being filtered (Fig. 14.4).

Commercially available filters are produced with a variety of pore-size specifications. It would be well to mention briefly one type of these modern filters, the Millipore filters (Fig. 14.5). Millipore filters are thin plastic membranes of cellulosic esters with millions of pores per square inch of filter surface. The pores are made to be extremely uniform in size and occupy approximately 80% of the filter membrane's volume, the remaining 20% being the solid filter material. This high degree of porosity permits flow rates much in excess of other filters having the same particle-retention capability. Millipore filters are made from a variety of polymers to provide membrane characteristics required for the filtration of almost any liquid or gas system. Also, the filters are made of various pore sizes to meet the selective filtration requirements of the operator. They are available in pore sizes from 14 to 0.025 μm. For comparative purposes, the period that ended the last sentence is approximately 500 μm in size. The size of the smallest particle visible to the naked eye is about 40 μm, a red blood cell is about 6.5 μm, the smallest bacteria, about 0.2 μm, and a polio virus, about 0.025 μm.

Although the pore size of a bacterial filter is of prime importance in the removal of microorgan-

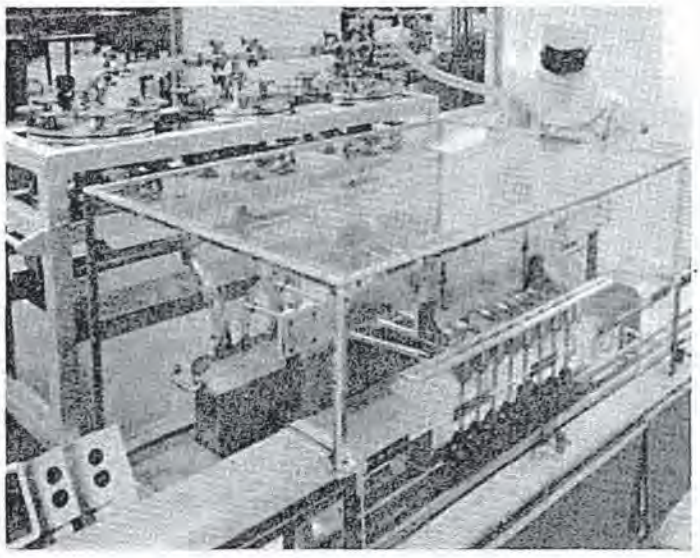

Fig. 14.4 *Sterilization by filtration. An eight-head bottle-filling machine using three large sterilizing filters for sterile filling of bottles in large scale pharmaceutical production. (Courtesy of Millipore Corporation.)*

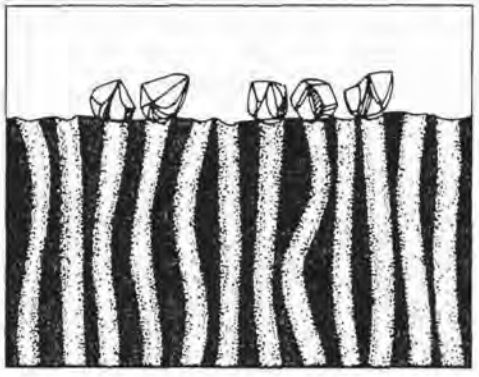

Fig. 14.5 *Membrane filters act as microporous screens that retain all particles and microorganisms larger than the rated pore size on their surface. (Courtesy of Millipore Corporation.)*

isms from a liquid, there are other factors such as the electrical charge on the filter and that of the microorganism, the pH of the solution, the temperature, and the pressure or vacuum applied to the system.

The major advantages of bacterial filtration include its speed in the filtration of small quantities of solution, its ability to sterilize effectively thermolabile materials, the relatively inexpensive equipment required, the development and proliferation of membrane filter technology, and the complete removal of living and dead microorganisms as well as other particulate matter from the solution.

The class of filter media lends itself to more effective standardization and quality control and also gives the user greater opportunity to confirm the characteristics or properties of the filter assembly before and after use. The fact that membrane filters are thin polymeric films offers many advantages but also some disadvantages when compared to depth filters such as porcelain or sintered material. Because much of the membrane surface is a void or open space, the properly assembled and sterilized filter offers the advantage of a high flow rate.

One disadvantage is that because the membrane is usually fragile, it is essential to determine that the assembly was properly made and that the membrane was not ruptured or flawed during assembly, sterilization, or use. The housing and filter assemblies that are chosen to be used should first be validated for compatibility and integrity by the user. This disadvantage is a circumstance not true of methods involving dry- or moist-heat sterilization in which the procedures are just about guaranteed to give effective sterilization. Also, filtration of large volumes of liquids would require more time, particularly if the liquid were viscous, than would, say, steam sterilization. In essence, the bacterial filters are useful when heat cannot be used and also for small volumes of liquids.

Bacterial filters may be used conveniently and economically in the community pharmacy to filter extemporaneously prepared solutions (as ophthalmic solutions) that are required to be sterile (Figs. 14.6, 14.7). Further, the membrane filter method is the most commonly used sterilization method used by hospitals. Occasionally, hospitals may use the autoclave (i.e., moist heat method) to sterilize IV solutions, such as caffeine citrate IV injection.

To date, there has been limited information about drug adsorption to membrane filters. Several studies, however, have demonstrated that membrane filters have the capacity to remove drug from solution (6–9). For example, 0.22 micron filters reduce the in vitro antimicrobial activity of amphotericin B (a colloidal suspension), while filtration of the amphotericin B through 0.85 and 0.45 micron filters did not. Butler et al. demonstrated that the potency of drugs administered intravenously and in small doses could be significantly reduced during in-line filtration with a filter containing a cellulose ester membrane (10). The pharmaceutical literature indicates that drugs administered in low doses might present the problem of the drug's bonding to the filter. Many filters in clinical use are nitrate or acetate esters of cellulose. These compounds are polar and have residual hydroxyl groups that might become involved with drug adsorption interactions. Hydrophobic interactions between hydrocarbon portions of drug molecules being filtered and linear cellulose molecules of filters are also thought to be involved in drug adsorption.

In general, current information suggests that little or no adsorption takes place with membrane filters. However, it is recommended that minute dosages of drugs (i.e., <5 mg) should not be filtered until sufficient data are available to demonstrate

Fig. 14.6 *Luer-Lock syringe adapted with a MILLEX Filter Unit and hypodermic needle. (Courtesy of Millipore Corporation.)*

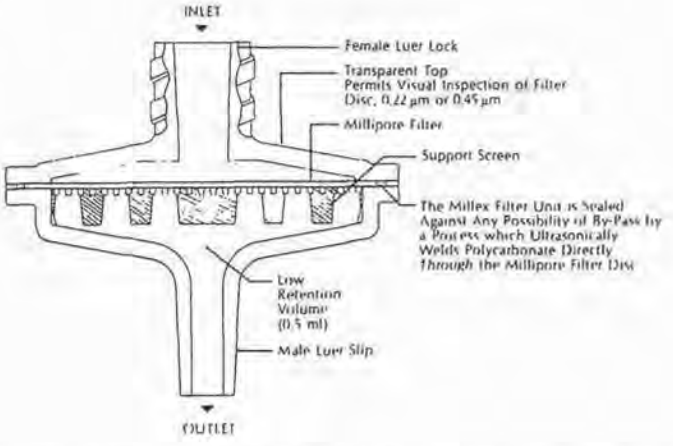

Fig. 14.7 *Cutaway showing composition of the MILLEX filter unit. (Courtesy of Millipore Corporation.)*

insignificant adsorption. With respect to amphotericin B, to assure the passage of the antibiotic colloidal dispersion, the filter's mean pore diameter should > 1 micron.

Membrane filter media which are now available include cellulose acetate, cellulose nitrate, fluorocarbonate, acrylic polymers, polycarbonate, polyester, polyvinyl chloride, vinyl, nylon, polytef, and even metal membranes, and they may be reinforced or supported by an internal fabric.

Gas Sterilization

Some heat-sensitive and moisture-sensitive materials can be sterilized much better by exposure to ethylene oxide or propylene oxide gas than by other means. These gases are highly flammable when mixed with air but can be employed safely when properly diluted with an inert gas such as carbon dioxide or a suitable fluorinated hydrocarbon. Such mixtures are commercially available.

Sterilization by this process requires specialized equipment resembling autoclaves, and many combination steam autoclaves-ethylene oxide sterilizers are commercially available. Greater precautions are required for this method of sterilization than for some of the others, because the variables—for instance, time, temperature, gas concentration, and humidity—are not as firmly quantitated as those of dry-heat and steam sterilization. In general, sterilization with gas is enhanced, and the exposure time required is reduced, by increasing the relative humidity of the system (to about 60%) and by increasing the exposure temperature (to between 50 and 60°C). If the material being sterilized cannot tolerate either the moisture or the elevated temperature, exposure time will have to be increased. Generally, sterilization with ethylene oxide gas requires from 4 to 16 hours of exposure. Ethylene oxide is thought to function as a sterilizing agent by its interference with the metabolism of the bacterial cell.

The great penetrating qualities of ethylene oxide gas make it a useful sterilizing agent in certain special applications, as in the sterilization of medical and surgical supplies and appliances such as catheters, needles, and plastic disposable syringes in their final plastic packaging just prior to shipment. The gas is also used to sterilize certain heat-labile enzyme preparations, certain antibiotics, and other drugs, with tests being performed to assure of the absence of chemical reaction or other deleterious effects on the drug substance.

Sterilization by Ionizing Radiation

Techniques are available for the sterilization of some types of pharmaceuticals by gamma rays and by cathode rays, but the application of such techniques is limited because of the highly specialized equipment required and the effects of irradiation on products and their containers.

The exact mechanism by which irradiation sterilizes a drug or preparation is still subject to investigation. One of the proposed theories involves an alteration of the chemicals within or supporting the microorganism to form deleterious new chemicals capable of destroying the cell. Another theory proposes that vital structures of the cell, such as the chromosomal nucleoprotein, are disoriented or destroyed. It is probably a combination of irradiation effects that causes the cellular destruction, which is complete and irreversible.

Validation of Sterility

Regardless of the method of sterilization employed, pharmaceutical preparations required to be sterile must undergo sterility tests to confirm the absence of microorganisms. The USP contains

monographs and standards for biologic indicators of a sterilization process. A *biologic indicator* is a characterized preparation of specific microorganisms resistant to a particular sterilization process. They may be utilized to monitor a sterilization cycle and/or to periodically revalidate the process. Biologic indicators are generally of two main forms. In one, spores are added to a carrier, as a strip of filter paper, packaged to maintain physical integrity while allowing the sterilization effect. In the other, the spores are added to representative units of the product being sterilized, with sterilization assessed based on these samples. In moist heat (i.e., steam) sterilization and ethylene oxide sterilization, spores of suitable strains of *Bacillus stearothermophilus* are commonly employed because of their resistance to this mode of sterilization. In dry heat sterilization, spores of *Bacillus subtilis* are commonly used. In sterilization by ionizing radiation, spores of suitable strains of *Bacillus pumilus, Bacillus stearothermophilus,* and *Bacillus subtilis* have been utilized.

The effectiveness of thermal sterilization procedures has been quantified through the determination and calculation of *F value* to express the time of thermal death. *Thermal death time* is defined as the time required to kill a particular organism under specified conditions. The F_0, at a particular temperature other than 121°C, is the time, in minutes, required to provide the lethality equivalent to that provided at 121° for a stated time.

Although heat distribution in an autoclave chamber is usually rapid with 121°C obtained nearly instantaneously throughout the autoclave, the product being sterilized may not achieve identical conditions due to a variety of factors of heat transfer, including the thermal conductivity of the packaging components, the viscosity and density of the product, container proximity, passage of steam around containers and other variables. F values may be computed from biologic data derived from the rate of destruction of known numbers of microorganisms, as shown in the following equation:

$$F_0 = D_{121}(\text{Log A} - \text{Log B})$$

where D_{121} = the time required for a one-log reduction in the microbial population exposed to a temperature of 121°C
A = the initial microbial population
B = the number of microorganisms that survive after a defined heating time (11).

Pyrogens and Pyrogen Testing

As indicated earlier, *pyrogens* are fever-producing organic substances arising from microbial contamination and responsible for many of the febrile reactions which occur in patients following injection. The causative material is thought to be a lipopolysaccharide from the outer cell wall of the bacteria and endotoxins. Because the material is thermostable, it may remain in water even after sterilization by autoclaving or by bacterial filtration.

Manufacturers of water for injection may employ any suitable method for the removal of pyrogens from their product. Because pyrogens are organic substances, one of the more common means of facilitating their removal is by oxidizing them to easily eliminated gases or to nonvolatile solids, both of which are easily separated from water by fractional distillation. Potassium permanganate is usually employed as the oxidizing agent, with its efficiency being increased by the addition of a small amount of barium hydroxide serving to impart alkalinity to the solution and to make nonvolatile barium salts of any acidic compounds that may be present. These two reagents are added to water that has previously been distilled several times, and the distillation process is repeated with the chemical-free distillate being collected under strict aseptic conditions. When properly conducted, this method results in a highly purified, sterile, and pyrogen-free water. However, in each instance the official pyrogen test must be performed for assurance of the absence of these fever-producing materials.

PYROGEN TEST. The USP Pyrogen Test utilizes healthy rabbits that have been properly maintained in terms of environment and diet prior to performance of the test. Normal, or "control" temperatures are taken for each animal to be used in the test. These temperatures are used as the base for the determination of any temperature increase resulting from the injection of a test solution. In a given test, rabbits are used whose temperatures do not differ by more than one degree from each other and whose body temperatures are considered to be unelevated. A synopsis of the procedure of the test is as follows.

Render the syringes, needles, and glassware free from pyrogens by heating at 250°C for not less than 30 minutes or by other suitable method. Warm the product to be tested to 37°C ± 2°C.

Inject into an ear vein of each of three rabbits 10 mL of the product per kg of body weight, completing each injection within 10 minutes after the start of administration. Record the temperature at 30-minute intervals between 1 and 3 hours subsequent to the injection.

If no rabbit shows an individual rise in temperature of 0.5° or more above its respective control temperature, the product meets the requirements for the absence of pyrogens. If any rabbit shows an individual temperature rise of 0.5° or more, continue the test using five other rabbits. If not more than three of the eight rabbits show individual rises in temperature of 0.5° or more and if the sum of the eight individual maximum temperature rises does not exceed 3.3°, the material under examination meets the requirements for the absence of pyrogens.

In recent years, it has been shown that an extract from the blood cells of the horseshoe crab (*Limulus polyphemus*) contains an enzyme and protein system that coagulates in the presence of low levels of lipopolysaccharides. This discovery has led to the development of the *Limulus* amebocyte lysate (LAL) test for the presence of bacterial endotoxins. The USP Bacterial Endotoxins Test utilizes LAL and is considered generally more sensitive to endotoxin than the rabbit test. The FDA has endorsed the test as a replacement for the rabbit test and it is used for a number of parenteral products.

Some parenteral products, however, cannot be tested with the LAL test because the active ingredient interferes with the test outcome. Such products include meperidine HCl and promethazine HCl, oxacillin sodium, sulfisoxazole, and vancomycin HCl, among others. These then, must be tested with the aforementioned USP Pyrogen Test.

Because the LAL test is so sensitive for the presence of bacterial endotoxins, in some cases, where the active ingredient of the small volume parenteral can interfere with the test, a strategy to overcome this interference is to dilute the product more than one twofold dilution. Such products include diphenhydramine HCl, ephedrine HCl, meperidine HCl, promethazine HCl, and thiamine HCl, among others, are thus tested in this manner.

The Industrial Preparation of Parenteral Products

Once the formulation for a particular parenteral product is determined, including the selection of the proper solvents or vehicles and additives, the production pharmacist must follow rigid aseptic procedures in preparing the injectable products. In most manufacturing plants the area in which parenteral products are made is maintained bacteria-free through the use of ultraviolet lights, a filtered air supply, sterile manufacturing equipment, such as flasks, connecting tubes, and filters, and sterilized work clothing worn by the personnel in the area (Fig. 14.8).

In the preparation of parenteral solutions, the required ingredients are dissolved according to good pharmaceutical practice either in water for injection, in one of the alternate solvents, or in a combination of solvents. The solutions are then usually filtered until sparkling clear through a membrane-type filter. After filtration, the solution is transferred as rapidly as possible and with the least possible exposure into the final containers. The product is then sterilized, preferably by autoclaving, and samples of the finished product are tested for sterility and pyrogens. In instances in which sterilization by autoclaving is impractical due to the nature of the ingredients, the individual components of the preparation that are heat or moisture labile may be sterilized by other appropriate means and added aseptically to the sterilized solvent or to a sterile solution of all of the other components sterilizable by autoclaving.

Suspensions of drugs intended for parenteral use may be prepared by reducing the drug to a very fine powder with a ball mill, micronizer, colloid mill, or other appropriate equipment and then suspending the material in a liquid in which it is insoluble. It is frequently necessary to sterilize separately the individual components of a suspension before combining them, as frequently the integrity of a suspension is destroyed by autoclaving. Autoclaving of a parenteral suspension may alter the viscosity of the product, thereby affecting the suspending ability of the vehicle, or change the particle size of the suspended particles, thereby altering both the pharmaceutic and the therapeutic characteristics of the preparation. If a suspension remains unaltered by autoclaving, this method is generally employed to sterilize the final product. Because parenterally administered emulsions, which are dispersions or suspensions of a liquid throughout another liquid, are generally destroyed by autoclaving, an alternate method of sterilization must be employed for this type of injectable.

