June 2001
Water Quality for Validated Cleaning Processes

The quality of the water used for aqueous cleaning is critical for performance. This includes the water quality for any pre-rinse, for the washing step itself, and for any rinses. What all three of these have in common is the necessity to control the quality of the water used. Quality includes chemical properties (pH, conductivity, hardness, TOC, etc.) and biological properties (including bioburden and endotoxin). Unfortunately, there are few regulatory guidelines that deal with this subject. One draft guidance will be covered later. However, there are a number of good scientific principles to utilize.

Water for washing

We'll start with water quality for washing, then cover rinsing, and finally cover pre-rinsing. For the washing process, perhaps the most critical of these is the water hardness (calcium and magnesium ions). Hardness ions are well known to affect the efficacy of cleaning of aqueous surfactant solutions. If tap (potable) water is used for cleaning, hardness can be accounted for by using chelants in the cleaning formulation. It can also be a problem if the hardness in the water varies, either seasonally or by source. For example, some municipalities obtain their water both from surface waters and from deep wells. The deep-well water is more likely to have higher hardness. If a cleaning process were designed using the surface water, that cleaning process might not be effective if the deep-well water (with higher hardness) were used. A second concern with hardness ions in any tap water source is that, if alkaline cleaning agents are used (for example, those with potassium or sodium hydroxide), hardness ions may precipitate as calcium carbonate at high pHs. Depending on the conditions of precipitation, that precipitation may cause a white residue on surfaces. That white residue may cause a surface to fail a "visually clean" criterion. This can be minimized by utilizing a cleaning agent with chelants, or by using an acidic post-rinse.

Water for rinsing

A general principle involving the manufacture of finished drugs utilizing water in the formulation is that the quality of the water for the final rinse should be at least as good as the quality of the water added in the next manufacturing process. For example, if a parenteral drug product is formulated with Water for Injection (WFI), then the final rinse of the previous cleaning process should be with WFI. If an oral drug product is formulated with Purified Water (PW), then the final rinse of the previous cleaning process should be with PW. The rationale for this is that any residues left behind from the final rinse are residues that would be added in the next product anyway. In this way, concerns with residues from the final rinse water itself are minimized. If water is used for rinsing and the subsequently manufactured product does not have water in the manufacturing process, then additional information is required. For example, if the product is a non-sterile oral, solid dose product, PW would be clearly acceptable for a final rinse. If the aqueous cleaning process involves cleaning an API made by an organic synthesis route (in which no water is used in the synthesis), the most common approach is to use deionized water as the final rinse (these facilities rarely have a validated Purified Water system). One additional concern about the final rinse quality is that one should also be aware that using a lower quality water for the final rinse may leave behind mineral deposits, which in and of itself would not be a problem; however, those mineral deposits may be visible when the rinse water dries, and would therefore cause the equipment to fail any "visually clean" criterion.

Water for Pre-rinsing

In most cases, the quality of the water for pre-rinsing is the least critical of the three cases. Water for pre-rinsing is solely used to flush residue out of the system prior to the washing step itself. Some companies will choose to recycle their water, and use for the pre-rinse the water from the previous final rinse (NOT from the initial post-rinses, for these will be highly contaminated with residues and cleaning agent). Choices of water quality to use for the pre-rinse are usually based on practicality, such as using the same water as used for the washing step.

Regulatory Guidance

The only regulatory guidance on water quality for cleaning processes is the EMEA's draft "Note for Guidance on Quality of Water for Phamraceutical Use.". The relevant comments regarding water for cleaning are as follows:

1. Section 3: "Potable water may be used … in the early stages of the cleaning of pharmaceutical manufacturing equipment." [Note: It is unclear whether "early stages" refers to APIs as opposed to finished drugs, or to a pre-rinse as opposed to a final rinse.]
2. Section 4.3 and Table 5: Under "Water used for cleaning/rinsing of equipment, containers and closures", Table 5 listed Purified Water as suitable for "General Use including CIP".
3. Table 5 also lists water quality for rinsing of containers/closure. These also might be extrapolated to equipment. Those guidelines call for Highly Purified Water [the new European category to cover WFI-quality water made by RO] for the initial rinse of containers/closures for sterile products, WFI for the final rinse of containers/closures for sterile parenteral products, and Highly Purified Water for the final rinse of containers/closures for sterile non-parenteral products.

Although not regulatory documents per se, some companies have received FDA 483's because they have used potable (tap) water for cleaning and did not have a monitoring program in place to measure/control its quality.

Overall choices

It should be realized that in any cleaning operation, there may have to be some adjustments to deal with what can be practically achieved. While it may be possible to justify the use of tap water as a pre-rinse, PW for the washing step, and WFI for the rinses, the engineering and quality concerns with having all three water sources piped for appropriate use may be a challenge. In addition, if tap water were chosen for any process step, assuring consistency of that water will be critical. That would usually include a comprehensive chemical and microbiological monitoring program.

The discussion in this Cleaning Memo is not mean to prescribe certain water qualities that must always be used. Rather this discussion is meant to explore how water quality might affect the various steps in the cleaning process. Such information can be critical in selecting the appropriate water quality for a given step or a given process.