

July 2002 Worst-case Process Conditions

Cleaning validation generally involves three PQ runs where one challenges the cleaning process under worst-case process conditions to demonstrate that within normal process variations, the cleaning process is effective. This generally involves stressing under worst-cases within normal process conditions. For example, if the cleaning process temperature were $70^{\circ} \pm 5^{\circ}\text{C}$, one would NOT conduct a worst-case process condition at 60°C . Even though that low temperature were a worst case, it does not represent conducting the cleaning process within normal parameters.

If one were considering temperature in the case discussed above, would one be expected to challenge under the worst-case condition of 65°C ? While that might be desirable, in most cases it is not practical. Why? If one were to establish a set point of 65°C , inevitably the temperature at some point would drop below the control range of $65\text{-}75^{\circ}\text{C}$, and would therefore incur a process deviation. As a practical matter, if the temperature could be controlled in a very narrow range, such as $\pm 2^{\circ}\text{C}$, then the process specification for temperature would be set at $70^{\circ} \pm 2^{\circ}\text{C}$. While it may be desirable to evaluate a lower temperature as part of a pre-validation study, in most cases it is not practical to use a “worst-case temperature” as a cleaning process challenge.

What, then, are appropriate challenges to the cleaning process? The most common is the dirty equipment hold time, or DEHT (see Cleaning Memo for October 2001), which is the time between the end of manufacture and the beginning of the cleaning process. In many cases the longest DEHT represents a worst-case, and therefore an appropriate challenge to the cleaning process. Other challenges would be specific to individual situations. However, some common challenges are:

1. Using different lots of cleaning agent for each of the three PQ runs
2. Using different operators for each of three PQ runs for manual cleaning processes
3. Different lots of API for manufacture of finished drugs

In a sense these three do not represent “worst cases”, but rather represent a challenge of possible variation. For example, if one specifies a cleaning agent concentration of $5.0\% \pm 0.5\%$, is 4.5% the worst case? In one sense it may be the worst-case for removing the soil, but 5.5% represents the worst case for rinsing of the cleaning agent. It should also be recognized that, in some situations, it may not be possible to challenge under any of these variations.

Another issue that comes up is whether each and every PQ run should be run under the worst case DEHT. The answer this is partly a matter of judgment. Some companies choose to make at least one of the DEHT at the maximum, while others choose to perform all three PQ runs at the maximum DEHT (certainly the most defensible). The former choice can be acceptable, but generally only if there is adequate information from prevalidation cleaning studies that the cleaning process is robust to handle this worst-case. In addition, if one specifies that only one PQ must be at the maximum DEHT, it is preferable that the other two PQ runs not both be at the minimum. In other words, if the maximum DEHT is 24 hours, one should challenge at 24 hours, at 12 hours and at 2 hours for the three PQ runs. Certainly if there is evidence that the DEHT has no effect on difficulty of cleaning (as with some dry products), then using a range of hold times for the three PQ runs is also appropriate.