Chapter 84

Parenteral Preparations

history
administration
components
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packaging
labeling

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The term parenteral (Gk, *para enteron* = beside the intestine) refers to the route of administration of drugs by injection under or through one or more layers of skin or mucous membrane. Since this route circumvents the highly efficient protective barriers of the human body, the skin and mucous membranes, exceptional purity of the dosage form must be achieved. The processes utilized in preparing the dosage form must embody good manufacturing practices that will produce and maintain the required quality of the product. New developments in process technology and quality control should be adopted as soon as their value and reliability have been established as a means for further improving the quality of the product.

History[1]

One of the most significant events in the beginnings of parenteral therapy was the first recorded injection of drugs into the veins of living animals, in about the year 1657, by the architect Sir Christopher Wren. From such a very crude beginning, the technique for intravenous injection and knowledge of the implications thereof developed slowly during the next century and a half. During the first half of the 19th century, the subcutaneous route of administration was being developed. In 1855 Dr. Alexander Wood of Edinburgh described what was probably the first subcutaneous injection of drugs for therapeutic purposes using a true hypodermic syringe.

The latter half of the 19th century brought increasing concern for safety in the administration of parenteral solutions, largely because of the work of Robert Koch and Louis Pasteur. While Charles Chamberland was developing both hot-air and steam sterilization techniques and the first bacteria-retaining filter (made of unglazed porcelain), H. Nordtmeyer was developing a filter made of kieselguhr (the Berkefeld filter), and Stanislaus Limousin was developing a suitable container, the all-glass ampul. Shortly after the beginning of the 20th century, attention focused on the disturbing chills and fever which often followed the intravenous injection of drugs. In the middle 1920s Dr. Florence Seibert provided proof that this reaction was caused by potent products of microbial growth, pyrogens, which could be eliminated from water by distillation and from glassware by heating at elevated temperatures. These developments were prominent among those that provided the foundation for increasing use of parenteral routes for the administration of drugs.

Administration

Injections may be classified in five general categories: (1) solutions ready for injection, (2) dry, soluble products ready to be combined with a solvent just prior to use, (3) suspensions ready for injection, (4) dry, insoluble products ready to be combined with a vehicle just prior to use, and (5) emulsions. These injections may be administered by such routes as intravenous, subcutaneous, intradermal, intramuscular, intraspinal, intracisternal, and intrathecal. The nature of the product will determine the particular route of administration that may be employed. Conversely, the desired route of administration will place requirements on the formulation. For example, suspensions would not be administered directly into the blood stream because of the danger of insoluble particles blocking capillaries. Solutions to be administered subcutaneously would require strict attention to tonicity adjustment, otherwise irritation of the plentiful supply of nerve endings in this anatomical area would give rise to pronounced pain. Injections intended for intraocular, intraspinal, intracisternal, and intrathecal administration require the highest purity standards because of the sensitivity of nerve tissue to irritant and toxic substances.

When compared with other dosage forms, injections possess select advantages. If immediate physiological action is needed from a drug, it usually can be provided by intravenous injection of an aqueous solution. Modification of the formulation or another route of injection can be used to slow the onset and prolong the action of the drug. The therapeutic response of a drug is more readily controlled by parenteral administration since the irregularities of intestinal absorption are circumvented. Also, since the drug normally is administered by a professionally trained person, it may be confidently expected that the dose was actually and accurately administered. Drugs can be administered parenterally when they cannot be given orally because of the unconscious or uncooperative state of the patient, or because of inactivation or lack of absorption in the intestinal tract. Among the disadvantages of this dosage form are the requirement of asepsis at administration, the risk of tissue toxicity from local irritation, the real or psychological pain factor, and the difficulty in correcting an error, should one be made. In the latter situation, unless a direct pharmacological antagonist is immediately available, correction of an error may be impossible. One other disadvantage is that daily or frequent administration poses difficulties, either for the patient to visit a professionally trained person or to learn to inject oneself.

Parenteral Combinations

Since there is a degree of discomfort for the patient with each injection, a physician will frequently seek to reduce this discomfort by combining more than one drug in one injection. This is most commonly encountered when therapeutic agents are added to large-volume solutions of electrolytes or nutrients, commonly called "IV additives," during intravenous administration. Since these preparations would be aqueous solutions, there is a high potential for chemical and physical interactions to occur. The pharmacist is the professional best qualified to cope with these incompatibilities. However, in the past, these have been handled largely at the patient's

bedside by the nurse and physician. Only recently has it been recognized that this professional area is the proper function of a pharmacist and has been so stated by the Joint Commission on Accreditation of Hospitals.[2]

As pharmacists have assumed increasing responsibility in this area, awareness has gradually developed of the widespread occurrence of visible, as well as invisible, physical, chemical, and therapeutic incompatibilities when certain drugs are combined or added to intravenous fluids.