Some injections are packaged as dry solids rather than in conjunction with a solvent or vehicle due to the instability of the therapeutic agent in the presence of the liquid component. These dry powdered drugs are packaged as the sterilized powder in the final containers to be reconstituted with the proper liquid prior to use, generally to form a solution or less frequently a suspension. The method of sterilization of the powder may be dry heat or another method that is appropriate for the particular drug

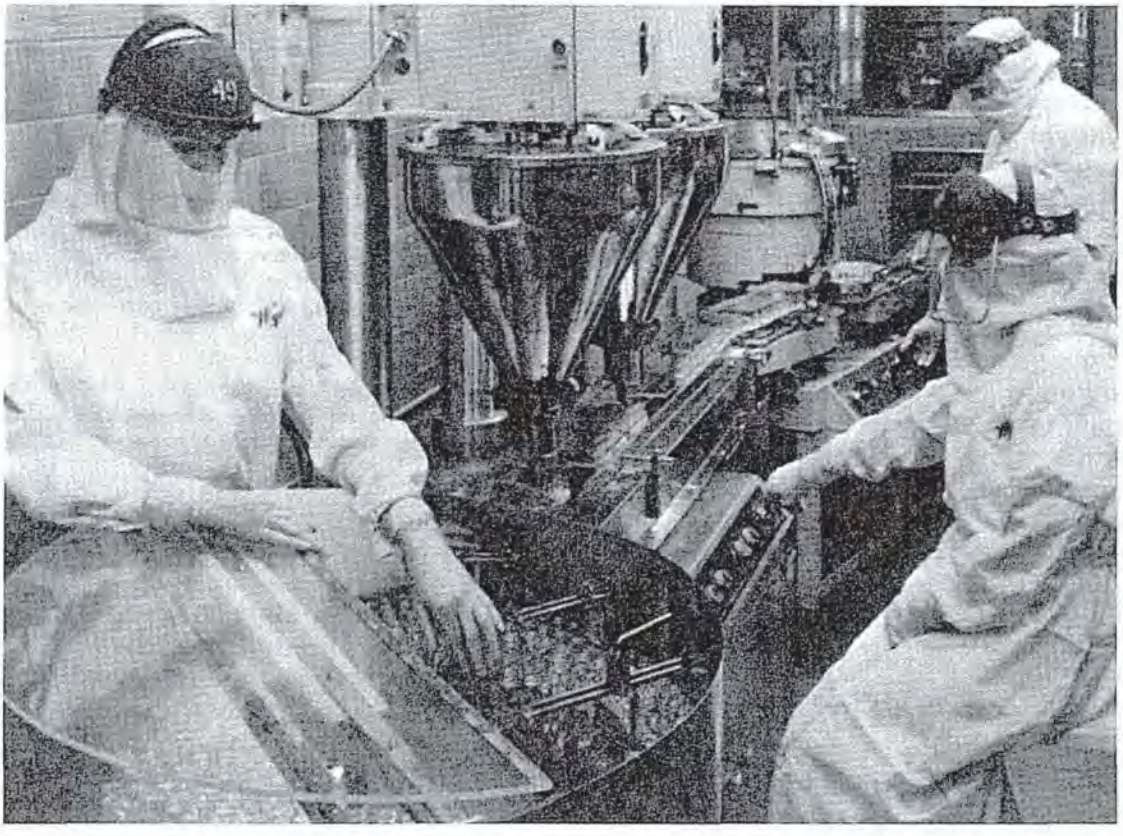

Fig. 14.8 *Sterile filling of vials. (Courtesy of Wyeth Laboratories.)*

involved. Examples of sterile drugs prepared and packaged *without* the presence of pharmaceutical additives as buffers, preservatives, stabilizers, tonicity agents, and other substances include:

Sterile Ampicillin Sodium
Sterile Ceftizoxime Sodium
Sterile Ceftazidime Sodium
Sterile Cefuroxime Sodium
Sterile Kanamycin Sulfate
Sterile Nafcillin Sodium
Sterile Penicillin G Benzathine
Sterile Streptomycin Sulfate
Sterile Tobramycin Sulfate

Antibiotics are prepared industrially in large fermentation tanks (Fig. 14.9).

Those sterile drugs formulated *with* pharmaceutical additives and intended to be reconstituted prior to injection include the following:

Cephradine for Injection
Cyclophosphamide for Injection
Dactinomycin for Injection
Erythromycin Lactobionate for Injection
Hyaluronidase for Injection
Hydrocortisone Sodium Succinate for Injection
Mitomycin for Injection
Nafcillin Sodium for Injection
Oxytetracycline Hydrochloride for Injection
Penicillin G Potassium for Injection
Vinblastine Sulfate for Injection

In certain instances, a liquid is packaged along with the dry powder for use at the time of reconstitution (Fig. 14.10). This liquid is sterile and may contain some of the desired pharmaceutical additives as the buffering agents. More frequently, the solvent or vehicle is not provided along with the dry product, but the labeling on the injection generally lists suitable solvents. Sodium chloride injection or sterile water for injection are perhaps the most frequently employed solvents used to reconstitute dry-packaged injections. The dry powders are packaged in containers large enough to permit proper shaking with the liquid component when the latter is aseptically injected through the container's rubber closure during its reconstitution. To facilitate the dissolving process, the dry powder is prevented from caking upon standing by the appropriate means including

Physical Pharmacy Capsule 14.1

Colligative Properties of Drugs

Drug molecules have properties that are often divided into additive, constitutive, or colligative.

Additive properties depend on the total contribution of the atoms in the molecule, or upon the sum of the properties of the constituents of the solution. An example is molecular weight.

Constitutive properties depend on the arrangement and, to a lesser extent, the number and kind of atoms in a molecule. Examples of this are the refraction of light, electrical properties, and surface and interfacial properties.

Colligative properties depend primarily on the number of particles in solution. Example properties include changes in vapor pressure, boiling point, freezing point and osmotic pressure. These values should be approximately equal for equimolar concentrations of drugs.

LOWERING OF VAPOR PRESSURE

A vapor, when in equilibrium with its pure liquid at a constant temperature, will exert a certain pressure known as the *vapor pressure*. When a solute is added to the pure liquid, it will alter the tendency of the molecules to escape the original liquid. In an ideal solution, or one that is very dilute, the partial vapor pressure of one component (p_1) is proportional to the mole fraction of molecules (N_1) of that component in the mixture:

$$p_1 = N_1 p_1^\circ$$

where p_1° is the vapor pressure of the pure component.

EXAMPLE 1

What is the partial vapor pressure of a solution containing 50 g dextrose in 1000 mL of water (the vapor pressure of water is given as 23.76 mm Hg).

1. (50 g dextrose)/(MW of 180) = 0.28 moles of dextrose
2. (1000 g water)/MW of 18) = 55.56 moles of water
3. 0.28 + 55.56 = 55.84 total moles
4. (55.56)/(55.84) = 0.995 mole fraction of water
5. p_1 = (0.995)(23.76 mm Hg) = 23.64 mm Hg

The vapor pressure of the solution is 23.64 mm Hg. The decrease in vapor pressure by the addition of the 50 g dextrose is 23.76 - 23.64 = 0.12 mm Hg.

INCREASE IN BOILING POINT

The *boiling point* of a liquid is that temperature when the vapor pressure of the liquid comes into equilibrium with the atmospheric pressure. The vapor pressure is reduced when a nonvolatile solute is added to a solvent, so the solution must be heated to a higher temperature to reestablish the equilibrium—hence, an increase in the boiling point. This is described in the following equation:

$$\Delta T_b = k_b m$$

where ΔT_b is the change in boiling point; k_b is the molar elevation constant of water, and m is the molality of the solute.

EXAMPLE 2

What is the boiling point elevation of a solution containing 50 g dextrose in 1000 mL of water (the molal elevation constant of water is 0.51).

1. (50 g dextrose)/(MW of 180) = 0.28 moles of dextrose in 1000 mL of water or 0.28 molal solution.
2. ΔT_b = (0.51) (0.28) = 0.143°C.

DECREASE IN FREEZING POINT

The *freezing point* of a pure liquid is the temperature at which the solid and liquid phases are in equilibrium at 1 atmosphere pressure. The freezing point of a solution is that temperature at which the solid phase of pure solvent and the liquid phase of solution are in equilibrium at 1 atmosphere pressure. When

Physical Pharmacy Capsule 14.1 **Colligative Properties of Drugs (Continued)**

a solute is added to a solvent, the decrease in freezing point is proportional to the concentration of the solute. The relationship is described by the following equation:

$$\Delta T_f = k_f m$$

where ΔT_f is the change in freezing point;
k_f is the molal freezing point depression constant of water; and
m is the molality of the solute.

EXAMPLE 3
What is the decrease in freezing point of a solution containing 50 g dextrose in 1000 mL of water (the molal elevation constant of water is −1.86°C).

1. (50 g dextrose)/(MW of 180) = 0.28 moles of dextrose in 1000 mL of water or 0.28 molal solution.
2. $\Delta T_f = (-1.86)\ (0.28) = -0.52°C$.

OSMOTIC PRESSURE

The pressure that must be applied to a more concentrated solution just to prevent the flow of pure solvent into the solution separated by a semipermeable membrane is called the *osmotic pressure*. This relationship can be expressed as follows:

$$PV = nRT$$

where P is the pressure (atm);
V is the volume (L);
n is number of moles of solute;
R is the gas constant (0.082 L-atm/mole deg), and
T is the absolute temperature in °C.

EXAMPLE 4
What is the osmotic pressure of 50 g dextrose in 1000 mL of water at room temperature (25°C)?

1. (50 g dextrose)/(MW of 180) = 0.28 moles of dextrose
2. 273°C + 25°C = 298°C
3. Volume will be 1 L
4. $P = [(0.28)(0.082)(298)]/(1) = 6.84$ atm

Deviations from reality in the above ideal examples of colligative properties are explained by the use of the Van't Hoff term, i. This "i" term considers that electrolytes exert more pressure than nonelectrolytes and is related to the number of ionic species present. These deviations may be caused by ionic interaction, degree of dissociation of weak electrolytes, or associations of nonelectrolytes.

MILLIEQUIVALENTS
An *equivalent weight* is the atomic weight, in grams, of a material divided by its valence, or charge. MilliEquivalents are related to equivalents, which are also considered measures of combining power, chemical activity, or chemical reactivity. Equivalency, or milliEquivalency, takes into consideration the total number of ionic charges in solution and the valence of the ions. Normally, plasma contains about 155 milliEquivalents of cations and anions in solution. The number of cations is always matched by the number of anions.

A *milliEquivalent* is the quantity, in mg, of a solute equal to 1/1000 of its gram-equivalent weight. Consider the following example.

EXAMPLE 1
What is the milliEquivalent weight of sodium?

1. The atomic weight of sodium is 23.
2. The valence of sodium is +1.

Physical Pharmacy Capsule 14.1 **Colligative Properties of Drugs (Continued)**

3. The equivalent weight of sodium is (23 g)/(1) = 23 g.
4. The milliEquivalent weight of sodium is (23 g)/1000 = 0.023 g, or 23 mg.
5. Therefore, one milliEquivalent of sodium weighs 23 mg.

MilliEquivalent calculations are commonly required in pharmacy practice today. The following are some examples.

EXAMPLE 2

How many milliEquivalents of potassium chloride are in a solution containing 74.5 mg/mL?

1. The atomic weight of potassium is 39 and chloride is 35.5. The combined molecular weight is 74.5.
2. Since the valence is 1 for both potassium and chloride, the equivalent weight for potassium chloride is 74.5 g and the milliEquivalent weight is 74.5 mg.
3. The solution contains 74.5 mg/mL, and the milliEquivalent weight is 74.5 mg; therefore, there is 1 mEq/mL of potassium chloride in the solution.

EXAMPLE 3

How many milliEquivalents of calcium are in 10 mL of 10% calcium chloride ($CaCl_2.2\ H_2O$) solution?

1. The formula weight for calcium chloride dihydrate is 147.
2. The equivalent weight is 147/2 = 73.5, since calcium is divalent.
3. Therefore, 1 milliEquivalent of calcium chloride weighs 73.5 mg.
4. (10 mL) (10%) = 1 g, or 1000 mg) of calcium chloride dihydrate.
5. (1000 mg)/(73.5 mg) = 13.6 mEq of calcium chloride dihydrate, which also is 13.6 mEq of calcium.

EXAMPLE 4

How many milliEquivalents of sodium are contained in a 1 liter bag of 0.9% sodium chloride solution?

1. (1000 mL) (0.009) = 9 g, or 9000 mg.
2. The formula weight for sodium chloride is 23 + 35.5 = 58.5.
3. The milliEquivalent weight for sodium chloride is 58.5 mg.
4. (9000)/(58.5) = 153.8 mEq, or 154 mEq.

In these cases, since sodium chloride is monovalent, there are 154 mEq of sodium, 154 mEq of chloride, or 154 mEq of sodium chloride.

OSMOLALITY AND TONICITY

Biologic systems are compatible with solutions having similar osmotic pressures, i.e., an equivalent number of dissolved species. For example, red blood cells, blood plasma, and 0.9% sodium chloride solution contain approximately the same number of solute particles per unit volume and are termed iso-osmotic and isotonic.

If solutions do not contain the same number of dissolved species i.e., they contain more (hypertonic) or less (hypotonic), then it may be necessary to alter the composition of the solution to bring them into an acceptable range.

An osmol (Osm) is related to a mole (gram molecular weight) of the molecules or ions in solution. One mole of glucose (180 g) dissolved in 1000 g of water has an osmolality of 1 Osm, or 1000 mOsm per kg of water. One mole of sodium chloride (23 + 35.5 = 58.5 g) dissolved in 1000 g of water has an osmolality of almost 2000 mOsm, since sodium chloride dissociates into almost two particles per molecule. In other words, a 1 molal solution of sodium chloride is equivalent to a 2 molal solution of dextrose.

Normal serum osmolality values are in the vicinity of 285 mOsm/kg (often expressed as 285 mOsm/L). Ranges may include values from about 275 to 300 mOsm/L). Pharmaceuticals should be close to this value to minimize discomfort on application to the eyes or nose, or when injected.

Physical Pharmacy Capsule 14.1

Colligative Properties of Drugs (Continued)

Some solutions may be iso-osmotic but not isotonic. This is because the physiology of the cell membranes must be considered. For example, the cell membrane of the red blood cell is not semi-permeable to all drugs. It allows ammonium chloride, alcohol, boric acid, glycerin, propylene glycol, and urea to diffuse freely. In the eye, the cell membrane is semi-permeable to boric acid, and a 1.9% solution of boric acid is an isotonic ophthalmic solution. But even though a 1.9% solution of boric acid is isotonic with the eye and is iso-osmotic, it is not isotonic with blood—since boric acid can freely diffuse through the red blood cells—and it may cause hemolysis.

Pharmacists are often called upon to calculate the quantity of solute that must be added to adjust a hypotonic solution of a drug to isotonic. This can be done using several methods, including the "L," sodium chloride equivalent, and cryoscopic methods.

One of the most frequently used methods for calculating the quantity of sodium chloride necessary to prepare an isotonic solution is the *sodium chloride equivalent method.* A "sodium chloride equivalent" is defined as the amount of sodium chloride that is osmotically equivalent to 1 g of the drug. For example, the sodium chloride equivalent of ephedrine sulfate is 0.23 (i.e., 1 g of ephedrine sulfate would be equivalent to 0.23 g of sodium chloride).

EXAMPLE 1

How much sodium chloride is required to make the following prescription isotonic?

Rx Ephedrine sulfate 2%
Sterile water, qs30 mL
M. isoton with sodium chloride.

1. (30 mL) (0.009) = 0.270 g sodium chloride would be required if only sodium chloride was present in the 30 mL of solution.
2. (30 mL) (0.02) = 0.6 g ephedrine sulfate is to be present.
3. (0.6 g) (0.23) = 0.138 g is the quantity of sodium chloride "represented" by the ephedrine sulfate present.
4. Since 0.270 g sodium chloride would be required if only sodium chloride is used, and the quantity of sodium chloride that is equivalent to 0.6 g of ephedrine sulfate is 0.138 g, then 0.270 − 0.138 g = 0.132 g of sodium chloride would be required to render the solution isotonic.
5. Therefore, to prepare the solution would require 0.6 grams of ephedrine sulfate, 0.132 grams of sodium chloride, and sufficient sterile water to make 30 mL.

its preparation by lyophilization (Fig. 14.11). Powders so treated form a honeycomb, lattice structure that is rapidly penetrated by the liquid, and solution is rapidly effected because of the large surface area of powder exposed.

Upjohn-Pharmacia has a newer Mix-O-Vial that incorporates the cover as part of the plunger. Once mixed, the small circle of plastic that covers the injection site is removed. This reduces the touch contamination potential.

The Abbott ADD-Vantage System IVPH is another example of a ready-to-mix sterile IV product designed for intermittent IV administration of potent drugs that do not have long-term stability in solution. With this system, antibiotics and other

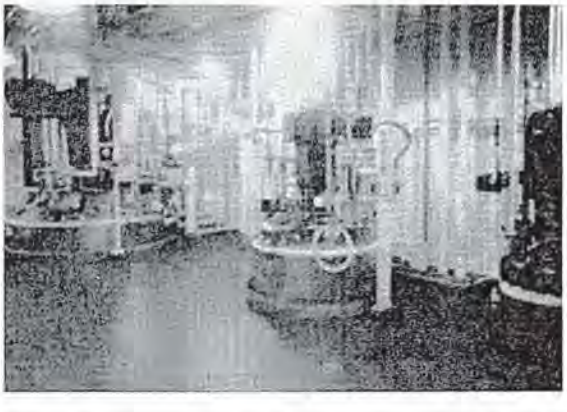

Fig. 14.9 *Fermentation tank in the preparation of antibiotics. (Courtesy of Schering-Plough.)*

Fig. 14.10 *The Mix-O-Vial shown above is a combination vial containing dry ingredients in the bottom compartment and a liquid diluent in the top compartment, separated by a specially formulated center seal. The bottom compartment can either be liquid filled, frozen and dried to make a lyophilized product, or it may be powder filled. The top diluent contains a preservative and may or may not contain one or more active ingredients. To use the vial, the dust cover is removed (as shown above), pressure is applied with the thumb to the top plunger which dislodges the center seal and the vial is shaken until the solution is effected. The top of the plunger is then swabbed with a disinfectant; the syringe needle inserted through the target circle on the plunger and the contents of the vial withdrawn into the syringe. The Mix-O-Vial offers stability of product (until it is activated), convenience, fast operation and safety as regards the right drug with the proper diluent in the correct proportions. (Courtesy of The Upjohn Company.)*

drugs do not have to be mixed until just prior to administration.

ADD-Vantage consists of two components (Fig. 14.12): a flexible plastic IV container partially filled with diluent and a glass vial of powdered or liquid drug. The vials containing the medication and the piggybacks (i.e., 50–250 mL of Dextrose 5% in Water Injection [D_5W] or Normal Saline Solution [NSS]) are specially designed to be used together. The vial locks into a chamber inside the plastic container, and the drug is released by removing the stopper on the vial, allowing the two components to mix. This simple process is performed by external manipulation of the container, thereby preserving the closed, sterile system.

The ADD-Vantage unit may be assembled in a number of locations. Microbiological tests and sterility tests have been conducted at various intervals following assembly of the units under a laminar flow hood, in a pharmacy on a countertop and in a patient's hospital room. The final admixtures were sterile, demonstrating that the ADD-Vantage unit can be aseptically assembled under the conditions tested. However, whenever possible, this system should be assembled under a laminar flow hood.

The assembled, but not activated ADD-Vantage System can be used within 30 days from the date that the diluent container was removed from the overwrap. ADD-Vantage enables hospitals to reduce drug waste, often caused by cancelled or changed prescriptions, and helps the pharmacy conserve labor and reduce material costs.

