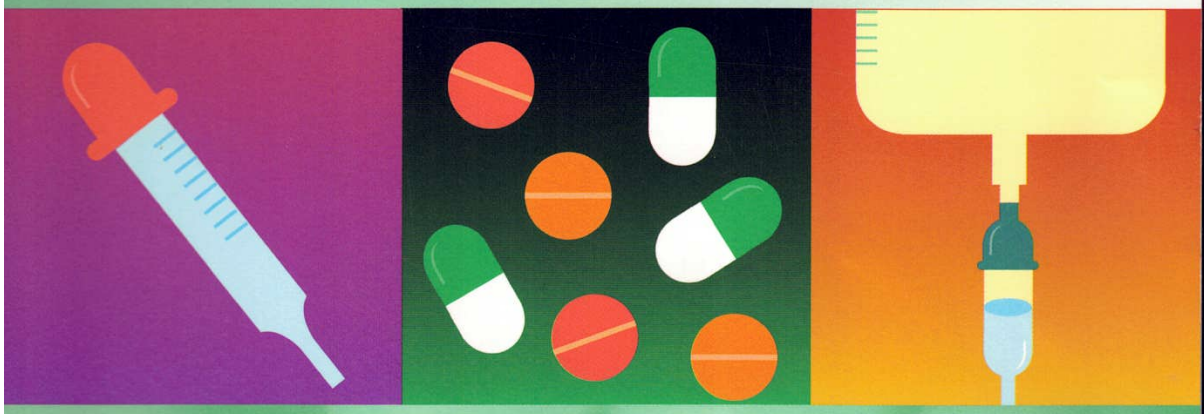
Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems

EIGHTH EDITION

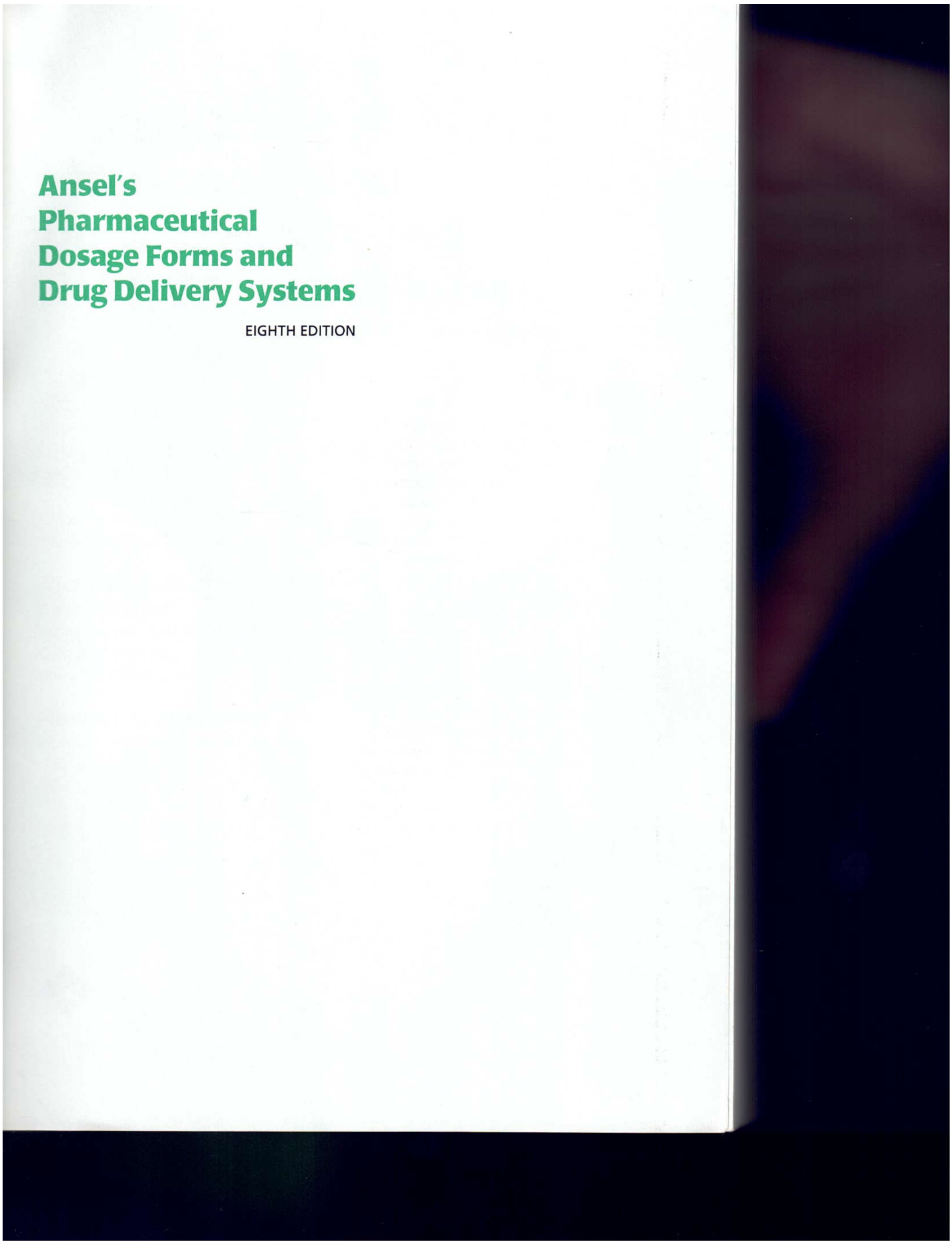


Loyd V. Allen, Jr.
Nicholas G. Popovich
Howard C. Ansel

LIPPINCOTT WILLIAMS & WILKINS

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EIGHTH EDITION



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Preface

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[a]Adapted with permission from O'Sullivan
Practice Manual: A Guide to the Clinical E

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Considered in this chapter are important pharmaceutical dosage forms with the common characteristic of sterility; that is, they are 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. Biologic preparations, including vaccines, toxoids, and antitoxins, also among this group are discussed in Chapter 16. Sterility in these preparations is essential 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, are discussed separately in Chapter 17.

Injections

Injections are sterile, pyrogen-free preparations intended to be administered parenterally. The term *parenteral* refers to the injectable routes of administration. It derives from the Greek words *para* (outside) and *enteron* (intestine) and denotes routes of administration other than the oral route. *Pyrogens*, fever-producing organic substances arising from microbial contamination, are responsible for many of the febrile reactions in patients following intravenous injection. Pyrogens and the determination of their presence in parenteral preparations are discussed later in this chapter. In general, the parenteral routes are used when rapid drug action is desired, as in emergencies; when the patient is uncooperative, unconscious, or unable to accept or tolerate oral medication; 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, physician's 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 is *home health care* programs, in which health professionals pay scheduled visits to patients at home, 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 at home while receiving appropriate medical care. The pharmacist supplies injectable preparations to the physician and nurse as required for 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 in 1888 in the first edition of the *National Formulary of the United States* (NF). Today, literally hundreds of drugs and drug products are 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*), joint fluid area (*intrasynovial*), spinal column (*intraspinal*), spinal fluid (*intrathecal*), arteries (*intra-arterial*), and in an emergency, even the heart (*intracardiac*). However, most injections go 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. 15.1).

Intravenous Route

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 thrombosis and embolism in the patients so treated. The invention of the hypodermic syringe toward the middle of the 19th century created new interest in intravenous techniques, and toward the turn of the 20th century, intravenous administration of solutions of sodium chloride and glucose became popu-

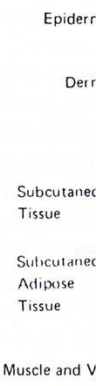


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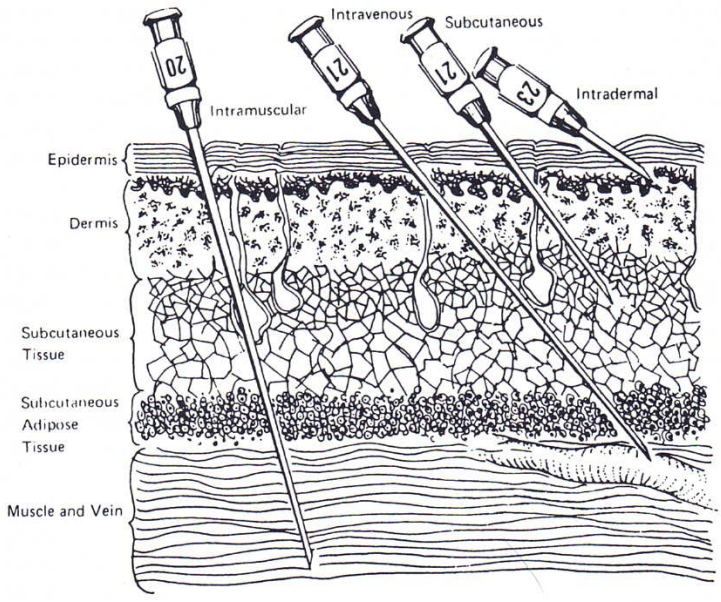


FIGURE 15.1 Routes of parenteral administration. Numbers on needles indicate gauge of needle (outside diameter of shaft). (Reprinted with permission from Turco S, King RE. Sterile dosage forms: their preparation and clinical applications, 3rd ed. Lea & Febiger, 1987.)

lar. Today intravenous administration of drugs is a routine occurrence in the hospital, although recognized dangers are still 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 a concern.

Intravenous 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 accuracy and immediacy not possible by other routes. In emergencies, intravenous administration of a drug may be lifesaving because of the placement of the drug directly into the circulation and the prompt action that 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 induction of vomiting after oral administration of the same drug. Furthermore, the intravenous dose may differ greatly from the oral dose. Thus, great care must be taken to prevent overdosing or underdosing. The beta-blocker drug class, such as metoprolol, is a perfect example of the vast differences between intravenous (three bolus injections of 5 mg each at about 2-minute intervals) and oral dosing (100 mg/day).

Although most superficial veins are suitable for venipuncture, the veins of the antecubital area (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 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, the health care worker

must withdraw the plunger of the syringe or squeeze a special bulb found on most intravenous sets to ensure that the needle has been properly seated. A backflow of blood into the administration set or syringe indicates proper placement of the needle in 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, plasma volume expanders, electrolytes, amino acids, and other therapeutic agents, are administered through an indwelling needle or catheter by continuous infusion. The infusion or flow rate may be adjusted according to the needs of the patient. Generally, flow rates for intravenous fluids are expressed in milliliters per hour and range from 42 to 150 mL/hour. Lower rates are used for keep-open (KO, KVO) lines. For intravenous infusion, the needle or catheter is placed in a prominent vein 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 thrombus formation induced by the catheter or needle touching the wall of the vein. Thrombi are most likely when the infusion solution is irritating to the biologic tissues. A *thrombus* is a blood clot formed within the blood vessel (or heart), usually because of slowing of the circulation or 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 block or occlusion referred to as an *embolism*. Such an obstruction may be a critical hazard to the patient, depending on the site and severity of the obstruction.

Intravenous drugs ordinarily must be in aqueous solution; they must mix with the circulating blood and not precipitate from solution. Such an event can lead to pulmonary microcapillary occlusion and blockage of blood flow. Intravenous fat emulsions (e.g., Intralipid, 10, 20, 30%, Clintec; Liposyn II, 10, 20%, Abbott; Liposyn III, 10, 20, 30%, Abbott) have gained acceptance for use as a source of calories and essential fatty acids for patients requiring parenteral nutrition for extended periods, usually more than 5 days. The product contains up to 30% 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 for blood transfusions, and it also serves as the point of exit for removal of blood from patients for diagnostic work and for donation.

In the late 1980s, automated intravenous delivery systems for intermittent self-administration of analgesics became commercially available. Patient-controlled analgesia (PCA) has been used to control the pain associated with a variety of surgical procedures, labor, sickle cell crisis, and 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 electromechanical unit. The unit, which may be compact enough to be worn on a belt or carried in a pocket (e.g., WalkMed PCA, McKinley, Wheat Ridge, CO), 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 from the manufacturer. The devices deliver intravenous bolus injections to produce rapid analgesia, along with slower infusion to produce steady-state concentrations for sustained pain control.

The advantage of the PCA is its ability to provide constant and uniform analgesia. The typical injection of an opioid into a depot muscular site may result in variable absorption, leading to unpredictable blood concentrations. Furthermore, 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 for breakthrough pain. It elimi-

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nates the delay between the perception of pain and receiving the medication. Furthermore, 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 opioids. When the side effect profile of PCA patients is compared to those of patients maintained on intramuscular opioids, nausea, sedation, and respiratory depression occur less often in the PCA group. Finally, patients accept the PCA as a favorable mode of relief, perhaps because of the sense of being in control and taking an active part in their pain relief.

PCA devices can be used for intravenous, subcutaneous, or epidural administration. Usually, these devices are either *demand dosing* (a fixed dose of drug is injected intermittently) or *constant-rate infusion plus demand dosing* (2). Regardless of type used, the physician or nurse establishes the loading dose, the rate of background infusion, dose per demand, lockout interval (minimum time between demand doses), and maximum dosage over a specified time. Figure 15.2 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.



FIGURE 15.2 PCA Plus II (LifeCare 4100): patient-controlled analgesic infuser. (Courtesy of Abbott Hospital Products Division.)

Intramuscular Route

Intramuscular injections of drugs provide effects that are less rapid but generally longer lasting 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, absorption rates vary widely. Drugs in solution are more rapidly absorbed than those in suspension, and drugs in aqueous preparations are more rapidly absorbed than oleaginous preparations. The physical type of preparation is based on the properties of the drug itself and on the therapeutic goals.

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, abscess, cyst, embolism, hematoma, sloughing of the skin, and scarring.

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. The muscle is poorly developed. An injection in this area may come 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 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 any blood entering the syringe. The volume of medication that may be conveniently administered by the intramuscular route is limited, generally to a maximum of 5 mL in the gluteal region and 2 mL in the deltoid of the arm.

The Z-track technique is useful for intramuscular injections of medications that stain upper tissue, such as iron dextran injection, and those that irritate tissue, such as diazepam, by sealing these medications in the lower muscle. Because of its staining qualities, iron dextran 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 used. To reduce further any staining of upper tissue, usually one needle is used to withdraw the iron dextran from its ampul and replaced with another for the injection.

Subcutaneous Route

The subcutaneous route may be used for injection of small amounts of medication. Injection of a drug beneath the skin is usually made in the loose interstitial tissue of the outer upper arm, the anterior thigh, or the lower abdomen. The site of injection is usually rotated when injections are frequently given, as with 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 24- to 26-gauge needles are used. These needles have cannula lengths of three-eighths of an inch to an inch. Most typically, subcutaneous insulin needles are 25 to 30 gauge with length of five-sixteenths to five-eighths of an inch. Upon insertion, if blood appears in the syringe, a new site should be selected.

Irritating drugs and those in thick suspension may produce induration, sloughing, or abscess and may be painful. Such preparations are 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 forearm. A short (three-eighths of an inch) and narrow (23- to 26-gauge) needle is usually employed. The needle is inserted horizontally into the skin with the bevel facing up. The injection is made with the bevel just disappearing into the corium. Usually only about 0.1 mL may be administered in this manner.

Specialized Access

When it is necessary to administer repeated injections over time, it is prudent to employ devices that provide continued access and reduce pain associated with administration.

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

The use of indwelling plastic catheters reduces the need for multiple punctures during intravenous therapy. Composed of polyvinyl chloride, Teflon, and polyethylene, these should be radiopaque to ensure that they are visible on radiographs. Usually, these must be removed within 48 hours after insertion. The choice of catheter depends on several factors, including

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Suspension, USP).

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length of time of the infusion, purpose of the infusion, and condition and 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. Developed to overcome catheter complications, they are designed to provide repeated access to the infusion site. The delivery catheter can be placed in a vein, cavity, artery, or the central nervous system. A Huber-point needle allows 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, injectable materials are separated into five general types. These may contain buffers, preservatives, and other added substances.

1. *Injection:* Liquid preparations that are drug substances or solutions thereof (e.g., Insulin Injection, USP).
2. *For injection:* Dry solids that upon addition of suitable vehicles yield solutions conforming in all respects to the requirements for injections (e.g., Cefuroxime for Injection, USP).
3. *Injectable emulsion:* Liquid preparation of drug substance dissolved or dispersed in a suitable emulsion medium (e.g., Propofol, USP).
4. *Injectable suspension:* Liquid preparation of solid suspended in a suitable liquid medium (e.g., Methylprednisolone Acetate Suspension, USP).
5. *For injectable suspension:* Dry solid that upon addition of suitable vehicle yields preparation conforming in all respects to the requirements for *injectable suspensions* (e.g., Imipenem and Cilastatin for Injectable Suspension, USP).

