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Dealing with Deviations in the DEHT

This month's topic is how to handle situations in which the dirty equipment hold time (DEHT) is exceeded in ordinary cleaning processes after a specific DEHT is validated in a cleaning validation protocol. For clarification, the DEHT is the time from the end of manufacture to the beginning of the cleaning process. It may be called a variety of things, such as dirty hold time or soiled hold time. For purposes of examples in this Cleaning Memo, I will use a DEHT of 72 hours; however, it should be noted that the specific time of the DEHT is in no way mandated by regulatory authorities. It is something that an individual manufacturer selects, incorporates as a challenge in the cleaning validation protocol (as a worst case condition), and then incorporates into the cleaning SOP.

If the validated DEHT is exceeded, for example, by not starting cleaning until 90 hours after the end of manufacturing, what does one do? There are several options, depending on the specifics of the situation. However, it should be clear that in all cases, this represents a deviation (or non-conformance), and that an investigation and report (perhaps with CAPA) according to the manufacturer's deviation policy is called for.

Let's take a look at three possible situations and possible responses in each case. The first situation is one where the manufacturer actually validates a longer DEHT than that specified in the cleaning SOP. By this I mean that the cleaning validation protocol validates a DEHT of 120 hours (for example), but that the cleaning SOP requires a DEHT of no more than 72 hours. The rationale for such a practice is precisely to deal with DEHT deviations. If the DEHT in a specific cleaning event is 90 hours, then I have justification for saying that cleaning with my regular cleaning SOP is going to be effective. Note that in this case, I will still treat it as deviation. I might also perform an investigation as to why the DEHT in the SOP was exceeded, and try to put into place preventive actions to help assure that I don't have such deviations in the future. This approach only works if the actual DEHT in the specific cleaning event is more than that specified in the SOP, but not greater than that validated in the protocol. [I should make it clear that I am not a big fan of this manner of dealing with the DEHT. My concern is that production people may become skeptical about various SOP practices, and come to believe that in all instances for all parameters, the actual validated value is more liberal than that specified in the SOP. If this leads to laxity in performing SOPs, the situation becomes counter to a GMP approach. That said, this approach does have a solid scientific rationale.]

A second situation is a case where the DEHT is known not to affect the difficulty of cleaning. For example, on a tablet press with residues of a dry drug product, the time after manufacture that cleaning is started may make no difference in terms of the difficulty of cleaning (there may be exceptions to this in cases such as hygroscopic powders). In this case, you might first ask "Why specify any DEHT in the SOP?" The reason is that some kind of reasonable DEHT must be specified. After all, if the DEHT in a specific situation was exceeded by 180 days (an extreme case!!), would you be concerned about the capability of the SOP to clean effectively? The answer is you would. So even though there is no problem with the difficulty of cleaning as the equipment sits there soiled, you want to set some kind of DEHT, such as 72 hours (representing the equipment soiled over a weekend). If this is the case, and you have set a DEHT in the protocol and in the SOP of 72 hours, and the actual DEHT in a specific situation were 90 hours, then you would still handle it as a deviation, with an investigation and with possible preventive actions. However, it may be released following cleaning with no additional testing required provided that the actual DEHT is no more than 2 or 3 days beyond the

DEHT time specified in the SOP. In some cases, manufacturers may choose to do more extensive visual examination following this cleaning after the deviation.

The third situation involves cases where cleaning may be more difficult as the SOP DEHT is exceeded. In this case, testing data after the cleaning process is generally required. However, the test data collected may not exactly replicate the test data collected in the original cleaning validation protocol. It may be possible to select as swab sampling locations, for example, only the “worst cases” of the worst case locations. It may also be possible to eliminate the testing for the cleaning agent. Bioburden probably should not be eliminated as a test if there is a possibility of additional proliferation of bioburden during the extended DEHT.

For this third situation, there are three options to consider for how to clean after the deviation. Option 1 is to clean with the same SOP as previously validated. Option 2 is to clean twice with the cleaning SOP previously validated. Option 3 is to clean with the same SOP previously validated with one or more cleaning parameters (such as cleaning time) extended. Note that in this last option the concentration of the cleaning agent should probably not be increased, unless one also increases the rinsing time or volume. Using a different cleaning agent should be avoided because you don’t want to perform analytical method validation for that new cleaning agent, and you don’t want to perform additional sampling recovery studies.

Why would one choose one option over another. Option 1 is certainly the simplest. If effective, it should be the main choice. The problem with it is that you don’t necessarily know it will be effective until you perform the testing. If the testing fails, it means you may have to repeat the cleaning and the testing again. The disadvantage of this situation is that there may be additional analytical testing and the downtime is increased. It is for these reasons (avoiding additional downtime and avoiding additional analytical testing) that some manufacturers will select Option 2 or Option 3. Yes, it requires additional cleaning time, but the overall downtime may be reduced and the additional testing is more likely to be avoided. Which option is selected is based on a risk analysis; it should be noted that this is a business risk. In all options, cleaning will be performed until it is documented to be effective in a cleaning verification mode.

The FDA has addressed this question to an extent in its Human Drug CGMP Note for the 2nd quarter of 2001. While answering questions related to cleaning validation, the following statement is made: “Also, equipment stored unclean for a longer time than during validation should be sampled to demonstrate that the cleaning procedure was effective.” Essentially that is suggesting/requiring cleaning verification be performed if the DEHT is exceeded. While I have given two situations where that may not be applicable (based on good scientific principles), clearly for the third situation this principle applies.

Manufacturers should consider what approach they would use in advance of the situation occurring. If faced with a situation where the DEHT is exceeded, it is preferable to take action sooner rather than later. Consideration of the various options in advance may make the appropriate response clearer if such a deviation were to occur. In addition to considering how to respond if such a deviation were to occur, it is also valuable to put practices and/or training (preventive actions) in place to help ensure that such deviations do not occur.