The Monovial Safety Guard (Becton Dickinson Pharmaceutical Systems) is a new IV infusion sys-

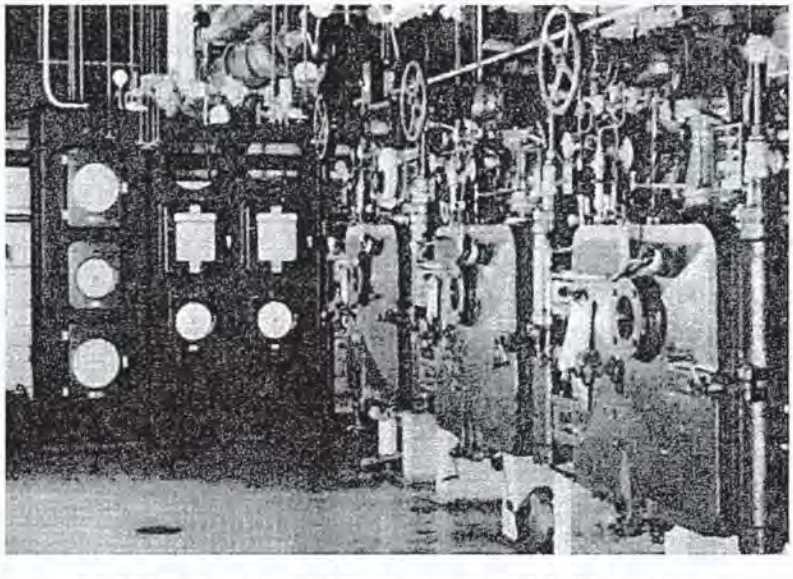

Fig. 14.11 *Antibiotic lyophilizers. (Courtesy of Abbott Laboratories.)*

Fig. 14.12 *ADD-Vantage system. (Courtesy of Abbott Laboratories.)*

tem for use in preparing extemporaneous small-volume infusions utilizing plastic minibags (Fig. 14.13). When compared to the two traditional methods of preparing small-volume infusions, i.e., the transfer needle and vial (TFN) method, the syringe and vial (SYR) method, the Monovial system performed quite favorably by saving time, used fewer materials, and was less costly (12).

This system is an integrated device (i.e., drug, transfer mechanism) with a protective shield surrounding the attached transfer needle. The reconstitution and transfer of the drug into an infusion bag is accomplished safely, quickly, and necessitates fewer materials. The needle is inserted into the port of the infusion bag and then the transfer set is pushed down toward the vial until a "click" is heard. With the Monovial upright, the infusion bag is squeezed several times to transfer fluid into the Monovial. The Monovial is then shaken a few times to reconstitute the drug. It is then inverted and then the minibag is squeezed and released to transfer the drug back into the infusion bag. This process is repeated until the vial is empty. Presently, diltiazem HCl (i.e., Cardizem) for injection is available with the Monovial Safety Guard.

Several manufacturers now ship to the hospital pharmacy reconstituted intravenous antibiotic solutions, e.g., cefazolin sodium, in the frozen state. When thawed these nonpyrogenic solutions are stable for a finite amount of time, e.g., reconstituted cefazolin is stable for 48 hours at room temperature and for 10 days refrigerated (5°C). The product is packaged in a small plastic bag for piggy-back use in intravenous administration to the patient.

Packaging, Labeling, and Storage of Injections

Containers for injections, including the closures, must not interact physically or chemically with the preparation so as to alter its strength or efficacy (Fig. 14.14). If the container is made of glass, it must be clear and colorless or of a light amber color to permit the inspection of its contents. The type of glass suitable and preferred for each parenteral preparation is usually stated in the individual monograph. Injections are placed either in single-dose containers or in multiple-dose containers (Figs. 14.15 through 14.17). By definition:

Fig. 14.13 *Monovial safety guard system. (Courtesy of Becton-Dickinson.)*

Fig. 14.14 *Testing compatibility of rubber closures with the solution with which they are in contact. (Courtesy of Abbott Laboratories.)*

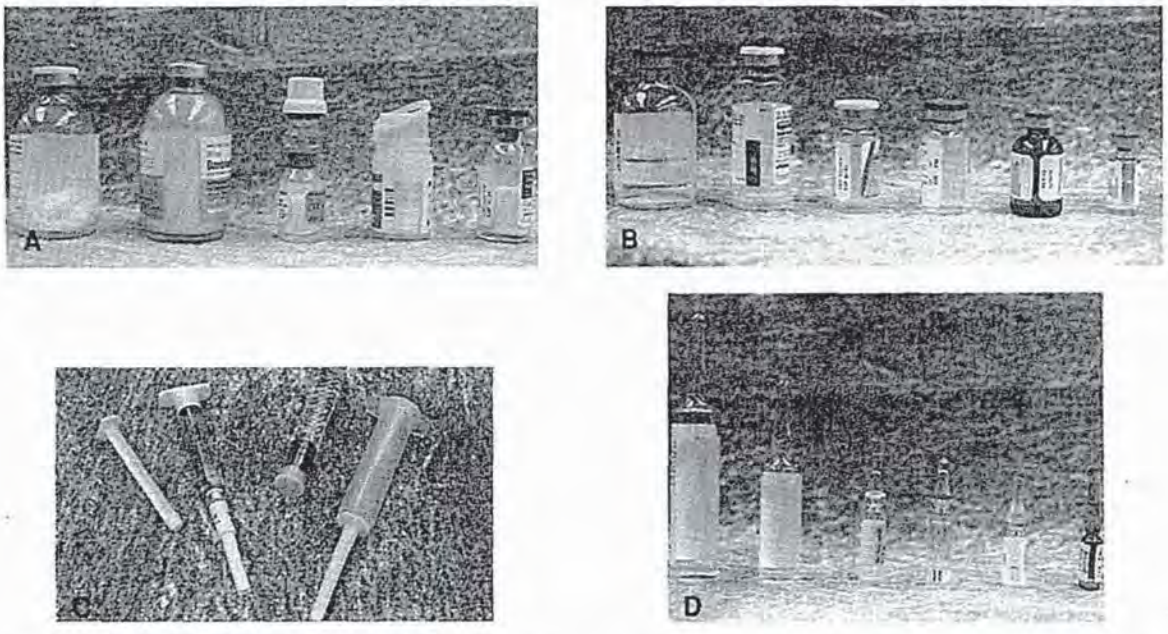

Fig. 14.15 *Examples of packaging of injectable products. A, Multiple-dose vials of suspensions and dry powders. B, Vials for solutions, including one with light-protective glass. C, Unit dose, disposable syringes. D, Various sizes of ampuls. (Courtesy of William B. French, PhD.)*

Fig. 14.16 *A typical vial used for sterile injectable products. It is made from Type I (borosilicate) glass. The rubber closure has been specially selected as regards compatibility with the product, desirable physical characteristics, etc. The overseal holds the closure in place and provides a means for ready access to the contents of the vial. (Courtesy of the Upjohn Company.)*

Single-dose container—A single-dose container is a hermetic container holding a quantity of sterile drug intended for parenteral administration as a single dose, and which when opened cannot be re-sealed with assurance that sterility has been maintained.

Multiple-dose container—A multiple-dose container is a hermetic container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion.

Single-dose containers may be ampuls or single-dose vials. Ampuls (Fig. 14.18) are sealed by fusion of the glass container under aseptic conditions (Figs. 14.19, 14.20). The glass container is made so as to have a neck portion that may be easily separated from the body of the container without fragmentation of the glass. After opening, the contents of the ampul should be withdrawn into a syringe with a 5-μm filter needle/straw apparatus. The filter needle or straw is then replaced with a regular needle. The filter needle or straw is used to trap any glass particles that have entered the sterile solution when the neck of the ampul was broken. Otherwise, if a filter needle is not available, the withdrawal of glass can be minimized by holding the ampul in the upright position, tilted slightly, when inserting the needle, and avoiding the outer surface of the neck of the ampul. The needle should not be lowered to the bottom of the ampul, but held slightly above, to avoid drawing glass particulate matter into the syringe.

Once opened, the ampul cannot be resealed, and any unused portion may not be retained and used at a later time, since the contents would have questionable sterility. Some injectable products are packaged in pre-filled syringes, with or without special administration devices (Figs. 14.21 to 14.23). The types of glass for parenteral product containers have already been pointed out in Chapter 5, and the student should recall that Types I, II, and III are suitable for parenteral products, with Type I being the most resistant to chemical deterioration. The type of glass to be used as the container for a particular injection is indicated in the individual monograph for that preparation.

One of the prime requisites of solutions for parenteral administration is clarity. They should be sparkling clear and free of all particulate matter, that is, all of the mobile, undissolved substances which are unintentionally present. Included are such contaminants as dust, cloth fibers, glass fragments, material leached from the glass or plastic containers or seals, and any other material which may find its way into the product during its manufacture or administration, or develop during storage.

To prevent the entrance of unwanted particles into parenteral products, a number of precautions

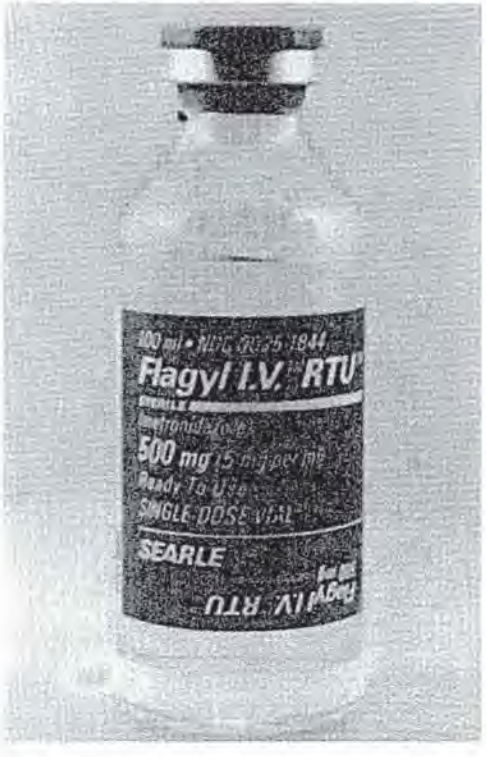

Fig. 14.17 *Example of a 100 mL single-dose vial for intravenous infusion in ready-to-use (RTU) form. (Courtesy of Searle Pharmaceuticals, Inc.)*

Fig. 14.18 *Ampul, before filling and sealing. (Courtesy of Owens Illinois.)*

must be taken during the manufacture, storage, and use of the products. During manufacture, for instance, the parenteral solution is usually final filtered before being placed into the parenteral containers. The containers are carefully selected to be chemically resistant to the solution being added and of the highest available quality to minimize the chances of container components being leached into the solution. It has been recognized for some time, that some of the particulate matter found in parenteral products is generated from leached material from the glass or plastic containers. Once the container is selected for use, it must be carefully cleaned to be free of all extraneous matter (Fig. 14.24). During container-filling, extreme care must be exercised to prevent the entrance of air-borne dust, lint or other contaminants into the container. The provision of filtered and directed air flow in production areas is useful in reducing the likelihood of contamination. Laminar flow hoods have been developed which allow for the draft-free flow of clean, filtered air over the work area. These hoods are commonly found in the hospital setting for both the manufacture and the incorporation of additives into parenteral and ophthalmic products (Fig. 14.25). The personnel involved in the manufacture of parenterals must be made acutely aware of the importance of cleanliness and aseptic techniques. They are provided uniforms made of monofilament fabrics that do not shed lint. They wear face hoods, caps, gloves, and disposable shoe covers to prevent contamination (Fig. 14.26).

After the containers are filled and hermetically sealed, they are visually (Fig. 14.27) or automatically (Fig. 14.28) inspected for particulate matter. Usually an inspector passes the filled container

Fig. 14.19 *Ampul filling. (Courtesy of Abbott Laboratories.)*

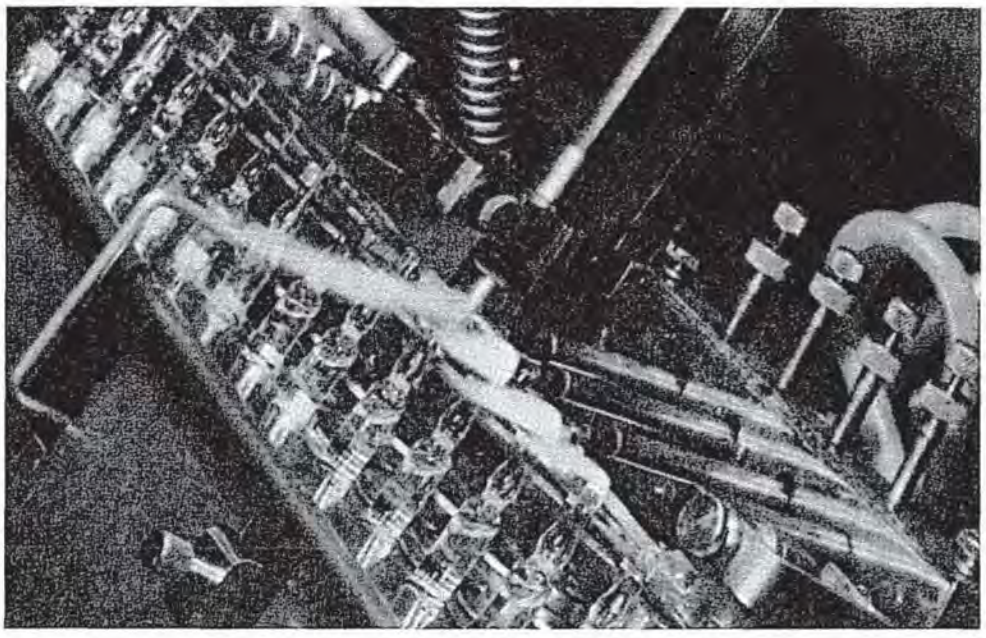

Fig. 14.20 *Ampul sealing. (Courtesy of Abbott Laboratories.)*

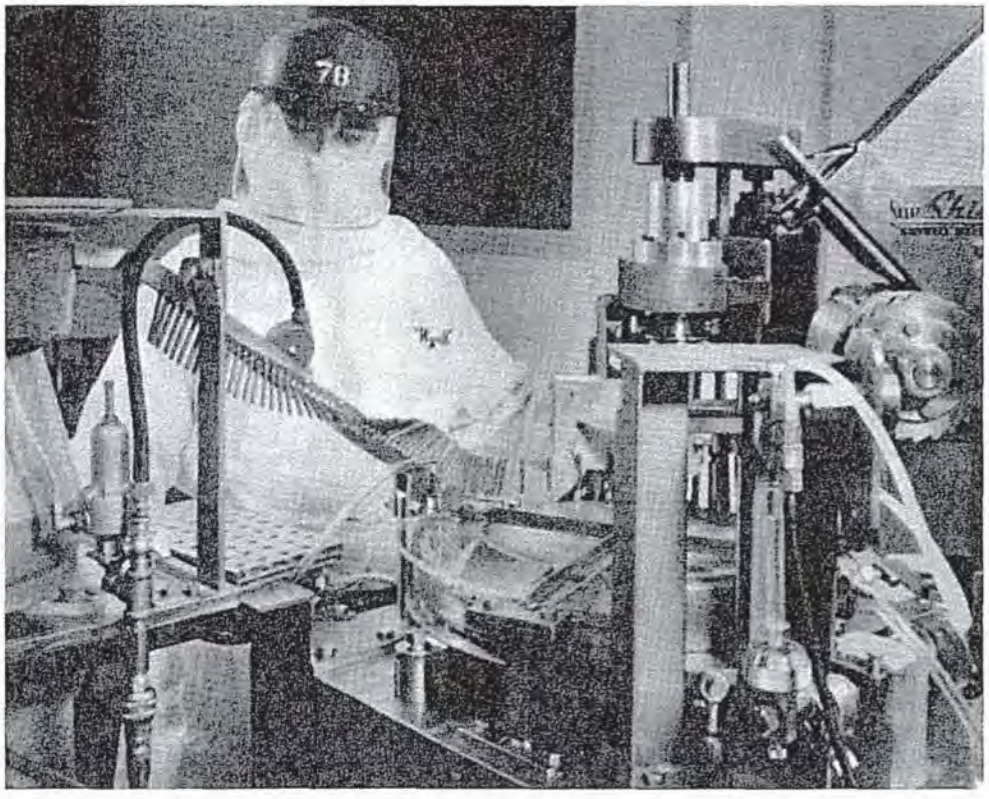

Fig. 14.21 *Operation of a TUBEX filling machine. (Courtesy of Wyeth Laboratories.)*

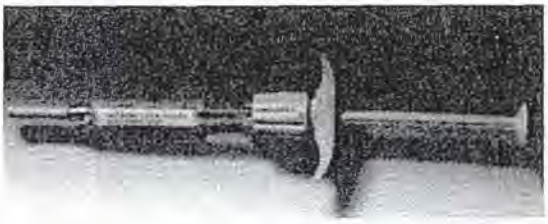

Fig. 14.22 *Tubex Injector. The ribbed collar and plunger rod securely hold a glass sterile cartridge-needle unit. Each prefilled unit contains a dose of medication with an attached sterile needle. After administration, the cartridge-needle unit is discarded; the Injector is reusable. (Courtesy of Wyeth-Ayerst Laboratories.)*

past a light source with a black background to observe for mobile particles. Particles of approximately 50 μm in size may be detected in this manner. Reflective particles, such as fragments of glass, may be visualized in smaller size, about 25 μm in size. Other methods are used to detect particulate matter smaller than that which may be detected by the unaided eye including microscopic examinations as well as the use of sophisticated equipment as the Coulter Counter which electronically counts particles present in a sample presented to it. Once past the inspection following production the product may be labeled. Prior to its use, however, the pharmacist should inspect each parenteral solution dispensed for evidence of particulate matter.

Although the total significance of injecting or infusing parenteral solutions containing particulate matter into a patient has not been ascertained, it is apparent that particulate matter has the potential of inducing thrombi and vessel blockage and depending upon the chemical composition of the particles the additional potential for introducing into the patient chemical agents which are undesired and possibly toxic.

In formulating a single-dose parenteral product, the pharmacist must consider not only the physicochemical aspects of the drug, but also the intended therapeutic use of the product itself. Some single-dose preparations are prepared to be administered rapidly in small volumes, but other preparations are allowed to infuse slowly into the circulatory system over a period of hours. Most small-volume parenterals are formulated so that a convenient amount of solution, say 0.5 to 2 mL, contains the usual dose of the drug although larger volumes of more diluted solutions are frequently administered intravenously and intramuscularly. Generally, several strengths of injections of a given drug are marketed to permit a wider dosage selection by the physician without being wasteful of the drug as would be the case if only part of a given single-dose parenteral solution was administered. The large-volume, single-dose preparations generally are those solutions used to expand the blood volume or to replenish nutrients or electrolytes and are given by slow intravenous infusion. However, in no instance may a single-dose parenteral container permit the withdrawal and administration of greater than 1000 mL. In addition, preparations intended for intraspinal, intracisternal, or peridural administration must be packaged only in single-dose containers as a precaution against contamination.