Development of a precipitate or a color change when preparations are combined is an immediate warning that an alteration has occurred. Such a combination should not be administered to the patient because the solid particles may occlude the blood vessels, the therapeutic agent may not be available for absorption, or the drug may have been degraded into toxic substances. Moreover, in other instances changes not visually apparent may have occurred which could be equally or more dangerous to the welfare of the patient.

The almost innumerable potential combinations present a complex situation even for the pharmacist. In an attempt to organize the information available and to aid the pharmacist in making rapid decisions concerning potential problems, a number of charts have been compiled based on the visible changes that may be observed when two or more preparations are combined. The value of such charts is limited by such factors as frequent changes in commercial products, variations in order of mixing or the proportions in the mixture, differences in concentration of each ingredient, or variations in the period of time that the combination is held before use.

As studies have been undertaken and more information has been gained, it has been shown that knowledge of variable factors such as pH and the ionic character of the active constituents aids substantially in understanding and predicting potential incompatibilities. Kinetic studies of reaction rates may be utilized to describe or predict the extent of degradation. Ultimately, a thorough study should be undertaken of each therapeutic agent in combination with other drugs and intravenous fluids, not only of generic but of commercial preparations, from the physical, chemical, and therapeutic aspects. Such studies are being undertaken and some have been reported.

Ideally, no parenteral combination should be administered unless it has been thoroughly studied to determine the effect of the combination on the therapeutic value and the safety of each such combination. However, such an ideal situation does not and may never exist. Therefore, it is the responsibility of the pharmacist to be as familiar as possible with the physical, chemical, and therapeutic aspects of parenteral combinations and to exercise the best possible judgment as to whether or not the specific combination extemporaneously prescribed is suitable for use in a patient. A service to pharmacists has been provided through reviews of this subject area.[3]

General Requirements

An inherent requirement for parenteral preparations is that they be of the very best quality and provide the maximum safety for the patient. Therefore, the pharmacist, being responsible for their preparation, must utilize skills and resourcefulness at the highest level of efficiency to achieve this end. Among the areas requiring dedicated attention are the following:

1. Possession and application of high moral and professional ethics. Even the thought of using inferior techniques or ingredients in a manufacturing process must not be countenanced by the pharmacist. The proper attitude of the person responsible for the preparation of the product is its most vital ingredient.
2. The pharmaceutical training received must be utilized to the fullest measure. The challenges to this knowledge bank will be many and varied.
3. Specialized techniques will be required for the manufacture of sterile preparations, employing them with alertness and sound judgment. These techniques must be subjected to continuous critical review for faults, omissions, and improvements.
4. Ingredients of the highest quality obtainable must be utilized. At times ingredients may require special purification beyond that of the commercial supply. This will normally require that cost factors be given second place in importance.
5. The stability and effectiveness of the product must be established with substantiating data, either from original or published sources. This must take into account process variations and differences in ingredient specifications from plant to plant.
6. A well-defined and controlled program must be established to assure the quality of the product and the repetition of valid production procedures. This involves evaluation of all ingredients, vigilant controls of all steps in the production procedures, and careful evaluation of the finished product.

Injections or other sterile products are rarely prepared in the community pharmacy because of the lack of adequate facilities necessary to prepare a reliable and safe product.

In some hospital pharmacies injections or irrigating fluids are manufactured, but in an increasing number aseptic processing is utilized primarily in the addition of various drugs to intravenous solutions for the individual patient. The vast majority of injectable products used clinically are prepared by the pharmaceutical industry.

General Process

The preparation of a parenteral product may be considered to encompass four general areas as follows: (1) procurement and selection of the components, (2) production facilities and procedures, (3) control of quality, and (4) packaging and labeling. The components of the product to be procured include vehicles, solutes, containers, and closures. The steps constituting production include the maintenance of facilities and equipment, preparing and controlling the environment, cleaning the containers and equipment, preparing the product, filtering the solution, filling containers with the product, sealing the containers, and sterilizing the product. Control of quality includes the evaluation of the components, validation of equipment and processes, determination that the production has been executed within prescribed requirements, and performance of necessary evaluative tests on the finished product. The final area of packaging and labeling includes all steps necessary to identify the finished product and enclose it in such manner that it is safely and properly prepared for sale and delivery to the user. In the following sections, these four areas and appropriate subtopics will be discussed in detail.

