16 Biologics

OBJECTIVES

After reading this chapter, the student will be able to:

1. Define, compare, and contrast the different types of immunity
2. List the standards and control requirements needed for the production of biologics
3. List various sources of valuable information for the proper use, storage, and administration of biologics
4. Compare and contrast the types of biologics for active immunity and their mechanism of action
5. List the sources of biologics for passive immunity
6. Describe the possible adverse drug reactions for biologics based on their mechanism of action, administration, and/or excipients
7. Describe the childhood and adult immunization schedules

The Food and Drug Administration (FDA) refers to immunizing agents as biologics. In an encompassing manner, a biologic is a substance produced by a living source; biologics include antibiotics, hormones, and vitamins, among others. The Advisory Committee on Immunization Practices (ACIP) refers to immunizing agents as *immunobiologics*.

According to the *Code of Federal Regulations*, a biologic product is any virus, therapeutic serum, toxin, antitoxin, or analogous product employed for prevention, treatment, or cure of diseases in humans. The purpose of these products is to help develop immunity in the person receiving them. Immunity is defined as natural or acquired resistance to disease.

Provision of immunity through the use of a biologic is immunization. *Vaccination* is the term more commonly used; it refers to the use of a biologic product (a vaccine) to develop active immunity in the patient.

The benefits of these products is apparent when one considers, for example, that the incidence of poliomyelitis fell dramatically after licensure of the inactivated polio vaccine in 1955 and the oral polio vaccine (OPV) in the 1960s. In the early 1950s, there were more than 20,000 cases of polio each year. By 1960, the number of polio cases had dropped to about 3,000, and by 1979, the last cases (about 10) of indigenously acquired polio in the United States were reported. Similarly, the largest annual number of cases of rubella, or German measles, an acute viral disease affecting people of all ages, occurred in the United States in 1969 (57,686 cases reported). Following rubella vaccine licensure in 1969, the incidence of this disease fell rapidly, and since 1992, the number of reported cases in the United States has been fewer than 500 per year.

TYPES OF IMMUNITY

Before discussing specific biologics, it is important to understand the different types of immunity. There are two main categories of immunity: natural and acquired.

Natural Immunity

Natural, innate, or native immunity depends on factors that are inborn and can be classified as species immunity, racial immunity, and individual immunity.

Species Immunity

In general, cold-blooded animals are not susceptible to diseases common to warm-blooded animals. Humans are not all susceptible to certain diseases of lower animals, such as chicken cholera. However, a number of infections that occur primarily in animals can be transmitted to humans. Among the most important are anthrax (in cattle, sheep, horses), plague (in rodents), and rabies (in cats, dogs, bats, and others). Correspondingly, many human diseases do not naturally occur in animals. Examples include gonorrhea, typhoid fever, influenza, measles, mumps, and poliomyelitis.

Racial Immunity

Human races differ in susceptibility to common infections (e.g., yellow fever, pneumonia, tuberculosis). Factors that determine racial immunity are elusive and not well known. Racial immunity should not be used synonymously or confused with environmental immunity. Environmental immunity may be the result of resistance to infection among individuals in a community resulting from the degree of acquired immunity and other factors (e.g., nutrition, genetic constitution, fatigue). For example, tuberculosis and smallpox wreaked havoc among the Eskimos and American Indians when these groups were first exposed to them. However, with the course of time, the disease tends to become less severe, and it may eventually reach the same level of incidence and severity as among other races with whom the disease has been endemic for a long time.

Individual Immunity

Apart from any specific immunity to a particular infectious agent, individuals vary in the ability to resist common microbiologic diseases. Some individuals have little capacity to resist skin disorders, the common cold, and other familiar diseases. The natural resistance of the same individual may vary from time to time.

General good health, demonstrated by healthy body tissues, skin, and mucous membranes; leukocytes in plentiful supply; and an active and positive lifestyle (i.e., little or no smoking, alcohol, social drug use), provides adequate barriers to bacterial infiltration. Resident bacteria in the gastrointestinal tract and upper respiratory tract, for example, provide resistance to infection. These play a vital role in resisting invasion by other species of microorganisms capable of producing infection. Also, stomach acid is to a degree capable of destroying ingested bacteria. Intestinal enzymes are also known to provide secondary defense mechanisms.

Acquired Immunity

Acquired immunity is a specific immunity that may be active or passive. *T lymphocytes* regulate cell-mediated immunity and are responsible for controlling certain bacterial and viral infections. These lymphocytes are responsible for mediating graft versus host disease, allograft rejection, and delayed hypersensitivity reactions.

T lymphocytes augment the activity of *B lymphocytes*, which are primarily involved with humoral immunity and antibody production. Once an antigen is introduced into the body, *B lymphocytes* differentiate into plasma cells that produce antibodies specific to the invading antigen. These antibodies, known synonymously as immunoglobulins, attach to the invading antigen and cause its destruction by phagocytes and the complement system.

Once exposed to an antigen, the *T* and *B lymphocytes* demonstrate memory that allows them to recognize and respond to a specific antigen when exposed again. The second response is far greater in magnitude to the first immunologic response. This memory of an antigen by the immune system allows sensitized individuals to resist infections on subsequent exposure.

Active Immunity

Active immunity develops in response to antigenic substances in the body. This may

occur by natural means, as by infection, in which case it is termed *naturally acquired active immunity*, or it may develop in response to administration of a specific vaccine or toxoid, in which case it is *artificially acquired active immunity*. In either case, the body builds up its own defense in response to the antigen.

Vaccines are administered primarily for prophylactic action, to develop acquired active immunity. Vaccines may contain living attenuated (weakened) or killed microorganisms or fractions of these microorganisms. Toxoids are bacterial toxins modified and detoxified with moderate heat and chemical treatment so that the antigenic properties remain while the substance is rendered nontoxic. Although toxoids do not cause disease, exposure of immunocompetent persons may result in antibody production that will protect the person against disease caused by the natural toxin. A problem with toxoids is that they produce inadequate immunologic responses when administered alone. Therefore, they are often combined with adjuvants (e.g., alum, aluminum phosphate, aluminum hydroxide) that enhance their antigenicity. These agents do so through their insoluble nature, which acts to keep the immunogens in tissue for longer periods and, thus, prolongs the immune response.

A vaccine composed of killed whole bacteria or viruses or substructures of these is known as an inactivated vaccine. Vaccines that contain live but significantly weakened microorganisms are attenuated vaccines. Both types are capable of producing immunity. However, the attenuated vaccines typically have more antigenicity so are more likely to confer permanent immunity. To maintain adequate antibody titers, inactivated vaccines must be administered again over time.

With live vaccines, caution must be exercised with immunocompromised patients. This group of patients includes those with HIV infection, thymic abnormalities, lymphoma, leukemia, generalized malignancy, or advanced debilitating diseases or who are receiving corticosteroids, alkylating agents, antimetabolites, or radiation chemotherapy. These patients are unable to mount immune responses against even weakened microorganisms. The result could be a disseminated bacterial or viral infection. Thus, inactivated vaccines should be employed for these patients.

Immunization during pregnancy is another concern. Live attenuated vaccines should be avoided for pregnant patients because of the danger of transmission of the microorganism to the fetus. For example, measles, mumps, and rubella (MMR) vaccine should not be administered during pregnancy, and pregnancy should be avoided for 1 month following vaccination with monovalent measles vaccine and 4 weeks following MMR or other rubella-containing vaccines.

Passive Immunity

Passive acquired immunity occurs by introduction of the immunoglobulins produced in another individual (human or animal) into the host, who is not involved in their production. In similar fashion to active acquired immunity, passive acquired immunity can be classified as natural or artificial.

Naturally acquired passive immunity occurs by placental transmission of immunoglobulin gamma (IgG) from the mother to the fetus. Because of the transfer of these immunoglobulins, the infant may have passive immunity to diphtheria, tetanus, measles, mumps, and other infections for the first 4 to 6 months of life.

Several biologic products containing immunoglobulins provide passive immunity. These are limited to provision of temporary prophylaxis to susceptible individuals, for example, during an epidemic, and to supplying immediate immunoglobulins for the treatment of infections and toxicities. Notable in this category are the antivenins for treatment of snakebite (e.g., North American coral snake antivenin) and spiders (e.g., black widow spider antivenin).

The acquired passive immunity provided by immunoglobulins is not long lasting, usually 1 to 2 weeks. Their important feature is that they offer the susceptible patient protection during a critical period of exposure (e.g., the patient exposed to diphtheria). Immunoglobulins do not last long because

their function is to bind to the pathogen as needed. Immunoglobulin is metabolized by the body if not needed for immunologic purposes.

PRODUCTION OF BIOLOGICS

Biologics are produced by manufacturers licensed to do so in accordance with the terms of the federal Public Health Service Act (58 Stat. 682) approved on July 1, 1944, and each product must meet specified standards as administered by the Center for Biologics Evaluation and Research of the FDA (1). Each lot of a licensed biologic is approved for distribution when it has been determined that the lot meets the specific control requirements for that product. Licensing includes approval of a specific series of production steps and in-process control tests as well as end product specifications that must be met lot by lot.

Generally, each lot of a biologic product must pass rigid control requirements before it may be distributed for general use. Provisions generally applicable to biologic products include tests for potency, general safety, sterility, purity, water (residual moisture), pyrogens, identity, and constituent materials. Constituent materials include preservatives, diluents, and adjuvants, which generally should meet compendial standards; extraneous protein in cell-cultured vaccines (which, if other than serum originating, is excluded); and antibiotics other than penicillin added to the production substrate of viral vaccines, for which compendial monographs on antibiotics and antibiotic substances are available. Additional safety tests on live vaccines and certain other items are also required.

Biologics to be administered by injection are packaged and labeled in the same manner as other injections. In addition, the label of a biologic product must include the title or proper name (the name under which the product is licensed under the Public Health Service Act); the name, address, and license number of the manufacturer; the lot number; the expiration date; and the recommended individual dose for multiple-dose containers. The package label also includes the preservative and its amount; the number of containers if more than one; the amount of product in the container; the recommended storage temperature; a statement, if necessary, that freezing is to be avoided; and such other information as FDA regulations may require to ensure safe and effective use of the product.

With few exceptions, most biologics are stored in a refrigerator (2°C to 8°C, or 35°F to 46°F), and freezing is avoided. Besides the biologic substance that is harmed by freezing, the container may be broken due to the expansion of an aqueous vehicle resulting in loss of product. Diluents packaged with biologics should not be frozen. Some products are to be held at specified temperatures during shipment.

The expiration date for biologic products varies with the product and the storage temperatures. Most biologic products have an expiration date of a year or longer after the date of manufacture or issue. The stated date on each lot determines the dating period, which begins on the date of manufacture and beyond which the product cannot be expected to retain the required safety, purity, and potency. The dating period may be comprised of an in-house storage period during which the lot is held under prescribed conditions followed by a period after issue. The individual monographs for biologics usually indicate both, the after-issue time frame for use and (in parentheses) the permissible in-house storage period.

STORAGE, HANDLING, AND SHIPPING OF BIOLOGICS

Biologics are sensitive to extreme temperatures, and exposure to heat or freezing can decrease their potency and dramatically reduce their effectiveness. Poor storage, handling, and shipping conditions for these products not only waste the intrinsic value of the products but waste money as well. Biologics are expensive and can add significantly to one's inventory costs. An inventory of vaccines and other immunologic products can amount to tens of thousands of dollars or more.

A real danger is that if damaged products are administered, the person may get little or none of the intended benefit. The person may not be able to build up immunity and may result in an infection or inadequate protection from the disease.

The overriding theme for the pharmacist in storage, handling, and shipping of biologic products is to maintain the cold chain (2). This implies continuity from the manufacturer's refrigerator to one's pharmacy, clinic, or office to administration. If the cold chain is maintained, the pharmacist can be assured that the quality of the product will not be diminished.

In the pharmacy, there should be a clear understanding of primary and secondary individuals who are responsible for receiving, handling, and shipping these products. A key ingredient is good storage equipment. Whenever possible, separate commercial refrigerators and freezers should be used for these products. For small-volume biologics, a standard refrigerator–freezer should be used. Frost-free freezers should be used because ice buildup interferes with the freezer's ability to maintain very low temperatures. Also, defrosting requires that product be removed to temporary storage.

Refrigerators and freezers cool by convection. Thus, cool air must have room to circulate around the product. Packing the refrigerator too tightly can lead to small incremental elevations in the temperature of the product.

A separate refrigerator dedicated to biologics is preferable to minimize the times the refrigerator door is opened. The World Health Organization recommends that the door not be opened more frequently than four times per day. Also, doors should be closed as quickly as possible after securing the product, and pharmacists should avoid using the inside of the refrigerator door to store product to avoid unacceptable temperature variations. The door shelving can be used to store diluents or bottles of water. This helps provide insulation and a thermal reserve (2).

If a vaccine must be kept outside of the refrigerator for a few minutes, it is advisable to put the product in an insulated container with coolant packs (thermal packs, blue ice packs, chemical packs) from the freezer. Coolant packs should be kept in the freezer and ready for use in shipping. An additional advantage of freezer packs is that they provide extra insulation and cooling power in the freezer in case of an interruption of electric power or outage.

Coolant packs that contain water have about as much cooling capacity as ethylene glycol packs. An easy way to create a coolant pack is to fill a plastic bottle with water and freeze it. It is important, however, that the product not come in direct contact with these coolant packs because the vial contents may freeze and be damaged. A towel or sheet of cardboard may be used to separate the product from the coolant pack (2).

Periodically, it is advisable for the pharmacist to test the temperature of the refrigerator and freezer. The National Immunization Program (NIP) recommends twice daily temperature monitoring and recording. Furthermore, logs of these temperatures should be kept for 3 years. Some adult immunization programs recommend that refrigerator temperature be checked daily and recorded in a log. Refrigerator temperatures should range between 2°C and 8°C, and freezers should stay well below 0°C. Usually, an optimal temperature is – 15°C (5°F).

With respect to personnel, pharmacists should educate and train every person who will handle biologics in good storage and handling procedures. These individuals should understand the importance of reporting any problems or interruptions associated with proper handling and storage guidelines. It is far more important to report a breach in handling and storage than to discount and overlook it intentionally. The use of a mishandled or poorly stored biologic could have devastating consequences on the person who receives it.

Store containers of the same vaccine together. To avoid selecting the wrong product or one having a similar sounding name or packaging, separate the products. A good example of this occurs with pediatric and adult dosage forms (e.g., tetanus–diphtheria

toxoids), which could be confused. Keep them separate. Look-alike packaging as well as sound-alike names can easily confuse any conscientious practitioner.

An online publication describing storage and handling requirements for currently recommended vaccines is available from the Centers for Disease Control and Prevention (CDC). Included in the publication are shipping and storage recommendations for specific vaccines, how to reconstitute them, information about vaccines' shelf life before and after reconstitution, and special handling instructions (3).

Biologics for Active Immunity

Bacterial Vaccines

A vaccine is a suspension of attenuated (live) or inactivated (killed) microorganisms or fractions thereof that are administered to induce immunity and prevent disease. Originally, the organism is grown in a suitable broth medium in a controlled environment of temperature, pH, and oxygen tension. To reduce the potential for hypersensitivity reactions to the finished product, the medium, whenever possible, should consist of chemically defined ingredients.

Following a suitable amount of time for bacterial growth, the culture is processed in two steps. If the vaccine is to be inactivated microorganisms, the organisms are treated with phenol or formaldehyde. Heat and phenol or heat and acetone are employed for the typhoid fever vaccine. Next, the organisms are separated from the medium through centrifugation and suspended in sterile water or 0.9% sodium chloride for injection. If necessary, the preparation may be further purified by several methods, including dialysis and/or additional centrifugation.

A live attenuated vaccine can also be produced by genetic alteration of the pathogenic organisms. This allows the organism to survive and multiply but not produce the disease. Usually, several base pairs of DNA in a key region of the gene structure are eliminated or altered. Thus, the organism is incapable of reverting to its more pathogenic form.

Another way to create a vaccine is to employ purified antigen subunits produced with use of recombinant DNA. With subunit vaccines, the genes that code for the desired antigen are introduced into the nonpathogenic organisms. There is no potential to harm the patient because there is no possibility that a pathogenic organism can be created from only a limited number of components of the original organism. Also, the subunit vaccine can be expected to have a lower incidence of side effects. As an example, the hepatitis B vaccine is produced through recombinant DNA technology by common baker's yeast, into which the gene for the hepatitis B surface antigen (HBsAg) has been inserted.

To date, subunit vaccines have had limited clinical utility because of inability to produce a sufficient, specific immune response. However, alternative biotechnologic strategies have been employed to produce subunit vaccine immunogens and adjuvant-active compounds that can be added to enhance the immune response.

The final vaccine may contain one single immunogen (monovalent), or it may contain multiple immunogens (polyvalent, trivalent) to promote immunity against the same disease state. The final product may also be a mixed vaccine. For example, MMR vaccine is a single product with three immunogens for three viral diseases. A mixed biologic may contain a vaccine and a toxoid in the same product, as with diphtheria, tetanus, and pertussis (DTP). Another example of a mixed biologic is the combination vaccine Pediarix (diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B [recombinant], and inactivated poliovirus vaccine [IPV]) introduced in late 2002.

The strength of a vaccine may be expressed as total number of organisms, total protective units per milliliter or dose, or micrograms of immunogen in each milliliter or in each dose of vaccine.

A current list of vaccines licensed in the United States is posted at www.fda.gov/cber/.

Viral Vaccines

Viruses cannot be grown on inanimate media employed to grow bacteria and so

are propagated on one of several types of animate media. Examples of animate media include embryonic egg, cell cultures of chick embryo, human diploid cell culture, monkey cell culture, skin of living calves, and intact mice.

In similar fashion to vaccine preparation, after growth of the culture, various techniques are employed to separate the virus from the host cell. Purification steps are taken to reduce the incidence of hypersensitivity reactions to animate media or host cells, most notably embryonic egg. The final viral product may contain a single immunogen (monovalent) or multiple immunogens (polyvalent) to elicit immunity against the same disease.

The vaccine may remain as the whole virion or be further chemically processed to split it into a subvirion vaccine, as is the case with the influenza virus vaccine. This virus is prepared yearly with three virus strains. Since 1977, influenza A (H1N1), influenza A (H3N2), and influenza B viruses have circulated globally. Each year's influenza vaccine contains a virus representing each of these three distinct influenza virus groups. The three viruses selected to be included for the 2008 to 2009 season vaccine were selected in February 2008 as the viruses that appeared most likely to be circulating during this influenza season (4). The 2008 to 2009 trivalent vaccine strains are A/Brisbane/59/2007-like (H1N1), A/Brisbane/10/2007-like (H3N2), and B/Florida/4/2006-like viruses. The degree of antigenic match between current influenza vaccine strains and the influenza viruses that are circulating this season will continue to be assessed as more viruses become available for analysis. To date, 91% of influenza A (H1N1) viruses sent to CDC for antigenic characterization were similar to A/Solomon Islands/3/2006, the influenza A (H1N1) component of the 2007 to 2008 influenza vaccine. Although the majority of influenza A (H3N2) and influenza B viruses are not optimally matched, vaccination with the trivalent influenza vaccine continues to be recommended because the vaccine can provide partial protection against related strains and reduce the risk for influenza-related complications and deaths. In addition, communities can experience outbreaks with more than one strain of influenza in a given year.

Strains are usually selected during the preceding February because of scheduling requirements for production, quality control, packaging, distribution, and vaccine administration before the onset of the next influenza season. Sometimes strains mutate and protection is not thorough as was the case for the 2007 to 2008 flu season. When there is a good match between the strains in the vaccine and those in the community, inactivated vaccine is 70% to 90% effective in preventing influenza in adults under 65 years of age.

To prolong stimulation of antibodies, the virion may be adsorbed onto aluminum phosphate, as is the case with rabies vaccine (adsorbed). Typically, viral vaccines are available as lyophilized (freeze-dried) products that require reconstitution prior to administration with the provided diluent. Some inactivated vaccines are available in suspensions for injection.

Belshe et al. (5) reported the effectiveness of a live attenuated, cold-adapted, trivalent influenza virus vaccine that was administered intranasally to more than 1,000 healthy school-aged children. This placebo-controlled trial demonstrated that children receiving the active vaccine had fewer febrile illnesses, including 30% fewer episodes of febrile otitis media, than the placebo group. This was one significant outcome of the study, because otitis media is a recognized complication of influenza in children, and the influenza virus has been isolated from middle ear fluid in children with influenza and middle ear effusion. The incidence of otitis media increases in the 14-day period after influenza virus infection. Furthermore, administration of inactivated influenza virus vaccine has been shown to reduce outbreaks of otitis media in day care centers (6). Thus, if efforts are employed to immunize more day care children, this might ultimately result in lower incidence of otitis media and less need for prescribed antibiotics.

Historically, the influenza vaccine was strongly recommended annually for children

aged 6 months or more with certain risk factors, including but not limited to asthma, cardiac disease, sickle cell disease, HIV, and diabetes. However, as of 2006, all children aged 6 to 59 months, and their household contacts and out-of-home caregivers should be vaccinated against influenza.

In June 2003, the live intranasal influenza virus vaccine (FluMist, Wyeth; MedImmune) was approved for active immunization against influenza A and B viruses in healthy children aged 5 to 17 and adults 18 to 49 years of age. It is the first vaccine approved in the United States for administration as a nasal mist. The introduction of a nasal vaccine has much implication to help overcome barriers to immunization (fear of side effects, the need for yearly immunizations, perception of low vaccine effectiveness). Widespread use of the nasal vaccine in high-risk children may, therefore, be more easily achievable than use of injected vaccines. This would be a very effective way to reduce the incidence of influenza in this population. The only downside is its expense (ranging from $50 to $70 per patient) and that the cold chain, discussed earlier in this chapter, must be maintained to guarantee adequate stability.

The strength of viral vaccines can be provided in tissue culture infectious doses, the quantity of virus estimated to infect 50% of inoculated cultures. Also, micrograms of immunogen, international units, D-antigen units, and plaque-forming units for yellow fever vaccine are employed for these products.

Cancer Vaccines

For more than a century, the role of the immune system and its relationship to cancer has been researched. Recently, however, the immune response is being clinically explored as a mode to prevent and treat cancer. Cancer vaccines in development are intended to increase recognition of cancer cells by the immune system.

This approach to cancer treatment is exciting, as it offers another modality to complement surgery, radiation therapy, and chemotherapy. Another cause for guarded optimism is that the development of these vaccines may play a role in preventing cancer in patients at high risk because of familial diseases.

For the immune system to recognize and kill a tumor cell, immune cells must recognize antigens on the tumor cell as foreign to the body and receive costimulatory signals. Otherwise, tumor cells go undetected by the immune system and proliferate. Thus, a goal of cancer vaccine development is to increase antigen awareness of the immune cells or increase costimulatory signals that induce an immune response.

T cells, lymphokine-activated killer cells, and *natural killer cells* have antitumor activity. Thus, tumor vaccine development is to stimulate these immune cells instead of antibody-producing cells, the operational model used to protect one from an infection. Tumor-killing cells recognize tumor-associated antigens (TAAs) on the surface of the tumor cells. These antigens have peptide fragments that appear on the cell surface either by the cancer cell or taken up by a phagocytic cell.

TAAs fall into one of three categories. These are patient specific, tumor specific, and shared. Antigens unique to a specific patient are patient specific, such as an antigen expressed on the surface of a B-cell malignancy. A tumor-specific TAA is unique to a particular tumor. Most notable is prostate-specific antigen, found in prostate tumors. Shared TAAs are created by tumor cells with a common histology. A notable example of this is the carcinoembryonic antigen on adenocarcinoma cells found in colon, ovarian, and lung tumors.

Four types of cancer vaccines are under investigation, and a thorough explanation of each is beyond the scope of this book. Nonetheless, these types are important. They are autologous, allogeneic, anti-idiotypic, and gene therapy–derived vaccines.

Autologous tumor vaccines are developed from antigenic material procured from the tumor of the patient. Tumor cells are isolated from tissue procured during biopsy or surgery. These cells are killed or attenuated and reinfused into the patient. Typically, to enhance immunogenicity, they are combined with an adjuvant, such as

bacille Calmette-Guérin (BCG) or *C. parvum*. A major problem with this approach is the work and cost associated with the production of vaccine for the individual patient. Also, some tumors escape the immune system because their antigens are not expressed on the tumor surface.

Allogeneic tumor vaccines use the concept of shared or tumor-specific antigens. These vaccines are produced from cell lines that express tumor-specific or shared TAAs. To induce an immune response, either the fragment of the allogeneic tumor cell or the whole cell is injected. The beneficial aspect of this vaccine is that it can be used in a wide population of patients.

Anti-idiotypic vaccines are three-dimensional immunogenic regions on the antibody that binds antigen. Antibodies that bind TAAs are isolated and injected into mice. The resulting antibodies are harvested and used to vaccinate another mouse. The resulting antibodies have a three-dimensional binding site that mimics the original structure of the TAA. These antibodies are combined with an adjuvant and given as a vaccine. Because the anti-idiotypic antibody closely resembles the antigen, these can be used to induce immune responses (cellular, antibody–antigen) to a given antigen.

Gene therapy allows a DNA template to be placed within a cell, transcribed into messenger RNA, and expressed as a costimulatory protein. One can then induce a cell to synthesize this protein as part of its normal function. A gene that encodes for interleukins or other costimulatory proteins can be placed in cells expressing TAAs. This stimulates the immune response. In June 2006, the FDA approved the first quadrivalent human papillomavirus (HPV) (Types 6, 11, 16, 18) recombinant vaccine (Gardasil by Merck). Approximately 70% of cervical cancer is caused by infection with HPV types 16 and 18, and approximately 90% of genital warts are caused by HPV types 6 and 11. As this is a prophylactic measure, at present, this vaccine is only indicated for women 9 to 26 years of age. Subsequently, in September 2008, this vaccine was approved to prevent vulvar and vaginal cancers. To test the vaccine, 15,000 women from earlier cervical cancer studies were evaluated for a 2-year period. In the group which did not receive the vaccine, 10 women developed precancerous vulvar lesions, and nine developed similar vaginal lesions. No women in the Gardasil-treated group developed such lesions.

Clinical trials are being undertaken for cancer vaccines for melanoma, colorectal cancer, renal cell carcinoma, breast and ovarian cancers, prostate cancer, and lung cancer.

Toxoids

In similar fashion to bacterial vaccines, bacteria are propagated, and after the required growth is achieved, the culture is filtered through a sterilizing membrane filter. The filtrate that contains the toxin (exotoxin) is then processed. Processing involves addition of a concentrated salt solution to precipitate the toxin from the filtrate. After the precipitated toxin is washed and dialyzed to purify it, the toxin is detoxified with formaldehyde.

The detoxified toxin (toxoid) may be plain or contain an adjuvant (e.g., alum, aluminum hydroxide, aluminum sulfate). The product may also contain single, multiple, or mixed immunogens (e.g., tetanus and diphtheria toxoids adsorbed for adult use, which contains two toxoids for active immunization against different toxins). A mixed biologic, such as diphtheria and tetanus toxoids and pertussis vaccine adsorbed for pediatric use, has two toxoids and a vaccine in a single-dosage form for active immunization against different toxicities and infection. Their advantage is broad immunization coverage and minimum number of injections.

These mixtures or types of biologics differ from polyvalent products, which are used for different strains of the same toxicity or infection (e.g., influenza virus vaccine, pneumococcal vaccine polyvalent).

The strength of a toxoid is in flocculating (Lf) units (e.g., tetanus toxoid, 4 to 5 Lf U/0.5 mL dose). A flocculating unit is the smallest amount of toxin that flocculates most rapidly one unit of standard antitoxin in a series of mixtures containing fixed amounts of antitoxin and varying amounts of toxin.

Biologics for Passive Immunity

Human Immune Sera and Globulins (Homologous Sera)

Human immune sera, or homologous sera, include immunoglobulin and hyperimmune sera for specific diseases. These contain the specific antibodies obtained from the blood of humans and produced as a result of having had the specific disease or having been immunized against it with a specific biologic product. The source of homologous sera is the pooled plasma of adult donors, either from the general population (for immunoglobulin) or from hyperimmunized donors (for immunoglobulins for specific diseases). Thus, these products confer passive immunity.

The pooled plasma from adult donors must be free of hepatitis B antigen and antibodies to HIV. Processing steps include fractional precipitation (e.g., with cold ethanol), maintaining rigorous control of pH and ionic strength. Further purification takes place with a finished biologic product that contains not <15% and not more than 18% protein. There are of course exceptions (e.g., varicella-zoster immunoglobulins [VZIGs] contain not <10% protein).

These preparations are for intramuscular (IM) injection and should not be administered intravenously. However, immunoglobulin intravenous (3% to 12% protein) and cytomegalovirus immunoglobulin are administered intravenously.

Sera have the greatest value for the treatment of acute disease, although they are also useful in some instances to prevent illness when immediate protection is needed. Immunity resulting from the injection of an immune serum is brief (a few weeks) because the foreign serum and the antibodies it produces are eliminated from the body within a few weeks.

Animal Immune Sera (Heterologous Sera)

Most commonly employed immune sera are prepared by immunization of horses against the specific immunogen (e.g., toxin, venom). After the plasma is harvested, it is separated by fractional precipitation into two components: immunologically active (immunoglobulins) and immunologically inactive (albumins, clotting factors) ones. The immunologically active component is treated with pepsin to remove the complement-activating component of the molecules and render it less immunogenic. Subsequently, the active component is recovered through dialysis and fractional precipitation or centrifugation.

This category of pharmaceuticals includes antitoxins and antivenins. Antitoxins are produced by inoculating horses with increasing doses of the toxoids and exotoxins. After several injections over weeks or months, the animal is bled with adequate safeguards to avoid contamination and the plasma harvested. Antivenins are produced similarly, by inoculating horses with the venom of selected species and harvesting the plasma.

Before using these products, precautions must be taken to ensure the safety of the patient, who may be sensitive to horse protein. Appropriate measures, including a sensitivity test with suitable controls, should be taken to detect any dangerous hypersensitivity.

Table 16.1 lists representative biologics by category. Although the scope of this book does not permit a thorough description of each according to its intended use, adverse effects, and so on, the list demonstrates the wide applicability of these products to produce active or passive immunity, provide prophylaxis, or serve as a diagnostic tool.

ADMINISTRATION AND TOXICITY ASSOCIATED WITH BIOLOGIC PRODUCTS

Table 16.1 lists examples of official biologics, and Table 16.2 lists the composition of some example biologic products.

Biologics must be dispensed in the original container to avoid contamination and deterioration. They are sterile when packaged and are injected by aseptic techniques. A few are administered by mouth.

Traditional vaccines, often constituted by inactivated whole cells, can cause unwanted side effects. Those developed from selected antigens have demonstrated fewer systemic

Table 16.1 EXAMPLES OF OFFICIAL BIOLOGIC PRODUCTS

BIOLOGIC PRODUCT	NATURE OF CONTENTS	ROUTE[a]	USE
Vaccines and Vaccine Combinations			
Anthrax adsorbed	Toxigenic, nonencapsulated strain of *Bacillus anthracis* culture, protective antigens (proteins common to all harmful strains), aluminum hydroxide as adjuvant to enhance antibody response	Subcutaneous	Active immunizing agent
BCG	Attenuated living culture of BCG strain of *Mycobacterium bovis*	Intradermal active immunizing agent from multidose vial	Active immunizing agent
Hepatitis B	Originally, biochemically, biophysically inactivated human HBsAg particles from chronic HBsAg carriers. Now, only recombinant vaccines produced in yeast cells are available in the United States.	IM	Active immunizing agent
Human papillomavirus	Recombinant vaccine from highly purified viruslike particles of capsid protein of HPV types 6, 11, 16, and 18	IM	Active immunizing agent
Influenza virus	Aqueous suspension of inactivated virus from allantoic fluid of infected chick embryo in phosphate-buffered isotonic NaCl injection	IM	Active immunizing agent
Influenza virus	Preservative-free, latex-free, egg-based aqueous solution. Each 0.5 mL contains ~ $1 \times 10^{6.5–7.5}$ tissue culture infectious doses of virus. Egg base provides protein to increase reproducibility of virus.	Intranasal	Active immunizing agent
Measles virus, live	Live attenuated Enders line measles virus from attenuated Edmonston strain in chick embryo cell cultures	SQ	Active immunizing agent
Measles, mumps, rubella virus, live	Propagated in chick embryo (measles, mumps) and in human diploid cell cultures (rubella)	SQ	Active immunizing agent
Measles, mumps, rubella, varicella virus, live	Live, attenuated preparation propagated in chick embryo cell cultures (measles, mumps) and in human fibroblasts (rubella, varicella)	SQ	Active immunizing agent
Measles, rubella virus, live	Measles virus grown on chicken embryo tissue and rubella virus on duck embryo tissue	SQ	Active immunizing agent
Mumps virus, live	Live attenuated Jeryl Lynn (B level) strain of virus propagated in chick embryo tissue	SQ	Active immunizing agent
Pneumococcal, polyvalent	Sterile solution of antigenic capsular polysaccharides from *Streptococcus pneumoniae*. Contains 23 capsular polysaccharide types. Each 0.5-mL dose contains 25 µg of each type of capsule polysaccharide in 0.9% NaCl injection. Also contains phenol or thimerosal preservative	IM, SQ	Active immunizing agent

Table 16.1 EXAMPLES OF OFFICIAL BIOLOGIC PRODUCTS (Continued)

BIOLOGIC PRODUCT	NATURE OF CONTENTS	ROUTE[a]	USE
Pneumococcal 7-valent conjugate	Sterile 0.5-mL-dose solution of saccharides of capsular antigens of *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F individually conjugated to diphtheria CRM197 to form glycoconjugate	IM	Active immunizing agent
Rabies	Inactivated virus from HDCV or RDCV cultures	HDCV, IM, ID; RDCV, IM only	Active immunizing agent
Rubella virus, live	Live rubella (German measles) virus propagated in human diploid (WI-38) cell culture	SQ	Active immunizing agent
Rubella and mumps, live	Rubella virus in human diploid cell culture and mumps virus on chicken embryo tissue	SQ	Active immunizing agent
Smallpox	Dried calf lymph live virus preparation of vaccinia virus	ID	Active immunizing agent
Typhoid	Parenteral form, solution of cell surface Vi polysaccharides extracted from *Salmonella typhi* Ty2 strain; oral form, enteric-coated capsules, lyophilized, live *S. typhi* of attenuated Ty21a strain	SQ or ID; oral	Active immunizing agent
Varicella virus, live	Varicella zoster, Oka/Merck strain, attenuated by multiple passages through cultures of human embryonic lung cell, embryonic guinea pig cell, WI-38 strain of human diploid cell, MRC-5 strain of human diploid cell	SQ	Active immunizing agent
Yellow fever	Dried frozen attenuated strain of living yellow fever virus cultured in living chick embryo, prepared, processed, freeze-dried, and sealed in nitrogen	SQ	Active immunizing agent
Zoster virus, live	Varicella zoster, Oka/Merck strain, attenuated by multiple passages through cultures of human embryonic lung cell, embryonic guinea pig cell, WI-38 strain of human diploid cell, MRC-5 strain of human diploid cell	SQ	Active immunizing agent
Toxoids			
Diphtheria and tetanus, adsorbed	Suspension of purified diphtheria toxoid, tetanus toxoid alum precipitated or adsorbed onto aluminum phosphate	Deep IM	Active immunizing agent
Tetanus	Suspension of formaldehyde-treated tetanus *bacillus* (*C. tetani*)	IM, SQ	Active immunizing agent
Tetanus, adsorbed	Suspension of toxoid alum precipitated or adsorbed onto aluminum phosphate	Deep IM	Active immunizing agent
Tetanus, diphtheria adsorbed for adult use	Suspension of toxoids, alum precipitated or adsorbed onto aluminum phosphate	IM	Active immunizing agent

(*Continued*)

Table 16.1 EXAMPLES OF OFFICIAL BIOLOGIC PRODUCTS (Continued)

BIOLOGIC PRODUCT	NATURE OF CONTENTS	ROUTE[a]	USE
Antitoxins			
Botulism	Solution of refined, concentrated proteins, chiefly globulins, with antitoxin from blood serum or plasma of healthy horses immunized against toxins produced by type A, B, and E strains of *C. botulinum*	IM or IV	Passive immunizing agent
Tetanus	Solution of refined, concentrated proteins, chiefly globulins, with antitoxic antibodies from blood serum or plasma of a healthy animal, usually horse, immunized against tetanus toxoid or toxin. More commonly from pooled human plasma. Lyophilized concentrate, which contains IgG with minimum of 100 IU/mL of antitetanus antibodies. Only selected plasma is used (HIV and HB5 negative).	IM or SQ (prophylactic) or IV (therapeutic)	Passive immunizing agent
Immune Sera			
Cytomegalovirus	IgG antibodies from large number of healthy persons who contributed to plasma pools	IV	Passive for kidney transplant recipients seronegative for CMV who receive kidney from CMV seropositive donor
Immunoglobulin IM	Nonpyrogenic solution of globulins with many antibodies normally in adult human blood prepared by cold alcohol fractionation of pooled plasma from venous blood of at least 1,000 individuals	IM	Passive immunity to hepatitis A and B, measles, varicella zoster, primary immunodeficiency diseases
Immunoglobulin IV	Nonpyrogenic solution of globulins with many antibodies normally in adult human blood prepared by cold alcohol fractionation of pooled plasma from venous blood of at least 1,000 individuals	IV	Primary immunodeficiency diseases, HIV, ITP, bone marrow transplant, beta cell CLL
Rh_o (D) globulin	From plasma or serum of adults with high titer of anti-Rh_o antibody to red blood cell antigen Rh_o (D); contains 10%–18% protein; not <90% IgG. Commercial solutions contain glycine as a stabilizer and thimerosal as a preservative; pH is adjusted with sodium carbonate or NaCl.	IM	Passive immunizing agent
Tetanus immunoglobulin	Solution of globulins derived from blood plasma of adult human donors hyperimmunized with tetanus toxoid	IM	Passive immunizing agent
Miscellaneous Biologic Products			
Antivenin (Crotalidae) polyvalent	Dried frozen solution of specific venom-neutralizing globulins from serum of healthy horses immunized against venoms of four species of pit vipers, *Crotalus atrox*, *C. adamanteus*, C. *durissus terrificus*, and *Bothrops atrox*	IM or IV	Neutralizes venom of crotalids native to the Americas

Table 16.1 EXAMPLES OF OFFICIAL BIOLOGIC PRODUCTS (Continued)

BIOLOGIC PRODUCT	NATURE OF CONTENTS	ROUTE[a]	USE
Candida albicans skin test antigen	From culture filtrate, cells of two strains of *C. albicans*	ID	Detects reduced cellular hypersensitivity, DTH; assesses diminished cellular immunity in HIV
Histoplasmin, USP	Standardized culture filtrates of fungus *Histoplasma capsulatum* grown on liquid synthetic medium	ID	Diagnostic aid (histoplasmosis)
Plasma Protein Fraction, USP	Blood plasma of adult human donors; contains ~ 5% protein, ~ 88% normal human albumin;, 12% *alpha* and *beta* globulins	IV	Blood volume expansion
Tuberculin, USP	Solution of concentrated soluble products of MTB. Old tuberculin, soluble partially purified product of MTB in special liquid medium free of protein (purified protein derivative)	ID	Diagnostic aid (tuberculosis)

[a]The doses to be administered and the schedule of doses vary widely with the patient's age, exposure, previous record of immunizations, and so on.
BCG, bacille Calmette-Guérin; IM, intramuscular; SQ, subcutaneous; HBsAg, hepatitis B surface antigen; HDCV, human diploid cell vaccine; RDCV, rhesus diploid cell vaccine; ID, intradermal; ITP, idiopathic thrombocytopenic purpura; CLL, chronic lymphocytic leukemia; IgG, immunoglobulin gamma; DTH, delayed-type hypersensitivity; MTB, *Mycobacterium tuberculosis*.

side effects. Liposomal delivery has decreased side effects while enhancing the vaccine's effectiveness.

Itching, erythema, pain, and tenderness around the injection site occur with subcutaneous, IM, and intradermal administration. Vaccines that contain adjuvants (e.g., BCG) can cause these adverse effects in addition to induration and ulceration at the site. Low-grade fever, myalgia, and arthralgia have occurred in patients who received a BCG-containing biologic product.

These adverse effects are controlled with the use of over-the-counter analgesic agents. However, before these are used, the patient's drug history should be obtained to ensure that the use of an analgesic is permissible given a patient's health status and other drug therapy.

The foremost adverse effect of concern with immunization is hypersensitivity, most notably anaphylaxis, ranging from pruritus or urticaria to bronchospasm, respiratory distress, laryngeal edema, circulatory collapse, and death. Life-threatening anaphylaxis is a rarity but quite possible. The risk of an anaphylactic reaction is in the range of one for every 600,000 to 6.4 million doses of vaccine distributed (7).

The immunopathologic classification of allergic drug reactions places anaphylactic reactions in type I. In this situation, initial exposure to an antigen results in production of specific IgE antibodies. Upon reexposure, antigen reacts with antibodies bound to the surface of mast cells or basophils, causing the release of histamine and other mediators. Several weeks are required after initial exposure to antigen and sensitization before an anaphylactic reaction can occur. Once sensitized, however, the patient can demonstrate an attack within minutes of reexposure to small amounts of the drug administered by any route.

Because of the rare nature of anaphylactic reactions, it is difficult to determine whether the patient is allergic to the proteins that make up the active antigenic portion of the vaccine or to the excipients (e.g., neomycin, gelatin, aluminum gels). Several viruses that constitute vaccines are grown in animate media, including embryonic egg and cell

Table 16.2 COMPOSITION OF SOME EXAMPLE BIOLOGICAL PRODUCTS

PRODUCT	ACTIVE	VEHICLE	TONICITY AGENT OR PRESERVATIVE	OTHER
Influenza				
Afluria	Influenza virus vaccine suspension, IM Single dose	Sterile water for injection	Sodium chloride	Monobasic sodium phosphate Dibasic sodium phosphate
	Multidose	Sterile water for injection	Sodium chloride Thimerosal	Monobasic potassium phosphate Potassium chloride Calcium chloride
Fluarix	Influenza virus vaccine	Sterile water for injection		Octoxynol-10 A-tocopheryl hydrogen succinate Polysorbate
Flulaval	Influenza virus vaccine		Thimerosal	Residual: Ovalbumin Formaldehyde Sodium deoxycholate
Fluvirin	Influenza virus vaccine Single dose			
	Multidose		Thimerosal	Residual: Ovalbumin Polymyxin Neomycin Beta Propiolactone Nonylphenol ethoxylate
Tetanus Toxoid and Combinations				
Boostrix	Tetanus toxoid Reduced diphtheria toxoid Acellular pertussis vaccine suspension, IM	Sterile water for injection		Aluminum hydroxide Sodium dihydrogen phosphate dihydrate
Infanrix	Diphtheria and tetanus toxoids and acellular pertussis vaccine, adsorbed		Sodium chloride	Aluminum hydroxide Residual: Formaldehyde Polysorbate 80
Kinrix	Diphtheria and tetanus toxoids and acellular pertussis vaccine, adsorbed		Sodium chloride	Aluminum hydroxide Residual: Formaldehyde Polysorbate 80
Pediarix	Diphtheria and tetanus toxoids and acellular pertussis adsorbed Hepatitis B and IPV		Sodium chloride	Aluminum salts Residual: Formaldehyde Polysorbate 80 Neomycin sulfate Polymyxin B

Table 16.2 COMPOSITION OF SOME EXAMPLE BIOLOGICAL PRODUCTS (Continued)

PRODUCT	ACTIVE	VEHICLE	TONICITY AGENT OR PRESERVATIVE	OTHER
Human Papillomavirus				
Cervarix	HPV bivalent vaccine, recombinant	Sterile water for injection		Aluminum hydroxide Sodium dihydrogen phosphate dehydrate
Gardasil	HPV quadrivalent	Sterile water for injection	Sodium chloride	Aluminum hydroxyphosphate sulfate Yeast protein L-histidine Polysorbate 80 Sodium borate
Hepatitis				
Havrix	Hepatitis A vaccine			Aluminum hydroxide Amino acids phosphate-buffered saline Polysorbate 20 Residual: Formalin Neomycin sulfate
Vaqta	Hepatitis A vaccine, inactivated	0.9% Sodium chloride solution		Residual: Bovine albumin Formaldehyde Neomycin pH adjusted with sodium borate
Engerix	Hepatitis B vaccine		Sodium chloride	Aluminum hydroxide Disodium phosphate dehydrate Sodium dihydrogen phosphate dihydrate
Recombivax	Hepatitis B vaccine (recombinant)	Sterile water for injection		Aluminum hydroxyphosphate Residual: Formaldehyde
Twinrix	Hepatitis A and hepatitis B (recombinant vaccine)	Sterile water for injection	Sodium chloride	Aluminum phosphate Aluminum hydroxide Amino acids Phosphate buffer Polysorbate
Haemophilus B				
Pedvaxhib	Haemophilus B conjugate vaccine	0.9% Sodium chloride solution		Aluminum hydroxyphosphate sulfate
Haemophilus B and Hepatitis B				
Comvax	Haemophilus B conjugate and hepatitis B	0.9% Sodium chloride solution		Aluminum hydroxyphosphate sulfate pH adjusted to sodium borate Residual: Formaldehyde

(*Continued*)

Table 16.2 COMPOSITION OF SOME EXAMPLE BIOLOGICAL PRODUCTS (Continued)

PRODUCT	ACTIVE	VEHICLE	TONICITY AGENT OR PRESERVATIVE	OTHER
Rabies Vaccine				
Rabavert	Rabies vaccine			Polygeline Human serum albumin Potassium glutamate Sodium EDTA
Rotavirus				
Rotarix	Rotavirus vaccine, live, oral			Dextran Sorbitol Xanthan Dulbecco's Modified Eagle Medium
Rotateq	Rotavirus vaccine, live, oral, pentavalent			Sucrose Sodium citrate Sodium phosphate monobasic monohydrate Sodium hydroxide Polysorbate 80 Fetal bovine serum
Meningococcal				
Menhibrix	Meningococcal groups C and Y and Haemophilus B tetanus toxoid conjugate vaccine	0.9% Sodium chloride solution		Tris–HCl Sucrose Residual: Formaldehyde
Menveo	Meningococcal oligosaccharide, diphtheria CRM conjugate vaccine	Sterile water for injection		Residual: Formaldehyde
Measles				
M-M-R II	Measles, mumps, and rubella virus vaccine live		Sodium chloride	Sorbitol Sodium phosphate Sucrose hydrolyzed gelatin Recombinant human albumin Fetal bovine serum Neomycin
Proquad	Measles, mumps, rubella, and varicella virus vaccine		Sodium chloride	Sucrose Hydrolyzed gelatin Sorbitol Monosodium-L-glutamate Sodium phosphate dibasic Human albumin Sodium bicarbonate Potassium phosphate monobasic Potassium chloride Potassium phosphate dibasic Residual: Neomycin Bovine calf serum

Table 16.2 COMPOSITION OF SOME EXAMPLE BIOLOGICAL PRODUCTS (Continued)

PRODUCT	ACTIVE	VEHICLE	TONICITY AGENT OR PRESERVATIVE	OTHER
Pneumococcal				
Pneumovax 23	Pneumococcal vaccine polyvalent	0.9% Sodium chloride solution	0.25% Phenol	
Varicella				
Varivax	Varicella virus vaccine live		Sodium chloride	Sucrose Hydrolyzed gelatin Monosodium-L-glutamate Sodium phosphate dibasic Potassium phosphate monobasic Potassium chloride Sodium phosphate monobasic EDTA Neomycin Fetal bovine serum
Zoster				
Zostavax	Zoster vaccine live		Sodium chloride	Sucrose Hydrolyzed porcine gelatin Monosodium-L-glutamate Sodium phosphate dibasic Potassium phosphate monobasic Potassium chloride

cultures of chick embryo. Even though purification techniques decrease dramatically the amount of egg protein in the final product, even picograms or nanograms can elicit a response.

Before a vaccination is administered, it is important that a complete and thorough history of previous allergic reactions be taken. This includes the names of the offending agents and the type of reaction. Also, one should determine how long ago the reaction took place. Not only should one inquire about drugs (e.g., neomycin, gelatin) but also foods (e.g., severe allergy to egg products). It may be necessary for an allergist to perform skin testing to determine whether a patient may demonstrate an immediate type I hypersensitivity reaction to a vaccine.

Even though anaphylactic reactions to immunizations are rare, they can occur. Therefore, at the time of immunization, adequate safeguards, including proper emergency supplies and trained personnel, must be in place to handle such an emergency.

Thimerosal has been used in vaccines as a preservative since the 1930s. It is effective for killing bacteria in several vaccines and for preventing bacterial contamination, especially in opened multidose vials. Previously, several of the vaccines routinely recommended for children in the United States contained thimerosal. In high doses, both forms of organic mercury (methylmercury and ethyl mercury) formed from metabolism of thimerosal can cause neurotoxicity. Definitive information regarding the dose of thimerosal that produces developmental effects in infants is not available. Therefore, in September 1999, the American Academy of Pediatrics (AAP) Committee on Infectious Diseases and Committee on Environmental Health urged government agencies and the pharmaceutical industry to work rapidly toward reducing children's exposure

to mercury from all sources, including vaccines. Specifically, these committees urged rapid elimination of thimerosal in vaccines. Since the end of 2001, all routine pediatric vaccinations contain either no thimerosal or only trace amounts, and it is estimated that the overall vaccine schedule for children now contains 98% less than it used to. The academy also issued guidelines to prevent exposure of women of childbearing age to amounts of mercury that might be toxic to the rapidly developing brain of the fetus, which is much more susceptible to toxicity than the adult brain. It also stated that the specific window of highest susceptibility is not known, but exposure after birth should be associated with less toxicity than in utero exposure.

When vaccines preserved with thimerosal have been administered in recommended doses, some hypersensitivity reactions have been reported, but no other harmful effects have been noted. However, massive overdoses with thimerosal-containing products have resulted in toxicity expressed in the central nervous system, kidneys, and immune system. Thus, as part of an ongoing review of biologic products in response to the FDA Modernization Act of 1997, the FDA determined that infants who would receive thimerosal-containing vaccines at several visits might be exposed to more mercury than recommended by federal guidelines.

Pichichero et al. (8) demonstrated that mercury does not accumulate in children who receive thimerosal-containing vaccines. After administration of such vaccines, mercury was measured in the urine, blood, and stool samples of 40 term infants <6 months old and in 21 control infants who received thimerosal-containing vaccines. The authors concluded from the data at 2 months and at 6 months of age that the amounts of mercury in the blood of infants receiving these vaccines are well below concentrations of mercury associated with toxicity. Thus, the conclusion was that thimerosal in these vaccines poses little risk to term infants, but should not be administered at birth to very low birth weight premature infants.

The AAP also recommended that the benefits and risks of thimerosal-containing vaccines be discussed with parents. It emphasized that the larger risk of not vaccinating the child (e.g., more than 20% will develop pneumonia) far outweigh any known risk of exposure to a thimerosal-containing vaccine. Infants and children who have received vaccines preserved with thimerosal do not need to have blood, urine, or hair tested for mercury because the concentrations of mercury would be quite low and would not require treatment.

All infants need protection against debilitating and potentially harmful childhood diseases as well as consequences from the vaccinations. One concern has been the development of autism in some infants who were administered the MMR vaccination. In a study attempting to resolve the question, Madsen et al. (9) identified more than 537,000 children in Denmark from 1991 to 1998, 82% of whom had received the MMR vaccine. The scientists determined that the relative risk of autistic disorders among vaccinated children was 8% less than among unvaccinated children, not statistically significant. Furthermore, the risk of other autistic spectrum disorders was found to be 17% lower with vaccination, statistically equivalent to the risk of unvaccinated children. In addition, no relationship was identified between the infants' ages at the time of vaccination, time since vaccination, or date of vaccination and the development of the autistic disorder. This study on the possible link between autism and the MMR vaccine should have allayed the fears of parents, and pharmacists have been endeavoring to educate them on this matter as well as the thimerosal-containing vaccinations. However, concern persists even though two additional hypotheses have emerged recently concerning environmental exposure like vaccines might cause autism. In addition to the thimerosal hypothesis, putative association has centered on the MMR vaccine and the large number of vaccines administered. Gerber and Offit (10) discussed the genesis of each theory and reviewed relevant epidemiological evidence. Suffice it to say,

20 epidemiological studies reviewed demonstrated that neither thimerosal nor MMR vaccine causes autism. In addition, Tozzi et al. (11) compared the neuropsychological performance 10 years after vaccination in two groups of children exposed randomly to varying amounts of thimerosal through immunization. There was no conclusive evidence that thimerosal had an effect on the neuropsychological development of the children, and an association between thimerosal exposure through vaccination in infancy and eventual neuropsychological deficits was unlikely or clinically negligible.

Typically, IM injection is the preferred route of administration. The vastus lateralis muscle of the thigh is the preferred site for injection for infants up to 12 to 18 months of age. The deltoid muscle of the shoulder is preferred for children older than 18 months of age. Needle overpenetration of the IM injection into the bone or periosteum can cause pain and/or damage. Further, it can cause the needle to detach from the syringe. For vaccination into the thigh muscle, a 7/8-inch or longer needle is used for all children aged 6 years or younger. For vaccination into the shoulder, needle lengths ranging from ½ inch to 7/8-1 inch are recommended depending upon the weight of the child (12).

Given their ability to affect complex processes in the body, biological products including vaccines have a higher likelihood of adverse effects than traditional or chemical agents. Nearly one third of boxed warnings for biological pharmaceuticals approved by the FDA from January 1995 through 2007 have been added within 2 years of the product's availability on the market (13). Thus, it is important for pharmacists to participate in extensive adverse event monitoring of new products.

Influenza continues to be a major cause of morbidity and mortality in the United States. The U.S. Public Health Service has targeted elimination of HIB in children <5 years of age. It is characterized by an abrupt onset of fever, myalgia, headache, severe malaise, cough, sore throat, and rhinitis. Although it resolves within a few days, it can exacerbate chronic conditions (e.g., asthma, diabetes mellitus) and lead to secondary bacterial pneumonia. The ACIP makes recommendations on a yearly basis concerning the use and composition of the influenza virus vaccine to children aged 6 months through 18 years. But in spite of efforts to vaccinate persons at high risk, the annual rate of influenza may reach as high as 40% in children, far above the 10% to 20% encountered in the general population.

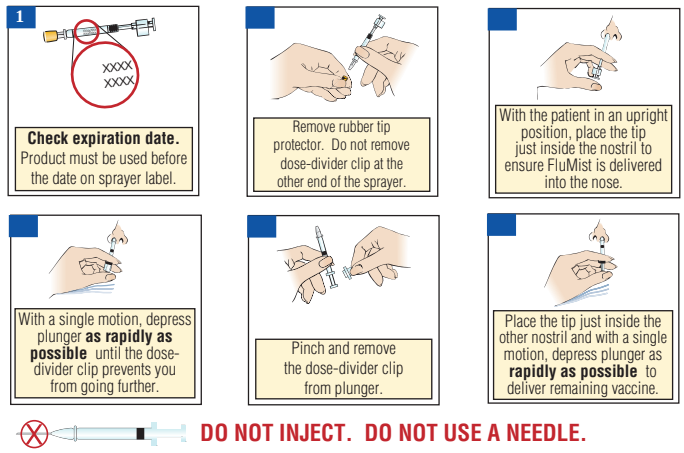
Influenza

Typically, the vaccine is administered parenterally, and it causes concern among parents over the threat of adverse reactions. As mentioned earlier, in June 2003, the first intranasal live attenuated influenza virus (LAIV) vaccine, FluMist, was approved for clinical use in the United States. However, its use was originally restricted to healthy children aged 5 to 17 and adults aged 18 to 49. For healthy individuals aged 5 to 49, LAIV is an acceptable alternative to the IM trivalent inactivated influenza vaccine (TIV). At that time, the FDA's Vaccines and Related Biological Products Advisory Committee determined that the vaccine was not safe for patients under age 5 due to concerns over increased rates of asthma within 6 weeks of vaccination. In a randomized clinical trial, FluMist and TIV were compared among children aged 6 to 59 months (14). Excluded children were those with medically diagnosed or treated wheezing within 42 days before enrollment, or a history of severe asthma. FluMist demonstrated a 55% greater efficacy compared with TIV in preventing culture-confirmed influenza illness.

Subsequently, on October 24, 2007, the ACIP recommended that either the LAIV or TIV can be used to vaccinate healthy nonpregnant persons aged 2 to 49 years. Healthy persons were defined as those who do not have an underlying medical condition that predisposes them to influenza complications. For patients 50 years of age and older, the safe and effective use of FluMist has not been established. Hence, it is restricted from use in this patient population. When

considering the use of the LAIV in children aged 2 to 4 years, health care providers should consult the medical record, when available, to identify children in this age group with recurrent wheezing that might indicate asthma. Parents should also be asked, "In the past 12 months, has a health care provider ever told you that your child had wheezing or asthma?" Children whose parents respond "yes" to the question or demonstrate an asthmatic or wheezing episode noted in the medical record within the last 12 months should not receive FluMist, and the injective TIV should be administered instead.

FluMist must be used cautiously and never administered parenterally. Patients with a history of anaphylactic reactions to eggs should not generally receive this vaccine. Children and adolescents receiving chronic aspirin therapy, because of the risk of Reye syndrome, and patients with a history of Guillain-Barré syndrome should not receive FluMist. Pregnant women should not receive FluMist. Whenever the nasal vaccine is administered, epinephrine injection should be available in case of an anaphylactic reaction. The most common adverse effects encountered with FluMist are nasal congestion, runny nose (45%), sore throat (28%), cough (14%), and chills (9%). Serious adverse events occurred at similar rates in healthy children aged 60 to 71 months receiving FluMist and those receiving the placebo dosage form. It is important that suspected adverse events be reported by telephone to the VAERS (1-800-822-7967). Three other changes in the use of FluMist and its 2007 to 2008 formulation should be noted: the amount of vaccine administered, the temperature at which FluMist is shipped and stored after delivery to the end user, and the minimum interval between doses have changed compared with the 2006 to 2007 influenza-season formulation. FluMist is now supplied in a prefilled, single-use sprayer containing 0.2 mL of vaccine instead of the previous 0.5-mL dose. Those administering the FluMist should spray 0.1 mL (i.e., one half of the total sprayer contents) into the first nostril while the recipient is in the upright position. The attached dose-divider clip should then be removed from the sprayer and the second half of the dose administered into the second nostril (Fig. 16.1). Previously, FluMist was shipped and stored frozen. It is now approved to be shipped to end users at 35°F to 46°F (2°C to 8°C). The product should be stored within this temperature range upon receipt and up to the time the expiration date



Note: Active inhalation (i.e., sniffing) is not required by the patient during FluMist administration

Figure 16.1 Instructions for intranasal administration of FluMist, live attenuated influenza vaccine. (Courtesy of MedImmune, LLC.)

is reached. Lastly, the recommended interval from the first to the second dose in children requiring two doses has changed from a minimum of 6 weeks to a minimum of 4 weeks, the same interval recommended between doses for TIV.

Because FluMist is a live vaccine, IM inactivated vaccine is preferred for health care workers and for family members and other close contacts of immunosuppressed patients. The package insert advises FluMist recipients to avoid close contact (e.g., within the same household) with any immunocompromised patients for at least 21 days.

Children aged 6 to 23 months are particularly susceptible to the risk of influenza-related hospitalizations, whereas those aged 24 to 59 months are at increased risk of influenza-related clinic and emergency room visits. Thus, the vaccination of children in these age groups is encouraged when feasible. ACIP has indicated that annual influenza vaccine will be recommended for children aged 6 to 59 months as well as their household contacts and out-of-home caregivers. In January 2009, the CDC recommended that influenza vaccine be administered on an annual basis to children aged 6 months through 18 years of age. Influenza vaccination is recommended annually for children over 6 months with certain risk factors (e.g., asthma, cardiac disease, sickle cell disease, HIV, diabetes, household members in groups at high risk) and can be administered to all others wishing to obtain immunity. Children <12 years old should receive vaccine in a dosage appropriate for their age, that is, 0.25 mL for ages 6 to 35 months and 0.5 mL for ages 3 years and older. Children <9 years old who are receiving influenza vaccine for the first time should receive two doses separated by at least 4 weeks. Two doses separated by at least 4 weeks should also be administered to those children <9 years old who were vaccinated for the first time last season and received only one dose.

A new catch-up immunization schedule for children and adolescents who start vaccinations late or who are more than 1 month behind has been published by the CDC (15). Minimum ages and minimum intervals between dosages are provided for each of the routinely recommended childhood and adolescent vaccines. The schedules are divided into two distinct age groupings, ages 4 months to 6 years and ages 7 to 18 years.

Toxins

Botulinum toxin type A (i.e., Botox) is indicated to treat axillary hyperhidrosis; cervical dystonia (CD), that is, to decrease the severity of abnormal head position and neck pain associated with CD; and strabismus and blepharospasm associated with dystonia. Botulinum toxin type A (i.e., Botox Cosmetic) is only indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugators and/or procerus muscle activity, that is, facial frown lines, in adult patients ≤65 years of age (16).

Botulinum toxin type A is available as a powder for injection in a single-use vial. Unopened vials are to be stored in a refrigerator (2°C to 8°C) for up to 24 months. It is to be administered within 4 hours of reconstitution and during this time period, must be stored in a refrigerator. The reconstituted injection should appear clear, colorless, and without particulate matter. Prior to injection, the vacuum-dried botulinum toxin type A is reconstituted with sterile normal saline without a preservative; 0.9% w/v sodium chloride injection is the recommended diluent.

As an example, for glabellar line injection, using Botox Cosmetic, a 21-gauge needle and an appropriately sized syringe are used to draw up a total of 2.5 mL of 0.9% sterile saline solution without preservative. The needle is inserted at a 45-degree angle, and the diluent is slowly injected into the botulinum toxin A (cosmetic) vial. The vial is discarded if a vacuum does not pull the diluent into the vial. The vial is gently rotated, and the date and time of the reconstitution are recorded on the label space. Then, at least 0.5 mL of the properly reconstituted toxin is

drawn up into the sterile syringe, preferably a tuberculin syringe, expelling air bubbles in the syringe barrel. The needle used for reconstitution is removed, and a 30-gauge needle is attached, and the concentration will be 4 U/0.1 mL and a total dose of 20 U in 0.5 mL. The duration of activity of botulinum toxin type A cosmetic for glabellar lines is approximately 3 to 4 months.

The safe and effective use of botulinum toxin type A depends upon the proper product storage, selection of the correct dose, proper reconstitution, and proper administration. Physicians administering botulinum toxin type A must have a clear understanding of the relevant neuromuscular or orbital anatomy of the area involved and any alterations to the anatomy caused by prior surgical procedures.

Botulinum toxin type A must not be confused with botulinum toxin type B. Botulinum toxin type B is a preservative-free injectable solution, that is, 5,000 U/mL. Type B is also indicated for CD. The clinical doses of botulinum toxin are not interchangeable between products.

RESPONDING TO BIOTERRORISM

In the wake of the events of September 11, 2001 (9/11), awareness of the necessity for vigilance to illness patterns and diagnostic clues that might indicate an unusual infectious disease outbreak heightened. Pharmacists and allied health professionals were asked to report any indication of suspicious symptoms to local and state health departments. Evidence of intentional release of biologic agents includes infection in these groups: (*a*) people in the same location with symptoms that suggest an infectious disease outbreak (e.g., unexplained febrile illness associated with sepsis, pneumonia, respiratory failure, rash, or botulism-like syndrome with flaccid muscle paralysis), (*b*) age groups not normally associated with the disease in question, and (*c*) numerous cases of acute flaccid paralysis with prominent bulbar palsies that suggest the release of botulinum toxin.