Frequently in the hospital, a physician may order an additional agent to be placed in a large-volume parenteral solution for infusion. In these instances, the person filling such an order must be certain that aseptic conditions are employed and that the additive is compatible with the contents of the original large volume parenteral solution (13). Care must also be exercised not to introduce particulate matter into

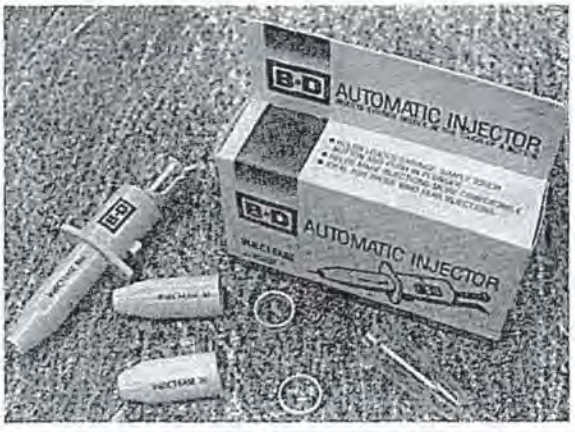

Fig. 14.23 *Inject-Ease automatically inserts the needle of an insulin syringe into the skin when activated. (Courtesy of William B. French, PhD.)*

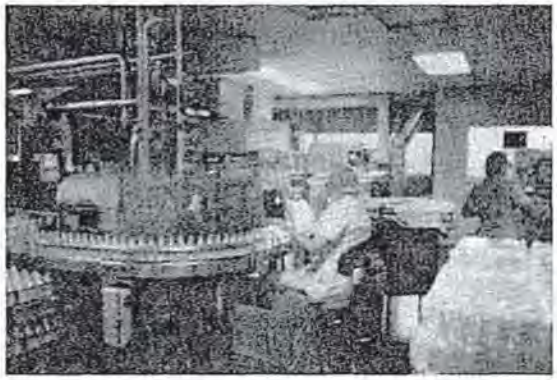

Fig. 14.24 *Production line in the preparation of vials for sterilization and filling. (Courtesy of Schering-Plough.)*

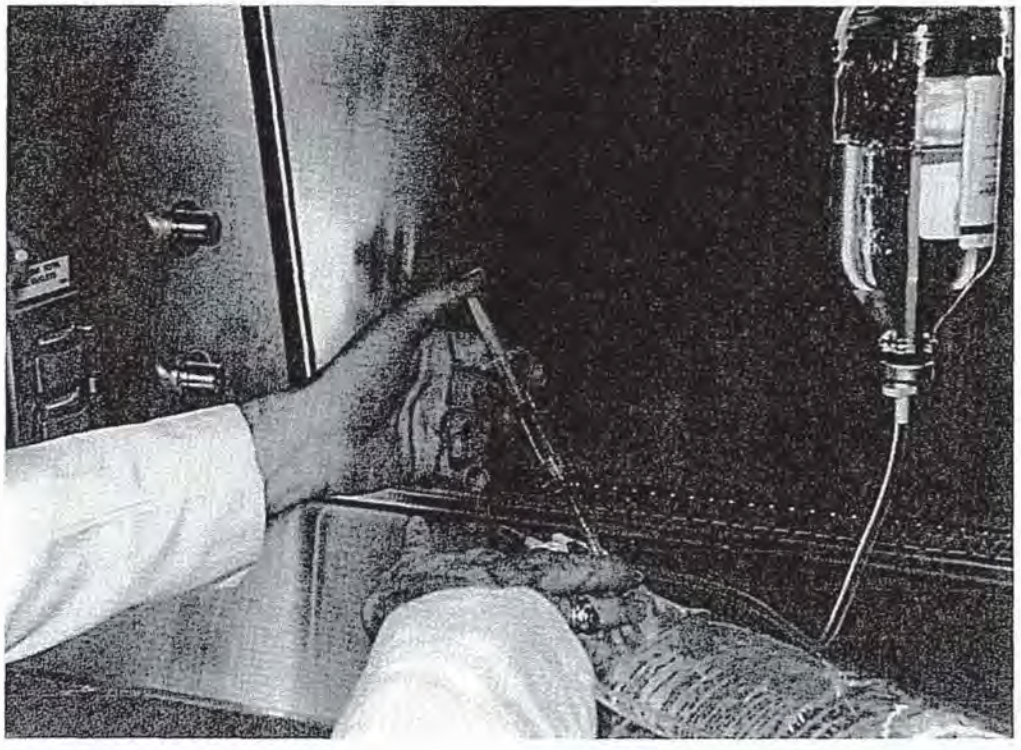

Fig. 14.25 *Hyperalimentation being prepared in a vertical laminae flow hood using millipore sterilization. (Courtesy of William B. French, PhD.)*

the solution. Many pharmaceutical companies have developed special devices for the aseptic transfer of pharmaceutical additives to large volume parenterals. An ordinary sterile needle and syringe, preferably affixed with a filtering device, may be effectively employed to transfer solutions from one parenteral product to another (Fig. 14.29). Many hospital pharmacies have established well controlled *IV additive* or *admixture* programs to assure additive-solution compatibility, safety and efficacy (14).

Multiple-dose containers are affixed with rubber closures to permit the penetration of a hypodermic needle without the removal or destruction of the closure. Upon withdrawing the needle from the container, the closure reseals and protects the contents from airborne contamination. The needle may be inserted to withdraw a portion of the prepared liquid injection, or it may be used to introduce a solvent or vehicle to a dry powder intended for injection. In either instance, the sterility of the injection may be maintained so long as the needle itself is sterile at the time of entry into the container. It

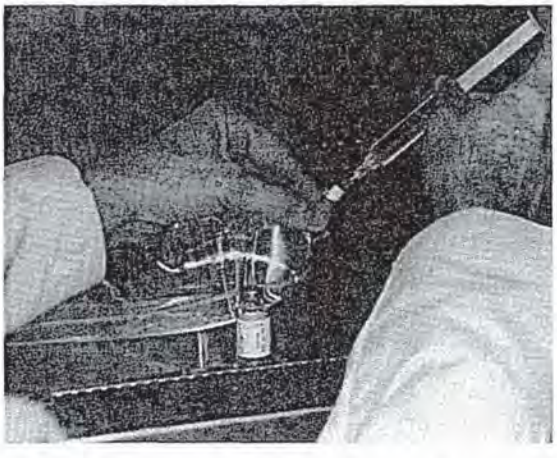

Fig. 14.26 *Pharmacist preparing a parenteral admixture in a laminar flow hood. (Courtesy of William B. French, PhD.)*

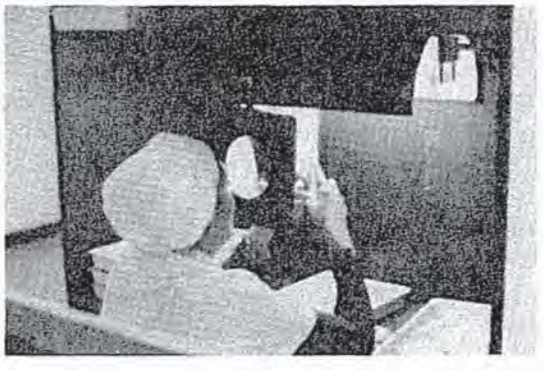

Fig. 14.27 *Industrial inspection of parenteral fluid for particulate matter. (Courtesy of Schering-Plough.)*

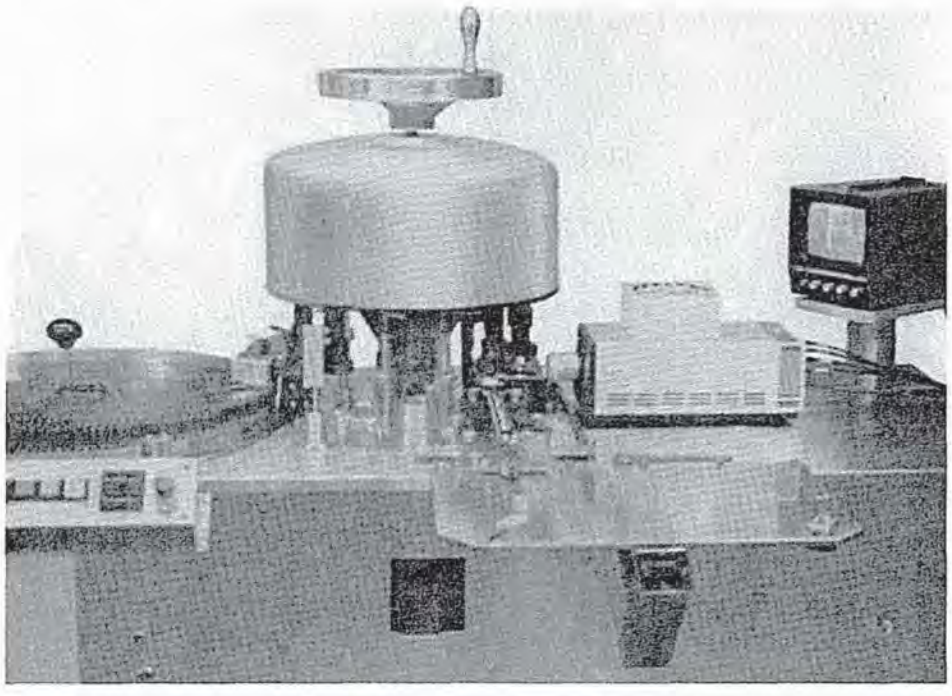

Fig. 14.28 *The AUTOSKAN industrial automatic inspection machine which detects the presence of particulate matter in injectables with a television camera and electronics, and automatically rejects them from the production line. (Courtesy of Lakso Company, Inc.)*

should be recalled that unless otherwise indicated in the monograph, multiple-dose injectables are required to contain added antibacterial preservatives. Also, unless otherwise specified, multiple-dose containers are not permitted to allow the withdrawal of greater than 30 mL in order to limit the number of penetrations made into the closure and thus protect against loss of sterility. The limited volume also guards against an excessive amount of antibacterial preservative being inadvertently co-administered with the drug when unusually large doses of an injection are required, in which case a non-preserved single-dose preparation is advisable. The usual multiple-dose container contains about ten usual doses of the injection, but quantity may vary greatly with the individual preparation and manufacturer.

Because it is impossible in practice to transfer the entire volume of a single-dose container or the last dose in a multiple-dose container into a hypodermic syringe, a slight excess in volume of the contents of ampuls and vials over the labeled "size" or volume of the package is permitted. Table 14.2 presents the recommended "overages" permitted by the USP to allow the withdrawal and administration of the labeled volumes.

For labeling purposes, a revised injectable product nomenclature process became official in the *United States Pharmacopeia* 23 (USP 23) on January 1, 1995. The main points of the revised process were as follows:

1. The term "Sterile" was eliminated from the titles of injectable products with the exception of appropriate monograph titles for WATER that are intended for parenteral use, e.g., Sterile Water for Injection.
2. For established names of injectable products, all

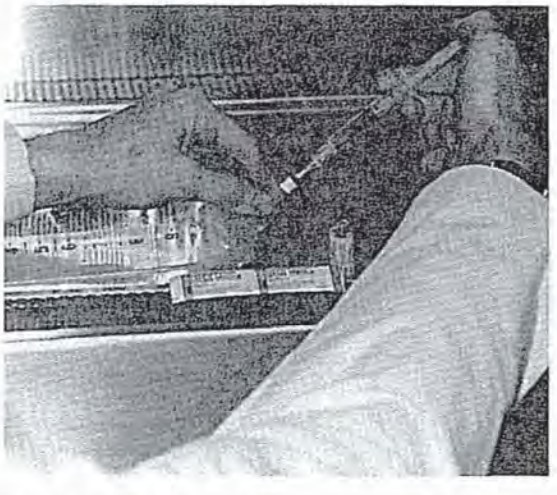

Fig. 14.29 *Utilization of a filter syringe for the aseptic addition of an additive to a large-volume parenteral solution. (Courtesy of William B. French, PhD.)*

Table 14.2. Recommended Overages for Official Parenteral Products

Labeled Size, mL	*Excess Volume for Mobile Liquids, mL*	*Excess Volume for Viscous Liquids, mL*
0.5	0.10	0.12
1.0	0.10	0.15
2.0	0.15	0.25
5.0	0.30	0.50
10.0	0.50	0.70
20.0	0.60	0.90
30.0	0.80	1.20
50.0 or more	2%	3%

of which are suitable for, and intended for parenteral administration, USP established the following criteria in determining the product's title:

a. Liquids
   1) *[Drug] Injection*—Title for liquid preparations that are drug substances or solutions thereof.
   2) *[Drug] Injectable Suspension*—Title for liquid preparations of solids suspended in a suitable liquid medium.
   3) *[Drug] Injectable Emulsion*—Title for liquid preparations of drug substances dissolved or dispersed in suitable emulsion medium.
b. Solids
   1) *[Drug] for Injection*—Title for dry solids that, upon the addition of suitable vehicles, yield solutions conforming in all respects to the requirements for *Injections*.
   2) *[Drug] for Injectable Suspension*—Title for dry solids that, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for *Injectable Suspensions*.

To facilitate this transition to a new nomenclature, the Center for Drug Evaluation and Research encouraged parenteral drug manufacturers to place a "flag" or reminder statement on the labels of the product for a six month period alerting practitioners to the changes. The intent was to facilitate practitioners becoming familiar with the revised rules. An example of a "flag" would be: "FORMERLY STERILE [Drug Name]."

In addition, the labels on containers of parenteral products must state: 1) the name of the preparation; 2) for a liquid preparation, the percentage content of drug or the amount of drug present in a specified volume, or for a dry preparation, the amount of active ingredient present and the volume of liquid to be added to the dry preparation to prepare a solution or suspension; 3) the route of administration; 4) a statement of storage conditions and an expiration date; 5) the name of the manufacturer and distributor; 6) an identifying lot number, which is capable of yielding the complete manufacturing history of the specific package, including all manufacturing, filling, sterilizing, and labeling operations. Injections for veterinary use are labeled to that effect. Preparations intended to be used as dialysis, hemofiltration or irrigation solutions should meet the requirements for injections, except those relating to volume present in the containers, and should bear a statement indicating that the solution is not intended for use by intravenous infusion. All containers appropriately labeled should allow a sufficient area of the container to remain free of label for its full length or circumference to permit inspection of the contents. Any injection which upon visual inspection reveals particulate matter other than normally suspended material should be discarded.

Each individual monograph for the official injection states the type of container (single-dose and/or multiple-dose) permitted for the injection, the type of glass preferred for the container, exemptions, if any, to usual package-size limitations, and any special storage instructions. Most injections prepared from chemically pure medicinal agents are stable at room temperature and may be stored without special concern or conditions. However, most biological products—insulin injection and the various vaccines, toxoids, toxins, and related products—are usually stored under refrigeration. Reference should be made to the individual monograph to find the proper storage temperature for a particular injection.

Quality Assurance for Pharmacy-Prepared Sterile Products

The American Society of Health System Pharmacists (formerly, the American Society of Hospital Pharmacists) publishes annually a technical assistance bulletin (TAB) on quality assurance for pharmacy-prepared sterile products (15). The TAB

was developed to help pharmacists establish quality assurance procedures for the component of practice that encompasses the preparation of sterile products. The recommendations of the TAB are appropriate to all practice settings in which pharmacists directly serve patients (e.g., hospitals, community pharmacies, nursing homes, home health care). Note that these are not intended to apply to the manufacturing of sterile pharmaceuticals as defined in state and federal laws and regulations. Nor are they to apply the preparation of medications (i.e., by pharmacists, nurses, physicians) intended for immediate administration (i.e., minimal delay between preparation and administration) to patients.

The term *sterile products* used within the TAB refers to sterile or nutritional substances that are prepared (e.g., compounded or repackaged) by pharmacy personnel, using aseptic technique and other quality assurance procedures.

The objectives of these recommendations are to enable pharmacists to provide:

1. Information to pharmacists on quality assurance and quality control activities that may be applied to the preparation of sterile products in pharmacies, and
2. A scheme to match quality assurance and quality control activities with the potential risks to patients posed by various types of products.

The TAB defines the purpose of these recommendations and encourages pharmacists to participate in quality improvement, risk management, and infection control programs within their organizations. In doing so, pharmacists would be expected to report findings about quality assurance in sterile products to appropriate staffs or committees, and to cooperate with managers of quality improvement, risk management, and infection control to develop optimal sterile product procedures.

Originally, in February 1992, the then American Society of Hospital Pharmacists had proposed guidelines that formed the basis of TAB (16). This original document distinguished between quality control (QC) and quality assurance (QA). By definition, *quality control* is the acceptance or rejection of raw materials and packaging components, in-process test materials, and inspections (17). *Quality assurance* is a systematic method to identify problems in patient care that are resolved via administrative, clinical, or educational actions to ensure that final products and outcomes meet applicable specifications (17).

The TAB classifies sterile products into three levels based on risk to the patient. The risk levels range

Table 14.3. ASHP Risk Level Classification of Pharmacy-Prepared Sterile Products[15]

Risk Level 1

1. Products
   A. Stored at room temperature and completely administered within 28 hours of preparation; or
   B. Stored under refrigeration for 7 days or less before complete administration to a patient over a period not to exceed 24 hours; or
   C. Frozen for 30 days or less before complete administration to a patient over a period not to exceed 24 hours.
2. Unpreserved sterile products prepared for administration to one patient, or batch-prepared products containing suitable preservatives prepared for administration to more than one patient.
3. Products prepared by closed-system aseptic transfer of sterile, nonpyrogenic, finished pharmaceuticals obtained from licensed manufacturers into sterile final containers (e.g., syringe, minibag, portable infusion-device cassette) obtained from licensed manufacturers.

Risk Level 2

1. Products stored beyond 7 days under refrigeration, or stored beyond 30 days frozen, or administered beyond 28 hours after preparation and storage at room temperature.
2. Batch-prepared products without preservatives that are intended for use by more than one patient. (*Note:* Batch-prepared products without preservatives that will be administered to multiple patients carry a greater risk to the patients than products prepared for a single patient because of the potential effect of product contamination on the health and well-being of a larger patient group.)
3. Products compounded by combining multiple sterile ingredients, obtained from licensed manufacturers, in a sterile reservoir, obtained from a licensed manufacturer, by using closed-system aseptic transfer before subdivision into multiple units to be dispensed to patients.

Risk Level 3 Products Exhibit Either Characteristic 1 or 2

1. Products compounded from nonsterile ingredients or compounded with nonsterile components, containers, or equipment, or
2. Products prepared by combining multiple ingredients—sterile or nonsterile—by using an open-system transfer or open reservoir before terminal sterilization or subdivision into multiple units to be dispensed.

from the least potential risk (level 1) to the greatest potential risk (level 3). The classification system is designed only to assist the pharmacist in selecting sterile preparation procedures. Pharmacists must exercise professional judgment in deciding which risk level applies to a specific sterile product or situation. Factors that increase risk (e.g., multiple system breaks, compounding complexities, high-risk administration sites, immunocompromised patients, microbial growth potential of the product, storage conditions) must be weighed by the pharmacist.