The form in which the manufacturer prepares a given drug for parenteral use depends on the nature of the drug itself with respect to its physical and chemical characteristics and on 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 administration, or it may be prepared as a suspension. If the drug is unstable in 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 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. Aqueous or blood-miscible solutions may be injected directly into the blood stream. Blood-immiscible liquids, such as oleaginous injections and suspensions, can interrupt the normal flow of blood, 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 its chemical form, the physical state of the injection (solution or suspension), and the vehicle. 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 because of the greater miscibility of the aqueous preparation with the body fluids after injection and the more rapid contact of the drug particles with the body fluids. Oftentimes long action is desired to reduce the frequency of injections. These long-acting injections are called repository or depot preparations.

The solutions and suspensions of drugs intended for injection are prepared in the same general manner as solutions (Chapter 13) and disperse systems (Chapter 14), with the following differences:

1. Solvents or vehicles must meet special purity and other standards ensuring their safety by injection.
2. The use of added substances, such 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, 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 used to ensure hermetic seal and sterile condition.
7. Each container of an injection is filled to a volume in slight excess of the labeled volume to be withdrawn. This overfill permits ease of withdrawal and administration of the labeled volumes.
8. The volume of injection permitted in multiple-dose containers is restricted, as are the types of containers (single-dose or multiple-dose) that 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*—that is, not more than 1 mg/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 to be sterilized after 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 after 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 packaged in single-dose containers not larger than 1 L. As with water for injection, it must be pyrogen free but does have an allowable endotoxin level, not more than 0.25 USP endotoxin units per milliliter. Also, it may not contain any antimicrobial agent or other added substance. This water may contain slightly more total solids than water for injection because of the leaching of solids from the glass-lined tanks during sterilization. This water is intended to be used as a solvent, vehicle, or diluent for already sterilized and packaged injectable medications. The 1-L 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 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 prefilled syringes or in vials containing not more than 30 mL of the water. The container label must state the names and proportions of the antimicrobial agent or agents. 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 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 be used only in par-

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Sodium Chloride
isotonic solution of

enterals that are administered in small volumes. Its use in parenterals administered in large volume is restricted by the excessive and perhaps toxic amounts of the antimicrobial agents that would be injected along with the medication. Generally, if more than 5 mL of solvent is 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 or agents with the particular medicinal agent being dissolved or suspended.

USP labeling requirements demand that the label state NOT FOR USE IN NEONATES. This statement was the result of problems encountered with neonates and toxicity of the bacteriostat, that is, benzyl alcohol. This toxicity results from the high cumulative amounts (milligrams per kilogram) 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 gasping syndrome. In one study, 10 premature infants developed this clinical syndrome characterized by the development of multiorgan 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 to 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 but has approximately 154 mEq each of sodium and chloride ions per liter. It may be used as a sterile vehicle in 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 intravenous line flush to maintain patency. Catheters or intravenous 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 0.9% renders the solution isotonic. For the reasons noted for bacteriostatic water for injection, this solution may not be packaged in containers larger than 30 mL. When this solution is used as a vehicle, care must be exercised to ensure compatibility of the added medicinal agent with the preservative or preservatives and with the sodium chloride.

Bacteriostatic sodium chloride injection is also used to flush a catheter or intravenous 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 as a result of liver immaturity. Because of their low physical weight, their acute illness and consequent need for medications, and the frequent use of the umbilical catheter for various purposes, these patients may receive much more flush solution relative to their body weight than adults. Thus, bacteriostatic sodium chloride injection also carries the warning NOT FOR USE IN NEONATES.

Suffice it to say that benzyl alcohol may 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 re-

ceived 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 used. However, if such a formulation is not available and there is no alternative, a medication preserved with benzyl alcohol may still be used if the physician's clinical judgment is that the risk-to-benefit ratio is appropriate.

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 those of physiologic fluids. Ringer's is employed as a vehicle for other drugs or alone as an electrolyte replenisher and plasma volume expander. *Lactated Ringer's Injection, USP*, has different quantities of the three salts in Ringer's injection, and it 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, it may be precluded by 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 not sensitizing. 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. Among the many considerations are the solvent's physical and chemical stability at various pH levels, viscosity, which must be such as to allow ease of injection (suitable for use in syringes); fluidity, which must be maintained over a fairly wide temperature range; boiling point, which should be sufficiently high to permit heat sterilization; miscibility with body fluids; low vapor pressure to avoid problems during heat sterilization; and constant purity or ease of purification and standardization. No single solvent is free of limitations; hence, cross-consideration and assessment of each solvent's advantages and disadvantages help the formulator determine the most appropriate solvent for a given preparation. Among the nonaqueous solvents employed in parenteral products are fixed vegetable oils, glycerin, polyethylene glycols, propylene glycol, alcohol, and a number of less often used agents, including ethyl oleate, isopropyl myristate, and dimethyl acetamide. 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 United States Pharmacopeia (USP) specifies restrictions on the fixed vegetable oils in parenteral products. For one thing, they must remain clear when cooled to 10°C (50°F) to ensure the stability and clarity of the injectable product during 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 on 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 toxicity of vegetable oils is 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. 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 (Physical Pharmacy Capsule 15.1).

By selective employment of solvent or vehicle, a pharmacist can prepare injectable preparations as solutions or suspensions in either an aqueous or nonaqueous vehicle. For the most part, oleaginous injections are administered intramuscularly. They must not be administered

PHYSICAL PHARMACY CAPSULE 15.1

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 on 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 are 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 in equilibrium with its pure liquid at a constant temperature will exert *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:

$$p_1 = N_1 p^\circ_1$$

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 the temperature at which 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 reach 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.

Physical Pharmacy Capsule 15.1 cont.

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. $\Delta T_b = (0.51)\,(0.28) = 0.143°C$.

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

Physical Pharmacy Capsule 15.1 cont.

3. Volume will be 1 L
4. P = [(0.28)(0.082)(298)]/(1) = 6.84 atm

Deviations from reality in these ideal examples of colligative properties are explained by the use of the Van't Hoff term i, which 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 milligrams of a solute equal to 1/1000 of its gram-equivalent weight. Consider the following example.

EXAMPLE 5

What is the milliequivalent weight of sodium?

1. The atomic weight of sodium is 23.
2. The valence of sodium is +1.
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 6

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

1. The atomic weight of potassium is 39, and that of 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 7

How many milliequivalents of calcium are in 10 mL of 10% calcium chloride ($CaCl_2 \cdot 2\ H_2O$) 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.

Physical Pharmacy Capsule 15.1 cont.

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 8

How many milliequivalents of sodium are contained in a 1-L bag of 0.9% sodium chloride?

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 is 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, that is, 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 contain more (hypertonic) or fewer (hypotonic) dissolved species, 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/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 on injection.

Some solutions are 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 semipermeable 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 semipermeable 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 L, sodium chloride equivalent, and cryoscopy.

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 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; that is, 1 g of ephedrine sulfate is equivalent to 0.23 g of sodium chloride.

EXAMPLE 9

How much sodium

Rx Ephedrine su
Sterile water, qs
M. isoton with s

1. (30 mL) (0.009)
   30 mL of solutio
2. (30 mL) (0.02) =
3. (0.6 g) (0.23) = (
4. Since 0.270 g sod
   chloride that is e
   0.132 g of sodiun
5. Therefore, the so
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Added Substance

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TABLE 15.1 SOME I

INJECTION
Dimercaprol
Estradiol cypionate
Estradiol valerate
Fluphenazine decanoate
Fluphenazine enanthate
Hydroxyprogesterone capr
Progesterone in Oil
Testosterone cypionate
Testosterone cypionate and
Testosterone enanthate
Testosterone enanthate and

Physical Pharmacy Capsule 15.1 cont.

EXAMPLE 9

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

Rx Ephedrine sulfate 2%
Sterile water, qs 30 mL
M. isoton with sodium chloride

1. (30 mL) (0.009) = 0.270 g sodium chloride is required if only sodium chloride is 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.
4. Since 0.270 g sodium chloride is 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 g – 0.138 g = 0.132 g of sodium chloride required to render the solution isotonic.
5. Therefore, the solution requires ephedrine sulfate 0.6 g, sodium chloride 0.132 g, and sufficient sterile water to make 30 mL.

intravenously, as the oil will occlude the pulmonary microcirculation. Some examples of official injections with oil as the vehicle are presented in Table 15.1.

Added Substances

The USP permits addition of suitable substances to official preparations intended for injection to increase stability or usefulness as long as the substances are not interdicted in the individual monographs, 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 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

TABLE 15.1 SOME INJECTIONS IN OIL

INJECTION	OIL	CATEGORY
Dimercaprol	Peanut	Antidote to arsenic, gold, and mercury poisoning
Estradiol cypionate	Cottonseed	Estrogen
Estradiol valerate	Sesame or castor	Estrogen
Fluphenazine decanoate	Sesame	Antipsychotic
Fluphenazine enanthate	Sesame	Antipsychotic
Hydroxyprogesterone caproate	Castor	Progestin
Progesterone in Oil	Sesame or peanut	Progestin
Testosterone cypionate	Cottonseed	Androgen
Testosterone cypionate and estradiol cypionate	Cottonseed	Androgen and estrogen
Testosterone enanthate	Sesame	Androgen
Testosterone enanthate and estradiol valerate	Sesame	Androgen and estrogen

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. Because many of the usual preservative agents are toxic in large 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 accompanying an injectable product is frequently replaced with an inert gas, such as nitrogen, to enhance the stability of the product by preventing a chemical reaction between oxygen and the drug.

Methods of Sterilization

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

1. Steam
2. Dry heat
3. Filtration
4. Gas
5. Ionizing radiation

The method 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 personnel.

Steam Sterilization

Steam sterilization is conducted in an autoclave and employs steam under pressure. It is usually the method of choice if the product can withstand it (Fig. 15.3).

Most pharmaceutical products are adversely affected by heat and cannot be heated safely to the temperature required for dry heat sterilization (about 150°–170°C, or 302°–338°F). When moisture is present, bacteria are coagulated and destroyed at a considerably lower temperature than when 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 be by denaturation and coagulation of some of the organism's essential protein. It is the hot moisture in the microbial cell that permits destruction at relatively low temperature. Death by dry heat is thought to be by dehydration of the microbial cell followed by slow oxidation. Because it is not possible to raise the temperature of steam above 100°C (212°F) under atmospheric conditions, pressure is employed to achieve higher temperatures. It is the temperature, not the pressure, that destroys the microorganisms, and the application of pressure is solely to increase the temperature of the system.



FIGURE 15.3 Autoclaving of intravenous electrolyte solutions. (Courtesy of Abbott Laboratories.)

Time is another imp
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autoclaves have gaug
erator the internal cc
and pressure and a tir
desired exposure tim
steam pressures, the
under these pressure
length of time requir
the system reaches th
are as follows:

10 lb pressure (11
minutes
15 lb pressure (121
minutes
20 lb pressure (126
minutes

As can be seen, the g
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and the less the time r

Most autoclaves rot
(250°F), as measured
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time of moist heat into
nature of the load, and
be adjusted to accoun
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exposure times. This pr
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yields a lower tempera
alone under the same pr
15 pounds pressure th
rated steam is 121.5°C,
parts of air and steam
112°C (234°F).

Time is another important factor in 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 lb pressure (115.5°C, or 240°F) for 30 minutes
15 lb pressure (121.5°C, or 250°F) for 20 minutes
20 lb pressure (126.5°C, or 260°F) 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.

Most autoclaves routinely operate at 121°C (250°F), as measured at the steam discharge line running from the autoclave. The temperature 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 moist heat into the load varies 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 121°C 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 to ensure adequate exposure times. This process depends on moisture and an elevated temperature, so air is removed from the chamber as sterilization begins, because a combination of air and steam yields a lower temperature than does steam alone under the same 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 (234°F).

In general, steam 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 aqueous solutions the moisture is already present, and all that is required is elevation of the temperature of the solution for the prescribed period. Thus, solutions in sealed containers, such as ampuls, are readily sterilized by this method. Sealed empty vials can be sterilized by autoclaving only if they contain a small quantity of water. Steam sterilization is also applicable to bulk solutions, glassware, surgical dressings, and instruments. It is not useful for oils, fats, oleaginous preparations, and other preparations not penetrated by the moisture or for exposed powders that may be damaged by the condensed moisture.

Dry Heat Sterilization

Dry heat sterilization is usually carried out in ovens 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 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 so as to permit free circulation of heated air throughout the chamber. Dry heat sterilization is usually conducted at 150° to 170°C for not less than 2 hours. Higher temperatures permit shorter exposure 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 (284°F), the lower temperature is used and the exposure time is increased.

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 is also an effective method for sterilizing glassware and surgical instruments. Dry heat 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 on the physical removal of microorganisms by adsorption on the filter medium or by a sieving mechanism, is used for heat-sensitive solutions. Medicinal preparations sterilized by this method must undergo extensive validation and monitoring because the effectiveness of the filtered product can be greatly influenced by the microbial load in the solution being filtered (Fig. 15.4).

Commercially available filters are produced with a variety of pore size specifications. It would be well to mention briefly one type of modern filter, the Millipore filter (Fig. 15.5). The Millipore filter is a thin plastic membrane of cellulosic esters with millions of pores per square inch. The pores are made to be extremely uniform in size and occupy approximately 80% of the membrane's volume, the remaining 20% being the filter material. This high degree of porosity permits flow rates much in excess of those of other filters having the same particle retention capability. Millipore filters are made from a variety of polymers to be suitable for filtration of almost any liquid or gas system. Also, the filters have various pore sizes, 14 to 0.025 μm, to meet the specific requirements. For comparative purposes, the period that ended the last sentence is approximately 500 μm. 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 poliovirus, about 0.025 μm.



FIGURE 15.5 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.)



FIGURE 15.4 Sterilization by filtration. An eight-head bottle-filling machine using three large filters in large-scale pharmaceutical production. (Courtesy of Millipore Corporation.)

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surface is a void or oper
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tage of a high flow rate.
One disadvantage is
brane tends to be fragil
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and that the membrane
flawed during assembly



FIGURE 15.7 Cutaway sh

Although the pore size of a bacterial filter is of prime importance in the removal of microorganisms from a liquid, 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, are also important

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

The class of filter medium lends itself to more effective standardization and quality control and also gives the user greater opportunity to confirm the 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 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 tends to be 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.



FIGURE 15.6 Luer-Lock syringe adapted with a Millex Filter Unit and hypodermic needle. (Courtesy of Millipore Corporation.)

The housing and filter assemblies should first be validated for compatibility and integrity. 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 requires more time, particularly if the liquid is viscous, than, say, steam sterilization. In essence, 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 must be sterile (Figs. 15.6 and 15.7). Furthermore, the membrane filter is the method most commonly used in hospitals. Occasionally, hospitals use the autoclave (moist heat) to sterilize intravenous solutions, such as caffeine citrate.

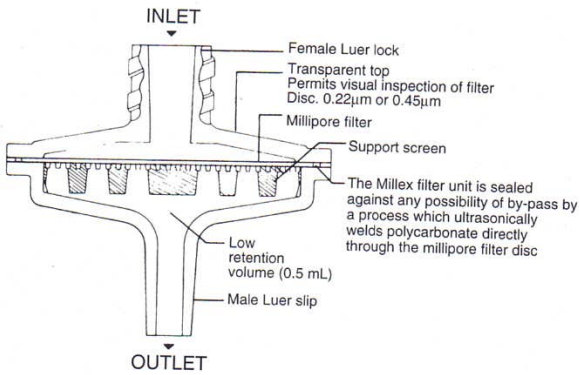


FIGURE 15.7 Cutaway showing composition of the Millex filter unit. (Courtesy of Millipore Corporation.)

To date, information about drug adsorption to membrane filters is limited. Several studies, however, have demonstrated that membrane filters can remove drug from solution (6–9). For example, 0.22-μm filters reduce the in vitro antimicrobial activity of amphotericin B (a colloidal suspension), while filtration of the amphotericin B through 0.85- and 0.45μm filters did not. Butler et al. (10) 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. The literature indicates that drugs administered in low doses might present a problem of 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 may adsorb drug. Hydrophobic interactions between hydrocarbon portions of drug molecules being filtered and linear cellulose molecules of filters are also thought to contribute to drug adsorption.

In general, current information suggests that little or no adsorption takes place with membrane filters. However, it is recommended that minute doses of drugs (<5 mg) should not be filtered until sufficient data demonstrate insignificant adsorption. With respect to amphotericin B, to ensure the passage of the antibiotic colloidal dispersion, the filter's mean pore diameter should be more than 1 μm.

Membrane filter media 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 an autoclave, and many combination steam autoclaves and 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 50° to 60°C. If the material being sterilized cannot tolerate either the moisture or the elevated temperature, exposure time must be increased. Generally, sterilization with ethylene oxide gas requires 4 to 16 hours of exposure. Ethylene oxide is thought to sterilize by interfering with the metabolism of the bacterial cell.

The great penetrating qualities of ethylene oxide gas make it a useful agent in certain special applications, such as 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, after testing to ensure absence of chemical reaction and other deleterious effects on the drug substance.