Pharmacists are also encouraged to participate in their community's disaster preparedness efforts. The pharmacist can bring an important and unique perspective to determining and preparing for health care needs during times of natural disasters or manmade crises. The American Pharmacists Association has attempted to assist involved pharmacists by creating a National Pharmacists Response Team. The 10 teams will assist communities with chemoprophylaxis or vaccinations during times of need. Interested pharmacists can apply for the team online at www.aphanet.org/pharmcare/NPRTform.pdf.

After 9/11, the news media concentrated on the threat of an anthrax outbreak without realizing there were other more prominent diseases with greater potential harm to the public. Those listed by the CDC as the biggest biologic threats in addition to anthrax included smallpox and pneumonic plague. Other agents of concern include *Clostridium botulinum* toxin (botulism), *Francisella tularensis* (i.e., tularemia), and hemorrhagic fevers.

Smallpox, caused by variola virus, has initial symptoms that include high fever, fatigue, headache, and backaches. These symptoms are followed by a rash. While most patients recover, up to 30% of cases result in death. This disease is spread by face-to-face contact. Routine vaccination against smallpox ended in 1972, so the level of immunity among persons vaccinated up until this time is unknown. Therefore, all individuals are considered susceptible. In 2002, after evaluating the risk of a bioterrorist attack and the adverse effects of the smallpox vaccine (e.g., lymph node swelling, rash, fever, scarring, severe skin reactions, encephalitis), the ACIP concluded that the risks outweighed the benefits and recommended that the general public not be inoculated against smallpox. It recommended that vaccinations be offered to a total of about 15,000 health care workers around the country who would be designated to investigate smallpox cases and provide direct care at designated hospitals.

In an attempt to determine whether more smallpox vaccines could be made available to the general population given supply questions, a recent study was conducted by the National Institute of Allergy and Infectious Disease (NIAID) (17). The study consisted of 680 adults <32 years of age who were never vaccinated for smallpox and who were assigned to three treatment groups. They received vaccine that was undiluted, diluted 1:5, or diluted 1:10 (18). The initial vaccination was successful in 97.8% of all three groups. There were no significant differences in the rate of vesicle formation (the end point demonstrating success of the vaccine) over the range of titers tested. When followed up with a second vaccination, the researchers demonstrated that the two dilutions were both effective against smallpox. The implication was that the 1:10 dilution could protect 10 times as many persons as would be protected by the administration of the undiluted vaccine.

Botulism is a muscle-paralyzing disease caused by the toxin produced by *C. botulinum*. Food-borne botulism is a public health emergency because the contaminated food may still be available to other people. This form of botulism occurs when the preformed toxin is ingested in contaminated food and causes illness within 6 hours to 2 weeks. Symptoms include double vision, blurred vision, drooping eyelids, slurred speech, difficulty swallowing, dry mouth, and muscle weakness that leads to paralysis of the breathing muscles. Botulism is not communicable from one person to the next.

Pneumonic plague occurs when *Yersinia pestis* infects the lung. The initial symptoms of this illness include fever, headache, weakness, and cough with a bloody or watery sputum. This disease progresses over 2 to 4 days and may cause septic shock. If treatment is not initiated, the result is death. This disease is communicable with face-to-face contact with the infected person. Early treatment with antibiotics (e.g., tetracycline, streptomycin, chloramphenicol) is imperative. There is no vaccine against this disease.

Anthrax has three forms: cutaneous (skin surface is exposed to anthrax particles and skin lesions develop), gastrointestinal (particles are ingested), and inhalation (often fatal). Cutaneous anthrax demonstrates typically on the arms or hands as a swelling of the skin that develops into a central area of ulceration or a depression, and then a dark, blackish-brown scab forms over the area. This manifestation of anthrax can be painless, and a fever may be present. Gastrointestinal anthrax is characterized by an acute inflammation of the intestines, loss of appetite, vomiting, and pain. This is followed by a bout of abdominal pain, vomiting of blood, and severe diarrhea. Initial symptoms of inhalation anthrax resemble the common cold and within a few days, progress to severe respiratory problems and shock.

Anthrax cannot be transmitted from one person to another. Treatment is with antibiotics (e.g., penicillin, doxycycline, fluoroquinolones), but only those exposed to this disease should be treated. Initially, with the anthrax scare after 9/11, prescriptions for Cipro, a fluoroquinolone, increased as concerned individuals were stockpiling to protect themselves and their families from the threat of anthrax. This was not a good practice because the drug should be used only by patients exposed to the disease and because storage conditions and validation of expiration dates cannot be ensured.

DIAGNOSTIC SKIN ANTIGENS

It may be necessary to use antigens in vivo as diagnostic tools. Typically, these are injected intradermally and the site inspected for development of a hypersensitivity reaction. A positive reaction is determined by the extent of induration (in millimeters) and degree of reaction, from slight induration to vesiculation and necrosis. These signs demonstrate sensitivity to the antigen and the presence of antibodies due to present or past infection with the particular organism.

The number of diagnostic skin biologics is relatively small. In the late 1970s, many were removed from the market as a result of the recommendations of the FDA panel on

PHARMACEUTICS CASE STUDY

SUBJECTIVE INFORMATION

You are in charge of providing a vaccine for a statewide program to vaccinate a select population of patients at 10 sites throughout the state. The vaccine will go to about 10,000 patients. What will you recommend to the organizing committee to ensure that the vaccine arrives intact, stable, and active?

OBJECTIVE INFORMATION

The vaccine is a lyophilized vaccine that must be stored in a freezer until it is reconstituted with sterile water for injection and administered. After reconstitution, it is stable for only 1 hour. Prior to reconstitution, it must remain in frozen, and if allowed to reach room temperature prior to reconstitution, it must be discarded after 3 hours.

ASSESSMENT

Of the 10 sites for administration, 2 are within 50 miles, 2 more within 100 miles, 3 more within 150 miles, and 3 within approximately 225 miles of your facility.

PLAN

The vaccine will be ordered to arrive at your facility, shipped overnight from the manufacturer with sufficient dry ice to keep it frozen, the week before it is to be shipped to the vaccination sites. On Monday of the week of the vaccinations, the vaccines will be packaged in sufficient dry ice and shipped overnight to arrive at each of the 10 sites the next morning (Tuesday). Upon arrival, the vaccine will be placed in freezers until used. The vaccinations can be scheduled for Wednesday through Friday of that week; this will minimize storage and potential handling problems of the vaccine.

Review of Skin Antigens (19). Specifically, the panel questioned the reliability of skin test antigens for trichinosis, lymphogranuloma venereum, and mumps and recommended that these be withdrawn from the market and not licensed.

Some diagnostic skin antigens are featured in Table 16.1. One of the more recent in vivo diagnostic biologics, *Candida albicans* skin test antigen, is useful in the assessment of diminished cellular immunity in persons infected with HIV. Because HIV infection can modify the delayed-type hypersensitivity (DTH) response to tuberculin, it is advisable to skin test HIV-infected patients at high risk for tuberculosis with antigens in addition to tuberculin, to assess their competency to react to tuberculin. Responses to DTH antigens also have prognostic value in patients with cancer.

The Multiple Skin Test Antigens (Multitest CMI, Merieux) is a skin test for multiple antigens consisting of a disposable applicator with eight sterile heads preloaded with seven delayed hypersensitivity skin test antigens and a glycerin negative control for percutaneous administration. The seven antigens are tetanus toxoid antigen, diphtheria toxoid antigen, *streptococcus* antigen, old tuberculin, *Candida* antigen, trichophyton antigen, and *Proteus* antigen. The intent of this multiple test is to detect anergy (lack of response to antigens) through delayed hypersensitivity skin testing.

CLINICAL CASE STUDY

PHARMACEUTICS CLINICAL CASE STUDY

Vaccines are antigenic substances administered for prophylactic purposes to achieve active immunity. The body's response helps to build up its own immune defenses. Vaccines may be living, attenuated, or killed microorganisms or fractions of microorganisms. They may also be a toxoid, a bacterial toxin that is modified and detoxified by use of moderate heat and chemical treatment. The end result of the processing is considered nontoxic, although the antigenic properties remain. Children and adults are vaccinated, and immunization schedules have been developed for both groups. For example, the pediatric immunization schedule includes 20 immunizations that are administered before the person is 2 years of age.

PHARMACEUTICAL CARE PLAN

S: J.C. is an 8-week-old female. Her mother brought J.C. to the emergency department at 3:00 PM. J.C. had been restless and crying inconsolably for the past 4 hours. J.C. was given her 2-month immunization of Pediarix yesterday by her pediatrician. Her mother took a rectal temperature today at 2:00 PM and found it to be elevated. J.C. has also had one seizure while in the emergency department.

O: Age, 8 weeks

Temperature (rectal) at 2:00 PM, 101°F per mother

Currently, 105°F in ER

A: The patient is reacting to the immunization Pediarix, a combination of diphtheria and tetanus toxoids and acellular pertussis adsorbed hepatitis B (recombinant) and IPV.

J.C. needs these immunizations to protect against many disease states. Diphtheria is an acute toxin-mediated infectious disease caused by toxigenic strains of *Corynebacterium diphtheriae*. Tetanus is a condition of neuromuscular dysfunction as a result of a potent exotoxin released from *Clostridium tetani*. Pertussis, or whooping cough, is a respiratory tract condition caused by *Bordetella pertussis*. Hepatitis B is a condition that affects the liver. Poliomyelitis is a highly contagious disease that can cause paralysis.

J.C. is most likely reacting to the acellular pertussis adsorbed component of Pediarix based on her presenting symptoms of fever above 105°F within 48 hours of Pediarix administration, inconsolable crying for longer than 3 hours within 48 hours of Pediarix administration, and seizure (with or without fever) within 3 days of Pediarix administration.

P: Because J.C. has had a reaction to the pertussis component, she may no longer be a candidate for immunization with Pediarix. Subsequent pertussis vaccinations must be withheld. Her 4- and 6-month immunizations will have to be individual injections of diphtheria and tetanus toxoid, hepatitis B vaccine, and IPV.

APPLYING THE PRINCIPLES AND CONCEPTS

Group Activities

1. Differentiate between currently available monovalent and polyvalent biological products.
2. Role-play a scenario between a health care professional and a parent in communicating the benefits versus risks of a child receiving a thimerosal-containing vaccine.
3. Compare and contrast the different methods for creating each type of biological product.
4. Create a flowchart for a patient to navigate a mass immunization event utilizing the information provided for immunizations from the Centers for Disease Control's website (www.cdc.gov).

Individual Activities

1. List vaccination resources: Health care providers can refer patients and caregivers to regarding scheduled vaccines for adults and children.
2. Define and explain the term "cold chain" as it relates to the storage, handling, and shipping of biologics.
3. Describe the different methods of inducing immunity via bacterial vaccines.
4. List the required components of maintaining permanent vaccination records.
5. Compare and contrast the different types of oncological vaccinations.

List the various populations who should receive an influenza vaccination and the timing of the vaccination. List those patient types in whom this vaccine is contraindicated.

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17 Special Solutions and Suspensions

OBJECTIVES

After reading this chapter, the student will be able to:

1. Describe ophthalmic, nasal, and inhalation drug delivery
2. List drugs that are typically administered by each of these drug delivery methods
3. Explain the advantages/disadvantages of using one of these drug delivery methods over oral administration
4. Describe the use of the various pharmaceutical adjuvants, which are employed in the formulation of these dosage forms
5. Differentiate between the various types of contact lens products and appropriate care products, which are employed for each
6. Explain the proper administration of each of these drug delivery systems
7. Explain how patients can misuse/abuse these products intentionally or unintentionally

Pharmaceutical dosage forms and drug delivery systems applied topically to the eye, nose, or ear can include solutions, suspensions, gels, ointments, and drug-impregnated inserts. This chapter builds on the general considerations of solutions and suspensions presented in Chapters 13 and 14 by describing additional requirements of these dosage forms when designed specifically for ophthalmic, nasal, or otic use.

OPHTHALMIC DRUG DELIVERY

Pharmaceutical preparations are applied topically to the eye to treat surface or intraocular conditions, including bacterial, fungal, and viral infections of the eye or eyelids; allergic or infectious conjunctivitis or inflammation; elevated intraocular pressure and glaucoma; and dry eye due to inadequate production of fluids bathing the eye. In treating certain ophthalmic conditions, such as glaucoma, both systemic drug use and topical treatments may be employed.

The normal volume of tear fluid in the cul-de-sac of the human eye is about 7 to 8 µL (1–4). An eye that does not blink can accommodate a maximum of about 30 µL of fluid, but, when blinked, can retain only about 10 µL (2). Because the capacity of the eye to retain liquid and semisolid preparations is limited, topical applications are administered in small amounts, liquids dropwise, and ointments as a thin ribbon applied to the margin of the eyelid. Larger volumes of liquid preparations may be used to flush or bathe the eye.

Excessive liquids, both normally produced and externally delivered, rapidly drain from the eye. A single drop of an ophthalmic solution or suspension measures about 50 µL (based on 20 drops/mL), so much of an administered drop may be lost. The optimal volume to administer, based on eye capacity, is 5 to 10 µL (1). Microliter-dosing medication

droppers are not generally available for personal use; consequently, loss of instilled medication using standard eye droppers is a common occurrence. The average dropper delivers about 25 to 50 µL/drop.

Because of the dynamics of the lacrimal system, the retention time of an ophthalmic solution on the eye surface is short, and the amount of drug absorbed is usually only a small fraction of the quantity administered. For example, following administration of pilocarpine ophthalmic solution, the solution is flushed from the precorneal area within 1 to 2 minutes, resulting in the ocular absorption of <1% of the administered dose (5,6). This necessitates repeated administration of the solution. Decreased frequency of dosing, increased ocular retention time, and greater bioavailability are achieved by formulations that extend corneal contact time, such as gel systems, liposomes, polymeric drug carriers, and ophthalmic suspensions and ointments (7,8). Systemic absorption of the active ingredient(s) that may result from drainage of the drug through the nasolacrimal duct and then swallowed can be minimized by applying gentle pressure to the lacrimal sac for 3 to 5 minutes after administration.

PHARMACOLOGIC CATEGORIES OF OPHTHALMIC DRUGS

The major categories of drugs applied topically to the eye are as follows:

- *Anesthetics*: Topical anesthetics, such as tetracaine, cocaine, and proparacaine, are employed to provide pain relief preoperatively, postoperatively, for ophthalmic trauma, and during ophthalmic examination.
- *Antibiotic and antimicrobial agents*: Used systemically and locally to combat ophthalmic infection. Among the agents used topically are azithromycin, gentamicin sulfate, sodium sulfacetamide, ciprofloxacin hydrochloride, ofloxacin, polymyxin B–bacitracin, and tobramycin.
- *Antifungal agents*: Among the agents used topically against fungal endophthalmitis and fungal keratitis are amphotericin B, natamycin, and flucytosine.
- *Anti-inflammatory agents*: Used to treat inflammation of the eye, as allergic conjunctivitis. Among the topical anti-inflammatory steroidal agents are fluorometholone, prednisolone, and dexamethasone salts. Nonsteroidal anti-inflammatory agents include diclofenac, flurbiprofen, ketorolac, and suprofen.
- *Antiviral agents*: Used against viral infections, as that caused by herpes simplex virus. Among the antiviral agents used topically are trifluridine, ganciclovir, and vidarabine.
- *Astringents*: Used in the treatment of conjunctivitis. Zinc sulfate is a commonly used astringent in ophthalmic solutions.
- *Beta-adrenergic blocking agents*: Agents such as betaxolol hydrochloride, levobunolol hydrochloride, metipranolol hydrochloride, and timolol maleate are used topically in the treatment of intraocular pressure and chronic open-angle glaucoma.
- *Miotics and other glaucoma agents*: Miotics are used in the treatment of glaucoma, accommodative esotropia, and convergent strabismus and for local treatment of myasthenia gravis. Among the miotics are pilocarpine, echothiophate iodide, and demecarium bromide. Several other types of agents are used in the treatment of glaucoma, including carbonic anhydrase inhibitors, such as acetazolamide (oral); beta-blockers, such as timolol; *alpha*-adrenergic agents, such as apraclonidine hydrochloride; sympathomimetics, such as dipivefrin hydrochloride; and an ester prodrug analog of prostaglandin F2a (e.g., bimatoprost, latanoprost, travoprost).
- *Mydriatics and cycloplegics*: Mydriatics allow examination of the fundus by dilating the pupil. Mydriatics having a long duration of action are termed *cycloplegics*. Among the mydriatics and cycloplegics are atropine, scopolamine, homatropine, cyclopentolate, phenylephrine, hydroxyamphetamine, and tropicamide.
- *Protectants and artificial tears*: Solutions employed as artificial tears or as contact lens fluids to lubricate the eye contain agents such as carboxymethyl cellulose,

methylcellulose, hydroxypropyl methylcellulose, and polyvinyl alcohol.

- *Vasoconstrictors and ocular decongestants*: Vasoconstrictors applied topically to the mucous membranes of the eye cause transient constriction of the conjunctival blood vessels. They are intended to soothe, refresh, and remove redness due to minor eye irritation. Among the vasoconstrictors used topically are naphazoline, oxymetazoline, and tetrahydrozoline hydrochlorides. Antihistamines, such as emedastine difumarate, ketotifen fumarate, and olopatadine hydrochloride, are included in some products to provide relief of itching due to pollen, ragweed, and animal dander.

PHARMACEUTICAL REQUIREMENTS

The preparation of solutions and suspensions for ophthalmic use requires special consideration with regard to sterility, preservation, isotonicity, buffering, viscosity, ocular bioavailability, and packaging.

Sterility and Preservation

Ophthalmic solutions and suspensions must be sterilized for safe use. Although it is preferable to sterilize ophthalmics in their final containers by autoclaving at 121°C (250°F) for 15 minutes, this method sometimes is precluded by thermal instability of the formulation. As an alternative, bacterial filters may be used. Although bacterial filters work with a high degree of efficiency, they are not as reliable as the autoclave. However, because final product testing is used to validate the absence of microbes, sterility may be ensured by either method. One advantage of filtration is the retention of *all* particulate matter (microbial, dust, fiber), the removal of which has substantial importance in the manufacture and use of ophthalmic solutions. Figures 17.1 and 17.2 show bacterial filtration equipment that may be used in the extemporaneous preparation of ophthalmic solutions.

To maintain sterility during use, antimicrobial preservatives generally are included in ophthalmic formulations; an exception is for preparations to be used during surgery or in the treatment of traumatized eyes because some preservatives irritate the eye. These preservative-free preparations are packaged in single-use containers.

FIGURE 17.1 Sterilization by filtration. The preparation of a sterile solution by passage through a syringe affixed with a microbial filter. (Courtesy of Millipore Corporation.)

During preformulation studies, antimicrobial preservatives must demonstrate stability, chemical and physical compatibility with other formulation and packaging components, and effectiveness at the concentration employed. Among the antimicrobial preservatives used in ophthalmic solutions and suspensions and their effective concentrations are benzalkonium chloride, 0.004%

FIGURE 17.2 Examples of sterilizing filters. (Courtesy of Millipore Corporation.)

to 0.01%; benzethonium chloride, 0.01%; chlorobutanol, 0.5%; phenylmercuric acetate, 0.004%; phenylmercuric nitrite, 0.004%; and thimerosal, 0.005% to 0.01%. Certain preservatives have limitations; for example, chlorobutanol cannot be autoclaved because it decomposes to hydrochloric acid even in moderate heat. This degradation renders a product susceptible to microbial growth and could alter its pH and thereby affect the stability and/or physiologic activity of the therapeutic ingredient.

In concentrations tolerated by the eye, all of the aforementioned preservative agents are *in*effective against some strains of *Pseudomonas aeruginosa*, which can invade an abraded cornea and cause ulceration and even blindness. However, preservative mixtures of benzalkonium chloride (0.01%) and either polymyxin B sulfate (1,000 USP U/mL) or disodium ethylenediaminetetraacetate (0.01% to 0.1%) *are* effective against most strains of *Pseudomonas*. The latter agent, which is commonly employed as a chelating agent for metals, renders strains of *P. aeruginosa* more sensitive to benzalkonium chloride.

Isotonicity Value

If a solution is placed behind a membrane that is permeable only to solvent molecules and not to solute molecules (a *semipermeable membrane*), *osmosis* occurs as the molecules of solvent traverse the membrane. If a solution-filled membrane is placed in a solution of a higher solute concentration than its own, the solvent, which has free passage in either direction, passes into the more concentrated solution until equilibrium is established on both sides of the membrane and an equal concentration of solute exists on the two sides. The pressure responsible for this movement is termed *osmotic pressure*.

The concentration of a solution with respect to osmotic pressure is concerned with the number of particles of solute in solution. That is, if the solute is not an electrolyte (as with sucrose), the concentration of the solution will depend solely on the number of molecules present. However, if the solute is an electrolyte (as with sodium chloride), the number of particles that it contributes to the solution will depend not only on the concentration of the molecules present but also on their degree of ionization. A chemical that is highly ionized will contribute a greater number of particles to the solution than will be the same amount of a poorly ionized substance. The effect is that a solution with a greater number of particles, whether they are molecules or ions, has higher osmotic pressure than does a solution having fewer particles.

Body fluids, including blood and tears, have an osmotic pressure corresponding to that of a 0.9% solution of sodium chloride. Thus, a 0.9% sodium chloride solution is said to be *iso-osmotic*, or having an osmotic pressure equal to that of physiologic fluids. The term *isotonic*, meaning equal tone, is commonly used interchangeably with iso-osmotic, although it is correctly used only with reference to a specific body fluid, whereas *iso-osmotic* is a physicochemical term comparing the osmotic pressure of two liquids that may or may not be physiologic fluids. Solutions with a lower osmotic pressure than body fluids or a 0.9% sodium chloride solution are commonly called *hypotonic*, whereas solutions having a greater osmotic pressure are termed *hypertonic*.

Theoretically, a hypertonic solution added to the body's system will have a tendency to draw water from the body tissues toward the solution in an effort to dilute and establish a concentration equilibrium. In the blood stream, a hypertonic injection can cause *crenation* (shrinking) of blood cells; in the eye, the solution can draw water toward the site of the topical application. Conversely, a hypotonic solution may induce hemolysis of red blood cells or passage of water from the site of an ophthalmic application through the tissues of the eye.

In practice, the isotonicity limits of an ophthalmic solution in terms of sodium chloride or its osmotic equivalent may range from 0.6% to 2% without marked discomfort to the eye. Sodium chloride itself does not have to be used to establish a solution's osmotic pressure. Boric acid in a concentration of 1.9% produces the same osmotic pressure as does 0.9% sodium chloride. All of an

ophthalmic solution's solutes, including the active and inactive ingredients, contribute to the osmotic pressure of a solution.

The calculations necessary to prepare iso-osmotic solutions may be made in terms of data relating to the colligative properties of solutions (9). Like osmotic pressure, the other colligative properties of solutions, namely, vapor pressure, boiling point, and freezing point, depend on the number of particles in solution. These properties, therefore, are related, and a change in any one of them will be accompanied by corresponding changes in the others. Although any one of these properties may be used to determine iso-osmoticity, a comparison of freezing points between the solutions in question is most used.

When 1-g molecular weight of a nonelectrolyte, such as boric acid, is dissolved in 1,000 g of water, the freezing point of the solution is about 1.86°C below the freezing point of pure water. By simple proportion, therefore, the weight may be calculated for any nonelectrolyte to be dissolved in each 1,000 g of water to prepare a solution iso-osmotic with lachrymal fluid and blood serum, which have freezing points of −0.52°C.

Boric acid, for example, has a molecular weight of 61.8, so 61.8 g in 1,000 g of water should produce a freezing point of −1.86°C. Therefore,

$$\frac{1.86(°C)}{0.52(°C)} = \frac{61.8\ (g)}{x(g)}$$

$$x = 17.3\ (g)$$

Hence, 17.3 g of boric acid in 1,000 g of water theoretically should produce a solution iso-osmotic with tears and blood.

The calculation employed to prepare a solution iso-osmotic with tears or blood when using electrolytes is different from the calculation for a nonelectrolyte. Since osmotic pressure depends on the number of particles, substances that dissociate have an effect that increases with the degree of dissociation; the greater the dissociation, the smaller the quantity required to produce a given osmotic pressure. If we assume that sodium chloride in weak solutions is about 80% dissociated, each 100 molecules yield 180 particles, or 1.8 times as many particles as are yielded by 100 molecules of a nonelectrolyte. This dissociation factor, commonly symbolized by the letter i, must be included in the proportion when we seek to determine the strength of an iso-osmotic solution of sodium chloride (molecular weight, 58.5):

$$\frac{1.86(°C) \times 1.8}{0.52(°C)} = \frac{58.5(g)}{x(g)}$$

$$x = 9.09\,g$$

Therefore, 9.09 g of sodium chloride in 1,000 g of water should make a solution iso-osmotic with blood or lacrimal fluid. As indicated previously, a 0.9% (w/v) sodium chloride solution is taken to be iso-osmotic (and isotonic) with the body fluids.

Simple iso-osmotic solutions, then, may be calculated by this general formula:

$$\frac{0.52 \times \text{molecular weight}}{1.86 \times \text{dissociation (i)}} = \begin{matrix}\text{g of solute per} \\ 1{,}000\ \text{g of water}\end{matrix}$$

Although the i value has not been determined for every medicinal agent that might be named, the following values may be generally used:

Nonelectrolytes and substances of slight dissociation	1.0
Substances that dissociate into 2 ions	1.8
Substances that dissociate into 3 ions	2.6
Substances that dissociate into 4 ions	3.4
Substances that dissociate into 5 ions	4.2

Since 0.9% sodium chloride is considered to be iso-osmotic and isotonic with tears, other medicinal substances are compared with regard to their "sodium chloride equivalency." An often used rule states (9):

> Quantities of two substances that are tonicic equivalents are proportional to the molecular weights of each multiplied by the i value of the other.

Using the drug atropine sulfate as an example,

Molecular weight of sodium chloride = 58.5;
i = 1.8

Molecular weight of atropine sulfate = 695; i = 2.6

$$\frac{695 \times 1.8}{58.5 \times 2.6} = \frac{1(g)}{x(g)}$$

x = 0.12 g of sodium chloride represented by 1 g of atropine sulfate

Thus, the *sodium chloride equivalent* for atropine sulfate is 0.12 g. To put it one way, 1 g of atropine sulfate equals the tonic effect of 0.12 g of sodium chloride. To put it another way, atropine sulfate is 12% as effective as an equal weight of sodium chloride in contributing to tonicity. When a combination of drugs is used in a prescription or formulation to be rendered isotonic, each agent's contribution to tonicity must be taken into consideration. For instance, consider the following prescription:

Atropine sulfate:	1%
Sodium chloride:	qs to isotonicity
Sterile purified water, ad:	30 mL

To make the 30 mL isotonic with sodium chloride, 30 mL × 0.9% = 0.27 g or 270 mg of sodium chloride would be required. However, because 300 mg of atropine sulfate is to be present, its contribution to tonicity must be taken into consideration. The sodium chloride equivalent of atropine sulfate is 0.12. Thus, its contribution is calculated as follows:

$$0.12 \times 300 \text{ mg} = 36 \text{ mg}$$

Thus, 270 − 36 mg = 234 mg of sodium chloride required.

Table 17.1 presents a short list of sodium chloride equivalents. A more complete list may be found in pharmaceutical calculations or physical pharmacy textbooks.

As a convenience, some earlier pharmacy reference books list amounts of some common ophthalmic drugs that may be used to prepare isotonic solutions. Some of the drugs and the related values are presented in Table 17.2. The data are used in the following manner. Of each of the drugs listed, 1 g added to purified water will prepare the corresponding volume of an isotonic solution. For instance, 1 g of atropine sulfate will prepare 14.3 mL of isotonic solution. This

Table 17.1 SOME SODIUM CHLORIDE EQUIVALENTS

SUBSTANCE	MOLECULAR WEIGHT	IONS	I	SODIUM CHLORIDE EQUIVALENT
Atropine sulfate·H_2O	695.0	3	2.6	0.12
Benzalkonium chloride	360.0	2	1.8	0.16
Benzyl alcohol	108.0	1	1.0	0.30
Boric acid	61.8	1	1.0	0.52
Chlorobutanol	177.0	1	1.0	0.18
Cocaine hydrochloride	340.0	2	1.8	0.17
Ephedrine sulfate	429.0	3	2.6	0.20
Epinephrine bitartrate	333.0	2	1.8	0.18
Ethylmorphine hydrochloride $2H_2O$	386.0	2	1.8	0.15
Naphazoline hydrochloride	247.0	2	1.8	0.27
Physostigmine salicylate	413.0	2	1.8	0.14
Pilocarpine hydrochloride	245.0	2	1.8	0.24
Procaine hydrochloride	273.0	2	1.8	0.21
Scopolamine hydrobromide $3H_2O$	438.0	2	1.8	0.13
Tetracycline hydrochloride	481.0	2	1.8	0.12
Zinc sulfate $7H_2O$	288.0	2	1.4	0.16

Table 17.2 ISOTONIC SOLUTIONS PREPARED FROM COMMON OPHTHALMIC DRUGS

DRUG (1 G)	VOLUME OF ISOTONIC SOLUTION (ML)
Atropine sulfate	14.3
Boric acid	55.7
Chlorobutanol (hydrous)	26.7
Cocaine hydrochloride	17.7
Colistimethate sodium	16.7
Dibucaine hydrochloride	14.3
Ephedrine sulfate	25.7
Epinephrine bitartrate	20.0
Eucatropine hydrochloride	20.0
Fluorescein sodium	34.3
Homatropine hydrobromide	19.0
Neomycin sulfate	12.3
Penicillin G potassium	20.0
Phenylephrine hydrochloride	35.7
Physostigmine salicylate	17.7
Physostigmine sulfate	14.3
Pilocarpine hydrochloride	26.7
Pilocarpine nitrate	25.7
Polymyxin B sulfate	10.0
Procaine hydrochloride	23.3
Proparacaine hydrochloride	16.7
Scopolamine hydrobromide	13.3
Silver nitrate	36.7
Sodium bicarbonate	72.3
Sodium biphosphate	44.3
Sodium borate	46.7
Sodium phosphate (dibasic, heptahydrate)	32.3
Streptomycin sulfate	7.7
Sulfacetamide sodium	25.7
Sulfadiazine sodium	26.7
Tetracaine hydrochloride	20.0
Tetracycline hydrochloride	15.7
Zinc sulfate	16.7

solution may be diluted with an isotonic vehicle to maintain the isotonicity while changing the strength of the active constituent in the solution to any desired level. For instance, if a 1% isotonic solution of atropine sulfate is desired, 14.3 mL of isotonic solution containing 1 g of atropine sulfate should be diluted to 100 mL (1 g atropine sulfate in 100 mL = 1% w/v solution) with an isotonic vehicle. By using sterile drug, sterile purified water, a sterile isotonic vehicle, and aseptic techniques, a sterile product may be prepared. In addition to being sterile and isotonic, the diluting vehicles generally used are buffered and contain suitable preservative to maintain the stability and sterility of the product.

Buffering

The pH of an ophthalmic preparation may be adjusted and buffered for one or more of the following purposes (10): (*a*) for greater comfort to the eye, (*b*) to render the formulation more stable, (*c*) to enhance the aqueous solubility of the drug, (*d*) to enhance the drug's bioavailability (i.e., by favoring unionized molecular species), and (*e*) to maximize preservative efficacy.

The pH of normal tears is considered to be about 7.4, but it varies; for example, it is more acidic in contact lens wearers (9). Tears have some buffer capacity. The introduction of a medicated solution into the eye stimulates the flow of tears, which attempts to neutralize any excess hydrogen or hydroxyl ions introduced with the solution. Most drugs used ophthalmically are weakly acidic and have only weak buffer capacity. Normally, the buffering action of the tears neutralizes the ophthalmic solution and thereby prevents marked discomfort. The eye apparently can tolerate a greater deviation from physiologic pH toward alkalinity (and less discomfort) than toward the acidic range (10). For maximum comfort, an ophthalmic solution should have the same pH as the tears. However, this is not pharmaceutically possible, because at pH 7.4 many drugs are insoluble in water. A few drugs—notably pilocarpine hydrochloride and epinephrine

bitartrate—are quite acid and overtax the buffer capacity of the tears.

Most drugs, including many used in ophthalmic solutions, are most active therapeutically at pH levels that favor the undissociated molecule (Physical Pharmacy Capsule 17.1). However, the pH that permits greatest activity may also be the pH at which the drug is least stable. For this reason, a compromise pH is generally selected for a solution and maintained by buffers to permit the greatest activity while maintaining stability.

PHYSICAL PHARMACY CAPSULE 17.1

pH and Solubility

pH is one of the most important factors in formulation. The effects of pH on solubility and stability are critically important. The effect of pH on solubility is critical in the formulation of liquid dosage forms, from oral and topical solutions to intravenous solutions and admixtures.

The solubility of a weak acid or base is often pH dependent. The total quantity of a monoprotic weak acid (HA) in solution at a specific pH is the sum of the concentrations of both the free acid and salt (A^-) forms. If excess drug is present, the quantity of free acid in solution is maximized and constant because of its saturation solubility. As the pH of the solution is increased, the quantity of drug in solution increases because the water-soluble ionizable salt is formed. The expression is

$$HA \overset{K_a}{\leftrightarrow} H^+ + A^-$$

where K_a is the dissociation constant.

At a certain pH level, the total solubility (S_T) of the drug solution is saturated with respect to both the salt and acid forms of the drug, that is, the pH_{max}. The solution can be saturated with respect to the salt at pH values higher than this, but not with respect to the acid. Also, at pH values less than this, the solution can be saturated with respect to the acid but not to the salt. This is illustrated in the accompanying figure.

To calculate the total quantity of drug that can be maintained in solution at a selected pH, either of two equations can be used, depending upon whether the product is to be above or below the pH_{max} (figure). The following equation is used when below the pH_{max}:

$$S_T = S_a\left(1+\frac{K_a}{[H^+]}\right) \qquad \textit{(Equation 17.1)}$$

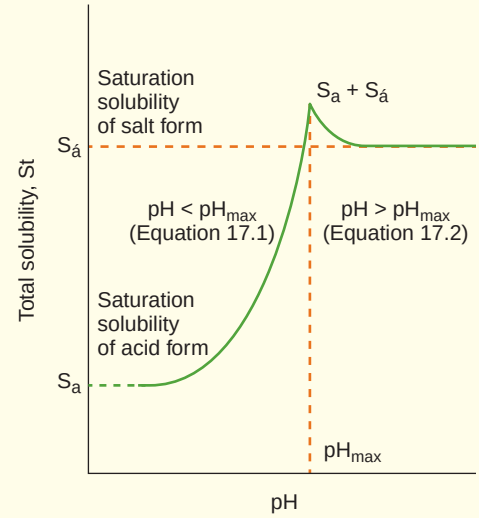
The next equation is used above the pH_{max}:

$$S_T = S'_a\left(1+\frac{[H^+]}{K_a}\right) \qquad \textit{(Equation 17.2)}$$

where

S_a is the saturation solubility of the free acid and

S'_a is the saturation solubility of the salt form.



PHYSICAL PHARMACY CAPSULE 17.1 CONT.

EXAMPLE

A pharmacist prepares a 3% solution of an antibiotic as an ophthalmic solution and dispenses it to a patient. A few days later, the patient returns the eye drops to the pharmacist because the product contains a precipitate. The pharmacist, checking the pH of the solution and finding it to be 6.0, reasons that the problem may be pH related. The physicochemical information of interest on the antibiotic includes the following:

Molecular weight:	285 (salt) 263 (free acid)
3% Solution of the drug:	0.1053 M solution
Acid form solubility (S_o):	3.1 mg/mL (0.0118 M)
K_a:	5.86×10^{-6}

Using Equation (17.1), the pharmacist calculates the quantity of the antibiotic in solution at pH 6.0 (pH 6.0 = $[H^+]$ 1×10^{-6}):

$$S_T = 0.0118\left(1+\frac{5.86\times10^{-6}}{1\times10^{-6}}\right) = 0.0809\,\text{M}$$

From this, the pharmacist knows that at pH 6.0, a 0.0809-M solution can be prepared. However, the concentration that was to be prepared was 0.1053 M; consequently, the drug is not in solution at that pH. The pH may have been all right initially but shifted lower over time, resulting in precipitation of the drug. At what pH (hydrogen ion concentration) will the drug remain in solution? This can be calculated using the same equation and the available information. The S_T value is 0.1053 M:

$$0.1053 = 0.0118\left(1+\frac{5.86\times10^{-6}}{[H^+]}\right)$$

$$[H^+] = 7.333\times10^{-7},\ \text{or a pH of } 6.135$$

The pharmacist prepares a solution of the antibiotic, adjusting the pH above about 6.2 using a suitable buffer system and dispenses the solution to the patient—with positive results.

An interesting phenomenon concerns the close relationship of pH to solubility. At pH 6.0, only a 0.0809-M solution could be prepared, but at pH 6.13, a 0.1053-M solution could be prepared. In other words, a difference of 0.13 pH units resulted in the following:

$$\frac{0.1053-0.0809}{0.0809} = 30.1\%\ \text{more drug in solution at the higher pH}$$

In other words, a very small change in pH resulted in about 30% more drug going into solution. According to the figure, the slope of the curve would be very steep for this example drug, and a small change in pH (x-axis) results in a large change in solubility (y-axis). From this, it can be reasoned that if one observes the pH–solubility profile of a drug, it is possible to predict the magnitude of the pH change on its solubility.

In recent years, more and more physicochemical information on drugs is being made available to pharmacists in routinely used reference books. This type of information is important for pharmacists in many types of practice, especially those who do compounding and pharmacokinetic monitoring.

An isotonic phosphate vehicle prepared at the desired pH (Table 17.3) and adjusted for tonicity may be employed in the extemporaneous compounding of solutions. The desired solution is prepared with two stock solutions, one containing 8 g of monobasic sodium phosphate (NaH_2PO_4) per liter and the other containing 9.47 g of dibasic sodium phosphate (Na_2HPO_4) per liter, the weights being on an anhydrous basis.

The vehicles listed in Table 17.3 are satisfactory for many ophthalmic drugs, excepting pilocarpine, eucatropine, scopolamine, and homatropine salts, which show instability in the vehicle. The vehicle is used effectively as the diluent for ophthalmic drugs already in isotonic solution, such as those prepared according to the method presented in Table 17.2. When drug substances are added directly to the isotonic phosphate vehicle, the solution becomes slightly hypertonic. Generally, this provides no discomfort to the patient. However, if such a solution is not desired, the appropriate adjustment can be made through calculated dilution of the vehicle with purified water.

Viscosity and Thickening Agents

Viscosity is a property of liquids related to the resistance to flow. The reciprocal of viscosity is *fluidity*. Viscosity is defined in terms of the force required to move one plane surface past another under specified conditions when the space between is filled by the liquid in question. More simply, it can be considered as a relative property, with water as the reference material and all viscosities expressed in terms of the viscosity of pure water at 20°C (68°F). The viscosity of water is given as 1 centipoise (actually 1.0087 cP). A liquid material 10 times as viscous as water at the same temperature has a viscosity of 10 cP. The centipoise is a more convenient term than the basic unit, the poise; 1 poise is equal to 100 cP.

Specifying the temperature is important because viscosity changes with temperature; generally, the viscosity of a liquid decreases with increasing temperature. The determination of viscosity in terms of poise or centipoise results in the calculation of *absolute* viscosity. It is sometimes more convenient to use the kinematic scale, in which the units of viscosity are *stokes* and *centistokes* (1 stoke equals 100 centistokes). The kinematic viscosity is obtained from the absolute viscosity by dividing the latter by the density of the liquid at the same temperature:

$$\text{kinematic viscosity} = \frac{\text{absolute viscosity}}{\text{density}}$$

Using water as the standard, these are examples of some viscosities at 20°C:

Table 17.3 ISOTONIC PHOSPHATE VEHICLE

MONOBASIC SODIUM PHOSPHATE SOLUTION (ML)	DIBASIC SODIUM PHOSPHATE SOLUTION (ML)	RESULTING BUFFER SOLUTION (PH)	SODIUM CHLORIDE REQUIRED FOR ISOTONICITY (G/100 ML)
90	10	5.9	0.52
80	20	6.2	0.51
70	30	6.5	0.50
60	40	6.6	0.49
50	50	6.8	0.48
40	60	7.0	0.46
30	70	7.2	0.45
20	80	7.4	0.44
10	90	7.7	0.43
5	95	8.0	0.42

Ethyl alcohol:	1.19 cP
Olive oil:	100.00 cP
Glycerin:	400.00 cP
Castor oil:	1,000.00 cP

Viscosity can be determined by any method that will measure the resistance to shear offered by the liquid. For ordinary Newtonian liquids, it is customary to determine the time required for a given sample of the liquid to flow at a regulated temperature through a small vertical capillary tube and to compare this time with that required to perform the same task by the reference liquid. Many capillary tube viscosimeters have been devised, and nearly all are modifications of the Ostwald type. With an apparatus such as this, the viscosity of a liquid may be determined by the following equation:

$$\frac{\eta_1}{\eta_2} = \frac{\rho_1 t_1}{\rho_2 t_2}$$

where

η_1 is the unknown viscosity of the liquid
η_2 is the viscosity of the standard
ρ_1 and ρ_2 are the respective densities of the liquids, and t_1 and t_2 are the respective flow times in seconds.

In the preparation of ophthalmic solutions, a suitable grade of methylcellulose or other thickening agent is frequently added to increase the viscosity and thereby aid in maintaining the drug in contact with the tissues to enhance therapeutic effectiveness. Generally, methylcellulose of 4,000 cP is used in concentrations of 0.25% and the 25-cP type at 1% concentration. Hydroxypropyl methylcellulose and polyvinyl alcohol are also used as thickeners in ophthalmic solutions. Occasionally, a 1% solution of methylcellulose without medication is used as a tear replacement. Viscosity for ophthalmic solutions is considered optimal in the range of 15 to 25 cP.

Ocular Bioavailability

Ocular bioavailability is an important factor in the effectiveness of an applied medication. Physiologic factors that can affect a drug's ocular bioavailability include protein binding, drug metabolism, and lacrimal drainage. Protein-bound drugs are incapable of penetrating the corneal epithelium because of the size of the protein–drug complex (1). Because of the brief time an ophthalmic solution may remain in the eye, the protein binding of a drug substance can quickly negate its therapeutic value by rendering it unavailable for absorption. Normally, tears contain 0.6% to 2% of protein, including albumin and globulins, but disease states (e.g., uveitis) can raise these protein levels (1). Although ocular protein binding is reversible, tear turnover results in the loss of both bound and unbound drug (2).

As in the case with other biologic fluids, tears contain enzymes (e.g., lysozyme) capable of metabolic degradation of drug substances. However, only a limited amount of research has been conducted on the ocular metabolism of pharmacologic agents, so the full extent to which drug metabolism occurs and affects therapeutic effectiveness is undetermined (11).

In addition to physiologic factors affecting ocular bioavailability, other factors, such as the physicochemical characteristics of the drug substance and product formulation, are important. Because the cornea is a membrane barrier containing both lipophilic and hydrophilic layers, it is permeated most effectively by drug substances having both lipophilic and hydrophilic characteristics (1).

As discussed previously, ophthalmic suspensions, gels, and ointments mix with lacrimal fluids less readily than do low-viscosity solutions and so remain longer in the cul-de-sac, enhancing drug activity.

Additional Considerations

Ophthalmic solutions must be sparkling clear and free of all particulate matter for comfort and safety. The formulation of an ophthalmic suspension may be undertaken when it is desired to prepare a product with extended corneal contact time, or it may be necessary when the medicinal agent is insoluble or unstable in an aqueous vehicle.

Drug particles in an ophthalmic suspension must be finely subdivided, usually

micronized, to minimize eye irritation and/or scratching of the cornea. The suspended particles must not associate into larger particles upon storage and must be easily and uniformly redistributed by gentle shaking of the container prior to use.

PACKAGING OPHTHALMIC SOLUTIONS AND SUSPENSIONS

Although a few commercial ophthalmic solutions and suspensions are packaged in small glass bottles with separate glass or plastic droppers, most are packaged in soft plastic containers with a fixed built-in dropper (Figs. 17.3 and 17.4). This type of packaging is preferred both to facilitate administration and to protect the product from external contamination. Ophthalmic solutions and suspensions are commonly packaged in containers holding 2, 2.5, 5, 10, 15, and 30 mL of product.

FIGURE 17.3 Commercial ophthalmic solution in a plastic container with built-in dropper device. (Courtesy of Alcon.)

FIGURE 17.4 Ophthalmic product packaging. Liquids are in 5- and 15-mL Drop-Tainer dispensers, and ointments are in tubes containing 3.5 g of product. (Courtesy of Alcon.)

Patients must be careful to protect an ophthalmic solution or suspension from external contamination. Obviously, the fixed-dropper containers are less likely to acquire airborne contaminants than screw-type bottles, which are fully opened when in use. However, each type is subject to contamination during use by airborne contaminants and by the inadvertent touching of the tip of the dropper to the eye, eyelids, or other surface.

Ophthalmic solutions used as eyewashes are generally packaged with an eye cup, which should be cleaned and dried thoroughly before and after each use.

PROPER ADMINISTRATION OF OPHTHALMIC SOLUTIONS AND SUSPENSIONS

Prior to the administration of an ophthalmic solution or suspension, the patient or caregiver should be advised to wash the hands thoroughly. If the ophthalmic drops are supplied with a separate dropper, the person should inspect the dropper to make sure it has no chips or cracks. Ophthalmic solutions should be inspected for color and clarity. Out of date or darkened solutions should be

discarded. Ophthalmic suspensions should be shaken thoroughly prior to administration to distribute the suspensoid evenly.

The cap of an eye drop container should be removed immediately prior to use and returned immediately after use. The combined dropper with container as shown in Figure 17.3 is used by holding it between the thumb and middle finger with the index finger on the bottom of the container. One or more drops are delivered by gently squeezing the container. A product packaged with a separate dropper is used by holding the dropper between the thumb and forefinger, then drawing up and discharging the medication dropwise in the usual and familiar manner.

To instill eye drops, the person should tilt the head back and, with the index finger of the free hand, gently pull downward the lower eyelid of the affected eye to form a pocket or cup. While looking up, and without touching the dropper to the eye, the prescribed number of drops should be instilled into the formed pocket. The lower eyelid should be released and the eye closed to allow the medication to spread over the eye. The eye should be held closed, preferably for a full minute, without blinking, rubbing, or wiping. While the eye is closed, gentle pressure should be applied just under the inner corner of the eye by the nose to compress the nasolacrimal duct to prevent drainage and enhance corneal contact time. Then, any excess liquid may be wiped away with a tissue.

During handling and administration, care must be taken not to touch the dropper to the eye, eyelid, or any other surface. If a separate dropper is used, it should be returned to the container and capped tightly. The dropper should not be rinsed or wiped off. If a combined dropper and container unit is used, the container cap should be returned and tightly closed.

In every case, the patient should be advised about the correct number of drops to instill, the frequency of application, the duration of treatment, proper storage of the medication, and usual side effects specific to the product. Among the side effects encountered with the use of ophthalmic medication are transient stinging or burning, foreign body sensation, itching, tearing, decreased vision, margin crusting, and occasionally a bad (drug) taste.

Examples of some commercially available ophthalmic solutions and suspensions are presented in Table 17.4.

Table 17.4 SOME OPHTHALMIC AGENTS BY CATEGORY

AGENT	COMMERCIAL PRODUCT	ACTIVE INGREDIENT (%)	COMMENTS
Decongestant			
Naphazoline HCl	Naphcon-A Ophthalmic Solution (Alcon)	0.025	Topical ocular vasoconstrictor
Antiallergic			
Cromolyn sodium	Opticrom Ophthalmic Solution (Fisons)	4	For allergic ocular disorders, for example, vernal conjunctivitis
Antibacterial			
Ciprofloxacin hydrochloride	Ciloxan Sterile Ophthalmic Solution (Alcon)	0.35	For superficial eye infections due to susceptible microorganisms
Gentamicin sulfate		0.3	
Tobramycin	Tobrex Ophthalmic Solution (Alcon)	0.3	
Sulfacetamide sodium	Sodium Sulamyd Ophthalmic Solution (Schering-Plough)	10, 30	

Table 17.4 SOME OPHTHALMIC AGENTS BY CATEGORY (Continued)

AGENT	COMMERCIAL PRODUCT	ACTIVE INGREDIENT (%)	COMMENTS
Sulfacetamide sodium and	Blephamide Ophthalmic	10%/0.2%	For steroid-responsive anti-inflammatory conditions
Prednisolone acetate	Suspension (Allergan)		
Antiviral			
Trifluridine	Viroptic Ophthalmic Solution (Monarch)	1	For herpes simplex keratitis
Artificial tears			
Dextran 70, hydroxypropyl methylcellulose	Tears Naturale II (Alcon)		For relief of dry eyes
Astringent			
Zinc sulfate	Zincfrin Ophthalmic Solution (Alcon)	0.25	Relief of discomfort, congestion of minor irritations to eyes, such as dust, fatigue, allergies
Anti-Inflammatory			
Dexamethasone sodium phosphate		0.1	Combats inflammation of mechanical, chemical, immunologic causes
Antibacterial–Anti-Inflammatory Combinations			
Tobramycin and dexamethasone	TobraDex Sterile Ophthalmic Suspension (Alcon)	0.3 tobramycin, 0.1 dexamethasone	
Beta-Adrenergic Blocking Agents			
Betaxolol HCl	Betoptic-S Sterile Ophthalmic Solution (Alcon)	0.5	For ocular hypertension, chronic open-angle glaucoma
Timolol maleate	Timoptic Sterile Ophthalmic Solution (Aton Pharma)	0.25, 0.5	For chronic open-angle glaucoma, aphakic patients with glaucoma
Cholinergic			
Pilocarpine HCl	Isopto Carpine Ophthalmic Solution (Alcon)	0.25–10	Miotic for glaucoma, esp. open-angle; neutralizes mydriasis following ophthalmoscopy or surgery
Cholinesterase Inhibitor			
Demecarium bromide	Humorsol Sterile Ophthalmic Solution (Merck & Co.)	0.125, 0.25	Intense miosis, ciliary muscle contractions by inhibiting cholinesterase. Used in open-angle glaucoma when shorter-acting miotics inadequate
Prostaglandin Analog			
Travoprost	Travatan Z Ophthalmic Solution	0.004%	Treatment of elevated intraocular pressure

CONTACT LENSES AND CARE AND USE SOLUTIONS

The number of persons wearing contact lenses grows each year, currently estimated to be over 30 million. About 87% of these persons utilize soft, hydrogel lenses, while the remainder use rigid lenses (*rigid gas permeable* [RGP]) with varying degrees of oxygen permeability. Over 50% of contact lens wearers use 1- to 2-week disposable lenses, and 15% use extended wear (up to 30 days) (12). Their popularity and increased use have fostered the development of new types of lenses and lens care products. To counsel patients properly, it is important for pharmacists to know the characteristics and features of the types of contact lenses and the products available for their care and use (13–15).

The three basic/general types of contact lenses are classified by their chemical composition and physical properties as hard, soft, and RGP.

Hard contact lenses provide durability and clear, crisp vision. The lenses are termed *hard* because they are made of a rigid plastic resin, polymethylmethacrylate (PMMA). The lenses are 7 to 10 mm in diameter and are designed to cover only part of the cornea. They float on the tear layer overlying the cornea. Hard lenses require an adaption period sometimes as long as a week for comfort (16). Even then, because of their rigidity, some patients find them difficult to wear. PMMA lenses are practically impermeable to oxygen and moisture (they absorb only about 0.5% water), a disadvantage to corneal epithelial respiration and to comfort. Care must be exercised to prevent the hard lens from resting directly on the corneal surface and causing physical damage to epithelial tissue. To prevent direct contact, solutions are used to wet the lens and provide a cushioning layer between the corneal epithelium and the inner surface of the lens.

Soft contact lenses are more popular than hard lenses because of their greater comfort. They range from about 13 to 15 mm in diameter and cover the entire cornea. Because of their size and coverage, soft lenses are less likely than hard lenses to dislodge spontaneously. They also are less likely to permit irritating foreign particles (e.g., dust or pollen) to lodge beneath them. However, for some patients, soft lenses do not provide the same high level of visual acuity as hard lenses. They are less durable than hard lenses and carry some risk of absorbing medication concomitantly applied to the eye.

Soft contact lenses are made of a hydrophilic transparent plastic, hydroxyethylmethacrylate, with small amounts of cross-linking agents that provide a hydrogel network (3). Soft lenses contain 30% to 80% water, which enables enhanced permeability to oxygen. There are two general types of soft contact lens: daily wear and extended wear. Whereas daily wear lenses must be removed at bedtime, extended wear lenses are designed to be worn for more than 24 hours, with some approved for up to 30 days of continuous wear. However, it is advisable that lenses not be left in the eye for longer than 4 to 7 days without removal for cleaning and disinfection, else the wearer can be predisposed to an eye infection.

Disposable soft lenses do not require cleaning and disinfection for the recommended period of use; they are simply discarded and replaced with a new pair. Patients should be advised to resist any temptation to wear the lenses for longer than recommended to avoid risk of an eye infection. *RGP* contact lenses take advantage of features of both soft and hard lenses. They are oxygen permeable but hydrophobic. Thus, they permit greater movement of oxygen through the lens than hard lenses while retaining the characteristic durability and ease of handling. RGP lenses are more comfortable than hard lenses. The basic type of lens is intended for daily wear; some of the newer superpermeable RGP lenses are suitable for extended wear.

There are advantages and disadvantages associated with each type of contact lens. Hard contact lenses and RGP lenses provide strength, durability, and relatively easy care regimens. They are easy to insert and remove and are relatively resistant to absorption of medications, lens care products, and environmental contaminants. These lenses provide visual acuity superior to that provided

by soft contact lenses. On the other hand, hard contact lenses and RGP lenses require a greater adjustment period for the wearer and are more easily dislodged from the eye. Soft contact lenses have a shorter adaption period and may be worn comfortably for longer periods. They do not dislodge as easily or fall out of the eye as readily as the hard lenses. However, they have a shorter life span than hard or RGP lenses, and the wearer must ensure that the lenses do not dry out.

Color Additives to Contact Lenses

Contact lens manufacturers produce clear and colored lenses. The use of color additives in medical devices, including contact lenses, is regulated by the U.S. Food and Drug Administration (FDA) through authority granted by the Medical Device Amendments of 1976. Color additives that come into direct contact with the body for a significant period must be demonstrated to be safe for consumer use. This includes the color additives used in contact lenses. The FDA permits the use of a specific color additive in contact lenses only after reviewing and approving a manufacturer's official *Color Additive Petition*. The petition must contain the requisite chemical, safety, manufacturing, packaging, and product labeling information for FDA review. Many colored contact lenses are prepared as a reaction product, formed by chemically bonding a dye, such as Color Index Reactive Red 180 (Ciba Vision) to the vinyl alcohol–methyl methacrylate copolymeric lens material.

Care of Contact Lenses

It is important that contact lenses receive appropriate care to retain their shape and optical characteristics and for safe use. Wearers should be instructed in the techniques for insertion and removal of the lenses in methods of cleaning, disinfecting, and storage.

With the exception of disposable soft contact lenses, all soft lenses require a routine care program that includes (*a*) cleaning to loosen and remove lipid and protein deposits, (*b*) rinsing to remove the cleaning solution and material loosened by cleaning, and (*c*) disinfection to kill microorganisms. If the lenses are not maintained at proper intervals, they are prone to deposit buildup, discoloration, and microbial contamination. The moist, porous surface of the hydrophilic lens provides an attractive medium for the growth of bacteria, fungi, and viruses. Thus, disinfection is essential to prevent eye infections and microbial damage to the lens material.

Hard contact lenses require a routine care program that includes (*a*) cleaning to remove debris and deposits from the lens, (*b*) soaking the lens in a storage disinfecting solution while not in use, and (*c*) wetting the lenses to decrease their hydrophobic characteristics.

To achieve the care needs of contact lenses, the following types of solutions are used: (*a*) cleaning solutions, (*b*) soaking solutions, (*c*) wetting solutions, and (*d*) mixed-purpose solutions.

Products for Soft Contact Lenses

Cleaners

Because of their porous composition, soft lenses tend to accumulate proteinaceous material that forms a film on the lens, decreasing clarity and serving as a potential medium for microbial growth. The two main categories of cleaners are *surfactants*, which emulsify accumulated oils, lipids, and inorganic compounds, and *enzymatic cleaners*, which break down and remove protein deposits. Surfactant agents are used in a mechanical washing device, by placing several drops of the solution on the lens surface and gently rubbing the lens with the thumb and forefinger, or by placing the lens in the palm of the hand and rubbing gently with a fingertip (about a 20- to 30-second procedure). The ingredients in these cleaners usually include a nonionic detergent, wetting agent, chelating agent, buffers, and preservatives. Enzymatic cleaning is accomplished by soaking the lenses in a solution prepared from enzyme tablets. This procedure is recommended at least once a week or twice a month in conjunction with regular surfactant cleansing. The enzyme

tablets contain papain, pancreatin, or subtilisin, which cause hydrolysis of protein to peptides and amino acids. Typically, these are added to saline solution, but one solution can be prepared using 3% hydrogen peroxide, which combines enzymatic cleaning with disinfection, that is, Ultrazyme Enzymatic Cleaner. After the lenses have been soaked for the recommended time, they should be thoroughly rinsed. This is important to do because a peroxide-soaked lens placed directly into the eye will cause great pain, photophobia, redness, and possible corneal epithelial damage.

Rinsing and Storage Solutions

Saline solutions for soft lenses should have a neutral pH and be isotonic with human tears, that is, 0.9% sodium chloride. Besides rinsing the lenses, these solutions are used for storage, because saline maintains their curvature, diameter, and optical characteristics. The solutions also facilitate lens hydration, preventing the lens from drying out and becoming brittle.

Because they are used for storage, some saline solutions contain preservatives, which while inhibiting bacterial growth can induce sensitivity reactions or eye irritation. Thus, some manufacturers make available preservative-free saline solutions and package them in aerosol containers or unit-of-use vials. The use of salt tablets to prepare a normal saline solution is discouraged because of the potential for contamination and risk of serious eye infections.

Disinfection and Neutralization

Disinfection can be accomplished by either of two methods: thermal (heat) or chemical (no heat). In the past, both methods were equally used; however, the introduction of hydrogen peroxide systems for chemical disinfection has become more popular.

For thermal disinfection, the lenses are placed in a specially designed heating unit with saline solution. The solution is heated sufficiently to kill microorganisms, perhaps for 10 minutes at a minimum of 80°C (176°F). It is important that after disinfection the lenses be stored in the unopened case until ready to be worn. The wearer must also ensure that the lenses have been thoroughly cleaned before using heat disinfection. Otherwise, heating can hasten lens deterioration.

In years past, chemical disinfection was conducted with products that contained thimerosal in combination with either chlorhexidine or a quaternary ammonium compound. Unfortunately, many wearers had sensitivity reactions, and these products and chemical disinfection fell into disfavor. The introduction of hydrogen peroxide systems for chemical disinfection revitalized this method of disinfection. It is thought that the free radicals chemically released from the peroxide react with the cell wall of the microorganisms, and the bubbling action of the peroxide is thought to promote removal of any remaining debris on the lens.

To prevent eye irritation from residual peroxide after disinfection, it is necessary that the lenses be exposed to one of three types of neutralizing agents: the *catalytic type* (an enzyme catalase or a platinum disk), the *reactive type* (such as sodium pyruvate or sodium thiosulfate), or the *dilution–elution* type.

Chemical disinfection systems may come as two-solution systems, which use separate disinfecting and rinsing solutions, or one-solution systems, which use the same solution for rinsing and storage. It is important that the wearer realizes that lenses must not be disinfected by heating when using these solutions.

Products for Hard Contact Lenses

Cleaners

Hard lenses should be cleaned immediately after removal from the eye. Otherwise, oil deposits, proteins, salts, cosmetics, tobacco smoke, and airborne contaminants can build up, interfere with clear vision, and possibly cause irritation upon reinsertion. A surfactant cleaner is used by applying the solution or gel to both surfaces of the lens and then rubbing the lens in the palm of the hand with the index finger for about 20 seconds. Too vigorous rubbing can scratch or warp the lens.

Soaking and Storage Solutions

Hard lenses are placed in a soaking solution once they are removed from the eye. Soaking solutions contain a sufficient concentration of disinfecting agent, usually 0.01% benzalkonium chloride and 0.01% edetate sodium, to kill surface bacteria. Overnight soaking is advantageous because it keeps the lenses wet and the prolonged contact time helps to loosen deposits that remain after routine cleaning.

Wetting Solutions

Wetting solutions contain surfactants to facilitate hydration of the hydrophobic lens surface and enable the tears to spread evenly across the lens by providing it with temporary hydrophilic qualities. These solutions also provide a cushion between the lens and the cornea and eyelid. Typical ingredients include a viscosity-increasing agent, such as hydroxyethyl cellulose; a wetting agent, such as polyvinyl alcohol; preservatives, such as benzalkonium chloride or edetate disodium; and buffering agents and salts to adjust the pH and maintain tonicity.

Combination Solutions

Combination solutions mix effects, such as cleaning and soaking, wetting and soaking, or cleaning, soaking, and wetting. While they are characterized by ease of use, combination products may lower the effectiveness of cleaning if the concentration of cleaning solution is too low to adequately remove debris from the lens. These combination solutions should be reserved for wearers who have a demonstrated need for simplification of lens care.

Products for RGP Contact Lenses

Care of RGP lenses requires the same general regimen as for hard contact lenses except that RGP-specific solutions must be used. One of two cleaning methods, either hand washing or mechanical washing, may be used. In the first method, the lens may be cleaned by holding the concave side up in the palm of the hand. The lens should not be held between the fingers because the flexibility of the lens may allow it to warp or turn inside out. Mechanical washing is advantageous because the possibility of the lens turning inside out or warping during cleaning is minimized.

After cleansing, the RGP lens should be thoroughly rinsed and soaked in a wetting or soaking solution overnight. After overnight soaking, the lens is rubbed with fresh wetting or soaking solution and inserted into the eye. To facilitate removal of stubborn protein deposits, weekly cleaning with enzymatic cleaners is recommended.

Clinical Considerations in the Use of Contact Lenses

Although most medicated eye drops may be used in conjunction with the wearing of contact lenses, some caution should be exercised and drug-specific information used, particularly with soft contact lenses, because this type of lens can absorb certain topical drugs and affect bioavailability (13,15).

Use of ophthalmic suspensions and ophthalmic ointments by contact lens wearers presents some difficulties. The drug particles in ophthalmic suspensions can build up between the cornea and the contact lens, causing discomfort and other undesired effects. Ophthalmic ointments not only cloud vision but may discolor the lens. Thus, an alternative dosage form, such as an ophthalmic solution, may be prescribed or lens wearing deferred until therapy is complete.

Some drugs administered by various routes of administration for systemic effects can find their way to the tears and produce drug–contact lens interactions. This may result in lens discoloration (e.g., orange staining by rifampin), lens clouding (ribavirin), ocular inflammation (salicylates), and refractive changes (acetazolamide) (13). In addition, drugs that cause ocular side effects have the potential to interfere with contact lens use. For example, drugs with anticholinergic effects (e.g., antihistamines, tricyclic antidepressants) decrease tear secretion and may cause lens intolerance and damage to the eye. Isotretinoin, prescribed for severe, recalcitrant acne, can induce marked dryness of the eye and may interfere with the use of

contact lenses during therapy. Drugs that promote excessive lacrimation (e.g., reserpine) or ocular or eyelid edema (e.g., primidone, hydrochlorothiazide, chlorthalidone) also may interfere with lens wear.

Use of ophthalmic vasoconstrictors occasionally causes dilation of the pupil, especially in people who wear contact lenses or whose cornea is abraded. Although this effect lasts only 1 to 4 hours and is not clinically significant, some patients have expressed concern. To allay their concern, the FDA has recommended that patients be advised of this side effect by product labeling stating PUPILS MAY BECOME DILATED (ENLARGED) (16).