Components and Containers

Establishing specifications to insure the quality of each of the components of an injection is of vital importance. These specifications will be coordinated with the requirements of the specific formulation and will not necessarily be identical for a particular component if used in several different formulations.

The most stringent requirements normally will be encountered with aqueous solutions, particularly if the product is to be sterilized at an elevated temperature where reaction rates will be greatly accelerated. Modification of aqueous vehicles to include a glycol, or replacement with a nonaqueous vehicle, will usually reduce reaction rates. Dry preparations pose relatively few reaction problems but may require definitive physical specifications for ingredients that must have certain solution or dispersion characteristics when a vehicle is added.

Containers and closures are herein considered components of the product because they are in prolonged, intimate contact with the product and may release substances or remove ingredients from the product. While not usually considered a part of a container, administration devices are a part of a container system and their effect upon the product must be assessed even though the contact period is usually brief.

Vehicles

Since most liquid injections are quite dilute, the component present in the highest proportion is the vehicle. A vehicle normally has no therapeutic activity and is nontoxic. However, it is of great importance in the formulation since it presents to body tissues the form of the active constituent for absorption. Absorption normally occurs most rapidly and completely when a drug is presented as an aqueous solution. Modification of the vehicle with water-miscible liquids or substitution with water-immiscible liquids normally decreases the rate of absorption. Absorption from a suspension may be affected by such factors as the viscosity of the vehicle, its capacity for wetting the solid particles, the solubility equilibrium produced by the vehicle, and the distribution coefficient between the vehicle and aqueous body systems.

The vehicle of greatest importance for parenteral products is water. Water of suitable quality for parenteral administration must be prepared either by distillation or by reverse osmosis. Only by these means is it possible to separate adequately various liquid, gas and solid contaminating substances from water.

Preparation of Water

In general, a conventional still consists of a boiler (evaporator) containing raw water (distillant), a source of heat to vaporize the water in the evaporator, a headspace above the level of distillant with condensing surfaces for refluxing the vapor and thereby returning nonvolatile impurities to the distillant, a means for eliminating volatile impurities before the hot water vapor is condensed, and a condenser for removing the heat of vaporization, thereby converting the water vapor to a liquid distillate.

It should be apparent that the specific construction features of a still and the process specifications will markedly affect the quality of distillate obtained from a still. Those required for producing high-purity water, such as Water for Injection USP, must be considerably more stringent than those required for Purified Water USP. Among the factors that must be considered are:

1. The quality of the raw water will affect the quality of the distillate. It may be necessary that the raw water be first deionized, treated by reverse osmosis or even distilled to obtain a final distillate of adequate quality.
2. The size of the evaporator will affect the efficiency. The evaporator should be large enough to provide a low vapor velocity, thus reducing entrainment of distillant either as a film on vapor bubbles or as separate droplets.
3. The baffles (condensing surfaces) determine the effectiveness of refluxing. They should be designed to efficiently remove entrainment at optimal vapor velocity, collecting and returning the heavier droplets contaminated with distillant.
4. Redissolving of volatile impurities in the distillate reduces purity. Therefore, volatile impurities should be separated efficiently from the hot water vapor and eliminated by aspirating to the drain or venting to the atmosphere.
5. Contamination of the vapor and distillate from the metal parts of the still can occur. Present standards for high-purity stills are that all parts contacted by the vapor or distillate should be constructed of metal coated with pure tin, of 304 or 316 stainless steel, or of chemically resistant glass.

Design features of a still also influence its efficiency of operation, relative freedom from maintenance problems, or the extent of automatic operation. Stills may be constructed of varying size, rated according to the volume of distillate that

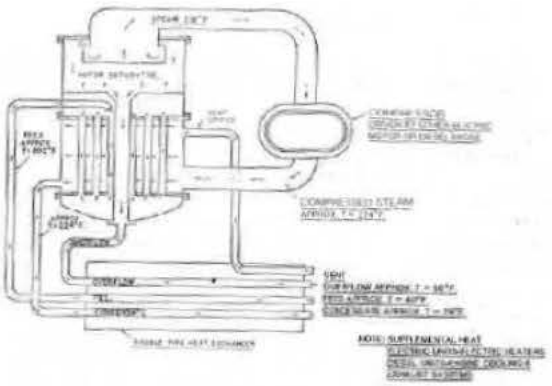

Fig. 84-1. Vapor compression still.

can be produced per hour of operation under optimum conditions. Only stills designed to produce high-purity water may be considered for use in the production of Water for Injection USP.