Sterilization by Ionizing Radiation

Techniques are available for sterilization of some types of pharmaceuticals by gamma rays and by cathode rays, but 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 is 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 nucleopro-

tein, 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, pharmaceutical preparations required to be sterile must undergo tests to confirm the absence of microorganisms. The USP contains monographs and standards for biologic indicators of sterilization. A *biologic indicator* is a characterized preparation of specific microorganisms resistant to a particular sterilization process. They may be used to monitor a sterilization cycle and/or periodically to revalidate the process. Biologic indicators are generally of two main forms. In one, spores are added to a carrier, such 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 assessment of sterilization based on these samples. In steam and ethylene oxide sterilization, spores of suitable strains of *Bacillus stearothermophilus* are commonly employed because of their resistance to these modes of sterilization. In dry heat, spores of *Bacillus subtilis* are commonly used. With ionizing radiation, spores of suitable strains of *Bacillus*, including *B. pumilus, B. stearothermophilus*, and *B. subtilis*, have been used.

The effectiveness of thermal sterilization 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 lethality equivalent to that provided at 121°C 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 because of 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} is the time required for a one-log reduction in the microbial population exposed to a temperature of 121°C,
A is the initial microbial population, and
B is 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 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 and water soluble, 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 removal of pyrogens from their product. Because pyrogens are organic, one of the more common means of removing them 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 increased by addition of a small amount of barium hydroxide 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 been distilled several times, and distillation is repeated, the chemical-free distillate being collected under strict aseptic conditions. When properly conducted, this method results in highly pure, sterile, and pyrogen-free water.

However, in each instance the official pyrogen test must be performed to ensure absence of these fever-producing materials.

Pyrogen Test The USP pyrogen test uses healthy rabbits that have been properly maintained in terms of environment and diet before 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 injection of a test solution. A given test uses rabbits whose temperatures do not differ by more than 1°C from each other and whose body temperatures are considered not to be elevated. 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 kilogram of body weight, completing each injection within 10 minutes of the start of administration. Record the temperature at 30-minute intervals 1 to 3 hours subsequent to the injection.

If no rabbit shows an individual rise in temperature of 0.5°C or more, the product meets the requirements for the absence of pyrogens. If any rabbit shows an individual temperature rise of 0.5°C 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°C or more and if the sum of the eight individual maximum temperature rises does not exceed 3.3°C, the material under examination meets the requirements for the absence of pyrogens.

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 led to the development of the *Limulus* amebocyte lysate (LAL) test for the presence of bacterial endotoxins. The Bacterial Endotoxins Test, USP, uses LAL and is considered generally more sensitive to endotoxin than the rabbit test. The FDA has endorsed it as a replacement for the rabbit test, and it is used for a number of parenteral products. The USP–NF has specific allowable endotoxin levels for various injections based on the dosage of the individual drugs to keep below a threshold level of administered endotoxins.

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

Because the LAL test is so sensitive for the presence of bacterial endotoxins, when 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 twofold. Diphenhydramine HCl, ephedrine HCl, meperidine HCl, promethazine HCl, and thiamine HCl, among others, are tested in this manner.

The Industrial Preparation of Parenteral Products

Once the formulation for a particular parenteral product is determined, including selection of the proper solvents or vehicles and additives, the production pharmacist must follow rigid aseptic procedures in preparing the products. In most manufacturing plants the area in which parenteral products are made is maintained bacteria free by use of ultraviolet lights; a filtered air supply; sterile manufacturing equipment, such as flasks, connecting tubes, and filters; and sterilized work clothing (Fig. 15.8).

In preparation of parenteral solutions, the required ingredients are dissolved according to good pharmaceutical practice in water for injection, in another solvent, or in a combination of solvents. The solutions are usually filtered through a membrane until sparkling clear. 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. If sterilization by autoclaving is impractical because of the nature of



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and added aseptically tc
solution of components

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suspended particles, alte
tical and therapeutic ch
pension remains unalter
method is generally emp
final product. Because



FIGURE 15.8 Sterile filling of vials. (Courtesy of Wyeth Laboratories.)

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 solution of components that can be autoclaved.

Suspensions of drugs 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, affecting the suspending ability of the vehicle, or change the particle size of the suspended particles, altering both pharmaceutical and therapeutic characteristics. If a suspension remains unaltered by autoclaving, this method is generally employed to sterilize the final product. Because parenteral emulsions, which are dispersions or suspensions of a liquid throughout another liquid, are generally destroyed by autoclaving, an alternative 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 because the therapeutic agent is unstable in the presence of the liquid component. These dry powders are packaged in the final container to be reconstituted, generally to a solution or less frequently a suspension. The method of sterilization of the powder may be dry heat or another appropriate method. These are examples of sterile drugs prepared and packaged *without* pharmaceutical additives such as buffers, preservatives, stabilizers, and tonicity agents:

Ampicillin sodium
Ceftizoxime sodium
Ceftazidime Sodium
Cefuroxime sodium

Kanamycin sulfate
Nafcillin sodium
Penicillin G benzathine
Streptomycin sulfate
Tobramycin sulfate

Antibiotics are prepared industrially in large fermentation tanks (Fig. 15.9).

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

Cyclophosphamide
Dactinomycin
Erythromycin lactobionate
Hydrocortisone sodium succinate
Mitomycin
Nafcillin sodium
Oxytetracycline hydrochloride
Penicillin G potassium
Vinblastine sulfate

Sometimes a liquid is packaged along with the dry powder for use at the time of reconstitution (Fig. 15.10). This liquid is sterile and may contain some of the desired pharmaceutical additives, such as the buffering agents. More frequently, the solvent or vehicle is not provided, but the label generally lists suitable solvents. Sodium chloride injection and sterile water for injection are perhaps most frequently employed 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 reconstitution. To facilitate dissolution, the dry powder is prevented from caking upon standing by the appropriate means, including lyophilization (Fig. 15.11). Powders so treated form a honeycomb lattice structure that is rapidly penetrated by the liquid, and solution is rapid because of the large surface area of powder exposed.

Pharmacia manufactures the Mix-O-Vial, which 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.

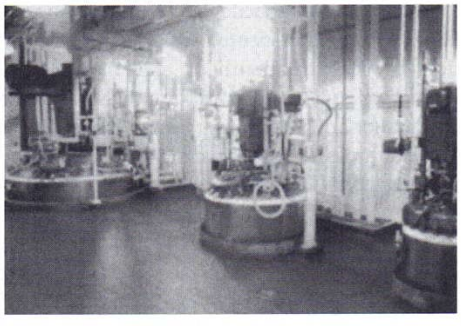


FIGURE 15.9 Fermentation tank for preparation of antibiotics. (Courtesy of Schering-Plough.)

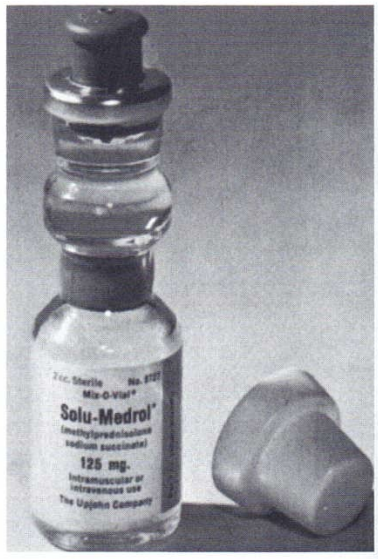


FIGURE 15.10 The Mix-O-Vial contains dry ingredients in the bottom compartment and a liquid diluent in the top, separated by a specially formulated center seal. The bottom compartment can be filled either with a liquid that is frozen and dried to make a lyophilized product or with a powder. The diluent in the top contains a preservative and sometimes one or more active ingredients. To use the vial, the dust cover is removed; pressure is applied with the thumb to the top plunger, which dislodges the center seal; and the vial is shaken well. 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 Pharmacia Company.)

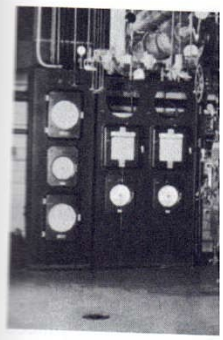


FIGURE 15.11 Antibiotic
bott Laboratories.)

The Abbott ADD-
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be mixed until just p
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(Fig. 15.12): a flexible
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vial of powdered or liq
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(50–250 mL of dextros
0.45% sodium chloride
designed to be used t
into a chamber inside th
the drug is released by r
the vial, allowing the tw
This simple process is
manipulation of the co
closed, sterile system.

The ADD-Vantage ur
a number of locations. M
sterility tests have been
intervals following asser
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Vantage system can be u

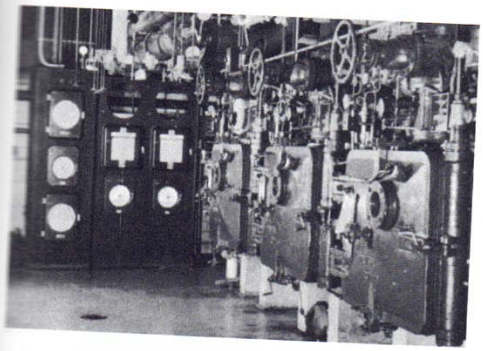


FIGURE 15.11 Antibiotic lyophilizers. (Courtesy of Abbott Laboratories.)



FIGURE 15.12 ADD-Vantage system. (Courtesy of Abbott Laboratories.)

The Abbott ADD-Vantage System IVPB is another example of a ready-to-mix sterile intravenous product designed for intermittent administration of potent drugs that do not have long-term stability in solution. With this system, antibiotics and other drugs do not have to be mixed until just prior to administration. ADD-Vantage consists of two components (Fig. 15.12): a flexible plastic intravenous container partially filled with diluent and a glass vial of powdered or liquid drug. The vials containing the medication and the piggybacks (50–250 mL of dextrose 5% in water injection, 0.45% sodium chloride solution) 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, preserving the closed, sterile system.

The ADD-Vantage unit may be assembled in a number of locations. Microbiologic 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 of removal of the diluent container from the outer wrapping. ADD-Vantage enables hospitals to reduce drug waste, often caused by canceled or changed prescriptions, and helps the pharmacy conserve labor and reduce material costs.

The Monovial Safety Guard (Becton Dickinson Pharmaceutical Systems) is a new intravenous infusion system for use in preparing extemporaneous small-volume infusions using plastic minibags (Fig. 15.13). When compared to the two traditional methods of preparing small-volume infusions, that is, the transfer needle and vial (TFN) and syringe and vial (SYR) methods, the Monovial system performed quite favorably, saving time, using fewer materials, and costing less (12).

This system is an integrated drug transfer mechanism with a protective shield surrounding the attached transfer needle. Reconstitution and transfer of the drug into an infusion bag are accomplished safely, quickly, and with few materials. The needle is inserted into



FIGURE 15.13 Monovial safety guard system. (Courtesy of Becton-Dickinson.)

the port of the infusion bag and the transfer set is pushed down toward the vial until it clicks. With the Monovial upright, the infusion bag is squeezed several times to transfer fluid into the Monovial. The Monovial is shaken a few times to reconstitute the drug and inverted. 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. Diltiazem HCl (Cardizem) for injection is available with the Monovial Safety Guard.

Several manufacturers ship to the hospital pharmacy reconstituted intravenous antibiotic solutions, for example cefazolin sodium, in the frozen state. When thawed, these nonpyrogenic solutions are stable for a finite period. Reconstituted cefazolin is stable for 48 hours at room temperature and for 10 days refrigerated (5°C, or 41°F). The product is packaged in a small plastic bag for piggyback use in intravenous administration.

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. 15.14). If the container is made of glass, it must be clear and colorless or light amber to permit inspection of its contents. The type of glass suitable 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. 15.15 to 15.17). By definition:

Single-dose container: A hermetic container holding a quantity of sterile drug intended for parenteral administration as a single dose; when opened, it cannot be resealed with assurance that sterility has been maintained.

Multiple-dose container: 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. 15.18) are sealed by fusion of the glass container under aseptic conditions (Figs. 15.19 and 15.20). The glass container is made so as to have a neck that may be easily separated from the body of the



FIGURE 15.14 Testing compatibility of rubber closures with a solution. (Courtesy of Abbott Laboratories.)

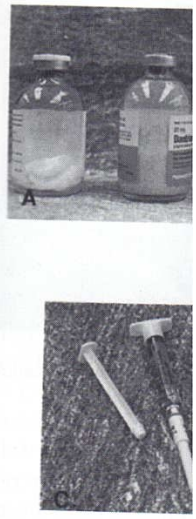


FIGURE 15.15 Packaging
lutions, including one wi
tesy of William B. French,

container without
opening, the content
withdrawn into a sy
needle or straw appa
replaced with a regu



FIGURE 15.16 A typical vial
made from type I (borosilic
has been specially selecte
product, desirable physical
overseal holds the closure ir
cess to the contents of the
Company.)

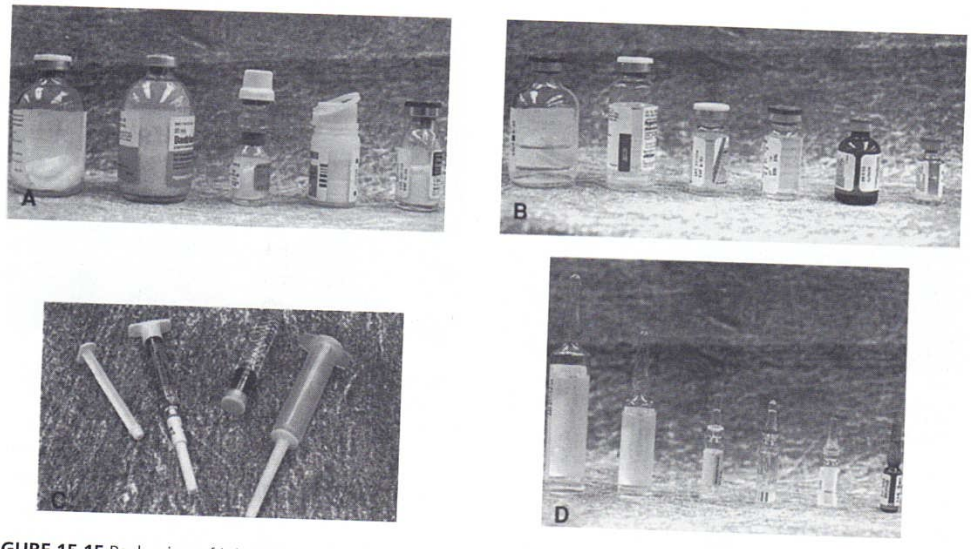


FIGURE 15.15 Packaging of injectable products. **A**. Multiple-dose vials of suspensions and dry powders. **B**. Vials for solutions, including one with light-protective glass. **C**. Unit dose, disposable syringes. **D**. Various sizes of ampuls. (Courtesy of William B. French, PhD.)

container without breaking the glass. After opening, the contents of the ampul should be withdrawn into a syringe with a 5-μm filter needle or straw apparatus. The filter needle is replaced with a regular needle. The filter needle is used to trap any glass particles that entered the sterile solution when the neck of the ampul was broken. If a filter needle is not available, withdrawal of glass can be minimized by holding the ampul upright, tilted slightly,



FIGURE 15.16 A typical vial for sterile injectable products, made from type I (borosilicate) glass. The rubber closure has been specially selected for compatibility with the product, desirable physical characteristics, and so on. The overseal holds the closure in place and provides ready access to the contents of the vial. (Courtesy of Pharmacia Company.)



FIGURE 15.17 Two 100-mL single-dose plastic bags for intravenous infusion. (Courtesy of Mr. Akinwale O. Onamade.)

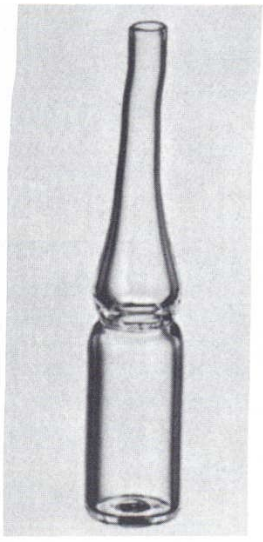


FIGURE 15.18 Ampul before filling and sealing. (Courtesy of Owens Illinois.)

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 into the syringe.



FIGURE 15.19 Ampul filling. (Courtesy of Abbott Laboratories.)

