Pumps burn out and parts wear away. Also, if pumps are static and not continuously in operation, their reservoir can be a static area where water will lie. For example, during a FDA inspection some years ago it was noted that a firm had to install a drain from the low point in a pump housing and this eventually resulted in a contamination of *Pseudomonas* species.

Piping in WFI systems usually consist of a high polished stainless steel. In a few cases, manufacturers utilize PVDF (polyvinylidene fluoride) piping. It is purported that this piping can tolerate heat with no extractables being leached. A major problem with PVDF tubing is that it requires considerable support. When this tubing is heated, it tends to sag and may stress the weld (fusion) connection and result in leakage. Additionally, initially at least, fluoride levels are high. This piping is of benefit in product delivery systems where low-level metal contamination may accelerate the degradation of drug product (e.g., biopharmaceuticals).

One common problem with piping is that of "dead-legs." The proposed large volume parenteral (LVP) regulations defined dead-legs as not having an unused portion greater in length than six diameters of the unused pipe measured from the axis of the pipe in use. It should be pointed out that this was developed for hot (75–80°C) circulating systems. With colder systems (65–75°C) any drops or unused portion of any length of piping has the potential for the formation of a biofilm and should be eliminated or have special sanitizing procedures. There should be no threaded fittings in a pharmaceutical water system. All pipe joints must utilize sanitary fittings or be butt-welded. Sanitary fittings will usually be used where the piping meets valves, tanks, and other equipment that must be removed for maintenance or replacement. Therefore, the firm's procedures for sanitization, as well as the actual piping, should be reviewed and evaluated during the inspection.

Water Purity

USP and EP monographs provide the official standards of purity for WFI and Sterile Water for Injection (SWFI). There are four primary quality standards to be met for WFI (Table 15-2). The chemical and physical standards for WFI have changed over the years. The only physical/chemical tests remaining are the new total organic carbon (TOC), with a limit of 500 ppb (0.5 mg/L), and conductivity, with a limit of 1.3 μS/cm at 25°C or 1.1 μS/cm at 20°C. The former is an instrumental method capable of detecting all organic carbon present, and the latter is a three-tiered instrumental test measuring the conductivity contributed by ionized particles (in microSiemens or micromhos) relative to pH. Since conductivity is integrally related to pH, the pH requirement of 5–7 in previous revisions has been eliminated (although with much controversy still remains for USP-packaged SWFI). The TOC and conductivity specifications are now considered to be adequate minimal predictors of the chemical/physical purity of WFI. However, the wet chemistry tests are still used when WFI is packaged for commercial distribution and for SWFI.

Biological requirements continue to be, for WFI, not more than 10 colony-forming units (CFUs)/100 mL and 0.25 USP endotoxin units/mL. The SWFI requirements differ in that since it is a final product, it must pass the USP Sterility Test. The real concern in WFI is endotoxins. Because WFI can pass the Limulus amebocyte lysate (LAL) endotoxin test and still fail the

Table 15-2 Quality Standards for Water for Injection (WFI), USP[a]

Quality standard	How measured	Specification
Inorganic content	Water conductivity at 25°C. USP <645>	≤1.3 μS/cm
Organic content	Total organic carbon, USP <643>	<0.5 mg/L
Pyrogen content	Limulus amebocyte lysate test, USP <85>	<0.25 EU/mL
Microbial content	Total bacterial count, USP <1231>	≤ 10 CFU/100 mL (generally considered maximum action level for WFI using microbial enumeration methodologies described in USP <1231>)

[a]USP, EP, and JP specifications are harmonized for the above standards. However, EP requires two additional tests—heavy metals (specification NMT 0.1 ppm) and nitrates (specification NMT 0.2 ppm). The JP does not have a requirement for nitrates, but does have a requirement for ammonium (NMT 0.05 mg/L).