Conventional commercial stills designed for the production of high-purity water are available from several suppliers.*

Compression Distillation—The vapor compression still, primarily designed for the production of large volumes of high purity distillate with low consumption of energy and water, is illustrated diagrammatically in Fig. 84-1. To start, the feed water is heated in the evaporator to boiling. The vapor produced in the tubes is separated from entrained distillant in the separator and conveyed to a compressor which compresses the vapor and raises its temperature to approximately 224°F. It then flows to the steam chest where it condenses on the outer surfaces of the tubes containing distillant; thereby the vapor is condensed and drawn off as distillate while giving up its heat to bring the distillant in the tubes to the boiling point.

Vapor compression stills are available in capacities from 50 to 2800 gal/hour (*Aqua-Chem, Barnstead, Meco*). In addition to their use by the pharmaceutical industry, they are utilized extensively by military and governmental installations for the production of potable water from sea and brackish well water.

Reverse Osmosis—Reverse osmosis has recently been added by the USP as a method suitable for preparation of Water for Injection. As the name suggests, the natural process of selective permeation of molecules through a semipermeable membrane separating two aqueous solutions of different concentrations is reversed. Pressure, usually between 200 and 400 psig, is applied to overcome osmotic pressure and force pure water to permeate through the membrane. Membranes, usually composed of cellulose esters or polyamides, are selected to provide an efficient rejection of contaminant molecules in raw water. The molecules most difficult to remove are small inorganic molecules such as sodium chloride. Passage through two membranes in series is sometimes utilized to increase the efficiency of removal of these small molecules and to decrease the risk of structural failure of a membrane to remove other contaminants, such as bacteria and pyrogens (for additional information concerning reverse osmosis see under this title in Chapter 77, and Fig. 77-21, in that chapter; also the discussion under *Water* in Chapter 83).

Currently, extensive validation is being undertaken to determine whether, in fact, this method is capable of consistently producing high-purity water of a quality equal or superior to that producible by distillation.

* *Am. Sterilizer, Barnstead, Consolidated, Corning, Finn-Aqua.*

Water for Injection USP

This is a high-purity water intended to be used as a vehicle for injectable preparations. Sterile Water for Injection USP is described in a separate monograph and differs in that it is intended as a packaged and sterilized product.

Storage—Water for Injection should be used immediately. This is usually not possible since the quantity required in production of a product must be accumulated over a period of time. When storage of water is necessary, the conditions for storage and subsequent delivery to the point of use must meet strict standards. Otherwise, recontamination may occur. To prevent such recontamination, Water for Injection should be collected in a scrupulously clean, closed system; in its simplest form, the outlet from the condenser should be connected directly to a closed storage tank. Such a system is shown in Fig. 84-2. To allow for changes in pressure during filling and emptying of the tank, an air vent should be provided through a filter so constructed that microorganisms and chemical vapors will be prevented from entering the tank. The material of construction for the tank and connecting lines should be of chemically resistant glass, of metal parts with a heavy internal coating of pure tin, or of 304 or 316 stainless steel.

Although water vapor should be sterile when condensed, contamination of distillate can occur even with a closed collection system. Therefore, if storage is to be at room temperature, it should not exceed 24 hours. For longer periods, the water must be kept under conditions that will prevent growth of microorganisms and ingress of other contaminants.

If small quantities of Water for Injection are to be collected and stored, clean, sterile bottles made of chemically resistant glass may be used. After filling, the bottles are sealed, sterilized by autoclaving and kept until needed. Intermediate quantities may be collected in closed tanks. In some instances storage is at room temperature with microbial growth controlled by use of an immersion ultraviolet lamp, as shown in Fig. 84-2. Most frequently, however, the water is held at an elevated temperature of about 80°C by means of steam-jacketed tanks, a temperature too high for microbial growth to occur. Where large quantities of water are needed in multiple locations in the plant, for example, in the production of large-volume parenterals, very sophisticated storage and distribution systems have been developed. Such systems encompass large jacketed stainless steel storage tanks, welded and insulated stainless steel pipes to circulate the water to remote points of use, piping systems designed with a continuous loop back to the tank with no "dead legs," stainless steel circulating pumps, and controls to be assured that the temperature of all water in the system remains within established limits.