There will be situations when the pharmacist must make risk vs. benefit decisions to prepare these products outside of the guidelines (e.g., the preparation of a sterile investigational drug in a compassionate-use protocol for a lifesaving effort). The risk assignments listed in Table 14.3 provide a logical template within which the pharmacist can evaluate risk. These do not, however, preclude the possibility of alternative, logical arrangements that could be based upon scientific information and professional judgment.

Risk level 1 represents the minimum QA guidelines. In risk levels 2 and 3, products must meet or exceed each of the risk level 1 guidelines. In those instances where the risk level assignment might be nebulous, guidelines for the higher risk level should be followed.

The TAB delineates the quality assurance components for each risk level. These include: policies and procedures; personnel education, training, and evaluation; process validation; storage and handling; facilities and equipment; garb; aseptic technique and product preparation; process evaluation; expiration dating; labeling; end-product evaluation; and documentation. Specific recommendations germane to each of these components at each risk level are made in the TAB; the reader may refer to them for additional information.

Available Injections

There are hundreds of injections on the market of various medicinal agents. Tables 14.4 through 14.7 present some examples of those packaged in small-volume and large-volume containers, the latter for intravenous infusion.

Small Volume Parenterals

Table 14.4 presents some commonly employed injections given in small volume. Some of these injections are solutions and others suspensions.

Premixed intravenous delivery systems have simplified the delivery process for small-volume parenterals in particular. A distinct advantage of these ready-to-use systems is that they require little or no manipulation to make them patient specific, and thus a viable alternative to the traditional labor-intensive method of compounding parenteral medications from partial-fill (i.e., individual dose/multiple doses of IV medications) vials and an appropriate parenteral solution. Since the introduction of the first ready-to-use systems in the late 1970s, the availability and variety of systems has increased (e.g., Baxter Healthcare Corporation, Kendall McGaw Laboratories, Abbott Laboratories) (refer to Table 14.5).

The traditional method for preparing small-volume parenteral therapy for patient-specific use from a partial-fill drug vial into a minibag can be labor-intensive and costly (e.g., labor supply and inventory costs for materials such as syringes and needles). The savings accrued through ready-to-use systems can be significant and have been documented (18). Another key advantage of these systems is extended stability dating and reduced wastage. Doses can be put together (but not activated) in cycles, then activated just prior to patient use and delivered to the nursing station by the pharmacy personnel (18).

The down side of these ready-to-use small parenteral products is that they do not offer flexibility in changing the volume or concentration of the product. This may then pose a problem to the fluid-restricted patient (18). But, the introduction of minibags in volumes of 100 mL, 50 mL, and 25 mL, have helped this problem somewhat. Another disadvantage of the ready-to-use products is that some manufacturers' premixed products require thawing. Microwave use for quick thawing poses stability problems for some of these products (e.g., cefazolin, cephalothin). For example, the high energy source of the microwave oven could cause a structural alteration of the cephalothin molecule. Another possibility is that of leaching of substance from the rubber stopper when frozen ampuls of Neutral Keflin are thawed using the microwave.

General precautions (19) required with the use of microwave ovens for thawing frozen premixed products include:

1. Being aware that the possibility of radiation leakage does exist. However, manufacturers of microwave ovens are required by law to comply with federal standards.
2. Safeguarding pharmacy personnel who are exposed to these ovens, especially those with cardiac pacemakers.
3. The possible leaching of rubber stopper material when the rubber material on the container is exposed to microwave heating.

Table 14.4. Examples of Some Injections Usually Packaged and Administered in Small Volume

Injection	*Physical Form*	*Category and Comments*
Butorphanol Tartrate Injection	solution	Narcotic Agonist-Antagonist Analgesic; administered IM or IV for relief of moderate to severe pain and as a preoperative or preanesthesia medication.
Chlorpromazine HCl Injection	solution	An antipsychotic drug with antiemetic (antidopaminergic) effects, this drug should not be administered sub-Q. It's injection should be IM slowly, deep into upper outer quadrant of the buttocks. Avoid injecting directly into the vein. The IV route is used ONLY for severe hiccoughs, surgery, or tetanus.
Cimetidine HCl Injection	solution	Histamine H_2 antagonist; administered IM or IV for patients with pathological GI hypersecretory conditions or intractable ulcers.
Dalteparin Sodium Injection	solution	A sterile, low molecular weight heparin which is indicated for prophylaxis against deep vein thrombosis (DVT) in patients undergoing abdominal surgery who are at risk. Available in a prefilled syringe, it is administered Sub-Q.
Dexamethasone Sodium Phosphate Injection	solution	Glucocorticoid; administered IM or IV for cerebral edema and unresponsive shock. Also used intra-articular, intralesional or soft tissue for joints, bursae, and ganglia.
Digoxin Injection	solution	Cardiotonic given IM (not preferred) or IV with highly individualized and monitored dosage.
Dihydroergotamine Mesylate Injection	solution	Alpha-adrenergic blocking agent specific in migraine, given IM or IV.
Diphenhydramine HCl Injection	solution	An ethanolamine, non-selective antihistamine administered intravenously or intramuscularly when oral administration is impractical and indicated for Type I (i.e., immediate) hypersensitivity reactions and active treatment of motion sickness.
Furosemide Injection	solution	Loop diuretic; administered IM or IV [slowly] for edema or acute pulmonary edema.
Granisetron HCl Injection	solution	5-HT_3 receptor antagonist indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin.
Heparin Sodium Injection	solution	Anticoagulant administered IV or SubQ, as indicated by activated partial prothrombin time (APTT) or actuated coagulation time (ACT).
Hydromorphone HCl Injection	solution	Narcotic analgesic used for the relief of moderate to severe pain; administered subcutaneously or IM or by slow IV injection.
Ibutilide Fumarate Injection	solution	An antiarrhythmic drug with predominantly class III (i.e., cardiac action potential prolongation) properties according to the Vaughn Williams Classification that is infused intravenously undiluted or diluted in 50 ml diluent.
Iron Dextran Injection	solution	A hematinic agent administered intravenously or intramuscularly for the treatment of patients with documented iron deficiency in whom oral administration is unsatisfactory or impossible.
Isoproterenol HCl Injection	solution	Adrenergic (bronchodilator) given IM, SubQ, or IV.
Ketorolac Tromethamine Injection	solution	Available in Tubex® syringes for IV/IM dosing, this NSAID is indicated for the short-term (< 5 days) management of moderately severe, acute pain that requires analgesia at the opioid level, usually in a postoperative setting.
Lidocaine HCl Injection	solution	Cardiac depressant given IV as an antiarrhythmic; also as a local anesthetic, epidurally, by infiltration, and in peripheral nerve block.
Magnesium Sulfate Injection	solution	Anticonvulsant/electrolyte; administered by IM or direct IV injection, IV infusion, or in other IV infusions for management of convulsive toxemia of pregnancy, hyperalimentation therapy, mild magnesium deficiency, or severe hypomagnesemia.
Meperidine HCl Injection	solution	Narcotic analgesic given IM, SubQ, or slow continuous IV infusion.

continued

Table 14.4. Examples of Some Injections Usually Packaged and Administered in Small Volume

Injection	*Physical Form*	*Category and Comments*
Metoclopramide Monohydrochloride Injection	solution	Gastrointestinal stimulant; administered IM, direct IV, or slowly as an IV admixture for the prevention of chemotherapy-induced emesis.
Midazolam HCl Injection	solution	A short-acting benzodiazepine CNS depressant administered IV or IM and indicated for preoperative sedation, anxiolysis and amnesia.
Morphine Sulfate Injection	solution	Narcotic analgesic. IM, IV, PCA.
Nalbuphine HCl Injection	solution	Narcotic Agonist-Antagonist Analgesic; administered SC, IM or IV for relief of moderate to severe pain and for preoperative analgesia.
Naloxone HCl Injection	solution	A narcotic antagonist which prevents or reverses the effects of opioids including respiratory depression, sedation and hypotension; administered IV, IM, or subcutaneously.
Oxytocin Injection	solution	Oxytocic, given IM (erratic) or IV obstetrically for the therapeutic induction of labor.
Phenytoin Sodium Injection	solution	Anticonvulsant; administered IM [erratic absorption] as a prophylactic dosage for neurosurgery or IV [slowly] for status epilepticus.
Phytonadione Injection	dispersion	Vitamin K (prothrombogenic) employed in hemorrhagic situations. An aqueous dispersion of phytonadione, a viscous liquid.
Procaine Penicillin G Injection	suspension	Anti-infective; administered IM for moderately severe infections due to penicillin-G sensitive microorganisms.
Prochlorperazine Edisylate Injection	solution	Antidopaminergic; administered IM or IV for control of severe nausea and vomiting associated with adult surgery.
Propranolol HCl Injection	solution	A beta-adrenergic receptor blocking agent indicated in the management of hypertension. Oral dosage (tablets) is usual; intravenous administration is reserved for life-threatening arrhythmias or those occurring under anesthesia.
Sodium Bicarbonate Injection	solution	Electrolyte; administered IV, either undiluted or diluted in other IV fluids for cardiac arrest and in less urgent forms of metabolic acidosis.
Sumatriptan Succinate Injection	solution	A selective 5-hydroxytryptamine$_1$ receptor, subtype agonist, used for acute migraine attacks with or without aura. Self-administered SubQ from unit-of-use syringes and *SELFdose* unit.
Verapamil HCl Injection	solution	Calcium channel blocking agent; administered as a slow IV injection over at least 2 minutes for supraventricular tachyarrhythmias.

4. A possible explosion that may result from the increase in internal pressure as a result of placing a closed or sealed container into the microwave oven.
5. The possibility of unequal distribution of heat because microwave ovens do produce heterogeneous heat.
6. Developing protocols to ensure that the final solution temperature does not exceed room temperature.

Some manufacturers allow frozen premixed products to be warmed using a water bath, but warn not to submerge during the thawing process because there is a distinct possibility that water from the bath could enter and contaminate the contents of the dosage form. Forced clean air at 25° C flowing over the bags may help. In fact, using an old laminar flow hood for thawing has been used with some success. However, room temperature thawing is a lengthy process. Thus, appropriate planning is required so that large numbers of these products that are thawed in advance are used and recycled efficiently. Otherwise, these small-volume parenteral products potentially increase waste. Finally, getting a prescription label to adhere to a thawed minibag can be a problem.

The available ready-to-use systems have not demonstrated much impact in the pediatric and neonatal population. The unique dosing and fluid requirements of these patients make these systems inappropriate. In some institutions, the unique dosing and fluid requirements of pediatric and neonate

Table 14.5. Representative Marketed Frozen, Premixed Products Illustrating Stability Data Frozen and After Thawing[a]

Drug	*Diluent*	*Expiration Dating*			
		Storage Stability	*Frozen Stability*	*Refrigerated Stability*	*Room Temperature*
Aztreonam 1g, 2g	Iso-osmotic in dextrose, 50 mL	Frozen	18 months	14 days	48 hours
Cefazolin sodium 500 mg, 1 g	Iso-osmotic in dextrose, 50 mL	Frozen	24 months	30 days	48 hours
Cefotaxime sodium, 1g, 2g	Iso-osmotic in dextrose, 50 mL	Frozen	15 months	10 days	24 hours
Cefoxitin sodium 1g, 2g	Iso-osmotic in dextrose, 50 mL	Frozen	18 months	21 days	24 hours
Ceftazidime sodium 1g, 2g	Iso-osmotic in dextrose, 50 mL	Frozen	9 months	7 days	24 hours
Ceftizoxime sodium 1g, 2g	Iso-osmotic in dextrose, 50 mL	Frozen	12 months	28 days	48 hours
Ceftriazone sodium 1g, 2g	Iso-osmotic in dextrose, 50 mL	Frozen	15 months	21 days	72 hours
Ticarcillin disodium and clavulanate potassium	Iso-osmotic in Water for Injection, 100 mL	Frozen	6 months	7 days	24 hours
Vancomycin HCl 500 mg	Iso-osmotic in dextrose, 100 mL	Frozen	12 months	30 days	72 hours

[a]Stability information provided by Baxter Healthcare Corporation.

patients are addressed by making dilutions of medications to standardized concentrations, filling and capping individual syringes, and administering these doses through a syringe pump.

Among the most used of the small volume injections are the various insulin preparations. Insulin, the active principle of the pancreas gland, is primarily concerned with the metabolism of carbohydrates, but also influences protein and fat metabolism. Insulin facilitates the cellular uptake of glucose and its metabolism in liver, muscle, and adipose tissue. It increases the uptake of amino acids and inhibits the breakdown of fats and the production of ketones. Insulin is administered to patients having abnormal or absent pancreatic beta cell function to restore glucose metabolism and maintain satisfactory carbohydrate, fat, and protein metabolism. It is used in the treatment of *diabetes mellitus*, in instances in which the condition cannot be controlled satisfactorily by dietary regulation alone or by oral hypoglycemic drugs. Insulin may also be used to improve the appetite and increase the weight in selected cases of nondiabetic malnutrition and is frequently added to intravenous infusions.

Insulin is administered by needle or jet injection (Figs. 14.30, 14.31, 14.32). A system for the

Fig. 14.30 *Medi-Jector II, an example of a jet injection device. The jet injection method utilizes pressure rather than a needle in providing the subcutaneous distribution of an injectable medication. The device shown can be used with U-100 insulin or a combination of insulins and can deliver 2 to 100 units in half-unit increments. (Courtesy of Derata Corporation.)*

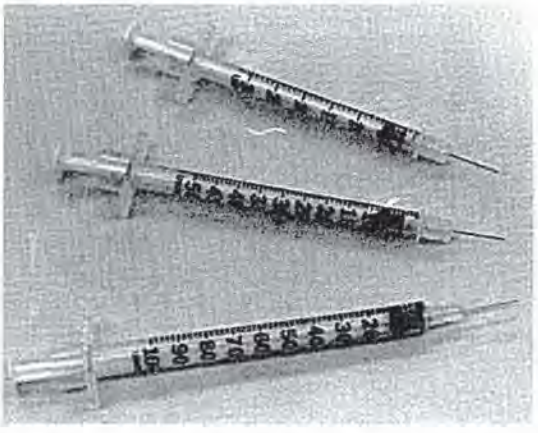

Fig. 14.31 *Examples of insulin syringes calibrated in units. (Courtesy of William B. French, PhD.)*

nasal administration of insulin is presently under study.

Since its introduction, U-100 insulin has been suggested as a replacement for the U-40 insulin strength, with the intention of making U-100 the single strength for in-home use by the patient. In December 1991, Eli Lilly announced that it would cease further production of U-40 insulins, and subsequently other insulin manufacturers also decided to cease production of this strength. The basis for this decision was a lack of patient demand (i.e., very low numbers of patient utilizing this strength). Recognizing, however, that lower strengths of insulin (i.e., under 100 U/mL) might still be needed (e.g., small children, veterinarian use), Lilly markets a diluting fluid for the Regular, NPH, and Lente insulins of U-100 strength. This fluid can be used to prepare any strength of insulin below 100 U/mL.

Age-associated sight difficulties and the vision deterioration associated with diabetes can interfere significantly with buying and using insulin products. Therefore, packaging of insulins must make allowances for the visual deficits of patients with diabetes. To facilitate identification of the proper medication at the site of purchase, the arrangement and size of the package lettering must make it easy for the insulin-dependent patient to recognize the insulin type and concentration of the product. In the case of Humulin insulins, an international symbol also appears on the cartons and bottles of all formulations. These symbols help assure that patients with diabetes secure the correct Humulin formulation anywhere in the world.

Insulin Injection (Regular)

Insulin Injection is a sterile aqueous solution of insulin. Commercially, the solution is prepared from beef or pork pancreas or both or through biosynthetic means (Human Insulin), discussed in the next section. The source must be stated on the labeling. In 1980, purified pork insulin [Iletin II, pork (Lilly)] became available for individuals allergic to or otherwise adversely affected by the mixed pork-beef product. The first insulin developed for clinical use was an amorphous insulin. This type has since been replaced by a more purified crystalline insulin composed of zinc-insulin crystals which produces a clear aqueous solution. Originally, insulin injection ("regular insulin") had been produced at a pH of 2.8 to 3.5. This was necessary, because particles formed in the vial when the pH was increased above the acid range. However, changes in the manufacturing methods resulting in the production of insulin of greater purity has allowed for the preparation of insulin injection having a neutral pH. The neutralized product has been shown to exhibit greater stability than the acidic product.

Insulin injection is prepared to contain 100 or 500 USP Insulin Units in each mL. The labeling must state the potency, in USP Insulin Units in each mL and the expiration date, which must not

Fig. 14.32 *Example of packaging of disposable sterile insulin syringes and needles. (Courtesy of William B. French, PhD.)*

be later than 24 months after the date of distribution from the manufacturer's storage. As an added precaution against the inadvertent use of the incorrect strength of insulin by the patient during self-administration of the drug, the package colors vary, depending on the strength of the insulin. For instance, all insulins (of the various types) containing 100 units per mL have orange and the 500 units per mL preparation has brown with diagonal white stripes. U-500 insulin is indicated for patients with a marked insulin requirement (more than 200 units per day) because a large unit/dose may be administered subcutaneously in a small volume.

Insulin injection is a colorless to straw-colored solution, depending upon its concentration; that containing 500 Units per mL is straw-colored. It is substantially free from turbidity. A small amount of glycerin (1.4 to 1.8%) is added for stability and 0.1 to 0.25% of either phenol or cresol is added for preservation. Insulin remains stable if stored in a cold place, preferably the refrigerator. However, because the injection of cold insulin is somewhat uncomfortable, the patient may store the vial being used at room temperature (59–86°F or 15–30°C) for up to 1 month. Any insulin remaining in the vial after that time should be discarded. Freezing should be avoided, as this reduces potency.

The various insulin preparations differ as to their rapidity of action (onset of action) after injection, their peak of action, and their duration of action (Table 14.6). Insulin injection, being a solution, is categorized as a prompt-acting insulin preparation. Insulin preparations that are suspensions are slower acting. Only insulin injection may be administered intravenously; all others, as well as insulin injection, are normally given subcutaneously, usually 1/2 to 2 hours before a meal so that its physiological effects will parallel the absorption of glucose. The dosage is individually determined, with the usual dosage range being 5 to 100 USP Units. The insulin injection containing 500 units per mL is employed in cases of insulin resistance requiring very large doses.

It is important to emphasize at this point that the pharmacist plays a vital role in the education of the diabetic patient, particularly as it relates to the proper use of insulin. The insulin dosage should always be checked to ensure it is correct. Because it is a solution, Regular Insulin can be used in emergency situations, i.e., ketoacidosis, to effect a rapid decrease in blood glucose levels. However, with the exception of diabetic ketoacidosis, it is rare for a patient to ever require a dose of Regular Insulin greater than 25 units. Typically, diabetic patients combine Regular Insulin with a modified insulin, i.e., NPH, to provide daily coverage using two injections (morning, late-afternoon) or now use available pre-mixed preparations. So it is important that the patient understand how much of each to use and know in what order these should be mixed in the insulin syringe. The unmodified insulin, i.e., Regular Insulin, is drawn up first into the syringe.

