the SOPs. There must be data demonstrating that the SOPs are valid and that the system is capable of consistently producing water that meets the desired specifications. And, there must be data to demonstrate that seasonal variations in the feed water do not adversely affect the operation of the system or the water quality.

The last part of the validation is the compilation of the data, including acceptance criteria, with any conclusions into the final report. The final validation report must be signed by individuals responsible for the operation and quality assurance of the water system.

The FDA Guide to Inspection of Bulk Pharmaceutical Chemicals (July, 1993) comments on the concern for the quality of the water used for the manufacture of drug substances, particularly those drug substances used in parenteral manufacture. Excessive levels of microbiological and/or endotoxin contamination have been found in drug substances, with the source of contamination being the water used in purification. At this time, WFI does not have to be used in the finishing steps of synthesis/purification of drug substances for parenteral use. However, such water systems used in the final stages of processing of drug substances for parenteral use should be validated to assure minimal endotoxin/microbiological contamination.

In the active pharmaceutical ingredient industry, particularly for parenteral grade substances, it is common to see UF and RO systems in use in water systems. While UF may not be as efficient in reducing pyrogens, they will reduce the high-molecular-weight endotoxins that are a contaminant in water systems. As with RO, UF is not absolute, but it will reduce numbers. Additionally, as previously discussed with other cold systems, there is considerable maintenance required to maintain the system.

The FDA Guide to Inspections of Sterile Drug Substance Manufacturers (July, 1994) contains the following paragraph under Section VIII. Water for Injection: "Some manufacturers have attempted to utilize marginal systems, such as single pass Reverse Osmosis (RO) systems. For example, a foreign drug substance manufacturer was using a single pass RO system with post RO sterilizing filters to minimize microbiological contamination. This system was found to be unacceptable. RO filters are not absolute and should therefore be in series. Also, the use of sterilizing filters in a Water for Injection system to mask a microbiological (endotoxin) problem has also been unacceptable."

Typical Problems with Water Systems

FDA and other government or even internal quality inspections for good manufacturing practice (cGMP) compliance often find problems with the tight control of water systems. Examples of problems cited include:

- The water system is not validated with respect to control of quality and purity of WFI.
- Inadequate in-process and routine monitoring for water quality, especially related to microbiological purity.
- Improper responses after failed monitoring results.
- The water system has poor design to begin with.
- Poor system operation and/or maintenance.
- Lack of SOPs for operation, maintenance, and/or monitoring.

If a water system has endotoxin problems, there may be WFI in the condenser at the start-up. Since this water could lie in the condenser for up to several days (i.e., over the weekend), this may produce unacceptable levels of endotoxin.

A common problem is the failure to adequately treat feed water to reduce levels of endotoxins. It must be kept in mind that conductivity meters used to monitor chemical quality have no meaning regarding microbiological quality. Many of the still fabricators will only guarantee a 2.5 log to 3 log reduction in the endotoxin content. Therefore, it is not surprising that in systems where the feed water occasionally spikes to 250 EU/mL, unacceptable levels of endotoxins may occasionally appear in the distillate (WFI). For example, three new stills, including two multi-effect, were found to be periodically yielding WFI with levels greater than 0.25 EU/mL. Pretreatment systems for the stills included only deionization systems with no UF, RO, or distillation. Unless a firm has a satisfactory pretreatment system, it would be extremely difficult for them to demonstrate that the system is validated.