Fig. 84-2. High-purity still and sealed-water storage system. *A:* Evaporator; *B:* high-purity baffle unit; *C:* condenser; *D:* storage tank with ultraviolet lamp; *E:* control panel (courtesy, Ciba-Geigy).

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

Purity—The USP monographs provide standards of purity for Water for Injection and for Sterile Water for Injection. A few of these standards require comment.

Sterile Water for Injection must meet the requirements of the USP Sterility Test, but Water for Injection need not since it is to be used in a product which will be sterilized. Both must meet the requirements of the USP Pyrogen Test (page 530).

The limits for total solids varies in the two monographs. The larger the surface area of the glass container per unit volume of water, the greater the amount of glass constituents that may be leached into the water, particularly during the elevated temperature of steam sterilization.

The Water for Injection monograph stipulates a maximum of 10 ppm of total solids. This is generally considered to be much too high to assure a quality of water that would permit stable formulation of many drugs. A relatively few metallic ions present can often render a formulation unstable. Therefore, it is common practice to set a limit of 0.1 ppm or less of ionic contaminants expressed as sodium chloride.

Ionic contaminant level is not the same as total solids, the former being a measurement of only the ionic content, while the latter is a measurement of undissociated constituents as well. The ionic content of water can be measured very easily by means of a conductivity meter, and is frequently used as an indication of the purity. The results are expressed in one of three terms; namely, as sodium chloride ions, as resistance in ohms or megohms, or as conductance in micromhos. Ohms and mhos have a reciprocal relationship to each other, but they are related to ppm sodium chloride by an experimentally determined curve. To give one point of comparison, 0.1 ppm sodium chloride is equal to approximately 1.01 megohms and 0.99 micromhos. It should be mentioned that conductivity measurements give no direct indication of pyrogen content of water since pyrogens are undissociated organic compounds.

Water for Injection may not contain an added substance. Sterile Water for Injection may contain a bacteriostatic agent when in containers of 30-ml capacity or smaller. This restriction is designed to prevent the administration of a large quantity of a bacteriostatic agent that probably would be toxic in the accumulated amount of a large volume of solution, even though the concentration was low.

Types of Vehicles

Aqueous Vehicles—Certain aqueous vehicles are recognized officially because of their valid use in parenteral formulations. Often they are used as isotonic vehicles to which

...ge may be added at the time of administration. The ad-...sional osmotic effect of the drug may not be enough to ...duce any discomfort when administered. These vehicles ...clude: Sodium Chloride Injection, Ringer's Injection, ...extrose Injection, Dextrose and Sodium Chloride Injection, ...d Lactated Ringer's Injection.

Water-Miscible Vehicles—A number of solvents that are ...scible with water have been used as a portion of the vehicle ...the formulation of parenterals. These solvents are used ...marily to effect solubility of certain drugs and to reduce ...drolysis. The most important solvents in this group are ...hyl alcohol, polyethylene glycol of the liquid series, and ...opylene glycol. Ethyl alcohol is used particularly in the ...paration of solutions of cardiac glycosides and the glycols ...solutions of barbiturates, certain alkaloids, and certain ...tibiotics. Such preparations are usually given intramus-...larly.

These solvents, as well as nonaqueous vehicles, have been ...viewed by Spiegel and Noseworthy.[4]

Nonaqueous Vehicles—The most important group of ...naqueous vehicles are the fixed oils. The USP provides ...ecifications for such vehicles. A few of these requirements ...ed to be discussed. The fixed oils must be of vegetable ...igin in order that they may be metabolized, will be liquid at ...om temperature, and will not become rancid rapidly. The ...st specification eliminates oils of mineral origin and the ...ter two, those of animal origin. To be liquid at room tem-...rature, a fixed oil must contain esters of unsaturated fatty ...ids. However, excessive unsaturation will produce tissue ...itation. Therefore, the USP stipulates upper and lower ...mits to the iodine value for the oil. The development of ...cidity must be prevented by the inclusion of antioxidants ...ch as tocopherol, a natural constituent of many fixed oils. ...e USP also prescribes an upper limit for free fatty acids in ...der to minimize the degree of tissue irritation. Other ...ecifications are included primarily to detect adulteration. ...e oils most commonly used are corn oil, cottonseed oil, ...anut oil, and sesame oil. It should be noted that the official ...nographs for some of these oils provide for greater latitude ...an the specifications required for the use of the oil as a ve-...icle for a parenteral. Therefore, parenteral vehicle oils must ...e select oils or specially purified to meet the more stringent ...quirements. Fixed oils are used particularly as vehicles for ...rtain hormone preparations. These and other nonaqueous ...hicles, such as ethyl oleate, isopropyl myristate and benzyl ...nzoate, may be used provided they are safe in the volume ...ministered and do not interfere with the therapeutic effi-...acy of the preparation or with its response to prescribed as-...ays and tests. The label also must state the name of the ...hicle so that the user may beware in case of known sensi-...ivity or other reactions to it.