In an institutional setting the pharmacist must make sure written insulin orders are correctly transcribed or transmitted. Errors in insulin dosage have occurred because of allied health professional error. Written orders for 6 U of insulin have been interpreted to mean 60 units, an order for 4 U has been read as 4 cc. Each of these occurred because

Table 14.6. Insulin Activity Profiles and Compatibility

	Insulin Preparations	*Onset (hr)*	*Peak (hr)*	*Duration (hr)*	*Compatible mixed with*
Rapid Acting	Insulin Injection (Regular)	0.5 to 1		8 to 12	All
	Prompt Insulin Zinc Suspension (Semilente)	1 to 1.5	5 to 10	12 to 16	Lente
	Lispro Insulin Solution	0.25	0.5 to 1.5	6 to 8	Ultralente, NPH
Intermediate Acting	Isophane Insulin Suspension (NPH)	1 to 1.5	4 to 12	24	Regular
	Insulin Zinc Suspension (Lente)	1 to 2.5	7 to 15	24	Regular, semilente
Long Acting	Protamine Zinc Insulin Suspension (PZI)	4 to 8	14 to 24	36	Regular
	Extended Insulin Zinc Suspension (Ultralente)	4 to 8	10 to 30	> 36	Regular, semilente
Premixed Insulins	Isophane Insulin Suspension 50% and Insulin Injection, 50%				
	Isophane Insulin Suspension 70% and Insulin Injection, 30%	0.5	2 to 12	18 to 24	Regular, NPH

the abbreviation "U" for units was read as a zero or a cc.

The patient should be instructed to rotate the site of insulin injections on a continual basis. Rotation of the site will help to avoid the development of lipohypertrophy, a buildup of fibrous tissue. Otherwise, if there is continual injection into one site, the tissue becomes spongy and avascular. The avascular nature of the site perpetuates the problem because the skin becomes anesthetized and the injection is not felt. This is a particular problem with children who continue to use the same site and do not realize that the absorption of insulin from this site becomes erratic and uncontrollable. Numerous brochures are available from manufacturers of diabetic supplies that demonstrate the appropriate rotation of insulin injection sites over the entire body.

Another encountered problem with insulin injection is the development of lipodystrophy. Generally, this problem appears within 2 months to 2 years following the beginning of insulin therapy and occurs predominantly in women and children. The etiology of the problem has been ascribed to the injection of refrigerated insulin (not giving enough time for it to warm up prior to injection), to a failure to rotate the injection site and to insulin impurities. The result is the formation of a subcutaneous indentation or "pothole" caused by a wasting or atrophy of the lipid tissue. It appears that the greater purity of current insulins significantly have decreased this problem, and a marked improvement in existing atrophic areas has been demonstrated by the injection of highly purified port or human insulin directly into or on the periphery of the atrophic areas.

Prior to use, the patient should be instructed to carefully inspect the insulin. Regular Insulin, a solution, should appear clear, while the other insulins which are suspensions should appear cloudy. With the insulins that are suspensions the patient should be instructed how to prepare the insulin, i.e., the vial is rotated slowly between the palms of the hands several times, prior to drawing the insulin into the syringe. This avoids frothing and bubble formation which would result in an inaccurate dose of insulin. The patient should not shake the insulin vial.

Proper storage should also be encouraged for insulins. These preparations should be stored in a cool place or a refrigerator. The patient should be warned to avoid having the insulin come into contact with extremes of temperature, i.e., freezing [overnight in the car during the wintertime], heat [glove compartment of a car, direct sunlight]. If this occurs, it is preferred that the patient discard the insulin and get a new bottle. Any bottle of insulin that appears "frosted" or "clumped" should be returned to the pharmacy where the purchase took place. Lastly, the patient should use the insulin in a timely fashion, but not beyond the expiration date indicated on the insulin vial.

Human Insulin

Biosynthetic human insulin was the first drug product developed through recombinant DNA techniques to receive approval by the federal Food and Drug Administration for marketing. This product, Humulin, Lilly, became available in 1983. It is produced by utilizing a special nondisease-forming laboratory strain of *Escherichia coli* and recombinant DNA technology. A recombined plasmid DNA coding for human insulin is introduced into the bacteria, and it is then cultured by fermentation to produce the A and B chains of human insulin. These A and B chains are freed and purified individually before they are linked by the specific disulfide bridges to form human insulin. The insulin produced is chemically, physically, and immunologically equivalent to insulin derived from the human pancreas. The biosynthetic insulin is free of contamination with *E. coli* peptides, and, is also free of the pancreatic peptides that are present as impurities in insulin preparations derived from animal pancreatic extraction. These latter impurities include proinsulin and proinsulin intermediates, glucagon, somatostatin, pancreatic polypeptide, and vasoactive intestinal peptide.

Pharmacokinetic studies in some normal subjects and clinical observations in patients indicate that formulations of human insulin have a slightly faster onset of action and a slightly shorter duration of action than their purified pork insulin counterparts. Two formulations of human insulin were initially marketed: Neutral Regular Human Insulin (Humulin R, Lilly) and NPH Human Insulin (Humulin N, Lilly). Neutral Regular human insulin consists of zinc-insulin crystals in solution. It has a rapid onset-of-action and a relatively short duration-of-action (6 to 8 hours). NPH human insulin is a turbid preparation that is intermediate-acting, with a slower onset-of-action and longer duration-of-action (slightly less than 24 hours) than regular human insulin.

Human insulins should be stored as other insulins, in a cold place, preferably a refrigerator. Freezing should be avoided.

Lispro Insulin Solution

Lispro insulin solution consists of zinc-insulin lispro crystals dissolved in a clear aqueous fluid. It is created when the amino acids at positions 28 and 29 on the insulin B-chain are reversed.

Lispro insulin solution is rapidly absorbed after subcutaneous administration and demonstrates no significant differences in absorption from abdominal, deltoid, and femoral sites of injection. Its bioavailability mimics that of regular insulin. Compared to regular insulin, however, peak serum levels of lispro insulin occur earlier, i.e., within 0.5 to 1.5 hours, are higher, and are shorter acting, i.e., 6–8 hours. Peak hypoglycemic effects are more pronounced with lispro insulin solution. Thus, hypoglycemia is the primary complication associated with its use. Comparative studies have demonstrated, however, that hypoglycemic episodes have been less frequent with lispro insulin than with regular insulin.

Lispro insulin solution administered fifteen minutes before meals has decreased the risk of hypoglycemic episodes and improved postprandial glucose excursions when compared to conventional regular insulin therapy. Some studies have demonstrated a greater impact on the quality of life with lispro insulin solution, and it has been shown to be more effective than regular insulin in reducing exercise-induced hypoglycemia when exercise is performed three hours after a meal. Thus, as a new insulin, it offers more flexibility for the diabetes patient and should be added to formularies as an alternative to regular insulin.

Lispro insulin solution should be stored in a refrigerator, but not in the freezer. If accidently frozen, it should not be used. If absolutely necessary, it may be stored at room temperature for up to 28 days. In this instance, storage temperature should be as cool as possible. The vial or cartridge containing this insulin should be kept away from direct light and heat. At the end of 28 days, any unused portion of the Lispro insulin solution should be discarded.

Isophane Insulin Suspension (NPH Insulin)

Isophane Insulin Suspension is a sterile suspension, in an aqueous vehicle buffered with dibasic sodium phosphate to between pH 7.1 and 7.4, of insulin prepared from zinc-insulin crystals modified by the addition of protamine so that the solid phase of the suspension consists of crystals composed of insulin, zinc, and protamine. Protamine is prepared from the sperm or the mature testes of fish belonging to the genus *Oncorhynchus* and others. As mentioned earlier during the discussion of the aqueous insulin solutions, suspensions of insulin with a pH on the alkaline side are inherently of a longer duration of action than those preparations that are solutions. Insulin is most insoluble at pH 7.2.

The rod-shaped crystals of isophane insulin suspension should be approximately 30 micrometers in length and the suspension free from large aggregates of crystals following moderate agitation. This is necessary for the insulin suspension to pass freely within the needle used in injection and for the absorption of the drug from the site of injection to be consistent from one manufactured batch of injection to another. When a portion of the suspension is examined microscopically, the suspended matter is largely crystalline with only traces of amorphous material. The official injection is required to contain glycerin and phenol for stability and preservation. The specified expiration date occurring in the labeling is 24 months after the immediate container was filled by the manufacturer. The suspension is packaged in multiple-dose containers having not less than 10 mL of injection. Each mL of the injection contains 100 units of insulin per mL of suspension. The suspension is best stored in a refrigerator, but freezing must be avoided.

As indicated earlier, isophane insulin suspension is an intermediate-acting insulin preparation administered as required mainly as hormonal replacement in diabetes mellitus. The usual dosage range subcutaneously is 10 to 80 USP Units.

The "NPH" used in some product names stands for "Neutral Protamine Hagedorn," since the preparation is about neutral (pH about 7.2), contains protamine, and was developed by Hagedorn. The term "isophane" is based on the Greek: *iso* and *phane*, meaning "equal" and "appearance" and refers to the equivalent balance between the protamine and insulin.

Isophane Insulin Suspension and Insulin Injection

In years past, patients needing a more rapid onset of insulin and the intermediate duration of activity approximately one day, would routinely mix isophane insulin suspension, an intermediate-acting insulin, with insulin injection, a rapid-acting insulin. Unexpected patient responses (e.g., hypo-

glycemic episodes) were encountered. It was not uncommon for the patient inadvertently to contaminate one of the vials during the mixing process. Subsequently, a premixed formulation of isophane insulin suspension and insulin injection became available. Currently there are two formulations, a 70/30 combination that consists of 70% isophane insulin suspension and 30% insulin injection, and a 50/50 combination that consists of 50% isophane insulin suspension and 50% insulin injection.

Humulin 50/50, for example, achieves a higher insulin concentration (C_{max}) and higher maximum glucose infusion rates with more rapid elimination than Humulin 70/30. However, as expected, the cumulative amounts of insulin absorbed (AUC) and the cumulative effects over 24 hours following injection are identical. Thus, the 70/30 combination provides an initial insulin response tempered with a more prolonged release of insulin. The 50/50 mixture would be useful in those situations where a greater initial response is required, and in those patients who have been using extemporaneously compounded insulin mixtures in a 50/50 ratio.

The Humulin 70/30 and 50/50 premixed insulins are cloudly suspensions with a zinc content of 0.01–0.04 mg/100 units. These insulins are neutral in pH and phosphate buffered. m-Cresol and phenol are the preservatives employed for both combinations. Protamine sulfate is used as the modifying protein salt.

Patients should not attempt to change the ratio of these products with the addition of NPH or regular insulin. If Humulin N and Humulin R mixtures are prescribed in a different proportion, the individual insulin products should be mixed in the amounts recommended by the physician.

Insulin Zinc Suspension

Insulin for Insulin Zinc Suspension is modified by the addition of zinc chloride so that the suspended particles consist of a mixture of crystalline and amorphous insulin in a ratio of approximately 7 parts of crystals to 3 parts of amorphous material. The sterile suspension is in an aqueous vehicle buffered to pH 7.2 to 7.5 with sodium acetate. In treating insulin with zinc chloride, it is possible to obtain both crystalline and amorphous zinc insulin. The amorphous form has the most prompt hypoglycemic effect, since the particles are the smallest and are absorbed into the system more rapidly after subcutaneous injection than are the zinc insulin crystals. Also, the larger the crystals the less prompt and the longer-acting will be the insulin suspension. By combining the crystalline and amorphous forms into one preparation, an intermediate-acting suspension is obtained. As noted in Table 14.6 the time-activity of insulin zinc suspension is only slightly different than that for isophane insulin suspension. The advantage of the former is that no additional foreign protein (other than the insulin) is present, such as protamine, which may produce local sensitivity reactions. Also, it may be combined as desired with either of the following two suspensions to produce an insulin preparation having the time-activity characteristics that most closely meet the desires and requirements of the individual patient. Suspensions available contain 100 USP Insulin Units per mL packaged in 10-mL vials. The individual crystalline and amorphous particles may be seen microscopically, with the crystals being predominantly between 10 to 40 μm in maximum dimension and the amorphous particles no greater than 2 μm in maximum dimension.

In addition to the sodium acetate as a buffer, the suspension contains about 0.7% sodium chloride for tonicity and 0.10% methylparaben for preservation. The expiration date of the suspension is 24 months after the immediate container was filled. The suspension must be stored in a refrigerator with freezing being avoided. As with all such preparations, the dose depends upon the individual needs of the patient, but generally ranges between 10 and 80 USP Units.

Extended Insulin Zinc Suspension

Extended insulin zinc suspension is a sterile suspension of zinc insulin crystals in an aqueous medium buffered to between pH 7.2 and 7.5 with sodium acetate. Present also are 0.7% sodium chloride for tonicity and 0.1% methylparaben for preservation. Because the suspended matter is composed solely of zinc insulin crystals, which are slowly absorbed, this preparation is classified as a long-acting insulin preparation. Because of the compatibility between the preparations, this suspension may be mixed with either insulin zinc suspension or prompt insulin zinc suspension to achieve the proper time-activity requirements of an individual patient. The usual dosage range is 10 to 80 USP Units. The suspension is commercially available in 10-mL vials providing 100 USP Insulin Units per mL. The suspension must be stored in a refrigerator with freezing being avoided. Under proper storage conditions, the expiration date of the injection is not later than 24 months after the immediate container was filled.

Prompt Insulin Zinc Suspension

The sterile suspension of insulin in Prompt Insulin Zinc Suspension is modified by the addition of zinc chloride so that the solid phase of the suspension is amorphous. The maximum dimension of the shapeless particles of zinc insulin must not exceed 2 micrometers. The suspension is available in 100 USP Insulin Units per mL in vials of 10 mL. This preparation has the same pH and additives as extended insulin zinc suspension, and they may be mixed as desired to achieve a preparation having the desired time-activity characteristics. This is a rapid-acting insulin preparation. It must be stored in a refrigerator and not permitted to freeze. Its expiration date is not greater than 24 months after the immediate container was filled.

Insulin Infusion Pumps

Insulin infusion pumps allow patients to achieve and maintain blood glucose at near-normal levels on a *constant basis*. Continuous infusion of insulin through use of these pumps eliminates the need for the patient to self-administer daily injections of insulin. This provides patient convenience, better patient compliance, and control over the disease. The main objective of pump therapy is the strict control of the blood glucose level between 70 to 140 mg/dL. This is the primary way to avoid complications in diabetic patients, such as gangrene and diabetic retinopathy.

Early insulin infusion pumps were large bedside units, used mainly in hospitals. Today, portable, battery-operated, and programmable units are available. These systems utilize microcomputers to regulate the flow of insulin from a syringe attached to a catheter (usually 18 gauge) connected to a 27- to 28-gauge needle inserted in the patient. The insulin may be delivered subcutaneously, intravenously, or intraperitoneally.

Patients who use infusion pumps for the continuous subcutaneous administration of insulin may develop hard nodules at the site of injection. Some patients may demonstrate nodules that are tender, develop a rock-hard consistency, and take several months to subside. Although the cause of this nodule formation is unknown, a change in insulin may be beneficial. Speculation as to the cause centers around the development of local trauma or hematoma formation with a subsequent local inflammatory response, stimulation of fibroblast replacement, or dystrophic calcification. The need to rotate sites of injection on a several day basis cannot be overemphasized. For additional information on infusion pumps, the reader is directed to the footnote reference at the end of this chapter (20).

Large Volume Parenterals (LVPs)

Common examples of large volume parenterals in use today were presented in Table 14.7. These solutions are usually administered by intravenous infusion to replenish body fluids, electrolytes, or to provide nutrition. They are usually administered in volumes of 100 mL to liter amounts and more per

Table 14.7. Examples of Some Injections Administered in Large Volume by Intravenous Infusion That May Be Administered in Volumes of 1 Liter or More, Alone, or With Other Drugs Added

Injection	*Usual Contents*	*Category and Comments*
Amino Acid Injection	3.5, 5, 5.5, 7, 8.5, 10% crystalline amino acids with or without varying concentrations of electrolytes or glycerin	Fluid and nutrient replenisher.
Dextrose Injection, USP	2.5, 5.0, 10, 20% dextrose, and other strengths	Fluid and nutrient replenisher.
Dextrose and Sodium Chloride Injection, USP	Dextrose varying from 2.5 to 10% and sodium chloride from 0.11 (19 mEq sodium) to 0.9% (154 mEq sodium)	Fluid, nutrient, and electrolyte replenisher.
Mannitol Injection, USP	5, 10, 15, 20 and 25% mannitol	Diagnostic aid in renal function determinations; diuretic. Fluid and nutrient replenisher
Ringer's Injection, USP	147 mEq sodium, 4 mEq potassium, 4.5 mEq calcium, and 156 mEq chloride per liter	Fluid and electrolyte replenisher.
Lactated Ringer's Injection, USP	2.7 mEq calcium, 4 mEq potassium, 130 mEq sodium and 28 mEq lactate per liter	Systemic alkalinizer; fluid and electrolyte replenisher.
Sodium Chloride Injection, USP	0.9% sodium chloride	Fluid and electrolyte replenisher; isotonic vehicle.

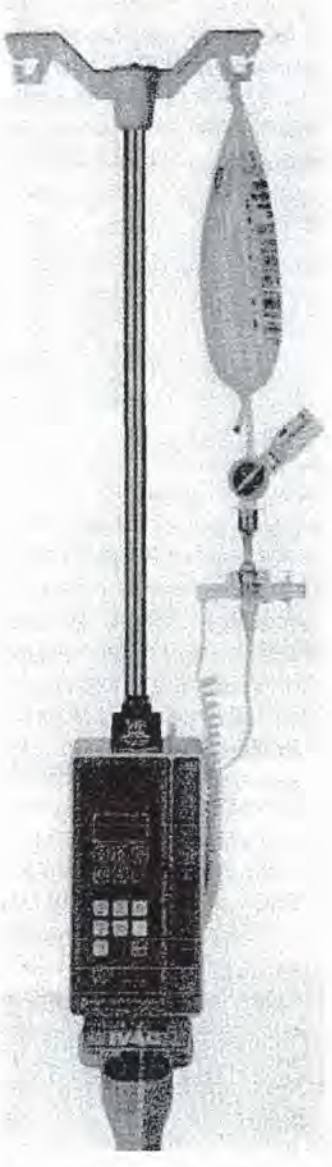

Fig. 14.33 *Accurate delivery of intravenous fluids and medications by use of a controlled rate infusion system (CRIS) for the drug vial and a volumetric infusion pump for the intravenous fluids. (Courtesy of Eli Lilly and Company.)*

day by slow intravenous infusion with or without controlled-rate infusion systems (Fig. 14.33). Because of the large volumes administered, these solutions must not contain bacteriostatic agents or other pharmaceutical additives. They are packaged in large single-dose containers (Figs. 14.34, 14.35).

