Remington's Pharmaceutical Sciences

Eighteenth Edition

NPS EX. 2054

Library of Congress Catalog Card No. 60-53334

ISBN 0-912734-04-3

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Printed in the United States of America by the Mack Printing Company, Easton, Pennsylvania

glass or a coating of pure tin. Such systems are very carefully designed and constructed and often constitute the most costly installation within the plant.

When the water cannot be used at 80°, 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 buildup on the filters and the consequential release of pyrogenic substances.

Purity—The USP monographs provide standards of purity for WFI and SWFI. A few of these standards require comment.

SWFI must meet the requirements of the USP Sterility Test, but WFI 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 492).

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 WFI 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 permits the stable formulation of many drugs. A relatively few metallic ions present often can 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 is a measure of only the ionic content, while the latter is a measure of the undissociated constituents as well. The ionic content of water can be measured very easily by means of a conductivity meter which frequently is used as an indicator of the purity. The results are expressed in one of three terms: 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 since pyrogens are undissociated organic compounds.

WFI may not contain an added substance. SWFI may contain a bacteriostatic agent when in containers of 30-mL capacity or less. 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 parenterals. Often they are used as isotonic vehicles to which a drug may be added at the time of administration. The additional osmotic effect of the drug may not be enough to produce any discomfort when administered. These vehicles include Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection and Lactated Ringer's Injection.

Water-Miscible Vehicles—A number of solvents that are miscible with water have been used as a portion of the vehicle in the formulation of parenterals. These solvents are used primarily to effect the solubility of certain drugs and to reduce hydrolysis. The most important solvents in this group are ethyl alcohol, polyethylene glycol of the liquid larly in the preparation of solutions of cardiac glycosides and the glycols in solutions of barbiturates, certain alkaloids and certain antibiotics. Such preparations usually are given intramuscularly.

These solvents, as well as nonaqueous vehicles, have been reviewed by Spiegel and Noseworthy.[6]

Nonaqueous Vehicles—The most important group of nonaqueous vehicles are the fixed oils. The USP provides specifications for such vehicles, indicating that the fixed oils must be of vegetable origin so that they will be metabolized, will be liquid at room temperature and will not become rancid readily. The USP also specifies limits for the degree of unsaturation and free fatty acid content. The oils most commonly used are corn oil, cottonseed oil, peanut oil and sesame oil. It should be noted that the official monographs for some of these oils provide for greater latitude than the specifications required for the use of the oil as a vehicle for a parenteral.

Fixed oils are used particularly as vehicles for certain hormone preparations. These and other nonaqueous vehicles, such as ethyl oleate, isopropyl myristate, and benzyl benzoate, may be used provided they are safe in the volume administered and do not interfere with the therapeutic efficacy of the preparation or with its response to prescribed assays and tests. The label also must state the name of the vehicle so that the user may beware in case of known sensitivity or other reactions to it.

Solutes

The requirements for purity of the medicinal compound used in an injection often make it necessary to undertake special purification of the usual chemical grade available. In a few instances, a special parenteral grade of a compound is available, for example, ascorbic acid freed from all traces of copper contamination. As a general rule, the best chemical grade obtainable should be used. It should be obvious that if a few ppm of ionic contaminants in WFI may cause stability problems, a similar level of contamination in the solute itself may, likewise, cause stability problems. Metallic catalysis of chemical reactions is one which is encountered frequently.

Other factors to be considered with respect to the quality of solutes include the level of microbial and pyrogenic contamination, 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 its quality. An added substance may

Effect solubility, as does sodium benzoate in Caffeine and Sodium Benzoate Injection.

Provide patient comfort, as do substances added to make a solution isotonic.

Enhance the chemical stability of a solution, as do antioxidants, inert gases, chelating agents and buffers.

Preserve a preparation against the growth of microorganisms. The term "preservative" sometimes is 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 their effect on the total formula-

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%.
Chlorobutanol 0.5%.

The above limit is rarely used for phenylmercuric nitrate, most frequently being employed in a concentration of 0.002%. Methyl *p*-hydroxybenzoate 0.18% and propyl *p*-hydroxybenzoate 0.02% in combination, and benzyl alcohol 2% also are used frequently. 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 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 80 or the reduction of phenylmercuric nitrate by sulfide residues in rubber closures. A physical reaction encountered is that bacteriostatic agents sometimes are removed from solution by rubber closures.

Buffers are used primarily to stabilize a solution against the chemical degradation that might occur if the pH changes 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 effect on the activity of the product must be evaluated carefully. The acid salts most frequently employed as buffers are citrates, acetates and phosphates.

Antioxidants are required frequently to preserve products because of the ease with which many drugs are oxidized. Sodium bisulfite 0.1% is used most frequently. The use of sulfites has been reviewed by Schroeter[7]. Acetone sodium bisulfite, sodium formaldehyde sulfoxylate and thiourea also are used sometimes. 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 may be anticipated contaminants in crude drugs, such as antibiotics produced by fermentation, or they may be present as unexpected and unwanted contaminants in a finished product as a result of inadvertent contamination during processing. The former must be eliminated during the purification steps of the drug. The latter can be eliminated best by preventing their introduction or development during the process. In general, the presence of pyrogens in a finished product is indicative of preparation under inadequately controlled clean conditions.

symptoms include chills, pains in the 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 microorganisms and, on this basis, have been used therapeutically. Recent findings indicate that bacterial pyrogens, when introduced into the body, stimulate the production of an endogenous (leukocytic) pyrogen that causes the familiar physiological responses.

Pyrogens are products of the growth of microorganisms. The most potent pyrogenic substances are produced by Gram-negative bacteria (endotoxins), but Gram-positive bacteria and fungi also produce pyrogenic substances of lesser potency. Chemically endotoxins have been shown to be a phospholipid attached to a polysaccharide carrier.

