2 Characteristics of sterile dosage forms

Sterile dosage forms are unique pharmaceutical dosage forms largely because of their seven primary characteristics that will be featured in this chapter (Table 2-1). Also, specific characteristics of sterile dosage forms that are discussed in the United States Pharmacopeia (USP), primarily general chapter <1> will be featured.

SEVEN PRIMARY CHARACTERISTICS OF STERILE DOSAGE FORMS

Safety

Sterile dosage forms, with some exceptions, are injected directly into the body and, thus, avoid the body's natural barriers for invasion of entities that could harm the body. Therefore, any component of an injectable product must be proven safe at the quantitative level it is injected. Certainly, any substance, if injected in large quantities, can be unsafe.

With respect to safety, formulation of sterile dosage forms can be both easier and more difficult compared to formulation of nonsterile dosage forms. This is because of safety considerations when selecting additives to combine with the active ingredient to overcome one or more problems related to drug solubility, stability, tonicity, and controlled or sustained delivery. If any of these problems exist with a nonsterile dosage form, the formulation scientist has a plethora of choice with respect to additives safe to use for administration other than by injection. However, for overcoming these problems with sterile dosage forms, the requirement for safety prohibits the use of many additives that could be effective.

Under the Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act, most pharmaceutical preparations are required to be tested for safety in animals. Because it is entirely possible for a parenteral product to pass the routine sterility test, pyrogen and/or endotoxin test, as well as the chemical analyses, and still cause unfavorable reactions when injected, a safety test in animals is essential, particularly for biological products, to provide additional assurance that the product does not have unexpected toxic properties.

The FDA has published guidance for safety evaluation of pharmaceutical ingredients (1) that is periodically updated. Many general chapters of the USP also provide specific instructions for safety evaluation of pharmaceutical excipients. Also, there exists the International Pharmaceutical Excipients Council (IPEC), a federation of three independent regional industry associations headquartered in the United States (IPEC-Americas), Europe (IPEC Europe), and Japan (JPEC). The following is a quote from their Web site:

- Each association focuses its attention on the applicable law, regulations, science, and business practices of its region. The three associations work together on excipient safety and public health issues, in connection with international trade matters, and to achieve harmonization of regulatory standards and pharmacopoeial monographs.
- Over 200 national and multinational excipient makers, producers, and companies, which use excipients in finished drug dosage forms are members of one or more of the three IPEC regional units. Over 50 U.S. companies are IPEC members. (2)

Sterility

Obviously, sterility is what defines/differentiates a sterile product. Achieving and maintaining sterility are among the greatest challenges facing manufacturers of these dosage forms. There are many factors that contribute to achieving and maintaining sterility and these will be covered in more detail in chapters 13, 17, 18, 21, and 23. Suffice to state at this point that the characteristic of sterility is achieved via valid sterilization procedures for all components during manufacturing of the product, valid procedure for sterile (better term is aseptic) filtration, design and maintenance of clean rooms meeting all requirements for preparing sterile products (discussed