6 Formulation components (solvents and solutes)

Sterile formulations, by necessity, must be as simple as possible. Safety considerations limit the number and choices of additives to use in formulations besides the active and, if stability is sufficient, a vehicle. The ideal parenteral formulation would contain the active ingredient and water and nothing else. In reality, the author is unaware of any sterile formulation that contains only active ingredient in a ready-to-use 2-year stable aqueous solution. Formulations that contain only the active ingredient typically are freeze-dried with the therapeutic dose of the active sufficient to produce an elegant cake that is constituted with a diluent vehicle prior to administration. Most sterile formulations contain at least one additive besides the active ingredient and a majority of formulations contain two or more additives. This chapter will describe the types and purposes of additives (solutes) and vehicles used in sterile formulations. References 1 through 8 provide reviews and listings of approved additives in marketed sterile product formulations including a valuable Food and Drug Administration Web site.

Care must be taken in selecting active pharmaceutical ingredients and excipients to ensure that their quality is suitable for parenteral administration. A low microbial level will enhance the effectiveness of either the aseptic or terminal sterilization process used for the drug product. Likewise, nonpyrogenic ingredients enhance the nonpyrogenicity of the finished injectable product. It is now a common GMP procedure to establish microbial and endotoxin limits on active pharmaceutical ingredients and most excipients. Chemical impurities should be virtually nonexistent in active pharmaceutical ingredients for parenterals, because impurities are not likely to be removed by the processing of the product. Depending on the chemical involved, even trace residues may be harmful to the patient or cause stability problems in the product. Therefore, manufacturers should use the best grade of chemicals obtainable and use its analytical profile to determine that each lot of chemical used in the formulation meets the required specifications.

Reputable chemical manufacturers accept the stringent quality requirements for sterile products and, accordingly, apply good manufacturing practices to their chemical manufacturing. Examples of critical bulk manufacturing precautions include the following:

- Using dedicated equipment or properly validated cleaning to prevent cross-contamination and transfer of impurities
- Using WFI for rinsing equipment
- Using closed systems wherever possible for bulk manufacturing steps not followed by further purification
- Adhering to specified endotoxin and bioburden testing limits for the substance

VEHICLES (SOLVENTS)

The solvent in injectable formulations typically is the largest component. Of course, the preferred solvent or vehicle is water for injection (WFI). For drugs that are not sufficiently soluble in water, water-miscible organic co-solvents may be used with limitations on the acceptable amounts from a safety viewpoint. For drugs completely insoluble in water and not required to be injected intravenously, oily (oleaginous) solvent systems of vegetable origin may be used.

Water

Since most liquid injections are quite dilute, the component present in the highest proportion is the vehicle. The vehicle of greatest importance for sterile products is water. Water of suitable quality for compounding and rinsing product contact surfaces may be prepared either by distillation or by reverse osmosis, to meet United States Pharmacopeia (USP) specifications for WFI. Preparation and quality standards of WFI and description of other types of compendial water are covered in chapter 15.