Solutes

The requirements for purity of the medicinal compound ...ed in an injection often make it necessary to undertake ...pecial purification of the usual chemical grade available. In ...few instances, a special parenteral grade of a compound is ...ailable, for example, ascorbic acid freed from all traces of ...opper contamination. As a general rule, the best chemical ...ade obtainable should be used. It should be obvious that ...few ppm of ionic contaminants in Water for Injection may ...use stability problems, a similar level of contamination in ...e solute itself may, likewise, cause stability problems. ...etallic catalysis of chemical reactions is one of the most ...portant problems.

Other factors to be considered with respect to the quality ...solutes include: the level of microbial and pyrogenic con-...mination, solubility characteristics as determined by the chemical or physical form of the compound, and freedom from gross dirt.

Added Substances—The USP includes in this category all substances added to a preparation to improve or safeguard the quality of the product. An added substance may effect solubility, as does sodium benzoate in Caffeine and Sodium Benzoate Injection, or provide patient comfort, as do substances added to make a solution isotonic. They may enhance the chemical stability of a solution, as do antioxidants, inert gases, chelating agents, and buffers, or they may preserve a preparation against the growth of microorganisms. The term "preservative" is sometimes applied only to those substances which prevent the growth of microorganisms in a preparation. However, such limited use is inappropriate, being better used for all substances that act to retard or prevent the chemical, physical, or biological degradation of a preparation.

While added substances may prevent a certain reaction from taking place, they may induce others. Not only may visible incompatibilities occur, but hydrolysis, complexation, oxidation, and other invisible reactions may decompose or otherwise inactivate the therapeutic agent. Therefore, added substances must be selected with due consideration and investigation of the effect of the substance on the total formulation.

Antimicrobial Agents—The USP states that antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to preparations contained in multiple-dose containers. They must be present in adequate concentration at the time of use to prevent the multiplication of microorganisms inadvertently introduced into the preparation while withdrawing a portion of the contents with a hypodermic needle and syringe. Among the compounds most frequently employed, with the concentration limit prescribed by the USP, are: phenylmercuric nitrate and thimerosal 0.01%, benzethonium chloride and benzalkonium chloride 0.01%, phenol or cresol 0.5%, and chlorobutanol 0.5%. The above limit is rarely used for phenylmercuric nitrate, being most frequently employed in a concentration of 0.002%. Methyl *p*-hydroxybenzoate 0.18% and propyl *p*-hydroxybenzoate 0.02% in combination, and benzyl alcohol 2% are also frequently used. In oleaginous preparations, no antibacterial agent commonly employed appears to be effective. However, it has been reported that hexylresorcinol 0.5% and phenylmercuric benzoate 0.1% are moderately bactericidal.

Antimicrobial agents must be studied with respect to compatibility with all other components of the formula. In addition, their activity must be evaluated in the total formula. It is not uncommon to find that a particular agent will be effective in one formulation but ineffective in another. This may be due to the effect of various componenis of the formula on the biological activity or availability of the compound; for example, the binding and inactivation of esters of *p*-hydroxybenzoic acid by macromolecules such as Polysorbate 80 or the reduction of phenylmercuric nitrate by sulfide residues in rubber closures. A physical reaction encountered is that bacteriostatic agents are sometimes removed from solution by rubber closures. These facts establish the principle that antimicrobial agents must be evaluated for their activity in the total formula to assure their activity when needed, normally at the time of use.

Buffers—Buffers are used primarily to stabilize a solution against the chemical degradation that would occur if the pH changed appreciably. Buffer systems employed should normally have as low a buffer capacity as feasible in order not to disturb significantly the body buffer systems when injected. In addition, the buffer range and the effect of the buffer on the activity of the product must be evaluated carefully. The acid salts most frequently employed as buffers are citrates, acetates, and phosphates.

Antioxidants—Antioxidants are frequently required to

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