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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. This term should not be so limited but should include 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%¹² and phenylmercuric benzoate 0.1%¹³ 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 components 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 80¹⁴ 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.¹⁵ 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.¹⁶ The acid salts most frequently employed as buffers are citrates, acetates, and phosphates.

Antioxidants—Antioxidants are frequently required to preserve products because of the ease with which many drugs are oxidized. Sodium bisulfite 0.1% is most frequently used. The use of sulfites as antioxidants has been reviewed by Schroeter.¹⁷ Acetone sodium bisulfite, sodium formaldehyde sulfoxylate, and thiourea are also sometimes used. The sodium salt of ethylenediaminetetraacetic acid has been found to enhance the activity of antioxidants in some cases, apparently by chelating metallic ions that would otherwise catalyze the oxidation reaction.

Pyrogens

Pyrogens are not predetermined components of parenteral preparations, but they may be present as unwanted contaminants. If they are present, the product may have to be discarded since it is very difficult to remove them without adversely affecting the product. The only safe and proper way to manage pyrogen contamination is to keep it out of the product. Presence of pyrogens, therefore, is indicative of an improperly prepared product.

Pyrogens cause a febrile reaction in human beings. Other symptoms include chills, pains in back and legs, and malaise. While pyrogens are rarely fatal, they produce significant discomfort for the patient. On the other hand, pyrogens have been shown to induce a general nonspecific resistance to microorganisms¹⁸ and, on this basis, have been used therapeutically.

Pyrogens are products of the growth of microorganisms. The most potent pyrogenic substances are produced by Gram-negative bacteria, but Gram-positive bacteria and fungi also produce pyrogenic substances. The potency varies with the species producing it. Chemically, pyrogenic material has been shown to be lipid in nature, sometimes containing phosphorus, and is attached to a polysaccharide or a protein or both. When so complexed, it is a weak antigen.¹⁹ A tolerance to pyrogens will develop in man and susceptible animals.

Pyrogens can be destroyed by heating at high temperatures. The recommended procedure for depyrogenation of glassware and equipment is heating at a temperature of 250°C for 45 min. It has been reported that 650°C for 1 min or 150°C for 4 hr will likewise destroy pyrogens. The usual autoclaving cycle will not do so. Although heating with strong alkali solutions will destroy pyrogens, the usual washing cycles, including detergent treatment, cannot be relied on to completely eliminate pyrogens from glassware. Heating with oxidizing agents, such as hydrogen peroxide, will destroy pyrogens. It has been reported that anion exchange resins will adsorb pyrogens from water.²⁰ However, the most reliable method for the elimination of these substances from water is distillation. Pyrogenic substances are not volatile and thus will remain in the distillate. The only method available for consideration for the removal of pyrogenic substances from solutions is filtration through asbestos filters. This method is quite limited, however, since asbestos fibers remove the pyrogen by adsorption and the same

physical phenomenon of adsorption of the constituents as well. In action is adsorption, saturated, the remaining through the filter. In pharmaceuticals, sometimes by dilute acid, or more often.

Sources of Pyrogens—Pyrogens may be introduced by any means, including microorganisms or the products of their action. Perhaps the greatest potential source of pyrogenic materials is the water used in distillation will provide, particular, but also to Reusing containers is a dangerous and a contamination. Residues of become bacterial cultures environment. Such with pyrogens. Even proposed to the atmosphere for microorganisms to destroy pyrogens, they long periods of time. by dry heat depyrogenation equipment suitable for use.

The solute also may be may be crystallized or liquids containing pyrogen process pyrogens may be layers. In such cases to recrystallization, precipitate to eliminate the pyrogens.

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Containers

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physical phenomenon may act to remove chemical constituents as well. In addition, since the mechanism of action is adsorption, once the fibers of asbestos are saturated, the remaining pyrogenic material will pass through the filter. In-process destruction of pyrogens in pharmaceutical preparations may be accomplished sometimes by careful heating with dilute alkali, dilute acid, or mild oxidizing agents.

Sources of Pyrogens.—Pyrogens may enter a preparation by any means that will introduce living or dead microorganisms or the products of their growth. Perhaps the greatest potential source of such contamination is the water used in products. However, proper distillation will provide pyrogen-free water. Another potential source of contamination is equipment. Pyrogenic materials adhere strongly to glass surfaces in particular, but also to the surface of other equipment. Reusing containers, as is often practiced in hospitals, is a dangerous and a significant source of pyrogenic contamination. Residues of solutions in used bottles often become bacterial cultures from septic patients or the environment. Such bottles will be heavily contaminated with pyrogens. Even washed bottles left wet and exposed to the atmosphere may contain sufficient nutrients for microorganisms to grow. Since drying does not destroy pyrogens, they may remain in equipment for long periods of time. Adequate washing accompanied by dry heat depyrogenation will render contaminated equipment suitable for use.