The following guidelines should be used by pharmacists in counseling patients: Contact lens wearers should wash their hands thoroughly with a nonabrasive, noncosmetic soap before and after handling lenses. Wearers should not rub the eyes when the lenses are in place, and if irritation develops, the lenses should be removed until these symptoms subside.

Only contact lens care products specifically recommended for the type of lens worn should be used. Also, to avoid differences between products of different manufacturers, it is preferable to use solutions made by a single manufacturer. Cleaning and storing lenses should be performed in the specific solution for that purpose. The patient should be instructed to discard cleansers and other lens care products if the labeled expiration date is exceeded. Lenses should not be stored in tap water nor should saliva be used to help reinsert a lens into the eye. Saliva is not sterile and contains numerous microorganisms, including *P. aeruginosa*.

When handling a contact lens over the sink, the drain should be covered or closed to prevent the loss of the lens. During cleansing, the patient should be advised to check the lens for scratches, chips, and/or tears. Similarly, the lens should be inspected for any particulate matter, particles, warpage, and/or discoloration. The patient must ensure the lens is cleaned thoroughly and rinsed thoroughly. Otherwise, these factors can lead to eye discomfort and irritation.

When cleaning a lens, the patient should be instructed to clean it back and forth and not in a circular direction. To avoid the "left-lens syndrome," the patient should be instructed to clean the second lens as thoroughly as the first lens. Oftentimes, the right lens is removed and cleaned first and the second less thoroughly, which will result in more deposits after cleaning.

As appropriate, contact lens users should be counseled with regard to cosmetic use. It is prudent to purchase makeup in the smallest container, because the longer a container is open and the more its contents are used, the greater the likelihood of bacterial contamination. Mascara and pearlized eye shadow should be avoided by women wearing hard lenses because particles of these products can get into the eye and cause irritation, with corneal damage a possibility. Aerosol hairsprays should be used before the lens is inserted and preferably applied in another room, since airborne particles may attach to the lens during insertion and cause irritation. Lenses should be inserted before makeup application because oily substances on the fingertips can smudge the lenses when they are handled. For similar reasons, lenses should be removed before makeup.

Wearers of contact lenses normally do not have ocular pain. If pain is present, it may be a sign of ill-fitting lenses, corneal abrasion, or other medical condition, and the patient should be advised to consult his or her ophthalmologist (15). Hard or soft contact lenses may occasionally cause superficial corneal changes, which may be painless and not evident to the patient. Thus, it is important that all contact lens wearers have their eyes examined regularly to make certain that no damage has occurred.

NASAL PREPARATIONS

Most preparations intended for intranasal use contain adrenergic agents and are employed for their decongestant activity on the nasal mucosa. Most of these preparations are in solution form and are administered as nose drops or sprays; however, a few are available as jellies. Examples of products for

FIGURE 17.5 Commercial packages of nasal solutions, showing drop and spray containers and a nasal inhaler.

intranasal use are shown in Figure 17.5 and in Table 17.5.

Nasal Decongestant Solutions

Most nasal decongestant solutions are aqueous, rendered isotonic to nasal fluids (approximately equivalent to 0.9% sodium chloride), buffered to maintain drug stability while approximating the normal pH range of the nasal fluids (pH 5.5 to 6.5), and stabilized and preserved as required. The antimicrobial preservatives are the same as those used in ophthalmic solutions. The concentration of adrenergic agent in most nasal decongestant solutions is quite low, ranging from about 0.05% to 1%. Certain commercial solutions are available in adult and pediatric strengths, the pediatric strength being approximately half of the adult strength.

Nasal decongestant solutions are employed in the treatment of rhinitis of the common cold, for vasomotor and allergic rhinitis including hay fever, and for sinusitis. Frequent or prolonged use may lead to chronic edema of the nasal mucosa, that is, rhinitis medicamentosa, aggravating the symptom that they are intended to relieve. Thus, they are best used for short periods (no longer than 3 to 5 days), and the patient should be advised not to exceed the recommended dosage and frequency of use.

The easiest but least comfortable approach to treat rebound congestion is complete withdrawal of the topical vasoconstrictor. Unfortunately, this approach will promptly result in bilateral vasodilation with almost total nasal obstruction. A more acceptable method is to withdraw application of drug in only one nostril, with the patient continuing to use the medication in the other nostril. Once the rebound congestion subsides in the drug-free nostril, after about 1 to 2 weeks, a total withdrawal is instituted. Another approach is substitution of a topical saline solution or spray for the topical vasoconstrictor. This keeps the nasal mucosa moist and provides psychologic assistance to patients who are dependent on placing medication into their nostrils.

Most of the adrenergic drugs used in nasal decongestant solutions are synthetic compounds similar in chemical structure, pharmacologic activity, and side effects to the parent compound, naturally occurring epinephrine. Epinephrine as a pure chemical substance was first isolated from suprarenal gland in 1901 and was called both suprarenin and adrenalin. Synthetic epinephrine was prepared just a few years later.

Most solutions for nasal use are packaged in dropper bottles or in plastic spray bottles, usually containing 15 to 30 mL of medication. The products should be determined to be stable in the container and the package tightly closed while not in use. The patient should be advised to discard the solution if it becomes discolored and/or contains precipitated matter.

The patient should also understand that there is a difference in the duration of the effect of topical decongestants. For example, phenylephrine should be used every 3 to 4 hours, whereas oxymetazoline, which is longer acting, should only be used every 12 hours. Patients should be advised to read and adhere to the directions for use to avoid misuse/overuse.

Inhalation Solutions

Inhalations are sterile drugs or sterile solutions of drugs administered by the nasal or oral respiratory route. The drugs may be administered for local action on the bronchial tree or for systemic effects through absorption from the lungs. Certain gases, such as oxygen and ether, are administered by inhalation,

Table 17.5 SOME COMMERCIAL NASAL PREPARATIONS

PRODUCT	MANUFACTURER	ACTIVE INGREDIENT	USE/INDICATIONS
Afrin nasal spray, Afrin nose drops	Schering-Plough	Oxymetazoline HCl 0.05%	Adrenergic, decongestant
Beconase AQ nasal spray	GlaxoSmithKline	Beclomethasone dipropionate 0.042%	Synthetic corticosteroid for relief of seasonal, perennial allergic, vasomotor rhinitis
Diapid nasal spray	Sandoz	Lypressin 0.185 mg/mL	Antidiuretic; control, prevention of diabetes insipidus of deficiency of endogenous posterior pituitary antidiuretic hormone
Imitrex nasal spray	GlaxoSmithKline	Sumatriptan 5 or 20 mg/100 µL	Acute treatment of migraines
Nasalcrom nasal spray	Pharmacia	Cromolyn sodium 4%	Prevention and treatment of symptoms of allergic rhinitis
Nasalide nasal solution	Dura	Flunisolide 0.025%	Symptoms of seasonal or perennial rhinitis
Neo-Synephrine nose drops, spray	Bayer Consumer Care	Phenylephrine HCl 0.125% to 1.0%	Adrenergic, decongestant
Neo-Synephrine maximum strength 12 h	Bayer Consumer Care	Oxymetazoline HCl 0.05%	Adrenergic, decongestant
Ocean mist	Wonder Labs	Sodium chloride 0.65%	Restore moisture, relieve dry, crusted, inflamed nasal membranes
Privine HCl nasal solution	Insight	Naphazoline HCl 0.05%	Adrenergic, decongestant
Rhinocort aqua	AstraZeneca	Budesonide 32 µg/spray	Anti-inflammatory corticosteroid
Syntocinon nasal spray	Sandoz	Oxytocin 40 U/mL	Synthetic oxytocin for initial milk letdown preparatory to breast feeding
Tyzine pediatric nose drops	Kenwood	Tetrahydrozoline HCl (0.05%)	Adrenergic, decongestant
Veramyst nasal spray	GlaxoSmithKline	Fluticasone furoate 27.5 µg/l50 µL spray	Treatment of allergic rhinitis

as are finely powdered drug substances and solutions of drugs administered as fine mists. Sterile Water for Inhalation, USP, and Sodium Chloride Inhalation, USP, may be used as vehicles for inhalation solutions.

As discussed in Chapter 14, a number of drug substances are administered through pressure packaged inhalation aerosols. For the inhaled drug substance or solution to reach the bronchial tree, the inhaled particles must be just a few microns in size.

A widely used instrument capable of producing fine particles for inhalation therapy is the nebulizer. This apparatus, shown in Figure 17.6, contains an atomizing unit in a bulbous glass chamber. A rubber bulb at the end of the apparatus is depressed, and the medicated solution is drawn up a narrow glass tube and broken into fine particles by the passing airstream. The particles produced range between 0.5 and 5 µm. The larger, heavier droplets of the mist do not exit the apparatus but fall back into the reservoir of medicated liquid. The lighter particles do escape with the airstream and are inhaled by the patient, who operates the nebulizer with the exit orifice in the mouth, inhaling while depressing the rubber bulb.

FIGURE 17.6 **A:** A handheld manual nebulizing device. **B:** An electronic nebulizing device. (Courtesy of DeVilbiss Co.)

The pharmacist should advise the patient on the proper technique to use the nebulizer and provide additional instructions, such as not to exceed physician's instructions and to use the smallest amount of product necessary to afford relief. The pharmacist may also advise on how to cope with any dryness of the mouth and should emphasize the need to clean the nebulizer after use and explain how to do it.

The common household vaporizer, like the one depicted in Figure 17.7, produces a fine mist of steam that may be used to humidify a room. When a volatile medication is added to the water in the chamber or to a medication cup, the medication volatilizes and is also inhaled by the patient. Humidifiers, as shown in Figure 17.8, are used to provide a cool mist to the air in a room. Moisture in the air is important to

FIGURE 17.7 A commercial vaporizer. (Photo provided by Kaz, Inc. Vicks is a registered trademark of The Procter & Gamble Co. Manufactured by Kaz, Inc under license from The Procter & Gamble Company, Cincinnati, OH, USA.)

prevent mucous membranes of the nose and throat from becoming dry and irritated. Vaporizers and humidifiers are commonly used in the adjunctive treatment of colds, coughs, and chest congestion.

The pharmacist can help a patient select a vaporizer or humidifier according to personal

Figure 17.8 A commercial humidifier. (Photo provided by Kaz, Inc, maker of Honeywell Portable Humidifiers. The Honeywell trademark is used by Kaz, Inc under license from Honeywell Intellectual Properties, Inc.)

needs. Both devices have advantages and disadvantages. Manufacturing guidelines and legal regulations, such as lock tops, have made vaporizers safer today than in years past, so the possibility of scalding due to an overturned vaporizer is less with newer models. Furthermore, the heat generated in a vaporizer kills any mold and bacteria in the water tank. Humidifiers are more costly but use less electricity than vaporizers. In addition, humidifiers are noisier, can deposit minerals on woodwork and furniture, and can cool down a room by 1°F to 3°F (a problem with young children). The patient should learn about these subtle differences from the pharmacist and/or caregiver.

Ultrasonic humidifiers are effective and operate at an almost noiseless level, but they apparently pose a health problem. While they are highly efficient at nebulizing water into fine droplets, they are also efficient at nebulizing up to 90% of water contaminants. These contaminants include mold, bacteria, lead, and dissolved organic gases, which could ultimately cause acute respiratory irritation or chronic lung problems in unsuspecting patients. Thus, patients should either be advised to run water through a high-grade demineralization filter before filling their ultrasonic humidifier or buy a humidifier with a built-in filter that works.

Examples of Medicated Inhalation Solutions

A number of inhalations pressure packaged as inhalation aerosols are discussed in Chapter 14. Several other inhalations used in medicine are solutions intended to be administered by nebulizer or other apparatus. Among these are isoetharine inhalation solution (Bronkosol, Sanofi) and isoproterenol inhalation solution (Isuprel Solution, Sanofi), both used to relieve bronchial spasms of bronchial asthma and related conditions.

Inhalants

Inhalants are drugs or combinations of drugs that by virtue of their high vapor pressure can be carried by an air current into the nasal passage, where they exert their effect. The device that holds the drug or drugs and from which they are administered is an inhaler.

Certain nasal decongestants are in the form of inhalants. For instance, propylhexedrine is a liquid that volatilizes slowly at room temperature. This quality makes it effective as an inhalant.

Amyl Nitrite Inhalant

Amyl nitrite is a clear yellowish volatile liquid that acts as a vasodilator when inhaled. It is prepared in sealed glass vials that are covered with a protective gauze cloth. Upon use, the glass vial is broken in the fingertips, and the cloth soaks up the liquid, from which the vapors are inhaled. The vials generally contain 0.3 mL of the drug substance. The effects of the drug are rapid and are used in the treatment of anginal pain.

Propylhexedrine Inhalant

Propylhexedrine (Benzedrex, VF Ascher) is a liquid adrenergic (vasoconstrictor) agent that volatilizes slowly at room temperature. This quality enables it to be effectively used as an inhalant. The official inhalant consists of cylindrical rolls of suitable fibrous material impregnated with propylhexedrine, usually aromatized to mask its amine-like odor and contained in a suitable inhaler. The vapor of the drug is inhaled into the nostrils when needed to relieve nasal congestion due to colds and hay fever. It may also be employed to relieve ear block and pressure pain in air travelers.

Each plastic tube of the commercial product contains 250 mg of propylhexedrine with aromatics. The containers should be tightly closed after each opening to prevent loss of the drug vapors. The counterpart commercial product is Benzedrex Inhaler (Menley & James Labs).

Proper Administration and Use of Nasal Drops and Sprays

To minimize the possibility of contamination, the pharmacist should point out to the patient that the nasal product should be used by one person only and kept out of the reach of children. If the nasal product is intended for a

child, the directions for use should be clear to the child if old enough to understand, the parent, or the caregiver. If an over-the-counter product is used, the parent should note the directions on the label.

Before using the drops, the patient should be advised to blow the nose gently and wash the hands thoroughly with soap and water. For maximum penetration with drops, a patient should lie down on a flat surface, such as a bed, hanging the head over the edge and tilting the head back as far as comfortable. The prescribed number of drops is then gently placed in the nostrils, and to allow the medication to spread in the nose, the patient should remain in this position for a few minutes. After this, the dropper should be replaced in the bottle and tightened.

Before using the spray, the patient should gently blow the nose to clear the nostrils and wash the hands thoroughly with soap and water. The patient should be told not to shake the plastic squeeze bottle but be sure to remove the plastic cap. While holding the head upright, the patient should insert the nose piece into the nostril, pointing it slightly backward, and close the other nostril with one finger. The patient should then spray the prescribed or recommended amount, squeezing the bottle sharply and firmly while sniffing. Remove the bottle tip from the nose while maintaining pressure on the bottle sides so as not to aspirate any nasal material into the bottle. Wipe the tip with alcohol or some other appropriate agent, release the pressure on the sides, and repeat the application as necessary. Sprays should always be administered with the patient upright. Spraying medicine into the nostrils should not be performed with the head over the edge of a bed (the preferred procedure for administration of nasal drops) because it could result in systemic absorption of the drug rather than a local effect.

The patient should be advised not to overuse the product. Some decongestant medicines, such as oxymetazoline and xylometazoline, can predispose the patient to rebound congestion if used for more than 3 to 5 consecutive days. The patient should also understand the normal time frame in which to see results and be advised to consult the physician after a certain number of days if relief is not achieved. Finally, patients should not share their medicated spray with another person to prevent the possibility of cross-contamination between individuals. Certain nasal medications, such as beclomethasone dipropionate (Vancenase, Schering), are available for administration through aerosol inhalers.

Nasal Route for Systemic Effects

The nasal route for drug delivery is of interest because of the need to develop a route that is neither oral nor parenteral for newly developed synthetic, biologically active peptides and polypeptides (17–22). Polypeptides, such as insulin, that are subject to destruction by the gastrointestinal fluids are administered by injection. However, the nasal mucosa has been shown to be amenable to the systemic absorption of certain peptides as well as to nonpeptide drug molecules including scopolamine, hydralazine, progesterone, and propranolol (20,21). The nasal route is advantageous for nonpeptide drugs that are poorly absorbed orally.

The adult nasal cavity has about a 20-mL capacity, with a large surface area (about 180 cm^2) for drug absorption afforded by the microvilli along the pseudostratified columnar epithelial cells of the nasal mucosa (19,21). The nasal tissue is highly vascularized, providing an attractive site for rapid and efficient systemic absorption. One great advantage to nasal absorption is that it avoids first-pass metabolism by the liver. However, identification of metabolizing enzymes in the nasal mucosa of certain animal species suggests the same possibility in humans and the potential for some intranasal drug metabolism (19).

For some peptides and small molecular compounds, intranasal bioavailability has been comparable to that of injections. However, bioavailability decreases as the molecular weight of a compound increases, and for proteins composed of more than 27 amino acids, bioavailability may be low (18). Various pharmaceutical techniques and

formulation adjuncts, such as surface-active agents, have been shown to enhance nasal absorption of large molecules (18,21).

Pharmaceuticals on the market or in various stages of clinical investigation for nasal delivery include oxytocin (Syntocinon, Sandoz), desmopressin (DDAVP, Sanofi-Aventis), vitamin B_{12} (Ener-B Gel, Nature's Bounty), progesterone, insulin, calcitonin (Miacalcin, Novartis), propranolol, and butorphanol (Stadol, Bristol-Myers Squibb) (17,18).

OTIC PREPARATIONS

Otic preparations are sometimes referred to as ear or aural preparations. Solutions are most frequently used in the ear, with suspensions and ointments also finding some application. Ear preparations are usually placed in the ear canal by drops in small amounts for removal of excessive cerumen (earwax) or for treatment of ear infections, inflammation, or pain. Because the outer ear is a skin-covered structure and susceptible to the same dermatologic conditions as other parts of the body's surface, skin conditions are treated using the variety of topical dermatologic preparations discussed in Chapter 10.

Cerumen-Removing Solutions

Cerumen is a combination of the secretions of the sweat and sebaceous glands of the external auditory canal. The secretions, if allowed to dry, form a sticky semisolid that holds shed epithelial cells, fallen hair, dust, and other foreign bodies that make their way into the ear canal. Excessive accumulation of cerumen in the ear may cause itching, pain, and impaired hearing, and it impedes otologic examination. If not removed periodically, the cerumen may become impacted and its removal made more difficult and painful.

Through the years, light mineral oil, vegetable oils, and hydrogen peroxide have been commonly used agents to soften impacted cerumen for its removal. Recently, solutions of synthetic surfactants have been developed for their ability to remove earwax. One commercial product uses carbamide peroxide in glycerin and propylene glycol (Debrox drops, GSK). On contact with the cerumen, the carbamide peroxide releases oxygen, which disrupts the integrity of the impacted wax, allowing its easy removal.

Cerumen removal usually involves placing the otic solution in the ear canal with the patient's head tilted at a 45-degree angle, inserting a cotton plug to retain the medication in the ear for 15 to 30 minutes, and followed by gentle flushing of the ear canal with lukewarm water using a soft rubber ear syringe.

Anti-Infective, Anti-Inflammatory, and Analgesic Ear Preparations

Drugs used topically in the ear for their anti-infective activity include such agents as ciprofloxacin, colistin sulfate, neomycin, ofloxacin, polymyxin B sulfate, and nystatin, the latter agent used to combat fungal infections. These agents are formulated into eardrops (solutions or suspensions) in a vehicle of anhydrous glycerin or propylene glycol. These viscous vehicles permit maximum contact time between the medication and the tissues of the ear. In addition, their hygroscopicity causes them to draw moisture from the tissues, reducing inflammation and diminishing the moisture available for the life process of the microorganisms. To assist in relieving the pain that frequently accompanies ear infections, a number of anti-infective otic preparations also contain analgesic agents, such as antipyrine, and local anesthetics, such as pramoxine hydrochloride and benzocaine.

Topical treatment of ear infections is frequently considered adjunctive, with concomitant systemic treatment with orally administered antibiotics.

Liquid ear preparations of the anti-inflammatory agents hydrocortisone and dexamethasone sodium phosphate are prescribed for their effects against the swelling and inflammation that frequently accompany allergic and irritative manifestations of the ear and for the inflammation and pruritus

that sometimes follow treatment of ear infections. In the latter instance, some physicians prefer the use of corticosteroids in ointment form, packaged in ophthalmic tubes. These packages allow placement of small amounts of ointment in the ear canal with a minimum of waste. Many commercial products used in this manner are labeled EYE AND EAR to indicate their dual use.

Aside from the antibiotic–steroid combinations that are used to treat otitis externa, or swimmer's ear, acetic acid 2% in aluminum acetate solution and boric acid 2.75% in isopropyl alcohol are used. These drugs help to reacidify the ear canal, and the vehicles help dry the ear canal. Drying the ear canal keeps in check growth of the offending microorganisms, usually *P. aeruginosa*. Pharmacists may also be called on for extemporaneous preparation of a solution of acetic acid 2% to 2.5% in rubbing alcohol (70% isopropyl alcohol or ethanol), propylene glycol, or anhydrous glycerin. The source of the acetic acid can be Glacial Acetic Acid, USP, or Acetic Acid, NF. Boric acid 2% to 5% dissolved in either ethanol or propylene glycol has also been recommended for use in the ear. This substance, however, may be absorbed from broken skin and be toxic. Thus, its use is usually limited, especially in children with burst eardrums.

Pain in the ear frequently accompanies ear infection or inflamed or swollen ear tissue. Frequently, the pain is far out of proportion to the actual condition. Because the ear canal is so narrow, even a slight inflammation can cause intense pain and discomfort. Topical analgesic agents generally are employed together with internally administered analgesics, such as aspirin, and other agents, such as anti-infectives, to combat the cause of the problem.

Most topical analgesics for the ear are solutions, and many contain the analgesic antipyrine and the local anesthetic benzocaine in a vehicle of propylene glycol or anhydrous glycerin (antipyrine 54 mg, benzocaine 14 mg, dehydrated glycerin qs 10 mL). Again, these hygroscopic vehicles reduce the swelling of tissues (and thus some pain) and the growth of microorganisms by drawing moisture from the swollen tissues into the vehicle. These preparations are commonly employed to relieve the symptoms of acute otitis media. Examples of some commercial otic preparations are presented in Table 17.6.

Table 17.6 SOME COMMERCIAL OTIC PREPARATIONS

PRODUCT	MANUFACTURER	ACTIVE INGREDIENT	VEHICLE	USE/INDICATIONS
Americaine otic	Insight Pharmaceuticals	Benzocaine	Glycerin, polyethylene glycol 300	Local anesthetic for ear pain, pruritus in otitis media, swimmer's ear, similar conditions
Cerumenex eardrops	Purdue Frederick	Triethanolamine polypeptide oleate condensate	Propylene glycol	Removes impacted earwax
Chloromycetin otic	Parke-Davis	Chloramphenicol	Propylene glycol	Anti-infective
Cortisporin otic solution	Glaxo Wellcome	Polymyxin B sulfate, neomycin sulfate, hydrocortisone	Glycerin, propylene glycol, water for injection	Superficial bacterial infections
Debrox drops	GlaxoSmithKline	Carbamide peroxide	Anhydrous glycerin	Earwax removal
PediOtic suspension	Glaxo Wellcome	Polymyxin B sulfate, neomycin sulfate, hydrocortisone	Mineral oil, propylene glycol, water for injection	Superficial bacterial infections

As determined on an individual product basis, some liquid otic preparations require preservation against microbial growth. When preservation is required, such agents as chlorobutanol 0.5%, thimerosal 0.01%, and combinations of the parabens are commonly used. Antioxidants, such as sodium bisulfite, and other stabilizers are also included in otic formulations as required. Ear preparations are usually packaged in 5- to 15-mL glass or plastic containers with a dropper.

Otic Suspensions

Subtle differences in the formulation of otic suspensions may be bothersome to the patient. This is so especially as it relates to differences in inactive or inert ingredients that are considered equivalent on the basis of active ingredients and strength. For example, several suspension combinations of polymyxin B sulfate, neomycin sulfate, and hydrocortisone have been shown to be more acidic at pH 3 to 3.5 than the standard product, Cortisporin-TC Otic (Monarch), whose pH is 4.8 to 5.1. Consequently, there is a risk that when drops are legally substituted, a burning and stinging sensation can occur when the drops are introduced into the ear of young children, especially those with tympanostomies. It has also been demonstrated that with time, the pH of these formulations, including Cortisporin, becomes more acidic, possibly pH 3. Thus, if it is stored over time, the acidity may irritate the ear canal on later use. For this reason, this antibiotic–hydrocortisone combination has been formulated into a new suspension product, PediOtic (Glaxo Wellcome), with a minimum pH of 4.1.

Proper Administration and Use of Otic Drops

When eardrops are prescribed, it is important for the pharmacist to determine how the drops are to be used. For example, earwax removal drops should be instilled and then removed with an ear syringe. Drops intended to treat external otitis infection are intended to be instilled and left in the ear.

The pharmacist should make sure the child, parent, or caregiver understands that administration is intended for the ear and the frequency of application. To facilitate acceptance, the pharmacist should point out that the bottle or container of medication should first be warmed in the hands and, if the product is a suspension, shaken prior to withdrawal into the dropper. The pharmacist should also explain the need to store the medication in a safe place out of the reach of children and away from extremes of temperature.

When instilled into the ear, to allow the drops to run in deeper, the earlobe should be held up and back. For a child, the earlobe should be held gently down and back. For convenience, it is probably easier to have someone other than the patient to administer the drops.

Some eardrops by virtue of their low pH may cause stinging upon administration. Parents and children should be forewarned, especially if a child has tympanostomy tubes in the ear. The patient or parent should also understand how long to use the product. For antibiotic eardrops it is not necessary to finish the entire bottle, because therapy could last 20 to 30 days, depending upon the dosage regimen. Therefore, patients should be instructed to continue using the drops for 3 days after symptoms disappear. Products for otitis externa may take up to 7 to 10 days to demonstrate efficacy.

If a child is prone to develop ear infections as a result of swimming or showering, it might be advisable to recommend that the parents consult a physician for prophylactic medication to use during swimming season and consider using ear plugs that fit snugly in the ear when swimming or showering. After the child emerges from the water or shower, the parents can be advised to use a blow dryer on a low setting to dry the ear quickly without trauma. The dryer should not be held too close to the child's ear.

PHARMACEUTICS CASE STUDY

SUBJECTIVE INFORMATION

Working as a pharmacist in a local hospital, you receive a prescription for 5 mL of fluorouracil 10 mg/mL ophthalmic solution for topical use in the eye. What is a reasonable technique to compound the preparation so the patient can begin treatment within a couple of hours?

OBJECTIVE INFORMATION

Fluorouracil is an antineoplastic agent that is used as ancillary treatment of glaucoma, pterygium, retinal detachment, and premalignant eye lesions. The 10 mg/mL is often used in the treatment of premalignant lesions of the cornea, conjunctiva, and eyelids.

Fluorouracil occurs as a white to practically white, practically odorless crystalline powder that is sparingly soluble in water and slightly soluble in alcohol. Fluorouracil is commercially available as a solution for injection at a concentration of 50 mg/mL in 10, 20, and 100 mL vials and a 10-mL ampule. The injection has a pH adjusted to approximately 8.6 to 9.4 with sodium hydroxide and hydrochloric acid as needed. It is also available as Fluorouracil Powder, USP, that can be used to compound the preparation.

ASSESSMENT

Fluorouracil is water soluble and can be prepared as a sterile, isotonic ophthalmic solution. Two options are available. First, the commercial injection dosage forms can be diluted with sterile sodium chloride injection to the proper concentration. Second, it can be prepared from the fluorouracil powder in sterile water for injection, adjusted to isotonicity with sodium chloride, and sterile-filtered into a sterile container.

PLAN

The physician would like to have this preparation soon, so you select the first option. You obtain a 10-mL vial of fluorouracil 50 mg/mL injection. Using aseptic technique, cytotoxic handling procedures, and an appropriate aseptic clean air environment, you remove 1 mL of the injection, add sufficient sterile 0.9% sodium chloride injection to make 5 mL, and mix well. You package the preparation and add an appropriate label, then dispose of the used materials appropriately for chemotherapy handling and disposal.

CLINICAL CASE STUDY

HPI: K.P. is a 22-year-old WM who presents to the pharmacy with a prescription for olopatadine hydrochloride (Patanol) for allergic conjunctivitis. K.P. explains to the pharmacist, "My allergies have been so bad this spring that they have been bothering my eyes too. I tried to use Visine, but that just helped with the redness." The patient continues to explain that his eyes are excessively watery, itchy, and burning, and at times, he can barely see because the tears make his vision so blurry. He further complains that he has not been able to wear his contacts for almost a week because of his eye problems. K.P. is a college student who just moved to campus and is new to the pharmacy. Before preparing his prescription, the pharmacist takes his medical history.

CLINICAL CASE STUDY CONT.

PMH: Seasonal allergic rhinitis since high school
Seasonal allergic conjunctivitis

SH: (+) EtOH: Drinks 3 to 4 beers/night on the weekends
(–) Tobacco
(–) Illicit drugs

FH: Mother (+) for allergic rhinitis
Father (+) for hypertension
Sister (+) for asthma

Allergies: PCN (rash, hives)

Meds: Loratadine 10 mg po qd
Visine prn red eyes
Tylenol 1,000 mg po prn headaches
Centrum 1 tab po qd

PHARMACEUTICAL CARE PLAN

S: Patient has itching, burning, watery red eyes. Excessive tearing is causing blurred vision.

O: Redness relieved by Visine

A: K.P. is a 22-year-old WM with uncontrolled allergic conjunctivitis. The patient is at high risk for seasonal allergic conjunctivitis because of his history of seasonal allergic rhinitis. K.P. also has a family history significant for allergic rhinitis. Although patient's allergic rhinitis symptoms are controlled by his use of loratadine 10 mg po qd, his ocular symptoms persist even though he uses Visine.

P: Based on patient's symptoms and medical and medication histories, olopatadine hydrochloride is an appropriate option for treatment of his allergic conjunctivitis. Thus, after verifying that K.P.'s prescription is complete, the pharmacist dispenses the medication.

The pharmacist should counsel K.P. on his medication. The prescribed dosage is one drop in each affected eye two times daily at an interval of at least 6 to 8 hours (e.g., morning and late afternoon or early evening). To administer the eye drops, the patient should follow these instructions:

Wash hands thoroughly before using the product.

With the index finger of the free hand, gently pull the lower outer eyelid down and away from the eye to create a pouch.

While tilting the head back, place the dropper over the eye without the tip of the dropper touching the eye.

Just prior to instilling a drop into the eye, look up toward the dropper.

As soon as the drop is instilled into the eye, release the eyelid slowly. Keep the eye closed for a full minute afterward.

While the eye is closed, use a finger to apply gentle pressure over the opening of the tear duct on the innermost (closest to the nose) portion of the eye. This serves to keep the medication in contact with the eye longer.

Excess solution may be gently wiped away with a tissue.

Replace the cap onto the ophthalmic product and keep it tightly closed when not in use.

Advise K.P. against wearing his contact lenses until his eye redness has resolved. Because the preservative in olopatadine hydrochloride may be absorbed by soft contact lenses, K.P. should follow necessary precautions if he decides to resume wearing his contact lenses. K.P. should wait at least 10 minutes after instilling the drops before inserting his contact lenses.

Explain to K.P. the common side effects associated with olopatadine hydrochloride use (e.g., burning or stinging, dry eyes, headache, sinusitis, blurred vision). In addition, K.P. should be instructed to discontinue using Visine while using his prescription.

Remind K.P. to store the eye drops at room temperature in an upright position with the cap tightly secured. He should follow the expiration date on the bottle. In addition, he should know not to rinse or tamper with the dropper.

APPLYING THE PRINCIPLES AND CONCEPTS

Group Activities

1. Select one ophthalmic, one nasal, and one inhalation product. In groups of three, one student serves as the pharmacist, the second the patient, and the third the observer. The pharmacist will counsel the patient on the specific product. After the session, the observer and patient provide constructive criticism on the session. The roles then should be rotated utilizing a different product until the three students have participated in each of the three roles.
2. Brainstorm how each one of these three dosage forms (ophthalmic, nasal, and inhalation) can be misused/abused by a patient and/or caregiver. Determine how a hard contact lens cleaning solution differs from a wetting solution, a wetting/soaking solution, and a rewetting/lubricating solution.
3. Go to the American Optometric Association web site, that is, www.aoa.org, and complete activity sheets no. 2 and 3, which are created for parents and educators (lower left corner).
4. Interview a fellow student who uses contact lenses. Determine the type of lens used, review use and care procedures, and identify any problems associated with the use of the lenses and care products.
5. Organize and execute a health care booth at a local high school event, for example, swimming meet. Provide information and education materials to parents and participants on common ear ailments, including otitis externa, *syn*. swimmer's ear.

Individual Activities

1. List eye care resources that health care providers can refer patients and caregivers to regarding proper use of contact lens products.
2. Go to the American Optometric Association website, that is, www.aoa.org, and perform the classroom exercises, which are created for parents and educators (lower left corner).
3. Describe the procedure for the chemical disinfection of an RGP or soft contact lens.
4. List precautions associated with contact lens use, and write out how you would counsel a patient to avoid adverse effects associated with misuse.
5. Isotonicity Calculation Exercise:
   a. How many milligrams of sodium chloride should be used to compound the following prescription? Given: Ephedrine sulfate SCE = 0.20

R_x:	Ephedrine sulfate	0.3
	Sodium chloride	*qs*
	Purified water *qsad*	30
Sig:	Use as directed	

   b. How many grams of anhydrous dextrose (SCE = 0.18) should be used to prepare one liter of a 0.5% isotonic ephedrine sulfate nasal spray?
6. Select a special solution/suspension product and develop step-by-step instructions (with illustrations) demonstrating its appropriate use. The student then instructs his/her fellow students on the selected product. Because each student's selection should differ from fellow classmates' instructions, these can be collected at the end of the exercise, duplicated, and handed out as a packet to the class as a whole.

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SECTION VIII

NOVEL AND ADVANCED DOSAGE FORMS, DELIVERY SYSTEMS, AND DEVICES

18 Radiopharmaceuticals

OBJECTIVES

After reading this chapter, the student will be able to:

1. Compare and contrast the three principal types of radioactive decay (i.e., alpha, beta, gamma)
2. Compare and contrast the use of radiopharmaceuticals in diagnostics and therapeutics
3. Identify the diagnostic and/or therapeutic role(s) and delivery method(s) for the following radiopharmaceuticals: ^{99m}Tc, ^{89}Sr, ^{90}Y, ^{201}Tl, ^{67}Ga, ^{111}In, ^{123}I/^{131}I, and ^{153}Sm
4. Describe the concept and therapeutic utility of positron emission tomography (PET)
5. Identify indications for the following nonradioactive pharmaceuticals in nuclear medicine: Prussian blue, acetazolamide, captopril, dipyridamole, adenosine, and furosemide
6. Describe the organization of a nuclear pharmacy in a community and hospital setting
7. Define the role of the nuclear pharmacist (e.g., radiopharmaceutical preparation, quality assurance, dispensing, safety, consultation)

By definition, a radiopharmaceutical is a radioactive pharmaceutical agent that is used for diagnostic or therapeutic procedures (1). For a product to be classified as a radiopharmaceutical agent safe for human use, the preparer must satisfy a state agency, the State Board of Pharmacy, and two branches of the federal government whose responsibilities in this category have overlapping jurisdictions. They are the Food and Drug Administration (FDA) and the Nuclear Regulatory Commission (NRC). The extent of oversight by the board of pharmacy differs between states. Because of the stringent regulations of the NRC, some state boards defer and do not have specific rules for nuclear pharmacies. Other state boards have rules within their pharmacy practice acts that relate to the practice of nuclear pharmacy.

Over the past four decades, the discipline of nuclear pharmacy, or radiopharmacy, has become highly specialized and contributed positively to the practice of nuclear medicine. Nuclear pharmacy, the first specialty in pharmacy recognized (in 1978) by the Board of Pharmaceutical Specialties, focuses on the safe and effective use of radioactive drugs or radiopharmaceuticals.

The application of radiopharmaceuticals is divided into two major areas, diagnostic and therapeutic. The diagnostic side is well established, while the therapeutic side of nuclear medicine is evolving. For example, more than 100 radiopharmaceutical products

are available, with the largest proportion of these having application in cardiology (e.g., myocardial perfusion), oncology (e.g., tumor imaging and localization), and neurology (e.g., cerebral perfusion). Diagnostically, they are also used for infection imaging and in nephrology. Historically, nuclear medicine has been well established as a therapeutic modality for thyroid cancer, Graves disease, hyperthyroidism, and bone pain palliation associated with skeletal metastasis. However, recent radiopharmaceuticals (e.g., ^{131}I or ^{123}I-labeled MIBG [*m*-iodobenzylguanidine]) are being used to treat pheochromocytoma and neuroblastoma, and radiolabeled somatostatin analogs are used for the treatment of neuroendocrine tumors (e.g., neuroblastoma) (2). Ongoing investigative studies involving radiopharmaceuticals are being conducted for numerous other diseases (e.g., primary bone cancers, ovarian cancer) using innovative means (e.g., targeting agents) to deliver the drug to the tumor. It is anticipated that many of these radiopharmaceuticals will become available for amelioration of diseases.

A radiopharmaceutical consists of a drug component and a radioactive component. Most radionuclides contain a component that emits *gamma* radiation. Substances that have varying numbers of protons and neutrons as compared to stable elements are called *radionuclides*. Nuclides may be stable or unstable; those that are unstable are radioactive because their nuclei undergo rearrangement while changing to a stable state, and energy is released.

An important distinction between radiopharmaceuticals and traditional drugs is lack of pharmacologic activity on the part of radiopharmaceuticals. For intensive purposes, radiopharmaceuticals have been used as tracers of physiologic processes. Their huge advantage is that their radioactivity allows noninvasive external monitoring or targeted therapeutic irradiation with very little effect on the biologic processes in the body. Indeed, radiopharmaceuticals have an excellent safety record, and their incidence of adverse effects is extremely low (3). However, in the past two decades, there has been committed interest to developing unsealed radionuclides for treatment of cancers arising from the diversity of newer molecular carriers (e.g., immune-derived molecules, receptor-avid tracers). Technologic advances in molecular pharmacology, combinatorial chemistry, and peptide biochemistry are providing innovative means (e.g., targeting vectors) to enhance radionuclide specificity and targeting cancerous cells in vivo.

Systemic administration of radiopharmaceuticals for site-specific use allows the physician to treat widely disseminated diseases. Optimally, therapeutic radiopharmaceuticals are designed for site specificity and based solely upon physiological function of the target organ even if the actual location of the cancerous tumor is unknown. The mechanism of localization of the radiopharmaceutical in a particular target organ depends upon processes as varied as antigen–antibody reactions, physical trapping of particles, receptor site binding, and transport of a chemical species across a cell membrane, among others. Ideally, the radiopharmaceutical will cause minimal or tolerable damage to healthy, adjacent tissue. However, a variety of factors related directly to the physical and chemical characteristics of the radiopharmaceutical make this goal difficult to achieve. Research will continue to address problems related to efficient radiopharmaceutical delivery to the target site. For example, the residence time of radioactivity at the target site, the in vivo catabolism and metabolism of the drug, and the optimization of relative rates of radiolabeled drug or drug metabolite clearance from the target site are factors to be determined. Development of an effective radiopharmaceutical for therapeutic use is a complex, difficult undertaking.

BACKGROUND INFORMATION

Not all of the atoms of an unstable radionuclide completely rearrange at the same instant. The time required for a radionuclide to decay to 50% of its original activity is termed its radioactive half-life. Radionuclides range widely in their half-life; for ^{14}C, it is 5,730 years, whereas for ^{24}Na, it is 15 hours, and for ^{81}Kr, it is 13 seconds.

The activity of radioactive material may be calculated by a decay equation that allows the clinician to predict the activity at any time, earlier, or later than the specific assay. The specific decay equation:

$$A_e = A_0 e^{-\lambda t}$$

where

A_e is the specific activity at time t,
A_0 is the initial activity, and
λ is the decay constant calculated as ln 2/half-life, and t is time.

Decay tables have been formulated for various radionuclides by calculating the last portion of the decay equation ($e^{-\lambda t}$). Thus,

$$A_e = A_0 \left(\text{decay factor}\right)$$

The activity of a radioactive material is expressed as the number of nuclear transformations per unit of time. Because of decay, all radioactivity decreases with time because fewer atoms remain as the atoms decay. The fraction of nuclei disintegrating with time is always constant, and fewer and fewer atoms are left. The larger the decay constant the faster the decay and the shorter the half-life. Thus, as demonstrated by the following, the half-life is inversely proportional to the decay constant:

$$t_{1/2} = \frac{0.69315}{\lambda}$$

where λ is the transformation or decay constant, which has a characteristic value for each radionuclide.

The fundamental unit of radioactivity is the *curie* (Ci), defined as 3.700×10^{10} nuclear transformations per second or disintegrations per second (dps). Multiplying this unit by 60 allows the definition to be expressed as disintegrations per minute. Multiples and submultiples (e.g., *millicurie* [mCi], *microcurie* [μCi], and *nanocurie* [nCi]) of the curie can be expressed also:

$$1\ \text{mCi} = 10^{-3}\ \text{Ci}$$
$$1\ \mu\text{Ci} = 10^{-6}\ \text{Ci}$$
$$1\ \text{nCi} = 10^{-9}\ \text{Ci}$$

In July 1974, at the meeting of the International Commission of Radiation Units and Measurements, a recommendation was made that within no less than 10 years, the curie would be replaced with a new SI (Système International d'Unites) unit, the reciprocal second (sec^{-1}) (4). The intent was that this new unit be used to express the unit of activity as a function of the rate of spontaneous nuclear transformations of radionuclides, as one per second (dps). It was further recommended that this new unit of activity be given the name *becquerel* and bear the symbol *Bq*. The intent was that the becquerel would be equivalent to 1 dps or approximately 2.703×10^{-11} Ci. For example, a 15-mCi dose of ^{99m}Tc would be referred to as a 555-megabecquerel (MBq) dose. To date, the conversion to SI units in the United States has been slow.

The amount of radiation absorbed by body tissue in which a radioactive substance resides is called the radiation dose. Traditionally, this is measured in rad (*r*adiation *a*bsorbed *d*ose); 1 rad = 100 ergs of energy absorbed by 1 g of tissue. The gray (Gy) is the international unit of absorbed dose, equal to 1 J of energy absorbed in 1 kg of tissue, that is, 1 Gy = 100 rad.

Radiopharmaceutical doses are dispensed to patients in units of activity, typically mCi or μCi. Traditional therapeutic agents are dispensed according to weight-based calculations to determine appropriate activity. The pharmacist remains responsible to ensure that the proper prescribed dose is prepared and dispensed. Because of the nature of radiopharmaceuticals, the amount of radioactivity in the unit dose at the time of preparation must be sufficient to allow for decay of radioactivity before the product is administered.

The three main types of radiation decay are alpha particles, beta particles, and gamma photons (or gamma rays). Of the three types, alpha particles have the largest mass and charge of radiation, consisting of two protons and two neutrons, identical with the helium nucleus. As an alpha particle loses energy, its velocity decreases. It then attracts electrons and becomes a helium atom. Most alpha

particles are unable to pierce the outer layers of skin or penetrate a thin piece of paper. However, because the charge is large, it does cause a great deal of damage to the immediate area by breaking down DNA. Beta particles may be either electrons with negative charge, *negatrons*, or positive electrons, *positrons*. These two particles, β^- and β^+, have a range of more than 100 feet in air and up to about 1 mm in tissue. Beta particles are not as destructive as alpha particles, but they can be used therapeutically. The beta particle possesses a lot of kinetic energy, thousands to millions of electron volts. Nuclear medicine depends mostly on radiopharmaceuticals that decay by gamma emission. Gamma rays are electromagnetic vibrations comparable with light but with much shorter wavelength. Because of their short wavelength and high energy, they are very penetrating.

Auger electrons originate from the orbital electrons rather than from the nucleus. Whenever there is a vacancy in a lower orbital, an electron from a higher orbital falls down into that lower orbital, and the difference in energy between the two orbitals is emitted in the form of a characteristic x-ray. Most of the time, the characteristic x-ray leaves the atom. But sometimes, the characteristic x-ray hits a higher orbital electron of the same atom. Then, the transfer of energy from the x-ray to the electron is enough to free it from the atom. This free electron, known as an auger electron, is similar to a beta particle except that it has much less energy, typically only tens to hundreds of electron volts. In materials with large atomic numbers, there are several higher electron orbitals, so several different auger electrons may be produced, each with a different kinetic energy. Thus, the term auger cascade is sometimes used to indicate the production of multiple different auger electrons.

The optimum dose of a radiopharmaceutical is that which allows acquisition of the desired information with the least amount of radiation dose or exposure to the patient. Consequently, the clinical utility of a radiopharmaceutical is determined mainly by the radionuclide's physical properties (e.g., radiation, energy, half-life). Therefore, the best diagnostic images at the lowest radiation dose are attained if the radionuclide has a short half-life and emits only gamma radiation. ^{99m}Tc is a prime example of a radionuclide with these properties. Its half-life is 6 hours, and gamma emission is in the order of 140 keV, efficiently detected by the gamma camera. It is commonly known as the "ideal" radionuclide for diagnostic imaging. For therapeutic use, however, radionuclides should emit particulate radiation (beta particles), which deposits the radiation within the target organ. ^{131}I is a prime example, used for hyperthyroidism and eradication of metastatic disease of the thyroid gland. Because ^{131}I emits both beta and gamma radiation, it can be used diagnostically (gamma rays) and therapeutically (beta particles).

Most radiopharmaceuticals are produced by nuclear activation in a nuclear reactor. In such a reactor, stable atoms are bombarded with excess neutrons in the reactor. The resulting neutron additions to the stable atoms produce unstable atoms and radionuclides. The facilities for the production, use, and storage of radioactive pharmaceuticals are subject to licensing by the NRC or, in certain instances, to appropriate state agencies. Many states, known as agreement states, have taken over licensing for the NRC. They agree to follow all NRC regulations and, in some instances, may be more stringent. As for all pharmaceuticals, the FDA enforces good manufacturing practice and proper labeling and use of the products. The Federal Department of Transportation regulates shipment of radiopharmaceuticals, as do state and local agencies.

Radiopharmaceuticals are used to diagnose disease or evaluate the progression of disease following specific therapy intervention. They can also be used to evaluate drug-induced toxicity and to an increasing extent are being used to treat diseased tissue.

The distribution pattern of radiopharmaceuticals can be used for imaging purposes to attain diagnostic information about organs or various body systems (5). Imaging procedures are classified as either *dynamic* or *static*. The dynamic study provides useful information through the rate of accumulation and

removal of the radiopharmaceutical from a specific organ. A static study merely provides perfusion and morphologic information, such as assessing adequacy of blood flow; organ size, shape, and position; and any space-occupying lesions.

DIAGNOSTIC IMAGING

Some radiopharmaceuticals are formulated to be placed within a target organ. ^{131}I is taken up actively by thyroid cells following absorption into the bloodstream after oral administration of a capsule or solution. The extent of uptake of the dose by the gland helps assess thyroid function, or an image of the gland can be obtained after administration. Alternatively, when ^{131}I was labeled with orthoiodohippuric acid (^{131}I-orthoiodohippurate, or OIH) and intravenously injected, kidney tubules would actively secrete this agent into urine. Measuring the time course of activity over the kidney with a gamma camera and plotting the rate of radioactivity accumulation and removal versus time yield a measure of kidney function. This dynamic study, termed a *renogram*, is particularly useful to assess renal function in patients with transplanted kidneys. The visualization of the entire kidney anatomically is known as a pyelogram (Fig. 18.1).

There are, however, limitations to the use of ^{131}I-orthoiodohippurate. Because of its beta emissions, the dose must be held from 200 to 400 μCi. The required lower dose with the 364-KeV gamma and beta emissions produces a poorer image than ^{99m}Tc-Mag-3, which has pure gamma emissions of 140 KeV, allowing for a higher dose and enhanced image quality without increasing the total body radiation burden. ^{99m}Tc-Mag-3 undergoes tubular secretion and glomerular filtration in the kidney and provides excellent renograms.

The most common diagnostic imaging procedure is myocardial perfusion imaging (MPI). For many years, this procedure was performed using ^{201}Tl-thallous chloride. However, in recent years, ^{201}Tl has been replaced as the "gold standard" in MPI by the ^{99m}Tc-based radiopharmaceuticals (e.g., ^{99m}Tc-sestamibi, ^{99m}Tc-tetrafosmin) (6).

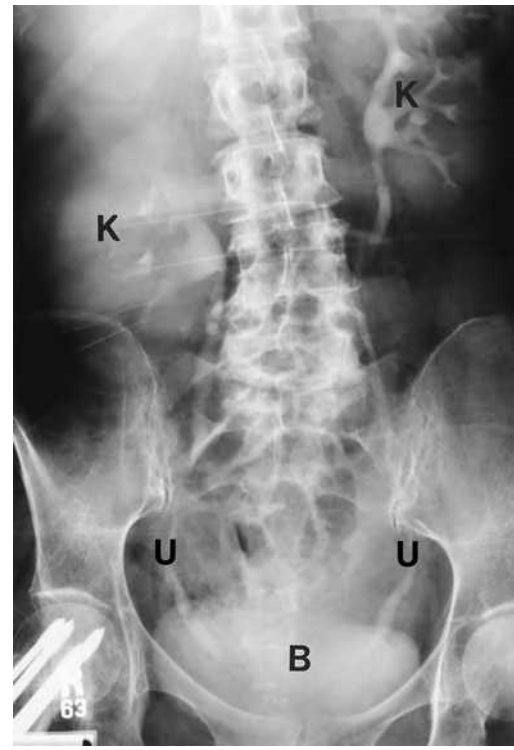

FIGURE 18.1 Intravenous pyelogram in an elderly patient. Note contrast visualization of the kidneys (*K*), ureters (*U*), and bladder (*B*). The patient also has fixation screws in her right hip to stabilize a hip fracture. (Reprinted with permission from Hunter TB, Walsh TK, Hall JN. Agents for diagnostic imaging. In: Block H, Beale JM Jr, eds. Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry. 11th Ed. Baltimore, MD: Lippincott Williams & Wilkins, 2004:478.)

Radiopharmaceuticals are useful to evaluate a patient's response to drug therapy and surgery. These agents can detect early changes in physiologic function that come before morphologic or biochemical end points. An example is perfusion lung imaging using ^{99m}Tc macroaggregated albumin particles to detect pulmonary embolism. Once the embolism is confirmed and thrombolytic and/or anticoagulant therapy initiated, this lung-perfusing agent can be administered again to evaluate its resolution with drug therapy. Cardiac radionuclide ventriculograms using ^{99m}Tc-labeled red blood cells are performed to assess left ventricular function (e.g., ejection fraction, regional wall motion) to evaluate the effect of surgery (e.g., coronary artery

bypass graft, valve repair) or the response to drug therapy. Also, a ^{99m}Tc ejection fraction study can be performed to assess the benefits of heart medications, such as digoxin.

Radiopharmaceuticals also find utility to help monitor drug therapy, including toxicity. For example, the ability of doxorubicin to cause irreversible heart failure is well known, and the cumulative dose of this drug should not exceed 550 mg/m^2. Because there is much variation in the individual response to this drug, serial determinations of left ventricular ejection fraction using ^{99m}Tc are useful to determine the risk of developing doxorubicin-induced heart failure on an individual basis.

THERAPEUTIC USE OF RADIOPHARMACEUTICALS

Therapeutic radiopharmaceuticals are radiolabeled molecules designed to deliver therapeutic doses of ionizing radiation to specific disease sites, such as cancerous tumors, with high specificity in the body. The design of each radiotherapeutic agent requires optimizing the balance between specific targeting of the disease, such as a cancerous tumor, and the clearance of radioactivity from nontarget radiosensitive tissues; it is also necessary to consider the physical radioactive decay properties of the radionuclide. As mentioned earlier, difficulties in the design and development of a highly selective radiolabeled drug carrier include drug delivery, maximizing the residence time of radioactivity at target sites, in vivo catabolism and metabolism of the drug, and optimization of relative rates of the radiolabeled drug or metabolite clearance from nontarget sites, among others.

Unsealed source radiolabeled agents have been used for treatment of cancers for more than five decades. Thyroid disease has been treated with sodium iodide, ^{131}I; polycythemia vera can be treated with sodium phosphate, ^{32}P; peritoneal effusions can be treated with chromic phosphate, ^{32}P; and ^{89}Sr-chloride, ^{153}Sm-EDTMP, and ^{186}Re-HEDP are used for pain relief associated with metastatic bone lesions. The intent is to use beta radiation to destroy diseased tissue selectively. Thus, a minimum sufficient dosage must be administered although this dose can be much larger than doses for diagnostics. In the case of ^{131}I, the therapeutic dose is 5 to 10,000 times the dose used to assess organ function. The major indications for radioiodine therapy include hyperthyroidism (diffuse toxic goiter or Graves disease and toxic multinodular goiter) and eradication of metastatic disease (thyroid cancer).

A major focus of current research is to enhance drug targeting to internal target sites (e.g., solid tumors, specific organs). The objective is to enhance the drug by concentrating it at the target site and minimize its effect in healthy sites. This approach is being investigated for cancer chemotherapy and radioimmunotherapy (RIT). RIT uses antigen-specific monoclonal antibodies (MABs) or their derived reagents to deliver therapeutic radionuclides to tumorous tissue (2). Improved bioengineered delivery vehicles (e.g., humanized and chimeric whole antibodies, Fv fragments, and hypervariable domain region peptides) have reinvigorated RIT, and more and more pretargeting protocols are becoming available (2).

Most chemotherapeutic drugs and radiotherapeutic peptides are small molecules. Consequently, low concentration of drug is obtainable at the target site, largely because of rapid excretion and metabolism by the kidneys and liver. This limits the amount of drug available for localization in the target site from the bloodstream. Increasing the dosage of drug is not an option because of the toxicologic implications for one or more body organ systems. Covalent conjugates of MABs were the first generation of drug-targeting agents that were employed to attain the concentrating effect in tumors (7).

In 1996, the FDA granted licenses to three manufacturers to market four radiolabeled antibodies for diagnostic imaging. CEA-Scan was a murine MAB fragment linked to ^{99m}Tc. It was reactive with carcinoembryonic antigen, a tumor marker for cancer of the colon and rectum and indicated with other standard diagnostic modalities for the detection of recurrent and/or metastatic colorectal cancer. Cytogen Corporation developed a

linker payload system with the attachment of diagnostic (OncoScint colorectal/ovarian) or therapeutic substances (cancer cell–killing yttrium in OncoRad ovarian and OncoRad prostate systems) on the carbohydrate region of MABs. After injection, the MABs bind to the targeted tumor antigen to facilitate diagnosis or treatment. While tumor targeting was somewhat successful with the large, long-circulating radiolabeled MABs, normal organ activity (e.g., blood, kidneys, liver, bone marrow) became problematic. Consequently, both CEA-Scan and OncoSCint colorectal/ovarian are now off the market.

In the past two decades, extensive research for radionuclide therapy has attempted to use ions (molecular weight or MW, 10^2), low molecular weight drugs (MW $10^{2–3}$), peptides (MW 10^3), radiolabeled antibody fragments and various proteins (MW 10^4), intact antibodies (MW 10^5), chase molecules, metabolizable linkers, local delivery, antibody-directed enzyme prodrugs, and liposomes for targeting purposes (MW 10^6) (8). The extensive size range demonstrated for a few of these molecules illustrates the several orders of magnitude that these substances cover with respect to molecular weight range (8). Thus, there is much potential for research involving an enormous number of agents with various properties.

One strategy to increase the concentration of a dose-limited, rapidly cleared radionuclide in a tumor was to couple it covalently to a large molecule (e.g., MAB directed against a tumor marker on the surface of the tumor) (9). Because of their large size, these radionuclide conjugates are not rapidly excreted by the kidneys; they are slowly removed from the systemic circulation over several days by the reticuloendothelial system (RES). Still, however, data demonstrate that while the radionuclide has high systemic circulation, very little is localized in the tumor. Thus, getting high tumor uptake with large antibody conjugates has posed a significant challenge. The most popular MAB pretargeting techniques employ either biotin and avidin or the hapten–antibody system and prodrug–enzyme systems or ligand–receptor systems (2). All of these methods employ a long-circulating targeting conjugate to get high tumor uptake with a diffusible, rapidly excreted effector molecule. The result is higher ratios of target to normal tissue and consequently less toxicity.

Molecular weight, lipophilicity, and charge of the targeting agents are important properties that influence hepatic and renal excretion. Small water-soluble peptides demonstrate effective excretion, which is beneficial in ridding the body of excess circulating radionuclide-labeled compounds. However, if excretion is too rapid, effective levels of the agent reaching the tumor are never achieved.

Creating a targeting agent with a very high molecular weight is thought to reduce the ability of the agent to diffuse through the capillary walls and thereby hinder the ability to target disseminated tumor cells in normally vascularized tissues. Thus, this may only allow tumor targeting in areas of pathologic tumor vasculature of the primary tumor or metastases. The limited passage through the capillary walls may also prolong systemic circulation and cause undesired exposure of normal tissue to radiation. Alternatively, enhanced circulation times may result in higher tumor uptake.

To avoid trapping and degradation of the agents by the RES, therapeutic entities must be designed not to be recognized by the RES (9). Pretherapeutic administration of nonradioactive antibodies (preload) can be used to saturate the RES and modify the distribution of the radiolabeled antibody. Pegylation and other preventive modifications have demonstrated some reduction in the RES's ability to uptake macromolecular agents.

In the spring of 2002, the FDA approved a new treatment regimen for low-grade B-cell non-Hodgkin lymphoma. It was the first regimen that combined a MAB with radionuclides. Rituximab is administered in a therapeutic regimen with ibritumomab tiuxetan (Zevalin). This therapy is recommended for patients who have not responded to standard chemotherapeutic treatments or to the prior use of rituximab (Rituxan). Rituximab and ibritumomab tiuxetan target the CD20 antigen on the surface of mature white blood cells (B cells) and B-cell lymphocytes occurring in

non-Hodgkin lymphoma. This is discussed further later in the chapter.

Peptides have been investigated to succeed antibodies as delivery vehicles for linked diagnostic or therapeutic agents. Peptides have the advantage over MABs of being more rapidly cleared from the body, potentially with a lower level of toxicity (7). Further, they provide physiologic evidence of the nature of the disease process or progress of treatment. Radiolabeled peptides are a new class of radiotracers that target a cell or tissue and deliver a diagnostic signal or therapeutic agent to the site of the disease. Peptides are naturally occurring or synthetic compounds that contain one or more amino acid sequences or groups. On their plasma membranes, cells express receptor proteins with high affinity for regulatory peptides, such as somatostatin. Changes in the density of these receptors during disease, such as the overexpression found in many tumors, provide the basis for new imaging and therapeutic applications (10). The first peptide analogs successfully applied for visualization of receptor-positive tumors were radiolabeled somatostatin analogs. The next step was to label these analogs with therapeutic radionuclides for peptide receptor radionuclide therapy (PRRT). Results from preclinical and clinical multicenter studies have already shown an effective therapeutic response to radiolabeled somatostatin analogs to treat receptor-positive tumors. Infusion of positively charged amino acids reduces kidney uptake, enlarging the therapeutic window. For PRRT of CCK-B receptor-positive tumors, such as medullary thyroid carcinoma, radiolabeled mini gastrin analogs are being successfully applied (7).

An example of this new class of radiopharmaceuticals is octreotide, a synthetic analog of the aforementioned peptide hormone, somatostatin, with the ^{111}In-labeled analog pentetreotide. The resulting product, OctreoScan, became the first radiolabeled peptide approved by the FDA. This agent has made possible the detection of small (0.5 to 1.0 cm) primary and metastatic tumors, including those of several brain tumor types, pancreatic islet tumors, neuroblastomas, carcinoids, thymomas, and melanomas, among others.

Small antimicrobial peptides are also thought to be candidates to be new antimicrobial agents. Lupetti et al. (11) have developed a scintigraphic approach to studying these pharmacokinetically in animals. These peptides, radiolabeled with ^{99m}Tc, demonstrated rapid accumulation at sites of infection but not at sites of sterile inflammation. This outcome indicated that these radiolabeled antimicrobial peptides could be used in infection detection and allows the effectiveness of antibacterial therapy in animals to be monitored. Another outcome of this research was that the process allowed reliable real-time whole-body imaging and quantitative biodistribution studies without the need to kill animals at each time interval.

RADIOPHARMACEUTICALS

The USP 35–NF 30 (10) lists 77 official radioactive pharmaceuticals (12). Examples are presented in Table 18.1. The following describes some of the radiopharmaceuticals frequently used in daily practice. Several of these radiopharmaceuticals are being used for the delivery of MABs, biotechnologic drugs. For a deeper understanding of these biotechnologic drugs, including terminology, see Chapter 19.

Technetium-99 m (^{99m}Tc)

Technetium-99 m (^{99m}Tc) possesses a relatively short half-life of 6 hours, which allows administration of higher amounts of activity for faster and clearer images while exposing the patient to a low radiation dose. It offers an abundance of gamma photons for imaging without the hazardous effects of beta particles. Also, its chemistry profile is flexible, which allows it to be used as a binding agent for several pharmaceuticals used for imaging. Kits are available for preparation of various technetium ^{99m}Tc compounds that assist in hepatobiliary imaging (mebrofenin) and ischemic heart disease (sestamibi, tetrofosmin).

^{99m}Tc has also been used as a radiolabel for MABs because of its wide availability in

Table 18.1 REPRESENTATIVE RADIOPHARMACEUTICAL DRUGS AND PRIMARY USES

DRUG	TRADE NAME	PRIMARY USES
^{111}In oxyquinoline	Indium-111 Oxine	Radiolabel autologous leukocytes and platelets
^{111}In capromab pendetide	ProstaScint	MAB for imaging prostate cancer
^{111}In pentetreotide	OctreoScan	Imaging of neuroendocrine tumors
^{123}I, sodium iodide	—	Thyroid imaging and uptake
^{131}I, sodium iodide	—	Thyroid imaging, uptake, therapy
^{131}I tositumomab	Bexxar	Treatment of non-Hodgkin lymphoma
^{131}I-*m*IBG	—	Treatment of neuroendocrine tumors
^{99m}Tc exametazime	Ceretex	Cerebral perfusion, radiolabeling autologous leukocytes
^{99m}Tc macroaggregated	Pulmonite	Pulmonary perfusion albumin
^{99m}Tc mebrofenin	Choletec	Hepatobiliary imaging
^{99m}Tc medronate (MDP)	—	Bone imaging
^{99m}Tc mertiatide	TechneScan MAG3	Renal imaging
^{99m}Tc oxidronate (HDP)	OctreoScan HDP	Bone imaging
^{99m}Tc pentetate (DTPA)	Techneplex, TechneScan DTPA	Renal imaging and function studies; radioaerosol ventilation imaging
^{99m}Tc pertechnetate	—	Imaging of thyroid, salivary glands, ectopic gastric mucosa, parathyroid glands, dacryocystography, cystography
^{99m}Tc red blood cells	Ultratag	Imaging of gastrointestinal bleeding, cardiac chambers, cardiac first pass, gated equilibrium imaging
^{99m}Tc sestamibi	Cardiolite, Miraluma	Imaging of myocardial perfusion, breast tumor
^{99m}Tc sulfur colloid		Imaging of RES, bone marrow, gastric emptying, gastrointestinal bleeding, lymphoscintigraphy, arthrograms
^{99m}Tc tetrofosmin	Myoview	Myocardial perfusion imaging
^{201}Tl	—	Myocardial perfusion imaging; parathyroid and tumor imaging
^{133}Xe	DuPont Xenon, Mallinckrodt Xenon, GE Healthcare Xenon	Pulmonary ventilation imaging
^{90}Y microspheres	TheraSphere	Therapy for biopsy-proven, unresectable hepatocellular carcinoma
^{90}Y ibritumomab tiuxetan	Zevalin	Non-Hodgkin lymphoma
^{153}Sm-lexidronam (EDTMP)	Quadramet	Palliation of bone pain of skeletal metastases
^{166}Ho-DOTMP	—	Bone cancer therapy
^{186}Re-HEDP	—	Bone cancer therapy

nuclear pharmacies and because it is relatively inexpensive and easy to obtain. It provides low radiation dosimetry and highly efficient detection of photons by planar scintigraphy. Unfortunately, widespread use of this radionuclide in immunoscintigraphy has been hindered by the lack of a simple, efficient, and stable method for attaching the ^{99m}Tc to the antibody molecule.