Once opened, the ampul cannot be resealed, and no unused portion may be retained and used later, since the contents would have lost sterility. Some injectable products are packaged in prefilled syringes, with or without special administration devices (Figs. 15.21 to 15.23). The types of glass for parenteral product containers are described in Chapter 5. 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 for a particular injec-

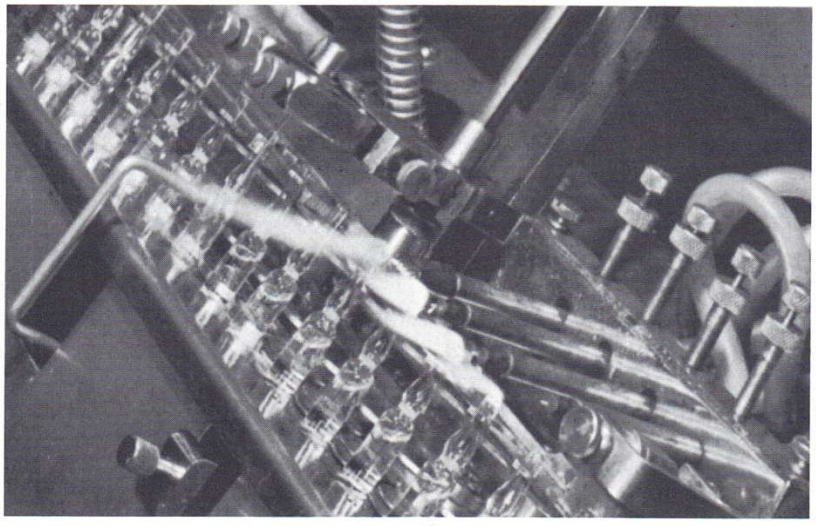


FIGURE 15.20 Ampul sealing. (Courtesy of Abbott Laboratories.)



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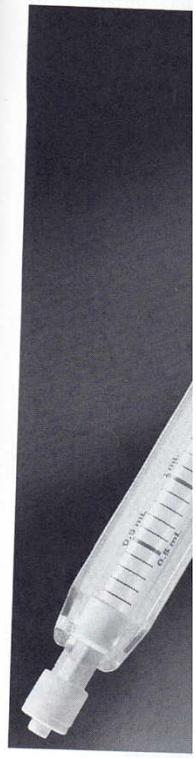


FIGURE 15.22 Carpuj
system that includes a
holder. (Courtesy of Ab



FIGURE 15.21 Medication-containing disposable sterile cartridges compatible with the Carpuject holder. (Courtesy of Abbott Hospital Products Division).

tion is indicated in the individual monograph for that preparation.

One of the prime requisites of parenteral solutions is clarity. They should be sparkling clear and free of all particulate matter; that is, no mobile undissolved substances should be present. Such contaminants include dust, cloth fibers, glass fragments, material leached from the glass or plastic container or seal, and any other material that may find its way into the product during manufacture or administration or develop during storage.

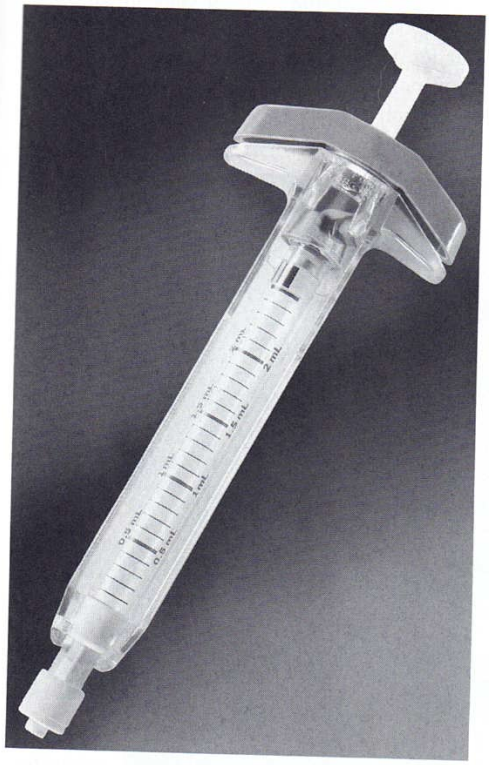


FIGURE 15.22 Carpuject, a prefilled unit dose injection system that includes a reusable clear plastic full-length holder. (Courtesy of Abbott Hospital Products Division.)



FIGURE 15.23 Inject-Ease automatically inserts the needle of an insulin syringe into the skin when activated. (Courtesy of William B. French, PhD.)

To keep unwanted particles out of parenteral products, a number of precautions must be taken during manufacture, storage, and use of the products. During manufacture the parenteral solution is usually filtered just before it goes into the container. The containers are carefully selected to be chemically resistant to the solution and of the highest available quality to minimize the chances of container components leaching into the solution. It has been recognized for some time that some particulate matter in parenteral products is leached material from the glass or plastic container. Once the container is selected, it must be carefully cleaned to be free of all extraneous matter (Fig. 15.24). During container filling, extreme care must be exercised to prevent the entrance of airborne dust, lint, or other contaminants. Filtered and directed airflow in production areas reduces the likelihood of contamination. Laminar flow hoods allow for draft-free flow of clean, filtered air over the work area. These hoods are commonly found in hospitals for both manufacture and incorporation of additives into parenteral and ophthalmic products (Fig. 15.25). The personnel who manufacture parenterals must be made acutely aware of the importance of cleanliness and aseptic techniques. They are provided uni-



FIGURE 15.24 Production line for preparation of vials for sterilization and filling. (Courtesy of Schering-Plough.)

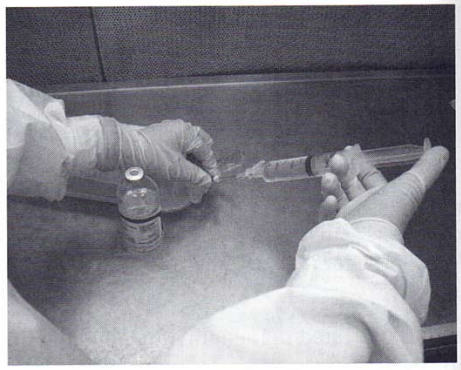


FIGURE 15.26 Pharmacist preparing a parenteral admixture in a laminar flow hood. (Courtesy of Ms. Amy Schuppert Smith)

forms of monofilament fabrics that do not shed lint. They wear face hoods, caps, gloves, and disposable shoe covers to prevent contamination (Fig. 15.26).

After the containers are filled and hermetically sealed, they are visually (Fig. 15.27) or automatically (Fig. 15.28) inspected for particulate matter. Usually an inspector passes the filled container past a light source with a black background to observe for mobile particles. Particles of approximately 50 μm may be detected in this manner. Reflective particles, such as fragments of glass, may be visualized in smaller size, about 25 μm. Methods to detect smaller particulate matter include microscopic examination and use of sophisticated equipment such as the Coulter Counter, which elec-



FIGURE 15.25 Hyperalimentation being prepared in a horizontal laminar flow hood. (Courtesy of Ms. Amy Schuppert Smith)



FIGURE 15.27 Industrial i
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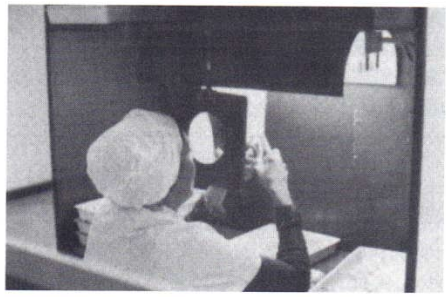


FIGURE 15.27 Industrial inspection of parenteral fluid for particulate matter. (Courtesy of Schering-Plough.)

tronically counts particles in samples. Having passed inspection, the product may be labeled. However, the pharmacist should inspect each parenteral solution 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 to induce thrombi and vessel blockage, and depending on the chemical composition of the particles, the additional potential to introduce into the patient agents that 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. Some single-dose preparations are to be administered rapidly in small volumes, but others infuse slowly into the circulatory system over 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 waste, 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 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 withdrawal and administration of more 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.

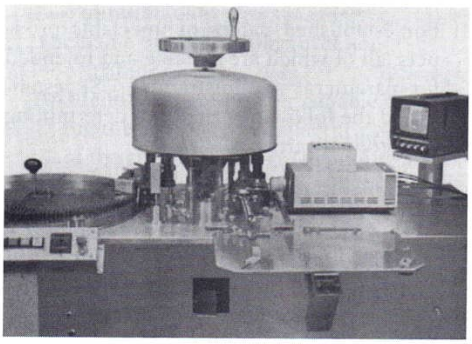


FIGURE 15.28 The Autoskan industrial automatic inspection machine, which detects particulate matter in injectables with a television camera and electronics and automatically rejects them from the production line. (Courtesy of Lakso Company.)

In the hospital, physicians commonly order an additional agent to be placed in a large-volume parenteral solution for infusion. The person filling such an order must be certain that aseptic conditions are employed and that the additive is compatible with the original solution (13). Care must also be exercised not to introduce particulate matter into the solution. Many pharmaceutical companies have developed special devices for aseptic transfer of pharmaceutical additives to large-volume parenterals. An ordinary sterile needle and syringe, preferably with a filtering device, may be effectively employed to transfer solutions from one parenteral product to another (Fig. 15.29). Many hospital pharmacies have established well-controlled *intravenous additive* or *admixture* programs to ensure compatibility, safety, and efficacy of the additive and solution (14).

Multiple-dose containers are affixed with rubber closures to permit penetration of a hypodermic needle without removal or destruction of the closure. Upon withdrawing the needle from the container, the closure reseals and



FIGURE 15.29 Use of a filter syringe for aseptic addition of an ingredient to a large-volume parenteral solution. (Courtesy of Ms. Amy Schuppert Smith)

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 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. Unless otherwise indicated in the monograph, multiple-dose injectables are required to contain antibacterial preservatives. Also, unless otherwise specified, multiple-dose containers are not permitted to allow withdrawal of more than 30 mL to limit the number of penetrations into the closure and thus protect against loss of sterility. The limited volume also guards against an excessive amount of antibacterial preservative being inadvertently administered with the drug when unusually large doses of an injection are required, in which case a preservative-free single-dose preparation is advisable. The usual multiple-dose container contains about 10 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 15.2 presents the recommended overages permitted by the USP to allow withdrawal and administration of the labeled volumes.

TABLE 15.2 RECOMMENDED OVERAGES FOR OFFICIAL PARENTERAL PRODUCTS IN MILLILITERS

LABELED SIZE	EXCESS VOLUME FOR MOBILE LIQUIDS	EXCESS VOLUME FOR VISCOUS LIQUIDS
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	2.00%	3.00%

For labeling purposes, revised injectable product nomenclature became official in the USP 23 on January 1, 1995, and continues. The main points of the revised process are as follows:

I. The term *sterile* was eliminated from the titles of injectable products except appropriate monograph titles for water intended for parenteral use, such as Sterile Water for Injection, USP.

II. For established names of injectable products, all of which are suitable and intended for parenteral administration, USP established the following criteria in determining the product's title:

A. Liquids

1. *Injection:* Title for liquid preparations that are drug substances or solutions thereof.
2. *Injectable suspension:* Title for liquid preparations of solids suspended in a suitable liquid medium.
3. *Injectable emulsion:* Title for liquid preparations of drug substances dissolved or dispersed in suitable emulsion medium.

B. Solids

1. *For injection:* Titl
upon the additic
cles, yield solutio
respects to the
Injections.
2. *For injectable susp*
solids that, upon
able vehicles, yiel
forming in all resp
ments for *Injectabl*

Originally, to facilitate
new nomenclature, the Cen
ation and Research encoura
manufacturers to place a
statement, on the labels of
months, alerting practitione
The intent was to help pract
miliar with the revised rule
flag: FORMERLY STERILE [DRU

In addition, the labels on
enteral products must state

The name of the preparat
For a liquid preparation,
content of drug or the
in a specified volume
For a dry preparation, the
ingredient present and
liquid to be added to th
tion to prepare a soluti
The route of administratic
A statement of storage cor
expiration date
The name of the manufact
distributor
An identifying lot number
ing the complete manuf
of the specific package,
manufacturing, filling, s
labeling operations

Injections for veterinary use
Preparations intended to be
hemofiltration, or irrigation s
meet the requirements for ir
those relating to volume in the
should bear a statement indica
lution is not intended for use
infusion. Appropriately labele

B. Solids
   1. *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. *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*.

Originally, 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 6 months, alerting practitioners to the changes. The intent was to help practitioners become familiar with the revised rules. An example of a flag: FORMERLY STERILE [DRUG NAME].

In addition, the labels on containers of parenteral products must state the following:

- The name of the preparation
- For a liquid preparation, the percentage content of drug or the amount of drug in a specified volume
- 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
- The route of administration
- A statement of storage conditions and an expiration date
- The name of the manufacturer and distributor
- An identifying lot number 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 so. Preparations intended to be used as dialysis, hemofiltration, or irrigation solutions should meet the requirements for injections except those relating to volume in the containers and should bear a statement indicating that the solution is not intended for use by intravenous infusion. Appropriately labeled containers 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 that visual inspection reveals to contain 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 biologic products—insulin injection and the various vaccines, toxoids, toxins, and related products—should be stored under refrigeration. Consult 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 guidelines on quality assurance for pharmacy-prepared sterile products (15). The guidelines were developed to help pharmacists establish quality assurance procedures for preparation of sterile products. The guidelines are appropriate to all practice settings in which pharmacists directly serve patients (e.g., hospitals, community pharmacies, nursing homes, home health care). These are not intended to apply to manufacture of sterile pharmaceuticals as defined in state and federal laws and regulations. Nor are they to apply to preparation of medications by pharmacists, nurses, and physicians intended for immediate administration (minimal delay between preparation and administration) to patients.

The term *sterile products* used within the guidelines refers to sterile or nutritional substances that are prepared (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 the following:

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

The guidelines define the purpose of these recommendations and encourage pharmacists to participate in quality improvement, risk management, and infection control programs in their organization. In doing so, pharmacists are 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, what was then the American Society of Hospital Pharmacists proposed guidelines that formed the basis of the Technical Assistance Bulletin (TAB) (16). This document distinguished between quality control (QC) and quality assurance (QA). By definition, *quality control* is 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 guidelines classify sterile products into three levels based on risk to the patient. The risk levels range 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 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.

Sometimes the pharmacist must make risk–benefit decisions to prepare these products outside of the guidelines (e.g., preparation of a sterile investigational drug in a compassionate-use protocol for a lifesaving effort). The risk assignments listed in Table 15.3 provide a logical template within which to evaluate risk. These do not, however, preclude alternative logical arrangements based on 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. If the risk level assignment is unclear, guidelines for the higher risk level should be followed.

The guidelines delineate 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 guidelines; see them for additional information.

The USP 27–NF 22 introduced a new general Chapter <797> "Pharmaceutical Compounding—Sterile Preparations," which establishes standards for aseptic compounding of all sterile dosage forms (18). This chapter explains in detail the various procedures and documentation necessary to prepare and dispense sterile drug products. It includes, among others, validation of sterilization and aseptic processes, personnel training, aseptic techniques, finished product release testing, storage, and beyond-use dating.

Available Injections

Hundreds of injections of various medicinal agents are on the market. Tables 15.4 to 15.7 present some examples of those packaged in small-volume and large-volume containers, the latter for intravenous infusion.

TABLE 15.3 ASHP STERILE PRODUC

1. Products
   A. Stored at room t
   B. Stored under ref riod not to exce
   C. Frozen for 30 da hours
2. Unpreserved sterile containing suitable
3. Products prepared b (e.g., from vials or a ringes, minibags, ela ufacturer

1. Products stored bey yond 28 hours after
2. Batch-prepared proc one patient. (Note: I tients carry a greate ity of inaccurate ing
3. Products compound censed manufacture closed-system asepti

1. Products compound tainers, or equipmer
2. Products prepared b transfer or open rese

Small-Volume

Table 15.4 presents ployed injections give of these injections are suspensions.

Premixed intraven simplified delivery fo als in particular. A di ready-to-use systems or no manipulation to cific. Thus they are a traditional labor-inte pounding parenteral n ual or multiple doses tions and an appropr Since the introductior

TABLE 15.3 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 B. Stored under refrigeration for 7 days or less before complete administration to a patient over a period not to exceed 24 hours 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 (e.g., from vials or ampuls) obtained from licensed manufacturer into sterile final containers (e.g., syringes, minibags, elastomeric containers, portable infusion device cassette) obtained from licensed manufacturer
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 (e.g., epidural products) intended for use by more than one patient. (Note: Batch-prepared products without preservatives to be administered to multiple patients carry a greater risk to patients than products prepared for a single patient because of the possibility of inaccurate ingredients or product contamination.)
3. Products compounded by complex or numerous manipulations of sterile ingredients obtained from licensed manufacturers in a sterile container or reservoir obtained from a licensed manufacturer by using closed-system aseptic transfer; for example, TPN solutions prepared with an automated compounder.
RISK LEVEL 3 (PRODUCTS EXHIBIT CHARACTERISTIC 1 OR 2)
1. Products compounded from nonsterile ingredients or compounded with nonsterile components, containers, or equipment before terminal sterilization.
2. Products prepared by combining multiple ingredients—sterile or nonsterile—by using an open-system transfer or open reservoir before terminal sterilization.

Small-Volume Parenterals

Table 15.4 presents some commonly employed injections given in small volume. Some of these injections are solutions and others are suspensions.