As indicated previously, therapeutic additives as electrolytes, vitamins, and antineoplastics are frequently incorporated into large volume parenterals for coadministration to the patient. It is the responsibility of the pharmacist to be knowledgeable of the physical and chemical compatibility of the

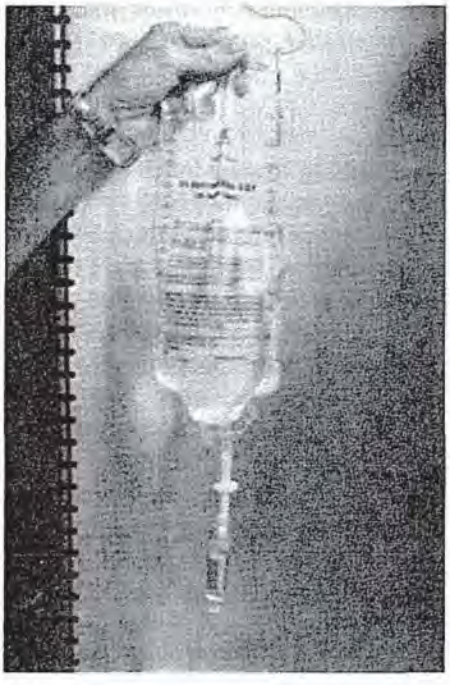

Fig. 14.34 *Intravenous solution packaged in pliable plastic.*

additive in the solution in which it is placed. Obviously, an incompatible combination which results in the formation of insoluble material or which affects the efficacy or potency of the therapeutic agent of the vehicle is not acceptable.

It is also important for the pharmacist to be vigilant of possible incompatibilities associated with multiple infusions that may be co-administered to a patient. A typical nursing question may involve, "can the dopamine infusion ('drip') be run in with the heparin infusion ('drip')?" To answer these questions, the pharmacist should become knowledgeable about parenteral therapy and be aware of incompatibilities through the literature. Numerous references (e.g., *Handbook of Injectable Drugs*, King's *Guide to Parenteral Admixtures* [Cutter Laboratories]) are available for sources listing and discussing par-

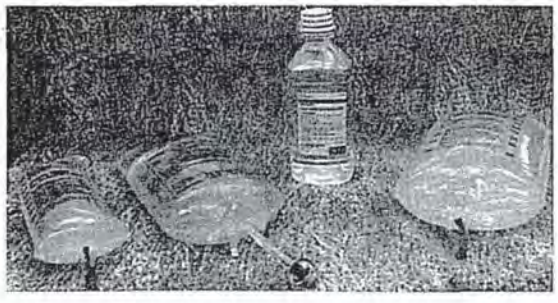

Fig. 14.35 *Examples of peritoneal dialysis and irrigation fluids. (Courtesy of William B. French, PhD.)*

enteral incompatibilities. However, the pharmacist should only use the most current editions of each of these references. Whenever possible, the pharmacist should attempt to answer these important questions and explain the incompatibilities that come to his/her attention as part of the daily routine. Further, the pharmacist should create a file of available data and add it from one's experience and the literature.

While it is impossible to chart every possible admixture incompatibility, principles can be learned and applied. For example, certain drugs are inactivated or precipitate at either high or low pH values, some drugs (e.g., sympathomimetics) encounter problems when added to IV fluids, and certain therapeutic large-volume solutions (e.g., sodium bicarbonate, urea, mannitol) should never contain additives.

Large volume parenteral solutions are employed in *maintenance therapy* for the patient entering or recovering from surgery, or for the patient who is unconscious and unable to obtain fluids, electrolytes, and nutrition orally. The solutions may also be utilized in *replacement therapy* in patients who have suffered a heavy loss of fluid and electrolytes.

Maintenance Therapy

When a patient is being maintained on parenteral fluids for only several days, simple solutions providing adequate amounts of water, dextrose, and small amounts of sodium and potassium generally suffice. When patients are unable to take oral nutrition or fluids for slightly longer periods, say 3 to 6 days, solutions of higher caloric content may be used. In instances in which oral feeding must be deferred for periods of weeks or longer, total parenteral nutrition must be implemented to provide all of the essential nutrients to minimize tissue break-down and to maintain normalcy within the body. Total nutrient admixtures (i.e., TNA, three-in-one) include all substrates necessary for nutritional support, e.g., carbohydrates, protein, fat, electrolytes, trace elements, that are usually mixed in a single plastic intravenous bag for more convenient administration.

These admixtures are very useful for patients undergoing chemotherapy, and for gastrointestinal patients, and anorexic patients. The use of three-in-one admixtures in pediatric patients, especially neonates is controversial. The concentration of calcium, phosphorus, and necessary warm administration conditions for pediatric TPNs do not lend themselves to stable preparations. As a result, many pediatric institutions will not compound three-in-one admixtures for their patients, but administer each component separately.

When using TNA, the pharmacist must consider the order of substrate mixing, differentiate between various brands of substrate and their physical-chemical properties, determine the type of plastic bag system that is most appropriate to use, determine whether (and by what mode) the TNA should be filtered prior to infusion, determine how the product should be stored, and assess any potential complications that might arise with the use of this method of administering nutritional products. For example, the use of "standard" total parenteral nutrition plastic bags may result in the leaching out of plasticizer into the solution, and be potentially injurious to the patient.

In April, 1994, the FDA issued a Safety Alert regarding the hazards of precipitation associated with parenteral nutrition (21). This was in response to two deaths and at least two other patient cases of respiratory distress associated with the use of three-in-one admixtures. Patient autopsies revealed diffuse microvascular pulmonary emboli linked to the presence of a calcium phosphate precipitate in the admixture. Consequently, the FDA Safety Alert recommends that a filter be used when infusing either central or peripheral parenteral nutrition admixtures. A 0.22-μm filter, containing both a bacterial-retentive and an air-eliminating filter, has been recommended for use with nonlipid (i.e., two-in-one) containing parenteral nutrient solutions.

Lipid emulsions and three-in-one admixture parenteral nutrient solutions can be safely filtered through filters with a pore size of ≥ 1.2 μm. A problem with the lipid emulsion in a three-in-one admixture is that it obscures the presence of any precipitate. Thus, if a lipid emulsion is needed, a preferable alternative is to employ a two-in-one admixture with a lipid infused separately via a Y-site.

Replacement Therapy

In instances in which there is a heavy loss of water and electrolytes, as in severe diarrhea or vomiting, greater than usual amounts of these materials may be initially administered and then maintenance therapy provided. Patients with Crohn's disease, AIDS, burn patients, or those experiencing trauma are candidates for replacement therapy.

Water Requirement

In normal individuals, the daily water requirement is that amount needed to replace normal and expected losses. Water is lost daily in the urine, feces, skin and from respiration. The normal daily requirement of water for adults is about 25 to 40 mL/kg of

body weight, or an average of about 2,000 mL per square meter of body surface area (22). Nomograms for the determination of body surface area from body height and weight are presented in Chapter 2, Figure 2.8. Children and small adults need more water per pound of body weight than do larger adults; water requirements correlate more closely with body surface area than with weight and an employed guideline to estimate normal daily requirement for water in these patients is as follows:

1. <10 kg: 100 mL/kg/day
2. 10–20 kg: 1000 mL plus 50 mL/kg/day for weight over 10 kg.
3. >20 kg to maximum of 80 kg: 1500 mL plus 20 mL/kg/day for weight over 20 kg.

However, in the newborn, the volume administered in the first week or two should be about half that calculated from body surface area.

In water replacement therapy for adults, 70 mL of water per kg per day may be required in addition to the maintenance water requirements; a badly dehydrated infant may require even a greater proportion (22). Thus, a 50-kg patient may require 3500 mL for replacement plus 2400 mL for maintenance. In order to avoid the consequences of fluid overload, especially in elderly patients, and those with renal or cardiovascular disorders, monitoring of blood pressure is desirable.

Because water administered intravenously as such may cause the osmotic hemolysis of red blood cells, and, since a patient who requires water generally requires nutrition and/or electrolytes, the parenteral administration of water is generally as a solution with dextrose or electrolytes in which the solution has sufficient tonicity (sodium chloride equivalency) to protect the red blood cells from hemolyzing.

Electrolyte Requirement

Potassium, the primary intracellular cation, is particularly important for normal cardiac and skeletal muscle function. The usual daily intake of potassium is about 100 mEq and the usual daily loss is about 40 mEq. Thus, any replacement therapy should include a minimum of 40 mEq plus the amount needed to replace additional losses. Potassium can be lost through excessive perspiration, repeated enemas, trauma (such as severe burns), uncontrolled diabetes, diseases of the intestinal tract, surgical operations, and the use of such medications as thiazide and loop diuretics. People who suffer from poor nutrition, those using very low-calorie diet products, and victims of anorexia nervosa or acute alcoholism also may have low potassium levels, i.e., hypokalemia, because they are not taking in enough of the mineral. Symptoms of potassium loss include a weak pulse, faint heart sounds, falling blood pressure, and generalized weakness. Severe loss of potassium can lead to death. Too much potassium is not a good thing, either. An excess may cause diarrhea, irritability, muscle cramps, and pain. Hyperkalemia can be caused by kidney failure or consuming excess amounts of potassium-rich foods. Prescribed potassium supplements, potassium-sparing diuretic therapy, angiotensin converting enzyme inhibitors (e.g., lisinopril) and the indiscriminate use of over-the-counter salt-substitute products have also been implicated to induce hyperkalemia.

In cases of severe potassium deficiency, electrolyte replacement through the intravenous administration of potassium is usually employed. The pharmacist who receives a prescription for intravenous potassium chloride must be careful and check the amount of potassium chloride in the prescription and the infusion rate at which the drug is to be administered to the patient. Potassium preparations must be diluted with a suitable large volume parenteral solution, mixed well, and given by slow IV infusion. They are not to be administered undiluted.

The most commonly used concentration of potassium chloride for continuous infusion, IV maintenance therapy is between 20–40 mEq/L. With a peripheral line, that concentration may increase to 60 mEq/L, and with a central line, the maximum concentration can be up to 80 mEq/L.

For intermittent potassium replacement therapy in patients suffering from hypokalemia, the usual infusion rate is 10 mEq/hr (maximum recommended rate is 20 mEq/hr). Because of potassium chloride's ability to effect ECG changes (e.g., progressive increase in height and peaking of T waves, lowering of the R wave, decreased amplitude and ultimate disappearance of the P waves), most hospitals establish a maximum infusion rate of 10 mEq/hr if the patient is not monitored by EKG. For patients monitored by EKG, the usual infusion rate is 20 mEq/hr with a maximum infusion rate of 40 mEq/hr depending upon the clinical condition of the patient.

For patients in need of aggressive potassium replacement, the potassium serum level should be assessed every 6 hours during the early intensive phase of therapy and once daily thereafter when normal potassium serum levels are achieved. For patients whose serum potassium is >2.5 mEq/L, the potassium level should be measured after the first 60 mEq are administered. For patients whose serum potassium is <2.5 mEq/L, the potassium

level should be measured after the first 80 mEq are administered.

Sodium, the principal extracellular cation, is vital to maintain normal extracellular fluids. Average daily intake of sodium is 135 to 170 mEq (8 to 10 g of sodium chloride). The body is able to conserve sodium when this ion is lost or removed from the diet. When there is sodium loss or a deficit, the daily administration of 3 to 5 g of sodium chloride (51 to 85 mEq of sodium) should prevent a negative sodium balance. A low sodium level in the body may result from excessive sweating, the use of certain diuretics, or diarrhea. Fatigue, muscle weakness, apprehension, and convulsions are among the symptoms of excessive sodium loss. Sodium concentrations can increase when a person does not drink enough water, especially in hot weather, or if kidney function is impaired. Dry, sticky mucous membranes, flushed skin, elevated body temperature, lack of tears, and thirst are among the symptoms of sodium excess. In about 20% of individuals who suffer from high blood pressure, sodium has been implicated as a causative factor. Chloride, the principal anion of the extracellular fluid is usually paired with sodium. Chloride is also important for muscle contraction, balancing the fluid levels inside and outside the cells, and maintaining the acid-base balance of the extracellular fluid. An adequate supply of chloride is necessary to prevent bicarbonate, the second most prevalent anion, from tipping the acid-base balance to the alkaline side. (In 1979, a lack of chloride in a brand of infant formula caused metabolic alkalosis in babies who had been exclusively fed that formula. As a result of this episode, Congress passed the Infant Formula Act of 1980, which spells out the nutrients that must be in formulas and establishes quality control procedures for the manufacture of these infant foods.) Although other electrolytes and minerals as calcium, magnesium, and iron are lost from the body, they generally are not required during short-term parenteral therapy.

Caloric Requirements

Generally patients requiring parenteral fluids are given 5% dextrose to reduce the caloric deficit that usually occurs in patients undergoing maintenance or replacement therapy. The use of dextrose also minimizes ketosis and the breakdown of protein. Basic caloric requirements may be estimated by body weight; in the fasting state, the average daily loss of body protein is approximately 80 g/day for a 70 kg man. Daily ingestion of at least 100 g of glucose reduces this loss by half.

Parenteral Hyperalimentation

This is the infusion of large amounts of basic nutrients sufficient to achieve active tissue synthesis and growth. It is employed in the long-term intravenous feeding of protein solutions containing high concentrations of dextrose (approximately 20%), electrolytes, vitamins, and in some instances insulin. Among the components utilized in parenteral nutrition solutions are the following, listed in quantities commonly provided per liter of fluid. The individual components and amounts administered to a patient would vary depending on the patient's needs.

Electrolytes:	
Sodium	25 mEq
Potassium	20 mEq
Magnesium	5 mEq
Calcium	5 mEq
Chloride	30 mEq
Acetate	25 mEq
Phosphate	18 mM
Vitamins:	
Vitamin A	3300 I.U.
Vitamin D	200 I.U.
Vitamin E	10 I.U.
Vitamin C	100 mg
Niacin	40 mg
Vitamin B_2	3.6–4.93 mg
Vitamin B_1	3–3.35 mg
Vitamin B_6	4–4.86 mg
Pantothenic Acid	15 mg
Folic Acid	400 mcg
Vitamin B_{12}	5 mcg
Biotin	60 mcg
Amino Acids: Essential Amino Acids	
L-Isoleucine	590 mg
L-Leucine	770 mg
L-Lysine acetate	870 mg
(free base	620 mg)
L-Methionine	450 mg
L-Phenylalanine	480 mg
L-Threonine	340 mg
L-Tryptophan	130 mg
L-Valine	560 mg
Nonessential Amino Acids	
L-Alanine	600 mg
L-Arginine	810 mg
L-Histidine	240 mg
L-Proline	950 mg
L-Serine	500 mg
Aminoacetic Acid	1.19 g

The large proportion of dextrose increases the caloric value of the solution, while keeping the vol-

ume required to be administered to a minimum. The solutions are administered slowly through a large vein, such as the superior vena cava. The superior vena cava is accessed through the subclavian vein, which is located immediately beneath the clavicle and near to the heart. This permits the rapid dilution of the concentrated hyperalimentation fluid and minimizes the risk of tissue or cellular damage due to the hypertonicity of the solution. Generally, final concentrations of dextrose (≤10%) can be given peripherally. Solutions containing dextrose (>10%) should be given via the central route, i.e., the superior vena cava.

Calcium (usually as calcium gluconate) and phosphate (usually as potassium or sodium phosphate) are frequently present in parenteral admixtures. A significant problem associated with their use is the formation of calcium phosphate, an insoluble precipitate. As mentioned earlier in this chapter, the formation of this and its resultant deposition of calcium phosphate crystals in lung tissue led to the 1994 FDA Safety Alert (21).

Many factors have been implicated in the formation of the insoluble precipitate. Among these are the concentration of the individual ions, the salt form of the calcium, the concentration and type of amino acids, the concentration of the dextrose, the temperature and pH of the TPN, the presence of other additives (e.g., cysteine), and the order of mixing. The potential of calcium phosphate precipitation is especially challenging for compounding neonate/pediatric TPN admixtures because of the small volume they are able to tolerate and the need for aggressive replacement therapy. Thus, pharmacists must be alert to recognize and to avoid this potential serious compatibility problem.

Figure 14.36 demonstrates a Nutrimix Macro TPN Compounder. This device can pump four nutritional solutions (i.e., dextrose, water, amino acids, fat) simultaneously to compound nutritional admixtures by gravimetric means. The user programs the volume and specific gravity of the fluid to be pumped and the device calculates the weight of the solution that has to be transferred from the source station to the patient bag. The fifth load cell serves as a confirmation of the weights programmed vs. weights delivered.

With the increasing use of parenteral solutions in the pediatric population, including parenteral nutrition solutions, pharmacists are frequently confronted with inquiries concerning the appropriate method of parenteral drug delivery (20). A dilemma with pediatric patients is that they often have a limited fluid capacity caused by disease (e.g., congestive heart failure, renal insufficiency) and limited vascular access. As a consequence, pharmacists are asked whether a medication can be administered along with a parenteral nutrition solution. Although this practice is to be discouraged, in the pediatric population it may be the only way to ensure that the patient is receiving adequate nutrition as well as appropriate drug therapy. Further, by administering the medication with the PN solution, rather than interrupting the PN to administer medication, rebound hypoglycemia is less likely to develop in the patient. The pharmacist must remember that the practice of administering medication through a central venous line intended for PN solutions is not without risks. Catheter sepsis and occlusion can result.

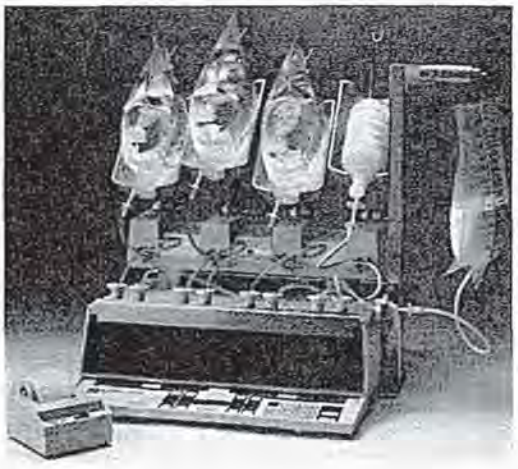

Fig. 14.36 *Nutrimix Macro TPN Compounder. (Courtesy of Abbott Hospital Products Division.)*

Formerly, TPNs were prepared one liter at a time. However, to conserve pharmacist and nursing time, a 24-hour supply is much more efficient and now the norm. Indeed, if a patient encounters a problem necessitating a bag to be remade, the cost difference between one or two liters and a 2000 mL bag is not that significant. Waste should not be a consideration because the attending physician should not use the TPN to minutely adjust for a patient's need. Typically, electrolyte requirements exceed the physical compatibilities of the TPN components (e.g., calcium/phosphate compatibilities in lipid containing TPNs), and when this occurs the pharmacist should encourage the physician to write for a separate infusion to make up the deficiency.