^{99m}Tc sulfur colloid is used for imaging areas of functioning reticuloendothelial (RE) cells in the liver, spleen, and bone

marrow (13). Phagocytosis, that is, physical entrapment, of the colloidal particles by the Kupffer cells in the RE system localizes the radiopharmaceutical to the specific target organ. In addition, it has also been used for other diagnosing purposes, for example, imaging of lymphatic vessels and nodes draining a particular organ or disease site. The subcutaneous, intradermal, and interstitial administration of this preparation causes pain and discomfort at the site of injection, and consequently, lidocaine HCl is used simultaneously in a separate injection prior to administration of the ^{99m}Tc sulfur colloid. Dura and Hinkle evaluated the stability of a mixture of the colloid mixture with lidocaine HCl 1% and determined that adding 0.2 mL of lidocaine HCl 1% to the colloidal mixture and storing the syringes up to 8 hours did not affect the radiochemical purity of the mixture or alter the pH of the mixture substantially (13).

Because of availability, cost, radiation dose, and image quality, ^{99m}Tc-DPTA (diethylenetriaminepentaacetic acids; pentetate) is preferred for use of cerebrospinal fluid procedures that require shorter imaging times via intrathecal injection. However, unlike indium-111 chloride (^{111}In)-DPTA, ^{99m}Tc-DPTA is not FDA approved for intrathecal injection (14).

Strontium-89 Chloride (^{89}Sr)

Strontium-89 chloride (^{89}Sr) (Metastron) is a sterile, nonpyrogenic aqueous solution for intravenous use and contains no preservative. It decays by beta emission, with a physical half-life of 51 days. This beta emission is very harmful to skeletal tissue, and thus, its clinical use is reserved for bone pain palliation associated with primary bone tumors and metastatic involvement (blastic lesions). An advantage of ^{89}Sr is that it is retained and accumulated in metastatic bone lesions much longer and in significantly greater concentration than in normal bone.

Following intravenous administration, strontium compounds demonstrate similar characteristics to calcium analogs. They clear rapidly from the bloodstream and selectively localize in bone mineral. The uptake of ^{89}Sr by bone occurs preferentially in sites of osteogenesis imperfecta, a condition characterized by the formation of brittle bones prone to fractures. Thus, as mentioned, it finds utility with primary bone tumors and metastatic bone lesions.

Prior to administration of ^{89}Sr, a risk-to-benefit ratio must be determined because of its bone marrow toxicity. It should be used with caution in patients with platelet counts below 60,000 and white cell counts below 2,400. After administration of ^{89}Sr, weekly blood tests should be performed and the patient's status monitored. Because the average hematologic recovery time is 6 months of treatment, at least 90 days is required prior to retreatment.

A small percentage of patients receiving ^{89}Sr report a transient increase in bone pain 36 to 72 hours after injection. This is usually mild, self-limiting, and controllable with analgesic therapy. Pain relief from the administration of ^{89}Sr typically manifests 7 to 20 days postinjection, and a key benefit of its use is a decreased dependence on opioids.

Yttrium-90 (^{90}Y)

Yttrium-90 (^{90}Y), a trivalent radioactive metal, is a pure beta-emitting radionuclide. It possesses a physical half-life of 64.2 hours (2.68 days) and is frequently used in human studies, in part because of its routine availability from commercial vendors as a sterile, pyrogen-free product with high specific activity (15). Its principal therapeutic application is in RIT of solid large tumors and lymphomas. In addition, it is employed in pain palliation involving soft tissue.

TheraSphere is a therapeutic device approved for use in patients with liver cancer (Fig. 18.2). It is being used for patients with biopsy-proven unresectable hepatocellular carcinoma. It is administered to a conscious patient via a catheter inserted into the femoral artery and is delivered directly into the hepatic artery in an interventional vascular radiology suite to go to the left or right lobe of the liver. Usually, patients receive two treatments to each liver lobe.

FIGURE 18.2 TheraSphere. (Courtesy of MDS Nordion.)

Patented in 1988, it consists of microspheres having a mean diameter of 20 to 30 mm (the approximate size of two red blood cells) that are bonded chemically to a radioactive pure beta emitter (^{90}Y). After injection, the product produces radiation to tissue with an average range of 2.5 mm and a maximum range of <1 cm. These lodge in end arterioles and capillaries in tumors, which minimizes or prevents delivery of the injected radionuclide to other body organs and tissues.

The sterile, pyrogen-free glass spheres are preformed by incorporating ^{89}Y oxide into the glass matrix. Subsequently, neutron bombardment is used to convert the ^{89}Y in the glass to ^{90}Y. Because the ^{90}Y is embedded in the spheres, it is not leached from the glass or metabolized. This prevents in vivo mobilization to distant body tissues and organs (15).

The ^{90}Y decays to stable zirconium-90. Each treatment delivers approximately 150 Gy or 15,000 rad to the liver lobe. Typically, 135 to 540 mCi of ^{90}Y (5 to 10 GBq) is delivered in 10 mL of saline that contains 2 million to 8 million microspheres. This is injected over a few minutes into the right or left hepatic artery. Patients are evaluated every month thereafter. Regular blood work that analyzes blood counts and liver function is performed, as is computed tomography (CT) or magnetic resonance imaging (MRI) of the liver.

Thallous-201 Chloride (^{201}Tl)

Thallous-201 chloride (^{201}Tl) is available as a sterile, isotonic nonpyrogenic solution for intravenous administration (Fig. 18.3). It demonstrates a physical half-life of 73.1 hours and decays by electron capture to mercury, ^{201}Hg. ^{201}Tl is a potassium analog that undergoes rapid active transport into the myocardium. Thus, it is an advantageous agent in MPI for the diagnosis and localization of myocardial infarction. It may also have prognostic value regarding survival. When administered to a clinically stable patient following the onset of myocardial infarct symptoms, it helps to assess the site and size of the perfusion defect. ^{201}Tl may also be used as an adjunct to the diagnosis of ischemic heart disease, that is, atherosclerotic coronary artery disease, when used in conjunction with exercise stress testing. Identified ischemia on ^{201}Tl scanning has been demonstrated to be a strong predictor of long-term mortality in

FIGURE 18.3 Product package of thallous chloride ^{201}Tl. (Courtesy of Mallinckrodt Medical.)

coronary artery disease (16). However, long-term survival after major vascular surgery is improved significantly if patients with moderate to severe ischemia on preoperative ^{201}Tl scanning undergo selective coronary revascularization (16).

When used in conjunction with exercise stress testing to help differentiate between ischemic and infarcted tissue, ^{201}Tl should be administered at the inception of a period of maximum stress sustained for 30 seconds after injection of the agent. Imaging commences within 10 minutes after administration to obtain maximum target-to-background ratios. If the patient is unable to undergo a treadmill stress exercise because of physical limitation, pharmaceutical agents (e.g., Adenoscan, Persantine) may be used to induce cardiac stress.

^{201}Tl undergoes fast redistribution in normal myocardium. Because of decreased blood flow, the uptake and washout of ^{201}Tl are not quick in ischemic cardiac tissue. If the image demonstrates no uptake, the tissue is classified as infarcted.

Gallium-67 Citrate (^{67}Ga)

Gallium-67 citrate (^{67}Ga) is available as a sterile, pyrogen-free aqueous solution. Chemically, this drug behaves similarly to ferric ion (Fe^{+3}) and demonstrates a half-life of 78 hours.

^{67}Ga can localize in certain viable primary and metastatic tumors and in focal sites of infection. Investigational studies demonstrate that perhaps ^{67}Ga accumulates in lysosomes and is bound to a soluble intracellular protein. ^{67}Ga may be useful in demonstrating the presence and extent of malignancies associated with Hodgkin disease, lymphomas, and bronchogenic carcinoma. It can also be useful for localization of focal inflammatory lesions (e.g., sarcoidosis, abscesses, pyelonephritis). Its most important use is in the diagnosis and monitoring of *Pneumocystis carinii* pneumonia of AIDS and can be used as a diagnostic screen in cases of prolonged fever when physical examination, laboratory tests, and other imaging studies have not disclosed the source of the fever (fever of undetermined origin) (17). This is because 2-[^{18}F], fluoro-2-deoxy-D-glucose (FDG) has replaced the other uses of ^{67}Ga.

Concurrent use of ferric ion can increase ^{67}Ga renal excretion from the body. Although the exact mechanism is not clear, it is thought that elevated serum iron levels may displace ^{67}Ga from plasma protein–binding sites and hasten its excretion, resulting in decreased tumor and abscess localization.

The optimal target-to-background concentration ratios are often obtained 48 hours postinjection, and delayed imaging is necessary to allow for the ideal target-to-background ratio. However, considerable biologic variation can occur in individuals, and acceptable imaging may be performed 6 to 120 hours after injection. The optimal target-to-background ratios also depend on the area of interest. For example, a lower abdominal scan can be hindered by ^{67}Ga fecal excretion. Thus, the use of laxatives facilitates faster scanning of the patient. Both ^{201}Tl and ^{67}Ga injections contain benzyl alcohol as their preservatives. This could be problematic for those patients who demonstrate hypersensitivity to this preservative.

Indium-111 Chloride (^{111}In)

Indium-111 chloride (^{111}In) has become a popular radionuclide as a label for MABs (Fig. 18.4). The advantage of using ^{111}In for immunoscintigraphy is its long half-life, which allows multiple images to be taken up to 10 to 14 days after administration. In addition, its dual photon peaks provide superior planar and tomographic images. Because it lacks beta emission, it can be administered in rather high doses. Lastly, unlike radioiodine complexes, ^{111}In–MAB complexes are relatively stable in the body.

Capromab pendetide (ProstaScint) is a MAB imaging agent linked to ^{111}In. This drug seeks out and attaches itself to prostate cancer and its metastases. ProstaScint images can aid management by helping identify when the cancer has metastasized from the prostate bed to regional lymph nodes or to distant soft tissues. It is also used as a diagnostic imaging agent in postprostatectomy

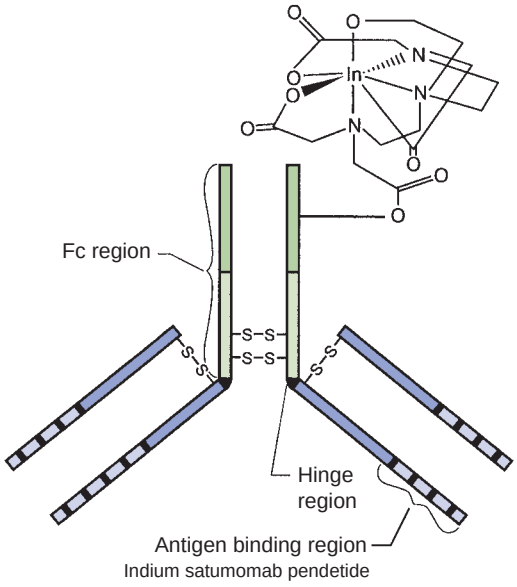

FIGURE 18.4 The indium satumomab pendetide molecule demonstrating attachment to the MAB. The antigen-binding region is also depicted. (Reprinted with permission from Hunter TB, Walsh TK, Hall JN. Agents for diagnostic imaging. In: Block JH, Beale JM Jr, eds. Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry. 11th Ed. Baltimore, MD: Lippincott Williams & Wilkins, 2004:470.)

patients with a rising prostate-specific antigen level and a negative or equivocal standard metastatic evaluation in whom there is a high clinical suspicion of occult metastatic disease. This product was approved for use by the FDA in late 1996.

Ibritumomab tiuxetan (Zevalin), approved for use in 2002, is a MAB that is separately labeled with ^{111}In and ^{90}Y in a two-phase regimen for the treatment of refractory low-grade follicular or transformed B-cell non-Hodgkin lymphoma, including patients with rituximab-refractory follicular non-Hodgkin lymphoma (Fig. 18.5). ^{111}In is used for the biodistributive study and administered 1 week prior to the final ibritumomab tiuxetan and ^{90}Y administration. This procedure ensures adequate biodistribution of the test dose. If the biodistribution is deemed unacceptable, the second step of the process is not implemented. This product works like a smart bomb. It is an antibody with a radionuclide attached that seeks and binds to cells with the CD20 receptor. Rituximab is administered

FIGURE 18.5 Product package of Zevalin. (Courtesy of Biogen Idec.)

prior to Zevalin (an unbound antibody) for both steps to clear most normal B cells and thus reduce the toxicity of the Zevalin.

The therapeutic regimen consists of two steps, as follows:

1. Initially, rituximab is infused in an amount equal to 250 mg/m^2 at 50 mg/h. The dose is increased by 50 mg/h every 30 minutes up to a maximum of 400 mg/h. During the infusion, the patient should be monitored for any hypersensitivity reaction and the infusion stopped if hypersensitivity occurs. If hypersensitivity does occur and is treated, the infusion is resumed at half the previous rate when symptoms improve. After rituximab infusion has been administered, within 4 hours, the diagnostic biodistribution dose of 5 mCi of ^{111}In-labeled ibritumomab tiuxetan is injected over 10 minutes with use of a syringe shield to reduce exposure during administration. The biodistribution of the drug is assessed by imaging within 2 to 24 hours and again 48 hours postinjection. If the biodistribution is acceptable, the second step is administered after 7 days of initial therapy. Alternatively, if the biodistribution is not acceptable, the therapy does not proceed to the second step.
2. Initiated within 7 to 9 days after step one, the patient receives another rituximab infusion of 250 mg/m^2 at an initial rate of 100 mg/h. The dosage is increased by 100 mg/h every 30 minutes to a maximum of 400 mg/h as tolerated. The therapeutic

dose is then administered according to the patient's platelet count. Because the most commonly reported adverse effect of this therapy is thrombocytopenia and neutropenia, after the rituximab infusion, if the patient's platelet count is above 150,000 cells/mm^3, a 0.4-mCi/kg dose of ^{90}Y-labeled ibritumomab tiuxetan is administered. If the patient's platelet count is between 100,000 and 150,000 cells/mm^3, a reduced dose of 0.3 mCi/kg of ^{90}Y-labeled ibritumomab tiuxetan is administered over 10 minutes. In any case, the total administered dose may not exceed 32 mCi. If the patient's platelet count is below 100,000 cells/mm^3, the drug is not administered.

The regimen is supplied in two distinct kits (Fig. 18.5) that contain all of the nonradioactive ingredients necessary to create the single doses of ibritumomab tiuxetan labeled with ^{111}In and ^{90}Y. Because ^{90}Y is a pure beta particle–emitting radionuclide, extreme precaution must be taken to protect the caregivers and the patient to keep radiation exposure levels to a minimum. While control of contamination is important in the handling of any radiopharmaceutical, it is paramount when handling a pure *beta* emitter, for example, ^{90}Y. A primary concern of handling a *gamma* emitter such as ^{99m}Tc is the shielding of its penetrating radiation, which is inversely proportional to the square of the distance from it. Radiation from pure *beta* emitters extends only a few millimeters from the source and may be shielded with acrylic shields, but skin contamination from these agents will result in a large tissue dose to caregivers.

Sodium Iodide-123 (^{123}I)

Sodium iodide-123 (^{123}I) is available as an oral capsule and is generally preferable to ^{131}I because it delivers lower radiation doses and has better imaging properties. It is used diagnostically to evaluate thyroid function and morphology. ^{123}I emits only gamma rays. In the euthyroid patient, 5% to 30% of the administered dose is concentrated in the thyroid gland at 24 hours and has an effective half-life of 13 hours. The remaining administered activity is distributed within the extracellular fluid and has an effective half-life of 8 hours. Although it is more expensive than ^{99m}Tc, ^{123}I produces a superior image because of its higher target-to-background ratio. Also, it gives a lower radiation dose.

Pharmacists must be aware that concurrently administered drugs can decrease the thyroid uptake of ^{123}I for a variety of reasons. Thus, it is recommended that these medications be withheld for a period prior to the administration of ^{123}I. For example, corticosteroids should be withheld 1 week prior to ^{123}I administration. Benzodiazepines should be withheld up to 4 weeks prior to ^{123}I administration. Vitamins, expectorants, antitussives, and topical medications containing iodine (e.g., clioquinol, Betadine) should be withheld for 2 to 4 weeks prior to the administration of ^{123}I.

Sodium Iodide-131 (^{131}I)

Sodium iodide-131 (^{131}I) is available as a volatile solution that can be purchased from a manufacturer or compounded by the nuclear pharmacist into an oral capsule or solution. In small amounts, it is used for thyroid function studies or thyroid uptake tests by determining the fraction of administered radioiodine activity taken up by the thyroid gland. The thyroid uptake test is used in the diagnosis of hyperthyroidism and in calculating the activity to be administered for radioactive iodine therapy.

Typically, the diagnostic dose of ^{131}I is 2 to 5 mCi. The therapeutic dose is higher, usually 5 to 200 mCi. The upper limit can be calculated to determine just how much radiation a particular patient can withstand. However, more than 200 mCi is usually not given.

^{131}I is also indicated for the evaluation of size, thyroid nodules, carcinoma, and masses in the lingual region, neck, and mediastinum and in the localization of functioning metastatic thyroid tumors. It finds utility in the preoperative and postoperative evaluation of patients with thyroid carcinoma and can be used to assess therapeutic effects in these patients.

The beta emissions from the ^{131}I destroy thyroid tissue and, in small amounts, can

be used for diagnostic thyroid imaging. It is not recommended for this use because of its relatively long half-life (8 days), its beta emission, and its poor resolution on gamma camera images. However, if cost is a consideration, ^{131}I is used *in lieu* of ^{123}I. It is also used when availability of ^{123}I is a concern.

The time to radioactivity visualization is generally 18 to 24 hours. However, imaging of functional thyroid metastases is generally performed at 24 to 96 hours to allow maximal uptake and minimal blood pool retention.

Tositumomab with ^{131}I (Bexxar) is a MAB product that has a radioactive substance, ^{131}I attached to it. The MAB seeks and binds to a protein receptor (CD20) on the surface of normal and malignant cells. It is indicated for treatment of patients with CD20-positive follicular non-Hodgkin lymphoma, with and without transformation, whose disease is refractory to rituximab, and who have relapsed following chemotherapy. Once it is bound to target cells, the product delivers radiation, which enhances the killing effect of the antibody. Normal B cells recover in about 9 months because the parent B cells do not possess the CD20 receptor.

Neuroendocrine tumors, such as neuroblastoma and pheochromocytoma, in adults are treated with ^{131}I-mIBG (11). Metaiodobenzylguanidine (i.e., mIBG, iobenguane) is a structural analog of guanethidine that has structural similarities to norepinephrine. This drug is selectively taken up by adrenergic neurons, the adrenal medulla, and some neuroendocrine cancer cells by an active uptake mechanism at the cell membrane. It is a good example of how targeted radionuclide therapy can be used for alternative treatment of neuroendocrine tumors, such as neuroblastoma, a heterogeneous pediatric cancer with clinical behavior related to the biologic features of the tumor. It is estimated that 50% of these patients have high-risk disease features, with overall survival rates less than 40%. Most of these children have significant tumor-related pain at the end of life. Often, too, the pain is difficult to treat. In targeted radiotherapy with submyeloablative doses, ^{131}I-MIBG has demonstrated effective palliation in highly refractory neuroblastoma. Most patients showed subjective improvement in pain and/or performance status (18). A retrospective review by Bomanji et al. (19) demonstrated that ^{131}I-MIBG also provides a good therapeutic response in adult patients with metastatic neuroendocrine tumors.

Samarium-153 (^{153}Sm)

Samarium-153 (^{153}Sm) has a short half-life, 46.3 hours (1.9 days), which can be advantageous for administering repeated doses; the difficulty is manufacturing and delivery. It is a low-energy beta emitter, which is advantageous for treating small clusters of tumorous cells. The range of its beta emissions is short and provides a good bone-to-marrow ratio. Myelotoxicity has been manageable at its approved dose schedule (1 mCi, or 37 MBq, per kilogram) (2).

^{153}Sm is chelated with ethylenediamine tetramethylene phosphonate (^{153}Sm-EDTMP, Quadramet) for the relief of pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on radionuclide bone scan (2). The recommended dose is 1.0 mCi (37 MBq)/kg administered intravenously over 1 minute through a secure indwelling catheter and followed with a saline flush. Excretion of this radiolabeled chelate occurs almost exclusively via the kidneys into urine. Within the first 15 minutes of administration of the complex, localization in the kidneys and the skeleton is high to all other organs and tissues. By 30 minutes postadministration, most of the non–bone-associated radioactivity is in the urine. The patient should be advised to urinate often after administration of the product to minimize radiation exposure to the bladder.

Several clinical trials have demonstrated significant pain relief in approximately 70% to 80% of patients studied at the standard intravenous dosage of 1 mCi/kg. Toxicity is limited to bone marrow suppression manifested by decreased leukocyte counts and thrombocytopenia. The nadir for this is 4 weeks postadministration with recovery to normal levels in 6 weeks.

^{153}Sm-labeled MABs are being used in animal research to study angiogenesis, the

development of new blood vessels from preexisting ones. Central to this process is the activator vascular endothelial growth factor, and research is being performed in laboratory animals using radiolabeled (^{153}Sm and ^{99m}Tc) antiendothelial MABs that localize in new cancerous vasculature (20).

Holmium-166 (^{166}Ho)

Holmium-166 (^{166}Ho) when complexed with 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylenephosphonic acid (^{166}Ho-DOTMP) has demonstrated potential to treat multiple myeloma and to ablate bone marrow. It is a bone-seeking complex that emits a high-energy beta particle (E_b (max) = 1.85 MeV). The long range of these beta particles produces excessive marrow suppression and destroys bone marrow cells remote from the surface of the bone where the ^{166}Ho-DOTMP deposits. Thus, it can be used for eradication of multiple myeloma cells and the normal stem cells in the marrow space.

^{166}Ho in a ferric hydroxide macroaggregate complex (^{166}Ho-FHMA) has been shown experimentally to provide beneficial outcomes for equine metacarpophalangeal and metatarsophalangeal joints. Inflamed equine joints with synovial lining hyperplasia could benefit from ^{166}Ho-FHMA–induced radiation synovectomy if excessive scar tissue formation can be avoided.

Lutetium-177 (^{177}Lu)

Lutetium-177 (^{177}Lu) is being investigated in more than 30 clinical applications, including treatment of colon cancer, metastatic bone cancer, non-Hodgkin lymphoma, ovarian cancer, and lung cancer. It is estimated that more than 500,000 new cases of these cancers occur each year in the United States and nearly 2 million cases worldwide. ^{177}Lu is a rare earth metal with a physical half-life of 6.75 days and beta emissions (E = 149 keV) that penetrate 0.2 to 0.3 mm in soft tissues. In comparison to ^{90}Y, a higher percentage of ^{177}Lu radiation energy will be absorbed in very small tumors and micrometastases (6).

^{177}Lu also emits two relatively low-abundance, low-energy gamma rays (113 and 208 keV) that allow imaging with a gamma camera but pose less radiation risk hazard to health care personnel than ^{131}I. Its most common side effects were delayed transient arthralgia and marrow suppression.

Rhenium-186 (^{186}Re) and Rhenium-188 (^{188}Re)

Rhenium-186 (^{186}Re) and Rhenium-188 (^{188}Re) are important radionuclides with therapeutic potential. The availability of ^{186}Re and ^{188}Re provides flexibility in design of radiolabeled agents that are compatible with their in vivo applications and pharmacokinetic properties. ^{188}Re has a higher beta particle energy and shorter half-life than ^{186}Re. Thus, it is generally more appropriate for larger tumor targeting and possesses a reasonably fast clearance from the blood and other nontarget tissues. Alternatively, ^{186}Re is a medium-energy beta particle emitter with a 3.7-day half-life, which makes it more appropriate for use with biomolecules that are not cleared from the bloodstream very rapidly. Its lack of availability as a high-specific-activity product limits ^{186}Re use to applications in which high–specific-activity formulations are not mandatory.

^{188}Rhenium-HEDP (Hydroxylethylene Diphosphonate)

^{188}Rhenium-HEDP (hydroxylethylene diphosphonate) is a new radiopharmaceutical for the treatment of metastatic bone pain. It is produced from a (188)W/(188)Re generator. It has a short physical half-life, 16.9 hours, and a maximal beta energy of 2.1 MeV. One study demonstrated a maximum decrease in metastatic bone pain from the third to eighth week after therapy initiation in 76% of the patients with human prostate cancer skeletal metastases. These patients described pain relief without an increase in analgesic intake (21).

POSITRON EMISSION TOMOGRAPHY

Since the early 1970s, positron emission tomography (PET) has been employed to study cerebral physiology (22). Since that time, it is a rapidly growing noninvasive

modality for the diagnosis and management of cancer. PET yields high-quality images that characterize substrate metabolism, cellular proliferation, receptor density, and other parameters used to identify cancer and evaluate its response to treatment (23). Radiolabeled tracers injected in nonpharmacologic doses are used to construct three-dimensional images by computer to demonstrate the location and concentration of the tracer of interest (24). PET allows the physician to secure an image that is essentially a low-resolution autoradiograph showing the regional concentration of a positron-emitting nuclide inside the body (25). It is a method for quantitative imaging of regional function and chemical reactions within various organs of the human body. Imaging applications of PET have shown great use, for instance, in mapping regional blood flow, oxygen metabolism, regional blood volume, rates of use of metabolic substrates, receptor-specific tracer binding, bone remodeling, tumor receptor density, and reporter gene expression (24).

The tracers used in PET imaging are natural biochemicals labeled with radionuclides of carbon, nitrogen, oxygen, and fluorine. This allows analysis in terms of physiology and biochemistry at a level of sophistication beyond that encountered in traditional nuclear medicine. No other technology can image body chemistry with such sensitivity, so that the moment-to-moment change in concentration of a tracer in the blood or tissue can be determined in absolute units. Other imaging modalities, such as CT and MRI, provide predominantly anatomic information, and this is thought to be the future of imaging. CT is based on portrayal of the distribution of attenuation of x-rays passing through the body. MRI exploits the variation in regional concentrations of hydrogen and nuclear relaxation parameters to generate image contrast and to provide information about free water content, relative blood flow, and the concentration of contrast agents. Clinical PET is being used with CT to combine anatomic information (CT) with functional molecular information (PET) to advance cancer management (24).

Chemical changes occur prior to anatomic changes in most disease states, and PET can detect functional abnormalities before anatomic changes have occurred. PET evolved with its main focus on studies of the brain and heart. However, it has emerged as a valued diagnostic tool for diagnosis and therapy monitoring of patients with lymphoma, as a means to assess estrogen receptors in primary and metastatic breast cancers and to identify resectable colorectal tumor recurrence. In epilepsy, PET and surface electroencephalography are used in concert with clinical assessment of symptoms and signs to try to localize areas of the brain that are the foci of epileptic seizures when surgical intervention is the only remaining method to prevent the seizures.

Tumors have more intermediary metabolism than normal tissue, and PET use is advantageous because it can qualitatively and quantitatively study metabolism. Several processes, including glycolysis, increased membrane glucose transfer capability, and RNA, DNA, and protein synthesis are demonstrated and/or accelerated in tumors. In the 1930s, Warburg demonstrated that glucose was used more in tumorous tissue than in normal tissue, and this remains today as a foundation for PET imaging in oncology (26). The radiopharmaceutical most widely used for evaluating tumors with PET imaging is [^{18}F]-fluorodeoxyglucose because it has been demonstrated useful for tracing glucose metabolism, for detecting malignant tissue, and for quantifying changes in tumor glycolysis during and after treatment. Thus, it is useful for diagnosis, staging, and monitoring various cancers, including lung, colorectal, melanoma, lymphoma, and head and neck, among others. [^{18}F]-FDG has a 110-minute half-life, which is much easier to work with than a 2-minute half-life. PET scanning has also been demonstrated to predict accurately a patient's clinical and pathological response and survival in patients who undergo preoperative chemotherapy on the treatment strategy for esophageal carcinoma (27).

When a radionuclide within the body decays by emission of a positron, that particle travels a very short distance (1 to 4 mm)

in body tissues or water before expending its kinetic energy and combining with an electron. This interaction, one positron annihilation, results in simultaneous emission of two photons, each having a specific energy (511 KeV) and emitted exactly 180° from each other. Therefore, two scintillation detectors are placed, one on either side of the tissue that contains the radionuclide. Detectors are connected to a coincident circuit that provides an output only when a certain level of gamma ray radiation can be simultaneously detected by both. The result is a low-background detector, highly specific for the particular radionuclide and providing excellent resolution.

Radionuclides that undergo positron decay generally have very short half-lives (e.g., ^{15}O; $t_{½}$ = 2.04 minutes), which permit administration of large doses of activity without subjecting the patient to excessive radiation exposure. The resulting high count rates facilitate collection of statistically significant images in a very short time and a dynamic study of physiologic processes that produces a quick fluctuation in tissue concentrations of the tracer. The short half-lives also allow repeat image studies within a brief time with no confounding background activity from the prior injection.

It is optimal to label radiopharmaceuticals using radionuclides with the shortest half-life that is compatible with the time scale of the physiologic process to be studied. However, a practical consequence of using short-lived ($t_{½}$ < 1 hour) radionuclides in diagnostic medicine is the necessity for the radionuclide production and radiotracer synthesis to occur in the hospital where the imaging procedure will be conducted. Originally, the major production of radionuclides for PET imaging (^{11}C, ^{13}N, ^{15}O, ^{18}F) was generally with in-house biomedical cyclotrons. Today, however, there are numerous commercial cyclotrons nationwide.

For tracers that have demonstrated great utility in PET imaging studies, robotic technique and automated systems have been created for routine radiopharmaceutical synthesis. These systems cannot reduce the personnel needed to supply PET radiopharmaceuticals, but the automated systems encourage frequent syntheses using large amounts of activity to be performed without exposing the personnel to unnecessary or excessive radiation exposure.

PET was once conducted primarily in large medical centers. A prime consideration was that PET radionuclides had short half-lives, often 2 to 20 minutes, which made it difficult to get them from commercial sources. However, commercial dispensing is now possible in certain markets where a PET cyclotron is adjacent to the pharmacy. In other markets, out of necessity, the production facility must be on-site, and after rapid synthesis, the pharmaceutical must be purified. Thus, research continues to focus upon sources of PET radionuclides other than cyclotrons, such as radionuclide generators, that would allow PET technology in community-based nuclear medicine and pharmacy environments.

Parent–daughter generator systems are now being investigated as a possible mode to produce PET radionuclides. Potentially, it would free PET imaging from its dependence on cyclotron generation within a hospital. Also, this could make PET a viable clinical diagnosis tool away from the hospital or large medical center. To date, very few positron emitters can be created by these systems, and only two radionuclides, ^{82}Rb and ^{68}Ga, have been extensively reported in the nuclear medicine literature. In late 2003, Ion Beam Applications was granted FDA approval of a generator (CardioGen-82) to make ^{82}Rb, a PET agent for the evaluation of coronary artery disease. It is capable of distinguishing normal from abnormal myocardium in patients with suspected myocardial infarction, and it helps identify patients most likely to benefit from further intervention while reducing the risks of unnecessary medical, radiologic, and/or surgical procedures. The use of this infusion system is growing and is especially useful in obese/diabetic patients who have more adipose tissue, which causes attenuation artifacts. A real perfusion defect may be exaggerated in size and severity using single-photon emission computed tomography. Alternatively, a real perfusion defect can

be hidden within an area of apparent attenuation. PET imaging, utilizing a transmission scan in addition to an emission scan, corrects this problem. It gives a truer picture of cardiac perfusion and viability during stress. Only pharmaceutical stressing agents can be used with this system.

The ^{82}Rb generator is very expensive and has a 30-day useful life. Typically, this generator was cost prohibitive unless the facility had a significant patient volume. Commercial nuclear pharmacies have developed a service that allows various departments to share a generator. They deliver and pick up generators on a daily basis.

Future studies of new drug entities will include pharmacokinetic determination using PET technology. Further, PET will allow the manufacturer to quantify how much of the drug reaches a specific drug receptor. Thus, comparative PET studies will shed light on which drug, for example, within a therapeutic category can attain the best distribution and concentration at the intended receptor site. It is also conceivable that PET technology will open new vistas for interpretation of drug interactions, particularly where there is competition by two drugs for one receptor site. PET imaging is also being investigated as a mechanism for the early diagnosis of infection and the capacity to distinguish between bacterial and sterile inflammation. Investigations have included radiolabeled antibiotics such as ^{18}F-ciprofloxacin and ^{18}F-fleroxacin (28). Attempts are being made to understand the mechanisms of binding and accumulation of radiopharmaceuticals to bacteria. The goal is to discover a specific, reliable method to image infection that can be used to replace or complement scintigraphy with radiolabeled autologous leukocytes or radiolabeled MABs to granulocyte antigens (28).

Longer-lived PET radionuclides, such as ^{89}Zr ($t_{½}$, 78.1 hours), ^{76}Br ($t_{½}$, 61.1 hours), ^{124}I ($t_{½}$, 4.15 days), and ^{64}Cu ($t_{½}$, 12.8 hours), are being investigated as radiolabels for MAB-based PET imaging. Early clinical research has demonstrated that these may be useful for detecting metastases smaller than 1.5 cm. About 2% to 4% of cancer patients have an initial diagnosis of cancer of unknown primary origin (29). In addition to cancer diagnosis, radiolabeled MABs have been used to evaluate cardiovascular disorders. Clinical uses of ^{111}In antimyosin include detection of acute myocardial infarct, perioperative myocardial damage assessment, detection of acute myocarditis, diagnosis of rejection and management of patients after heart transplantation, and diagnosis of active rheumatic carditis, among others. The European Council of Nuclear Cardiology published its position paper that summarized the current and future potential of PET as a clinical cardiovascular diagnostic imaging tool (30). Included in the statement was evidence demonstrating the superior diagnostic accuracy of PET and its value to guide clinical decision making.

Table 18.2 lists PET radiopharmaceuticals used in common imaging procedures, and the following section highlights a few of the more frequently used PET radiopharmaceuticals.

Carbon-11 Radiopharmaceuticals

^{11}C has been incorporated into a number of organic molecules (e.g., carboxylic acids, alcohols, glucose) for use in diagnostic imaging despite its relatively long half-life (20 minutes). To date, palmitic acid is the carboxylic acid used most in PET imaging. As a tracer, it has found utility in the study of myocardial metabolism.

Glucose randomly labeled with ^{11}C has been produced photosynthetically for use in studies of cerebral glucose metabolism. The use of ^{11}C glucose for cerebral glucose metabolism requires imaging less than 5 minutes after injection.

Nitrogen-13 Radiopharmaceuticals

^{13}N ammonia has been used as a tracer for cerebral and myocardial blood flow and demonstrates a half-life of 10 minutes. It undergoes a relatively long extraction into these organs and exhibits prolonged retention, as a major fraction of extractor tracer is metabolically incorporated into amino acids.

Table 18.2 POSITRON-EMITTING RADIOPHARMACEUTICALS USED IN COMMON PET IMAGING PROCEDURES

RADIOPHARMACEUTICAL	APPLICATION	TYPICAL DOSE (mCi), PROCEDURE[a]
[^{15}O]-oxygen	Cerebral oxygen extraction, metabolism	50–100
[^{15}O]-carbon monoxide	Cerebral blood volume	50–100
	Myocardial blood volume	50–100
[^{15}O]-water	Cerebral blood flow	80
	Myocardial blood flow	150
[^{13}N]-ammonia	Myocardial blood flow	15–25
[^{11}C]-acetate	Myocardial metabolism	30
[^{11}C]-*N*-methyl spiperone	Dopamine receptor binding	20
[^{18}F]-fluorodeoxyglucose	Cerebral glucose metabolism	5–20
	Myocardial glucose metabolism	
	Tumor glucose metabolism	
[^{82}Rb]-Rb^{+}	Myocardial blood flow	10–40

[a]Many PET studies combine imaging procedures (e.g., measurements of both blood flow and metabolism); the doses given here are typical of those actually used in each procedure of the study. For a single imaging procedure, an allowable dose (a dose that does not lead to excessive radiation exposure) may be significantly higher than these values.

For study of pulmonary ventilation, ^{13}N gas is superior to the radioactive noble gases because of its lower solubility in blood.

Oxygen-15 Radiopharmaceuticals

^{15}O is the radionuclide of oxygen with the longest half-life, 2.04 minutes. Because very little time is available for tracer synthesis, PET imaging studies employing ^{15}O are restricted to use of a few relatively simple molecules.

Four ^{15}O radiopharmaceuticals are available for clinical use. These are ^{15}O oxygen gas (^{15}OO), ^{15}O carbon monoxide (C^{15}O), ^{15}O carbon dioxide (CO^{15}O), and ^{15}O water ($H_2{}^{15}O$) having been used in hemodynamic studies that take advantage of their short half-life to allow administration of large doses of activity (up to 100 mCi) in imaging studies that can be repeated within 8 to 10 minutes with no carryover effect.

Labeled oxygen gas, that is, ^{15}OO, can be used directly in studies of oxygen metabolism or can be converted to carbon monoxide, carbon dioxide, or water. C^{15}O can be safely administered via inhalation and serves as a tracer for red blood cell volume upon binding of the C^{15}O to hemoglobin.

$H_2{}^{15}O$ can be used in equilibrium studies of tissue water content and finds its greatest use as a tracer for regional blood flow. Commonly used as a tracer in PET evaluation of cerebral and myocardial perfusion, its 2-minute half-life outweighs its limitation of ability to diffuse freely across the blood–brain barrier at high flow rates.

Fluorine-18 Radiopharmaceuticals

^{18}F has a relatively long half-life among positron emitters, 110 minutes. Compared to radiopharmaceuticals with a shorter half-life, this presents several distinct advantages for synthesis and allows delivery of the radionuclide to imaging centers at a distance from the generating cyclotron.

^{18}F also demonstrates specific activity that makes it attractive for use as a receptor-specific tracer binding. It is taken up by cells, is phosphorylated by hexokinase whose mitochondrial form is greatly elevated in rapidly growing malignant tumors, and is retained by tissues that demonstrate high metabolic activity, for example, malignant tumors. As a result, its major use has expanded beyond the imaging of cerebral, myocardial, and tumor

metabolism with 2-[^{18}F]-FDG to include colorectal cancer, breast cancer, melanoma, and lung cancer (31). In brain imaging procedures, FDG maps normal brain metabolic activity and highlights glucose consumption patterns within the hippocampus and identifies specific images associated with normal brain function, mild cognitive impairment, and different types of dementia, including Alzheimer disease (32). In cardiac studies, it identifies ischemic regions in which glucose metabolism increases as a consequence of decreased fatty acid metabolism. As mentioned earlier, glucose metabolism increases in tumor tissue, and FDG localization in that tissue is extremely helpful in the imaging study (33).

Gallium-68 Radiopharmaceuticals

^{68}Ga is rapidly bound by the iron-binding sites of transferrin following intravenous injection of ^{68}Ga citrate and is very useful in studies of regional plasma volume. When combined with a C^{15}O measurement of regional blood cell volume, the ^{68}Ga-transferrin PET study allows calculation of the regional hematocrit. ^{68}Ga-transferrin has also been employed in pulmonary studies of vascular permeability.

DRUG ANTIDOTE FOR RADIATION EXPOSURE

In October 2003, the FDA approved Prussian blue (ferric hexacyanoferrate, Radiogardase) to treat patients from the harmful levels of ^{137}Cs or thallium radiation exposure and contamination (Fig. 18.6). These are radioactive agents that terrorists might conceivably use to release from a dirty bomb that would be inhaled or ingested by victims. The two radioactive substances can cause serious illness and death when they gain entry, as the organs absorb high doses of radiation. At lower doses, these agents can cause cancer. Conventionally, ^{137}Cs is used in a wide range of devices to treat certain cancers. Nonradioactive thallium is used industrially and as a rat poison. In small quantities, radioactive thallium is used for medical imaging.

FIGURE 18.6 Radiogardase capsules. (Courtesy of Heyltex Corporation.)

Prussian blue was first manufactured in 1704 as a dye for Prussian military uniforms. To treat cesium and/or thallium radiation exposure, Prussian blue is administered orally in a dose of 3 g three times daily in adults and adolescents. In children aged 2 to 12 years, the dosage is 1 g/d. It works by trapping cesium and thallium ions in the gastrointestinal tract and interrupts their reabsorption back into the systemic circulation. Prussian blue is not absorbed from the gastrointestinal tract to a significant degree. Studies have demonstrated that 99% of the oral dose is excreted in the stool. The duration of treatment depends on the extent of exposure. Preferably, it should be administered as soon as possible after exposure and is continued for 30 days. After this treatment period, the patient should be reassessed.

Counseling a patient prescribed Prussian blue is very important. Food has been demonstrated to increase its effectiveness by stimulating bile secretion. If it is more convenient, as for patients (e.g., young children, geriatric patients) who cannot swallow solid doses, the capsules may be opened and mixed with liquid or bland food. Patients should be forewarned that constipation may occur, and if so, they should increase their dietary fiber. In addition, because the drug is a dye, it may discolor the stool blue, and if it is administered as a liquid or with bland food, it may discolor the lining of the mouth.

It is important that pharmacists help the patient identify the source of the radiation and take appropriate safety measures to minimize exposure to others. Also, men should urinate in a stool rather than a urinal and flush the toilet several times after relieving

themselves. Prussian blue is available as an artist's dye, so patients should be forewarned and dissuaded from using that source as a means to treat themselves, as it is not prepared in accordance with pharmaceutical safety procedures.

NONRADIOACTIVE PHARMACEUTICAL USE IN NUCLEAR MEDICINE

The advantage of radiopharmaceutical imaging is that it is a noninvasive modality in the diagnosis and workup of a disease. Generally, radiopharmaceuticals used diagnostically help to monitor a physiologic process without altering it. Sometimes, however, the information gained from the procedure is inadequate to address the clinical questions. To overcome this deficiency, interventional pharmaceutical drugs are used to complement the radiopharmaceutical (34).

These interventional pharmaceutical drugs alter the physiologic process being studied with radiopharmaceuticals. When the interventional drug is used in conjunction with nuclear medicine, the amount of information gained is greatly improved. This intervention improves the information about the process under study and may increase the specificity and sensitivity of the procedure or decrease the time necessary for imaging.

Acetazolamide (Diamox)

Acetazolamide (Diamox), an agent used to treat glaucoma by diuretic action, has been shown to increase cerebral blood flow following intravenous administration. On average, it can increase cerebral blood flow 23% ± 8% in normal vessels. Its use in cerebral perfusion studies is to enhance the differentiation between normal vessels and diseased vessels, which cannot easily dilate. It is indicated for use in patients with transient ischemic attack, carotid artery disease, or a cerebrovascular accident to help identify areas of the brain that are at risk for an infarct. The drug also is used in other neurologic conditions (e.g., Alzheimer disease, multiinfarct dementia) with which cerebral perfusion is far from optimal.

Captopril (Capoten)

Captopril (Capoten) is used to help diagnose renovascular hypertension in hypertensive patients with abdominal bruits, declining renal function, and poorly controlled hypertension with drug therapy. As an angiotensin-converting enzyme inhibitor, this drug blocks conversion of angiotensin I to angiotensin II and prevents vasoconstriction of the efferent arterioles of the kidney. This decreases glomerular filtration pressure in the affected kidney.

Cimetidine

Among children, Meckel diverticulum, a congenital anomaly of the gastrointestinal tract, presents itself in about a quarter of the cases as rectal bleeding and abdominal pain. This diverticulum, an abnormal remnant of the developing gastrointestinal tract, contains gastric mucosa that bleeds abnormally. This gastric mucosa concentrates ^{99m}Tc-pertechnetate as normal mucosa, and cimetidine (i.e., Tagamet) demonstrates usefulness in Meckel diverticulum imaging by virtue of its action as a histamine H_2 receptor antagonist. Cimetidine reduces the volume and concentration of stomach acid, and following its administration in a Meckel's study, the cells of the gastric mucosa continue to accumulate ^{99m}Tc-pertechnetate, but secretion of acid into the gastric lumen is reduced or prevented. This allows for continual ^{99m}Tc-pertechnetate accumulation in the gastric mucosa with little transit through the intestinal tract. This results in an enhanced ability to visualize the small area of ectopic gastric mucosa.

Dipyridamole (Persantine) and Adenosine (Adenocard)

Dipyridamole (Persantine) is used as an alternative to a treadmill stress test prior to cardiac imaging. Typically, patients who are candidates to receive pharmaceutical stress as part of the imaging procedure rather than perform the stress test are those with cardiac, respiratory, and/or orthopedic problems; those maintained on beta-blocker or calcium channel blocker medications; and those with poor motivation. Dipyridamole blocks

adenosine deaminase, the enzyme responsible for the degradation of adenosine, a potent coronary vasodilator. Adenosine can increase coronary blood flow up to four to five times the resting values. Blood flow through stenosed arteries is less than normal.

Adenosine (Adenocard) is an ideal agent in combination with MPI agents. It possesses an ultra short half-life, less than 10 seconds, and is a potent coronary vasodilator. This drug can increase coronary blood flow four to five times that of rest and can be beneficial as a pharmaceutical stress agent to help diagnose and identify stenosed arteries.

Dipyridamole and adenosine are available from commercial nuclear pharmacies in patient-specific unit dosage forms. In preparation for the use of adenosine or dipyridamole, theophylline- and caffeine-containing drugs, beverages, and foods must be discontinued, and the patient must take nothing by mouth overnight. An advantage of adenosine use over dipyridamole is that adverse effects caused by adenosine (e.g., chest pain; pain in the throat, jaw, or arm; headache; flushing; and dyspnea) generally disappear within 1 to 2 minutes after discontinuation of the infusion. Dipyridamole has a longer half-life (15 to 30 minutes) with a peak effect 2 to 3 minutes after infusion. When this agent is used, chest pain, headache, and dizziness occur most often.

To reverse the effects of adenosine and dipyridamole, aminophylline can be given intravenously if necessary. Nitroglycerin can be given to relieve the chest pain that follows dipyridamole administration.

Furosemide (Lasix)

Furosemide (Lasix), a loop diuretic, is administered to help confirm or rule out mechanical renal obstruction during renal scintigraphy when significant retention of radioactivity is noted in the renal pelvis. It inhibits the reabsorption of electrolytes, most notably sodium, in the ascending limb of the loop of Henle and in the proximal and distal tubules. In an obstructed kidney, furosemide diuresis will have little effect on clearance of the radioactivity retained in the kidney. An unobstructed kidney will rapidly clear the radioactivity into the bladder following furosemide administration, and the renograms will show rapid emptying with a steeply declining radioactivity curve.

Vitamin B_{12}

Schilling test determines a patient's capability to absorb radioactive vitamin B_{12} from the intestine. Normally, vitamin B_{12} is released from food sources (e.g., meat, eggs, milk) and bound to intrinsic factor in the stomach. Ultimately, this intrinsic factor–vitamin B_{12} complex is absorbed in the ileum and stored in the liver. Once the liver's storage capacity for this complex is exceeded, vitamin B_{12} is excreted in urine. In cases of vitamin B_{12} deficiency, it is crucial to determine the cause of the deficiency, either lack of a proper diet or inadequate absorption. For the procedure, 1 mg of nonradioactive vitamin B_{12} is given intramuscularly 2 hours before the ^{57}Co-labeled vitamin B_{12} is administered orally. This large dose is intended to saturate the storage sites and helps flush absorbed radiolabeled B_{12} into the urine. Thus, the excreted radioactivity demonstrates the amount absorbed. Excretion of 5% or less is diagnostic of B_{12} malabsorption. Typical urinary excretion of B_{12} ranges from 15% to 40%.

PRACTICE OF NUCLEAR PHARMACY

As nuclear medicine has evolved from a research tool into a mainstream clinical, diagnostic, and therapeutic tool, so has the practice of pharmacy evolved within nuclear medicine. The skills of pharmacists play an important role in the safe and efficient operation of nuclear pharmacies and modern PET facilities. In particular, the role of the pharmacist in PET increases as the use of PET radiopharmaceuticals grows from research to clinical to commercial environments.

Internal dose models and methods in use for many years are well established in nuclear medicine. These allow calculation of radiation doses to stylized models representing reference individuals. In the future, kinetic analyses will have to be carefully planned, and dose conversion factors that are most similar to the subject in question should

be chosen to increase patient specificity. The important point is that the pharmacist uses his or her expertise to become a part of this and use patient image data to construct individualized models for more detailed and patient-specific dose calculations (35).

The Nuclear Pharmacy Practice Guidelines were created by the American Pharmacists Association Academy of Pharmacy Practice and Management Section of Nuclear Pharmacy. They were adopted in 1994, and the Specialty Council on Nuclear Pharmacy of the Board of Pharmaceutical Specialties validated them in 1995. The Specialty Council surveyed all board-certified nuclear pharmacists about the importance and frequency of each domain, task, and knowledge statement in the guidelines. This validation served as the underpinning for creation of the board examination in nuclear pharmacy. It established the proportion allotted to each of the nine identified domains on the nuclear pharmacy specialty examination (36).

Nuclear pharmacy is a patient-oriented service that embodies the scientific knowledge and professional judgment required to improve and promote health through safe and efficacious use of radioactive drugs for diagnosis and therapy. The pharmacist is expected to understand nuclear medicine procedures and their advantages and disadvantages for diagnostic or therapeutic purposes (37).

Typically, nuclear pharmacy practice occurs primarily in two settings: a large teaching hospital or a centralized commercial operation. Approximately, 95% of radiopharmaceuticals are produced in the commercial setting. With practice site differences, activities may not be all-inclusive at each site. The nine general activities encompassing nuclear pharmacy practice are procurement, compounding, quality assurance, dispensing, distribution, health and safety, provision of drug information and consultation, monitoring patient outcomes, and research and development.

Procurement and Storage

Nuclear pharmacists are responsible for securing radiopharmaceuticals, other appropriate drugs, supplies, and materials necessary to effect appropriate outcomes. The effectiveness of some diagnostic radiopharmaceuticals is enhanced or toxicity lessened by coadministration of other drugs. For example, some patients (e.g., elderly, obese, those with orthopedic problems) may not be capable of undergoing an exercise stress test prior to administration of a radiopharmaceutical intended to visualize cardiac perfusion. Thus, as mentioned earlier in this chapter, dipyridamole, a vasodilator, can be used as a substitute for the exercise stress test.

The short half-life of radiopharmaceuticals poses a special problem to the pharmacist in that the traditional pathways (e.g., drug wholesaler) to secure the drug may take longer than the lifetime of the drug. Typically, in the past, the nuclear pharmacist would order the drug directly from the manufacturer, primarily by overnight delivery. Therefore, knowledge of calibration time, shipping and delivery schedules, and radioactive decay associated with the ordered radiopharmaceutical weigh heavily in ordering. Limited quantities also played a vital role in the attempt to obtain products. All of this has led to the rise of centralized radiopharmacies.

Commercial radiopharmacies set up two distinct areas. The first includes general office workspace (e.g., storage, break rooms, restrooms). The second area is dedicated as a laboratory or pharmacy area. The latter area having restricted access, thus, is called the "restricted area." Within the "restricted area," there are separate areas for radioactive material storage, compounding and dispensing, quality control testing, and packaging and distribution. Dose calibration (i.e., counting) is performed in the compounding and dispensing area. Typically, this is an area that consists of laminar flow hoods and counter space. Each laminar flow hood contains a dose calibrator so that each unit dose can be "counted" by the dispensing pharmacist or nuclear pharmacy technician. There is no patient treatment area. Imaging clinics (e.g., cardiology, oncology, general nuclear), typically, purchase unit dose radiopharmaceuticals from a commercial nuclear pharmacy.

Typically, hospital nuclear pharmacies are separate from the hospital pharmacy

and are adjacent to the nuclear medicine or radiology departments. Usually, doses are prepared in the hospital nuclear pharmacy area and transported to the nuclear medicine department for administration by a nurse or certified nuclear medicine technologist in a treatment/administration room or private patient area. The patient is then brought to the "camera room" for imaging.

Preparation of the Radiopharmaceutical

Compounding of the radiopharmaceutical can be a simple (e.g., reconstituting reagent kits with ^{99m}Tc sodium pertechnetate) to very complex task (e.g., operating a cyclotron). Aside from the typical compounding procedures with a normal prescription (e.g., receipt of order, validation, safety of dose, supplies and equipment to prepare), the preparation of a radiopharmaceutical is confounded by issues of radioactivity and chemical reactions.

Compounding of a radiopharmaceutical involves chemical reactions to label a molecule with a radionuclide. For most ^{99m}Tc-labeled compounds, stannous chloride is used to reduce Tc(VII) pertechnetate to a lower oxidation state. This then is followed by chelation of the technetium atoms by multidentate ligands. For other radiopharmaceuticals, covalent bonding, transchelation, and coordination complexation reactions are used.

Manufacturers produce ready-to-use radiopharmaceuticals (e.g., ^{201}Tl-thallous chloride) and radionuclides used in compounding radiopharmaceuticals at the nuclear pharmacy. Expense, limited availability, and shipping schedules, however, dictate that some radiopharmaceuticals be created on-site at a central radiopharmacy using a cyclotron, particularly for PET due to their very short half-lives. Because of this necessary path of preparation, these are usually more expensive than those purchased directly from the manufacturer. A significant number of radiopharmaceuticals use ^{99m}Tc in the form of sodium pertechnetate plus sodium chloride for isotonicity. ^{99m}Tc is formed by decay of ^{99}Mo, a radioactive radionuclide of molybdenum obtained by neutron bombardment of ^{98}Mo. Commonly, a generator or "cow" containing ^{99}Mo (half-life, 67 hours) produces the sodium pertechnetate ^{99m}Tc at a rate that permits daily elutions of the generator (Fig. 18.7). "Milking the cow" is slang for eluting the generator to obtain the sodium pertechnetate. Other cyclotron-produced radiopharmaceuticals (e.g., ^{111}In, ^{123}I, ^{201}Tl) may be ordered for the next day. Many cyclotrons are operated as manufacturers and follow cGMP guidelines although this has not been mandated as yet by the FDA. It is anticipated that a mandate will be forthcoming and compliance will be expected in 2 years thereafter. At this writing, the publishing of the final rule is anticipated soon. As a result, many independent nuclear pharmacy owners have expanded and installed cyclotrons. The elution or the process of elution is related to the act of obtaining a radiopharmaceutical from a solid column generator or "cow." The eluate can then be used as is or added to another "cold" pharmaceutical to compound a radiopharmaceutical. The elution process usually uses a liquid, that is, 0.9% sodium chloride solution (NSS), but there have been generators that use gas, for example, air and oxygen. This process is similar, for example, to ion-exchange chromatography.

A significant majority of radiopharmaceuticals are produced for parenteral administration. Aseptic technique and methods must be maintained during preparation of the radiopharmaceutical and when radiolabeling biologic products (e.g., MABs, peptides). For example, to compound a vial of ^{99m}Tc radiopharmaceutical, the pharmacist takes an elution and removes the required amount of eluent and injects it aseptically into a vial and then adds a sufficient amount of NSS to bring it to its proper concentration. Further, strict adherence to universal precautions and appropriate infection control handling are a necessity when radiolabeling patient blood cells.

There are no differences between commercially available products and pharmacy compounded products other than the fact that the compounded products are dispensed in syringes. With solid, commercially available oral dosage forms such as capsules, there might be different colors of capsules or sizes,

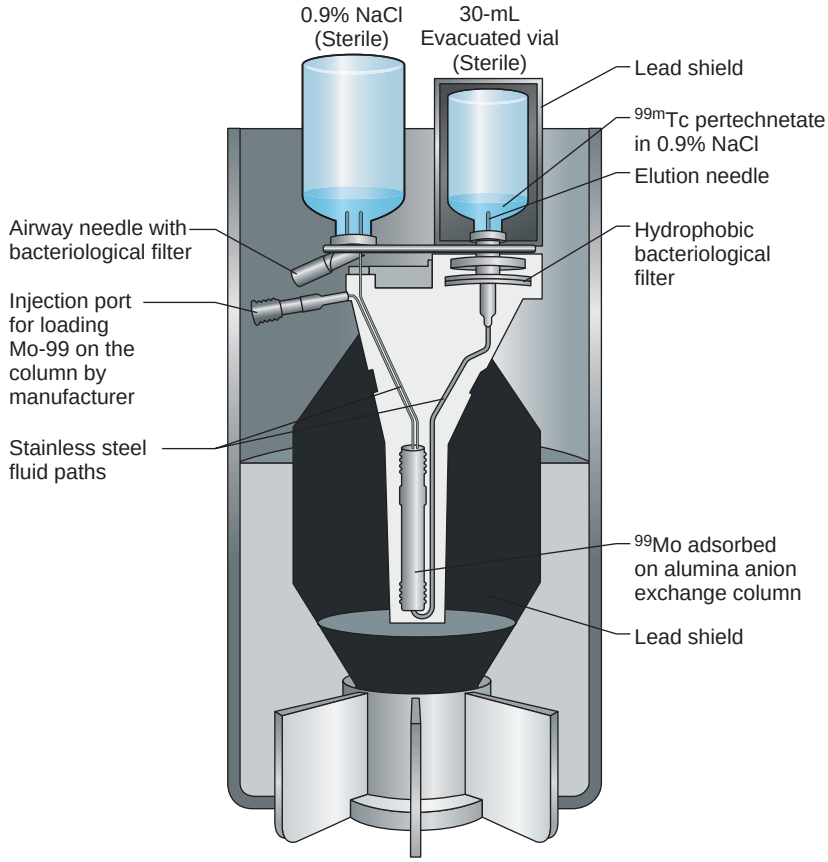

FIGURE 18.7 Cross section of a radionuclide generator for production of ^{99m}Tc by sterile 0.9% sodium chloride elution of a sterile alumina (Al_2O_3) column that has ^{99}Mo adsorbed onto it. (Reprinted with permission from Hunter TB, Walsh TK, Hall JN. Agents for diagnostic imaging. In: Block JH, Beale JM Jr, eds. Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry. 11th Ed. Baltimore, MD: Lippincott Williams & Wilkins, 2004;462. Courtesy of Dupont-Pharma, Billerica, MA.)

but other than physical appearance of the dosage form, they look alike and work the same.

Hung et al. (38) identified potential deficiencies in manufacturers' product package insert instructions for the preparation of radiopharmaceutical products. Five categories were identified as follows: (*a*) absent or incomplete instructions, particularly with respect to quality assurance procedures; (*b*) restrictive directions, such as specific instructions for chromatography solvents, counting devices, and reconstitution processes; (*c*) inconsistent instructions, such as different reconstituted volumes for the same final drug product, and unworkable expiration dates; (*d*) impractical directions, such as unrealistically low reconstituted activity limits and dangerously high numbers of radiolabeled particulate matter; and (*e*) vague instructions, such as use of "should," "may," and "recommend." The authors concluded that the manufacturers' instructions for the preparation of these products should be viewed as standard guidance rather than as requirements. They also advocated that nuclear pharmacists be allowed to use alternative validated methods to prepare radiopharmaceutical products as long as they do not conflict with normal pharmacy practice.

Quality Assurance

To ensure the safe use of radiopharmaceuticals in patients, the pharmacist must carry out appropriate tests (e.g., chemical,

physical, biologic). USP monographs dictate that radiopharmaceuticals meet delineated specifications, including radionuclidic purity, radiochemical purity, chemical purity, pH, particle size, sterility, pyrogenicity (or bacterial endotoxin), and specific activity. When the pharmacist uses an already prepared radionuclide (e.g., ^{201}Tl, ^{123}I, ^{131}I), these qualities are assured by the manufacturer.

Radionuclidic purity is the proportion of activity present as the stated nuclide. It can be measured by gamma ray spectroscopy, half-life measurement, and/or other physical measurements that help to detect the presence of extraneous nuclides. Examples of the lack of radionuclidic purity are ^{198}Au contaminated with ^{199}Au and ^{99m}Tc contaminated with ^{99}Mo.

Radiochemical purity is the fraction of the stated radionuclide in the stated chemical form. If there are nonradioactive contaminants, the radioactive drug may be radiochemically pure but not chemically pure. Similarly, if there are small amounts of radioactive contaminants, the material may be chemically pure but not radiochemically pure. Column or thin-layer chromatography is useful for purity determination.

Dispensing of a Radiopharmaceutical

A distinct difference between radiopharmaceutical dispensing and the traditional mode by which ordinary prescriptions are dispensed is that radiopharmaceuticals never go directly to the patient; they are provided to trained health care professionals at the hospital or clinic and then administered to the patient. Also, because of the nature of the product, radiopharmaceuticals typically are dispensed in unit doses and, typically, as injectables.

When the radiopharmaceutical is ordered, the dispensing pharmacist must ensure that the ordered dose is safe for the patient. Thus, the pharmacist must weigh and consider patient factors such as age, weight, surface area, and gamma camera sensitivity with each order. Usually, prescriptions are ordered and shipped. Therefore, radioactive decay must be considered to accommodate the time from manufacture to administration. Because the product is a radiopharmaceutical, it is subject to special labeling requirements (e.g., standard radiation symbol, CAUTION—RADIOACTIVE MATERIAL).

Radiopharmaceuticals compounded from sterile components in closed sterile containers and with a volume of 100 mL or less for a single-dose injection or not more than 30 mL taken from a multiple-dose container are designated as and conform to the USP <797> standards for Low-Risk Compounded Sterile Products (CSPs) (39). Radiopharmaceuticals are to be compounded using appropriately shielded vials and syringes in a properly functioning and certified ISO class 5, primary engineering control room located in an ISO class 8 or cleaner air environment to permit compliance with special handling, shielding, and negative air flow requirements.

Radiopharmaceutical vials designed for multiuse, compounded with ^{99m}Tc, exposed to ISO class 5 environment, and punctured by needles with no direct contact contamination may be used up to the time indicated by the manufacturer's recommendations. Storage and transport of properly shielded vials or radiopharmaceutical CSPs may occur in a limited access ambient environment without a specific ISO class designation.

^{99m}Tc/^{99}Mo generator systems are to be stored and eluted under conditions recommended by the manufacturer and applicable state and federal regulations. Such generator systems are to be eluted in an ISO class 8 or cleaner air environment to permit special handling, shielding, and air flow requirements. To limit acute and chronic radiation exposure of inspecting personnel to a level that is as low as reasonably achievable (i.e., ALARA), direct visual inspection of radiopharmaceutical CSPs containing high concentrations of radioactivity doses shall be conducted in accordance with ALARA.

Radiopharmaceuticals prepared as low-risk level CSPs with 12-hour or less beyond-use date are to be prepared in a segregated compounding area. A line of demarcation defining the segregated compounding area shall be established. Materials and garb exposed in a patient care and treatment area

shall not cross a line of demarcation into the segregated compounding area.

Radiopharmaceuticals for PET compounding conform to the USP <823> standards (40). This section of the USP provides the requirements for the control of components, materials, and supplies of the PET radiopharmaceuticals. In addition, compounding procedure verification and stability testing and expiration dating are provided. USP <823> also delineates PET radiopharmaceutical compounding for human use. In this section, quality control procedures are to be established by a designated, qualified, and trained individual who is responsible to ensure that the activities are conducted and properly completed by qualified and trained personnel.