Premixed intravenous delivery systems have simplified delivery 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. Thus they are a viable alternative to the traditional labor-intensive method of compounding parenteral medications from individual or multiple doses of intravenous medications 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) (Table 15.5).

The traditional method for preparing small-volume parenteral therapy from a partial-fill drug vial into a minibag can be labor intensive and costly in materials. The savings accrued through ready-to-use systems can be significant (19). 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 use and delivered to the nursing station by the pharmacy personnel (19).

The down side of these ready-to-use small parenteral products is that they do not offer

TABLE 15.4 SOME INJECTIONS USUALLY PACKAGED AND ADMINISTERED IN SMALL VOLUME

INJECTION	PHYSICAL FORM	CATEGORY AND COMMENTS
Botulinum toxin type A	Powder for injection	For temporary improvement in appearance of moderate to severe glabellar lines associated with corrugator or procerus muscle activity in adult patients 65 years or younger; administered IM.
Butorphanol tartrate	Solution	Opioid agonist-antagonist analgesic; administered IM or IV for relief of moderate to severe pain, as preoperative or preanesthesia medication.
Chlorpromazine HCl	Solution	Antipsychotic drug with antiemetic (antidopaminergic) effects; should not be administered SQ. Injection should be IM slowly, deep into upper outer quadrant of buttocks. Avoid injecting directly into vein. IV route used ONLY for severe hiccoughs, surgery, tetanus.
Cimetidine HCl	Solution	Histamine H_2 antagonist; IM or IV for pathologic GI hypersecretory conditions or intractable ulcers.
Dalteparin sodium	Solution	Sterile low-molecular-weight heparin for prophylaxis of deep vein thrombosis in patients at risk who are undergoing abdominal surgery. Available in a prefilled syringe; administered SQ.
Dexamethasone sodium phosphate	Solution	Glucocorticoid; IM or IV for cerebral edema, unresponsive shock. Also intra-articular, intralesional, in soft tissue for joints, bursae, and ganglia.
Digoxin	Solution	Cardiotonic given IM (not preferred) or IV with highly individualized and monitored dosage.
Dihydroergotamine mesylate	Solution	Alpha-adrenergic blocking agent specific for migraine, IM or IV.
Diphenhydramine HCl	Solution	Ethanolamine, nonselective antihistamine; IV or IM when PO impractical; indicated for type I (immediate) hypersensitivity reactions, active treatment of motion sickness.
Furosemide	Solution	Loop diuretic; IM or IV slowly for edema or acute pulmonary edema.
Granisetron HCl	Solution	5-HT_3 receptor antagonist for prevention of nausea and vomiting of cancer therapy, including high-dose cisplatin.
Heparin sodium	Solution	Anticoagulant IV or SQ as indicated by activated partial prothrombin time or actuated coagulation time.
Hydromorphone HCl	Solution	Opioid analgesic for relief of moderate to severe pain; SQ, IM, or slow IV.
Ibutilide fumarate	Solution	Antiarrhythmic with predominantly class III (cardiac action potential prolongation) properties according to Vaughn Williams Classification; infused IV undiluted or diluted in 50 mL diluent.
Iron dextran	Solution	Hematinic agent; IV or IM for documented iron deficiency when oral administration is unsatisfactory or impossible.
Isoproterenol HCl	Solution	Adrenergic (bronchodilator) given IM, SQ, or IV.
Ketorolac tromethamine	Solution	NSAID for < 5 days of moderately severe acute pain that requires analgesia at opioid level, usually postoperatively.
Lidocaine HCl	Solution	Cardiac depressant given IV as antiarrhythmic; also local anesthetic epidurally, by infiltration, and in peripheral nerve block.

(continued)

TABLE 15.4 SO
SMALL VOLUM
INJECTION
Magnesium sulfate
Meperidine HCl
Metoclopramide monohydrochlorid
Midazolam HCl
Morphine sulfate
Nalbuphine HCl
Naloxone HCl
Oxytocin
Phenytoin sodium
Phytonadione
Procaine penicillin G
Prochlorperazine edisylate
Propranolol HCl
Sodium bicarbonate
Sumatriptan succinate
Verapamil HCl

flexibility in changin
tration of the produc
lem to the fluid-restri
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mL, 50 mL, and 25 m
lem somewhat. Anotl
ready-to-use products
turers' premixed pro
Microwave use for qui

TABLE 15.4 SOME INJECTIONS USUALLY PACKAGED AND ADMINISTERED IN SMALL VOLUME

INJECTION	PHYSICAL FORM	CATEGORY AND COMMENTS
Magnesium sulfate	Solution	Anticonvulsant/electrolyte; IM or direct IV injection, IV infusion, other IV administration for convulsive toxemia of pregnancy, parenteral nutrition therapy, mild magnesium deficiency, severe hypomagnesemia.
Meperidine HCl	Solution	Opioid analgesic given IM, SQ, or slow continuous IV infusion.
Metoclopramide monohydrochloride	Solution	Gastrointestinal stimulant; administered IM, direct IV, or slow IV admixture to prevent chemotherapy emesis.
Midazolam HCl	Solution	Short-acting benzodiazepine CNS depressant; IV or IM; for preoperative sedation, anxiolysis, amnesia.
Morphine sulfate	Solution	Opioid analgesic. IM, IV, PCA.
Nalbuphine HCl	Solution	Opioid agonist-antagonist analgesic; administered SQ, IM, IV for moderate to severe pain, preoperative analgesia.
Naloxone HCl	Solution	Opioid antagonist; prevents or reverses effects of opioids, including respiratory depression, sedation, hypotension; IV, IM, SQ.
Oxytocin	Solution	Oxytocic, given IM (erratic) or IV obstetrically for therapeutic induction of labor.
Phenytoin sodium	Solution	Anticonvulsant; IM (erratic absorption) prophylaxis for neurosurgery or slow IV for status epilepticus.
Phytonadione	Dispersion	Vitamin K (prothrombogenic) for hemorrhage. Aqueous dispersion of phytonadione, a viscous liquid.
Procaine penicillin G	Suspension	Anti-infective; IM for moderately severe infections of penicillin G–sensitive microorganisms.
Prochlorperazine edisylate	Solution	Antidopaminergic; IM or IV for control of severe nausea and vomiting associated with adult surgery.
Propranolol HCl	Solution	Beta-adrenergic receptor blocker for hypertension. Oral dosage (tablets) is usual; IV administration is reserved for life-threatening arrhythmias and those occurring under anesthesia.
Sodium bicarbonate	Solution	Electrolyte; IV, undiluted or diluted for cardiac arrest, less urgent forms of metabolic acidosis.
Sumatriptan succinate	Solution	Selective 5-hydroxytryptamine$_1$ receptor, subtype agonist, for acute migraine with or without aura. Self-administered SQ from unit-of-use syringe, *SELFdose* unit.
Verapamil HCl	Solution	Calcium channel blocker; slow IV over at least 2 minutes for supraventricular tachyarrhythmias.

flexibility in changing the volume or concentration of the product. This may pose a problem to the fluid-restricted patient (19). 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). For example, before it was removed from the market, the high energy microwave oven could cause a structural alteration of the cephalothin molecule. Another possibility was that substance would leach from the rubber stopper when frozen ampuls of Neutral Keflin were thawed in the microwave, and oftentimes thawing was not

TABLE 15.5 REPRESENTATIVE MARKETED FROZEN, PREMIXED PRODUCTS ILLUSTRATING STABILITY DATA FROZEN AND AFTER THAWING[a]

			EXPIRATION DATING		
DRUG[b]	STRENGTH	DILUENT	FROZEN STABILITY	REFRIGERATED STABILITY	ROOM TEMPERATURE
Aztreonam	1 g, 2 g	Iso-osmotic in dextrose, 50 ml	12 months	14 days	48 hours
Cefazolin	500 mg, 1 g	Iso-osmotic in dextrose, 50 ml	24 months	30 days	48 hours
Cefotaxime sodium	1 g, 2 g	Iso-osmotic in dextrose, 50 ml	9 months	10 days	24 hours
Cefotetan	1 g, 2 g	Iso-osmotic in dextrose, 50 ml	12 months	21 days	48 hours
Cefoxitin	1 g, 2 g	Iso-osmotic in dextrose, 50 ml	18 months	21 days	24 hours
Ceftazidime sodium	1 g, 2 g	Iso-osmotic in dextrose, 50 ml	9 months	7 days	24 hours
Ceftizoxime	1 g, 2 g	Iso-osmotic in dextrose, 50 ml	12 months	28 days	48 hours
Ceftriaxone	1 g, 2 g	Iso-osmotic in dextrose, 50 ml	15 months	21 days	72 hours
Nafcillin	1 g, 2 g	Iso-osmotic in dextrose, 50 ml, 100 ml	18 months	21 days	72 hours
Oxacillin sodium	1 g, 2 g	Iso-osmotic in dextrose, 50 ml	18 months	21 days	48 hours
Ticarcillin disodium and clavulanate potassium	3.1 g	Iso-osmotic in water, 100 ml	6 months	7 days	24 hours
Vancomycin HCl	500 mg	Iso-osmotic in dextrose, 100 ml	12 months	30 days	72 hours

[a]Stability information provided by Baxter Healthcare Corporation.

[b]Stability data based on packaging drug in a Galaxy[R] container.

even, with the periphery thawed and the central portion still frozen.

General precautions (20) were once published for using a microwave to thaw frozen products. However, this practice is no longer suggested. Instead, many hospital pharmacies use the Sāf-Thaw (MMI of Mississippi, Crystal Springs). This apparatus provides a layer of conditioned air continuously circulating around the frozen product. The thawing surface facili-

TABLE 15.6 INSULIN ACTIVITY PROFILES AND COMPATIBILITY

PREPARATION	ONSET (HR)	PEAK (HR)	DURATION (HR)	COMPATIBLE WITH
Rapid acting				
Insulin Lispro	0.25	0.5–1.0	3	Ultralente; NPH
Insulin Aspart	0.25	0.5–1.0	3	None
Short acting				
Regular insulin	0.5	2–5	5–8	All
Intermediate acting				
Isophane (NPH) insulin	1–2	6–10	16–20	Regular
Insulin zinc (Lente)	1–2	6–12	18–24	Regular, semilente
Long acting				
Insulin zinc extended (Ultralente)	4–6	10–18	24–28	Regular, semilente
Insulin glargine	2	None	>24	None
Mixtures				
Isophane/regular insulin 70/30, 50/500.75	7–12	16–24	—	
NPL/Lispro Mix 75/25	5 min	7–12	1–24	—

TABLE 15.7 SOM VOLUMES OF 1

INJECTION
Amino acid
Dextrose Injection, U
Dextrose and Sodium Chloride Injection,
Mannitol Injection, U
Ringer's Injection, USI
Lactated Ringer's Injection, USP
Sodium Chloride Injection, USP

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TABLE 15.7 SOME INTRAVENOUS INFUSIONS THAT MAY BE ADMINISTERED IN VOLUMES OF 1 L OR MORE, ALONE OR WITH OTHER DRUGS

INJECTION	USUAL CONTENTS	CATEGORY AND COMMENTS
Amino acid	3.5, 5, 5.5, 7, 8.5, 10% crystalline amino acid with or without varying concentrations of electrolytes or glycerin	Fluid and nutrient replenisher
Dextrose Injection, USP	2.5, 5, 10, 20% dextrose, other strengths	Fluid and nutrient replenisher
Dextrose and Sodium Chloride Injection, USP	Dextrose 2.5–10%; NaCl 0.11–0.9% (19–154 mEq sodium)	Fluid, nutrient, electrolyte replenisher
Mannitol Injection, USP	5, 10, 15, 20, 25% mannitol	Diagnostic aid in renal function; diuretic; fluid and nutrient replenisher
Ringer's Injection, USP	147 mEq sodium, 4 mEq potassium, 4.5 mEq calcium, 156 mEq chloride per liter	Fluid and electrolyte replenisher
Lactated Ringer's Injection, USP	2.7 mEq calcium, 4 mEq potassium, 130 mEq sodium, 28 mEq lactate per liter	Systemic alkalinizer; fluid and electrolyte replenisher
Sodium Chloride Injection, USP	0.9% NaCl	Fluid and electrolyte replenisher; isotonic vehicle

tates recirculating the conditioned air in the unit and thereby prevents collection of unconditioned air or moisture from the room where the Sāf-Thaw is operating. The frozen product is placed on the thawing surface, which is approximately 37°C (99°F), warm to the touch when the unit is in operation. Several dozen frozen products can be placed on the thawing surface at one time, depending on their size.

In years past, some manufacturers recommended warming frozen premixed products in a water bath, with a warning not to submerge the product because there was a distinct possibility that water from the bath could enter and contaminate the product. Now manufacturers recommend that the frozen container be thawed at room temperature or in a refrigerator (e.g., for 1 hour) and prohibit the use of a water bath or microwave. Thawed floor stock is usually available for emergency orders. Generally, these are kept in refrigerators and warm up quickly (e.g., 20 minutes) to room temperature.

The ready-to-use systems have not been used much 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 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 with 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* that 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. 15.30 to 15.32). A system for nasal administration of insulin is under study.



FIGURE 15.30 Medi-Jector II, a jet injection device. The jet injection method uses pressure rather than a needle to provide subcutaneous distribution of medication. This device 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 Antares Pharm Inc.)

U-100 insulin has been suggested as a replacement for U-40 insulin, 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 production of U-40 insulins, and subsequently other insulin manufacturers also decided to cease production of this strength. The basis for this decision was lack of demand (very low numbers of patients using this strength). Recognizing, however, that insulin under 100 U/mL might still be needed, as for small children and veterinary use), Lilly markets a diluting fluid for the Regular, NPH, Lente, and Ultra-Lente insulins of U-100 strength. This fluid can be used to prepare any strength of insulin below 100 U/mL. The diluting solutions are identical to the diluent in the insulin in every way (e.g., preservative agent, buffer, pH) except for the presence of insulin. The recommended storage condition for opened and unopened diluting solutions is controlled room temperature, 25°C (77°F). Once the diluting solutions are opened, the material can be used for a month.

Age-associated sight difficulties and the vision deterioration associated with diabetes can interfere significantly with buying and using



FIGURE 15.31 Insulin syringes calibrated in units. (Courtesy of William B. French, PhD.)

insulin products. Therefore, packaging of insulins must make allowances for visual deficits. 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 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 ensure that patients with diabetes secure the correct Humulin formulation anywhere in the world.

The goal of insulin therapy is to achieve tight blood glucose control by mimicking insulin secretion by the normal pancreas. Normal insulin secretion consists of two components, basal and bolus insulin. These components are mimicked by the administration of two types of insulins. Basal insulins are intermediate-acting or long-acting insulins that mimic basal secre-

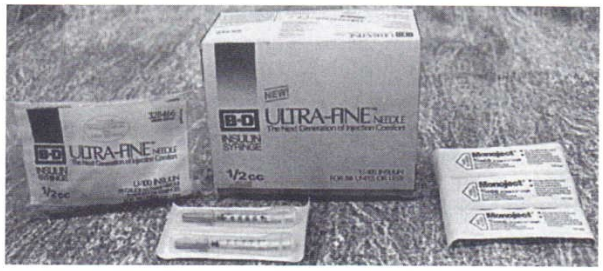


FIGURE 15.32 Packaging of disposable sterile insulin syringes and needles. (Courtesy of William B. French, PhD.)

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tion of insulin. This is the small amount that the pancreas secretes continuously. These products help to suppress hepatic glucose production between meals and overnight. Basal insulins provide approximately 50% of a person's daily requirements. Bolus insulins are rapid-acting or short-acting insulins that mimic the extra insulin the pancreas secretes in response to the postprandial rise of blood glucose levels. Postprandial blood glucose values contribute significantly to hemoglobin A_{1C} values and consequently to the long-term complications of diabetes if these blood glucose values are not controlled. Thus, postprandial control of blood glucose is essential for optimal management. Bolus injections are estimated to provide 10 to 20% of a patient's total daily insulin requirement at each meal.

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 and beef product. The first insulin developed for clinical use was amorphous. This type has since been replaced by a purer zinc–insulin crystalline product that produces a clear aqueous solution. Originally, insulin injection (regular insulin) was 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 manufacturing to produce insulin of greater purity has allowed for insulin injection with a neutral pH. The neutral product is more stable than the acidic product.

Insulin injection is prepared to contain 100 or 500 USP insulin units per milliliter. The labeling must state the potency in USP insulin units per milliliter and the expiration date, which must not be later than 24 months after the date of manufacture. As an added precaution against inadvertent use of the incorrect strength, the packages are color coded for strength. For instance, all insulins of the various types containing 100 U/mL have orange, and the 500 U/mL preparation has brown with diagonal white stripes. U-500 insulin is indicated for patients with a marked insulin requirement (more than 200 U per day) because a large dose may be administered subcutaneously in a small volume.

