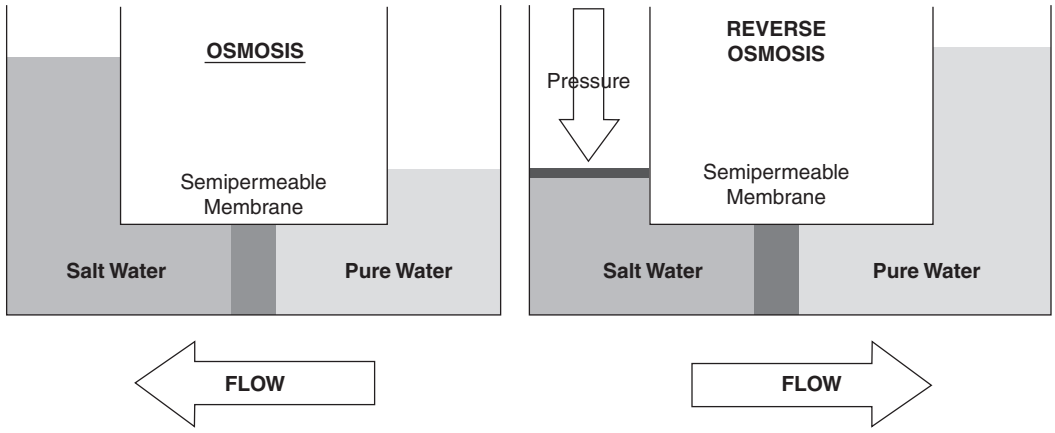

Figure 15-3 Schematic of reverse osmosis compared to osmosis. *Source:* Courtesy of Vertex Hydropore.

pressure instruments (osmometers that typically measure freezing point depression of the solution). In reverse osmosis, pressure, usually between 200 and 400 psig, is applied to overcome natural osmotic flow and force pure water to permeate through the membrane (Fig. 15-3). Membranes, usually composed of cellulose esters or polyamides, are selected to provide an efficient rejection of contaminant molecules (solutes) in raw water. The molecules most difficult to remove are small inorganic ones such as sodium chloride. Passage through two membranes in series is sometimes used to increase the efficiency of removal of these small molecules and to decrease the risk of structural failure of a membrane to remove other contaminants, such as bacteria and pyrogens. With the recognition of microbiological problems, some manufacturers have installed heat exchangers immediately after the RO filters to heat the water to 75–80°C to minimize microbiological contamination.

RO systems can be wall-mounted and fed by a single-pass RO unit that many small biotechnology companies use to produce high-purity water. Most of these systems employ polyvinyl chloride (PVC) or other type of plastic tubing. Because the systems are typically cold, the many joints in the system are subject to contamination. Another potential problem with PVC tubing is the release of extractables. These systems also contain 0.2-μm point-of-use filters to eliminate microbiological contamination and, therefore, reduce the source of endotoxins. However, 0.2-μm filters will not eliminate endotoxins already present. If filters are used in a water system, there should be a stated purpose for the filter, that is, particulate removal or microbial reduction, and a standard operating procedure (SOP) stating the frequency with which the filter is to be changed based on data generated during the validation of the system.

Because of the volume of water actually tested (0.1 mL for endotoxins vs. 100 mL for WFI), the microbiological test offers a good index of the level of contamination in a system. Therefore, unless the water is sampled prior to the final 0.2-μm filter, microbiological testing will have little meaning.

A strong trend in the sterile product manufacturing industry is to utilize both RO and distillation systems for generation of the highest quality water as well as combining highly purified water, RO, and electrodeionization systems (1). Since feed water to distillation units can be heavily contaminated, and, thus, affect the operation of the still, water is first run through RO units to eliminate contaminants. RO systems are available in a range of production and laboratory sizes.

Whichever system is used for the preparation of WFI, validation is required to be sure that the system, consistently and reliably, will produce the chemical, physical, and microbiological quality of water required. Such validation should start with the determined characteristics of the source water and include the pretreatment, production, storage, and distribution systems. All of these systems together, including their proper operation and maintenance, determine the ultimate quality of the WFI.