Quality control tests to be performed on individual batches of PET radiopharmaceuticals, the analytical procedures, and the corresponding acceptance criteria are to be established in writing. The procedures are for PET radiopharmaceuticals labeled with a nuclide having a $t_{½}$ > 20 minutes and PET radiopharmaceuticals labeled with a nuclide having a $t_{½}$ < 20 minutes. For each batch of PET radiopharmaceutical intended for parenteral administration, a membrane filter integrity test must be performed immediately after completion of product filtration. In addition, an in-process 20-minute endotoxin "limit test" and a standard 60-minute bacterial endotoxin test on each batch or quality control subbatch of the radiopharmaceutical must be performed prior to release for human use.

Written procedures for the performance of quality control tests must be established on batches of PET radiopharmaceuticals intended for human use. Verification testing of equipment and procedures used for quality control testing of PET radiopharmaceuticals must be conducted. For example, using internal or external standards, the correct operation of analytical equipment, for example, gas chromatography, must be confirmed upon initial installation or upon major repair. After the performance of quality control tests on PET batches of radiopharmaceuticals, the results must be initialed. Acceptance or rejection of individual batches of PET radiopharmaceuticals must be based on conformity of quality control test results with established acceptance criteria. Each batch that is acceptable must be signed and the date approved indicated. Unacceptable quality control test results must be investigated and the outcome documented.

USP <823> also delineates procedures for PET radiopharmaceutical sterilization and sterility assurance. This includes compounding equipment and components, environmental controls, and microbiological testing of the prepared products.

Distribution of Radiopharmaceuticals

Institutional procedures and policies dictate how a radiopharmaceutical is distributed within a health care facility. Generally, a lead-lined syringe container shipped in Department of Transportation–approved and tested cases are used with appropriate identifying information. Some nuclear pharmacies are converting from lead to tungsten containers. Tungsten is lighter, which results in less weight per shipment, and is less hazardous than lead. Local, state (e.g., State Board of Pharmacy), and federal (e.g., Department of Transportation, NRC) regulations are relevant when a radiopharmaceutical is distributed from a central nuclear pharmacy to another institution. Generally, these requirements relate to packaging, labeling, shipping papers, record keeping, shipper and carrier licensing, and personnel training.

Health and Safety

The NRC establishes and enforces radiation safety standards (e.g., limits for radiation doses, levels of radiation in an area, concentrations of radioactivity in air and waste water, waste disposal, precautionary procedures) for the compounding facility. Beyond the radiopharmaceuticals, related aspects of health and safety are a necessity. Hazardous chemicals (e.g., chromatography solvents) must be stored appropriately, handled safely, and disposed of properly. Attention must also be paid to the use of personal protective devices, containers, and the physical environment in which the radiopharmaceuticals are prepared. Personal monitoring devices

are used to monitor and track annual radiation exposure (e.g., whole-body exposure [film badges or optically stimulated luminescence badges] and extremity exposure [ring badges]). Both are evaluated weekly or monthly, and the information is used to refine handling processes continually to manage occupational radiation exposure in accordance with the ALARA concept, that is, to keep occupational radiation exposures as low as is reasonably achievable.

Provision of Drug Information and Consultation

It is very important that the nuclear pharmacist possess oral and written communication skills. His or her knowledge and expertise are useful only when they can be conveyed to an allied health professional, the patient, and the patient's caregiver, among others. The nuclear pharmacist must be able to answer inquiries and know where to find requested information.

The type of information can include, among others, the following:

- Biologic effects of radiation
- Radiation physics and protection
- Radiopharmaceutical chemistry, compounding, quality assurance, and products
- Diagnostic and therapeutic applications of radiopharmaceuticals
- Ancillary medications used to enhance radiopharmaceutical procedures
- Drug interactions associated with radiopharmaceuticals (Tables 18.3 to 18.6)
- Precautions associated with the use of radiopharmaceuticals
- Regulatory requirements affecting the use of radiopharmaceuticals
- This information can be used for educational purposes (e.g., allied health professionals, consumer groups), for setting policies and procedures, and for diagnostic or therapeutic value in the care of patients.

Table 18.3 CONCURRENT ADMINISTERED DRUGS KNOWN TO INTERFERE WITH TUMOR AND ABSCESS LOCALIZATION SCINTIGRAPHY

INTERFERING DRUG	EFFECT ON IMAGE
Phenytoin	Localization of RP in mediastinum, pulmonary hilar structures (patients without clinical evidence of lymphadenopathy)
Amiodarone, bleomycin, busulfan, nitrofurantoin, bacille Calmette-Guérin, chemotherapy, lymphangiographic contrast media, addictive drugs of abuse	Diffuse pulmonary localization (sometimes local pulmonary uptake)
Metoclopramide, reserpine, phenothiazines, oral contraceptives, diethylstilbestrol	Localization of RP in breast
Methotrexate, cisplatin, gallium nitrate, mechlorethamine HCl, vincristine, various chemotherapeutic agents, iron	Increased skeletal uptake Increased renal elimination Decreased hepatic accumulation Decreased tumor or abscess uptake
Clindamycin	Localization of RP in bowel
Calcium gluconate, IM injections	Soft tissue accumulation of RP
Ampicillin, sulfonamides, sulfinpyrazone, ibuprofen, cephalosporins, hydrochlorothiazide, methicillin, erythromycin, rifampin, pentamidine, phenylbutazone, gold salts, allopurinol, furosemide, phenazone, phenobarbital, phenytoin, phenindione	Increased accumulation of RP in the kidneys
Chemotherapeutic agents, antibiotics	Localization of RP in the thymus

RP, radiopharmaceutical.

Table 18.4 DRUGS KNOWN TO INTERFERE WITH BRAIN IMAGING

INTERFERING DRUG	EFFECT ON IMAGE
Cancer chemotherapeutic agents	Patchy increased uptake of RP as a result of chemoneurotoxicity
Corticosteroids	Decreased uptake into brain lesions
Psychotropic drugs	Rapid accumulation of RP in nasopharyngeal area during arterial or capillary phase (cerebral radionuclide angiography)

RP, radiopharmaceutical.

Table 18.6 DRUGS KNOWN TO INTERFERE WITH RENAL IMAGING

INTERFERING DRUG	EFFECT ON IMAGE
Iodinated contrast agents, aminoglycosides	Decrease in effective plasma flow values; decreased glomerular filtration rate
Cyclosporine, cisplatin	Decreased urinary excretion; decreased tubular function
Furosemide	Misleading renogram and flow curves resulting in false positive/negative studies
Probenecid	Decreased renal accumulation and accumulation

Monitoring Patient Outcome

Patient safety and optimal outcomes are the goal of the nuclear pharmacist and a central tenet of pharmaceutical care. In that regard, the nuclear pharmacist can be instrumental in providing quality patient care. The nuclear pharmacist can, among other things,

- Develop institutional standards for the rationale and appropriate use of radiopharmaceuticals.
- Prospectively screen and review patient data to ensure appropriate use of radiopharmaceuticals and ancillary medicines.

Table 18.5 CONCURRENT ADMINISTERED DRUGS KNOWN TO INTERFERE WITH MYOCARDIAL PERFUSION SCINTIGRAPHY

INTERFERING DRUG	EFFECT ON IMAGE
Beta-blockers, nitrates, calcium channel blockers	Decreases number and size of exercise-induced ^{201}Tl perfusion defects
Vasopressin	Appearance of myocardial defects in patients without coronary artery disease
Propranolol, cardiac glycosides, procainamide, lidocaine, phenytoin, doxorubicin	Decreased myocardial localization, increased liver localization

- Ensure that patients are selected appropriately for radionuclide therapy and monitored after therapy to prevent complications and/or provide necessary therapy.
- Evaluate the safety and effectiveness of radiopharmaceuticals and ancillary medications.
- Ensure proper preparation of patients prior to administration of the radiopharmaceutical and ancillary medications.
- Prevent, minimize, and/or rectify clinical problems associated with the use of radiopharmaceuticals and ancillary medications.
- Monitor patients for potential adverse effects following administration of a radiopharmaceutical or interventional medication.
- Discontinue incompatible medications before the nuclear medicine study, restart them after the study, and appropriately manage the patient during discontinuation.
- Ensure that patients with special needs, problems, or conditions (e.g., pregnancy, nursing mothers, dialysis patients, children, and the elderly) are given appropriate consideration before, during, and after radiopharmaceutical administration.
- Ensure that information gained from the nuclear medicine procedure is considered during development of the patient's therapeutic plan.
- Perform and enhance the effectiveness of nuclear pharmacy procedures, including administration of therapeutic or diagnostic radiopharmaceuticals and ancillary medications to the patient.

An example of a nuclear pharmacist intervention is use of radiopharmaceuticals in a breast-feeding woman. Specifically, recommendations are made for interruption of breast-feeding in patients who are undergoing a nuclear medicine diagnostic procedure. The nuclear pharmacist should review the patient's data, especially if the woman is of childbearing age. These recommendations include the following:

- Breast-feeding should be noted in the patient history from the attending physician.
- A member of the interdisciplinary team should inquire about the patient's breast-feeding status and notify the nuclear physician when a patient is breast-feeding.
- Breast-feeding should be interrupted for the period during which radioactivity is known to appear in the breast milk.
- Close contact with an infant should be restricted to 5 hours within 24 hours of the procedure for ^{99m}Tc MIBI, ^{99m}Tc-labeled red blood cells, and ^{131}I (> 3 mCi) whether or not the mother is breast-feeding (41).

Indirectly, the nuclear pharmacist can provide clinical services that include consultation with other caregivers (e.g., explain a nuclear medicine study), prepare institutional guidelines for the use of radiopharmaceuticals and ancillary medications, provide information and literature reviews related to specific questions or studies, formulate special drugs and/or dosage forms, and conduct drug use evaluation studies or drug use reviews.

REGULATORY PROCESS

Pharmacist expertise and experience in the drug regulatory process are very important in nuclear pharmacy practice, and the role of the pharmacist in nuclear medicine is complementary to all health professions practicing within it. The role of the pharmacist will become even more important in the future, with more players entering the marketplace, particularly in the domain of PET. Already there is a variety of corporate and institutional facility partnerships, and with the continual evolution of PET, this should exponentially increase the clinical demand for these agents and increase the role of nuclear pharmacy even further.

PHARMACEUTICS CASE STUDY

SUBJECTIVE INFORMATION

You are a pharmaceutical researcher assigned to work on a new drug, Radhot-1. Your project is to determine where Radhot-1 localizes in the body and the rate at which its two major metabolites are eliminated from the body.

OBJECTIVE INFORMATION

Radhot-1 contains carbon, hydrogen, sulfur, iodine, and nitrogen; it has been determined that these can be labeled appropriately for the study.

ASSESSMENT

To determine its location in the body, you use a gamma-emitting radionuclide. To follow the elimination of the two major metabolites, you label the two different parts of the molecule with two different beta-emitting radionuclides that can be counted separately.

PLAN

Radhot-1 will be prepared with a gamma-emitting iodine, beta-emitting carbon in one part of the molecule, and a beta-emitting hydrogen in a second part of the molecule, the two parts for beta counting being on the two separate parts of the molecule that split when metabolized. External body counting will be used to determine the source of the iodine localization. Urine samples will be collected and analyzed for the two different beta-emitting isotopes and the data plotted.

CLINICAL CASE STUDY

M.G. is a 56-year-old woman who presents to her family physician with blood pressure of 210/120. Following thyroid function tests, ultrasound, a nuclear medicine scan, and fine-needle biopsy, she was diagnosed with Hashimoto thyroiditis and papillary carcinoma of the thyroid gland.

The patient underwent a total thyroidectomy 4 weeks ago and is scheduled today for a 100-mCi radioactive ^{131}I ablation of any residual thyroid tissue. Upon questioning, the patient states that she is allergic to iodine, having had a severe rash following the administration of iodinated contrast medium in the past. The nuclear medicine technologist calls the nuclear pharmacist for advice on how to handle the situation.

SUBJECTIVE INFORMATION

Patient with history of allergy to iodine scheduled to receive ^{131}I ablation.

PMH:	HTN 20 years
	Anxiety disorders × 10 years
	Autoimmune thyroid disorder × 1 year
	Thyroidectomy × 4 weeks
Meds:	Calcium carbonate (TUMS) 500 mg po qid
	KCl 10 mEq po bid
	Diovan 160/12.5 mg po qd
	Levoxyl 0.175 mg po qd
	Meprobamate 400 mg po tid prn
	Calcitriol 0.5 mg po qd
	Diltiazem 240 mg po qd
Family history:	Father HTN × 20 years
Social history:	(–) Smoking
	(–) Alcohol
	(–) Illicit drugs
Insurance:	IPDA
Allergies:	Penicillin, iodine

OBJECTIVE INFORMATION

BP: 134/72 **Ca:** 8.6 (8.7 to 10.5 mg/dL)
Wt: 195 **Ca, ionized:** 4.5 (4.7 to 5.2 mg/dL)
Pulse: 67
TSH: 75 (normal 0.35 to 5.5 ulU/mL) (TSH was 0.275 prior to thyroidectomy)

PHARMACEUTICAL CARE PLAN

1. Potential allergic reaction to ^{131}I. The recommended daily allowance is 0.15 mg of dietary iodine per day. The total therapeutic dose given in this situation would be 0.0008 mg of iodine. This amount would not likely cause an allergic reaction to iodine even in the most iodine-allergic patient.
2. Potential pregnancy teratogenicity. The patient is postmenopausal, and no pregnancy test was ordered.
3. Patient education on radioactive ablation therapy. Patient was educated on procedure and precautions to be taken regarding close contact with other people, particularly children and pregnant women, after radionuclide therapy. Patient was also educated about radioactive ablation therapy and had her questions answered, and written, informed consent was secured.
4. In 4 months, will follow-up with endocrinologist who will order a thyrogen-stimulating thyroglobulin test.
5. Reference: Radiopharmaceuticals in Nuclear Medicine Practice, Kowalski and Perry, 1987

APPLYING THE PRINCIPLES AND CONCEPTS

Group Activities

1. Create a comparative table of radiopharmaceuticals for diagnostic use inclusive of indication(s), dosage regimen, adverse drug reactions, precautions, and route of administration.
2. Create a comparative table of radiopharmaceuticals for therapeutic use inclusive of dosage regimen, adverse drug reactions, precautions, and route of administration.
3. Interview a nuclear pharmacist, and determine how practice in a nuclear pharmacy differs from that of community and hospital pharmacy practice.
4. Identify a new radiopharmaceutical through the primary literature, and prepare a group PowerPoint presentation to educate the remainder of the recitation session students.

Individual Activities

1. Secure an article from the primary literature, which features a radiopharmaceutical for either diagnostic or therapeutic use. Critique it, and prepare and deliver a journal club presentation.
2. List typical adverse drug reactions encountered by radiopharmaceuticals, and describe the treatment/antidote for each.
3. Describe patient circumstances, for example, age, gender, pharmacogenetic background, and organ function, which contraindicate the use of certain radiopharmaceutical drugs, and determine an alternative mode to pursue to take care of the patient.
4. Search an electronic database, and be able to discover within 5 minutes all significant drug interactions between the drugs and the radiopharmaceutical, and be capable to explain the interaction.

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19 Products of Biotechnology

OBJECTIVES

After reading this chapter, the student will be able to:

1. Differentiate between the various techniques using living organisms in the production or modification of biotechnology drugs
2. Describe the classification of products of biotechnology used in clinical practice
3. Provide examples of biotechnology drugs for each classification of biotechnology drug type
4. Summarize important concepts associated with biotechnology product handling, storage, and administration
5. Describe the mission of the Food and Drug Administration (FDA) Office of Biotechnology Products and its structure
6. Discuss the general composition of biotechnology products

The term *biotechnology* encompasses any technique that uses living organisms (e.g., microorganisms) in the production or modification of products. The classic example of biotechnologic drugs was proteins obtained from recombinant DNA (rDNA) technology. However, biotechnology now encompasses the use of tissue culture, living cells, or cell enzymes to make a defined product. rDNA and monoclonal antibody (MAb) technologies have provided exciting opportunities for the development of more pharmaceuticals and approaches to the diagnosis, treatment, and prevention of disease.

The biotechnology pharmaceutical market in the United States for 2009–2013 forecasts the biotechnology pharmaceutical market to grow at a compound annual growth rate of 7.7% with blood modifiers accounting for the largest share of the market at 36.3%. The major growth factors include

1. Increased demand for biotechnology drugs with enhanced efficiency, safety, and popularity
2. Revised regulations and standards in encouraging more companies to invest in the field
3. Increased aging population and chronic and age-related illnesses (1)

Biotechnologic products will continue to have a marked impact upon the practice of pharmacy. Research will continue to generate potent new medications that require custom dosing for the individual patient and concomitant pharmacists' expertise in the use of and familiarity with sophisticated drug delivery systems.

Pharmacogenomics is the application of genomic technology to genetic variation in response to pharmaceutical compounds. It is an emerging discipline and an outgrowth of pharmacogenetics that seeks to describe the genetic basis for interindividual differences in drug effectiveness and toxicity, using genome-wide approaches to identify genes that govern an individual's response to specific medications. The initial draft of the human genome has demonstrated that the human genome

has more than 1.4 million single nucleotide polymorphisms, with more than 60,000 of these residing in the coding regions of human genes. Some of these have already been associated with significant changes in metabolism or effects with commonly used medications. Some genetic polymorphisms (e.g., thiopurine S-methyltransferase, CYP2D6) have a marked effect on drug pharmacokinetics, such that appropriate dosages of drugs are significantly different from traditional dosages. The ultimate goal of pharmacogenomics is to define the contributions of inherited differences in drug disposition and/or targets to drug response and thereby improve safety and effectiveness of medications through genetically guided individualized treatments.

Biotechnology drugs have become known synonymously as specialty pharmaceuticals that hold great promise for people living with an increasing number of chronic diseases (3). Coupled with advances in genetic-based diagnostic techniques, specialty drugs could conceivably redefine the way illnesses will be treated in the future. As the use of novel technologies is incorporated into routine clinical practice, opportunities exist to make pharmaceutical care even more personalized. The goal is to create oral administered products to supplant injection or infusion administration. Accompanying this will be increased costs. Because of their uniqueness, these agents often require special handling, administration, patient education, and clinical support, all of which add to cost. Specialty products are conveniently placed into one of the three categories: (*a*) self-administered therapies (e.g., rheumatoid arthritis, multiple sclerosis, psoriasis); (*b*) products injected or infused in an office or clinical setting (e.g., vaccines, asthma, immune disorders); and (*c*) office-/clinic-administered chemotherapeutic agents (e.g., cancer, neutropenia, anemia).

As a result of the increased risk of clinically important and/or unusual/potentially harmful adverse effects, these agents dictate increased safety surveillance. The U.S. Food and Drug Administration (FDA) has mandated the implementation of a risk minimization action plan (i.e., RiskMAP) for those products with high risk. The plan is a strategic risk assessment plan designed to minimize product risk while preserving its benefits to the patient (4). Given their ability to affect complex processes in the body, biological products including vaccines have a higher likelihood of adverse effects than traditional or chemical agents. Nearly one-third of boxed warnings for biological pharmaceuticals between January 1995 and 2007 have been added within 2 years of the products' approval by the FDA. Thus, it is important for pharmacists to participate in extensive adverse event monitoring of new products.

It is important to indicate that specialty products are not constituted solely with biotechnology products, which typically implies peptide products developed with recombinant technology. There are some nonpeptide injectables, for example, treprostinil sodium, and some oral specialty products, for example, bosentan and imatinib, for rare diseases that fall under this umbrella definition. Thus, the definition of specialty products will continue to evolve.

The first of the novel *biotechnologic* pharmaceuticals were proteins, but eventually an increasing number will be smaller molecules, discovered through biotechnology-based methods that will determine just how proteins work. Clearly, biotechnology has established itself as a mainstay in pharmaceutical research and development, and new products will continue to enter the market at an increasing pace in the future. Biotechnologic products are produced through highly complex processes from genetically engineered cell cultures, rather than synthesized chemically like small-molecule pharmaceuticals. Unlike small-molecule pharmaceuticals, there is no generic competition for biotechnology drugs in the United States that, in some instances, cost patients tens of thousands of dollars per year. The European Union recently instituted a system in an attempt to bring down the cost of biologics for patients through the use of biosimilars (5).

Biosimilars, also known as follow-on biologics, are biologic medical products whose active drug substances are made by a living organism or derived from a living organism by means of recombinant DNA or controlled gene

expression methods. These terms are used to describe officially approved subsequent versions of innovator biopharmaceutical products made by a different sponsor following patent and exclusivity expiration on the innovator product.

Biologics differ from the more common small-molecule drugs as they generally exhibit high molecular complexity and may be quite sensitive to changes in manufacturing processes. The manufacturers of biosimilars do not have access to the originator's molecular clone and original cell bank, to the exact fermentation and purification process, or to the active drug substance. However, they do have access to the commercialized innovator product. Since differences in impurities and/or breakdown products can potentially have serious health implications, there is a concern that copies of biologics might perform differently than the original branded version of the product. Consequently, only a few subsequent versions of biologics have been authorized in the United States through the simplified procedures allowed for small-molecule generics (menotropins, January 1997, and enoxaparin, July 2010) and additional biologics through another mechanism.

In February 2012, the FDA issued "Guidance for Industry on Biosimilars: Q & As Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act)" regarding the topic of biosimilarity.

Health insurers may view these as potentially cost-saving equivalents. However, biopharmaceuticals are large molecules that are difficult to characterize fully because of the complex processes utilized to manufacture the product. As yet, the FDA has not established guidelines how to evaluate the therapeutic equivalence of biosimilars and innovator products.

A vast number of biotechnology-derived medications have been approved and made available since human insulin became the first therapeutic recombinant protein drug in 1982. The commercial success of biotechnology spurred the entry of many additional products into the development pipelines since that time. This abundant activity grew out of entrepreneurism among many small venture-funded, narrowly focused groups. Several of these small companies have by now prospered to the point of becoming fully integrated pharmaceutical companies. It was anticipated then that patients with hemophilia, serious sepsis, skin ulcers, rheumatoid arthritis, and a number of cancers would benefit in future years as drugs in clinical trials secured market approval, and this has come to fruition. As some of those biotechnologic products are now on the market (e.g., ReFacto for hemophilia, Fuzeon for HIV therapy, Kineret for mild to moderate rheumatoid arthritis in patients who have failed one or more disease-modifying antirheumatic drugs [DMARDs], Xigris for severe sepsis), it is anticipated that this trend will continue.

As of 2006, there were more than 250 specialty medicines that have been approved by the FDA, and it is estimated 350 agents were in late-stage trials (6). At present, 250 specialty products are on the market and nearly 350 agents in late-stage trials. The growth of this grouping of pharmaceuticals is fueled with higher costs for existing specialty products (e.g., $10,000 treatment regimen cost per month), the introduction of new drugs to treat conditions where few drug alternatives exist, new indications for existing drugs, and an increasing degree of off-label use.

TECHNIQUES USED TO PRODUCE BIOTECHNOLOGIC PRODUCTS

Numerous techniques are used to create biotechnologic products. These include rDNA technology, MAb technology, polymerase chain reaction, gene therapy, nucleotide blockade or antisense nucleic acids, and peptide technology. The following section describes each of these techniques.

Recombinant DNA

DNA, deoxyribonucleic acid, has been called the substance of life. It is DNA that constitutes genes, allowing cells to reproduce and maintain life. Of more than 1 million kinds of plants and animals known today, no two are exactly alike; however, the similarity within

families is the result of genetic information stored in cells, duplicated, and passed from cell to cell and from generation to generation. It is DNA that provides this continuity.

DNA was first isolated in 1869. Its chemical composition was determined in the early 1900s, and by the 1940s, it had been proved that the genes within cell chromosomes are made of DNA. It was not until the 1950s when James D. Watson and Francis H.C. Crick postulated the structure of DNA that biologists began to comprehend the molecular mechanisms of heredity and cell regulation. Watson and Crick described their model of DNA as a double helix, two strands of DNA coiled about themselves like a spiral staircase. It is now known that the two strands of DNA are connected by the bases adenine, guanine, cytosine, and thymine (A, G, C, and T). The order of arrangement of these bases with the two strands of DNA comprises a specific gene for a specific trait. A typical gene has hundreds of bases that are always arranged in pairs. When A occurs on one strand, T occurs opposite it on the other; G pairs with C. A gene is a segment of DNA that has a specific sequence of these chemical base pairs. The pattern constitutes the DNA message for maintaining cells and organisms and building the next generation. To create a new cell or a whole new organism, DNA must be able to duplicate (clone) itself. This is done by unwinding and separating the two strands and attaching new bases to each from within the cell according to the A-T/C-G rule. The result is two new double strands of DNA, each of the same structure and conformation.

DNA also plays an essential role in the production of proteins for cellular maintenance and function. DNA is translated to messenger RNA (mRNA), which contains instructions for production of the 23 amino acids from which all proteins are made. Amino acids can be arranged in a vast number of combinations to produce hundreds of thousands of proteins. In essence, a cell is a miniature assembly plant for production of thousands of proteins. A single *Escherichia coli* bacterium is capable of making about 2,000 proteins.

The ability to hydrolyze selectively a population of DNA molecules with a number of endonucleases promoted a technique for joining two different DNA molecules: recombinant DNA, or *rDNA*. This technique uses other techniques (replication, separation, identification) that permit production of large quantities of purified DNA fragments. These combined techniques, referred to as *rDNA technology*, allow the removal of a specific piece of DNA out of a larger, more complex molecule. Consequently, rDNAs have been prepared with DNA fragments from bacteria combined with fragments from humans, viruses with viruses, and so forth. The ability to join two different pieces of DNA at specific sites within the molecules is achieved with two enzymes: a restriction endonuclease and a DNA ligase.

With rDNA technology, scientists can use nonhuman cells (e.g., a special strain of *E. coli*) to manufacture proteins identical to those produced in human cells. This process has enabled scientists to produce molecules naturally present in the human body in large quantities previously difficult to obtain from human sources. For example, approximately 50 cadaver pituitary glands were required to treat a single growth hormone–deficient child for 1 year until DNA-produced growth hormone became available through the new technology. Further, the biosynthetic product is free of viral contamination than the cadaver source. Human growth hormone (hGH) and insulin were the first rDNA products to become available for patients' use.

DNA probe technology is being used to diagnose disease. It uses small pieces of DNA to search a cell for viral infection or for genetic defects. DNA probes have application in testing for infectious disease, cancer, genetic defects, and susceptibility to disease. Using DNA probes, scientists can locate a disease-causing gene, which in turn can lead to the development of replacement therapies. In producing a DNA probe, the initial step is synthesis of the specific strand of DNA with the sequence of nucleotides that matches those of the gene being investigated. For instance, to test for a particular virus, first the DNA strand is developed to be identical to one in the virus. The second step is to tag

the synthetic gene with a dye or radioactive isotope. When introduced into a specimen, the synthetic strand of DNA acts as a probe, searching for a matching or complementary strand. When one is found, the two hybridize or join together. When the probe is bound to the virus, the dye reveals the location of the viral gene. If the synthetic DNA strand carries a radionuclide isotope, it will bind to the viral strand of DNA and reveal the virus through gamma ray scanning.

Monoclonal Antibodies

When a foreign body or antigen molecule enters the body, an immune response begins. This molecule may contain several different epitopes, and lines of beta lymphocytes will proliferate, each secreting an immunoglobulin (antibody) molecule that fits a single epitope.

By contrast, MAbs are produced as a result of perpetuating the expression of a single beta lymphocyte. Consequently, all of the antibody molecules secreted by a series of daughter cells derived from a single dividing parent beta lymphocyte are genetically identical. Through the development of hybridoma technology emanating from Kohler and Milstein's research (7), it became possible to produce identical monospecific antibodies in almost unlimited quantities. These are constructed by the fusion of beta lymphocytes, stimulated with a specific antigen, with immortal myeloma cells (8). The resultant hybridomas can be maintained in cultures and produce large amounts of antibodies. From these hybrid cells, a specific cell line or clone producing monospecific immunoglobulins can be selected.

A significant number of antibodies now in use belong to the immunoglobulin G (IgG) subclass. The IgG molecule has a molecular weight between 150 and 180 kDa and consists of two heavy and two light polypeptide chains connected by disulfide bonds (Fig. 19.1). The heavy and the light chains can be divided into a variable and a constant domain. The constant domain amino acid sequence is relatively conserved among immunoglobulins of a specific class (e.g., IgG, IgM). The variable domains of an antibody population are highly heterogeneous. It is the variable domain that gives the antibody

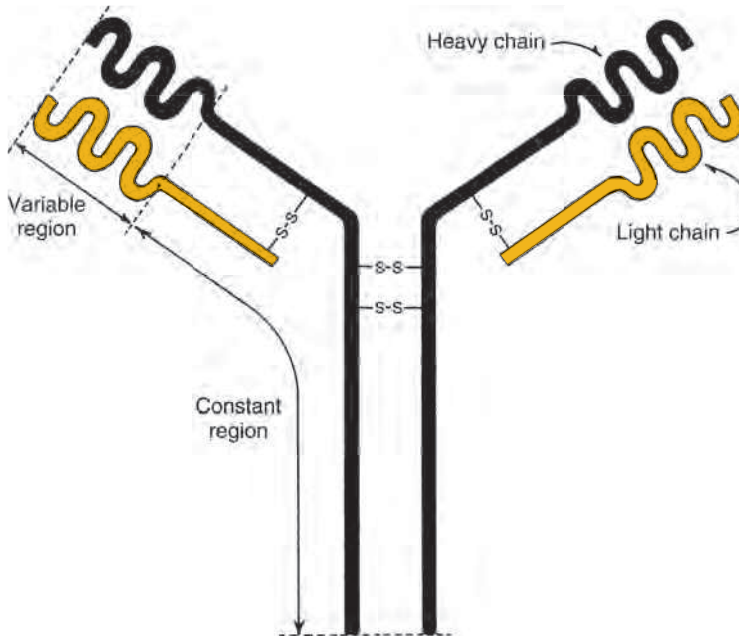


FIGURE 19.1 Basic shape of an immunoglobulin molecule akin to the class IgG, a heterogeneous population of molecules sharing a y-shaped structure composed of a heavy and light molecular chain linked by disulfide bonds. (Illustration by Alan J. Slade.)

its binding specificity and affinity. Thus, the antibody engineer must be cautious to maintain the tertiary structure and orientation of the complementary determining region.

Most of the MAbs in clinical trials have been derived from mice, and patients exposed to them have developed human anti–mouse antibody (HAMA) responses. This has limited the number of treatments that patients can receive. Typically, patients develop detectable antibody responses against the foreign MAb within 2 to 4 weeks. If the patient receives additional doses of the antibody, a typical allergic reaction is elicited (chills, urticaria, wheezing) and the antibody is rapidly cleared from the serum. In response to this problem, antibody therapy now includes a variety of molecules apart from the conventional immunoglobulin molecule.

Failed efforts with murine MAbs led to the development of MAbs with human components. Advances in the understanding of immunoglobulin structure through three-dimensional studies using nuclear magnetic resonance, x-ray crystallography, and increased computer-assisted molecular modeling capabilities combined with recombinant approaches have led to the evolution of a new class of antibody-like molecules, or *man-made antibodies* (9). Consequently, chimeric and humanized antibodies have been constructed to overcome the lack of intrinsic antitumor activity and the immunogenicity of many murine MAbs. These MAbs retain the binding specificity of the original rodent antibody determined by the variable region but have the potential to activate the human immune system through their human constant region (10).

As an example, smaller fragments that contain intact immunoglobulin-binding sites, such as F[ab']$_2$ and Fab', do not contain the lower binding domain of the molecule (Fig. 19.2). A smaller molecule will tend to be less immunogenic when administered systemically and is more likely to have a greater tumor penetration than a larger structure (9). Also, in diagnostic imaging applications, smaller fragments have demonstrated greater renal, biliary, and colonic uptake at 24 hours than the whole IgG, because of filtering by the kidneys and excretion via the biliary system of small protein compounds. All three smaller antibody forms have had success at detecting smaller (<2 cm) lesions not seen on computed tomography (CT) and are superior to the IgC anticarcinoembryonic antigen antibody.

Another example is the smaller Sfv molecule, which contains the heavy and light chains of the binding sites joined by the shorter link (Fig. 19.2). These molecules also have been engineered to attach toxins, cytokines, radiolabeled elements, or genes, thus broadening their ability as delivery vehicles for cancer therapy.

Today, fully human MAbs are produced in the mouse whose murine genes are inactivated and replaced by human sequences. The immunogenicity of fully human MAbs is low because they are 100% human and contain no mouse protein. At present, there are

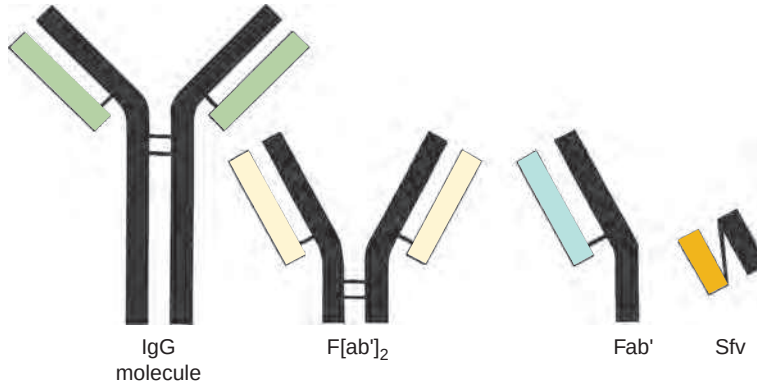


FIGURE 19.2 An IgG molecule and its fragments. (Illustration by Alan J. Slade.)

four types of MAbs. The suffix used in the name of the MAb demonstrates the source. The suffix *-omab* indicates murine, the earliest type of MAb derived entirely from mice, that is, mouse protein. The suffix *-ximab* indicates chimeric, which has a human constant region and a murine variable region. This was the second-generation MAb and emerged because of the high incidence of HAMA reactions with murine MAbs. The immune response and incidence of HAMA reactions were much lower for chimeric MAbs than with murine MAbs. Further, there was now a broader range of antigenic specificities, enhanced effector functions and cellular toxicity, and more optimal pharmacodynamic (i.e., increased affinity for the antigen) and pharmacokinetic changes (e.g., longer $t_{1/2}$). The third generation of MAbs was the humanized MAbs that are 90% human, containing only 10% mouse protein in the variable region. The suffix *-zumab* indicates a humanized MAb. Eventually, the fourth-generation MAb was created and fully human. The suffix is *-umab*, and these MAbs are created in mice whose murine genes are inactivated and replaced with human sequences. As would be expected, the immunogenicity of fully human MAbs is low because there is no mouse protein. In addition, the fourth-generation MAbs are cleared at a slower rate from plasma due to the lack of the mouse component.

Polymerase Chain Reaction

Polymerase chain reaction is a biotechnologic process whereby there is substantial amplification (more than 100,000-fold) of a target nucleic acid sequence (a gene). This enzymatic reaction occurs in repeated cycles of a three-step process. First, DNA is denatured to separate the two strands. Next, a nucleic acid primer is hybridized to each DNA strand at a specific location within the nucleic acid sequence. Finally, a DNA polymerase enzyme is added for extension of the primer along the DNA strand to copy the target nucleic acid sequence.

Each cycle duplicates the DNA molecules. This cycle is repeated until sufficient DNA sequence material is copied. For example, 20 cycles with a 90% success rate will yield 375,000 amplification of a DNA sequence.

Gene Therapy

Gene therapy is a process in which exogenous genetic material is transferred into somatic cells to correct an inherited or acquired gene defect. Also, it is intended to introduce a new function or property into cells. These common and life-threatening diseases include cystic fibrosis, hemophilia, sickle cell anemia, and diabetes.

Scientific technology has developed safe and efficient means to transfer genes into cells. Consequently, genetic and molecular delineation of the underlying pathophysiology of many of the primary immunodeficiency disorders has occurred, and gene-based therapy is now a viable option as long as the transferred genetic material can be delivered to the appropriate target cell or tissue.

Controversial ethical considerations over genetic intervention of germ line cells have fostered bioengineering to focus on gene therapy of somatic cells. Because somatic cells are end-stage differentiated cells, research has examined the use of a self-renewing stem cell population for therapeutic transfer of genetic material. Stem cells can renew themselves, and the inserted gene will remain in place through subsequent generations of differentiated cells or tissue populations.

As an example, a patient's cells (e.g., T lymphocytes) are harvested and grown in the laboratory. The cells receive the gene from a viral carrier (e.g., Moloney murine leukemia virus) and start to produce the missing protein necessary to correct the deficiency. These cells with the extra functional gene are then returned to the patient, and the normal protein is produced and released, alleviating the disease.

The genetic cause of numerous primary immunodeficiency disorders has been discovered and described. As a result, gene therapy can now be used as an alternative therapy, particularly in patients for whom bone marrow transplantation may not be suitable (e.g., a bone marrow donor cannot be identified, or preparation for transplantation carries substantial risk to the patient).

The first primary immunodeficiency disease to be defined was adenosine deaminase (ADA) deficiency. The gene encoding for ADA is found on chromosome 20. Gene deletions and point mutations result in a loss or severe reduction in ADA enzymatic activity, leading to a clinical presentation of severe combined immunodeficiency disease (SCID) and often causing death in childhood or adolescence.

The first human protocol for gene therapy was performed in ADA patients in 1990 at the National Institutes of Health. Since that time, the genetic defects of several other primary immunodeficiency disorders have been defined, and the defects have been at least partially corrected by gene therapy using hemopoietic stem cells in vitro. For SCID and other diseases, gene therapy is lifesaving (11).

Nucleotide Blockade/Antisense

Nucleotide blockade and antisense technology focuses on the study of function of specific proteins and intracellular expression. The sequence of a nucleotide chain that contains the information for protein synthesis is called the sense sequence. The nucleotide chain that is complementary to the sense sequence is called the antisense sequence. Antisense drugs recognize and bind to the nucleotide sense sequence of specific mRNA molecules, preventing synthesis of unwanted proteins and actually destroying the sense molecules in the process.

The introduction of antisense nucleic acids into cells has provided new ideas to explore how proteins, whose expression has been selectively repressed in a cell, function within that cell. Another goal is to arrest the expression of dysfunctional mRNA or DNA and control disease processes. Antisense technology is part of a new approach termed *reverse genetics*.

Antisense RNA, for example, can be introduced into the cell by cloning. The specific gene of interest is cloned in an expression vector in the wrong orientation so that complementary mRNA is created to match abnormal mRNA. Then when the two mRNA strands complex together, translation of the mRNA to form disease-producing proteins is prevented. Anti-DNA strands also can be created to complex with DNA to form a triple helix. Oligonucleotides, or short single strands of nucleic acids, instead of the full mRNA, also can be employed to block RNA expression. This form of biotechnology is being used for viral disease (e.g., herpes simplex, HIV) and cancer (oncogenes).

Peptide Technology

Peptide technology entails screening for polypeptide molecules that can mimic larger proteins. This is intended to afford relatively simple products that can be stable and easy to produce. These peptides can serve as either protein receptor agonists or antagonists.

Formulation Composition

Most of the biotechnology products are proteins, but some may soon be smaller peptide-like molecules. Proteins are inherently unstable molecules, and their degradation profiles can be quite complex. Biotechnology products differ from conventional small-molecule drug products in their method of preparation and in the potential problems presented in their formulation. Pharmacists involved in compounding with biologically active proteins will be interested in their stabilization, formulation, and delivery.

In working with biotechnologically derived drugs, one must be cognizant of both the active drug constituent and the total drug delivery system, or carrier. Protein drugs are extremely potent and are generally used in quite low concentrations. The bulk of most compounded preparations may be the excipients. In addition to the vehicle, buffers, and the like, stabilizers are often incorporated in these products. A number of different stabilizers can be used, including surfactants, amino acids, polyhydric alcohols, fatty acids, proteins, antioxidants, reducing agents, and metal ions. Table 19.1 describes agents used as stabilizers.

pH is one of the key factors in developing a stable product. The optimal pH range for a specific product can be achieved through the selection of appropriate physiologic buffers. Usually, buffer concentrations are in the range of 0.01 to 0.1 M. In general, an increase in the buffer concentration means an increase in pain on injection.

Table 19.1 STABILIZING AGENTS FOR BIOTECHNOLOGY PREPARATIONS

CLASS	AGENT	ACTION
Amino acids	Alanine	Serves as a solubilizer
	Arginine	Serves as a buffer
	Aspartic acid	Inhibits isomerism
	Glycine	Serves as a stabilizer
	Glutamic acid	Serves as a thermostabilizer
	Leucine	Inhibits aggregation
Antioxidants	Ascorbic acid, cysteine hydrochloride, glutathione, thioglycerol, thioglycolic acid, thiosorbitol	Help stabilize protein conformation
Chelating agents	EDTA salts	Inhibit oxidation by removing metal ions, glutamic acid, and aspartic acid
Fatty acids	Choline, ethanolamine, phosphatidyl	Serve as stabilizers
Proteins	Human serum albumin	Prevents surface adsorption; stabilizes protein conformation; serves as a complexing agent and cryoprotectant
Metal ions	Ca^{2+}, Ni^{2+}, Mg^{2+}, Mn^{2+}	Help stabilize protein conformation
Polyhydric alcohols	Ethylene glycol	Serves as a stabilizer
	Glucose	Strengthens conformation
	Lactose	Serves as a stabilizer
	Mannitol	Serves as a cryoprotectant
	Propylene glycol	Prevents aggregation
	Sorbitol	Prevents denaturation and aggregation
	Sucrose	Serves as a stabilizer
	Trehalose	Serves as a stabilizer
Polymers	PEG, povidone	Prevent aggregation
Surfactants	Poloxamer 407	Prevents denaturation and stabilizes cloudiness
	Polysorbate 20 and polysorbate 80	Retard aggregation

Source: Bontempo JA. Development of Biopharmaceutical Parenteral Dosage Forms. New York, NY: Marcel Dekker, 1997:112–113.

Chelating agents can be incorporated to bind trace metals such as copper, iron, calcium, and manganese. Ethylenediaminetetraacetic acid (EDTA) is commonly used at a concentration of about 0.01% to 0.05%.

Antioxidants are often incorporated because oxidation is one of the major factors in protein degradation. Ascorbic acid, sodium disulfide, monothioglycerol, and α-tocopherol are frequently used at a concentration of about 0.05% to 0.1%.

Preservatives may be necessary; these could include phenol (0.3% to 0.5%), chlorobutanol (0.3% to 0.5%), and benzyl alcohol (1.0% to 3.0%).

Polyols are good stabilizers and are commonly used in concentrations from 1% to 10%.

Tonicity-adjusting agents include sodium chloride and dextrose in concentrations necessary to achieve isotonicity with 0.9% sodium chloride solution, or approximately 290 mOsm/L.

Preparation

A general rule for working with biotechnology formulations is to keep procedures as simple as possible. Sterility must be maintained in any preparation of parenteral products, since most do not contain a preservative. It is recommended that only one dose be prepared from each vial or container to minimize contamination. Many times this is not practical, however, as specific manipulations are needed to meet patient needs. Facilities should be clean, and proper techniques

should be used. A kit for testing aseptic technique in preparing formulations is available from equipment suppliers. At a minimum, a laminar-airflow hood should be used and appropriate attire worn. All equipment must be sterile. Any additive used in compounding parenteral drug products must be free of pyrogens; if a preparation becomes contaminated with pyrogens, it should be discarded. Two special considerations in working with biotechnologically derived preparations—the use of filters and the sorption of these drugs to containers—are discussed in the following sections.

The use of filters in manipulating biotechnology products can result in some loss of the drug available to the patient. For example, muromonab-CD3 (Orthoclone OKT3) injection should be filtered with a low–protein-binding filter of 0.2 to 0.22 µm. Many biotechnology products should not be filtered at all. If a filtration device is part of the IV administration apparatus, biotechnology drugs should generally be administered distal to the site of the filter. Filters that have been shown to minimize protein adsorption are those made from polyvinylidene difluoride, polycarbonate, polysulfone, and regenerated cellulose. As a precaution, low–protein-binding filters should be used.

Sorption of proteins to containers can result in drug loss. This loss can be minimized either by the use of albumin or by siliconization. Adding about 0.1% albumin to the product can decrease the sorption of proteins to containers. If glass mixing vessels are used, the albumin solution should be added before the drug. If siliconization is used, the compounding pharmacist should prepare a silicon solution or emulsion and soak or rinse the glass vials in it. The drained vials should then be placed in an oven at about 250°C for 5 to 6 hours. This procedure will minimize protein adsorption to glass; it can be used for both the preparation equipment and the packaging containers.

Physicochemical Considerations

To retain a drug's biologic activity up to the time of administration to the patient, some factors associated with handling proteins must be considered: selecting an appropriate vehicle for drug delivery, individualizing dosages, administering drugs through novel drug delivery systems, preparing drugs for delivery through these systems, monitoring their efficacy, and counseling patients on their use.

Some issues specific to protein pharmaceuticals are

- Their high molecular weight and potential for aggregation (i.e., a small change in structure can result in a change in activity)
- Their immunogenic potential, because some are produced by a fermentation-type process and proteins can copurify with proteins
- The assignment of potency to the reference standards (when traditional pharmaceuticals are about 98% pure, these materials may be only 0.1% to 1% active, with their activity assigned by potentially variable assays)
- The use of micropipettes, which can require frequent calibration
- Concern that constituted products can be less stable than lyophilized products
- The effect of agitation on a product's stability
- Possible interaction of the product with the inner wall of the glass vial and with the elastomeric closure
- The effectiveness of the preservative if a multidose product is mixed with other products

Physicochemical factors to be considered in compounding protein drug products include the structure of the protein drug, isoelectric point, molecular weight, solubility and factors affecting solubility (e.g., surfactants, salts, metal ions, pH), stability and factors affecting stability (e.g., pH, temperature, light, oxygen, metal ions, freeze–thaw cycles, mechanical stress), polymorphism, stereoisomers, filtration media compatibility, shear, and surface denaturation.

Solubility depends on a number of factors, including chemical structure, pH, and temperature. Proteins are generally more soluble in their native environment or medium

or in a matrix that mimics their native environment, such as sodium chloride, trace elements, lipids, and other proteins in an aqueous medium. Before compounding these products, pharmacists must consider the ingredients' effects on the solubility of the active drug, especially because most of the products are currently administered parenterally. This task is critical because the actual drug is present in a small quantity and can go unnoticed if it precipitates. Sterile water for injection and 0.9% sodium chloride solution usually are good vehicles for use in a formulation.

The pH of the compound should be maintained close to the pH of the originally approved, manufactured product; changes in pH can affect proteins in numerous ways. Chemical degradation rate constants are pH related, and hydrogen ion concentration can affect the actual structure of proteins (i.e., quaternary structure). Buffer systems may be needed in compounding; they should be prepared at the minimum buffer strength required to produce the most stable drug product.

Chemical instability of proteins is the modification of protein structures by bond formation or cleavage to yield a new compound. *Physical instability* generally involves changes in structure, conformation, or behavior in a particular environment. Stability, both chemical and physical, depends on pH, temperature, and agitation, as well as on the overall environment in which the drug is contained.

Sorption is a problem with colony-stimulating factors (CSFs) and with aldesleukin (Proleukin) at low concentrations. To minimize "sticking" of the protein to the glass, it may be helpful to add about 0.1% albumin to the product to occupy the potential binding sites in the container. Pharmacists must consider this problem before making any changes in packaging.

Agitation, which is frothing created by the physical decomposition of the protein, can adversely affect the product in two ways. First, frothing can cause difficulties in using a syringe to withdraw the required amount of drug from a vial. To avoid this problem, the formulator should mix the product by rolling the vial in the hands or gently swirling it. Second, excessive agitation can cause changes in a protein's quaternary structure that often reduce or eliminate a drug's therapeutic activity. Some products, such as filgrastim (Neupogen) and sargramostim (Leukine), are reconstituted by directing a soft stream of diluent against the inside of the container wall. Others, such as recombinant tissue plasminogen activator (tPA; alteplase), are reconstituted by directing a stream of diluent directly into the product at the bottom of the vial.

Quality Control

The compounding pharmacist should follow standard quality control procedures. The compounded preparations can be tested for pH, final volume, sterility, and pyrogenicity and physically observed for clarity, presence of gas bubbles and particulate matter, and change in color.

PRODUCTS OF BIOTECHNOLOGY

Biotechnologic drugs fall into major classes, such as antisense, clotting factors, hematopoietic factors, hormones, interferons, interleukins (ILs), MAbs, tissue growth factors, and vaccines. Biotechnologic drugs are distinguished by whether they are physiologic or nonphysiologic peptides or new biotechnology products.

Physiologic peptides can be further subdivided by intended use. For example, those for substitution include clotting factors, insulin, hGH, and erythropoietin. Biotechnologic products intended for therapeutic purposes in nonphysiologic concentrations include interferons, cytokines, tPA, and urokinase. Nonphysiologic peptides include mutants of physiologic peptides, vaccines, thrombolytic agents, and antithrombics.

The following sections describe by classification products of biotechnology that have been approved by the FDA or are being developed for submission for approval (Table 19.2). The section describing indication also lists in brackets for some biotechnology drugs and products proposed uses under the Orphan

Table 19.2 REPRESENTATIVE BIOTECHNOLOGY PRODUCTS IN USE IN THE UNITED STATES

GENERIC NAME	TRADE NAME (MANUFACTURER)	INDICATIONS [PROPOSED USE][a]
Aldesleukin	Proleukin (Prometheus)	Metastatic renal cell carcinoma, melanoma; primary immunodeficiency disease of T-cell defects
Alteplase	Activase (Genentech)	Ischemic stroke
Conjugate vaccine	PedvaxHIB (Merck & Co.)	Routine immunization of children aged 2–71 mo
Efavirenz	Sustiva (Bristol-Myers Squibb)	Treatment of HIV-1 in combination with 2, 3, or 4 other anti-HIV drugs
Epoetin alfa	Epogen (Ortho Biotech, Procrit)	Certain anemias; chronic renal disease; AIDS; cancer chemotherapy; [anemia associated with end-stage renal disease or HIV infection or treatment; myelodysplastic syndrome; anemia of prematurity in preterm infants]
Filgrastim G-CSF	Neupogen (Amgen)	Decrease incidence of infection (febrile neutropenia) in nonmyeloid malignancies treated with myelosuppressive drugs. Reduce duration of neutropenia, neutropenia-related sequelae in nonmyeloid malignancies treated with myeloablative chemotherapy followed by bone marrow transplant [severe chronic neutropenia (absolute neutrophil count < 500/mm^3); neutropenia of bone marrow transplant; CMV retinitis of AIDS treated with ganciclovir; mobilization of peripheral blood progenitor cells for collection prior to myeloablative or myelosuppressive chemotherapy; reduce duration of neutropenia, fever, antibiotic use, hospitalization following induction, consolidation for acute myeloid leukemia.]
Haemophilus B conjugate vaccine	ActHIB (Aventis Pasteur)	Routine immunization of children against invasive diseases of HIB
Hepatitis B vaccine	Engerix-B (GlaxoSmithKline), Recombivax HB (Merck)	Hepatitis B prophylaxis
Human growth hormone	Protropin (Genentech), Humatrope (Lilly)	hGH deficiency in children
Human insulin	Humulin (Lilly), Rapid, Velosulin (Novo Nordisk)	Insulin-dependent diabetes mellitus
Imciromab pentetate	Myoscint (Centocor)	[Detection of early necrosis as indication of rejection of orthotopic cardiac transplant]
Infliximab	Remicade (Centocor)	Active and fistulizing Crohn disease
Interferon a-2b	Intron A (Schering)	Hairy cell leukemia; AIDS-related Kaposi sarcoma; chronic hepatitis B and C (non-A, non-B); condylomata acuminate
Interferon a-n3	Alferon N (Hemispherx Biopharma)	Condylomata acuminata
Interferon B	Betaseron (Bayer)	Multiple sclerosis
Interferon y-1b	Actimmune (Intermune)	Chronic granulomatous disease
Muromonab-CD3	Orthoclone (Ortho Biotech), OKT 3 (Biotech)	Acute allograft rejection in renal transplant patients

(Continued)

Table 19.2 REPRESENTATIVE BIOTECHNOLOGY PRODUCTS IN USE IN THE UNITED STATES (Continued)

GENERIC NAME	TRADE NAME (MANUFACTURER)	INDICATIONS [PROPOSED USE][a]
Recombinant factor VIII	Kogenate (Bayer), Recombinate (Baxter)	Hemophilia A
Rituximab	Rituxan (Biogen, IDEC/ Genentech)	Relapsed or refractory low-grade or follicular CD20-positive beta-cell NHL
Sargramostim (GM-CSF)	Leukine (Genzyme)	Myeloid reconstitution after bone marrow transplantation [Leukine: neutropenia of bone marrow transplant, graft failure, delay of engraftment, promotion of early engraftment; reduce neutropenia, leukopenia; decrease incidence of death from infection in AML]
Somatropin	Genotropin (Pfizer), Humatrope (Lilly), Norditropin (Novo Nordisk),	[Long-term treatment of children with growth failure of inadequate endogenous growth hormone; growth failure in children with inadequate growth hormone; idiopathic or organic growth hormone deficiency in children with growth failure; enhancement of nitrogen retention in hospitalized patients with severe burns; short stature in Turner syndrome; adults with growth hormone deficiency]
Somatropin for injection	Humatrope (Lilly), Nutropin (Genentech)	Long-term treatment for growth failure in children who lack endogenous growth hormone secretion. [Long-term treatment of children with growth failure of inadequate secretion of normal endogenous growth hormone; short stature in Turner syndrome; growth retardation in CRF; catabolism/weight loss in AIDS; children with AIDS-associated failure to thrive, including wasting; replacement therapy for growth hormone deficiency in adults with epiphyseal closure]
tPA (alteplase)	Activase (Genentech)	Management of AMI in adults to improve ventricular function, reduce incidence of CHF and mortality of AMI. Management of acute ischemic stroke in adults to improve neurologic recovery, reduce disability. Management of acute massive PE, lysis of acute PE, defined by obstruction of blood flow to a lobe or multiple segments of the lungs, and for lysis of PE with unstable hemodynamics
Reteplase	Retavase (Centocor)	Management of AMI in adults to improve ventricular function following AMI, reduce incidence of CHF, reduce mortality of AMI
Trastuzumab	Herceptin (Genentech)	Treatment of metastatic breast cancer or cancer spread beyond breast and lymph nodes under arm. Used alone in patients with primary failure with other chemotherapies or as a first-line treatment of metastatic disease in combination with paclitaxel. Approved as part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel and as part of a regimen with docetaxel and carboplatin. Both are for adjuvant treatment of HER2-overexpressing, node-positive, or high-risk node-negative breast cancer

[a]Listing includes proposed uses for orphaned drugs in [brackets]. The Orphan Drug Act defines an orphan drug as a drug or biologic product for the diagnosis, treatment, or prevention of a rare disease or condition. A rare disease is one that affects fewer than 200,000 persons in the United States or more than 200,000 persons but without reasonable expectation that the cost of developing and marketing the drug will be recovered from sales in the United States.

Drug Act. (the FDA Office of Orphan Products Development provides an information packet that includes an overview of the FDA's orphan drug program, a brief description of the orphan products grant program, and a current list on designated orphan products.)

Anticoagulant Drug: Lepirudin (Refludan)

Lepirudin (rDNA), a recombinant hirudin derived from yeast cells, is a highly specific direct inhibitor of thrombin. It is the first of the hirudin class of anticoagulants. The polypeptide is composed of 65 amino acids and has a molecular weight of 6,979.5 Da. Natural hirudin is produced in trace quantity as a family of highly homologous isopolypeptides by the leech *Hirudo medicinalis*. Biosynthetic lepirudin is identical to natural hirudin except for substitution of a leucine molecule for isoleucine at the N-terminal end of the molecule and the absence of a sulfate group on the tyrosine molecule at position 63.

The activity of this anticoagulant is measured in a chromogenic assay. One antithrombin unit (ATU) is the amount of lepirudin that neutralizes one unit of the World Health Organization (WHO) preparation 89/588 of thrombin. The specific activity of lepirudin is about 16,000 ATU/mg. One molecule of lepirudin binds to one molecule of thrombin and blocks its activity.

Lepirudin is indicated for heparin-induced thrombocytopenia (HIT) and associated thromboembolic disease to prevent further thromboembolic complications. The formation of antihirudin antibodies have been observed in approximately 40% of HIT patients treated with the drug. This ultimately may increase the anticoagulant effect of the lepirudin because of delayed renal elimination of active lepirudin–antihirudin complexes.

Initial dosage for anticoagulation in patients with HIT and associated thromboembolic disease is 0.4 mg/kg (<110 kg) slowly intravenously (e.g., over 15 to 20 seconds) as a bolus dose followed by 0.15 mg/kg (<110 kg per hour) as a continuous intravenous infusion for 2 to 10 days or longer if clinically necessary. The initial dose depends on the patient's weight and is valid up to 110 kg. For those who weigh more than 110 kg, the dose should not be increased beyond that for 110-kg body weight. The maximum initial bolus dose is 44 mg, and the maximal infusion dose is 16.5 mg per hour.

Therapy with lepirudin is monitored using the activated partial thromboplastin time (aPTT) at a given time over a reference value, usually median of the laboratory normal range. The patient's baseline aPTT should be determined prior to administration of the drug because lepirudin should not be given to patients with a baseline aPTT ratio of 2.5 or more to avoid initial overdosing.

Lepirudin powder for injection (Refludan) of 50 mg should be reconstituted only with water for injection, 0.9% sodium chloride injection, or 5% dextrose injection. For rapid complete reconstitution, 1 mL of diluent is injected into the vial and the vial shaken gently. After reconstitution, a clear, colorless solution is obtained in no more than 3 minutes.

The reconstituted solution should be used immediately, and it remains stable for 24 hours at room temperature (e.g., during infusion). Prior to administration, it should be warmed to room temperature.

Antisense Drugs

Fomivirsen Sodium (Vitravene)

Fomivirsen sodium injectable is an antisense drug approved for local treatment of cytomegalovirus (CMV) in patients with AIDS who are intolerant of or have a contraindication to other treatments for CMV retinitis. Also, it may be used after other treatment fails.

Fomivirsen sodium, a phosphorothioate oligonucleotide, is administered by direct injection into the vitreous body (the transparent gelatinous mass filling the eyeball behind the lens) of the eye. This oligonucleotide is targeted specifically to the CMV genetic information so that it can shut down the CMV virus but not interfere with the functioning of human DNA.

Two induction doses of the drug are injected into the eye under local anesthesia on days 1 and 15, followed by a monthly injection of 330 mg. This is advantageous for

the management of CMV retinitis because it obviates intravenous therapies. Also, it may offer avoidance of surgical implants and their complications and less frequency of intravitreal injections than other antiviral compounds, and it may be a suitable adjunct to oral ganciclovir therapy.

Efavirenz (Sustiva)

Efavirenz is a nonnucleoside reverse transcriptase inhibitor and the first anti-HIV drug to be approved by the FDA for once-daily dosing in combination with other anti-HIV drugs.

Clinical trials demonstrated that efavirenz reduces plasma viral RNA to below quantifiable levels in a majority of HIV-1-infected naïve and treatment-experienced individuals in two-, three-, and four-drug combinations.

Efavirenz is available as an oral capsule and can be taken once a day on an empty stomach, preferably at bedtime to improve any nervous system symptoms. However, if taken with food, it is advised that it should not be administered with high-fat meals, because this interaction may increase the drug's systemic absorption.

Clotting Factors

Hemophiliacs bleed internally because of a lack of clotting protein factors. Historically, treatment has been infusions of protein derived from human blood. Now, genetic engineering can create, without donor blood, factors that produce more nearly contaminant-free products and therefore expose the patient to fewer contaminants.

Systemic Antihemophilic Factors (Kogenate, Recombinate)

Recombinant antihemophilic factor (AHF) is indicated for the treatment of classical hemophilia A, in which there is a demonstrated deficiency of activity of plasma clotting factor (factor VIII). Human recombinant AHF (rAHF) is a sterile, nonpyrogenic concentrate with biologic and pharmacokinetic activity comparable to that of plasma-derived AHF. Additional clinical trials are being conducted to determine whether antibodies to rAHF form more often than with plasma-derived products (11).

rAHF contains albumin as a stabilizer and trace amounts of mouse, hamster, and bovine proteins. These products are made by modifying hamster cells so that they produce a highly purified version of AHF factor VIII.

Each vial of AHF is labeled with the AHF activity expressed in international units (IU). The assignment of potency is referenced to the WHO International Standard. One IU of factor VIII activity, approximately equal to the AHF activity of 1 mL of fresh plasma, increases the plasma concentration of factor VIII by 2%. The specific factor VIII activity ranges from 2 to 200 AHF IU per milligram of total protein.

The dose–response relation is linear, with an approximate yield of a 2% rise in factor VIII activity for each unit of factor VIII per kilogram transfused. The following formulas provide a guide for dosing calculations:

$$\text{Expected factor VIII increase (\%normal)} = \frac{\text{dose AFH / IU administered} \times 2}{\text{body weight (kg)}}$$

$$\text{AFH / IU required} = \text{body weight (kg)} \times \text{desired factor VIII increase (\% normal)} \times 0.5$$

Kogenate is available in strengths of 250 IU (with 2.5 mL sterile water for injection provided as diluent), 500 IU (with 5 mL sterile water for injection provided as diluent), and 1,000 IU (with 10 mL sterile water for injection provided as the diluent). Each strength contains 2 to 5 mmol of calcium chloride, 100 to 130 mEq/L of sodium, 100 to 130 mEq/L of chloride, 4 to 10 mg/mL of human albumin, and nanogram quantities of foreign protein (mouse, hamster) per IU. Kogenate is supplied in a single-dose vial along with the diluent, a sterile filter needle, and a sterile administration set.

Recombinate is available in strengths of 250, 500, and 1,000 IU, each with 10 mL sterile water for injection provided as diluent. Each strength contains 12.5 mg/mL of human albumin, 180 mEq/L of sodium, 200 mEq/L of calcium, and a small quantity of foreign protein.

Dry concentrates of rAHF should be stored at 2°C to 8°C (35°F to 46°F) and the diluent protected from freezing. Kogenate may be stored at room temperatures not exceeding 25°C for 3 months. After reconstitution, the solution should not be refrigerated.

The diluent and dry concentrate should be brought to room temperature (~ 25°C) prior to reconstitution. These may be allowed to warm to room temperature, or in an emergency warmed via water bath to a range of 30°C to 37°C (86°F to 98.6°F). Once reconstituted, the solution should not be shaken, because shaking could make it foam. The solution should be administered within 3 hours of reconstitution and any partially used vial discarded. This preparation should be administered alone through a separate line, without mixing with other intravenous fluids or medications.

Kogenate may be administered intravenously over 5 to 10 minutes and Recombinate up to 10 mL per minute. The comfort of the patient should guide the rate at which rAHF is administered. If a significant increase in pulse rate occurs, the infusion should be slowed or halted until the pulse rate returns to normal. The risk of an allergic reaction to product proteins (mouse, hamster, bovine) may be present in the MAb-derived and rAHF products.

Recombinant Factor VIII (ReFacto)

Approved for clinical use in March 2000, recombinant factor VIII is indicated for control and prevention of bleeding episodes and surgical prophylaxis to reduce the frequency of spontaneous bleeding episodes (Fig. 19.3). This product is the only factor VIII product indicated for short-term routine prophylaxis.

Hemophilia A is the most common form of hemophilia, an inherited blood disorder. Approximately, 17,000 American patients have hemophilia A. This form of the disease is the result of deficiency in blood clotting factor VIII.

Recombinant technology allows preparation of clotting factors without human blood or plasma products. This eliminates the risk of blood-borne viral contamination associated with nonrecombinant factor VIII products prepared from pooled human blood.

FIGURE 19.3 The product package of ReFacto. (Courtesy of Genetics Institute.)