Insulin injection is a colorless to straw-colored solution, depending on its concentration; the 500 U/mL product is straw colored. It is substantially free from turbidity. A small amount of glycerin (1.4–1.8%) 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 injection of cold insulin is uncomfortable, the patient may store the vial being used at room temperature (15–30°C or 59–86°F) 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 onset of action, peak of action, and duration of action (Table 15.6). Insulin injection, being a solution, is categorized as prompt acting. Insulin suspensions are slower acting. Only insulin injection may be administered intravenously; all others, as well as insulin injection, are normally given subcutaneously, usually 30 minutes to 2 hours before a meal so that physiologic effects will parallel absorption of glucose. The dosage is individually determined, with the usual range being 5 to 100 U. The insulin injection containing 500 U/mL is employed in cases of insulin resistance requiring very large doses.

The pharmacist plays a vital role in the education of the diabetes patient, particularly in the proper use of insulin. The insulin dose should always be checked to ensure it is correct. Because it is a solution, regular insulin can be used in emergencies, such as ketoacidosis, to effect a rapid decrease in blood glucose levels. However, with the exception of diabetic ketoacidosis, it is rare for a patient to require a dose of regular insulin greater than 25 U. Typically, diabetes patients combine regular insulin with a

modified insulin, such as NPH, to provide daily coverage in two injections (morning, late afternoon) or use premixed preparations. So it is important that the patient understand how much of each to use and in what order to mix them in the syringe. 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. Allied health care workers have made errors in insulin dosage. Written orders for 6 U of insulin have been interpreted to mean 60 U, and an order for 4 U has been read as 4 cc. Each of these occurred because the abbreviation U for units was read as a zero or cc.

The patient should be instructed to rotate the site of insulin injections. Rotation of the site will help to avoid lipohypertrophy, a buildup of fibrous tissue. With 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 from manufacturers of diabetes supplies demonstrate the appropriate rotation of insulin injection sites over the entire body.

Another problem with insulin injections 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. Its cause has been ascribed to injection of refrigerated insulin (not giving enough time for it to warm up prior to injection), to failure to rotate the injection site, and to impurities in the insulin. The result is the formation of a subcutaneous indentation or pothole caused by wasting or atrophy of the lipid tissue. It appears that the greater purity of current insulins has significantly decreased this problem, and a marked improvement in existing atrophic areas has been demonstrated by injection of highly purified pork or human insulin directly into or on the periphery of the atrophic areas.

Prior to use, the patient should be instructed to inspect the insulin carefully. Regular insulin and insulin glargine solutions should appear clear, while the other insulins, which are suspensions, should appear uniformly cloudy. With the suspensions the patient should be instructed how to prepare the insulin: the vial is rotated slowly and gently between the palms of the hands several times before the insulin is drawn into the syringe. This avoids frothing and bubble formation, which would result in an inaccurate dose. The patient should not shake the insulin vial.

Proper storage should also be encouraged. These preparations should be stored in a cool place or a refrigerator. The patient should be warned to avoid allowing the insulin to come into contact with extremes of temperature, that is, freezing, such as overnight in the car in the winter and heat, as in the glove compartment of a car in the summer or in direct sunlight. If this occurs, the patient should 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. Finally, the patient should use the insulin in a timely fashion, not beyond the expiration date indicated on the insulin vial.

Human Insulin

Biosynthetic human insulin was the first recombinant DNA drug product to receive approval from FDA. This product, Humulin (Lilly), became available in 1983. It is produced by using a special non–disease-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

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as impurities in insulin preparations extracted from animal pancreas. 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 at 6 to 8 hours. NPH human insulin is an intermediate-acting turbid preparation 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. However, peak serum levels of lispro insulin occur within 0.5 to 1.5 hours and are higher, and it is shorter acting, that is, 6 to 8 hours, than regular insulin. 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 15 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 hypoglycemia associated with exercise within 3 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 accidentally frozen, it should not be used. If absolutely necessary, it may be stored at room temperature for up to 28 days, but storage temperature should be as cool as possible. The vial or cartridge 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.

Insulin Aspart

Insulin aspart is a recombinant ultra–short-acting insulin using *Saccharomyces cerevisiae* (baker's yeast) as the production organism. It is homologous with regular human insulin except for a single substitution of the amino acid proline by aspartic acid in position B28. This insulin was developed to control postprandial glucose concentrations when administered 5 to 10 minutes before mealtime in a manner similar to that for insulin lispro. The dosage is individualized to the patient's needs.

Insulin aspart demonstrates pharmacokinetics very similar to those of lispro insulin solution in terms of onset of action (0.25 hours), peak effect (0.5–1 hour), and duration of action (3 hours).

Because of its very short duration of action, higher doses of NPH insulin are needed in combination with it than with regular insulin. In a meal-related regimen, 50 to 70% of this requirement may be provided by the insulin aspart and the remainder provided by the intermediate-acting or long-acting insulin. A few studies have demonstrated that patients treated with insulin aspart had better glucose control

and fewer nocturnal hypoglycemic episodes than patients using regular insulin. These studies demonstrate that insulin aspart is a viable alternative therapy for patients who use regular insulin.

Mixing insulin aspart with NPH human insulin immediately before injection may produce some attenuation in the peak concentration of the insulin aspart. However, the time to peak concentration and the total bioavailability of the insulin aspart should not be affected. When insulin aspart is mixed with NPH human insulin, the insulin aspart should be drawn up first. This combination should be injected immediately after mixing. Insulin aspart should not be mixed with crystalline zinc insulin preparations because compatibility data are lacking.

Isophane Insulin Suspension (NPH Insulin)

Isophane insulin suspension is a sterile suspension in an aqueous vehicle buffered with dibasic sodium phosphate to pH 7.1 to 7.4. It is prepared from zinc insulin crystals modified by the addition of protamine so that the solid phase of the suspension consists of crystals 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 in the discussion of the aqueous insulin solutions, suspensions of insulin with a pH on the alkaline side inherently have a longer duration of action than solutions. Insulin is least soluble at pH 7.2.

The rod-shaped crystals of isophane insulin suspension should be approximately 30 μm long and the suspension free of large aggregates of crystals following moderate agitation. This is necessary for it to pass freely through the needle and for absorption of the drug to be consistent from one batch 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 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 milliliter contains 100 U of insulin. The suspension is best stored in a refrigerator, but freezing must be avoided.

As indicated earlier, isophane insulin suspension is an intermediate-acting preparation administered as required mainly as hormonal replacement in diabetes mellitus. The usual dose range subcutaneously is 10 to 80 U. Its effects are comparable with those of a mixture of 2 to 3 parts of regular insulin and 1 part of protamine zinc insulin.

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* (equal) and *phane* (appearance) and refers to the equivalent balance between the protamine and insulin.

Isophane Insulin Suspension and Insulin Injection

In years past, patients needing a rapid onset of action and 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 responses, such as hypoglycemic episodes, were encountered. It was fairly common for the patient to contaminate one of the vials during mixing. Subsequently, a premixed formulation of isophane insulin suspension and insulin injection became available, and now there are two formulations. The 70/30 combination consists of 70% isophane insulin suspension and 30% insulin injection, and the 50/50 combination consists of 50% isophane insulin suspension and 50% insulin injection. These combinations are stable and absorbed as if injected separately.

Humulin 50/50 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 (area under the curve, or AUC) and the cumulative effects over 24 hours following injection are identical. Thus, the 70/30 combina-

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tion provides an initial response tempered with a more prolonged release of insulin. The 50/50 mixture is useful when a greater initial response is required and for patients who have been using extemporaneously compounded insulin mixtures in a 50/50 ratio.

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

Patients should not attempt to change the ratio of these products by adding 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.

Humalog Mix

Humalog Mix is a manufactured premixed insulin consisting of insulin lispro and neutral protamine lispro (NPL) in a fixed ratio. Humalog Mix 50/50 consists of 50% insulin NPL suspension and 50% insulin lispro injection. Humalog Mix 75/25 contains 75% insulin NPL suspension and 25% insulin lispro injection. It is estimated that these premixed combinations are used by more than 40% of diabetes patients who inject insulin twice daily.

These fixed combinations were developed to give better control for diabetes patients who use a combination of short- and long-acting insulin. In comparison to Humulin 70/30, Humalog Mix 75/25 demonstrated lower postprandial blood glucose levels and no difference between the afternoon and overnight glucose values. Furthermore, insulin NPL suspension was developed as an alternative to combinations employing NPH insulin. NPH insulin was unstable over weeks to months when mixed with lispro insulin.

Insulin Zinc Suspension

Insulin zinc suspension contains 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 with sodium acetate to pH 7.2 to 7.5. 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 crystals. Also, the larger the crystals, the less prompt and the longer-acting will be the suspension. By combining the crystalline and amorphous forms into one preparation, an intermediate-acting suspension is obtained. As noted in Table 15.6, the time activity of insulin zinc suspension is only slightly different from that for isophane insulin suspension. The advantage of the former is that it contains no foreign protein, 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 that most closely meets the desires and requirements of the individual. Suspensions contain 100 U/mL in 10-mL vials. The individual crystalline and amorphous particles may be seen microscopically, with the crystals being predominantly 10 to 40 μm in maximum dimension and the amorphous particles no greater than 2 μm.

In addition to the sodium acetate buffer, the suspension contains about 0.7% sodium chloride for tonicity and 0.1% 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 without freezing. As with all such preparations, the dose depends on the individual needs of the patient but generally ranges between 10 and 80 U.

Insulin Glargine

Insulin glargine is a long-acting (up to 24 hours) basal insulin preparation intended for once daily subcutaneous administration at bedtime in the treatment of type I diabetes mellitus in adults and children. It can also be used

by adults with type II diabetes who require long-acting insulin. It is created when the amino acids at position 21 of human insulin are replaced by glycine and two arginines are added to the C terminus of the B chain.

Insulin glargine is a recombinant human insulin analogue. Formulated at a pH of 4.0, it is completely soluble at that pH. However, once it is injected into subcutaneous tissue, it is neutralized, which causes formation of microspheres. This peakless insulin begins working in 2 hours and mimics basal insulin secretion more closely than other long-acting insulins for 24 hours. This allows for once-daily dosing. Because insulin glargine provides only basal coverage, it is often used in conjunction with other insulins or oral hypoglycemic drugs. However, because of the unique release characteristics of insulin glargine, it should not be mixed with any other insulin. Differences in pH can cause clumping. If it has to be used in combination with a short-acting insulin, the injections must be administered separately.

The unique release characteristics of insulin glargine may help to decrease the number of required injections of long-acting insulin from twice daily to once daily. Clinical studies have demonstrated no relevant differences in insulin glargine absorption after abdominal, deltoid, or thigh administration.

If the patient is changing over to insulin glargine from an intermediate- or long-acting regimen, the dosage may or may not have to be adjusted. When patients are transferred from twice-daily NPH to insulin glargine once daily at bedtime, to reduce the risk of hypoglycemia, the initial dose is usually decreased by approximately 20% from the total daily dose of NPH product for the first week of treatment and then adjusted to the patient's response. However, when patients are transferred from once-daily NPH or ultralente insulin to once-daily insulin glargine, the initial dose is usually not changed.

Extended Insulin Zinc Suspension

Extended insulin zinc suspension is a sterile suspension of zinc insulin crystals in an aqueous medium buffered with sodium acetate to pH 7.2 to 7.5. It also contains 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 long acting. It may be mixed with either insulin zinc suspension or prompt insulin zinc suspension to achieve the proper time activity of an individual patient. The usual dosage range is 10 to 80 U. It is commercially available in 10-mL vials providing 100 U/mL. The suspension must be stored in a refrigerator without freezing. The expiration date of the properly stored injection is not later than 24 months after the immediate container was filled.

Insulin Infusion Pumps

Insulin infusion pumps allow patients to achieve and maintain blood glucose at nearly normal levels on a *constant basis*. Continuous infusion of insulin through use of these small and lightweight pumps eliminates the need for the patient to adhere rigidly to a regimen of multiple daily injections of insulin. This provides convenience, better adherence, and control over the disease process. The main objective of pump therapy is strict control of the blood glucose level at 70 to 140 mg/dL. This is the primary way to avoid complications such as gangrene and diabetic retinopathy.

Early insulin infusion pumps were large bedside units used mainly in hospitals. Today an insulin pump is the size and weight of a personal pager. It is a plastic-encased computer device that can be worn in a pocket or bra or on a belt. A computer chip in the pump allows the patient to program the amount of insulin for the pump to release. Inside the pump, a syringe reservoir holds up to 300 U of U-100 insulin. Unlike conventional insulin therapy, which normally combines rapid-acting and intermediate-acting insulin, the infusion pump delivers either short-acting or rapid-acting insulin. Frequently a rapid-acting insulin, such as aspart (Novolog) or lispro (Humalog) is preferred.

The reservoir delivers insulin through a plastic infusion set, available in 24-inch or 42-inch lengths. The triggering device inserts the infusion set's flexible catheter into the subcutaneous tissue. Once the catheter is inserted,

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Large-Volume

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Most patients insert the infusion set into the abdomen. Here the insulin is rapidly and consistently absorbed. It is crucial that the set be inserted subcutaneously and not intramuscularly. Patients should understand not to place it where their clothing may rub against it (e.g., underwear area, waistline, a 4-inch area around the umbilicus) and to make sure to rotate the insertion site.

For optimal working efficiency, the patient should change the infusion site every 2 or 3 days or whenever blood glucose is above 240 mg/dL for two tests in a row. This may indicate that the infusion set is not working properly.

It is very important that patients understand the necessity to monitor their blood glucose so they know to adjust their dosage of insulin. Patients should check their blood glucose level before each meal, at bedtime, and whenever they have symptoms of hypoglycemia (sweating, shakiness, nausea, headache, difficulty concentrating) or hyperglycemia (polyuria, polydipsia, polyphagia, nocturnal enuresis, weakness, fatigue, blurred vision, alteration in mental status).

Infection at the site is a concern and a problem. Prevention is the best treatment; however, if the site becomes infected, the patient's health care provider should be informed and antibiotics ordered to treat it. In the meantime, the infusion set should be moved to another site, or insulin may be administered manually until the infection is cured.

At night, the insulin pump can be placed on the night stand close to the bed, in the bed next to the patient, or in a pajama pocket. When bathing, the patient can place the pump on the bathroom floor and allow the tubing to drape over the side of the tub. For showering, the pump can be placed in a special plastic bag and hung around the patient's neck or on the faucet handle.

Large-Volume Parenterals

Common examples of large volume parenterals in use today are presented in Table 15.7. These solutions are usually administered by intravenous infusion to replenish body fluids or electrolytes or to provide nutrition. They are usually administered in volumes of 100 mL to 1 L or more per day by slow intravenous infusion with or without a controlled-rate infusion system (Fig. 15.33). 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. 15.34 and 15.35).

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

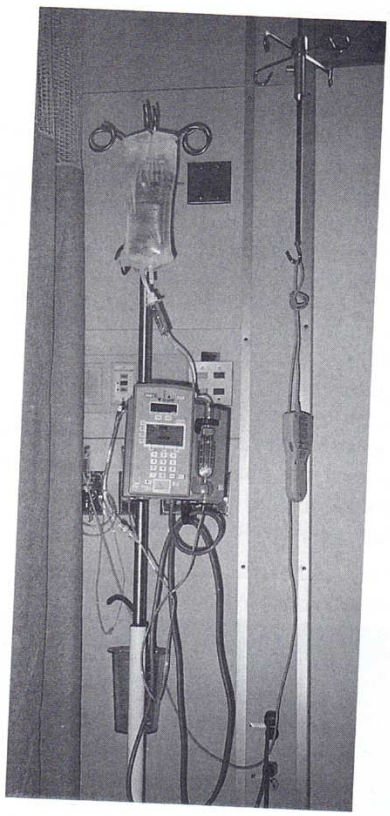


FIGURE 15.33 Accurate delivery of intravenous fluids and medications by use of a controlled-rate infusion system (Alaris Medical Systems) for the drug vial and a volumetric infusion pump for the intravenous fluids. (Courtesy of Mr. Akinwale O. Onamade.)