The following abbreviations may be used in the hospital in describing the desired order for parenteral nutrition:

CVTPN (Central Vein TPN)
TPN (Total Parenteral Nutrition)
PPN (Peripheral Parenteral Nutrition)

Enteral Nutrition

As appropriate, hospitalized and home care patients may be provided their nutritional needs through *enteral* rather than *parenteral* means. Enteral nutrition products may be administered orally, via nasogastric tube, via feeding gastrostomy, or via needle-catheter jejunostomy. These products are formulated to contain a variety of vitamins, minerals, carbohydrates, proteins, fats and caloric requirements to meet the specific needs of patients. While parenteral feeding is appropriate for short-term use in a hospital or long-term care facility, or when the gastrointestinal tract is unable to absorb nutrients, enteral feeding is preferable whenever possible. It is just as effective as a source of nutrients, less expensive than parenteral feeding, and has a low potential to cause serious complications.

The defined formula diets may be monomeric or oligomeric (i.e., amino acids or short peptides and simple carbohydrates) or polymeric (more complex protein and carbohydrate sources). Modular supplements are used for individual supplementation of protein (ProMod powder, Propac powder), carbohydrate (Moducal powder), or fat (Lipomul liquid) when formulas do not offer sufficient flexibility. For example, a physician may order a powder reconstituted one-quarter strength, half-strength, or full strength for a particular patient and then have this administered via a nasogastric tube, a feeding gastrostomy, or a needle-catheter jejunostomy.

There is no single classification system for these products, and there are different criteria for evaluating and categorizing them. Caloric density (generally in the range of 1, 1.5, or 2 kcal/mL) influences the density of other nutrients. Protein content is also a major determinant in these products. For those patients who experience diarrhea and cramping, high osmolality formulas may present difficulty. Low-fat-content products should be suggested for patients with significant malabsorption, hyperlipidemia, or severe exocrine pancreatic insufficiency. Medium chain triglycerides (MCT), while providing a useful source of energy in patients with malabsorption, do not provide essential fatty acids.

Originally, enteral feedings contained lactose and presented problems in lactase-deficient individuals. This ingredient has been eliminated from many of the nutritionally complete enteral formulas. For those patients with hepatic or renal disease, the sodium and potassium content of the formulations must be considered. For patients maintained on warfarin therapy, consideration should be focused on the content of Vitamin K in the formulation. Although many products now have less Vitamin K than before, caution is still warranted to avoid hypoprothrombinemic alterations in warfarin therapy.

Specific enteral products are selected according to the patient type they serve. For example, a requirement for less than 2000 calories per day, or increased protein typically involves an elderly, bedfast patient who is not physically active. This level of support is also advocated for postsurgical patients, and those who suffer from infection or fractured bones. While requiring fewer calories, these individuals still need normal nutrients, including protein. Such products as Ensure HN, Sustacal, and Osmolite HN are appropriate in this circumstance. Alternatively, most persons fall within the 2000 to 3000 calorie per day category, inclusive of patients with poor appetite or those suffering from cancer. The last category of patients are those with daily caloric needs which exceed 3000 calories. These individuals usually have high protein losses from severe trauma, e.g., burns, sepsis, multiple trauma. As in the first example there are numerous products for the latter two patient categories.

The pharmacist can be helpful in the selection of these products because these do differ in the amount of their carbohydrate, fat, and protein content, and in fiber. Further, these products differ in taste and consumer acceptability criteria, e.g., "mouth feel," cost. Pharmacists may encounter consumers who wish to self-administer an enteral product. If the intent is to supplement calories or protein in an otherwise healthy individual who simply wishes to assure a balanced dietary intake, a complete formula can be recommended. However, if it is intended to help a person regain weight which has been lost unexpectedly, the individual should be instead referred to a doctor. Sudden weight loss may indicate a serious pathologic problem requiring medical attention.

Pharmacists can also be helpful in cost management associated with these products. Composition (oligomeric or polymeric) and form (ready-to-use vs. powder) of the product influence cost. Generally, the polymeric products are less expensive than the oligomeric products. While powder forms may be less expensive compared to ready-to-use formulations, there is an indirect cost of labor required in the powder preparation.

Intravenous Infusion Devices

Since the early 1970s, the use of the intravenous route to administer drugs has become increasingly popular. In 1989, it was estimated that about 40% of all drugs and fluid administered in the hospital setting are done through intravenous administra-

tion (22). This increase has affected the development and use of mechanical infusion devices. Advances in infusion technology and computer technology have resulted in devices with extremely sophisticated drug-delivery capabilities (e.g., multiple-rate programming, pump or controller operation) (23). As a result, these cost-efficient devices provide greater accuracy and reliability of drug delivery than the traditional gravity-flow infusion methods. They also help reduce the fluid volume attributable to the medication infusion and decrease the need for monitoring fluid input (thus, decreased nursing time). Further, multiple-drug dosages can be administered, and incompatible drugs can be administered separately (22).

There are disadvantages associated with these mechanical devices, however, including the initial capital investment and extensive in-service education. Further, the influence of infusion pump devices on the delivery of a drug has not been fully recognized by clinicians. For example, intrinsic factors (operating mechanisms, flow accuracy, flow continuity, occlusion detection) and an extrinsic factor (backpressure) may alter the rate of drug delivery and the corresponding therapeutic response of the patient.

Pumps are classified by their *mechanism of operation* (peristaltic, piston, diaphragm), *frequency or type of drug delivery* (continuous or intermittent, bolus dosing, single-solution or multiple-solution), or *therapeutic application* (patient-controlled analgesia [PCA]) (24). Current research focuses upon the influence of drug delivery by these devices and the creation of new technologies (e.g., implantable pumps, pumps with chronobiological applications, osmotic-pressure devices, and open- or closed-loop systems) (24). Table 14.8 demonstrates several infusion devices which are used in parenteral nutrition support, including features associated with each.

Special Considerations Associated with Parenteral Therapy

Adsorption of Drugs

Numerous studies have demonstrated that some drugs are adsorbed onto the inner lining of IV containers and tubing or administration sets. Some of the drugs that have been implicated in this phenomenon and lost from aqueous solutions during infusion through plastic IV delivery systems include:

- Chlorpromazine HCl
- Diazepam
- Insulin
- Promazine HCl
- Promethazine HCl
- Thiopental sodium
- Thioridazine HCl
- Trifluoperazine HCl
- Warfarin sodium

Thus, pharmacists must be cognizant of this and take appropriate steps to prevent their occurrence. The significance of the loss is magnified with drugs that are used in lower quantities because a small amount lost to adsorption results in a higher percentage loss of the drug being delivered to the patient. One method to minimize this, is to administer infusions through short lengths of small-diameter tubing made of inert plastics.

Nitroglycerin, for example, should always be prepared in glass containers, and is adsorbed (40–80% of total dose) to polyvinylchoride (PVC), a plastic commonly used in administration components and some infusion containers. Thus, nitroglycerin for IV use is packaged with special non-PVC tubing by some manufacturers to avoid loss (<5%) of the drug into the tubing during administration. The amount of the adsorption depends upon such factors as concentration, flow rate, surface area of the tubing, and contact time with the tubing.

Intravenous nitroglycerin should be regulated by automatic infusion equipment (i.e., pumps, controllers) to enhance consistent dose administration. However, a problem may occur in that infusion pumps may fail to occlude the non-PVC infusion sets completely because the non-PVC (i.e., polyethylene) tubing is less pliable (i.e., more stiff) than standard PVC tubing. Excessive flow at low infusion rate settings may occur, causing alarms or unregulated gravity flow when the infusion pump is stopped. This could lead to overinfusion of nitroglycerin.

Some practitioners have responded by using the PVC containing tubing with the nitroglycerin and working around the problem. This is justified by some in that even though a great amount of drug is lost, the amount of drug the patient receives is based on hemodynamic functions. But, when the previous set is replaced, retitration of the drug is necessary. To allay this problem, several manufacturers have made available non-PVC containing pump administration sets.

The adsorption of insulin onto glassware and tubing depends upon several factors (i.e., concentration of insulin, contact time of insulin with glass and tubing, flow rate of the insulin infusion, presence of negatively charged proteins [human serum albumin]). Plastic IV infusion sets have reportedly removed up to 80% of a dose, but 20% to 30% is more common. The percent adsorbed is inversely

Table 14.8. Selected Infusion Devices Used in Parenteral Nutrition Support[1]

Pump	*Manufacturer*	*Cost ($)*	*Alarms, Features*
Volumetric infusion pumps			
AVI 2000 #200	AVI, 3M HealthCare Group	2800	Safety alarms; variable occlusion pressure limits; automatic KVO rate switch when volume limit reached.
Flo-Gard 8100	Baxter Healthcare	2800	Visual/audible alarms for flow rate error, improperly loaded cassette or drop sensor, infusion complete, low battery, occlusion; disposable cassette, gravity control plunger eliminates "run-aways" and allows for use on pump or by gravity, adjustable differential occlusion detection.
IMED	IMED	2600	Alarms for air in line, door open, low battery, malfunction, occlusion; automatic priming, dual-rate sequential piggybacking, syringe-use, selectable tamper-proof modes.
Multiple-rate programmable pumps			
CADD-TPN	Sims Deltec	3500	Alarms for infusion period completed, low reservoir volume, invalid rate, high pressure, system error; ambulatory system, may be stored and operated in backpack, programmable taper features.
Volumetric infusion pumps			
Provider One	Pancretec	2995	Alarms for air in line, computer error, end of infusion, low battery, low reservoir, occlusion, programming error; ability to taper up, down, or both, ability to adjust flow rate automatically, convenient carry case.
Quest 521 Intelligent	McGaw	2895	Alarms for air in line, check set, door open, low battery, repair, set volume; selectable variable pressure limits, 9 programmable cycles of time and rate.
Multiple-solution programmable pumps			
Gemini PC-2	IMED	4250	Alarms for check i.v. set, open-close door, air in line, occlusion inpatient or fluid side; 2 channels allowing delivery of 2 fluids at independent rates, can be operated as pump, controller, or both.
LifeCare 5000 Plum	Abbott	3500	Alarms for high or low flow, distal and proximal air in line or occlusion, dose end, low battery; history bank with last 15 alarms, variable pressure limits, tubing conversion to gravity flow, allows delivery of 2 fluids at independent rates, can be operated as pump, controller, or both.
Omni-Flow 4000	Abbott	4995	Alarms for air in line, cassette unlocked, empty container, low battery, occlusions in patient lines or upstream; automatic air elimination, can deliver up to 4 fluids simultaneously in continuous or intermittent modes.

[1]Copyright permission, American College of Clinical Pharmacy

proportional to the insulin concentration and will take place within 30 to 60 minutes. Because this phenomenon cannot be easily and accurately predicted, patient monitoring is essential.

Handling/Disposal of Chemotherapeutic Agents for Cancer

In the 1980s awareness developed among health care personnel about environmental contamination that was possible after handling cytotoxic agents. Mutagenic and allergic case reports began to emerge in the literature, and in response in 1985, the then American Society of Hospital Pharmacists (now the American Society of Health-System Pharmacists) published a technical assistance bulletin on handling cytotoxic and hazardous drugs. This bulletin has been updated through the years and is now found in the *Practice Standards of ASHP* (25).

In theory, "correct and perfect preparation and handling techniques will prevent drug particles or droplets from escaping from their containers while they are being manipulated" (25). However, near perfect technique is uncommon and quite impossible. Thus, there must be structured training and quality-assurance programs in place within institutions that use these hazardous drugs, and the pharmacist must play a vital role in creating and executing these.

At potential risk for harm are those personnel who handle cytotoxic drugs, and steps should be taken to minimize unnecessary exposure by implementing basic steps and following common sense (26). These basic steps include:

1. Utilizing vertical laminar flow hoods (or bacteriological glove boxes) for the preparation and reconstitution of cytotoxic drugs.
2. Wearing protective gloves and mask during product preparation.
3. Handling and disposing of cytotoxic drugs centrally utilizing specially designed waste containers and incineration.
4. Periodic monitoring of personnel involved with handling admixtures of cytotoxic drugs (e.g., CBC, blood chemistry screen, differential cell count).
5. Informing personnel handling cytotoxic drugs that a potential risk to their health exists.
6. Instituting specialized labeling of containers to ensure proper handling and disposal of the cytotoxic agent.

Other Injectable Products—Pellets or Implants

Historically, pellets or implants were sterile, small, usually cylindrical-shaped solid objects about 3.2 mm in diameter and 8 mm in length, prepared by compression and intended to be implanted subcutaneously for the purpose of providing the continuous release of medication over a prolonged period of time. The pellets, which are implanted under the skin (usually of the thigh or abdomen) with a special injector or by surgical incision, are used for potent hormones. Their implantation provides the patient with an economical means of obtaining long-lasting effects (up to many months after a single implantation) and obviates the need for frequent parenteral or oral hormone therapy. The implanted pellet, which might contain 100 times the amount of drug (e.g., desoxycorticosterone, estradiol, testosterone) given by other routes of administration, release the drug slowly into the general circulation.

Pellets were formulated with no binders, diluents, or excipients, to permit total dissolution and absorption of the pellet from the site of implantation. Recently, a levonorgestrel implant contraceptive system was developed. Rather than dissolute entirely, the surgically implanted capsules are intended to be removed subsequently by surgery after an appropriate amount of time (up to 5 years).

Levonorgestrel Implants

These are a set of six flexible, closed capsules of a dimethylsiloxane/methylvinylsiloxane copolymer, each containing 36 mg of the progestin levonorgestrel (27). These are found in an insertion kit to facilitate surgical subdermal implantation through a 2 mm incision in the mid-portion of the upper arm about eight to ten cm above the elbow crease. These are implanted in a fan-like pattern, about 15° apart, for a total of 75°. Appropriate insertion facilitates removal by the end of the fifth year. This system provides long-term (up to 5 years) reversible contraception.

Diffusion of the levonorgestrel through the wall of each capsule provides a continuous low dose of progestin. Initially, the dose of levonorgestrel is about 85 mcg/day, followed by a decline to about 50 mcg/day by 9 months, and to about 35 mcg/day by 18 months, with a further decline thereafter to about 30 mcg/day. The resulting blood levels are substantially below those generally observed among users of combination oral contraceptives containing the progestins norgestrel or levonorgestrel. Because of the range of variability in blood levels and variation in individual response, blood levels alone are not predictive of the risk of pregnancy in an individual woman (27).

Irrigation and Dialysis Solutions

Solutions for irrigation of body tissues and for dialysis resemble parenteral solutions in that they are subject to the same stringent standards. The difference is in their use. These solutions are not injected into the vein, but employed outside of the circulatory system. Since they are generally used in large volumes, they are packaged in large volume containers, generally of the screw-cap type which permits the rapid pouring of the solution.

Table 14.9. Examples of Irrigation Solutions

Solution	*Description*
Acetic Acid Irrigation, USP	This solution is employed topically to the bladder as a 0.25% solution for irrigation. It has a pH of between 2.8 and 3.4 and a calculated osmolarity of 42 mOsm/L, and is employed during urologic procedures. It is administered to wash blood and surgical debris away while maintaining suitable conditions for the tissue and permitting the surgeon an unobstructed view.
Neomycin and Polymyxin B Sulfates Solution for Irrigation, USP	This sterile urogenital solution contains 57 mg neomycin sulfate (40 mg of neomycin) and Polymyxin B Sulfate 200,000 Units (of polymyxin B) per ml and is employed as a topical antibacterial in the continuous irrigation of the bladder. It has a pH between 4.5 to 6.0. One ml of this solution is added to 1 L of 0.9% sodium chloride solution and administered via a 3-way catheter at the rate of 1 L every 24 hours (i.e., approximately 40 mL/hr).
Ringer's Irrigation, USP	This solution contains sodium chloride (8.6 g/L), potassium chloride (0.3 g/L), and calcium chloride (0.33 g/L) in purified water, in the same proportions, as is present in Ringer's Injection. The solution is sterile and pyrogen-free. It is used topically as an irrigation and must be labeled "not for injection." It has a pH between 5.0 and 7.5 and a calculated osmolarity of 309 mOsm/L.
Sodium Chloride Irrigation, USP	This sterile solution of sodium chloride in water for injection contains 77 or 154 mEq/L each of sodium and chloride in the 0.45 and 0.9% solution, respectively. Sodium chloride irrigation has a pH of approximately 5.3, and the 0.45 and 0.9% solutions have a calculated osmolarity of 154 and 308 mOsm/L, respectively. The solution is employed topically to wash wounds and into body cavities where absorption into the blood is not likely. The solution may also be employed rectally as an enema; for simple evacuation, 150 mL is usually employed and for colonic flush, 1500 mL may be used.
Sterile Water for Irrigation, USP	This is water for injection that has been sterilized and suitably packaged. The label designations "for irrigation only" and "not for injection" must appear prominently on the label. The water must not contain any antimicrobial or other added agent.

Irrigation Solutions

Irrigation solutions are intended to bathe or wash wounds, surgical incisions, or body tissues. Examples are presented in Table 14.9.

Dialysis Solutions

Dialysis may be defined as a process whereby substances may be separated from one another in solution by taking advantage of their differing diffusibility through membranes. *Peritoneal dialysis* solutions, allowed to flow into the peritoneal cavity, are used to remove toxic substances normally excreted by the kidney. In cases of poisoning or kidney failure, or in patients awaiting renal transplants, dialysis is an emergency life-saving procedure. Solutions are commercially available containing dextrose as a major source of calories, vitamins, minerals, electrolytes, and amino acids or peptides as a source of nitrogen. The solutions are made to be hypertonic (with dextrose) to plasma to avoid absorption of water from the dialysis solution into the circulation.

Peritoneal dialysis involves the principles of osmosis and diffusion across the semipermeable peritoneal membrane and includes the osmotic and chemical equilibration of the fluid within the peritoneal cavity with that of the extracellular compartment. The semipermeable peritoneal membrane restricts the movement of formed elements (e.g., erythrocytes) and large molecules (e.g., protein) but allows the movement of smaller molecules (e.g., electrolytes, urea, water) in both directions across the membrane according to the concentration on each side of the membrane, with net movement occurring in the direction of the concentration gradient. Instillation of dialysis solutions containing physiologic concentrations of electrolytes intraperitoneally allows for the movement of water, toxic substances and/or metabolites across the membrane in the direction of the concentration gradient, resulting in removal of these substances from the body following

drainage of the solution from the peritoneal cavity (i.e., outflow).

Hemodialysis is employed to remove toxins from the blood. In this method, the arterial blood is shunted through a polyethylene catheter through an artificial dialyzing membrane bathed in an electrolyte solution. Following the dialysis, the blood is returned to the body circulation through a vein.

Various dialysis solutions are available commercially and the pharmacist may be called upon to provide them or to make adjustments in their composition.

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