Also, ReFacto does not contain human serum albumin, whereas previously approved recombinant products (e.g., Kogenate, Bayer) add albumin during the cell culture phase and during the final product formulation. This procedure theoretically increases the possibility of viral contamination in the final product.

Colony-Stimulating Factors

CSFs are four glycoprotein regulators that bind to specific surface receptors and control the proliferation and differentiation of marrow cells into macrophages, neutrophils, basophils, eosinophils, platelets, or erythrocytes (12,13). These recombinant human CSFs have demonstrated use in oncology (e.g., chemotherapy-induced leukopenia, cancer patients having marrow transplants), inherited disorders (e.g., congenital neutropenia), and infectious disease (e.g., AIDS) (14). Patients with low amounts of endogenous CSFs are prone to secondary infections because of diminished resistance associated with some forms of cancer or more commonly, suppressed marrow function after the use of myelotoxic chemotherapy.

Granulocyte Colony–Stimulating Factor (Filgrastim)

Produced by rDNA technology, this drug stimulates the production of neutrophils in the bone marrow. It is approved for chemotherapy-related neutropenia and is

indicated (to decrease the incidence of infection, as manifested by febrile neutropenia) in patients with nonmyeloid malignancies who are receiving myelosuppressive anticancer drugs and exhibiting severe neutropenia with fever. This drug can also be used as an adjunct to myelosuppressive cancer chemotherapy to help speed the recovery of neutrophils after treatment and to reduce serious infection risk.

For chemotherapy-induced neutropenia, filgrastim is administered intravenously (short infusion, 15 to 30 minutes), as a subcutaneous bolus or continuous intravenous or subcutaneous injection, in a starting dose of 5 mg/kg once daily, beginning no earlier than 24 hours after administration of the last dose of cytotoxic chemotherapy. This regimen is continued for up to 2 weeks, until the absolute neutrophil count reaches 10,000/mm^3 following the *nadir* (the lowest neutrophil count, usually occurring 7 to 10 days after chemotherapy).

Filgrastim injection contains no preservative and should be stored at 2°C to 8°C. It is not to be frozen. Before use, the injection may be allowed to reach room temperature for a maximum of 24 hours, after which time it should be discarded. A clear, colorless solution, it should be inspected visually prior to injection. This product is supplied as a 1- or 1.6-mL single-dose vial (Fig. 19.4). Filgrastim is also available as a 0.5- or 0.8-mL Singleject prefilled syringe with a concentration of 300 µg/0.5 mL with no preservatives. Each syringe is protected with an Ultrasafe needle guard.

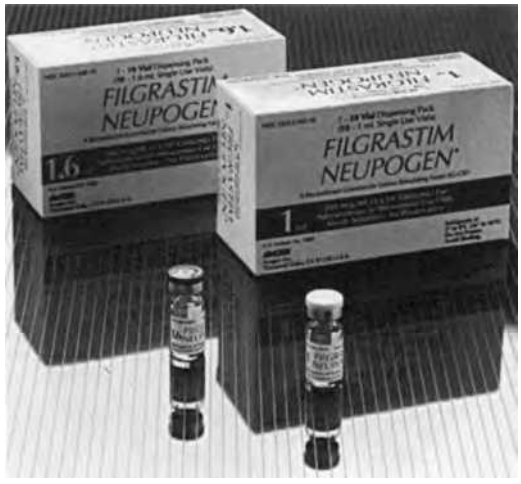


FIGURE 19.4 The product package of Filgrastim. (Courtesy of Amgen, Inc.)

Filgrastim is supplied in boxes containing 10 glass vials, which are packaged in a gel–ice insulating container with a temperature indicator to detect freezing. For convenience and to minimize the risk of breakage, filgrastim should be dispensed to the patient in its original packaging and the patient instructed to refrigerate the product promptly after arriving home.

If the patient has to travel a considerable distance or the outside temperature is high, it may be necessary to place the medication in a small cooler with a gel refrigerant (e.g., blue ice) for transport. It is suggested that the vials be wrapped in a towel to avoid direct contact between them and the blue ice. The drug must be physically separated from the refrigerant to prevent freezing. Dry ice should not be used because of the possibility of freezing the product through inadvertent contact.

It is conceivable that when it is used as an adjunct to cancer chemotherapy, prescriptions for this product will be written for 7 to 10 vials. Indeed, patients may have extra vials of this product at home from previous courses of cancer chemotherapy. The pharmacist should question such patients about having any unexpired, properly stored unused vials from the previous course of therapy. Filgrastim injection repackaged in 1-mL plastic tuberculin syringes stored at 2°C to 8°C remains sterile for 7 days.

Because granulocyte CSF (G-CSF) is a protein, it can be denatured if severely agitated. If the vial is shaken vigorously, the solution may foam or appear frothy, making withdrawal difficult. Thus, the pharmacist should instruct the patient or caregiver to avoid shaking the vial before use. If it is shaken, the vial should be allowed to stand until the froth diminishes.

If it is necessary to dilute filgrastim, use 5% dextrose injection. When filgrastim is diluted to concentrations ranging between 5 and 15 mg/mL, it should be protected from inadvertent adsorption to plastic materials

by the addition of albumin (human) to a final concentration of 2 mg/mL. When diluted in 5% dextrose injection or 5% dextrose plus albumin, filgrastim is compatible with glass bottles, polyvinyl chloride and polyolefin intravenous bags, and polypropylene syringes. Filgrastim should never be diluted with saline at any time, as the product may precipitate.

The manufacturer of filgrastim has developed a step-by-step guide to subcutaneous self-injection. However, the pharmacist should always emphasize the use of proper aseptic technique when preparing and administering the drug, to avoid product contamination and possible infection.

Granulocyte Colony–Stimulating Factor and Monomethoxypolyethylene Glycol (Pegfilgrastim)

Pegfilgrastim was approved in late January 2002 by the FDA for use in conjunction with myelosuppressive anticancer drugs to decrease the incidence of infection and neutropenic fever in patients with nonmyeloid malignancies. It is marketed under the trade name Neulasta (Fig. 19.5). It is derived by adding a 20-kDa monomethoxypolyethylene glycol (PEG) molecule to the N-terminal methionine residue of filgrastim. The covalent conjugation of the recombinant human G-CSF filgrastim and PEG alters the pharmacokinetic properties of filgrastim. The pegylation of filgrastim significantly prolongs the drug's half-life ($t_{1/2}$, 15 to 80 hours) over that of filgrastim ($t_{1/2}$, 3 to 4 hours) by altered clearance. As a result, it is administered as a single fixed dose of 6 mg injected per chemotherapy cycle. This is in comparison to 10 to 14 injections normally needed for filgrastim during a chemotherapy cycle. The significantly lower number of injections required with pegfilgrastim is anticipated to increase adherence to the regimen and decrease the demands on medical personnel. Furthermore, early experience suggests that pegfilgrastim may be slightly more effective in reducing febrile neutropenia in breast cancer patients receiving docetaxel and doxorubicin.

FIGURE 19.5 The product package of pegfilgrastim. (Courtesy of Amgen, Inc.)

Granulocyte–Macrophage Colony-Stimulating Factor (Sargramostim)

Sargramostim is a recombinant human granulocyte–macrophage CSF (GM-CSF) produced by rDNA technology in a yeast (*Saccharomyces cerevisiae*) expression system. GM-CSF is a growth factor that stimulates proliferation and differentiation of hematopoietic progenitor (precursor) cells into neutrophils and monocytes. It is a glycoprotein composed of 127 amino acids. The sequence of rGM-CSF differs from the natural human GM-CSF at position 23, where leucine is substituted.

This drug is indicated for acceleration of myeloid (marrow) recovery in patients with non-Hodgkin lymphoma (NHL), acute lymphoblastic leukemia (ALL), and Hodgkin disease undergoing autologous bone marrow transplantation (a procedure in which the patient's bone marrow is removed, treated to destroy malignant cells, and reinfused into the patient). It is also indicated in failure of bone marrow transplantation or engraftment delay (it takes 3 to 4 weeks for the new marrow to begin to produce new white blood cells).

GM-CSF accelerates engraftment by promoting the production of white blood cells. Health care costs are controlled, because patients treated with it demonstrate significant earlier increases in white blood cell counts, a reduced need for antibiotics,

and a shorter hospitalization. For myeloid reconstitution after autologous bone marrow transplantation, it is administered at 250 mg/m^2/day for 21 days as a 2-hour intravenous infusion beginning 2 to 4 hours after the autologous bone marrow infusion and not less than 24 hours after the last dose of chemotherapy and 12 hours after the last dose of radiation therapy. For bone marrow transplantation failure or engraftment delay, the dose remains the same, but the duration is 14 days, again using a 2-hour intravenous infusion. The dose can be repeated after 7 days of therapy if engraftment has not occurred.

Sargramostim is available in a multidose solution vial of 500 mg/mL and a preservative-free single-dose vial of 250 mg powder for reconstitution. It is reconstituted with 1 mL Sterile Water for Injection, USP (without preservative). The reconstituted solution should appear clear and colorless, and will be isotonic, with a pH of 7.4 ± 0.3. During reconstitution, the Sterile Water for Injection, USP, should be directed at the side of the vial and the contents gently swirled to avoid foaming during dissolution. The product must not be shaken or vigorously agitated. It can also be diluted for intravenous infusion in 0.9% Sodium Chloride Injection, USP. If the final concentration of GM-CSF is below 10 mg/mL, human albumin (0.1%) should be added to the saline before adding GM-CSF. This prevents adsorption of the drug to the components of the drug delivery system. To create a 0.1% albumin solution, the pharmacist should add 1 mg albumin (human) per milliliter of 0.9% sodium chloride injection.

An inline membrane filter for intravenous administration of this drug should not be used. In the absence of compatibility and stability information, other medications should not be admixed to infusion solutions containing sargramostim. Only 0.9% sodium chloride injection should be used to prepare the drug for intravenous infusion.

Because this product is preservative free, it should be administered as soon as possible and within 6 hours following reconstitution or dilution for intravenous infusion.

Erythropoietins

Erythropoietin is a sialic acid–containing glycoprotein that enhances erythropoiesis by stimulating the formation of proerythroblasts and the release of reticulocytes from bone marrow. It is secreted by the kidney in response to hypoxia and transported to the bone marrow in the plasma. It resembles an endocrine hormone more than any other cytokines (15).

Anemia (a deficiency of red blood cell production) is a frequent complication of chronic renal failure (CRF), cancer, and cancer therapy. Although it is easily corrected with blood transfusions, erythropoietins are available to treat only the severest forms of anemia and not to maintain the red blood cell mass required for normal activity and well-being. As anemic patients with solid tumors often have lower serum levels of erythropoietin, correction of the erythropoietin deficiency through erythropoietin therapy may be as beneficial for these cancer patients as it has been for uremic patients (15).

Kidney disease also impairs the body's ability to produce this substance and thus results in anemia. In the past, patients received blood transfusions. However, a problem with transfusions was possible exposure to infectious agents (hepatitis, HIV). Now, genetically engineered drugs, such as epoetin alfa and darbepoetin, are available to stimulate erythropoiesis. Although expensive, these drugs may prove beneficial for patients who require extensive transfusions because of the high cost of transfusions, the risk of infectious disease, and the consequent additional health care costs.

Epoetin Alfa (Epogen, Procrit)

Epoetin alfa, a glycoprotein produced by rDNA technology, contains 165 amino acids in an identical sequence to that of endogenous human erythropoietin. Erythropoietin also effects the release of reticulocytes from the bone marrow into the blood stream, where these mature into erythrocytes. It is approved for anemia related to cancer chemotherapy, chronic dialysis, and zidovudine (AZT) therapy.

Epoetin alfa stimulates erythropoiesis in anemic patients, dialyzed or not. The first evidence of a response to this drug is an increase within 10 days of the reticulocyte count. Coupled with this are subsequent increases in the red blood cell count, hemoglobin, and hematocrit, usually within 2 to 6 weeks. Once the hematocrit reaches the suggested target range, 30% to 36%, that level can be sustained in the absence of iron deficiency and concurrent illnesses by epoetin alfa therapy.

Epoetin alfa is administered intravenously or subcutaneously at 50 to 100 IU/kg body weight three times per week. It is given intravenously to patients with available access (e.g., patients who undergo hemodialysis) and either intravenously or subcutaneously to other patients. If after 8 weeks of therapy the hematocrit has not increased at least five to six points and is still below the target range of 30% to 36%, the dosage may be increased.

Epoetin alfa is available in 1-mL preservative-free single-dose vials (Fig. 19.6) in strengths of 2,000, 3,000, 4,000, 10,000, 20,000, and 40,000 U/mL. Each vial contains human albumin of 2.5 mg to prevent adsorptive losses. The product should be refrigerated at 2°C to 8°C and protected from freezing. The vial of epoetin alfa, recombinant injection, should not be shaken because this may denature the glycoprotein and render it biologically inactive. Each vial should be used to administer a single dose only, and any unused portion of the solution must be discarded.

The 10,000 U/mL is available in a 2-mL multidose vial. The 20,000 U/mL injection is available in a 1-mL multidose vial. These are preserved with 1% benzyl alcohol and contain 2.5 mg albumin (human) per milliliter. These vials should be stored at 2°C to 8°C after initial entry and between doses and discarded 21 days after initial entry.

FIGURE 19.6 The product package of Epogen. (Courtesy of Amgen, Inc.)

Epoetin alfa should not be administered in conjunction with other solutions. However, just before subcutaneous administration, the solution can be admixed in a syringe at a ratio of 1:1 with bacteriostatic 0.9% sodium chloride injection with benzyl alcohol 0.9%. The benzyl alcohol, a local anesthetic, may ameliorate pain associated with subcutaneous injection.

In early 2003, a counterfeit version of epoetin alfa (Procrit) was discovered. It posed a serious health threat because it contained a concentration of the active ingredient one twentieth of the expected and was contaminated with two types of bacteria. The FDA identified three batches of the fake drug product. Ortho Biotech Products, the manufacturer of the legitimate drug, advised consumers to check for differences on the packaging and vials. For example, the aluminum seal on a vial of real Procrit is smooth, not dented. Also, the closure seals on the outer carton of the real Procrit have writing on the underside and leave a residue when peeled away. In years past, counterfeit drugs were a problem in developing countries. Now, however, these drugs are becoming problematic in the United States, with the FDA investigating more than a half dozen counterfeit drug cases in 2002.

Darbepoetin Alfa (Aranesp)

Darbepoetin alfa, a recombinant erythropoietic protein, was first approved for the treatment of anemia associated with chronic kidney disease or CRF. It is now approved for the treatment of chemotherapy-induced anemia in patients with nonmyeloid malignancies (Fig. 19.7).

Darbepoetin alfa is an erythropoiesis-stimulating protein that is produced in Chinese hamster ovary cells by rDNA technology. It is administered intravenously or subcutaneously as a single weekly injection. The recommended starting dose for anemia in CRF patients is 0.45 mg/kg body weight. The doses are titrated not to exceed a

FIGURE 19.7 The product package of Aranesp. (Courtesy of Amgen, Inc.)

target hemoglobin concentration of 12 g/dL. Increased hemoglobin levels are not generally observed until 2 to 6 weeks after therapy initiation. Usually, the appropriate maintenance dosage is lower than the starting dose. Once therapy is initiated, hemoglobin should be assessed weekly until it is stabilized and the maintenance dose established. After a dosage adjustment, the hemoglobin should be assessed once weekly for at least 4 weeks until it has been confirmed that the hemoglobin levels have stabilized in response to the dosage adjustment. Thereafter, the hemoglobin levels should be assessed at regular intervals.

Dosage with darbepoetin must be individualized to ensure that hemoglobin levels are maintained but not to exceed 12 g/dL. For cancer patients, the recommended starting dose of darbepoetin alfa is 2.25 mg/kg administered as a weekly subcutaneous injection. Again, the dosage is adjusted to achieve and maintain the appropriate hemoglobin level.

Darbepoetin alfa is available as a solution for injection. The injection is preservative free in 1-mL single-dose vials. The polysorbate injection contains polysorbate 80, sodium phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous, and sodium chloride. The albumin solution contains human albumin, sodium phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous, and sodium chloride.

Prior to administration, the vial should be visually inspected for particulate matter and any discoloration. Vials demonstrating particulate matter and/or discoloration should not be used. The vial should not be shaken, as this will denature the darbepoetin and render it inactive. It should not be diluted or administered with other drug solutions. If there is any unused portion, it should be discarded and not pooled with other unused portions. The product should be stored in a refrigerator (2°C to 8°C), not frozen, and protected from light.

Darbepoetin alfa is available in strengths ranging from 25 mg/0.42 mL to 500 mg/mL. All solutions for injection are preservative-free in polysorbate or albumin solutions in single-dose prefilled, Singleject syringes and single-dose, prefilled SureClick autoinjectors. Several strengths are available in less than 1 mL solutions. Thus, the pharmacist has to be careful not to miscalculate the dosage required from the latter by assuming that the solution contains the drug in 1 mL.

Drotrecogin Alfa (Activated) (Xigris)

Drotrecogin alfa (activated) is recombinant human activated protein C (APC). Produced naturally in the liver, protein C is converted to APC through interaction with the thrombin–thrombomodulin complex. APC demonstrates antithrombotic activity through inhibition of factors Va and VIIIa (16).

Approved by the FDA in November 2001, drotrecogin alfa is indicated for a reduction of mortality in patients with severe sepsis associated with acute organ system dysfunction (Fig. 19.8). Sepsis remains a significant cause of death in patients who are critically ill. It has been estimated that more than 750,000 cases of sepsis occur yearly in the United States, with a mortality rate of about 30%.

Drotrecogin alfa (activated) should be administered by continuous intravenous infusion at 24 mg/kg/h for 96 hours. Because compatibility data are sparse, it should be administered via a dedicated line or dedicated lumen of a multilumen central venous

FIGURE 19.8 The product package of Xigris. (Courtesy of Eli Lilly and Co.)

FIGURE 19.9 The product package of Fuzeon. (Courtesy of Roche/Trimeris.)

catheter. Administration must be conducted within 12 hours of reconstitution. Periods during which the infusion is interrupted for procedures with an inherent risk of bleeding do not count toward the 96-hour duration of therapy.

Fusion Inhibitors: Enfuvirtide (Fuzeon)

Fusion inhibitors act through a unique mechanism. Enfuvirtide is a 36-amino acid synthetic peptide that corresponds to the C-terminal heptad repeat region (HR2) of the transmembrane subunit of the HIV-1 envelope surface glycoprotein gp41. Enfuvirtide binds to gp41 on the surface of the HIV and prevents the HIV from binding with T cells. Thus, it prevents the virus from infecting healthy cells. Once bound, it inhibits the conformational change in HIV-1 transmembrane glycoprotein gp41 that is required for fusion between HIV-1 and target cell membranes, blocking cell fusion and viral entry into the CD4 cell.

Approved in March 2003, enfuvirtide (known as T-20) is indicated only for patients older than 6 years who have used other anti-HIV medications and have ongoing evidence of viral replication despite ongoing antiretroviral therapy (Fig. 19.9). The dosage of enfuvirtide is 90 mg (1-mL sterile water for injection) subcutaneously twice daily into the upper arm, anterior thigh, or abdomen. Because enfuvirtide is a protein, it must be injected under the skin, making it the first injectable HIV drug. Adherence to the regimen is extremely important, as studies on antiretroviral therapy have demonstrated increased resistance unless nearly every dose is properly administered and on time. The goal is 100% compliance because rates of compliance <95% can lead to further resistance (17). If a patient misses a dose, it should be administered as soon as possible, but not if it is almost time for the next dose. In this instance, the patient should know to administer only one dose.

Patient education including proper injection technique is crucial. For convenience, patients may mix both daily doses at the same time, but the second dose must be refrigerated

until shortly before it is to be injected. As with insulin, it should be warmed to room temperature prior to injection. The patient should realize the importance of inspecting the injectable, and if particles are observed floating in the vial after mixing, it should not be used. Other injectable medications should not be mixed with enfuvirtide.

This drug is prescribed for patients with drug-resistant HIV infection, so the patient should understand to take precautions, discarding the syringes and needles into a sharps container. They are not to be discarded into the household garbage.

Growth Factor: Becaplermin (Regranex)

Endogenous platelet-derived growth factor increases the proliferation of cells that repair wounds and form granulation tissue. This factor promotes the chemotactic recruitment and proliferation of cells that participate in wound repair and enhances the formation of granulation tissue.

Becaplermin is a recombinant human platelet-derived growth factor for topical adjunctive treatment of diabetes ulcers, a form of pressure ulcer, of the lower extremities that extend into subcutaneous tissue or beyond, having a sufficient blood supply. It is reasonable to assume that it may find utility as an adjunct to good pressure ulcer care.

A measured quantity of the 0.01% gel formulation is spread evenly over the ulcerated area to yield a thin, continuous 1/16 inch thickness over the ulcerated area. The prescribed calculated length of the gel is placed on a clean, firm, nonabsorbent surface (e.g., waxed paper). A clean cotton swab, tongue depressor, or similar aid applicator is used to spread the gel over the surface of the ulcer to obtain an even layer, and the ulcer is covered with a saline-moistened gauze dressing.

After approximately 12 hours, the ulcer should be gently rinsed with saline or water to remove the residual gel and covered with a saline-moistened gauze dressing without the gel for the remainder of the day. The process is repeated daily until the ulcer has healed. The ulcer should demonstrate size reduction (about 30%) within 10 weeks. If complete healing has not occurred within 20 weeks, the therapy should be reassessed. To facilitate acceptance and convenience, bedtime application can be considered.

Becaplermin gel must be refrigerated for stability but need not be allowed to come to room temperature before it is applied. However, the cold gel may cause discomfort when it is applied. The gel itself has an expiration date of 9 months from the manufacture date, but because one tube lasts for about 2 to 4 weeks, pharmacists can dispense the gel up to a month prior to its expiration date.

Human Growth Hormone

The pituitary gland secretes hGH, which stimulates growth. It is estimated that approximately 15,000 American children are deficient in hGH and consequently will not achieve normal height as an adult.

In the late 1950s, cadaver pituitaries were harvested to produce hGH and treat these children. Besides the enormous expense, this method exposed the children to the risk of infection from viral contamination of the hormone (18). Genetic engineering now produces highly purified hGH.

Systemic Growth Hormone (Humatrope, Protropin)

Somatrem (Protropin) is a biosynthetic single polypeptide chain of 192 amino acids produced by rDNA in *E. coli*. This drug has one more amino acid (methionine) than natural hGH. Somatropin recombinant (Humatrope), biosynthetically produced by another rDNA process, possesses amino acid sequencing identical to the naturally occurring hGH (191 amino acids).

This hormone stimulates linear growth by affecting the cartilaginous growth areas of long bones. It also stimulates growth by increasing the number and size of skeletal muscle cells, influencing the size of organs, and increasing red cell mass through erythropoietin stimulation.

Somatrem for injection is initially administered intramuscularly or subcutaneously. The dosage, individualized at up to 0.1 mg/kg (0.26 IU/kg), is administered subcutaneously

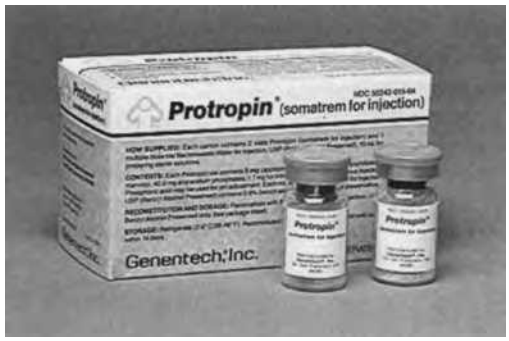


FIGURE 19.10 The product package of Protropin. (Courtesy of Genentech, Inc.)

or intramuscularly three times a week. The 5- and 10-mg single-dose vials (Fig. 19.10) are reconstituted using standard aseptic technique with 1 to 5 mL of Bacteriostatic Water for Injection, USP (benzyl alcohol preserved) only. Because of the toxicity of benzyl alcohol in newborns, when administering to this patient population, this product should be reconstituted with water for injection. The vial should then be swirled gently to dissolve the contents. If cloudy, the solution should not be used. When prepared with the manufacturer's provided diluent, the reconstituted solution should be stored in the refrigerator and used within 14 days. When water for injection is used to reconstitute this product, each vial should be used for one dose only and the unused portion discarded.

Somatropin, recombinant, for injection, is administered subcutaneously at 0.16 to 0.24 mg/kg body weight per week divided into six or seven subcutaneous injections. This drug is available in various strengths ranging from 1.5 mg (~ 4 IU/mL) to 10 mg (~ 30 IU/vial). As Genotropin, for example, the 5.8-mg Intra-Mix two-chamber cartridge (with preservative) is preassembled in a reconstitution device and packaged with a pressure release needle. The front chamber contains 1.5 mg of recombinant somatropin (~ 4.5 IU), glycine, sodium dihydrogen phosphate anhydrous, and disodium phosphate anhydrous. The rear chamber contains 1.13 mL of water for injection. Depressing the stopper allows the two components to mix. If the diluent and somatropin are in separate vials, aseptic technique must be used to add the desired amount of diluent (1.5 to 5 mL) provided by the manufacturer or sterile water for injection to a 5-mg vial. Like Somatrem, somatropin is stable when refrigerated for up to 14 days following reconstitution with the diluent containing a preservative provided by the manufacturer. When sterile water for injection is used to reconstitute this product, each vial should be refrigerated and used within 24 hours because there is no preservative.

Interferons

In 1957, two British scientists, Alick Isaacs and Jean Lindenmann, found that infected chick embryo cells released a naturally produced glycoprotein that allowed uninfected cells to resist viral infection. They named this factor *interferon* because it appeared "to interfere with the transmission of infection." Later, these researchers demonstrated that interferon does not activate viruses directly but rendered the host cells resistant to viral multiplication. Interferons exert virus-nonspecific but host-specific antiviral activity. By the mid-1970s, it appeared that interferon might also curtail the spread of certain types of cancer (e.g., small cell lung cancer, renal cell carcinoma, basal cell carcinoma).

As a class, interferons are a part of the large immune regulatory network within the body that includes lymphokines, monokines, growth factors, and peptide hormones. Interferons are classified into two types: type I, alpha and beta, which share the same molecular receptor, and type II, gamma or immune, which have a different receptor (19).

Interferon Beta-1b (Betaseron)

Interferon beta-1b (IFNB-1b) is a type I interferon made in *E. coli* using recombinant technology; it differs from natural IFNB-1b only by the substitution of a serine residue for a cysteine at position 17. This manipulation enhances the stability of the drug while retaining the specific activity of natural IFNB-1b.

IFNB-1b is effective in the treatment of relapsing and remitting types of multiple sclerosis, an inflammatory demyelinating disease of the central nervous system, at 0.25 mg (8 mIU) injected subcutaneously every other

day (20). This form of disease is characterized by recurrent attacks followed by complete or incomplete recovery.

The effectiveness of lower doses has not been documented, and there is no evidence of efficacy when this drug is used longer than 2 years.

Lyophilized IFNB-1b (Fig. 19.11) 0.3 mg (9.6 mIU) is reconstituted using a sterile syringe and needle to inject 1.2 mL of supplied diluent (sodium chloride 0.54%) into the vial. The diluent should be added down the side of the vial and the vial then gently swirled, but not shaken, to dissolve the drug completely. After reconstitution with the accompanying diluent, the solution has a strength of 0.25 mg/mL. This product also contains dextrose and albumin (often used in recombinant protein products to prevent sorption of the product to the glass vial, plastic tubing, or syringe). Reconstituted solution 1 mL is withdrawn from the vial into a sterile syringe fitted with a 27-gauge needle, and the drug is injected subcutaneously. For purposes of self-injection, the sites may include the arms, abdomen, hips, and thighs.

Because the product has no preservative, the vial is suitable for single use only. Before and after reconstitution, the product should be refrigerated. No more than 3 hours should elapse between reconstitution and use.

Interferon Beta-1a (Avonex, Rebif)

IFNB-1a was approved for use in multiple sclerosis therapy in 1996, 3 years after IFNB-1b was approved. It is indicated for the treatment of relapsing forms of multiple sclerosis to slow the progression of physical disability and decrease the frequency of clinical exacerbations.

FIGURE 19.11 The product package of Betaseron. (Courtesy of Bayer Health Care Pharmaceuticals, Inc.)

The dosage regimen of IFNB-1a is 30 mg IM once per week. Its advantage over IFNB-1b is less administration during the week. The lyophilized powder for injection, that is, Avonex, is reconstituted by using a sterile syringe and Micro Pin to inject 1.1 mL of the supplied diluent and swirled gently to dissolve the active ingredient. One mL is withdrawn from the vial into the sterile syringe. A sterile 23-gauge, 1.25-inch needle is used to inject IM. The prepared product should be used as soon as possible but no later than 6 hours after reconstitution, if stored at 2°C to 8°C. Avonex is also available in a prefilled, single-use syringe, 30 mg/0.5 mL.

Rebif, available in prefilled syringes, is administered subcutaneously with a targeted dosage of 22 and 44 mg, three times weekly. If possible, administration should be consistent, preferably in the late afternoon or evening, on the same 3 days, for example, Monday, Wednesday, and Friday, at least 48 hours apart. Initial therapy should be 20% of the targeted dose three times per week and scaled upward over a 4-week period to the targeted dosage. Thus, the 8.8 mg/0.2 mL prefilled syringe is used for this purpose.

Vials of IFNB-1a must be refrigerated (2°C to 8°C), and if refrigeration is not available, the product can be stored at 25°C (77°F) for up to 30 days. A recent pharmacoeconomic study demonstrated Avonex to be cost-effective relative to other interferon therapies for multiple sclerosis (21).

Interleukins

Originally, ILs were thought to oversee interactions among white blood cells, key components of the immune system. Now, however, it is known that these substances affect a wider variety of cell types. Most clinical interest centers on IL-1, secreted primarily by the monocyte–macrophage that activates T cells and B cells, and IL-2, secreted by the T cell that supports growth

and differentiation of T cells and B cells. There are 14 known ILs.

IL-1 was discovered in 1972, and within 7 years, its structure and function were delineated. It was first manufactured by rDNA technology in 1984. This substance is a key immune system regulator. It sets into motion a chain reaction that intensifies the immune response. IL-1 responds to the initial presence of an antigen. It activates T cells to mature, proliferate, and produce other *cytokines* (a generic term for soluble substances produced by cells that communicate with other cells to trigger or suppress cellular activity after interaction with an antigen).

IL-1 also intensifies the production of collagenase, prostaglandins, and antibodies. Because of this activity, excessive IL-1 is suspected to be behind many inflammatory disorders (collagenase breaks down connective tissue; prostaglandins are associated with inflammation). Patients with rheumatoid arthritis have an imbalance in which nine times as much IL-1 as IL-1a is present in the synovium. This imbalance favors agonist-derived inflammation and destruction. The cytokine may also be responsible for the fever, headache, fatigue, and weakness of influenza.

IL-2, like other cytokines, was initially greeted with much enthusiasm. Since that time, it has been found to be an essential component in the development of antigen-specific and antigen-nonspecific immune responses but has found few applications (21). Discovered in 1976, it became available through rDNA technology in 1984. When applied to white blood cells removed from patients and then reinfused as "lymphokine-activated killer cells" along with a booster injection of IL-2, spectacular remissions occurred in some patients with devastating conditions such as advanced malignant melanoma. Unfortunately, highly toxic side effects occurred because appropriate dosing was unknown. A combination of lower doses and physician experience managing its side effects will make IL-2 safer to use in the future.

Other ILs are in the research pipeline. IL-11 is being investigated in vitro and in mice to stimulate platelet function. If successful, this substance could help counter the platelet-depleting effects of chemotherapeutic agents. IL-6 (also known as beta-2 interferon) may also be a stimulator of platelet growth, and it is being investigated as an antiproliferative treatment for breast, colon, and skin cancer.

Aldesleukin (Proleukin)

Aldesleukin is synthetically produced by an rDNA process involving genetically engineered *E. coli* containing an analog of the human IL-2 gene. An expression clone that encodes a modified human IL-2 results from genetic engineering used to modify the human IL-2 gene. Aldesleukin differs from naturally occurring IL-2 in that it is not glycosylated because it is derived from *E. coli*, the molecule has no N-terminal alanine, and the molecule has serine substituted for cysteine at amino acid position 125.

Designated as an orphan drug, aldesleukin is approved for the treatment of metastatic renal carcinoma (about 10,000 cases diagnosed annually) in adults (over 18 years), melanomas, and primary immunodeficiency disease associated with T-cell defects. Aldesleukin is being investigated in phase II clinical trials for efficacy with zidovudine for HIV.

Because of its life-threatening toxicities (drug-related mortality rate is 4%), the physician should consider the benefit-to-risk ratio for the patient. The dosage of IL-2 is usually expressed in units of activity in promoting proliferation in a responsive cell line. Conversion to units from milligrams of protein varies with the source of IL-2. The strength and dosage of commercially available aldesleukin are expressed in IUs; 18 million IU equals 1.1 mg protein.

For metastatic renal carcinoma, high-dose therapy involves an intravenous infusion over 15 minutes, 600,000 IU/kg of body weight (0.037 mg/kg body weight) every 8 hours for a total of 14 doses. Following a rest period of 9 days, the schedule is repeated for another 14 doses, for a maximum of 28 doses per course. The manufacturer of aldesleukin recommends that plastic bags be used as the dilution containers (as opposed to glass bottles and polyvinyl chloride bags) for more consistent drug delivery. Inline filters are

not recommended because of the risk of adsorption of aldesleukin to the filter.

Each single-use vial contains 22 million IU (1.3 mg of drug) reconstituted for intravenous or subcutaneous injection by addition of 1.2 mL of sterile water for injection. The diluent should be directed to the side of the vial and the contents swirled gently to avoid foaming. The resultant solution should be clear and colorless to slightly yellow. It contains 18 million IU (1.1 mg) per milliliter. The vial should not be shaken. The appropriate dose is withdrawn, diluted in 50 mL of 5% dextrose injection, and infused over 15 minutes. Neither bacteriostatic water for injection nor 0.9% sodium chloride injection should be used to reconstitute this product because of the increased aggregation of the product.

Because the vial has no preservative, the reconstituted and diluted solutions should be refrigerated. However, it should be brought back to room temperature prior to administration. Reconstituted solutions should be used within 48 hours.

FIGURE 19.12 The product package of Kineret. (Courtesy of Amgen, Inc.)

Anakinra (Kineret)

Approved in November 2001, anakinra is a recombinant IL-1 receptor antagonist. It competitively binds to the IL-1 receptor, thereby blocking the biologic action of IL-1. Anakinra is an unglycosylated form of human IL-1ra, which occurs naturally but in insufficient amounts to compete for higher levels of IL-1 in the synovium.

Anakinra is indicated for use in adult patients who have been treated unsuccessfully with at least one DMARD. It can be used as the sole agent or combined with other DMARDs except the tumor necrosis factor (TNF)-α–blocking agents, specifically because of the increased risk of infection. The recommended dosage of anakinra is 100 mg per day subcutaneously. Clinical trials demonstrated a mild pain sensation at the site of injection and some inflammation, redness, and/or bruising. Anakinra is packaged in single-use prefilled syringes (Fig. 19.12). These contain no preservatives and should be stored in the refrigerator and protected from light. Patients and caregivers should be educated on the importance of proper disposal and caution against the reuse of needles, syringes, and drug product. The patient should have a puncture-resistant container available for the disposal of used syringes.

Oprelvekin (Neumega)

Patients receiving chemotherapy commonly have neutropenia and thrombocytopenia. These hematologic effects make it difficult to maintain the dose and dosing schedule of the chemotherapy regimen. Managing neutropenia became easier with the approval of the CSFs filgrastim and sargramostim. However, before the approval of oprelvekin, the only treatments for chemotherapy-related thrombocytopenia were platelet transfusion or a reduction in chemotherapy dosage.

Oprelvekin is a recombinant human IL-1 l (rhIL-1 l), a multifunctional cytokine used primarily as a thrombopoietic growth factor. IL-1 l interacts with IL-1 l receptors on the surface of myeloid progenitor cells to stimulate production of megakaryocytes and platelets.

Oprelvekin was approved specifically for prevention of severe thrombocytopenia and platelet transfusion following myelosuppressive chemotherapy in nonmyeloid malignancy patients (Fig. 19.13). Allowing the maintenance of dose intensity of chemotherapy may increase the probability that cancer patients will remain in remission for 5 years.

Oprelvekin is produced from *E. coli* by rDNA technology. It is supplied as 5 mg of lyophilized powder in a single-use vial. A 5-mL vial of sterile water for injection is supplied for reconstitution, which is confusing, because only 1 mL is needed for reconstitution. Predictably, medication errors have occurred because of overdilution of the product. The manufacturer is attempting to provide a suitable preservative-free 1-mL diluent. When reconstituted appropriately, this provides a daily dose up to 50 mg/kg for a 100-kg patient. There are no preservatives in the vial, as each vial is for single use. The reconstituted solution can be stored in the vial at room temperature or under refrigeration for up to 3 hours.

Oprelvekin is administered subcutaneously as a single daily injection in the abdomen, thigh, hip, or upper arm. Oprelvekin administration should commence 6 to 24 hours after completion of chemotherapy, and platelet counts should be monitored during therapy. The drug should be discontinued when the platelet count reaches more than 50,000/mm^3 after the nadir. Typically, therapy ranges from 10 to 21 days and should be discontinued at least 2 days before the start of the next chemotherapy cycle.

FIGURE 19.13 The product package of Neumega. (Courtesy of Genetics Institute.)

Monoclonal Antibodies

Historically, MAbs have found use in laboratory diagnostics, site-directed therapies, immunology, and home test kits (e.g., pregnancy, ovulation prediction). In the 1980s, monoclonals were expected to provide a tremendous potential for tumor therapy and immunomodulation. By coupling tracers and toxins to antibodies, tissue-selective or cell-specific targets can be attained. However, initial clinical trials demonstrated less than expected results because of (*a*) insufficient characterization of the product and its performance in vitro; (*b*) inadequate preclinical testing; (*c*) unrealistic expectations of clinical performance, for example, short circulating half-lives (patients frequently developed antibodies to the mouse-derived proteins); and (*d*) inadequately designed clinical trials.

Advances in genetic engineering provided more ways to design MAbs, and from 1980 to 2005, a total of 206 unique therapeutic MAbs were studied in clinical trials for a variety of cancer indications (22). By 2004, 13 intact, unconjugated, MAb antibodies; three intact immunoconjugates; and one Fab fragment were approved in the United States for therapeutic use in organ transplantation, rheumatoid arthritis, Crohn disease, breast cancer, and colorectal cancer, among others (23). MAbs are purified antibodies produced by a single source or clone of cells. These substances are engineered to recognize and bind to a single specific antigen. Thus, a MAb will target a particular protein or cell having the specific matching antigenic feature. When coupled with a drug molecule, radioactive isotope, or toxin, a MAb theoretically can target the desired cells or tissues with great precision. Specificity for the target antigen is the primary characteristic for the MAb and reflects affinity and strength of binding for the target antigen and cross-reactivity with normal cells. The ideal target organ antigen, hopefully, serves a vital biological function necessary for tumor cell survival because the tumor cell growth can continue unaffected if a target organ is not vital or can be circumvented. In addition, there must be sufficient antigen quantity to mediate a disease-relevant

response. Also, the target organ antigen should not be shed or secreted because such antigens bind to, neutralize, and clear MAbs without causing an antitumor effect.

Diagnostically, the specificity of MAbs helps to detect the presence of endogenous hormones (e.g., luteinizing hormone [LH], human chorionic gonadotropin) in the urine to establish the test results (24). They are also used to detect allergies, anemia, and heart disease, and commercial MAb diagnostic kits are available for drug assays, tissue and blood typing, and infectious diseases including hepatitis, AIDS-related CMV, streptococcal infections, gonorrhea, syphilis, herpes, and chlamydia. When covalently linked with radioisotopes, contrast agents, or anticancer drugs, MAbs can be used to diagnose and treat malignant tumors (8).

Adalimumab (Humira)

Adalimumab was approved by the FDA in early 2003 for reducing signs and symptoms in rheumatoid arthritis patients who have not responded to previous treatments with methotrexate and other DMARDs (Fig. 19.14). Administered subcutaneously every 2 weeks, this drug now offers an attractive alternative for patients who require TNF-a blocker therapy (25). TNF-a is responsible for much of the pain and inflammation associated with rheumatoid arthritis. Adalimumab is also indicated for psoriatic arthritis, ankylosing spondylitis, and Crohn disease.

Adalimumab was approved for monotherapy or combination treatment with methotrexate or other DMARDs. Compared with other biologic response–modifying rheumatoid arthritis medications, it offers an easier, that is, subcutaneous, and less frequent dosing regimen chronically, that is, every other week. Enbrel, another TNF-a blocker, requires twice weekly injections, and natalizumab, that is, Remicade, another TNF-a blocker, requires an infusion for administration in the physician's office.

Adalimumab is administered subcutaneously as an easy-to-use, single-use, prefilled syringe or disposable, single-use pens for subcutaneous injection (40 mg/0.8 mL). The injections should be kept refrigerated but not frozen. The injectables should be removed from the refrigerator 15 to 20 minutes prior to injection and the patient should select an injection site on his/her thigh or stomach that is at least 1 inch from the previous site of injection (i.e., rotating the injection sites) and 2 inches from the navel. The drug should not be injected into skin that is inflamed, tender to the touch, bruised, or hard. The medication should also be protected from light and stored in its original carton until it is to be administered.

FIGURE 19.14 The product package of Humira. (Courtesy of Abbott Laboratories.)

Basiliximab (Simulect)

Basiliximab is an IL-2 receptor antagonist. It is an example of a chimeric (murine–human) MAb (IgG_{1K}) produced by rDNA technology. It functions as an immunosuppressive agent, specifically binding to and blocking the IL-2 receptor alpha chain (IL-2Ra, also known as the CD25 antigen), which is selectively expressed on the surface of activated T lymphocytes. This high-affinity binding specificity of the drug to IL-2Ra competitively inhibits IL-2–mediated activation of lymphocytes, a critical pathway in the cellular immune response of allograft rejection.

Like daclizumab, basiliximab is indicated for the prophylaxis of acute organ rejection in patients receiving renal transplants. It is used as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids.

Basiliximab demonstrates an adverse effect profile similar to that of daclizumab. Administration of this drug is by central or peripheral intravenous infusion only. The dilute reconstituted basiliximab (20 mg/5 mL) is brought to a 50-mL volume with 0.9% sodium chloride injection or 5% dextrose injection and administered as an intravenous infusion over 20 to 30 minutes.

The recommended regimen for an adult is two doses of 20 mg each. The first dose is administered within 2 hours prior to transplantation surgery. The second dose is administered 4 days after surgery. For children and adolescents aged 2 to 15 years, the recommended regimen is two doses of 12 mg/m^2 each, up to a maximum of 20 mg per dose. The schedule is the same as for an adult.

Bevacizumab (Avastin)

Approved by the FDA in 2004, bevacizumab is used in combination with IV 5-fluorouracil–based chemotherapy for first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum. It is a recombinant humanized IgG MAb that binds with vascular endothelial growth factor A (VEGF-A), a target antigen that binds to VEGF tyrosine kinase receptors on the surfaces of endothelial cells, signaling intracellular tyrosine kinases resulting in angiogenesis (26). Angiogenesis is a term used to describe the growth of new blood vessels and plays a crucial role in the development and maturation of tissues. It also plays a central feature in a number of diseases. In cancer, this process supplies the increased demand for oxygen and nutrients that facilitate tumor growth and metastasis. Thus, inhibition of angiogenesis is a possible treatment for some cancers.

This drug is available for injection, 25 mg/mL in single-use 4- and 16-mL vials. It is diluted for infusion using aseptic technique and the necessary amount withdrawn and diluted in a total volume of 100 mL 0.9% sodium chloride injection. The initial dosage is delivered over 90 minutes as an IV infusion following chemotherapy. If the first infusion is well tolerated, the second infusion may be administered over a 60-minute period. If the second, 60-minute infusion is well tolerated, subsequent infusions can be administered over a 30-minute period.

The vials for injection must be refrigerated at 2°C to 8°C and protected from light. Freezing must be avoided and the vials not shaken. Diluted bevacizumab solutions for infusion may be stored at 2°C to 8°C for up to 8 hours.

Daclizumab (Zenapax)

Daclizumab is an immunosuppressive humanized IgG1 MAb produced by rDNA technology that binds specifically to the alpha unit (Tac subunit) of the human high-affinity IL-2 receptor that is expressed on the surface of activated lymphocytes. Daclizumab is a composite of human (90%) and murine (10%) antibody sequences.

Daclizumab is indicated for the prophylaxis of acute organ rejection in patients receiving renal transplants. It is used as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids.

The recommended dose is 1 mg/kg intravenously as part of an immunosuppressive regimen. The calculated volume of daclizumab is mixed with 50 mL of sterile 0.9% sodium chloride injection and administered via a peripheral or central vein over 15 minutes. The standard course of daclizumab therapy is five doses. The first dose is administered not more than 24 hours before transplantation, and the remaining four doses are given at intervals of 14 days. Daclizumab is supplied in single-use glass vials that should be stored between 2°C and 8°C, but not frozen. The vials should not be shaken and the undiluted solution protected from direct sunlight. Diluted daclizumab is stable for 24 hours at 4°C or for 4 hours at room temperature.

Gemtuzumab Ozogamicin (Mylotarg)

Gemtuzumab ozogamicin targets myeloid leukemic cells, leaving precursor pluripotent stem cells relatively unscathed and is

less toxic than daunorubicin and cytarabine. It was the first drug specifically approved for treating relapsed AML. It is a MAb linked to a highly potent chemotherapeutic agent, calicheamicin. The antibody targets CD33, a glycoprotein on the surface of most AML cells. Thus, it is now also indicated for patients who are older than 60 years and who demonstrate CD33-positive AML and not considered candidates for conventional therapy.

The recommended dose is 9 mg/m^2 administered as a 2-hour intravenous infusion followed by a repeat dose 14 days later. This drug can be administered in an ambulatory setting. Treatment causes chills, fever, nausea, and vomiting and less commonly hypotension and dyspnea during the first 24 hours after administration. Vital signs should be monitored for at least 4 hours post administration. Methylprednisolone administered prior to gemtuzumab infusion may help to ameliorate infusion-related symptoms. Further, it is advised to administer 50 mg diphenhydramine and 650 to 1,000 mg acetaminophen 1 hour prior to administration of gemtuzumab ozogamicin to reduce the risk of an infusion reaction. Two additional doses of acetaminophen may be needed.

The product is light sensitive and must be protected from direct and indirect sunlight and unshielded fluorescent light during the preparation and administration of the infusion. In a shielded fluorescent-lighted hood, the contents of each vial should be reconstituted with 5 mL sterile water for injection using sterile syringes. The vial is gently swirled and inspected to assure complete dissolution of contents. The final concentration of the prepared solution should be 1 mg/mL.

Ibritumomab Tiuxetan (Zevalin)

Approved by the FDA in February 2002, ibritumomab tiuxetan is the first commercially available radiolabeled antibody for cancer therapy. When infused into the patient, the antibody binds to the surface of the specific cells and delivers radiation directly to the cancer cells. It is indicated for the treatment of relapsed or refractory low-grade follicular or transformed B-cell NHL.

The ibritumomab tiuxetan therapeutic regimen is administered in two steps. On day 1, rituximab (Rituxan) 250 mg/m^2 is administered intravenously. Within 4 hours of completion, ^{111}In-ibritumomab tiuxetan 5 mCi containing 1.6 mg of the ibritumomab antibody is administered over a 10-minute period. This initial dose clears peripheral blood of beta cells and maximizes biodistribution of the ibritumomab tiuxetan. Biodistribution of the ^{111}In-ibritumomab should be assessed by imaging at 2 to 24 hours and at 48 to 72 hours postinjection to assess whether the antibody is settling in tumor sites and not in other organs. If biodistribution is adequate, the second regimen is administered.

The second step in the ibritumomab regimen, implemented on days 7 to 9, consists of a second infusion of rituximab 250 mg/m^2. This is followed by ^{90}Y-ibritumomab tiuxetan 0.4 mCi/kg of actual body weight for patients with a platelet count above 150,000 cells/mm^3 and 0.3 mCi/kg of actual body weight for patients whose platelet count is 100,000 to 149,000/mm^3. Regardless of actual body weight, the maximum dose of the ^{90}Y-ibritumomab tiuxetan component is 32 mCi. This regimen is not implemented in patients demonstrating a platelet count below 100,000 cells/mm^3.

Because the nuclear pharmacist will be working with a pure beta particle–emitting radionuclide, ^{90}Y, extreme care will be necessary when handling the agent to protect fellow employees and patients' radiation exposure and keep it as low as possible.

Infliximab (Remicade)

Infliximab is the only approved drug therapy specifically indicated for the treatment of fistulizing Crohn disease, an inflammation of the intestine.

Approved in 1998, infliximab was originally indicated for short-term treatment. In 2002, this indication was expanded to reduction of the signs and symptoms of and induction and maintenance of clinical remission in patients with moderate to severely active Crohn disease who demonstrated an inadequate response to conventional therapies. In addition, in 1999, infliximab was approved

for the treatment of rheumatoid arthritis, an indication that was expanded in 2002 to include improvement of physical function in patients without an adequate response to methotrexate therapy.

This MAb binds and neutralizes TNF-a, one of the primary cytokines that propagate the inflammatory response in patients with Crohn disease and rheumatoid arthritis. Thus, infliximab reduces the intestinal inflammation indicative of this disease process. Administration of single induction doses of infliximab when patients with Crohn disease are not receiving immunosuppressive drugs can lead to the development of antibodies to the chronic MAb itself. When antibodies to infliximab are present in high concentrations, patients demonstrate shortened duration of benefit, complete loss of response, and/or infusion reactions to the drug itself.

Infliximab is supplied in single-use 20-mL vials containing 100 mg of the drug. It has been associated with hypersensitivity reactions, including urticaria, dyspnea, and hypotension, and should be discontinued in case of a severe reaction. Additionally, anti-TNF therapy may result in the formation of autoimmune antibodies and rarely in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome and is positive for antibodies against double-stranded DNA, infliximab therapy should be discontinued.

Muromonab-CD3 (Orthoclone OKT3)

Muromonab-CD3 is a murine MAb that reacts with a T3 (CD3) molecule linked to an antigen receptor on the surface membrane of human T lymphocytes. It blocks both generation and functions of the T cells in response to antigenic challenge and is indicated for the treatment of organ transplant rejection. Usually, it is combined with azathioprine, cyclosporine, and/or corticosteroids to prevent acute rejection of renal transplants. Simultaneously, the amount of immunosuppressive drugs a patient must receive has been reduced, effecting better outcomes.

Muromonab-CD3 injection is administered by IV push over a period not less than 1 minute. For acute renal allograft rejection, it is given IV at 5 mg per day for 10 to 14 days. To decrease the incidence of reactions resulting from the first injection of muromonab, methylprednisolone sodium succinate 8 mg/kg should be administered intravenously 1 to 4 hours beforehand. The patient's temperature should not exceed 37.8°C at the time of administration.

Muromonab-CD3 injection should be drawn into the syringe through a low–protein-binding 0.2- to 0.22-mm filter. The filter should be discarded and the needle for the intravenous bolus injection attached. Because the drug is a protein solution, it may develop a few fine translucent particles that do not affect its potency. This solution has no preservative and so must be used immediately upon opening and the unused portion discarded. As with other protein products, it must not be shaken.

Omalizumab (Xolair)

Omalizumab is the first humanized therapeutic antibody for the treatment of asthma and the first approved therapy designed to target immunoglobulin E (IgE) in the management of asthma. It was approved by the FDA in 2003 for subcutaneous treatment of moderate to severe persistent asthma in patients more than 12 years of age who demonstrate a positive skin test or in vitro reaction to a perennial aeroallergen (Fig. 19.15). Another requisite for its use is that the patient is inadequately controlled with inhaled corticosteroids.

Omalizumab is administered subcutaneously every 2 to 4 weeks. Dosing is based on

FIGURE 19.15 The product package of Xolair. (Courtesy of Genentech, Inc.)

the patient's body weight and IgE level and may have to be repeated early in therapy to attain the dose necessary to be effective as a prophylactic agent. The usual dose is 150 to 375 mg, and the doses and frequency are determined by pretreatment serum total IgE levels and body weight using tables available in product labeling. Doses over 150 mg should be divided and administered in multiple sites. Not more than 150 mg should be injected into one site.

Palivizumab (Synagis)

Palivizumab is a humanized MAb (IgG_{1K}) produced by rDNA technology, directed to the epitope in the A antigenic site of the F protein of respiratory syncytial virus (RSV). It is a composite of human (95%) and murine (5%) antibody sequences.

Palivizumab demonstrates neutralizing and fusion-inhibitory activity against RSV, and is used to prevent serious lower respiratory tract disease caused by RSV in children. The safety and efficacy of this drug were established in infants with bronchopulmonary dysplasia (BPD) and infants with a history of prematurity (≤35 gestational weeks).

Palivizumab is for intramuscular use only, and the single-use vials of the drug do not contain a preservative. The injection must be administered within 6 hours after reconstitution.

The recommended dosage of palivizumab is 15 mg/kg intramuscularly in the anterolateral aspect of the thigh (preferable location). The use of the gluteal muscle is not advocated as a site of injection because of the risk of sciatic nerve damage. Patients, including those who develop an RSV infection, should receive monthly doses throughout the RSV season. The first dose is to be administered prior to the onset of the RSV season. In the northern hemisphere, the RSV season commences usually in November and lasts through April. However, it may be earlier or later.

Rituximab (Rituxan)

In November 1997, rituximab was the first MAb approved to treat cancer. It is a chimeric human–murine MAb directed against the CD20 antigen found on the surface of normal and malignant beta lymphocytes. The Fab domain of rituximab binds to the CD20 antigen on beta lymphocytes, and the Fc domain recruits immune effector functions to mediate beta-cell lysis in vitro.

Rituximab is used to treat patients with relapsed or refractory low-grade or follicular CD20-positive beta-cell NHL. The recommended dosage is 375 mg/m^2 given as an intravenous infusion weekly for four doses (days 1, 8, 15, and 22). It may be administered in an outpatient setting.

The first infusion is administered at 50 mg per hour. If no hypersensitivity or infusion-related events occur, the infusion is escalated in increments of 50 mg per hour every 30 minutes to a maximum of 400 mg per hour. If hypersensitivity or infusion-related reactions (e.g., fever, chills, nausea, urticaria, fatigue, headache, bronchospasm) develop, the infusion is interrupted or slowed. These reactions generally present within 30 minutes to 2 hours of the first infusion. Subsequent infusions can be administered at a higher rate (100 mg per hour) and increased by 100 mg per hour increments up to a maximum of 400 mg per hour as tolerated.

Premedication with acetaminophen and diphenhydramine may attenuate infusion-related events. Because hypotension may occur during infusion, it is suggested that one consider withholding any antihypertensive medication 12 hours prior to rituximab infusion.

Rituximab (as Rituxan) is available in 10- and 50-mL single-unit vials (10 mg/mL). The required amount of drug is withdrawn and diluted to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% sodium chloride or 5% dextrose injection. The bag is gently inverted to mix the solution. Any unused portion is discarded.

Satumomab Pendetide (OncoScint CR/OV Kit)

OncoScint CR/OV-In (^{111}In-satumomab pendetide) is a diagnostic imaging agent that is indicated for determining the extent and location of extrahepatic malignant disease in patients with known ovarian carcinoma.

Satumomab pendetide is a conjugate produced from the murine MAb CYT-099 (MAb B72.3). MAb B72.3 is a murine MAb of the IgG_{1K} subclass, which is directed to, localizes, and binds with a high molecular weight tumor–associated glycoprotein (TAG-72) that is expressed differentially by adenocarcinomas. (Adenocarcinoma is a technical name for a malignant tumor derived from a gland or glandular tissue or a tumor whose gland-derived cells form gland-like structures.) In vitro immunohistologic studies have reported MAb B72.3 to be reactive with about 83% of colorectal adenocarcinomas, 97% of common epithelial ovarian carcinomas, and most breast, non–small cell lung, pancreatic, gastric, and esophageal cancers evaluated.

OncoScint CR/OV is prepared by site-specific conjugation of the linker–chelator, glycyl tyrosyl-(*N*,e-diethylenetriamine pentaacetic acid)-lysine hydrochloride, to the oxidized oligosaccharide component of MAb B72.3. Each kit contains all of the nonradioactive ingredients necessary to produce a single-unit dose of OncoScint CR/OV-In for use as an intravenous injection. Each kit contains two vials. A single-dose vial of OncoScint CR/OV, formulated with sterile water for injection, contains 1 mg of satumomab pendetide in 2 mL of sodium phosphate–buffered saline solution adjusted to pH 6 with hydrochloric acid. OncoScint CR/OV is sterile, pyrogen-free, clear, and colorless, and it may contain some translucent particles. A vial of sodium acetate buffer contains 136 mg of sodium acetate trihydrate in 2 mL of water for injection adjusted to pH 6 with glacial acetic acid. It is sterile, pyrogen-free, clear, and colorless. Neither solution contains a preservative. Each kit also contains one sterile 0.22-mm Millex GV filter, prescribing information, and two identification labels. The kit should be stored upright in a refrigerator (2°C to 8°C) but not frozen.

Proper aseptic technique and precautions for handling radioactive materials should be employed. Waterproof gloves should be worn during radiolabeling. Consistent with the instructions provided, the sodium acetate buffer solution must be added to the ^{111}In chloride solution to buffer it prior to radiolabeling satumomab pendetide. After radiolabeling with ^{111}In, the immunoscintigraphic agent, OncoScint CR/OV-In (^{111}In-satumomab pendetide) is formed. The injection should be administered within 8 hours after radiolabeling.

Tocilizumab (Actemra)

IL-6, a proinflammatory cytokine, plays a primary role in causing local and systemic manifestations of rheumatoid arthritis. Tocilizumab is the first IL-6 receptor inhibiting MAb for the treatment of rheumatoid arthritis. It competitively inhibits the binding of IL-6 to its receptor, thereby preventing IL-6 signal transduction to inflammatory mediators to summon B and T cells.

Tocilizumab is a fusion of murine and human components. The drug was engineered by grafting the antigen-binding regions of the murine antihuman IL-6R antibody to the human IgG1 framework, which is associated with complement fixation. The resulting antibody has a longer half-life, that is, 240 hours, achieved after the third dose of 8 mg/kg in humans. The drug is administered as an IV infusion every 4 weeks for 3 months. The final assessment is performed 4 weeks after the third infusion. Because the drug is a humanized antibody, infusion-related adverse effects, that is, hypersensitivity reactions, might be expected.

Trastuzumab (Herceptin)

In September 1998, trastuzumab became the second MAb approved to treat cancer. It is indicated for the treatment of metastatic breast cancer or cancer that has spread beyond the breast and lymph nodes under the arm. The drug is approved for monotherapy in certain patients who have attempted chemotherapy with little success or as a first-line treatment of metastatic disease in combination with paclitaxel (Taxol) in first-line metastatic breast cancer therapy patients whose tumors overexpress the HER2 protein. In 2008, it was approved as part of a treatment regimen containing doxorubicin, cyclophosphamide, and docetaxel (Taxotere) and as part of a regimen with docetaxel and carboplatin.

Both are for adjuvant treatment of HER2-overexpressing, node-positive, or high-risk node-negative breast cancer.

Specifically, trastuzumab is a chimeric human–murine MAb that binds to the HER2 (or c-erbB2) protooncogene found on the surface of normal cells and plays a role in regulating cell growth. In the case of metastatic breast cancer cells, approximately 25% to 30% of tumors overexpress excess amounts of HER2. Thus, only patients who have tumors with this characteristic have shown benefit from trastuzumab. It should be used to treat only tumors that have HER2 protein overexpression. The trastuzumab–paclitaxel cycle is 21 days of treatment for six cycles.

The labeling of trastuzumab contains a black box warning regarding the risk of ventricular dysfunction and congestive heart failure (CHF). The patient receiving this medicine must be monitored closely. The recommended loading dose is 4 mg/kg as a 90-minute intravenous infusion along with 175 mg/m^2/dose on day 1 of therapy and must not be administered as an IV push or bolus. Subsequent weekly 2 mg/kg doses of trastuzumab can be administered as a 30-minute IV infusion if the first infusion was well tolerated on days 8 and 15 except for day 1 of the first cycle. Herceptin is available in a 440 mg/21 mL multidose vial and can be administered in an outpatient setting. Reconstituted trastuzumab must be discarded after 28 days.

TISSUE PLASMINOGEN ACTIVATORS

tPAs are substances produced in small quantity by the inner lining of blood vessels and by the muscular wall of the uterus. They prevent abnormal blood clotting by converting plasminogen, a component of blood, to the enzyme plasmin, which breaks down fibrin, the main constituent of a blood clot.

Genetic engineering has prepared these substances artificially, and they are used as *thrombolytic agents* (agents that dissolve blood clots). They are used for conditions such as heart attack, angina, and occluded arteries. Unlike other anticoagulant drugs, tPA acts only on the site of the clot.

Recombinant Alteplase (Activase)

Alteplase, a tPA produced by rDNA, is used in the management of acute myocardial infarction (AMI), acute ischemic stroke, and pulmonary embolism (PE). It is a sterile, purified glycoprotein of 527 amino acids. It is synthesized using the complementary DNA for natural human tissue-type plasminogen activator obtained from a human melanoma cell line.

The biologic activity of alteplase is determined by an in vitro clot lysis assay. The activity is expressed in IUs as tested against the WHO standard. Its specific activity is 580,000 IU/mg. Alteplase is an enzyme (serine protease) that has the property of fibrin-enhanced conversion of plasminogen to plasmin. It produces limited conversion of plasminogen in the absence of fibrin. When administered, alteplase binds to fibrin in a thrombus and converts the trapped plasminogen to plasmin. This initiates local fibrinolysis with limited systemic proteolysis.

An appropriate volume of the accompanying sterile water for injection (without preservatives) is added to the vial containing the lyophilized powder (2, 50, or 100 mg) (Fig. 19.16). Reconstitution should be with a large-bore (e.g., 18 gauge) needle and the stream of sterile water for injection directed into the lyophilized cake. A slight foaminess can be expected; when allowed to stand undisturbed, it should dissipate within several minutes. The resultant solution appears as a colorless to pale yellow transparent solution having a pH of approximately 7.3 and containing 1 mg/mL.

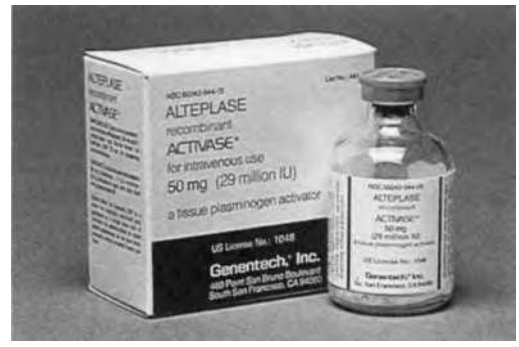


FIGURE 19.16 The product package of Activase (Alteplase). (Courtesy of Genentech, Inc.)

There are no antibacterial preservatives in the product, so it should be prepared just before use. Because the alteplase molecule is large, it cannot easily diffuse across biologic membranes and must be administered parenterally, usually intravenously. The solution may be used for direct intravenous administration within 8 hours of reconstitution when stored at 2°C to 30°C (36°F to 86°F). Before diluting or administering the product, it is necessary to inspect it visually for particulate matter and discoloration whenever the solution and container permit.

This product may be administered as reconstituted at 1 mg/mL, or the reconstituted solution may be diluted further immediately preceding administration with an equal volume of 0.9% sodium chloride injection or 5% dextrose injection. Alteplase is stable for up to 8 hours in these solutions at room temperature, and either polyvinyl chloride bags or glass bottles are acceptable. Light exposure has no influence upon stability.