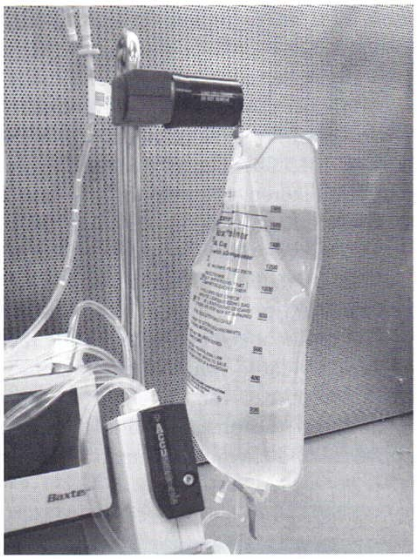


FIGURE 15.34 Intravenous solution packaged in pliable plastic. (Courtesy of Ms. Amy Schuppert Smith)

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

It is also important to be vigilant for incompatibilities associated with multiple infusions coadministered to a patient. A typical nursing question may be, "Can the dopamine drip be run in with the heparin drip?" To answer these questions, the pharmacist must know about parenteral therapy and be aware of incompatibilities reported in the literature. Numerous references (e.g., *Handbook on Injectable Drugs, King's Guide to Parenteral Admixtures* [King Guide Publications]) are available for sources listing and discussing parenteral incompatibilities. However, the pharmacist should use only the most current edition of these references. Whenever possible, the pharmacist should attempt to answer these important questions and explain the incompatibilities that come to his or her attention as part of the daily routine. Furthermore, the pharmacist should create a file of data and add to it from experience and the literature. Internet-accessible services (e.g., Micromedex) can also be employed to check incompatibilities. These reference the *Handbook on Injectable Drugs* and *King's Guide to Parenteral Admixtures*.



FIGURE 15.35 Peritoneal dialysis and irrigation fluids. (Courtesy of William B. French, PhD.)

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 intravenous 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 and for the patient who is unconscious and unable to take fluids, electrolytes, and nutrition orally. The solutions may also be used in *replacement therapy* for patients who have suffered a heavy loss of fluid and electrolytes.

Maintenance Therapy

When a patient is receiving parenteral fluids for only a few 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. If oral feeding must be deferred for periods of weeks or longer, total parenteral nutrition (TPN) must be implemented to provide all of the essential nutrients to minimize tissue breakdown and to maintain

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normalcy within the body. Total nutrient admixtures (TNA, three-in-one) include all substrates necessary for nutritional support—carbohydrates, protein, fat, electrolytes, trace elements—mixed in a single plastic intravenous bag for convenient administration.

These admixtures are very useful for chemotherapy, gastrointestinal, and anorexic patients. The use of three-in-one admixtures in pediatrics, especially for neonates, is controversial. The concentrations of calcium, phosphorus, and necessary warm administration for pediatric TPN do not lend themselves to stable preparations. As a result, many pediatric institutions do not compound three-in-one admixtures for their patients but administer the fat emulsion separately.

When using TNA, the pharmacist must consider the order of substrate mixing, differentiate between various brands of substrate and their physicochemical properties, determine the type of plastic bag system that is most appropriate, 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. For example, the use of "standard" TPN plastic bags may result in plasticizer leaching into the solution and injuring 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 cases of respiratory distress associated with the use of three-in-one admixtures. Autopsies revealed diffuse microvascular pulmonary emboli linked to 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 lipid-free (two-in-one) parenteral nutrient solutions.

Lipid emulsions and three-in-one parenteral nutrient solutions can be safely filtered at a pore size of at least 1.2 μm. A problem with the lipid emulsion in a three-in-one admixture is that it obscures 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

When the patient has undergone 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, burns, or trauma are candidates for replacement therapy.

Water Requirement

In normal individuals, the daily water requirement is the amount needed to replace normal and expected losses. Water is lost daily in the urine and feces and from the skin and 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 L/m^2 of body surface area (22). Nomograms for determination of body surface area from height and weight are presented in Figure 2.10. 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 a 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/kg/day may be required in addition to maintenance water requirements; a badly dehydrated infant may require an even greater proportion (22). Thus, a 50-kg patient may require 3500 mL for replacement plus 2400 mL for maintenance. To avoid 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 osmotic hemolysis of red blood cells and because a patient who requires water generally requires nutrition and/or electrolytes, parenteral administration of water is generally as a solution with dextrose or electrolytes with 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, disease of the intestinal tract, surgical operation, and the use of such medications as thiazide and loop diuretics. Poorly nourished people, those using very low-calorie diet products, and victims of anorexia nervosa or acute alcoholism also may have low potassium levels (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 general 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 excessive consumption of potassium-rich foods. Prescribed potassium supplements, potassium-sparing diuretic therapy, angiotensin-converting enzyme inhibitors (e.g., lisinopril) and the indiscriminate use of OTC salt substitutes have also been implicated to induce hyperkalemia.

In cases of severe potassium deficiency, intravenous electrolyte replacement 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. Potassium preparations must be diluted with a suitable large-volume parenteral solution, mixed well, and given by slow intravenous infusion. They are not to be administered undiluted. Undiluted potassium chloride administered intravenously has killed people.

The most commonly used concentration of potassium chloride for continuous-infusion maintenance therapy is 20 to 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 with hypokalemia, the usual infusion rate is 10 mEq/hour (maximum recommended rate is 20 mEq/hour). Because of potassium chloride's ability to effect electrocardiographic (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/hour if the patient is not monitored by ECG. For patients monitored by ECG, the usual infusion rate is 20 mEq/hour with a maximum infusion rate of 40 mEq/hour, depending on 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 after normal potassium serum levels are achieved. For patients whose serum potassium is more than 2.5 mEq/L, the potassium level should be measured after the first 60 mEq is administered. For patients whose serum potassium is less than 2.5 mEq/L, the potassium level should be measured after the first 80 mEq is administered.

Sodium, the principal extracellular cation, is vital to maintain normal extracellular fluids. Average daily intake of sodium is 135 to 170 mEq (8–10 g). 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) should prevent a negative sodium balance. A low sodium level in the body may result from excessive sweating, use of certain diuretics, or diarrhea. Fatigue,

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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. Sodium has been implicated as a causative factor in about 20% of cases of high blood pressure. 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, 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, including 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 Nutrition

Parenteral nutrition is infusion of enough basic nutrients to achieve active tissue synthesis and growth. It is characterized by 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 used in parenteral nutrition solutions are the following, listed in quantities commonly provided per liter of fluid. The individual components and amounts vary with the patient's needs.

Electrolytes	
Sodium	35 mEq
Potassium	30 mEq
Magnesium	5 mEq
Calcium	5 mEq
Chloride	40 mEq
Acetate	35 mEq
Phosphate	15 mM
Vitamins	
Vitamin A	3300 IU
Vitamin D	200 IU
Vitamin E	10 IU
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 μg
Vitamin B_{12}	5 μg
Biotin	60 μg
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 volume required to be administered to a minimum. The solution is administered slowly through a large vein, such as the superior vena cava. The superior vena cava is accessed through the subclavian vein immediately beneath the clavicle and near the heart. This permits 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 (not more than 10%) can be given peripherally. Solutions containing more than 10% dextrose should be given via 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, formation of calcium phosphate and deposition of its crystals in lung tissue led to the 1994 FDA safety alert (21).

Many factors have been implicated in 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 for calcium phosphate precipitation is especially challenging for compounding neonate and 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 avoid this serious compatibility problem.

Figure 15.36 demonstrates a four-station Nutrimix Macro TPN Compounder. This device can pump four nutritional solutions (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 bag. The fifth load cell

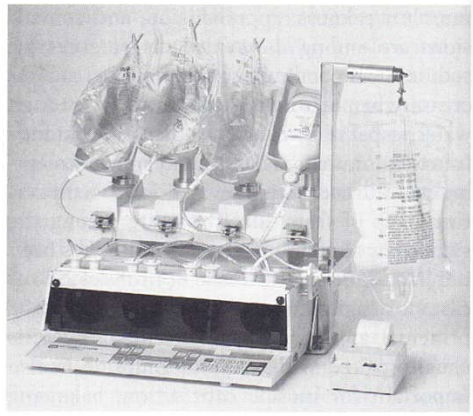


FIGURE 15.36 Nutrimix Macro TPN Compounder. (Courtesy of Abbott Hospital Products Division.)

serves as a confirmation of the weights programmed versus weights delivered. The picture demonstrates big flexible containers and the fat emulsion in glass. Figure 15.37 demonstrates the Nutrimix Micro TPN Compounder. This automatically dispenses small-volume nutritional additives into flexible containers that already contain a base nutritional admixture. The figure depicts 10 stations of small vials.

With the increasing use of parenteral solutions in children, including nutritional solu-

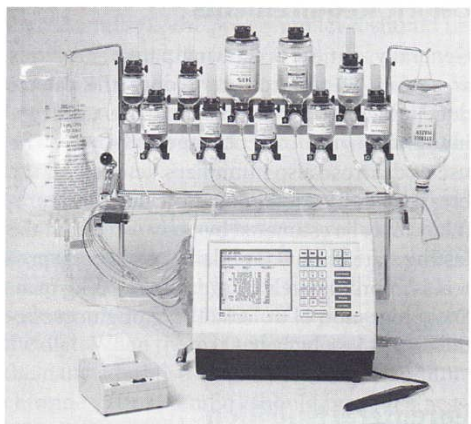


FIGURE 15.37 Nutrimix Micro TPN Compounder. (Courtesy of Abbott Hospital Products Division)

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tions, pharmacists are frequently confronted with inquiries concerning the appropriate method of parenteral drug delivery (23). A dilemma with young 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, it may be the only way to ensure that the patient is receiving adequate nutrition as well as appropriate drug therapy. Furthermore, administering the medication with the nutritive solution, rather than interrupting the feeding to administer medication, makes rebound hypoglycemia less likely. However, the practice of administering medication through a central venous line intended for parenteral nutrition solutions is not without risks. Catheter sepsis and occlusion can result.

Formerly, TPN was prepared 1 L at a time. However, to conserve time, a 24-hour supply is much more efficient and now the norm. Indeed, if a patient encounters a problem necessitating remake of a bag, the cost difference between 1 or 2 1000 mL bags 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 adjust minutely 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 order 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 receive 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 (amino acids or short peptides and simple carbohydrates) or polymeric (complex protein and carbohydrates). 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 have the preparation 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 patients with diarrhea and cramping, high-osmolality formulas may present difficulty. Low-fat products should be suggested for patients with significant malabsorption, hyperlipidemia, or exocrine pancreatic insufficiency. Medium-chain triglycerides, 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 patients with hepatic or renal disease, the sodium and potas-

sium content of the formulations must be considered. For patients receiving 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 applies to an elderly, bedfast patient who is not physically active. This level of support is also advocated for postsurgical patients and those with 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. Most persons, including those with poor appetite or cancer, need 2000 to 3000 calories per day. The last category of patients is those with daily caloric needs that exceed 3000 calories. These individuals usually have high protein losses from severe trauma, such as burns, sepsis, or multiple trauma. As in the first example, there are numerous products for these patient categories.

The pharmacist can help select these products, because they do differ in amounts of carbohydrate, fat, protein, and fiber. Furthermore, these products differ in taste and consumer acceptability criteria, such as mouth feel and 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 ensure a balanced dietary intake, a complete formula can be recommended. However, if it is intended to help a person regain weight 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 help manage the cost of these products. Composition (oligomeric or polymeric) and form (ready to use vs. powder) influence cost. Generally, the polymeric products are less expensive than the oligomeric products. While powder forms may be less expensive than ready-to-use formulations, there is an indirect cost of labor required in 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 drugs and fluid used in hospitals was administered intravenously (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) (24). 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, saving nurses' time. Furthermore, multiple-drug dosages can be administered, and incompatible drugs can be administered separately (22).

Originally, the disadvantages associated with these mechanical devices included the initial capital investment and extensive in-service education. Furthermore, the influence of infusion pump devices on the delivery of a drug was not fully recognized by clinicians. For example, intrinsic factors (e.g., operating mechanisms, flow accuracy, flow continuity, occlusion detection) and an extrinsic factor (back pressure) may have altered the rate of drug delivery and the therapeutic response of the patient.

Pumps were 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* (PCA) (25). Current research focuses on the influence of drug delivery by these devices and the creation of new technologies (e.g., implantable pumps, pumps with chronobiologic applications, osmotic pressure devices, and open- or closed-loop systems) (25). Today several features are to
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Table 15.8 lists several
parenteral nutrition su
ciated with each.

SmartDose, market
zinische Produktions-u
www.smartdose.com/e

eral features are to be considered in selecting an infusion pump system. Most important is patient safety, then convenience and versatility of the device and cost efficiency.

In terms of enhanced safety, there should be a flow check occlusion alarm system that monitors in-line resistance of incremental back pressure. Also, does the device have a flow rate calculation system that is automatic after the volume and time are selected? Does it protect against inadvertent gravity free flow? Against tampering?

In terms of greater convenience and versatility, does the infusion device possess programmed delivery? Is the system user friendly, easy to understand and use? Does it have an incremental flow rate, and what is the minimum amount that can be delivered incrementally? Some newer infusion devices can deliver 0.1 mL/hour. Does it have an automatic restart feature once an occlusion clears, and can automatic piggybacking be employed to accommodate secondary medications? What is the volume capacity? Some infusion devices can accommodate a range of volumes from 0.1 to 9,999 mL (e.g., Baxter's 6060 Multitherapy Infusion Pump, 0.1–999.9 mL in 0.1-mL increments or 1000–9999 mL in 1-mL increments).

In terms of cost efficiency, can the device be used with standard administration sets? For example, the Baxter Laboratories standard administration sets are compatible with the Flo-Gard 6201 Volumetric Infusion Pump. This eliminates the need for costly disposable sets and reduces the potential for waste.

ALARIS Medical Systems (http://www.alarismed.com/products/infusion_medley.shtml) markets a variety of infusion systems. One of these is the Medley System, which uses modularity, a common user interface, and the Guardrails Safety Software suite of applications, which improve medication safety by using total quality management (TQM) principles for administration at the point of care. Table 15.8 lists several infusion devices used in parenteral nutrition support and features associated with each.

SmartDose, marketed by Pro-Med Medizinische Produktions-und Handels-AG (http://www.smartdose.com/eng/html/pump.shtml),

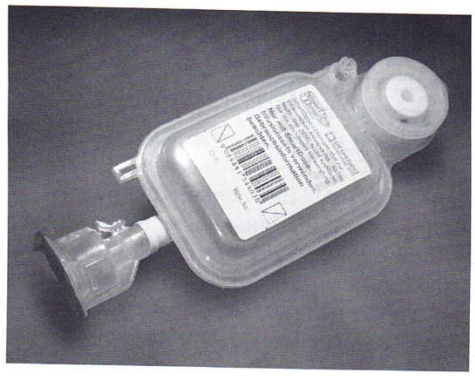


FIGURE 15.38 SmartDose, a portable disposable system for infusion or irrigation therapy. (Courtesy of Pro-Med AG.)

is a portable disposable system for infusion or irrigation therapy that allows the patient a high degree of mobility in a hospital or ambulatory environment (Fig. 15.38). It provides the precision of an electronic pump and the simplicity of an infusion bag. A chemical reaction in the attached power cell creates controlled gas pressure that is applied to dispense the liquid content in an accurate fashion through the dedicated administration set.

Special Considerations Associated With Parenteral Therapy

Look-Alike Products

To prevent mixups in which one drug product is selected in error because of its similarity in appearance to another, storage shelves should be labeled to warn about this possibility. A recent example of a serious medication error occurred when Lupron Depot-Ped 11.25 mg (Leuprolide acetate-TAP), a 1-month gonadotropin-releasing analogue used to treat central precocious puberty, was confused with Lupron Depot 3 Month. The latter is administered every 3 months to women with endometriosis or uterine leiomyomata (fibroids). The product releases its active ingredient over 3 months. Inadvertently, the second product was administered to children and caused them to receive therapy that was too low. It led attending physicians to

TABLE 15.8 SELECTED INFUSION DEVICES USED IN PARENTERAL NUTRITION SUPPORT

PUMP	MANUFACTURER	FEATURES
Breeze Lifecare 175	Abbott	Uses standard Abbott non-cassette gravity tubing. Includes both primary and secondary infusion capability, titration, built-in free-flow protection, adjustable occlusion pressure sensitivity (4 or 8 PSI), alarm history log, and optional flow detector. Air-in-line alarms, proximal and distal occlusion alarms. Indicated for various types of infusion, including parenteral and enteral, TPN, lipids, antibiotics and nitroglycerin therapies.[1]
Colleague 3	Baxter	Micro and macro rate range, basic delivery programming, piggybacking secondary medications, special programming functions for dosing, attachment to a remote nurse call system. A variety of systems exist which enable alert and alarm conditions to be transmitted to a remote location via the communications port on the rear panel assembly of the pump. Auto restart: allows the pump channel to automatically restart if an occlusion is relieved within one minute after detection.[2]
Flo-Gard 6201	Baxter	Flow check occlusion alarm (an in-line resistance display of incremental back pressure), flow rate calculation is automatic after volume and time are selected, slide clamp option offers an additional step to protect against inadvertent gravity free flow, front panel lock-out protects against tampering, automatic restart once occlusion clears, automatic piggybacking of secondary medication, programmed delivery profile allows up to 10 steps, individualizing control of infusion ramping and tapering.[3]
Horizon Nxt	B. Braun	Can deliver fluid from a negative head height (when the I.V. fluid container is lower than the pump), provides clinically accepted volumetric accuracy for all standard I.V. fluids, including blood, lipids and TPN. Profile Delivery mode incorporates a standard ramped delivery regimen, and the Programmable Delivery mode can be set up to sequentially deliver up to nine user-selected volumes of fluid each at a user-selected rate. Both modes are designed for ease of use and can be adapted to home-care settings. Automatically calculates the rate when dose information is entered, or the dose when rate information is entered. Distinct audible and visual alarm signals to indicate KVO, low battery, and actual alarm conditions. alarms: air-in-line, container empty, door open, downstream occlusion, hold time exceeded, low battery, low flow from container, close roller clamp, system error, upstream occlusion.[4]
Sabratek 6060	Baxter	Ambulatory multi-therapy device that can be used for enteral, epidural, subcutaneous, arterial and intravenous applications, using rotary peristaltic operation. It has five different methods of delivery: can be programmed using either milligrams or milliliters, and provides the option of programming using rate (ml/hr.) or time (volume delivered over a specific time period). Memory is indefinite until parameters are changed by the user, and if the pump is stopped during delivery, it will begin at the same point in the infusion when restarted. The pump uses YES/NO response to on-screen questions to facilitate easy programming, also uses a remote bolus cord.[5]

Footnotes

1. http://www.msdistributors.com/biomed/meh/LIFECARE.HTM
2. http://www.ardusmedical.com/products/baxter_colleague.htm
3. http://www.infusingsolutions.com/Assets/FG6201.pdf
4. http://www.ardusmedical.com/products/mcgraw_hor_nxt.htm
5. http://www.ardusmedical.com/products/baxter_6060.htm

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the following:

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

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believe the drug therapy was a failure. One reason for the confusion was that the pharmacy staff inadvertently selected the wrong computer code during order entry, and this was repeated when, after referencing patients' drug profiles for monthly refills, staff continued to select the 3-month dosage form instead of the monthly pediatric dosage form (26).