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° for 45 min. It has been reported that 650° for 1 min or 180° for 4 hr likewise will destroy pyrogens. The usual autoclaving cycle will not do so. Heating with strong alkali or oxidizing solutions will destroy pyrogens. It has been claimed that thorough washing with detergent will render glassware pyrogen-free if protected during manufacture and storage from heavy pyrogenic contamination. Likewise, plastic containers and devices must be protected from pyrogenic contamination during manufacture and storage since known ways to destroy pyrogens will affect the plastic adversely. It has been reported that anion-exchange resins will adsorb pyrogens from water and reverse osmosis will eliminate them. However, the most reliable method for their elimination from water is distillation.

A method that has been used for the removal of pyrogens from solutions is adsorption on adsorptive agents. However, since the adsorption phenomenon also may cause selective removal of chemical substances from the solution and the filtrate may be contaminated with the agent, this method has limited application. Other in-process methods for their destruction or elimination include selective extraction procedures and careful heating with dilute alkali, dilute acid or mild oxidizing agents. In each instance, the method must be studied thoroughly to be sure it will not have an adverse effect on the constituents of the product. New developments in ultrafiltration now make possible pyrogen separation on a molecular weight basis and the process of tangential flow increasingly is making large-scale processing a reality.

Sources of Pyrogens—Pyrogens may enter a preparation by any means that will introduce living or dead microorganisms. Perhaps the greatest potential source of such contamination is the water used in processing. Although proper distillation will provide pyrogen-free water, storage conditions must be such that microorganisms are not introduced and subsequent growth is prevented.

Another potential source of contamination is equipment. Pyrogenic materials adhere strongly to glass and other surfaces. Residues of solutions in used equipment often become bacterial cultures with subsequent pyrogenic contamination. Even washed equipment left wet and exposed to the atmosphere may contain sufficient nutrients for microorganism growth. Since drying does not destroy pyrogens, they may remain in equipment for long periods. Adequate washing greatly will reduce and subsequent dry-heat treatment will render contaminated equipment suitable for use.

The solute may be a source of pyrogens. Solutes 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

The manufacturing process 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 processed completely within one working day, including sterilization.

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.

Table I provides a generalized comparison of the three compatibility properties—leaching, permeation and adsorption—of container materials most likely to be involved in the formulation of aqueous parenterals. Further, the integrity of the container/closure system depends upon a series of characteristics which determine the effectiveness with which it achieves its role. These considerations have been reviewed by Morton.[8]

Plastic

Thermoplastic polymers have been established as packaging materials for sterile preparations such as large-volume parenterals, ophthalmic solutions and, increasingly, for small-volume parenterals. For such use to be acceptable a thorough understanding of the characteristics, potential problems and advantages for use must be developed. One thorough review of these factors relative to pharmaceuticals has been prepared by Autian.[9] He stated that three principal problem areas exist in using these materials; namely,

1. Permeation of vapors and other molecules in either direction through the wall of the plastic container.
2. Leaching of constituents from the plastic into the product.
3. Sorption (absorption and/or adsorption) of drug molecules or ions on the plastic material.

Permeation, the most extensive problem, may be troublesome by permitting volatile constituents or selected drug molecules to migrate through the wall of the container to the outside and thereby be lost. The reverse of this also may occur by which oxygen or other molecules may permeate to the inside of the container and cause oxidative or other degradation of susceptible constituents. Leaching may be a problem when certain constituents of the plastic material migrate into the product. This potential problem often may be controlled by careful formulation of the polymer mixture with a minimum of additives. Sorption seems to be a limited problem in the packaging of parenterals and is found most commonly in association with polyamides such as nylon.

One of the principal advantages of using plastic packaging materials is that they are not breakable as is glass; also, there is a substantial weight reduction. The flexibility of the low-density polyethylene polymer, for ophthalmic preparations, makes it possible to squeeze the side wall of the container and discharge one or more drops without introducing contamination into the remainder of the product. The flexible bags of polyvinyl chloride or select polyolefins, currently in use for large-volume intravenous fluids, have the added advantage that no air interchange is required; the flexible wall simply collapses as the solution flows out of the bag.

Most plastic materials have the disadvantage that they are not as clear as glass and, therefore, inspection of the contents is impeded. In addition, many of these materials will soften or melt under the conditions of thermal sterilization. However, careful selection of the plastic used and control of the autoclave cycle has made thermal sterilization of some products possible, large-volume parenterals in particular. Eth-

Table I—Comparative Compatibility Properties of Container Materials

	Leaching		Permeation		Adsorption (selective)
	Extent[a]	Potential Leachables	Extent[a]	Potential Agents	Extent[a]
Glass					
Borosilicate	1	Alkaline earth and heavy metal oxides	0	N/A	2
Soda-lime	5	Alkaline earth and heavy metal oxides	0	N/A	2
Plastic Polymers					
Polyethylene					
Low density	2	Plasticizers, antioxidants	5	Gases, water vapor, other molecules	2
High density	1	Antioxidants	3	Gases, water vapor, other molecules	2
PVC	4	HCl, especially plasticizers, antioxidants, other stabilizers	5	Gases, especially water vapor and other molecules	2
Polyolefins	2	Antioxidants	2	Gases, water vapor, other molecules	2
Polypropylene	2	Antioxidants, lubricants	4	Gases, water vapor	1
Rubber Polymers					
Natural and related synthetic	5	Heavy metal salts, lubricants, reducing agents	3	Gases, water vapor	3
Butyl	3	Heavy metal salts, lubricants, reducing agents	1	Gases, water vapor	2
Silicone	2	Minimal	5	Gases, water vapor	1