Recombinant Reteplase (Retavase)

Reteplase is a nonglycosylated deletion mutein of tPA containing 355 of the 527 amino acids of native tPA. It is produced by rDNA in *E. coli*. Its mechanism of action is the same as that of alteplase.

Reteplase is indicated for management of AMI in adults, improvement of ventricular function following an AMI, reduction of the incidence of CHF, and reduction in mortality associated with an AMI.

Reteplase is for intravenous administration only. It is administered as a 10 + 10 U double-bolus injection. Each 10-mL bolus is administered intravenously over 2 minutes. The second bolus is given 30 minutes after initiation of the first bolus injection. An important requirement is that the bolus injection be given via a line in which no other medication is being injected or infused. If reteplase must be injected through an intravenous line containing heparin, the health professional should flush the line with 0.9% sodium chloride injection or 5% dextrose injection before and after reteplase administration.

The lyophilized powder for injection of reteplase should be reconstituted only with sterile water for injection (without preservatives) immediately before use. A colorless solution should be created containing 1 U/mL. A slight foaminess at this point is fairly common, and allowing the solution to stand undisturbed for a few minutes will allow dissipation of any large bubbles.

Reteplase (as Retavase) is available in kits. Each kit contains a two single-use reteplase vials of 10.8 U (18.8 mg), two single-use diluent vials for reconstitution (10 mL sterile water for injection), two sterile 10-mL syringes with 20-gauge needle attached, two sterile dispensing pins, two sterile 20-gauge needles for dosage administration, and two alcohol swabs.

Recombinant Tenecteplase (TNKase)

This thrombolytic agent is marketed with a needleless administration set that can be used to deliver the medication with just one dose in only 5 seconds. It is packaged in a 10-mL syringe, a dual-cannula device, and a 10-mL vial of sterile water for injection. Doses are calculated on the basis of body weight. After reconstitution of the lyophilized powder, patients will receive 6 to 10 mL. The agent is administered via an intravenous line with saline, as dextrose may cause precipitation. This product contains no bacteriostatic agent and so must be prepared immediately before administration. However, if it is not used immediately, it can be refrigerated for use within 8 hours.

Produced in Chinese hamster ovary cells using rDNA technology, it demonstrated comparable effectiveness (demonstrated mortality rates) and safety (intracranial hemorrhage, major bleeding episodes) as an accelerated infusion of recombinant alteplase in the ASSENT-2 (ASsessment of the Safety and Efficacy of a New Thrombolytic agent) trial. The tenecteplase protein is a modified form of natural tPA. The three letters in the name derive from amino acid substitutions at three regions of the tPA protein. These substitutions have provided a prolonged half-life that enables single-bolus dosing, an enhanced specificity for fibrin (which reduces the agent's disruption of other parts of the coagulation system), and an increased level of resistance to plasminogen activator inhibitor, which can

otherwise interfere with the drug's therapeutic action. To be effective, tenecteplase, like the other clot busters, must be used within the first hours of a heart attack.

Tyrosine Kinase Inhibitor

The Philadelphia (Ph) chromosome, a truncated chromosome 22, was the first consistent chromosomal abnormality identified in human malignancy (27). Improved chromosome banding techniques demonstrated that this chromosome was the result of a reciprocal translocation between the long arms of chromosomes 9 and 22. The molecular consequences cause the fusion of the c-Abl oncogene (chromosome 9) and the Bcr sequence (chromosome 22) into the Bcr-Abl gene. This fusion catalyzes the phosphorylation of tyrosine residues from adenosine triphosphate (ATP). Ultimately, this activates several other multiple signaling pathways that affect cell growth, adhesion, and proliferation.

The size of the protein generated by this fusion gene depends on the breakpoint in the Bcr region. For example, 95% of patients with chronic myelogenous leukemia (CML) and up to approximately 20% of adult patients with ALL will demonstrate a 210-kDa fusion protein. Alternatively, a 185-kDa fusion protein is observed in 10% of adult patients with ALL and is the predominant Bcr-Abl fusion protein in Ph chromosome–positive children with ALL. The product of this fusion gene is a constitutively active tyrosine kinase with markedly enzymatic activity when compared to the Abl kinase. Because all of these events (cell growth, adhesion, proliferation) depend on the increased tyrosine kinase activity of the fusion protein, it is apparent that inhibition of the enzymatic activity of Bcr-Abl would be an effective treatment of CML. Bcr-Abl is present in most patients with CML, and the causative abnormality of the disease and its kinase activity are central for transformation.

Imatinib Mesylate (Gleevec)

Imatinib mesylate demonstrates potent and selective inhibitory activity in vivo against Abl tyrosine kinases, such as Bcr-Abl, through competitive inhibition at the ATP-binding site (28) (Fig. 19.17). It does so without any significant effect on normal cells or other cells affected by the tyrosine oncogenes. Phase I clinical trials of the drug (as ST1571) conducted in June 1998 demonstrated significant activity against CML even in patients who were interferon refractory. A significant finding was that the drug is most advantageous when used early in the disease, in the chronic phase. Thus, some experts have proposed a treatment algorithm that calls for all CML patients to receive imatinib while transplantation is being evaluated. In patients whose condition responded to imatinib and for whom the risk of death from transplantation is higher (all except the youngest patients with sibling donors), the procedure could be withheld or deferred.

FIGURE 19.17 The product package of Gleevec. (Courtesy of Novartis, Inc.)

The chronic phase dosage is 400 to 600 mg daily. The accelerated phase or blast crisis dosage ranges from 600 to 800 mg daily. The patient should be instructed to take this medication with food and a large glass of water because of mild gastrointestinal effects. Serum concentrations of imatinib are affected by medications that inhibit or induce the CYP 3A4 enzyme. Other common adverse effects

include edema, muscle cramps, hemorrhage, and musculoskeletal pain. But these have been mild compared with those of other chemotherapeutic agents.

Nilotinib (Tasigna)

Nilotinib, a Bcr-Abl tyrosine kinase inhibitor, was approved in late 2007 for the treatment of chronic and accelerated-phase CML in adults resistant or intolerant to prior therapies, including imatinib. The dosage regimen of nilotinib is 400 mg orally every 12 hours, and the capsule dosage form should be swallowed whole at least 2 hours after a meal. The patient should then refrain from eating for 1 hour. Grapefruit juice should not be consumed while taking this drug.

Nilotinib is metabolized by the CYP3A4 liver enzymes, and therefore, patients should consult their health care provider prior to initiating any other drug therapy. Similarly, patients receiving concurrent therapy with CYP3A4 inhibitors or inducers should be monitored closely and dosage adjustments made accordingly. Nilotinib can cause QT prolongation, and patients are educated to be aware of possible symptoms, for example, irregular heartbeat and fainting.

Vaccines

Genetically engineered vaccines use a synthetic copy of the protein coat of a virus to fool the body's immune system into mounting a protective response. This avenue avoids the use of live viruses and minimizes the risk of causing the disease the vaccine was intended to prevent. Further, these vaccines will all but eliminate concern about the natural vaccine, which could be derived from blood donor carriers who may harbor the AIDS virus.

The first genetically engineered vaccine for use in the United States was approved by the FDA in 1986 for hepatitis B, a widespread liver infection. This vaccine has now replaced the plasma-derived vaccine.

Hepatitis B Vaccine Recombinant (Engerix-B, Recombivax HB)

The plasma-derived hepatitis B vaccine is no longer being produced in the United States, and its use is limited to hemodialysis patients, other immunocompromised patients, and persons with known allergies to yeast. Recombinant hepatitis B vaccine has demonstrated an ability to induce antibody to hepatitis B surface antigen (anti-HBs) that is biochemically and immunologically comparable to antibody induced by the plasma-derived hepatitis B vaccine. Studies demonstrate that the two are interchangeable in use.

Hepatitis B recombinant vaccine is indicated for immunization of persons of all ages against infection caused by all types of hepatitis B virus. A dialysis formulation (Recombivax HB Dialysis Formulation) is indicated for immunization of adult predialysis and dialysis patients. The vaccine should be administered by intramuscular injection into the deltoid muscle (outer aspect of the upper arm) for immunization of adults and older children. The anterolateral thigh is recommended for infants and younger children. For patients with a risk of hemorrhage following intramuscular injection, the vaccine may be administered subcutaneously, although the subsequent antibody titer may be lower and there may be an increased risk of a local reaction.

Haemophilus B Conjugate Vaccine (HibTITER, Liquid PedvaxHIB, ActHIB)

Prior to the introduction of *Haemophilus B* conjugate vaccines, *Haemophilus influenzae* type B (HIB) was the most frequent cause of bacterial meningitis and leading cause of serious systemic bacterial disease among children worldwide. HIB disease occurred primarily in children <5 years of age in the United States prior to the initiation of a vaccine program and was estimated to account for nearly 20,000 cases of invasive infections annually, about 12,000 of which were meningitis. The mortality rate from HIB meningitis is about 5%. Among children, the most prevalent cause of *H. influenzae* meningitis is by the capsular strains of type B. In addition to meningitis, *Haemophilus B* is responsible for numerous other invasive disease processes (e.g., epiglottitis, sepsis, septic arthritis, osteomyelitis, pericarditis).

HIB conjugate vaccines use a new technology, covalent bonding of the capsular

polysaccharide of HIB to diphtheria toxoid, diphtheria CRM_{197} protein, or an outer membrane protein complex (OMPC) of *Neisseria meningitidis*, to produce an antigen that is postulated to convert the T-independent antigen to a T-dependent antigen. The protein carries both its own antigenic determinants and those of the covalently bound polysaccharide. Thus, the polysaccharide is theorized to be presented as a T-dependent antigen, resulting in both an enhanced antibody response and an immunologic memory.

Liquid PedvaxHIB is available as an injection of 7.5 mg *Haemophilus B* PRP, 125 mg *Neisseria meningitidis* OMPC, and 225 mg aluminum (as aluminum hydroxide) per 0.5 mL in a single-dose vial. HibTITER is also available as an injection of 10 mg purified *Haemophilus B* saccharide capsular oligosaccharide and about 25 mg diphtheria CRM_{197} protein/5 mL in 1- and 10-mL dose vials. ActHIB is available as a lyophilized powder for injection containing 10 mg purified *Haemophilus B* capsular polysaccharide and 24 mg tetanus toxoid/5 mL. This is available in single-dose vials with 7.5-mL vials of diphtheria and tetanus toxoids and pertussis vaccine as diluents or with 0.6-mL vial containing 0.4% sodium chloride diluent.

Others

Rasburicase (Elitek)

Rasburicase is a recombinant urate oxidase enzyme produced by a genetically modified *S. cerevisiae* strain. In humans, uric acid is the final step in the catabolic pathway of purines. Rasburicase catalyzes enzymatic oxidation of uric acid into an inactive and soluble metabolite, allantoin. Rasburicase is active only at the end of the purine catabolic pathway.

Rasburicase is indicated for initial management of elevated plasma uric acid levels in children with leukemia, lymphoma, and solid tumor malignancies who are receiving oncologic therapy expected to result in tumor lysis.

The recommended dosage of rasburicase is 0.15 or 0.2 mg/kg as a single daily dose for 5 days. Because the safety and effectiveness of the drug have not been determined for more than one administration or beyond 5 days, more than one course of therapy is not recommended. The chemotherapy regimen is implemented 4 to 24 hours after the first dose of rasburicase. The drug is administered as an intravenous infusion over 30 minutes.

Recombinant Human DNase I (Pulmozyme)

In 1989, the cystic fibrosis gene was discovered, and it has helped to lay the groundwork for new therapies to treat this disease, which is the most common inherited fatal disease affecting whites. Cystic fibrosis transmembrane conductance regulator, the protein product of the cystic fibrosis gene, is defective in its ability to facilitate ion transport across the airway epithelial cells in the lung. This defective regulator allows excessive absorption of sodium and adequate amounts of chloride across the cell membrane. Consequently, water from the mucus of the lung gets absorbed into the cell, and the mucus dries out, resulting in thick, tenacious mucus that accumulates in the small airways of the lung. This leads to a domino effect of chronic infection and inflammation, followed by chronic lung disease, pulmonary hypertension, and heart failure.

DNase (recombinant human deoxyribonuclease I), or dornase alfa, is a DNA enzyme indicated for the treatment of symptoms of cystic fibrosis. This enzyme specifically cleaves extracellular DNA, such as that found in the thick, sticky, mucous secretions of cystic fibrosis patients. As a result, airflow in the lung improves, and the risk of bacterial infection may decrease. This drug offers hope for breaking the cycle of chronic lung infection and inflammation associated with cystic fibrosis disease, and it demonstrates no effect upon the DNA of intact cells.

Indicated to treat cystic fibrosis in patients aged 5 years and older, DNase is available in 2.5-mL single-use polyethylene ampuls for use with compressed air nebulizers (Fig. 19.18). Six nebulizer systems are recommended, and the safety and efficacy of the administration of DNase with other nebulizer systems have not been demonstrated.

FIGURE 19.18 The product package of Pulmozyme. (Courtesy of Genentech, Inc.)

Clinical trials have been performed with and support the use of DNase with the following nebulizers:

- Marquest Acorn II nebulizer with Pulmo-Aide compressor
- Hudson T Updraft II nebulizer with Pulmo-Aide compressor
- Pari LC Jet plus nebulizer with the Pari Proneb compressor
- Pari Baby nebulizer with Pari Proneb compressor
- Durable Sidestream nebulizer with Mobilaire compressor
- Durable Sidestream nebulizer with Porta-Neb compressor

Patients who are unable to inhale or exhale orally throughout the entire nebulization period may use the Pari Baby nebulizer.

Portable jet models and ultrasonic nebulizers should not be used to administer DNase. The ultrasonic nebulizers may heat the protein enough to alter its structure. The portable jet nebulizers simply may not be capable of generating enough force or appropriate particle size to ensure optimal delivery of the drug into the lung.

To make administration efficient, it may be tempting to coadminister other compounds (e.g., albuterol, tobramycin) with DNase. However, no other medication should be mixed in the nebulizer system with this drug because of the possibility that a pH change could alter the DNase protein structure. Bronchodilator and antimicrobial agents that are delivered via nebulizer should be administered to patients sequentially, not mixed together. To date, no literature suggests the optimal sequence for all of these drugs to be administered.

The ampuls have an 18-month expiration date when stored in the refrigerator at 2°C to 8 °C and should be protected from strong light. The product cannot be exposed to room temperatures for more than 24 hours. The patient or caregiver should discard the solution if it is cloudy or discolored and should be told to make sure that the product is within the expiration date on the ampul. Unused ampuls should be stored in their protective foil pouch under refrigerated.

THE FUTURE OF BIOTECHNOLOGY PRODUCTS

The future will continue to demonstrate the development of more protein-based pharmaceuticals as a result of modern biotechnologic strategies. These protein-based drugs present unique challenges because of intrinsic instability, multifaceted metabolic properties, and limited gastrointestinal absorption. Their problems include variable tissue penetration (because of the size of the molecules) and toxicity related to the stimulation of an immune or allergic reaction.

A distinct advantage of these biotechnologic proteins over proteins from natural sources is enhanced purity. Hepatitis B virus and the HIV are capable of contaminating proteins and enzymes from human plasma. If their presence is known, they can be isolated or neutralized. However, sometimes their presence has been confirmed only after disastrous results. Products derived from recombinant technology will not have coextracted contaminants.

Research is also directed toward the discovery of new methods of delivery for these agents. Delivery systems being explored include transdermal and nasal routes, other forms of injectables, and oral tablets for smaller proteins. Few protein biopharmaceutical products can be administered orally because of their instability in the strong acid environment of the stomach and the low

systemic absorption through gastrointestinal mucosa. A challenge is to deliver regulatory proteins (e.g., insulin, growth hormone) to distant organs or tissue without biotransformation. One strategy that is bearing fruit is nanotechnology defined as the study, manipulation, and manufacture of ultrasmall structures made of as few as one molecule.

The past two decades has resulted in nanoparticle-based diagnostic and therapeutic drugs developed for the treatment of cancer, diabetes, pain relief, asthma, and allergy, among others (29). Nanotechnology involves the control of matter in the 1- to 100-nm dimension range. Nanomaterials demonstrate unique physicochemical properties, for example, ultrasmall size, large surface area-to-mass ratio, and high reactivity, which differ from bulk materials of the same composition.

To date, nanoparticle-based drug delivery has demonstrated distinct advantages. For example, the solubility of poorly water-soluble drugs is improved; by reducing immunogenicity, a prolongation of a drug's systemic circulation is shown; the release of the drug is sustained, and consequently, administration frequency is reduced. Further, drugs are delivered in a target manner that is advantageous to minimize systemic effects. This technology can also deliver two or more drugs at the same time to effect combination therapy, thereby generating a synergistic effect and allaying drug resistance (29).

Among the nanoparticle-based products, the primary products are liposomal drugs and polymer–drug conjugates. Liposomes encapsulate the protein-based compound in a lipid complex and, typically, are composed of some combination of phosphatidylcholine, cholesterol, phosphatidylglycerol, other glycolipids, and/or phospholipids (30,31). These are water-filled vesicular structures composed of several phospholipid layers surrounding an aqueous core, with the outer shell capable of providing direction to specific target cells (e.g., tumors). Usually, liposomes concentrate the drug in cells of the reticuloendothelial system of the liver and spleen and reduce drug intake in the heart, kidney, and gastrointestinal tract. Liposomes are popular among particulate carriers because of their relatively low toxicity and the versatility of their release characteristics and disposition in vivo, which can be altered by changing preparation techniques and bilayer constituents. Depending on their size, charge, and bilayer rigidity, among other characteristics, liposomes circulate only for a short time (minutes) in the circulation before degradation and uptake by macrophages of the mononuclear phagocyte system. Sometimes, their residence in the systemic circulation can be for hours and even days if they are stable and not recognized as foreign bodies by the mononuclear phagocyte system.

For example, use of liposome-associated doxorubicin reduces cardiotoxicity, and liposome-associated amphotericin B reduces nephrotoxicity and other adverse effects. Doxil is doxorubicin produced within microscopic pegylated lipid spheres that are grafted to the liposome surface. The pegylated drug delivery platform is an example of a polymer–drug conjugate. The pegylated liposomal shell protects the inner compartment. A single lipid bilayer membrane composed of hydrogenated soy phosphatidylcholine and cholesterol separates this internal aqueous compartment from the external medium. In essence, the drug, doxorubicin, is encapsulated within this internal compartment by the pegylated polymer layer, which protects the drug from rapid capture and clearance from the blood stream by the liver, spleen, and bone marrow (32). It is theorized that the long residence times and stability of pegylated doxorubicin in plasma are related to a steric stabilization effect provided by the PEG coating (32). This provides a protective layer and suppresses recognition by opsonins. An opsonin is any molecule that acts as a binding enhancer for the process of phagocytosis. The previously mentioned pegylated doxorubicin and pegfilgrastim are prime examples of this strategy. The polyethylene coating reduces mononuclear phagocyte system uptake and provides long plasma residence times and plasma stability.

Insoluble polymers composed of PEG are now used to form a protective sheath around a drug, inhibiting its degradation (32). PEG

is a highly hydrated flexible polymer chain. It reduces plasma protein adsorption and biofouling, that is, the accumulation of undesired substances onto the membrane of nanoparticles that decrease renal clearance of the relatively small drug molecules, thus effecting a prolonged half-life. Other advantages of PEG include it being nontoxic and nonimmunogenic. Other hydrophilic polymers that are grafted to liposomes and demonstrate increased circulation times include poly(acryloyl morpholine), polyvinylpyrrolidone, and poly(2-oxazoline).

Studies have shown that liposome size is critical to the effective delivery of encapsulated drugs when the desired outcome requires deposition of liposomes outside of the capillary bed (32). Most solid tumors exhibit unique features (e.g., extensive angiogenesis, hyperpermeable and defective vasculature, impaired lymphatic drainage, increased production of mediators that enhance vascular permeability). Liposomes extravasate in solid tumors through gaps in the normally continuous vascular endothelium. The gaps in these solid tumors have been found to be no larger than 380 to 780 nm (32). If the liposome is too big, it will not be able to extravasate through defects in the capillary endothelium. However, if it is too small, the liposome may have an inadequate amount of drug encapsulated to be effective.

Additional nanoscale systems for drug delivery include phospholipid micelles, pluronic micelles, poly(L-amino acid) micelles, polyester micelles, nanoemulsions, drug nanoparticles, solid nanoparticles, lipid-based nanoparticles, ceramic-based nanoparticles, albumin nanoparticles, nanogels, and dendrimer nanocomposites for drug deliver. As research continues forward in nanomedicine, research moving toward developing smaller and smaller agents will require larger, multidisciplinary teams from numerous disciplines including medicine, pharmacy, engineering, materials science, information technology, and physics (32).

It is entirely feasible that in the future, engineered protein complexes will combine a transporting protein with one that encodes the gene sequence to produce a therapeutic protein in the target tissue. In this instance, the gene will become functional only in certain tissue, decreasing delivery to an unintended site. There is also a growing knowledge base and research about signaling transduction pathways. This has led to the creation of antibodies that target receptors, enzymes, or other growth-regulating molecules.

The future should also see the creation of more diagnostic products for in-home testing. MAb-based diagnostic tests that are now restricted to physician use are under development for home testing. These include products for infectious disease processes (e.g., AIDS, *Chlamydia trachomatis*, streptococcal throat infections). In addition, it is anticipated that MAb-based tests will also be available to assay blood or plasma concentrations of a number of drugs (e.g., digoxin, phenytoin, theophylline).

THE FDA OFFICE OF BIOTECHNOLOGY PRODUCTS

In 1989, the FDA Office of Biotechnology was created. The office did not evaluate submissions to the FDA for approval of clinical investigations or for product marketing approvals; these functions were executed by the appropriate FDA centers. Nor was this office intended to perform laboratory research or mandate research priorities to the FDA centers. Instead, it was created to serve a central coordinating, problem-solving, and advisory role within the Office of the Commissioner. It was to become an effective point of contact with the FDA for those outside of the agency on issues related to new biotechnology.

Originally, the FDA Office of Biotechnology had the following responsibilities:

1. It was to advise and assist the commissioner and other central officials about scientific issues related to biotechnology policy, direction, and long-range goals.
2. It represented the FDA on biotechnologic issues to other governmental agencies and intergovernmental groups, state and local governments, industry, consumer organizations, Congress, national and international organizations, and the scientific community.

3. It provided leadership and direction on scientific and regulatory issues related to biotechnology through an agency-wide coordinating group, the Biotechnology Coordinating Committee, to promote communication and consistency on biotechnology matters across organizational lines.
4. It provided a problem-solving function for individuals, companies, associations, and organizations with concerns, questions, or complaints about biotechnology policies or procedures or about product jurisdiction and other aspects of product regulation.
5. It coordinated and facilitated guidance on cross-cutting or controversial biotechnology program policies.

Subsequently, the Office of Biotechnology has given way to the Office of Biotechnology Products. The mission of the Office of Biotechnology Products is to protect the public health by assuring the quality, safety, efficacy, availability, and security of recombinant therapeutic protein and MAb products. The Office of Biotechnology Products has two divisions: the Division of Therapeutic Proteins and the Division of Monoclonal Antibodies. The Office is also supported by a Biological Products Facility Staff in the Center for Drug Evaluation and Research Office of Compliance.

The Division of Monoclonal Antibodies (http://www.fda.gov/cder/biologics/research/dma.htm) ensures that safe, efficacious, and high-quality MAb products are available to the American people to diagnose, prevent, and treat the illnesses that afflict them. Its main activities include application review (Chemistry, Manufacturing, and Controls: CMC), facility inspection (Prior Approval Inspections and biannual Good Manufacturing Practices), research supporting biotechnology policy, policy and guidance document development, as well as training (internal and external).

PATIENT INFORMATION FROM THE PHARMACIST

For products that can be parenterally self-administered, the pharmacist should instruct patients in the use of aseptic technique. Appropriate verbal instruction that reinforces the printed information sheet should also be provided when the product requires reconstitution. It is desirable to perform the first injection under the supervision of an appropriately qualified health care professional to ensure that the patient understands the technique and can perform the injection. Some products (e.g., Betaseron) come with a training video that demonstrates reconstitution and self-administration techniques.

Patients who self-administer these products must be taught how to prepare (Fig. 19.19) and give the injection and how to rotate injection sites (Fig. 19.20). Some products provide a schematic illustration of this on the patient information sheet. Patients should understand that changing sites each time helps avoid injection reactions and gives the site opportunity to bounce back from the previous injection. It is important that the patient understands not to administer an injection into the same area as the prior injection or in areas that are tender, red, or hard. The pharmacist should provide a method for the patient to record where previous injections were made. One simple way is to suggest that the patient note the injection site on a calendar.

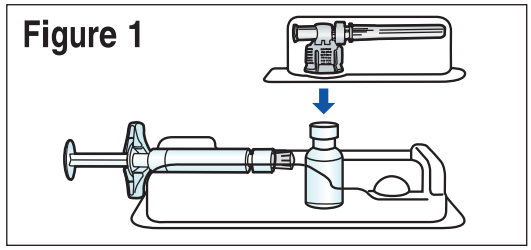
Patients should be advised about the proper disposal of needles and syringes. In this day of the cost-conscious consumer, patients must be advised against reusing needles and syringes. It is advantageous to provide the patient with a puncture-resistant container for disposal of used needles and syringes along with instruction for the safe disposal of full containers.

The patient should understand that periodic injection site reactions may occur. These may be transient (as in the case of IFNB-1b) and not require discontinuation of the therapy. It is advisable, however, periodically to reevaluate the patient's understanding and use of aseptic self-administration technique and procedures.

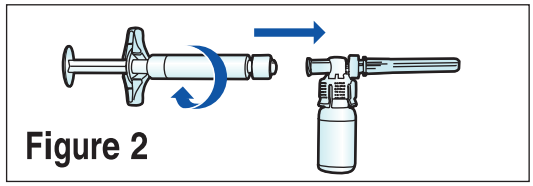
Patients should be educated about the proper storage, for example, 2°C to 8°C, and when necessary, the need to protect these products from light (Table 19.2). In addition, some products must be accompanied by an FDA-approved medication guide. Some products are also classified as Institute for Safe Medication Practices (ISMP) High Alert

Reconstituting Betaseron

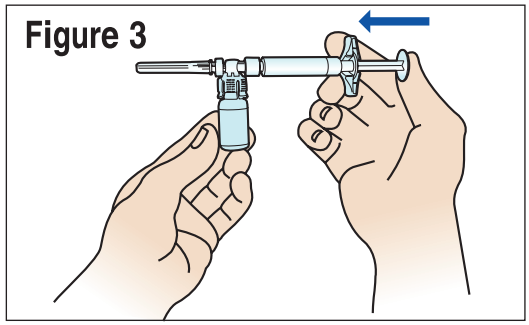
1. Remove the Betaseron vial from the well and take the cap off the vial.
2. Place the vial back into the vial holder. Use an alcohol prep pad to clean the top of the vial. Move the prep pad in one direction. Leave the alcohol prep pad on top of the vial until step 4.
3. Peel the label off the blister pack with the vial adapter in it, but do not remove vial adapter. The vial adapter is sterile; avoid touching the vial adapter.
4. Remove the alcohol prep pad from the top of the Betaseron vial. Keeping the vial adapter in the blister pack, place the adapter on top of the Betaseron vial and push down on the adapter until it pierces the rubber top of the Betaseron vial and snaps in place (**Figure 1**). Remove the blister packaging from the vial adapter.



5. Remove the rubber cap from the diluent syringe using a twist and pull motion. Discard the rubber cap.
6. Remove the vial with the vial adapter attached from the tray. Be careful not to pull the vial adapter off the top of the vial.
7. Connect the syringe with the yellow label to the vial adapter by turning clockwise and tighten carefully. This will form the syringe assembly (**Figure 2**).



8. Slowly push the plunger of the diluent syringe all the way in. This will transfer all of the diluent in the syringe to the Betaseron vial (**Figure 3**). Continue to hold the plunger in during the mixing process; otherwise the plunger may return to its original position after you release it.

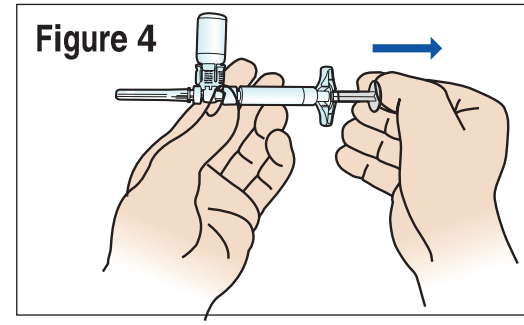


9. Gently swirl the vial to completely dissolve the white cake of Betaseron. Do not shake. Shaking can cause Betaseron to foam; even gently mixing the solution can cause foaming. If there is foam, allow the vial to sit undisturbed until the foam settles.
10. After the cake is dissolved, look closely at the solution to make sure the solution is clear and colorless and does not contain particles. If the mixture contains particles, or is discolored, do not use. Repeat the steps to prepare your dose using a new tray of Betaseron, prefilled syringe, vial adapter and alcohol prep pads. Contact Bayer HealthCare Pharmaceuticals Inc. at 1-800-788-1467 to obtain replacement product.

Preparing the Injection

You have completed the steps to reconstitute your Betaseron and are ready for the injection. The injection should be given immediately after mixing and allowing any foam in the solution to settle. If you must delay giving yourself the injection, you may refrigerate the solution and use within three hours of reconstitution. Do not freeze.

1. With your thumb still pushing the plunger, turn the syringe assembly so that the vial is on top. (The syringe is horizontal.)



2. Slowly pull the plunger back to withdraw the entire contents of the Betaseron vial into the syringe (**Figure 4**).

NOTE: The syringe barrel is marked with numbers from 0.25 to 1.0 mL. If the solution in the vial cannot be drawn up to the 1.0 mL mark, discard the vial and syringe and start over with a new tray containing a Betaseron vial, prefilled diluent syringe, vial adapter and alcohol prep pads.

3. Turn the syringe assembly so that the needle end is pointing up. Remove any air bubbles by tapping the outer wall of the syringe with your fingers. Slowly push the plunger to the 1.0 mL mark on the syringe (or to the amount prescribed by your doctor).

NOTE: If too much solution is pushed into the vial, repeat steps 1, 2, and 3.

4. Turn the syringe assembly so that the vial is at the bottom. Remove the vial adapter and the vial from the syringe by twisting the vial adapter as shown in Figure 5. This will remove the vial adapter and the vial from the syringe, but will leave the needle on the syringe (**Figure 5**).

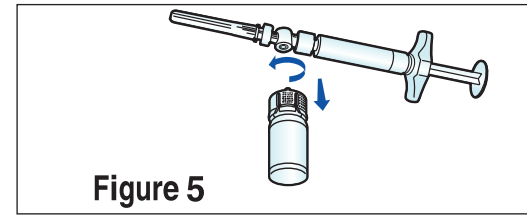


FIGURE 19.19 Preparing Betaseron for injection. (Courtesy of Bayer Health Care Pharmaceuticals, Inc.)

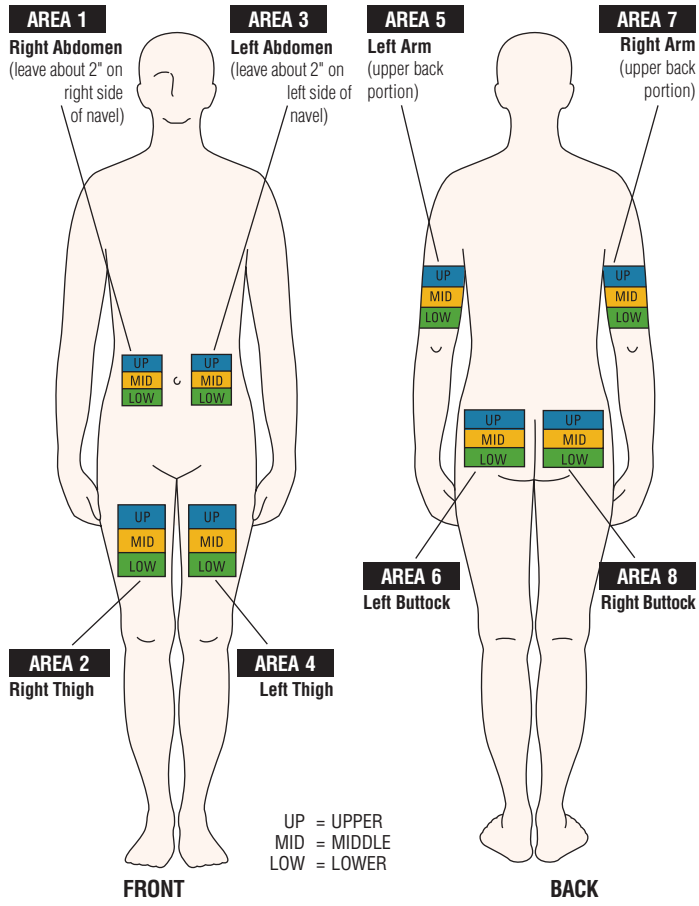


FIGURE 19.20 Rotation of injection sites. (Courtesy of Bayer Health Care Pharmaceuticals, Inc.)

Medications requiring special handling. As with traditional "sound alike–look alike" products, biotechnology product names can be confused, and pharmacists have to be very careful to avoid medication errors as well.

It is very important for the patient to understand that these products should not be agitated or shaken. Otherwise, there is the possibility of product (protein) denaturation and resultant ineffectiveness. Much like the suspension forms of insulin, which should be rolled (or rotated) in the palms of the hands, these products should be gently swirled to dissolve their contents.

Whenever possible, pharmacists must emphasize the need for compliance with dosage regimens. Betaseron, for example, is administered every other day. A calendar reminder system may be helpful for a patient using this medication.

PHARMACIST SELF-HELP WITH BIOTECHNOLOGY DRUGS

The advent of biotechnology drugs poses a real dilemma to some pharmacists. They may be reluctant to stock these medications because of their high cost and special storage and handling requirements and because of poor understanding of the drug's therapeutics (including side effects and counseling information required) and/or the difficult issue of reimbursement. These products also are far more expensive than ordinary pharmaceuticals. Table 19.3 demonstrates some representative biotechnology products illustrating storage conditions, handling and storage precautions, possible sound-alike/look-alike precautions, and other considerations.

Most biotechnologic drugs must be administered parenterally, which poses a

Table 19.3 REPRESENTATIVE BIOTECHNOLOGY PRODUCTS FEATURING STORAGE AND HANDLING REQUIREMENTS, SOUND-ALIKE/LOOK-ALIKE COMPARISONS, AND SPECIAL CONSIDERATIONS

DRUG	STORAGE	FREEZE	SHAKE	PROTECT FROM LIGHT	SOUND-ALIKE/LOOK-ALIKE ISSUES	OTHER
Aranesp (darbepoetin alfa)	2°C–8°C	No	No	Yes	Darbepoetin alfa may be confused with epoetin alfa.	Do not dilute with other drug solutions
Avastin (bevacizumab)	2°C–8°C	No	No	Yes	Bevacizumab may be confused with cetuximab.	ISMP High Alert Medication, do not mix with dextrose containing solutions
Avonex, Rebif (interferon beta-1a)	2°C–8°C	No	No	Yes	Avonex may be confused with Avelox.	Allow to warm to room temperature prior to use; FDA-approved medication guide must be given to the patient; some formulations contain albumin.
Betaseron (interferon beta-1b)	15°C–30°C, refrigerate if not used immediately after reconstitution	No	No	No	N/A	FDA-approved medication guide must be given to the patient, contains albumin.
Combivir (zidovudine and lamivudine)	2°C–30°C	No	N/A	No	Combivir may be confused with Combivent or Epivir; AZT is an error-prone abbreviation (mistaken as azathioprine, aztreonam).	None
Copaxone (glatiramer acetate)	2°C–8°C; excursions to room temperature for up to 1 wk do not have a negative impact on potency.	No	No	No	Copaxone may be confused with Compazine.	Antigenic, not for IV administration
Enbrel (etanercept)	2°C–8°C	No	No	Yes	N/A	Reconstituted vials should be administered immediately (if not, Enbrel may be stored at 2 °C–8 °C for up to 14 d); do not filter reconstituted solution during preparation.
Epogen, Procrit (epoetin alfa)	2°C–8°C	No	No	No	Epoetin alfa may be confused with darbepoetin alfa.	None

(Continued)

Table 19.3 REPRESENTATIVE BIOTECHNOLOGY PRODUCTS FEATURING STORAGE AND HANDLING REQUIREMENTS, SOUND-ALIKE/LOOK-ALIKE COMPARISONS, AND SPECIAL CONSIDERATIONS (Continued)

DRUG	STORAGE	FREEZE	SHAKE	PROTECT FROM LIGHT	SOUND-ALIKE/LOOK-ALIKE ISSUES	OTHER
Epzicom (abacavir and lamivudine)	15°C–30°C	No	N/A	No	N/A	FDA-approved medication guide and warning card must be given to the patient.
Erbitux (cetuximab)	2°C–8°C	No	No	No	Cetuximab may be confused with bevacizumab.	Do not dilute.
Evista (raloxifene)	15°C–30°C	No	N/A	No	Evista may be confused with Avinza.	Pregnancy Category X
Fluvirin (influenza virus vaccine)	2°C–8°C	No	N/A	Yes	Influenza virus vaccine (human strain) may be confused with the avian strain (H5N1) of influenza virus vaccine.	Influenza virus vaccine may be confused with tetanus toxoid and tuberculin products. Medication errors have occurred when tuberculin skin tests (PPD) have been inadvertently administered instead of tetanus toxoid products and influenza virus vaccine. These products are refrigerated and often stored in close proximity to each other. Some formulations are manufactured with chicken/egg protein or gentamicin. Some products may contain thimerosal or latex.
Forteo (teriparatide)	2°C–8°C	No	No	Yes	N/A	None
Gamunex (IVIG)	2°C–8°C for 36 mo or ≤25°C for up to 6 mo anytime during the 36-mo shelf life	No	No	No	N/A	Product of human plasma; may contain maltose or sucrose
Genotropin (somatropin)	2°C–8°C	No	No	Yes	Somatropin may be confused with somatrem or sumatriptan.	None

Gleevec (imatinib)	15°C–30°C	No	N/A	No	N/A	ISMP High-Alert Medication. **Special handling required: hazardous agent;** protect from moisture.
Herceptin (trastuzumab)	2°C–8°C	No	No	No	N/A	ISMP High-Alert Medication. **Special handling required: hazardous agent**; do not prepare with D5W; do not mix or dilute with other drugs.
Humira (adalimumab)	2°C–8°C	No	N/A	Yes	Humira may be confused with Humulin.	Packaging (needle cover) contains latex; store in original container.
Integrilin (eptifibatide)	2°C–8°C, can be kept at room temperature for 2 mo	No	N/A	Yes (until administration)	N/A	Discard unused portion left in vial.
Neulasta (pegfilgrastim)	2°C–8°C; allow to reach room temperature prior to injection (may be kept at room temperature for 48 h).	No	No	Yes	Neulasta may be confused with Neumega or Lunesta.	Packaging (needle cover) contains latex.
Neupogen (filgrastim)	2°C–8°C	Protect from freezing/ temperatures >30°C—if inadvertently frozen, thaw in a refrigerator and use within 24 h.	No	Yes	Neupogen may be confused with Epogen, Neumega, Neupro, or Nutramigen.	Packaging of some dosage forms contain latex.
Pegasys (peginterferon alfa-2a)	2°C–8°C	No	No	Yes	N/A	FDA-approved medication guide must be given to the patient; Pregnancy Category X when given with ribavirin; discard unused solution.
Remicade (infliximab)	2°C–8°C	No	No	No	Remicade may be confused with Renacidin or Rituxan; infliximab may be confused with rituximab.	FDA-approved medication guide must be given to the patient.

(Continued)

Table 19.3 REPRESENTATIVE BIOTECHNOLOGY PRODUCTS FEATURING STORAGE AND HANDLING REQUIREMENTS, SOUND-ALIKE/LOOK-ALIKE COMPARISONS, AND SPECIAL CONSIDERATIONS (Continued)

DRUG	STORAGE	FREEZE	SHAKE	PROTECT FROM LIGHT	SOUND-ALIKE/LOOK-ALIKE ISSUES	OTHER
Rituxan (rituximab)	2°C–8°C	No	No	Yes	Rituxan may be confused with Remicade; rituximab may be confused with infliximab.	ISMP* High Alert Medication; rituximab dose is NOT based on BSA; FDA-approved medication guide must be given to the patient.
Sustiva (efavirenz)	15°C–30°C	No	N/A	No	N/A	None
Synagis (palivizumab)	2°C–8°C	No	No	No	Synagis may be confused with Synalgos-DC or Synvisc.	Do not dilute; store in original container.
Tarceva (erlotinib)	15°C–30°C	No	N/A	No	Erlotinib may be confused with gefitinib.	ISMP High Alert Medication. **Special handling required: hazardous agent**
Trizivir (abacavir, lamivudine, and zidovudine)	15°C–30°C	No	N/A	No	N/A	FDA-approved medication guide must be given to the patient.
Truvada (emtricitabine and tenofovir)	15°C–30°C	No	N/A	No	N/A	None
Varivax (varicella virus vaccine)	–15°C, may be stored at 2°C–8°C for 72 h prior to reconstitution	Yes (do NOT freeze reconstituted vaccine)	No	Yes (before reconstitution)	N/A	Store diluent separately at room temperature or in the refrigerator; discard if reconstituted vaccine is not administered within 30 min.
Viread (tenofovir)	15°C–30°C	No	N/A	No	N/A	None
Xolair (omalizumab)	2°C–8°C, may be shipped at room temperature	No	No	Yes (following reconstitution)	N/A	FDA-approved medication guide must be given to the patient.

Approved Biotechnology Drugs. http://www.bio.org/speeches/pubs/er/approveddrugs.asp#P. (Accessed August 1, 2007).
Lamb E. Top 200 prescription drugs of 2006. *Pharma Times*. 2007;May:34–37.
Lexi-Comp/Lexi-Drugs Online. (Accessed August 1, 2007).
Prepared by Nicole Costa Purdue University Doctor of Pharmacy Class of 2008.

threat to some pharmacists, who are wary of this administration route and cognizant of their limitations in counseling the patients in appropriate technique. Suffice it to say that the pharmacist should assume the professional responsibility to secure educational materials (videotapes, print) from the manufacturer. Self-injection products contain instruction sheets that offer a step-by-step guide for preparing and administering the injection at home.

Aside from being knowledgeable about such things as therapeutic use, side effects, precautions, and drug interactions, the pharmacist must also be able to identify monitoring parameters to ensure safety and efficacy. For physiologic peptide molecules used for substitution therapy (e.g., insulin, clotting factors, erythropoietin), therapeutic drug monitoring (measurement of serum drug concentrations) is not indicated because alternative methods are routinely available to assess the efficacy and toxicity of these compounds. As an example, in insulin-dependent diabetes mellitus patients, insulin is routinely monitored through the use of blood glucose measurements and glycosylated hemoglobin measurements. For clotting factors, efficacy is assessed by measuring the specific factor being monitored or prothrombin time or partial thromboplastin time.

PHARMACEUTICS CASE STUDY

SUBJECTIVE INFORMATION

Working for an up-and-coming biotechnology company, you have been assigned to formulate a new GM-CSF product called CSF-110.

OBJECTIVE INFORMATION

CSF-110 is a glycoprotein consisting of 143 amino acids and a dose of 100 to 200 mg. It is stable for only 24 hours in aqueous solution at a pH in the range of 6.5 to 7.5 and less stable outside of this pH range. It is adsorbed to the interior of glass vials in aqueous solution. A reasonable shelf life is required, so the drug can be commercially marketed.

ASSESSMENT

This product will be marketed as a dry powder for reconstitution; the powder may be simply preblended or lyophilized. Due to the difficulty of maintaining uniform blends during packaging of a product containing particles of different densities, it may be best to prepare the solutions and lyophilize them in the vials in which they are dispensed. This may also be supported by the coating action of human serum albumin on the interior of the vials in solution form to minimize sorption of the drug to the vial after reconstitution.

PLAN

A lyophilized product that can be reconstituted with sterile water for injection prior to use may be feasible. The product could include the drug, a 0.05-M phosphate buffer system at pH 7.0, 0.1% human albumin to minimize sorption, and sodium chloride for tonicity adjustment. The solution will be prepared, poured into vials, lyophilized, labeled, and packaged.

CLINICAL  CASE STUDY

SUBJECTIVE INFORMATION

CC: J.S. is a 31-year-old WF who arrives at the clinic with her husband. He explains that J.S. has been feeling depressed ever since she started her new drug therapy a year ago. He is extremely concerned because she does not have any interest in the activities that she normally enjoyed to do.

HPI: J.S. was diagnosed with multiple sclerosis a year ago, when she had complaints of blurred vision, fatigue, and tingling sensations in her right leg. She received intravenous corticosteroid therapy for her acute exacerbation. Since then, J.S. has been receiving interferon therapy (Betaseron).

PMH: MS diagnosed 1 year ago
DM type I since age 5
Pneumonia 2 months ago, treated and resolved
Upper neck injury and concussion from a rugby game at age 22
Automobile accident at age 17 (concussion and shattered left)

Meds: Regular 30 U SQ q12h for DM, started at age 5
IFNB-1b (Betaseron) 0.25 mg QOD (powdered vial) for MS, started 1 year ago

OTC: Patient denies taking herbal, homeopathic medications, other supplements

PSH: Left elbow replacement surgery at age 17

FH: Father: H/o DM (type unknown), died of stroke at age 57
Mother: HTN since age 55
Brother: DM type I

SH: (+) Tobacco: smoked for 5 years, quit 6 years ago
(−) ETOH
(−) Caffeine
(−) Illicit drugs

Exercise/ daily activities: Used to run and lift weights two to three times per week, hiking and mountain biking during summers

Diet: Eats fast food and snacks of chips and candy; meal timing varies

The patient used to play professional rugby in Europe. Now she is a sales manager for Nike.

The patient lives with husband, married for 5 years.

ALL: NKA

MS: The patient reports that blurred vision, fatigue, and tingling sensations have subsided after Betaseron therapy. No allergic reactions or injection site reactions have been reported. The patient has been very compliant with therapy. The patient complains of difficulty in reconstituting the Betaseron.

CLINICAL CASE STUDY CONT

DM: The patient reports no sings/symptoms (s/s) of hyperglycemia or hypoglycemia. The patient is not aware of the recommended American Diabetic Association (ADA) diet. The patient also reports compliance with insulin shots but denies any glucose monitoring at home. The patient made an effort to exercise three times per week, but after interferon therapy, the patient does no exercise anymore.

OBJECTIVE INFORMATION

A 31-year-old WF

Ht:	5'8" Wt: 63.6 kg
BP:	121/78 P: 72 T: 98° RR: 19
Pain:	None
	137\104\13/112
	4.3/25/0.8\
	6.3\13.1/269\
	/40\
HgbA1c:	6.5
LFT:	wnl

ASSESSMENT

Betaseron therapy is effective in reducing recurrence of symptoms and exacerbations, but the patient has depression induced by Betaseron therapy. Studies indicate that interferon in Betaseron is responsible for the depression by suppressing circulating tryptophan and therefore serotonin synthesis. According to the patient's husband, the depression is interfering with the patient's quality of life.

Based on the patient's blood glucose and HgbA1c levels, the patient's diabetes is controlled.

PLAN

Recommend cessation of Betaseron therapy and substitute with glatiramer acetate (Copaxone). Although there are reports that using serotonin-specific reuptake inhibitors (SSRIs) (citalopram, paroxetine) may treat depression associated with interferon therapy, J.S. states having trouble reconstituting vials, and Copaxone comes as a prefilled syringe and is not associated with depression. In addition, follow-up on depression may be time consuming and cost money, and the side effect associated with SSRIs is another reason not to continue patient on Betaseron. Evaluate therapy at each clinic visit by monitoring side effects and s/s of disease progression, and magnetic resonance imaging should be done at least once a year to assess the reduction of neuronal lesions. Check complete blood count, perform a neurologic examination, and monitor the patient's compliance at each clinic visit. Monitor resolution of depression at next visit and encourage the patient to exercise regularly and to begin hobbies and activities (avoid activities that put the patient at high risk for trauma).

Continue insulin therapy. Recommend J.S. to obtain a glucose monitor and monitor blood glucose daily at home. Also recommend keeping a glucose diary (goal fasting blood glucose [FBG], 60 to 110 mg/dL; goal HgbA1c, 4% to 6%). Educate the patient on the importance of eating a healthy diet and following a consistent daily meal schedule. Recommend J.S. to start a 1,800-cal ADA diet. Also recommend the patient to check foot and skin daily and teeth and gums every 6 months and to get an annual eye and foot examination. Monitor for s/s of hypoglycemia and hyperglycemia at each clinic visit and perform urinary analysis (U/A) every 6 months. Recommend the patient to obtain a medical bracelet in case of emergency. Encourage J.S. to slowly begin exercising again.

APPLYING THE PRINCIPLES AND CONCEPTS

Group Activities

1. Describe the various technologies used in producing biotechnology drugs.
2. Select five biotechnology drugs featured in this chapter and determine the average patient cost of each for a 1-year period.
3. Select a high-risk biotechnology product and investigate the implementation of a risk minimization action plan (i.e., RiskMAP) for the specific product.
4. Make a listing of "biosimilars" instituted by the European Union.
5. Identify three examples of biotechnology drugs that are classified by the ISMP as "High Alert Medications" and explain the reasoning for the classification.
6. Create a table of disease states treated with biotechnological drug products and classify their treatment in which the drug products are self-administered, administered in a clinic/office, or as clinic/office administered chemotherapy.

Individual Activities

1. Create a table of biotechnology products within a specific product classification and include indication(s), contraindication(s), adverse effect profile, dosage, and storage and administration.
2. Select a biotechnology product that is available for patient or caregiver administration, and develop a counseling information sheet to facilitate its appropriate use by the patient or his/her caregiver.
3. Create a listing of pharmacist precautions needed when handling, storing, and dispensing biotechnology products.
4. Create a patient advisory brochure to facilitate patient or caregiver administration of an injectable biotechnology drug product.
5. Create a list of factors that might make a patient apprehensive about using a biotechnological product and describe how each factor can be overcome to allay patient apprehension.

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20 Novel Dosage Forms and Drug Delivery Technologies

OBJECTIVES

After reading this chapter, the student will be able to:

1. Describe the benefits of new, innovative drug delivery systems
2. Describe the mechanisms utilized to develop new, novel dosage forms
3. List novel drug delivery systems for each topical, oral, vaginal, ophthalmic, and parenteral route
4. List drugs that are typically administered by each of these drug delivery systems
5. Explain the advantages each novel delivery system may or may not have over traditional oral administration
6. Describe the principles of iontophoresis and phonophoresis and their benefits in advancing topical drug administration
7. Differentiate between liposomes for parenteral administration and standard parenteral solutions; describe a situation where liposomes for parenteral administration would be the preferred therapeutic dosage form over standard parenteral solutions
8. Identify the appropriate indication for two implantable medications and describe the mechanism of drug release for each

This chapter discusses novel drug delivery systems that are modifications of those previously presented, are relatively new on the market, or do not fit into the categories in the previous chapters. They may be relatively new, use new or relatively new delivery systems, or use unique delivery systems or unique devices before, during, or after administration. Dramatic changes have been introduced, with new technology and new devices now on the market. In some cases, traditional capsules and ointments have been replaced by osmotic pumps, wearable ambulatory pumps, electrically assisted drug delivery, and a host of other delivery methods based on various polymer technologies. Feedback mechanisms are now feasible: Actual drug delivery may be a response to a sensor detecting variations in certain body chemicals and prompting infusion of a drug to correct the imbalance.

Changes are coming about as new technologies are developed and reduce the limitations of existing therapies. In some cases, the new drugs require new delivery systems because the traditional systems are inefficient or ineffective; this may be true especially of some of the recombinant DNA and gene therapies of the future. We may soon be manipulating genes as active drugs and as drug

delivery systems and even work in nanotechnology (nanopharmacy) in the future. Some therapies may become very site specific and require very high concentrations of drugs in selected sites of the body, as more controlled drug delivery systems will be available in the very near future. Traditional oral medications may not be as effective in some of these cases.

New drug delivery system development is largely based on promoting the therapeutic effects of a drug and minimizing its toxic effects by increasing the amount and persistence of a drug in the vicinity of a target cell and reducing the drug exposure of nontarget cells. This is still largely based on Paul Ehrlich's magic bullet concept.

New drug delivery systems can provide improved or unique clinical benefits, such as (*a*) improvement of the patient's compliance, (*b*) improved outcomes, (*c*) reduction of adverse effects, (*d*) improvement of the patient's acceptance of the treatment, (*e*) avoidance of costly interventions such as laboratory services, (*f*) allowing the patients to receive medication as outpatients, and possibly (*g*) a reduction in the overall use of medicinal resources.

Novel drug delivery systems can include those based on physical mechanisms and those based on biochemical mechanisms. Physical mechanisms, also referred to as controlled drug delivery systems, include osmosis, diffusion, erosion, dissolution, and electrotransport. Biochemical mechanisms include monoclonal antibodies, gene therapy and vector systems, polymer drug abducts, and liposomes.

Therapeutic benefits of some of the new drug delivery systems include optimization of the duration of action of the drug, decreasing dosage frequency, controlling the site of release, and maintaining constant drug levels. Safety benefits include reducing adverse effects, decreasing the number of concomitant medications a patient must take, decreasing the need for interventions, and reducing the number of emergency department visits. Economic benefits of novel drug delivery systems include simplifying administration regimens, enhancing the patient's compliance, and an overall reduction of health care costs.

COMPOSITION

Associated with the various mechanisms that are characteristic of or the basis of the newer drug delivery systems, their composition can be quite variable—ranging from naturally derived substances, such as gelatin and sugars, to the more complex polymers. New drug delivery systems also incorporate mechanical, electronic, and computer components.

The therapeutic efficacy of selected products can be enhanced, and in some cases, the toxicity can be decreased by incorporating novel polymer technology. For example, degradable bonds can be used to attach an active drug to a synthetic or naturally occurring polymer. Upon delivery to the target site and in the presence of certain enzymes or through hydrolysis or a comparable mechanism, the product can be cleaved, releasing the active drug at a specific site of action. Oral, topical, parenteral, and implantable drugs have the potential to be used with this approach.

A number of release profiles using polymers are possible, as are actual penetration into specific tissues and selection of specific target sites. Potential problems of polymers include the following: (*a*) Their high molecular weight may cause them to be very slowly excreted from the body. (*b*) Because of their size, permeability through various membranes may be slow. (*c*) Immunologic or toxic reactions may occur. (*d*) Because they are complex, they may be labor intensive and expensive to develop. Novel drug delivery systems will be discussed in the general categories of topical, oral, vaginal, implanted, ophthalmic, and parenteral preparations.

TOPICAL ADMINISTRATION

The basis for the development of transdermal drug delivery systems (patches) involves percutaneous absorption. See Chapters 10 and 11 for background information on transdermal systems and penetration enhancers. Novel topical systems also include iontophoresis (IP) and phonophoresis.

Iontophoresis

IP is an electrochemical method that enhances the transport of some solute molecules by creating a potential gradient through the skin with an applied electrical current or voltage. It induces increased migration of ionic drugs into the skin by electrostatic repulsion at the active electrode: Negative ions are delivered by the cathode and positive ions by the anode. A typical IP device consists of a battery, microprocessor controller, drug reservoir, and electrodes.

Advantages of IP include (*a*) control of the delivery rates by variations of current density, pulsed voltage, drug concentration, and ionic strength; (*b*) eliminating gastrointestinal incompatibility, erratic absorption, and first-pass metabolism; (*c*) reducing side effects and variation among patients; (*d*) avoiding the risks of infection, inflammation, and fibrosis associated with continuous injection or infusion; and (*e*) enhancing compliance with a convenient and noninvasive therapeutic regimen.

The main disadvantage of IP is skin irritation at high current densities; this can be eliminated or minimized by reducing the current.

IP is gaining increasing acceptance in the pharmaceutical industry with small, efficient iontophoretic patches projected to be on the market within the next few years. Miniaturization is now possible with smaller, more powerful batteries and electronics. The next generation of IP patch may also include an electronic record of the date, time, and quantity of each dose delivered, providing information for determining patient compliance. Also, units may soon be capable of reverse IP that serves to collect a sample noninvasively and determine the analyte levels in the body with feedback mechanisms for dosing. Currently, however, most IP involves the use of an iontophoretic device attached to electrodes containing a solution of the drug.

As previously mentioned, IP involves the use of small amounts of physiologically acceptable electric current to move charged, or ionized, drugs through the skin. Placing an ionized solution of the drug in an electrode of the same charge and applying a current repel the drug from the electrode into the skin. This method of drug delivery has been around for at least 100 years. Since the 1930s, IP of pilocarpine has been used to induce sweating in the diagnosis of cystic fibrosis. More recently, IP has been used in the topical delivery of fluoride to the teeth, dexamethasone as an anti-inflammatory into joints, and lidocaine as a topical anesthetic. Drugs such as corticosteroids, nonsteroidal anti-inflammatory agents, and anesthetics are commonly delivered via IP. Other drugs under study include a number of analgesics, nicotine, anti-AIDS drugs, cancer drugs, insulin, and proteins. IP is also useful in veterinary medicine.

In the IP process, the current, beginning at the device is transferred from the electrode through the ionized drug solution as ionic flow. The drug ions move to the skin, where the repulsion continues, moving the drug through whatever pathways are available, namely, pores, and possibly through a disrupted stratum corneum. The drug-containing electrode is termed the active electrode, and the other electrode, the passive electrode, is placed elsewhere on the body. Current densities up to 0.5 mA/cm^2 can be tolerated with little or no discomfort. The larger the electrode surface, the greater the current the device must supply to provide a current density for moving the drug.

The delivery of a drug iontophoretically is quite complex, depending on the interactions between the drug and the vehicle electrolyte or buffer, partitioning of the drug between the vehicle and the skin, and then diffusion through a highly heterogeneous membrane under the influence of both chemical and electrical potential gradients.

The movement of ions across the skin is described by the relationship known as the Nernst-Planck equation:

$$J_i = -D_i \frac{dC_i}{dX} - Z_i mFC_i \frac{dE}{dX}$$

where

J_i is flux;
D_i is diffusivity;
dC_i/dx is concentration gradient;

z_i is valence of the species I;
m is mobility;
F is Faraday constant;
C_i is concentration; and
dE/dx is electrostatic potential gradient.

Variables affecting IP include aspects of the current, the physicochemical properties of the drug, formulation factors, biologic factors, and electroendosmotic flow.

The *current* can be direct, alternate, or pulsed and can have various waveforms, including square, sinusoidal, triangular, and trapezoidal. There may not be much advantage to the more complex forms, as direct current is most commonly used at this time.

Physicochemical variables include the charge, size, structure, and lipophilicity of the drug. The drug should be water soluble, low dose, and ionizable with a high charge density. Smaller molecules are more mobile, but large molecules are also usable.

Formulation factors include drug concentration, pH, ionic strength, and viscosity. Increasing drug concentration usually results in greater drug delivery to a certain degree. Buffer ions in a formula will compete with the drug for the delivery current, decreasing the quantity of drug delivered, especially because buffer ions are generally smaller and more mobile than the larger active drug. The pH of solutions can be adjusted and maintained by larger molecules, such as ethanolamine: ethanolamine HCl rather than the smaller hydrochloric acid and sodium hydroxide. An increase in ionic strength of the system will also increase the competition for the available current, especially because the active drugs are generally potent and present in a small concentration as compared to these extraneous ions.

Biologic factors pertain to the skin to which the electrodes are applied, its thickness, permeability, presence of pores, and so on.

Electroendosmotic flow results when a voltage difference is applied across a charged porous membrane, resulting in a bulk fluid flow in the same direction as the flow of counter ions. This fluid flow can actually carry a drug with it into the skin, especially positively charged, cationic, drugs. Neutral drugs can also be carried via electroendosmotic flow.

Iontophoretic devices have changed remarkably over the years, ranging from the galvanometers of the past to the small, specially designed units of today. Example IP units and electrodes are shown in Figures 20.1 to 20.3.

Iontophoretic units will soon be sized similarly to today's transdermal patches. They may be slightly thicker to accommodate the power source and small microprocessor controllers. The future may include IP patches capable of sampling and testing (e.g., glucose levels) and adjusting the delivery rate of a drug (e.g., insulin), all in the same IP system. Reverse IP can be used to extract chemicals or drugs from the body for testing. Many types of patches with electrodes may require pharmacists to add the drug prior to dispensing, as is done today in filling reservoirs for parenteral administration. Drugs currently administered using IP are listed in Tables 20.1 (human) and 20.2 (veterinary). Because most solutions designed specifically for IP are not commercially available, they must be compounded. It is best to have only the drug and water present to minimize competition for the active ions.

An IP system called Numby Stuff (IOMED) is used to achieve local anesthesia of the skin and is promoted as a painless, needleless system.

Iontophoretic administration is also used in veterinary pharmacy, using drugs such as those listed in Table 20.2. Because of the difference in the size and anatomy of the animal patient, different electrodes may be required. IP has been studied to enhance ungula penetration for the treatment of fungal infections in the nails. IP does moderately increase penetration as compared to passive diffusion (1).

Phonophoresis

Phonophoresis (syn, ultrasound, sonophoresis, ultrasonophoresis, ultraphonophoresis) is the transport of drugs through the skin using ultrasound; it is a combination of ultrasound therapy with topical drug therapy to achieve therapeutic drug concentrations at selected sites in the skin. It is widely used by physiotherapists. In this technique, the drug

FIGURE 20.1 The DuPel iontophoresis system showing the connections to which a passive and an active (drug-containing) electrode will be attached.

is generally mixed with a coupling agent, usually a gel, but sometimes a cream or ointment, that transfers ultrasonic energy from the phonophoresis device to the skin. The ultrasonic unit has a sound transducer head emitting energy at 1 MHz at 0.5 to 1 W/cm^2. Although the exact mechanism is not known, it may involve a disruption of the stratum corneum lipids, allowing the drug to pass through the skin.

Originally, the drug-containing coupling agent was applied to the skin and immediately

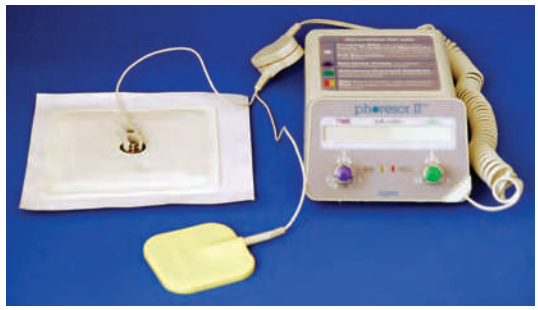


FIGURE 20.2 The Phoresor II iontophoresis system with example electrodes attached.

followed by the ultrasound unit. Today, the product is applied to the skin, and some time is allowed for the drug to begin absorption into the skin; then the ultrasound unit is applied. The ultrasound emitted from the unit is actually sound waves outside the normal human hearing range. As ultrasound waves, they can be reflected, refracted, and absorbed by the medium, just as regular sound waves can. Consequently, these are factors that must be considered as affecting phonophoresis efficiency.

Three effects of ultrasound are cavitation, microstreaming, and heat generation. Cavitation is formation and collapse of very small air bubbles in a liquid in contact with ultrasound waves. Microstreaming, closely associated with cavitation, results in efficient mixing by inducing eddies in small-volume elements of a liquid; this may enhance dissolution of suspended drug particles, resulting in a higher concentration of drug near the skin, for absorption. Heat results from the conversion of ultrasound energy to heat energy and can occur at the surface of the skin as well as in deeper layers of the skin.