The solute also may be a source of pyrogens. Solute may be crystallized or precipitated from aqueous liquids containing pyrogenic contamination. In the process pyrogens may be trapped within the particle layers. In such cases the solute must be purified by recrystallization, precipitate washing, or other means to eliminate the pyrogens.

The manufacturing process also must be carried out with great care and as rapidly as possible to minimize the risk of microbial contamination. Preferably, no more product should be prepared than can be completely processed within one working day, including sterilization. By far the best procedure is to prevent the introduction of pyrogens rather than to attempt to remove them, a task which well may be virtually impossible.

Containers

Containers are an integral part of the formulation of an injection and may be considered a component, for there is no container that is totally insoluble or does not in some way affect the liquid it contains, particularly if the liquid is aqueous. Therefore, the selection of a container for a particular injection must be based on a consideration of the composition of the container, as well as of the solution, and the treatment to which it will be subjected.

Plastic

Thermoplastic polymers are being considered and a few are being used as the container material for selected sterile products, particularly ophthalmic solutions. However, it is generally conceded that thermoplastic compounds have not been studied sufficiently to prove their nonreactivity, or to establish a definite reactivity pattern to define their safety for the packaging of injections.

Autian has thoroughly reviewed the use of plastic materials in pharmaceutical practice.²⁰ He and others have shown that extractives are obtained from thermo-

plastic materials and, with certain polymers, sorption (absorption and or adsorption) of drug molecules or ions may occur.²¹ The latter is observed in particular with polyamides such as nylon.

The lack of sufficiently high standards in the manufacture of plastics and the fact that the lower-cost polymers cannot be sterilized by thermal methods are also deterrents to their use. These and other problems are receiving concentrated attention. It seems reasonable to expect that eventually thermoplastic materials will be used for containers of selected injectable preparations. At present, however, the use of these materials is limited largely to components of disposable injection units where contact with the solution is brief.

For ophthalmic preparations the flexibility of the low-density polyethylene polymer provides a significant use characteristic, making it possible to squeeze out and administer one or more drops of the preparation. Therefore, several ophthalmic formulations have been adapted to plastic containers.²²

When thermoplastic containers are used for sterile solutions, the empty container must be sterilized by means of ethylene oxide or ionized radiations and filled aseptically with a sterile solution. Considerable attention is being given to the small amount of ethylene oxide residue in plastics after sterilization and its potential toxic effects.²³ See Chapter 91 on *Plastics*.

Glass

Glass is employed as the container material of choice for most injections. It is composed principally of silicon dioxide with varying amounts of other oxides such as those of sodium, potassium, calcium, magnesium, aluminum, boron, and iron. The basic structural network of glass is formed by the silicon oxide tetrahedron.²⁴ Boric oxide will enter into this structure, but most of the other oxides do not. The latter are only loosely bound, are present in the network interstices, and are relatively free to migrate. These migratory oxides may be leached into a solution in contact with the glass, particularly during the increased reactivity of thermal sterilization. The oxides thus dissolved may hydrolyze to raise the pH of the solution, catalyze reactions, or enter into reactions. In a manner as yet uncertain, some glass compounds will be attacked by solutions and, in time, dislodge glass flakes into the solution. Disturbing reactions such as these can, however, be minimized by the proper selection of the glass composition.

Types.—The USP has aided in this selection by providing a classification of glass; namely, Type I, a borosilicate glass; Type II, a soda-lime treated glass; Type III, a soda-lime glass; and NP, a soda-lime glass not suitable for containers for parenterals. Type I glass is composed principally of silicon dioxide and boric oxide, with low levels of the nonnetwork-forming oxides. It is a chemically resistant glass (low leachability) also having a low thermal coefficient of expansion. Type II and Type III glass compounds are composed of relatively high proportions of sodium oxide and calcium oxide. This makes the glass chemically less resistant. Both of these types melt at a lower temperature, are easier to mold into various shapes, and have a higher thermal coefficient of expansion than Type I. While there is no one standard formulation for glass among manufacturers of these USP type categories, Type II glass usually has a lower concentration of the migratory