15 Water and air quality in sterile manufacturing facilities

This chapter focuses exclusively on the basic highlights of water systems and air handling systems employed in the production of sterile products and the quality requirements of each system. Like almost all other chapters, general references are provided at the end of this chapter for recommended reading to the reader who desires broader and more in-depth coverage of these topics.

WATER

Water is the most commonly used component in sterile product formulations. Like everything else in nature, water has many applications in the sterile product manufacturing industry:

- Solvent in formulations
- Cleaning of components and equipment
- Solvent in cleaning, sanitizing, disinfectant solutions
- Source of clean steam
- Source of cooling water for freeze-dryer compressors
- Source of water for chillers, necessary for
  - Air compressors
  - Rubber closure processors
  - Cooling of depyrogenation tunnels

Water of suitable quality for compounding and rinsing product contact surfaces may be prepared either by distillation or by reverse osmosis (RO) to meet United States Pharmacopeia (USP) and other compendial specifications for Water for Injection (WFI). In active pharmaceutical ingredient manufacturing and in some foreign companies, ultrafiltration (UF) is employed to minimize endotoxins in those drug substances administered parenterally. For some ophthalmic products, such as the ophthalmic irrigating solutions, and some inhalation products, such as Sterile Water for Inhalation, where there are pyrogen specifications, it is expected that WFI be used in their formulation.

Table 15-1 provides a summary of the types of water found in USP monographs. Similar qualities and titles of water exist in other compendia, although this author did not attempt to compare compendial water monographs. Only by distillation or RO is it possible to separate adequately various liquid-, gas-, and solid-contaminating substances from water. With the possible exception of freeze-drying, there is no unit operation more important and none more costly to install and operate than the one for the preparation of WFI.

Preparation

The sources of water used in sterile product manufacture originate from any one of several natural sources—lakes, streams, wells, reservoirs, city water systems, and so forth. Such water, of course, is totally unsuitable for injecting into people and animals because of all the contamination with natural suspended mineral and organic substances, dissolved mineral salts, colloidal material, viable bacteria, bacterial endotoxins, industrial or agricultural chemicals, and other particulate matter. The source water must be pretreated by a combination of the following treatments: chemical softening, filtration, deionization, carbon adsorption, and/or RO purification (Fig. 15-1).

WFI can be prepared by distillation or by membrane technologies (RO or UF). The European Pharmacopeia (EP) only permits distillation as the process for producing WFI. The USP and Japanese Pharmacopeia (JP) allow application of all these technologies.

Distillation is a process of converting water from a liquid to its gaseous form (steam). Since steam is pure gaseous water, all other contaminants in the feed water are removed. Potential