The vehicle containing the drug must be formulated to provide good conduction of the ultrasonic energy to the skin. The product must be smooth and not gritty, as it will be rubbed into the skin by the head of the transducer. The product should have relatively low viscosity for ease of application and ease of movement of the transducer head. Gels work very well as a medium. Emulsions have been used, but the oil–water interfaces in emulsions can disperse the ultrasonic waves, reducing the intensity of the energy reaching the skin. It may also cause some local heat. Air should not be incorporated into the product, as air bubbles may disperse the ultrasound waves, resulting in heat at the liquid–air interface.

Hydrocortisone is the drug most often administered, in concentrations ranging from 1% to 10% in a phonophoresis gel.

FIGURE 20.3 Sample electrodes used in IP. The active electrode will generally receive up to 3 mL of a solution containing the drug to be delivered.

Tapes

A tape is a dosage form suitable for delivering active pharmaceutical ingredients to the skin. It consists of the drug(s) impregnated into a durable yet flexible woven fabric or extruded synthetic material that is coated with an adhesive agent. The active drug is generally in the dry state. The adhesive layer is designed to hold the tape securely in place without the need for additional bandaging. Unlike transdermal patches, tapes are not designed to control the release rate of the drug. The drug content of tapes is expressed as the amount per surface area with respect to the tape surface exposed to the skin. The use of an occlusive dressing with the tape enhances the rate and extent of delivery of the drug to deeper layers of the skin and may result in greater systemic absorption of the drug.

Table 20.1 DRUGS USED IN IP

DRUG SOLUTION	CONCENTRATION (%)	USE/INDICATION	POLARITY
Acetic acid	2–5	Calcium deposits, calcified tendonitis	Negative
Atropine sulfate	0.001–0.01	Hyperhidrosis	Positive
Calcium chloride	2	Myopathy, myospasm, immobile joints	Positive
Sodium chloride	2	Sclerolytic, scar tissue, adhesions, keloids	Negative
Copper sulfate	2	Astringent, fungus infection	Positive
Dexamethasone sodium phosphate	0.4	Tendonitis, bursitis, arthritis, tenosynovitis, Peyronie disease	Negative
Estriol	0.3	Acne scars	Positive
Fentanyl citrate		Analgesic	Positive
Fluoride sodium	2	Desensitize teeth	Positive
Gentamicin sulfate	0.8	Ear chondritis	Positive
Glycopyrronium bromide	0.05	Hyperhidrosis	Positive
Hyaluronidase	150 U/mL solution	Absorption enhancement, edema, scleroderma, lymphedema	Positive
Idoxuridine	0.1	Herpes simplex	Negative
Iodine ointment	4.7	Sclerolytic, antimicrobial, fibrosis, adhesions, scar tissue, trigger finger	Negative
Iron/titanium oxide		Skin pigmentation	Positive
Lidocaine hydrochloride	4 (with or without epinephrine 1:50,000–1:100,000)	Skin anesthesia, trigeminal neuralgia	Positive
Lithium chloride	2	Gouty arthritis	Positive
Magnesium sulfate	2	Muscle relaxant, vasodilator, myalgias, neuritis, deltoid bursitis, low back spasm	Positive
Mecholyl chloride	0.25	Vasodilator, muscle relaxant, radiculitis, varicose ulcers	Positive
Meladinine sodium	1	Vitiligo	Negative
Methylphenidate hydrochloride		Attention deficit disorder	Positive
Morphine sulfate	0.2–0.4	Analgesic	Positive
Pilocarpine hydrochloride		Sweat test for cystic fibrosis	Positive
Poldine methyl sulfate	0.05–0.5	Hyperhidrosis	Negative
Potassium iodide	10	Scar tissue	Negative
Sodium salicylate	2	Analgesic, sclerolytic, plantar warts, scar tissue, myalgias	Negative
Tretinoin		Acne scars	Positive
Water	100	Palmar, plantar, axillary hyperhidrosis	Both
Zinc oxide suspension	20	Antiseptic, ulcers, dermatitis, wound healing	Positive

Table 20.2 DRUGS USED IN VETERINARY IP

DRUG SOLUTION	COMMERCIAL CONCENTRATION (MG/ML)	TOTAL/6 ML ELECTRODE (MG)	POLARITY
NSAIDs			
Phenylbutazone	200	1,200	Negative
Flunixin meglumine	50	300	Negative
Ketoprofen	100	600	Negative
Corticosteroids, anti-inflammatory agents			
Dexamethasone sodium phosphate	2 or 4	12 or 24	Negative
Betamethasone	4	24	Negative
Prednisolone sodium succinate	10 or 50	60 or 300	Negative
Antibiotics			
Gentamicin sulfate	50 or 100	300 or 600	Positive
Amikacin sulfate	50	300	Positive
Ceftiofur sodium	50	300	Negative
Local anesthetic			
Lidocaine hydrochloride	20	120	Positive

Tapes should be stored in tight containers and protected from light and moisture. They should be labeled "For External Use Only." To use, one cuts a patch slightly larger than the area that will be treated. The backing paper is removed from the adhesive side and the tape applied to the skin. To ensure optimal adhesion, the tape should not be applied to folds in the skin. To minimize systemic absorption and to ensure good adhesion, tapes should be applied to dry skin.

ORAL ADMINISTRATION

Films

A film is a thin, flexible sheet of material, usually composed of a polymer material that is actually used in various routes of administration for oral administration in a rapidly dissolving form. They are prepared by mixing the polymer with the drug, sweetener, and flavor and casting, forming, drying, and packaging.

Mucoadhesive System

The Striant mucoadhesive testosterone buccal system is designed to adhere to the gum or inner cheek to provide a controlled and sustained release of testosterone through the buccal mucosa (2). Using a Striant system twice daily, morning and evening, provides continuous systemic delivery of testosterone to the patient. Each Striant buccal system contains 30 mg of testosterone, along with the inactive ingredients such as anhydrous lactose, Carbomer 934P, hypromellose, magnesium stearate, lactose monohydrate, polycarbophil, colloidal silicon dioxide, starch, and talc. When used as directed in hypogonadal males, the circulating testosterone levels should approximate the physiologic levels in healthy men at 300 to 1,050 ng/dL.

When applied, Striant begins hydrating, and testosterone is absorbed through the gum and cheek surfaces that are in contact with it. Venous drainage from the mouth into the superior vena cava circumvents first-pass (hepatic) metabolism. Following initial application, the serum testosterone concentration rises to a maximum within 10 to 12 hours; steady-state levels are usually obtained after the first two Striant systems are used. When removed and not reapplied, the serum testosterone levels fall below the normal range within 2 to 4 hours.

What is the effect of food when using Striant? No specific studies were reported in the package literature. The effects of toothbrushing, mouthwashing, chewing gum, and drinking alcoholic beverages on the use and absorption of testosterone from the Striant system were not specifically studied but were allowed in the phase 3 clinical studies, and no significant effect was attributed to these activities.

Medicated Gums

A medicated gum is a semisolid confection that is designed to be chewed rather than swallowed. Medicated gums release their active ingredient(s) into the saliva and can deliver therapeutic agents for both local action or for systemic absorption. Most medicated gums are manufactured using the conventional melting process of the confectionary industry, or, alternatively, they may be directly compressed from gum powder. They are formulated from insoluble synthetic gum bases, such as polyisoprene, polyisobutylene, isobutylene–isoprene copolymer, styrene butadiene rubber, polyvinyl acetate, polyethylene, ester gus, or polyterpenes.

Softening agents, or plasticizers such as propylene glycol, glycerin, oleic acid, or vegetable oils, are added to maintain pliability and aid in the incorporation of the active and inactive ingredients, including sweeteners and flavoring agents. Sugars and artificial sweeteners and flavorings are added to improve taste. Some medicated gums are coated with magnesium stearate to reduce tackiness and improve handling during packaging; sometimes a preservative may be added.

Preparation by melting includes melting the gum base to about 115°C until it achieves the viscosity of a thick syrup, at which point it is filtered through a fine-mesh screen. Then sweeteners, plasticizers, and active drugs are added with mixing. Colorings, flavorings, and preservatives are added and mixed while the melted gum is cooling. It is then shaped by extrusion or rolling and cutting. Any additional coating is applied to improve taste and aid in bulk packaging.

Preparation by direct compression involves using the gum base in a free-flowing granular powder. It is dry blended with sweeteners, flavors, the active drug, and a lubricant. It is then processed using a conventional tablet press into the desired shape and size. The tablets can be further coated with sugar or sugar-free excipients and packaged in blister or bottles as desired.

Osmotic Pump

Numerous drug delivery devices now use osmosis as the driving force. As shown in Figure 20.4, the Alzet (Alza osmotic minipump) is used in research laboratories to provide constant-rate delivery and programmed delivery of a drug. It consists of a flexible impermeable diaphragm surrounded by a sealed layer containing an osmotic agent that is enclosed within a semipermeable membrane. A stainless steel or polyethylene tube or catheter is inserted into the inner chamber from which the drug is channeled. When the unit is subjected to an aqueous medium, the water flows through the rate-controlling semipermeable membrane and dissolves the osmotic agent that provides the pressure on the flexible lining and forces the

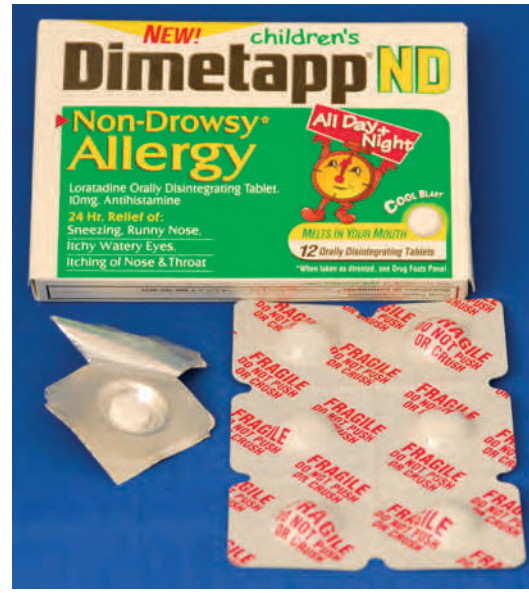


FIGURE 20.4 Diagram of an osmotic pump.

drug through the tube or catheter. The unit can be presterilized and prefilled using a filling tube.

With the Alzet pump, the drug reservoir is a liquid solution inside an impermeable collapsible polyester bag coated with a layer of an osmotically active salt. It is sealed within a rigid structure coated with a semipermeable membrane. As the salt dissolves, it creates an osmotic pressure gradient, and the drug compartment is reduced in volume, forcing the drug solution out. The delivery rate can be changed by changing the drug concentration (3).

VAGINAL ADMINISTRATION

Intravaginal Drug Delivery System

Vaginal administration of drugs, especially hormones, has several advantages, including self-insertion and removal, continuous drug administration at an effective dose level, and good patient compliance. The continuous release and local absorption of drug minimize systemic toxicity that may result from oral peak-and-valley drug administration.

In a polymeric vaginal drug delivery system, such as a resilient medicated vaginal ring, shown in Figures 20.5 and 20.6 or a copper-containing intrauterine contraceptive device, the drug may be uniformly distributed throughout the polymeric matrix. Upon administration and when in contact with vaginal fluids, the drug will slowly dissolve and migrate out of the device. Drug inside the device will diffuse toward the surface along a concentration gradient, resulting in a long-acting drug delivery system. Mirena (levonorgestrel-releasing intrauterine system) consists of a T-shaped polyethylene frame with a steroid reservoir (hormone elastomer core) around the vertical stem. It is designed to prevent pregnancy for up to 5 years (4).

Intrauterine Progesterone Drug Delivery System

The Progestasert System shown in Figure 20.7 slowly releases an average of 60 mg of progesterone per day for 1 year after insertion.

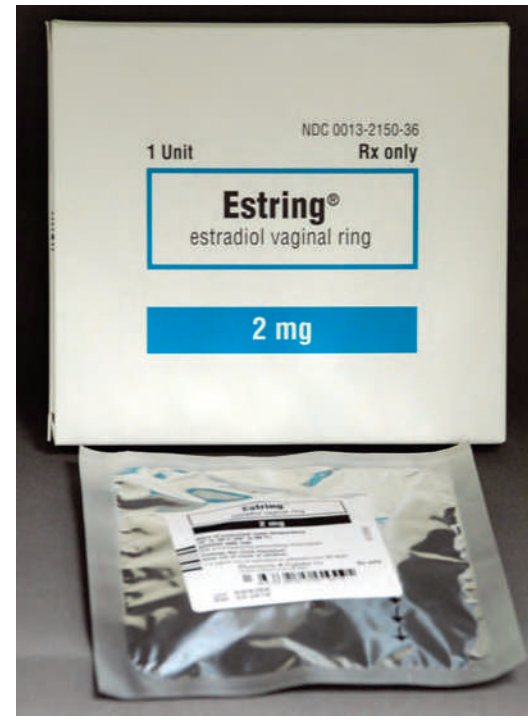


FIGURE 20.5 Estring (estradiol vaginal ring) commercial package. The ring is enclosed in a foil pouch inside the carton.

The continuous release of progesterone into the uterine cavity provides local rather than systemic action. Two hypotheses for the contraceptive action have been offered:

FIGURE 20.6 The Estring (Pharmacia & Upjohn), a polymeric vaginal drug delivery system. (Courtesy of Pharmacia & Upjohn.)

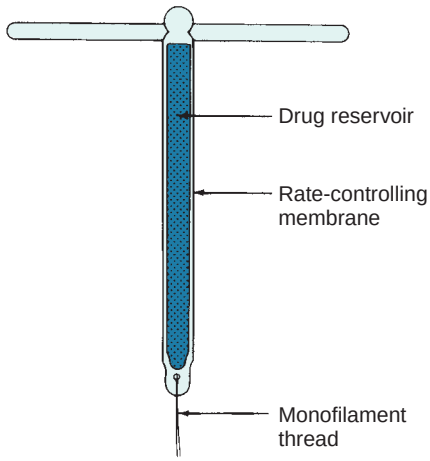


FIGURE 20.7 Schematic of the Progestasert intrauterine drug delivery system.

progesterone-induced inhibition of sperm capacity for survival and alteration of the uterine milieu to prevent nidation. The intrauterine device contains 38 mg of progesterone, a much smaller amount than would be taken by other routes of administration over the same period for the same purpose. The intrauterine device is replaced annually for the maintenance of contraception (5).

The Progestasert provides contraception without the need for daily self-medication and has the advantages of (*a*) using a natural hormone; (*b*) containing no estrogens; (*c*) using a T-shaped delivery device to ensure comfort, safety, and retention, which minimizes mechanically induced irritation; and (*d*) confining the hormonal action to the uterus.

The device contains the progesterone suspended in silicone oil; barium sulfate is added to make it radiopaque. The ethylene vinyl acetate (EVA) membrane surrounding the drug core controls the rate of drug release. Titanium dioxide is added to the EVA for a white color. At the end of a year, the device will contain approximately 14 mg of progesterone, the excess being required to maintain the thermodynamic activity of the drug reservoir.

Dinoprostone Vaginal Insert

Dinoprostone (Cervidil, Forest Pharmaceuticals) is a thick, flat, rectangular polymeric slab enclosed in a pouch of a knitted polyester retrieval system. The buff-colored semitransparent polymeric hydrogel slab contains 10 mg of dinoprostone. The retrieval system is in the shape of a long knitted tape used to retrieve, or remove, the unit after the dosing interval is complete. The product is designed to release dinoprostone in vivo at a rate of about 0.3 mg per hour. The unit contains 10 mg of dinoprostone in 236 mg of a cross-linked polyethylene oxide–urethane polymer slab that measures 29 mm by 9.5 mm and is 0.8 mm thick. When placed in a moist environment, the unit absorbs water, swells, and releases dinoprostone.

It is indicated for initiation and/or continuation of cervical ripening in patients at or near term when there is medical or obstetrical indication for labor induction.

The product is dosed at 10 mg of dinoprostone (1 unit) inserted vaginally and removed upon onset of active labor or 12 hours after insertion. After administration, the patient should remain supine for 2 hours but may be ambulatory after that time.

This product should be stored in a freezer at – 20°C to – 10°C (– 4°F to 14°F); it is packaged in foil and is stable in the freezer for 3 years. After opening and upon exposure to humidity, it is hygroscopic, and the release characteristics of the dinoprostone may be altered if it is improperly stored (6). An example is shown in Figure 20.8.

Estring

A unique method of administering estradiol is through the use of the estradiol vaginal ring (Estring, Pharmacia Corp., A Division of Pfizer) shown in Figures 20.5 and 20.6. The core of the ring contains a reservoir of estradiol, which is released immediately and then at a continuous rate of 75 mg per 24 hours over 90 days. The ring, composed of silicone polymers and barium sulfate, has an outer diameter of 55 mm and a core diameter of 2 mm. The ring is inserted into the upper third of the vaginal vault and is worn continuously for the treatment of urogenital symptoms associated with postmenopausal atrophy of the vagina.

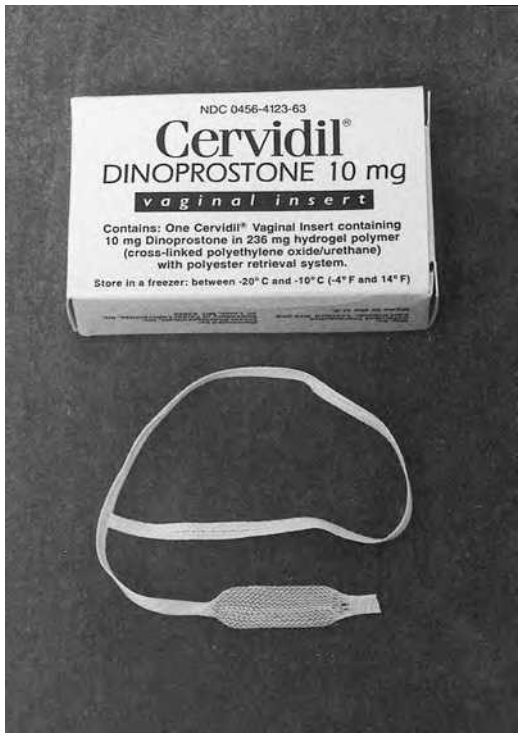


FIGURE 20.8 Cervidil (dinoprostone) vaginal insert. The polymeric slab containing the dinoprostone is encased in a pouch of a knitted polyester delivery and retrieval system. (Courtesy of Forest Pharmaceuticals.)

Crinone Gel

Another type of vaginal product with extended action is the bioadhesive vaginal gel Crinone Gel (Wyeth-Ayerst), which contains micronized progesterone and the polymer polycarbophil in an oil-in-water emulsion system. The polymer, which is insoluble in water, swells within the vagina and forms a bioadhesive gel coating on the walls of the vagina. This allows the absorption of progesterone through the vaginal tissue over 25 to 50 hours. The product is used to assist in reproduction and is shown in Figure 20.9.

OPHTHALMICS

One of the problems associated with the use of ophthalmic solutions is the rapid loss of administered drug due to the blinking of the eye and the flushing effect of lacrimal fluids. Up to 80% of an administered dose may be lost through tears and the action of nasolacrimal drainage within 5 minutes of installation. Extended periods of therapy may be achieved by formulations that increase the contact time between the medication and the corneal surface. This may be accomplished by the use of agents that increase the viscosity of solutions, by ophthalmic suspensions in which the drug particles slowly dissolve, by slowly dissipating ophthalmic ointments, or by the use of ophthalmic inserts.

FIGURE 20.9 Crinone (progesterone 8% gel). Commercial package contains six single-use, individually wrapped prefilled applicators.

Gels Extended Release

Although ophthalmic dosage forms are discussed at length in Chapter 17, it is useful to note here certain preparations designed to extend drug action. The following are but two examples of proprietary products that use viscosity-increasing agents to increase corneal contact time. Pilocarpine (Pilopine HS Gel, Alcon) employs Carbopol 940, a synthetic high molecular weight cross-linked polymer of acrylic acid. Timolol maleate (Timoptic-XE, Merck) employs gellan gum (Gelrite), which forms a gel upon contact with the precorneal tear film.

Ophthalmic Inserts

Lacrisert

Lacrisert (Merck) is a rod-shaped water-soluble form of hydroxypropyl cellulose.

The insert is placed in the inferior cul-de-sac of the eye once or twice daily for the treatment of dry eyes. The inserts soften and slowly dissolve, thickening the precorneal tear film and prolonging the tear film breakup.

Pilocarpine Insert

Pilocarpine is available in a membrane-controlled reservoir system that is used in the treatment of glaucoma. Pilocarpine is sandwiched between two EVA membranes. It also contains alginic acid, a seaweed carbohydrate, which serves as a carrier for pilocarpine. The small, clear device has a white annular border made of EVA copolymer impregnated with titanium dioxide (pigment) that makes it easier for the patient to see. The insert is placed in the cul-de-sac, where it will float with the tears. The pilocarpine will diffuse from the device and exert its pharmacologic effect (Figs. 20.10 and 20.11).

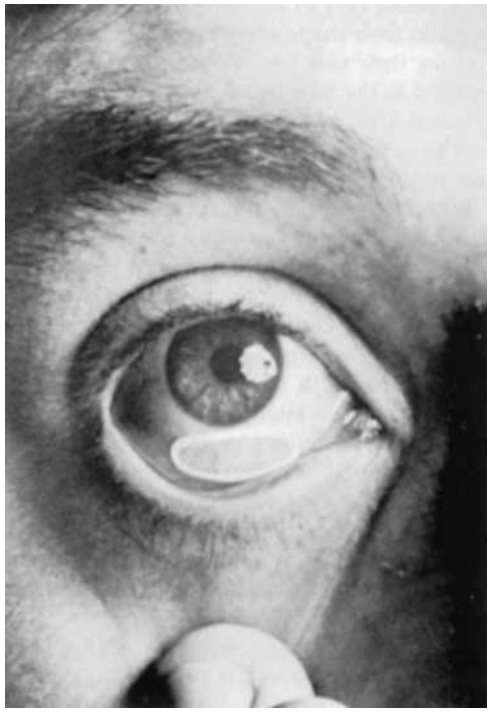


FIGURE 20.10 Ocusert ocular therapeutic systems are thin, flexible wafers placed under the eyelid to provide a week's dose of pilocarpine in the treatment of glaucoma. Ocusert systems cause less blurring of vision than conventional pilocarpine eye drops, which must be administered four times daily.

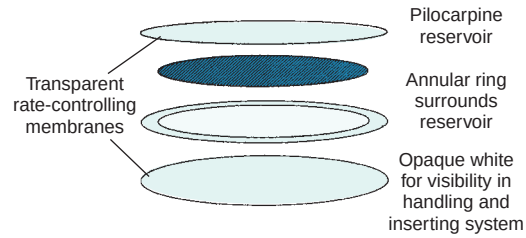


FIGURE 20.11 Construction of the Ocusert ocular therapeutic system containing pilocarpine between transparent rate-controlling membranes.

The tear fluid penetrates the microporous membrane, dissolving the pilocarpine. The release rate of pilocarpine is in the range of 20 or 40 mg per hour for 4 to 7 days. One advantage to this system is enhanced compliance, as the patient does not have to remember to instill the drops and has no blurred vision or slight discomfort that occurs when applying drops to the eyes.

The release rate of pilocarpine from the EVA system is shown in the following equation:

$$\frac{dm}{dt} = \frac{ADK\Delta C}{h}$$

where

dm/dt is the release rate;
D is the diffusion coefficient of the drug in the membrane;
K is the partition coefficient, that is, the ratio of drug concentration at equilibrium inside the membrane to that outside the membrane;
ΔC is the difference of the drug concentration between the inside and the outside walls of the membrane; and
A and h are the area and thickness of the system, respectively.

Under routine conditions, the concentration of the drug in the tears is negligible (2 to 3 mg/mL) compared to that inside the membrane, which is essentially the solubility of the drug, so the equation can be rewritten

$$\frac{dm}{dt} = \frac{ADKS}{h}$$

The systems are designed to release at 20 or 40 mg per hour for 1 week. Over a week's time, the total drug released by the system is

3.4 or 6.7 mg, for the 20 or 40 mg per hour units, respectively. The units contain either 5 or 11 mg of drug initially and are designed to retain about 40% of the initial quantity of drug to provide for a constant delivery rate and a safety margin of an extra day's delivery of drug.

PARENTERAL ADMINISTRATION

Long-Acting Parenteral Systems

Extended rates of drug action following injection may be achieved in a number of ways, including the use of crystal or amorphous drug forms having prolonged dissolution characteristics, slowly dissolving chemical complexes of the drug entity, solutions, or suspensions of drug in slowly absorbed carriers or vehicles (e.g., oleaginous vehicle), large particles of drug in suspension, or injection of slowly eroding microspheres of drug (7). The duration of action of the various forms of insulin, for example, is based in part on its physical form (amorphous or crystalline), complex formation with added agents, and dosage form (solution or suspension) (8).

Matrix carrier systems based on biodegradable materials for parenteral application have been examined as a potential means of delivering peptides and proteins (see "Gliadel Wafer Implant"). In such systems, a material such as purified insoluble collagen is used as a matrix that releases the drug contents through controlled diffusion and enzymatic matrix degradation.

In addition to these means of achieving extended drug action, the rate and duration of drug delivery may be controlled mechanically using controlled-rate drug infusion pumps.

Examples of proprietary parenteral products having long-acting features are presented in Table 20.3. Conventional parenteral products and methods of administration are discussed in Chapter 15.

Liposomes

Liposomes are composed of small vesicles of a bilayer of phospholipid encapsulating an aqueous space ranging from about 0.03 to 10 mm in diameter. They are composed of one or many lipid membranes enclosing discrete aqueous compartments. The enclosed vesicles can encapsulate water-soluble drugs in the aqueous spaces, and lipid-soluble drugs can be incorporated into the membranes. Liposomes can be administered parenterally, topically, by inhalation, and possibly by other routes of administration. Current products are administered parenterally.

The following is an oversimplification but will serve to illustrate the preparation

Table 20.3 EXAMPLES OF PROPRIETARY EXTENDED ACTION PARENTERAL PRODUCTS

PRODUCT	CONTENTS AND COMMENTS
Bicillin C-R Injection (Monarch)	Contains penicillin G benzathine and penicillin G procaine, which have low solubility, are slowly released from IM injection sites. Hydrolyze to penicillin G. Hydrolysis plus slow absorption results in prolonged blood serum levels. Usual dose interval, 2–3 d
Decadron-LA Sterile Suspension (Merck)	Contains dexamethasone acetate, very insoluble ester of dexamethasone. Repository IM injection may be repeated as needed at 1–3 wk.
Depo-Provera Contraceptive Injection (Pharmacia)	Medroxyprogesterone acetate, water-insoluble, in aqueous suspension. Single IM dose is repeated q3mo.
Abelcet Amphotericin B Lipid Complex Injection (Enzon)	Suspension of amphotericin B complexed with two phospholipids administered by IV infusion qd
Lupron Depot for Suspension (TAP Pharmaceuticals)	Sterile lyophilized microspheres; mixed with diluent, form IM injection suspension q3–4 mo

IM, intramuscular; IV, intravenous.

of liposomes. Prepare a solution of a lipid (lecithin) in an organic solvent (acetone, chloroform) in a beaker. Allow the solvent to evaporate, leaving a thin film of the lipid on the walls of the container. Add an aqueous solution of the drug to the beaker and place it in an ultrasonic bath. As the lipid is displaced from the beaker walls, it forms spheres or cylinders, trapping the aqueous solution inside. The liposomes can be collected, sized, and used.

Numerous configurations are possible for liposomes, including spheres and cylinders. Spherical liposomes can be unilamellar (only one layer) or multilamellar (many layers). They are often designated LUV (large unilamellar vesicle), SUV (small unilamellar vesicle), and MLV (multilamellar vesicle). The smaller vesicles, or liposomes, generally range in size from 0.02 to 0.2 mm and the large vesicles from about 0.2 mm to more than 10 mm. The MLVs may have an onion-skin structure of several layers.

The phospholipids composing liposomes are amphipathic, possessing both a hydrophilic or polar head and a hydrophobic or nonpolar tail. This is similar to the hydrophilic–lipophilic balance (HLB) and wedge orientation theories of emulsification. The hydrophobic tail is composed of fatty acids containing generally 10 to 24 carbon atoms, and the polar end may contain phosphoric acid bound to a water-soluble portion; the composition may vary considerably. Lecithin (phosphatidylcholine) is a backbone structure that has been studied extensively. When these phospholipids are exposed to water and line up, they do so in a manner that the fatty acid tails associate together as the lipophilic phase and the polar head groups associate toward the bulk water phase. Depending on the system and the water solubility of the drug, the drug may be in the aqueous compartments (if water soluble) or in the lipophilic bilayers (if oil soluble).

Some liposomes are unique because they can be selectively absorbed by tissues rich in reticuloendothelial cells, such as the liver, spleen, and bone marrow. This can serve as a targeting mechanism, but it also removes liposomes from the circulation rather rapidly. To extend the half-life of liposomes in the body, "stealth liposomes" have been developed by coating the liposomes with materials, such as the polymer polyethylene glycol (PEG), enabling liposomes to evade detection through the components of the body's immune system. This extends their half-life and may also alter their biodistribution.

Advantages of liposomes include the following: (*a*) Liposome-encapsulated drugs are delivered intact to various tissues and cells and can be released when the liposome is destroyed, enabling site-specific and targeted drug delivery. (*b*) Liposomes can be used for both hydrophilic and lipophilic drugs without chemical modification. (*c*) Other tissues and cells of the body are protected from the drug until it is released by the liposomes, decreasing the drug's toxicity. (*d*) The size, charge, and other characteristics can be altered depending on the drug and the intended use of the product.

Disadvantages of liposomes include their tendency to be taken up by cells of the reticuloendothelial system (RES) and the slow release of the drug when the liposomes are taken up by phagocytes through endocytosis, fusion, surface adsorption, or lipid exchange.

Many advances in liposome preparation, including composition, sizing, classification, and enhancing stability, have been made. Stability has been a problem, but stable liposomes can now be prepared. Liposomes have been investigated for a number of years as potential drug delivery systems, and now are on the market.

One product is Abelcet Injection (Enzon). It is a sterile, pyrogen-free suspension for intravenous infusion consisting of amphotericin B complexed with two phospholipids in a 1:1 drug-to-lipid molar ratio. The two phospholipids, L-alpha-dimyristoyl phosphatidyl choline (DMPC) and L-alpha-dimyristoyl phosphatidyl glycerol (DMPG), are present in a 7:3 molar ratio. The product is yellow and opaque with a pH in the range of 5 to 7. The formulation per milliliter is provided as the following (9):

Amphotericin B, USP, 5 mg
DMPC 3.4 mg

DMPG 1.5 mg
Sodium Chloride, USP, 9 mg
Water for Injection, USP, qs 1 mL

The product contains the following bolded note:

> NOTE: Liposomal encapsulation or incorporation in a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated or nonlipid-associated drug. In addition, different liposomal or lipid-complexed products with a common active ingredient may vary from one another in the chemical composition and physical form of the lipid component. Such differences may affect functional properties of these drug products.

AmBisome is amphotericin B liposome for injection. It is a sterile, nonpyrogenic lyophilized product for intravenous infusion; each vial contains 50 mg amphotericin B intercalated into a liposomal membrane consisting of approximately 213 mg of hydrogenated soy phosphatidylcholine, 52 mg of cholesterol, 84 mg of distearoyl phosphatidylglycerol, 0.64 mg of alpha-tocopherol, 900 mg of sucrose, and 27 mg of disodium succinate hexahydrate as a buffer. When reconstituted with sterile water for injection, the pH of the solution is between 5.0 and 6.0. AmBisome is a true, single bilayer liposomal drug delivery system. When the powder is reconstituted, multiple concentric bilayer membranes are formed; these are changed by microemulsification into single bilayer liposomes using a homogenizer. AmBisome contains liposomes that are less than 100 nm in diameter. Amphotericin B is a macrocyclic polyene antifungal antibiotic that is produced from a strain of *Streptomyces nodosus*.

Amphotec (amphotericin B cholesteryl sulfate, Sequus Pharmaceuticals) is a sterile, pyrogen-free lyophilized powder for reconstitution and intravenous administration. It is a 1:1 molar ratio complex of amphotericin B and cholesteryl sulfate that upon reconstitution forms a colloidal dispersion of microscopic disk-shaped particles. Each 50-mg single-dose vial contains amphotericin B 50 mg, sodium cholesteryl sulfate 26.4 mg, tromethamine 5.64 mg, disodium edetate dihydrate 0.372 mg, lactose monohydrate 950 mg, and hydrochloric acid *qs*. The 100-mg single-dose vial contains amphotericin B, 100 mg; sodium cholesteryl sulfate, 52.8 mg; tromethamine, 11.28 mg; disodium edetate dihydrate, 0.744 mg; lactose monohydrate, 1,900 mg; and hydrochloric acid, *qs*.

Amphotec is indicated for the treatment of invasive aspergillosis in patients when renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate in effective doses and in patients with aspergillosis when prior amphotericin B deoxycholate therapy has failed.

The drug is reconstituted with sterile water for injection by rapidly adding the water to the vial; it is shaken gently by hand, rotating the vial until all the solids have dissolved. The fluid may be opalescent or clear. For infusion, it is further diluted in 5% dextrose injection. The product should not be reconstituted with any fluid other than sterile water for injection; do not reconstitute with dextrose or sodium chloride solutions. Also, for further dilution, it should not be admixed with sodium chloride or electrolytes. Solutions containing benzyl alcohol or any other bacteriostatic agent should not be used, as they may cause precipitation. An inline filter should not be used, and the infusion admixture should not be mixed with other drugs. If infused using a Y-injection site or similar device, flush the line with 5% dextrose injection before and after infusion of Amphotec.

After reconstitution, the drug should be refrigerated and used within 24 hours; do not freeze. If further diluted with 5% dextrose injection, it should be refrigerated and used within 24 hours (10).

Daunorubicin citrate liposome injection (DaunoXome, Gilead Sciences) is an aqueous solution of daunorubicin citrate encapsulated with liposomes composed of distearoyl phosphatidylcholine and cholesterol (2:1 molar ratio), with a mean diameter of about 45 nm (range 35 to 65 nm). The weight ratio of lipid to drug is 18.7:1 (total lipid–daunorubicin base), equivalent to a 10:5:1 molar ratio of distearoyl phosphatidylcholine, cholesterol, and daunorubicin, respectively.

DaunoXome is formulated to maximize the selectivity of daunorubicin for solid tumors in situ. The liposomal formulation helps to protect the daunorubicin from chemical and

enzymatic degradation, minimizes protein binding, and generally decreases uptake by normal tissues.

The product should be diluted 1:1 with 5% dextrose injection prior to administration. Each vial contains the equivalent of 50 mg daunorubicin base at a concentration of 2 mg/mL after preparation; it is recommended to be diluted to 1 mg/mL for administration. The only fluid recommended for preparation is 5% dextrose injection; it must not be mixed with a solution containing sodium chloride or benzyl alcohol or with any other solution. An inline filter should not be used for the intravenous infusion of DaunoXome. The final product appears as a red translucent dispersion of liposomes that does scatter light, but it should not be used if it appears opaque or has precipitate or foreign matter in it. It should be stored in a refrigerator (2°C to 8°C; 36°F to 46°F); do not freeze and protect from light (11).

Stealth Liposomes

Liposome research has resulted in liposomes that avoid detection by the body's immune system, specifically the cells of the RES. These liposomes are known as "stealth liposomes" and are prepared with PEG on the outside of the membrane. The PEG coating, which is inert in the body, allows for longer circulatory life for the drug delivery mechanism. In addition to the PEG coating, most stealth liposomes also have some type of biological species attached as a ligand to the liposome in order to enable binding via a specific expression on the targeted drug delivery site. These targeting ligands could be monoclonal antibodies (making an immunoliposome), vitamins, or specific antigens. Targeted liposomes can target nearly any cell type in the body and deliver drugs that would naturally be systemically delivered. Naturally toxic drugs can be much less toxic if delivered only to diseased tissues. In case of tumor development, certain anticancer drugs like doxorubicin (Doxil) and daunorubicin are provided through liposomes.

Doxorubicin hydrochloride (Doxil) liposome injection consists of the drug encapsulated in stealth liposomes for intravenous administration. Doxorubicin is a cytotoxic anthracycline antibiotic that is isolated from *Streptomyces peucetius* var. *caesius*. The product is available as a sterile translucent red liposomal dispersion containing in each 10-mL single-use glass vial 20 mg doxorubicin HCl at a pH of 6.5. The stealth liposomes consist of 3.19 mg/mL of *N*-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt, 9.58 mg/mL of fully hydrogenated soy phosphatidylcholine, and 3.19 mg/mL of cholesterol; also, each milliliter contains approximately 2 mg ammonium sulfate along with histidine as a buffer, sucrose for tonicity, and hydrochloric acid and/or sodium hydroxide for adjustment of pH. The doxorubicin is at least 90% encapsulated in the stealth liposomes. These stealth liposomes are protected from detection by the mononuclear phagocyte system by the coating with surface-bound methoxy PEG; this increases blood circulation time. These liposomes have a half-life of approximately 55 hours in humans (12).

PEGYLATED DOSAGE FORMS

Neulasta (pegfilgrastim) is a covalent conjugate of recombinant methionyl human granulocyte colony-stimulating factor (G-CSF) (filgrastim) and monomethoxy-PEG. Filgrastim is a water-soluble 175-amino acid protein obtained from bacterial fermentation of a strain of *Escherichia coli*; it has a molecular weight of approximately 19 kDa. Pegfilgrastim is produced by covalently bonding a 20-kDa PEG molecule to the N-terminal methionyl residue of filgrastim, resulting in an average molecular weight of pegfilgrastim of approximately 39 kDa. Neulasta is available in 0.6-mL prefilled syringes for subcutaneous injection. The syringe contains 6 mg of pegfilgrastim (based on protein weight) in a clear, colorless, sterile, preservative-free solution containing 0.35 mg acetate, 30 mg sorbitol, 0.02 mg polysorbate 20, and 0.02 mg sodium in water for injection; the pH of the injection is 4.0.

Pegasys (peginterferon *alfa*-2a), used in the treatment of hepatitis C virus, is a covalent

conjugate of recombinant *alfa*-2a interferon (molecular weight ~20 kDa) with a single-branched bis-PEG chain of approximately 40-kDa molecular weight. The PEG moiety is linked at a single site to the interferon *alfa* moiety *via* a stable amide bond to lysine; the final product has an approximate molecular weight of 60 kDa.

Each vial of Pegasys contains approximately 1.2 mL of solution to deliver 1 mL of drug for subcutaneous administration. The 1-mL volume delivers 180 mg of drug product (expressed as the amount of interferon *alfa*-2a), 8 mg sodium chloride, 0.05 mg polysorbate 80, 10 mg benzyl alcohol, 2.62 mg sodium acetate trihydrate, and 0.05 mg acetic acid; the solution has a pH of 6.0 ± 0.01 and is colorless to light yellow.

Pegasys produces maximal serum concentrations at 72 to 96 hours after dosing that are sustained for up to 168 hours. In comparison to Roferon-A, the mean systemic clearance for Pegasys was 94 mL per hour, which is approximately one-hundredth of that for Roferon. The mean terminal half-life after subcutaneous dosing in patients with chronic hepatitis C was 80 hours (range 50 to 140 hours) compared to 5.1 hours (range 3.7 to 8.5 hours) for Roferon-A (13).

PEG-Intron (peginterferon alfa-2b Powder for Injection) is a covalent conjugate of recombinant *alfa* interferon with PEG; approximate molecular weight of the PEG portion is 12 kDa, and the approximate molecular weight of the PEG-Intron molecule is 31 kDa. The product is a white to off-white lyophilized powder supplied in 2-mL vials for subcutaneous use. Each vial contains 74, 118.4, 177.6, or 222 mg of PEG-Intron and 1.11 mg dibasic sodium phosphate anhydrous, 1.11 mg monobasic sodium phosphate dihydrate, 59.2 mg sucrose, and 0.074 mg polysorbate 80. After reconstitution with 0.7 mL of the supplied diluent, which is sterile water for injection, each vial contains PEG-Intron in strength of 100, 160, 240, or 300 mg/mL.

Compared to interferon *alfa*-2b, PEG-Intron has one-seventh the mean apparent clearance and a fivefold greater mean half-life, permitting a reduced dosing frequency. At effective therapeutic doses, PEG-Intron has approximately a 10-fold greater maximum concentration (C_{max}) and a 50-fold greater area under the curve than interferon *alfa*-2b (14).

FUSION PROTEIN: SPECIAL HANDLING

Ontak

Denileukin diftitox (Ontak) is included in this chapter because of its unusual nature and handling. Ontak is a fusion protein designed to direct the cytocidal action of diphtheria toxin to cells that express the interleukin-2 (IL-2) receptor. Ontak is a recombinant DNA–derived cytotoxic protein composed of the amino acid sequences for diphtheria toxin fragments A and B (Met_1-Thr_{387})-His followed by the sequences for IL-2 (Ala_1-Thr_{133}); it is produced in an *E. coli* expression system. Ontak has a molecular weight of 58 kDa. The single-use vials (2 mL) contain 300 mg of recombinant denileukin diftitox in a sterile solution of 20 mM citric acid, 0.05 mM ethylenediaminetetraacetic acid (EDTA), and <1% polysorbate 20 in water for injection; the pH of the solution is between 6.9 and 7.2.

The drug is indicated in the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor. It should be used only by physicians experienced in the use of antineoplastic therapy and management of patients with cancer. Use of this drug should be in patients managed in a facility equipped and staffed for cardiopulmonary resuscitation and where the patients can be closely monitored for an appropriate period based on their health status.

Ontak requires special handling as follows: (*a*) It must be brought to room temperature before preparing the dose. The vials may be thawed in the refrigerator for not more than 24 hours or at room temperature for 1 to 2 hours. (*b*) The solution in the vial may be mixed by gentle swirling: *Do not vigorously shake Ontak solution*. (*c*) After thawing, a haze may be visible. This haze should clear when the solution is at room temperature.

(*d*) Ontak solution must not be used unless the solution is clear, colorless, and without visible particulate matter. (*e*) *Ontak must not be refrozen*. The following are a few administration items of interest: (*a*) Diluted Ontak solution should be prepared and held in plastic syringes or soft plastic intravenous bags. *Do not use a glass container* because adsorption to glass may occur in a dilute state. (*b*) The concentration of Ontak must be at least 15 mg/mL in all steps in the preparation of the solution for intravenous infusion. This is best accomplished by withdrawing the calculated dose from the vial or vials and injecting it into an empty infusion bag. Then, for each 1 mL of Ontak, no more than 9 mL of sterile saline without preservative should be added to the intravenous bag. (*c*) Ontak solution should not be physically mixed with any other drugs. (*d*) Do not administer Ontak solution through an inline filter. (*e*) Prepared solutions of Ontak should be administered within 6 hours, using a syringe pump or intravenous infusion bag. (*f*) Unused portions of Ontak should be discarded immediately.

Prior to handling this drug, pharmacists, nurses, and physicians should carefully read and understand all of the precautions explained in the package labeling (15).

IMPLANTS

Implants are long-acting dosage forms that provide continuous release of the drug, often for periods of months to years. They are administered by the parenteral route; for systemic delivery, they may be placed subcutaneously, or for local delivery, they can be placed in a specific region in the body. They can be made by compression, melting, or sintering. They generally consist of the drug and rate-controlling excipients. Several types are available including pellets, resorbable microparticles, polymer implants, in situ–forming gel/solid implants, metal/plastic implants, and drug-eluting stents.

Pellet implants are small, sterile, solid masses of the active drug with or without excipients and are usually administered using a suitable special injector (e.g., trocar) or by surgical incision. The size and rate of erosion will influence the release rate, which is generally first-order kinetics.

Resorbable microparticles or microspheres generally range from 20 to 100 μm in diameter composed of the drug dispersed within a biocompatible, bioresorbable polymeric excipient (matrix). The microparticles are administered as an aqueous suspension subcutaneously or intramuscularly for systemic delivery, or they may be injected into a specific location in the body.

Polymer implants can be formed as a single mass, such as a cylinder. The polymer matrix must be biocompatible and can be either biodegradable or nonbiodegradable. Shaped implants are administered by means of a suitable injector; release rates are not zero order but can approach zero-order kinetics. They are used to deliver potent small molecules, including steroids, and large molecules, including peptides. An advantage to the biodegradable implants is that they do not require removal after release of all the drug.

Liquid–gel/solid implants are initially liquid formulations comprising a polymer, active drug, and solvent (either aqueous or organic). After administration, a gel or a solid polymeric matrix is formed trapping the drug and extending the release of the drug for days or months.

Metal/plastic implants may be formulated from titanium or other suitable materials and are administered by an injector or surgical installation. A solution of the drug, located inside the implant, is released via an osmotically driven pump inside the implant and may last as long as 1 year or more; release follows zero order.

Drug-eluting stents combine the mechanical effect of the stent with a prolonged pharmacologic effect of the incorporated drug. The metal stent can be coated with a nonbiodegradable or biodegradable polymer-containing drug.

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 that 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 mg of the progestin (16). 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 degrees apart for a total of 75 degrees. 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 mg per day, declining to about 50 mg per day by 9 months, about 35 mg per day by 18 months, and thereafter to about 30 mg per day. The resulting blood levels are substantially below those generally observed among users of combination oral contraceptives containing the progestins norgestrel and 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 (17).

Gliadel Wafer Implant

Polifeprosan 20 with carmustine implant (Gliadel Wafer), shown in Figures 20.12 to 20.14, is a sterile off-white to pale yellow wafer approximately 1.45 cm in diameter and 1 mm thick. Each wafer contains 192.3 mg of a biodegradable polyanhydride copolymer and 7.7 mg of carmustine. Polifeprosan 20 consists of poly[bis(*p*-carboxyphenoxy) propane–sebacic acid] in a 20:80 molar ratio and is used to control the local delivery of carmustine, which is distributed uniformly throughout the copolymer matrix.

Gliadel is designed to deliver the carmustine directly into the surgical cavity created when a brain tumor is resected, with numerous wafers being used depending upon the desired dose. When exposed to the aqueous environment in the resection cavity, the anhydride bonds in the copolymer are hydrolyzed, releasing the carmustine, carboxyphenoxypropane, and sebacic acid. The active drug, carmustine, is released from the wafer and diffuses into the surrounding brain tissue, producing an antineoplastic effect by alkylating DNA and RNA.

FIGURE 20.12 Gliadel wafer (polifeprosan 20 with carmustine implant) and packaging components. (Courtesy of Guilford Pharmaceuticals.)

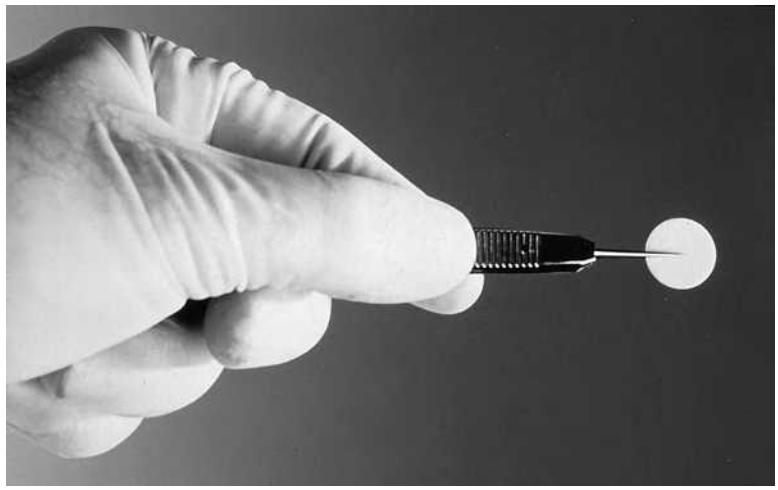


FIGURE 20.13 Gliadel wafer removed from sterile foil pouch in preparation for implantation. (Courtesy of Guilford Pharmaceuticals.)

In 3 weeks, more than 70% of the copolymer degrades, with carboxyphenoxypropane being eliminated by the kidney and sebacic acid being metabolized by the liver and expired as carbon dioxide.

Each wafer contains 7.7 mg of carmustine, and when eight wafers (the recommended dose) are used, a dose of 61.6 mg is delivered. The wafers are supplied in a single-dose treatment box containing eight individually pouched wafers. Each wafer is double-pouched in foil. The inner pouch is sterile; upon removing the outer foil pouch in an aseptic working environment, the inner pouch is treated as a sterile item. Gliadel wafers must be stored at or below – 20°C (18).

Goserelin Implant (Zoladex)

Goserelin acetate implant (Zoladex, AstraZeneca) is a sterile, biodegradable product containing goserelin acetate, equivalent to 3.6 mg of drug, designed for subcutaneous injection with continuous release over 28 days. Goserelin acetate is dispersed in a matrix consisting of D,L-lactic and glycolic

FIGURE 20.14 Gliadel wafer implanted in the brain. (Courtesy of Guilford Pharmaceuticals.)

acid copolymer (13.3 to 14.3 mg/dose) containing <2.5% acetic acid and up to 12% goserelin-related substances. It is a sterile white to cream-colored cylinder 1 mm in diameter, preloaded in a special single-use syringe with a 16-gauge needle. The unit is packaged in a sealed light- and moisture-proof aluminum foil laminate pouch containing a desiccant capsule.

Zoladex is indicated for a number of disorders, including the palliative treatment of advanced carcinoma of the prostate, offering an alternative to orchiectomy and/or estrogen administration when the standard treatments are not indicated or are unacceptable to the patient. It is also used in the treatment of endometriosis and advanced breast cancer.

Zoladex is also available as Zoladex 3-Month, containing the equivalent of 10.8 mg of goserelin. The base consists of a matrix of D,L-lactic and glycolic acid copolymer (12.82 to 14.76 mg/dose) containing <2% acetic acid and up to 10% goserelin-related substances and presented as a sterile white to cream-colored cylinder 1.5 mm in diameter, preloaded in a special single-use syringe with a 14-gauge needle and overwrap, as previously described. This preparation is designed for administration every 3 months (19).

In 1998, the FDA approved the combination of Zoladex (3.6- and 10.8-mg goserelin acetate depots) and Eulexin (flutamide) for the management of locally confined stage B2 to C prostate carcinoma. The treatment is initiated 8 weeks prior to radiation therapy and continued during radiation therapy. The treatment regimen for prostate cancer uses one 3.6-mg implant subcutaneously into the upper abdomen every 28 days or a 10.8-mg implant subcutaneously into the abdominal wall every 12 weeks.

Goserelin is administered as a subcutaneous implant. Along with leuprolide acetate (Lupron Depot), it was one of the first polymer systems to have received FDA approval for controlled release of a peptide. This drug is available in a 3.6-mg biodegradable and biocompatible sterile white to cream-colored 1-mm by 1.5-mm cylinder about the size of a grain of rice preloaded into a special single-use syringe (Fig. 19.18). The drug is dispersed in a matrix of D,L-lactic acid and glycolic acid copolymer.

Histrelin (Vantas) Implant

The Vantas (histrelin) implant is a sterile nonbiodegradable, diffusion-controlled reservoir drug delivery system designed to deliver histrelin continuously for 12 months upon subcutaneous implantation. It contains 50 mg of histrelin acetate, a synthetic nonapeptide analog of the naturally occurring gonadotropin-releasing hormone (GnRH) or luteinizing hormone–releasing hormone (LH-RH). The device must be removed after 12 months, and another implant may be inserted to continue therapy.

The sterile implant contains a 50-mg histrelin acetate drug core inside a nonbiodegradable, 3.5 cm by 3 mm cylindrically shaped hydrogel reservoir that also contains stearic acid. The hydrogel reservoir consists of a hydrophilic polymer cartridge composed of 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, trimethylolpropane trimethacrylate, benzoin methyl ether, Perkadox-16, and Triton X-100. It is packaged in a glass vial containing 2 mL of 1.8% sodium chloride solution and is primed for release upon insertion (20).

Leuprolide Acetate (Lupron, Lupron Depot-Ped, Lupron Depot-3 Month)

Leuprolide is a synthetic GnRH analog. Like the naturally occurring LH-RH, initial and intermittent administration of this drug stimulates the release of LH and FSH from the anterior pituitary. As with goserelin, continuous administration of leuprolide suppresses the secretion of LH and FSH, with a concomitant drop in testosterone concentrations and subsequent medical castration.

The usual adult dose for prostatic carcinoma is a subcutaneous injection of 1 mg per day. There is also a monthly (every 28 to 33 days) depot intramuscular injection. The 7.5-mg strength is used for prostatic carcinoma. The powder for intramuscular injection is reconstituted with a special diluent composed of D-mannitol, purified gelatin,

D,L-lactic and glycolic acid copolymer, polysorbate 80, and acetic acid.

Lupron should be refrigerated until dispensed, but patients may store the product at room temperature (no more than 30°C, or 86°F). The product should be protected from light and the vial stored in the carton until use. Following reconstitution, the suspension is stable for 1 day. However, because the product has no preservative, it should be discarded if not used immediately.

Viadur Implant

The Viadur (leuprolide acetate) implant is a sterile, nonbiodegradable, osmotically driven miniaturized implant designed to deliver leuprolide acetate for 12 months at a controlled rate. It contains 65 mg of leuprolide (as 72 mg of the acetate), which is a synthetic nonapeptide analog of naturally occurring GnRH or LH-RH. After 12 months, the implant must be removed, and another may be inserted if indicated. Viadur is indicated in the palliative treatment of advanced prostate cancer. The drug is dissolved in 104 mg of dimethyl sulfoxide. The reservoir houses a polyurethane rate-controlling membrane, an elastomeric piston, and a polyethylene diffusion moderator. The contained osmotic tablets are composed of sodium chloride, sodium carboxymethylcellulose, povidone, magnesium stearate, and sterile water for injection. PEG fills the space between the osmotic tablets and the reservoir. The implant weighs about 1.1 g. As aqueous fluid diffuses through the membrane and is slowly taken up by the osmotic tablets, the piston will move and force out a controlled amount of the drug through the diffusion moderator orifice (21).

Vitrasert Implants

Vitrasert implants contain 4.5 mg of the antiviral drug ganciclovir and are used to treat AIDS-related cytomegalovirus (CMV) retinitis. Ganciclovir does not cure the CMV retinitis, but helps to decrease its progression. The dosage form is surgically implanted into the vitreous cavity of the eye in an outpatient intraocular procedure.

Each implant contains 4.5 mg of ganciclovir, contains magnesium stearate (0.25%) as an inactive ingredient, and is embedded into a polymer-based system that slowly releases the drug over a 5- to 8-month period. Follow-up ophthalmological examinations are required, and the Vitrasert is removed and replaced with a new implant once the contents of the original implant have been depleted. The Vitrasert implant only treats the eye in which it has been implanted and does not demonstrate any systemic effect. Clinical trials reported adverse effects, for example, loss of visual acuity, vitreal hemorrhage, and retinal detachment, which were observed in 10% to 20% of patients. Most patients experienced a loss in visual acuity from 2 to 4 weeks after implantation. Currently, Vitrasert is pregnancy category C, and its use in pediatric patients <9 years of age has not been established. Vitrasert is associated with carcinogenicity and mutagenicity and should be handled and disposed of properly according to antineoplastic guidelines.

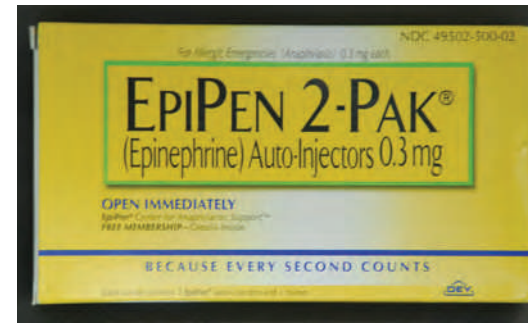
OTHER NOVEL DELIVERY SYSTEMS

Definity is a vial of perflutren lipid microspheres for preparing an injectable suspension. The vial contains components that upon activation yield perflutren lipid microspheres that are used as a diagnostic agent for contrast enhancement during echocardiographic procedures; it is administered intravenously. Prior to activation, the Definity vial contains 6.52 mg/mL octafluoropropane in the head space; each milliliter of the clear liquid contains 0.75 mg of a specific lipid blend, 103.5 mg of propylene glycol, 126.2 mg of glycerin, and 6.8 mg of sodium chloride in water for injection. The pH may be adjusted to 5.8 to 7.0 with either sodium hydroxide or hydrochloric acid. The perflutren vial must be activated prior to use with a mechanical shaking device (Vialmix). Upon activation, each milliliter of the milky white suspension contains a maximum of 1.2×10^{10} perflutren lipid microspheres and about 150 mL/mL of octafluoropropane. The microsphere particles have an average diameter of 1.2 to 3.3 mm (22).

Minocycline hydrochloride (Arestin) microspheres are subgingival sustained-release products containing minocycline

hydrochloride in a bioresorbable polymer, poly(glycolide-co-DL-lactide), or PGLA; it is for professional administration into periodontal pockets. Each unit dose cartridge delivers minocycline hydrochloride equivalent to 1 mg of minocycline free base (23).

Doxycycline hyclate (Atridox) 10% in the Atrigel delivery system is for controlled release in subgingival applications. It is composed of a two-syringe mixing system. Syringe A contains 450 mg of the Atrigel delivery system, which is a bioabsorbable, flowable polymeric formulation composed of 36.7% poly(D,L-lactide) dissolved in 63.3% *N*-methyl-2-pyrrolidone. Syringe B contains doxycycline hyclate that is equivalent to 42.5 mg doxycycline. Once prepared, the product is a pale yellow to yellow viscous liquid with a concentration of 10% doxycycline hyclate in the gel. After professional application and upon contact with the crevicular fluid, the liquid product solidifies and allows for controlled release of drug over 7 days. Doxycycline is a broad-spectrum semisynthetic bacteriostatic tetracycline (24).



A

B

FIGURE 20.15 EpiPen 2-Pak commercial epinephrine autoinjectors, each containing 0.3 mg of epinephrine. **A:** Front of package. **B:** Back of package.

Autoinjection Systems

The EpiPen and EpiPen Jr. automatic injectors contain 2 mL of epinephrine injection for emergency intramuscular use. Each latex-free injector delivers 0.3 mg of Epinephrine Injection, USP, 1:1,000 in a 0.3-mL volume. The remaining 1.7 mL (2.0 to 0.3 mL) remains in the injector after use and is not to be used. Each 0.3 mL of the solution contains 0.3 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust the pH of the solution to 2.2 to 5.0, and water for injection (25).

Both EpiPen autoinjectors are designed as emergency supportive therapy of allergic reactions (anaphylaxis) and are not a replacement or substitute for immediate medical or hospital care. Epinephrine is a sympathomimetic amine that deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin. The EpiPen injectors should be checked immediately prior to use, and if there is any evidence of discoloration, they should be replaced. The activation cap on the units should not be removed until ready for use. The EpiPen injector should be stored in the provided tubes, because it is light sensitive, at room temperature; the units are not to be refrigerated. Figures 20.15 and 20.16 show prefilled pen injection systems.

Humulin N Pen contains NPH human insulin (rDNA origin) isophane suspension in a disposable insulin delivery device. It is packaged containing five 3-mL disposable insulin delivery devices containing NPH insulin 100 U/mL.

FIGURE 20.16 Exenatide 250 mg/mL; 1.2-mL prefilled pen injection. Each prefilled pen will deliver 60 subcutaneous doses at 5 mg per dose.

Safe Needle Systems

With the implementation of the Needlestick Safety and Prevention Act, which requires the evaluation and implementation of "safer medical devices" as well as Occupational Safety and Health Administration (OSHA) requirements, new devices will be entering the market to enhance the safety of personnel responsible for injecting medications in patients.

Enoxaparin sodium injection (Lovenox) is available in a prefilled syringe with an automatic safety device (26). The device allows the use of normal injection technique; the needle shield is removed; the injection proceeds as usual; and the syringe/needle is removed from the injection site with the finger still on the plunger rod. Next, the syringe/needle is pointed away from the administrator of the injection and others, and the safety device is activated by firmly pushing on the plunger rod. The protective sleeve automatically covers the needle, and an audible click is heard to confirm that the shield has been activated and covers the needle. The syringe/needle is then safely disposed of in the nearest sharps container.

MICRONEEDLE ARRAYS

Microneedle Arrays

Microneedle arrays are promising devices for the delivery of drugs and vaccines into or the skin. Unique microneedle arrays can be prepared from various materials. They rapidly take up skin interstitial fluid upon skin insertion to form continuous, unblockable, conduits from attached patch-type drug reservoirs to the dermal microcirculation. Microneedles that can be fabricated in a wide range of patch sizes and microneedle geometries can be easily sterilized, resist hole closure while in place, and are removed completely intact from the skin. Delivery of macromolecules is no longer limited to what can be loaded into the microneedles themselves, and transdermal drug delivery can now be controlled by the cross-link density of the hydrogel system rather than the stratum corneum. This technology has the potential to overcome the limitations of conventional microneedle designs and to greatly increase the range of the type of drug that is deliverable transdermally, with ensuing benefits for industry, health care providers, and, ultimately, patients.

However, little is known about the safety of the microneedles. One study reported on the ability of microneedles to disrupt the skin barrier, which was evaluated by transepidermal water loss (TEWL). The study also determined the safety in terms of skin irritation (skin redness and blood flow) and pain sensation. The microneedle arrays used in the study are able to overcome the barrier function of the skin in human volunteers, are painless, and cause only minimal irritation. This opens the opportunity for dermal and transdermal delivery of drugs and vaccines.

Needle-free delivery has the potential to enhance parenteral administration efficacy and safety, as well as facilitate cost-effective global vaccine distribution and storage, especially for vaccines. To this end, microneedle arrays provide the ability for pain-free, safe, and convenient materials delivery through disruption of the outer layers of the skin to access potent immunocompetent cell populations residing within the epidermal/dermal tissues. These systems also have the capability of two-way activities; drug delivery and sensing capabilities potentially to monitor and adjust drug delivery(27).

APPLYING THE PRINCIPLES AND CONCEPTS

Group Activities

1. In groups of three, create a brief patient handout describing the appropriate use and varying administration techniques for Lamictal chewable dispersible tablets. Be specific in your recommendations and suggestions.
2. Select two ophthalmic and one oral inhalation products. In groups of three, one student serves as the pharmacist, the second the patient, and the third the observer. The pharmacist–student role player will counsel (and demonstrate) the patient on the specific product. After the session, the observer and patient provide constructive feedback on the session. The roles then are rotated utilizing a different product until each of the three students has participated in each of the three roles.
3. To realize the need for novel dosage forms of vaginal administration, access http://www.livestrong.com/video/1945-menopause-health-byte/. View the menstrual cycle health video (1:18 minutes) and the menopause health video (2:09 minutes). Brainstorm possible delivery systems that might be used for intravaginal administration.
4. Interview a classmate who acknowledges using an oral inhalation product, for example, Advair Diskus. Discuss with him or her his or her ability to use the product appropriately, the product's effectiveness, and any concerns he or she might have had when it was prescribed and/or might have presently.
5. In groups of two (one student serves as the pharmacist, the second the patient), have the pharmacist explain to the patient the reason for dispensing a pilocarpine ocusert versus his/her traditional pilocarpine eye drop solution. This is intended to be an interactive exercise; the patient is expected to ask a series of pertinent follow-up questions.

Individual Activities

1. Conduct a literature search to discover five different drugs that utilize liposomal injection technology.
2. Create a pharmacokinetic figure that demonstrates general pharmacokinetic properties (i.e., absorption, distribution, metabolism, excretion) of the Striant mucoadhesive testosterone buccal system against an orally administered testosterone medication.
3. Provide examples of drugs administered parenterally for a long-acting effect utilizing techniques shared in this chapter, for example, slowly dissolving chemical complexes of the drug entity, solutions or suspensions of drugs in slowly absorbed carriers or vehicles, and large drug particles in suspension.
4. Compare and contrast the administration techniques utilized for the EpiPen, Humulin N Pen, Byetta Pen, and a Glucagon Emergency Rescue Kit.

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