The manufacturer actually anticipated the problem and placed a picture of either an adult or a child to help discriminate the products. Unfortunately, price stickers were placed directly over the pictures and obscured the visual cues. To compound the problem, the products were taken to the pediatricians' offices, where the nurses administering the product also failed to note the mistake. The mistake might not have been detected except that a parent of one of the children questioned the pharmacy to ask about the increased prescription cost; Lupron Depot 3-Month costs more than Lupron Depot-Ped.

Adsorption of Drugs

Numerous studies have demonstrated that some drugs are adsorbed to the inner lining of intravenous 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 intravenous delivery systems include the following:

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

Pharmacists must be cognizant of this and take appropriate steps to prevent it. The significance of the loss is magnified with drugs that are used in small quantities because a small amount lost to adsorption results in a higher percentage loss of the drug 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 (NTG), for example, should always be prepared in glass and/or a plastic known to be compatible with it. It is adsorbed (40–80% of total dose) to polyvinyl chloride (PVC), a plastic commonly used in administration components and some infusion solution bags and intravenous tubing. Previously, some manufacturers packaged NTG for intravenous use with special non-PVC tubing to avoid loss (<5%) of the drug into the tubing during administration. However, many manufacturers have discontinued supplying NTG IV in the U.S. market. Baxter Healthcare and Abbott Laboratories still manufacture NTG IV. Baxter Healthcare markets nitroglycerin 25, 50, and 100 mg in a glass bottle, 250 mL in 5% dextrose. However, the administration set, including tubing, is sold separately from the medication.

Special high-density polyethylene administration sets are recommended for NTG IV administration. Hard solid plastics, such as polyethylene and polypropylene, generally do not adsorb NTG. The amount of NTG adsorption depends on such factors as concentration, flow rate (e.g., a slow flow rate and long tubing increase the loss of NTG), surface area of the tubing, and contact time with the tubing.

Intravenous NTG should be regulated by automatic infusion equipment (pumps, controllers) to enhance consistent dose administration. However, infusion pumps may fail to occlude the non-PVC infusion sets completely because the non-PVC tubing is stiffer 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 NTG.

Some practitioners have responded by using the PVC tubing with the NTG 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 market non–PVC-containing pump administration sets.

The adsorption of insulin onto glassware and tubing depends on several factors, including concentration of insulin, contact time of insulin with glass and tubing, flow rate of the infusion, and presence of negatively charged proteins (human serum albumin). Plastic intravenous infusion sets have reportedly removed up to 80% of a dose, but 20 to 30% is more common. The percent adsorbed is inversely proportional to the insulin concentration and will take place within 30 to 60 minutes. Because this phenomenon cannot be easily and accurately predicted, it is essential to monitor the patient.

Handling and Disposal of Chemotherapeutic Agents for Cancer

In the 1980s health care personnel became aware of environmental contamination from handling cytotoxic agents. Mutagenic and allergic case reports began to emerge in the literature, and in 1985, in response, 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* (27).

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" (27). However, nearly perfect technique is uncommon and perfection is quite impossible. Thus, institutions that use these hazardous drugs must have structured training and quality assurance programs, and the pharmacist must play a vital role in creating and executing them.

At risk for harm are personnel who handle cytotoxic drugs, and steps should be taken to minimize unnecessary exposure by implementing basic steps and following common sense (28). These basic steps include the following:

1. Using vertical laminar flow hoods or bacteriologic glove boxes for preparation and reconstitution of cytotoxic drugs
2. Wearing protective gloves and mask during product preparation
3. Handling and disposing of cytotoxic drugs centrally using specially designed waste containers and incineration
4. Periodic monitoring of personnel who handle admixtures of cytotoxic drugs (e.g., CBC, blood chemistry screen, differential cell count)
5. Informing personnel handling cytotoxic drugs of the risk to their health
6. 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 solid objects about 3.2 mm in diameter and 8 mm long, prepared by compression and intended to be implanted subcutaneously to provide continuous release of medication over 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. Implantation provides the patient with an economical means of obtaining long-lasting effects (up to many months after a single implantation) and obviates frequent parenteral or oral hormone therapy. The implanted pellet, which may 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 dissolve entirely, the surgically implanted capsules are intended to be removed by surgery after an appropriate amount of time (up to 5 years).

Levonorgestrel Implants

Levonorgestrel implants are a set of six flexible closed capsules of a dimethylsiloxane–methyl vinyl Siloxane copolymer, each containing 36

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arm about 8 to 10 c
They are implanted
15° apart for a total
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TABLE 15.9 EXAM

SOLUTION
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Neomycin and Polymyx Sulfates Solution for Irrigation, USP
Ringer's Irrigation, USP
Sodium Chloride Irrigat USP
Sterile Water for Irrigat USP

mg of the progestin (29). They are found in an insertion kit to facilitate subdermal implantation through a 2-mm incision in the mid upper arm about 8 to 10 cm above the elbow crease. They are implanted in a fanlike 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 μg/day, declining to about 50 μg/day by 9 months, about 35 μg/day by 18 months, and thereafter to about 30 μg/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 blood levels and variation in individual response, blood levels alone are not predictive of the risk of pregnancy in an individual woman (29).

Irrigation and Dialysis Solutions

Solutions for irrigation of body tissues and for dialysis are subject to the same stringent standards as parenteral preparations. The difference is in use. Irrigation and dialysis solutions are not injected into the vein but employed outside of the circulatory system. Because they are generally used in large volumes, they are packaged in large containers, generally of the screw-cap type, which permits rapid pouring. Dialysis solutions generally appear similar to intravenous bags, and irrigation solutions are screw-capped or bagged, so caution is necessary to avoid selecting the wrong product.

Irrigation Solutions

Irrigation solutions are intended to bathe or wash wounds, surgical incisions, or body tissues. Examples are presented in Table 15.9.

TABLE 15.9 EXAMPLES OF IRRIGATION SOLUTIONS

SOLUTION	DESCRIPTION
Acetic Acid Irrigation, USP	0.25% solution applied topically to bladder for irrigation; pH 2.8–3.4, calculated osmolarity 42 mOsm/L; during urologic procedures, washes away blood, surgical debris while maintaining suitable conditions for tissue and permitting unobstructed view.
Neomycin and Polymyxin B Sulfates Solution for Irrigation, USP	Sterile urogenital solution contains 57 mg neomycin sulfate (40 mg neomycin) and polymyxin B sulfate 200,000 U/mL; topical antibacterial in continuous irrigation of bladder; pH 4.5–6; 1 mL added to 1 L 0.9% NaCl, administered via 3-way catheter at 1 L/24 hr (40 mL/hr approx.).
Ringer's Irrigation, USP	NaCl 8.6 g/L, potassium chloride 0.3 g/L, calcium chloride 0.33 g/L in purified water, in same proportions as in Ringer's injection. Sterile and pyrogen free; used topically to irrigate; must be labeled NOT FOR INJECTION; pH 5–7.5, calculated osmolarity 309 mOsm/L.
Sodium Chloride Irrigation, USP	NaCl in water for injection; 77, 154 mEq/L each sodium, chloride in 0.45 and 0.9% solutions, respectively; NaCl irrigation pH 5.3 approx.; 0.45, 0.9% solutions calculated osmolarity 154, 308 mOsm/L, respectively. Employed topically to wash wounds and body cavities where absorption into blood not likely; also employed as enema; for simple evacuation, 150 mL; for colonic flush, 1500 mL may be used.
Sterile Water for Irrigation, USP	Sterilized and suitably packaged. Label designations FOR IRRIGATION ONLY, NOT FOR INJECTION must appear prominently. Must not contain any antimicrobial or other added agent.

Dialysis Solutions

Dialysis is separation of substances 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 lifesaving 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 uses the principles of osmosis and diffusion across the semipermeable peritoneal membrane and includes 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. Intraperitoneal instillation of dialysis solutions containing physiologic concentrations of electrolytes allows for movement of water, toxic substances, and/or metabolites across the membrane in the direction of the concentration gradient, removing 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.

PHARMACEUTICS CASE STUDY

Subjective

You have been asked to prepare progesterone injection 200 mg/mL in sesame oil for a physician's office. How will you formulate it?

Objective

Progesterone is only sparingly soluble in vegetable oils, and cosolvents must be used to obtain the 200 mg/mL concentration. Hormone injections in oil sometimes contain benzyl alcohol and/or benzyl benzoate. Benzyl alcohol, in addition to being a solvent, has preservative and anesthetic properties. Benzyl benzoate can be metabolized to benzyl alcohol and benzoic acid.

Assessment

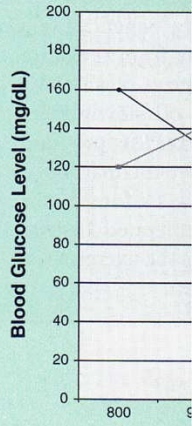
It is apparent that a cosolvent system must be used, possibly consisting of sesame oil, benzyl alcohol, and benzyl benzoate, similar to other hormone injections. The product must be sterilized and suitably packaged.

Plan

After reviewing the literature and the formulations for other hormone in oil injections, you determine that the formula will consist of benzyl alcohol 20%, benzyl benzoate 20%, and sesame oil 60%. The progesterone will be dissolved in the solvent system and be placed in a suitable container for dry heat sterilization. The dry heat sterilization will be validated but will start with 150° C for 1 hour. After sterilization, the injection will be aseptically packaged and labeled.

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Meds: Humulin (
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CLINICAL CASE STUDY

M.N. is an 18 y/o AA female diagnosed with type 1 diabetes mellitus 3 months ago. Today she presents to the clinic for her regular checkup. Yesterday, she had her local pharmacist download her blood glucose (BG) levels for the past month from her home monitor. M.N. takes these to her physician for interpretation. M.N. tells her physician that she is "concerned about some of her BG levels, especially in the morning." She notes that her morning BG levels are usually around 160 mg/dL. She also states that she has been waking up from nightmares around 3 A.M. a few times every week. Three nights ago, after waking up, she checked her BG level at 3 A.M. and her value was 192 mg/dL. She repeated the test to ensure that there was no error with her technique, and her reading was 188 mg/dL. Upon further questioning, the physician determines that M.N.'s knowledge of diabetes is increasing. However, the physician believes that M.N. would benefit from further education on diet and exercise. Because M.N. is newly diagnosed, the physician also wants her to review her insulin injection technique "from start to finish."

Meds: Humulin (NPH/Regular) 70/30 18 U before breakfast and 9 U before dinner.

Develop a pharmaceutical care plan addressing the following problems:
Hyperglycemia at 3:00 A.M., 8:00 A.M.
Nutrition and Exercise
Insulin injection technique

Pharmaceutical Care Plan

S: M.N. is seen in the clinic for a regular checkup by her primary care physician. She is concerned with some BG levels that she has recorded over the past month. She says she has had nightmares a few times every week in that time. M.N. has been compliant with her insulin regimen and has requested additional education on insulin injection technique along with nutrition and exercise information.

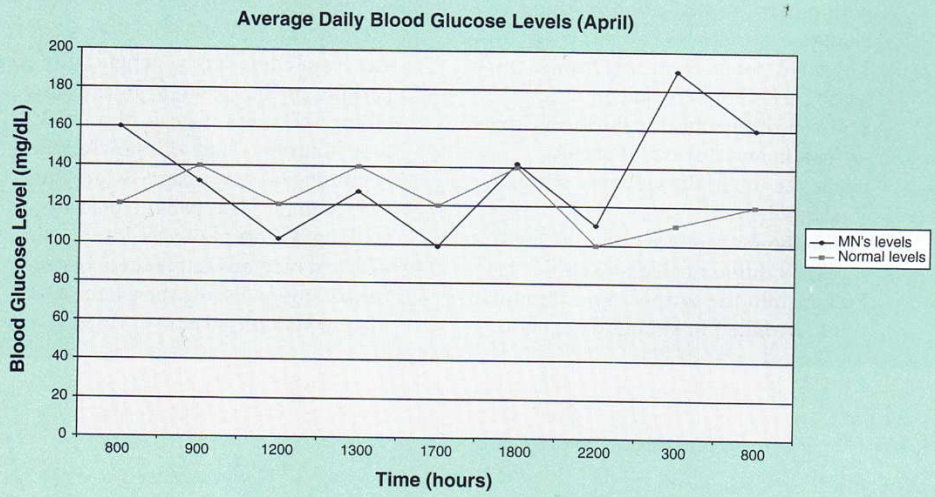
O: Weight: 120 lb (54.5 kg)

See graph for average BG levels for April.

Current medications:

Humulin (NPH/Regular) 70/30 18 U before breakfast and 9 U before dinner.

A: 1. M.N.'s BG is uncontrolled with hyperglycemia at 3:00 A.M. and 8:00 A.M. Hyperglycemia at these times is most likely because the patient is without appropriate insulin coverage throughout the night. M.N. checked her BG



Clinical Case Study cont.

level at 3:00 A.M. after awakening from a nightmare, and the level was found to be elevated. The nightmares are an indication of high BG levels during sleep.

2. M.N. would like to review appropriate insulin injection preparation and administration technique with the pharmacist.
3. M.N. is a newly diagnosed patient and would like further information regarding diet and exercise.

P: 1. Because M.N.'s BG levels at 3:00 A.M. and 8:00 A.M. have been running high, it is appropriate to adjust the dinnertime dose of insulin. With a dinnertime dose of less than 10 U, the UKPDS suggests that the dose of insulin be increased by 1 U (if particular injection dose is more than 10 U, increase by 2 U). Therefore, M.N.'s Humulin 70/30 dose may be increased to 11 U at dinnertime to provide control during the night. M.N. should be instructed to monitor her 8:00 A.M. BG levels and three consecutive 3:00 A.M. BG levels and report these to her physician. If M.N. finds that her BG level after dinner is falling too low, she should increase her meal with one additional carbohydrate exchange.

2. The main points regarding insulin injection technique include in order:
   Roll vial of insulin in palms to warm insulin and disperse it evenly.
   Swipe the top of the vial once with an alcohol swab.
   Swipe the body site for the injection with a different alcohol swab.
   Pull air into the syringe. The amount of air pulled in should be equal to the amount of insulin that will be needed for the injection.
   Insert the needle into the vial using the anticoring technique (demonstrated to the patient) and push the air into the vial.
   While holding onto the vial and the syringe, invert both and remove the desired dose of insulin.
   Remove syringe from vial.
   At injection site, gather a fold of skin.
   Insert needle at 90° angle to injection site.
   Inject insulin.
   Remove needle from skin.
   Discard syringe in designated container for disposal.
3. Refer patient to registered dietitian for tailored meal planning. Some points M.N. should keep in mind:
   Eat three scheduled meals per day. Skipping meals can cause BG to be uncontrolled.
   Watch for serving sizes and control portion sizes.
   Balance diet between carbohydrates, proteins, and fats.
   It is important to monitor BG levels regularly.
   Instruct patient to make exercise a regular part of her day. Explain that exercise can help lower BG levels and any extra effort can be beneficial (e.g. parking further away from the store, taking the stairs instead of an elevator). Caution: Start off slowly when beginning a new exercise program. For example, the patient may begin walking 3 days per week for 20 minutes and increase as tolerated. Instruct the patient to discuss the exercise regimen with a physician.

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