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Dirty Equipment Hold Times

There are two aspects of "hold times" generally evaluated for validated cleaning processes in pharmaceutical manufacturing. One is the time from the end of manufacturing until the beginning of the cleaning process. The other is the time from the end of the cleaning process until the beginning of the use of the cleaned equipment for manufacture of the next product. This "Cleaning Memo" addresses the former hold time, which will be abbreviated DEHT ("dirty equipment hold time") for simplicity. Next month's Cleaning Memo will address the latter hold time (for clean equipment).

Why is the DEHT important for the control of a cleaning process? Simply put, the nature of the "soil" on the equipment surfaces may change over time. Those changes include drying of the soil and/or microbial proliferation. Such changes may make the soil more difficult to remove by the cleaning process. Since the clean-ing process should be designed to adequately clean the equipment under the worst cases of normal operating conditions, a demon– stration of effectiveness under the worst-case (usually the longest) DEHT should be documented. It should be noted that there might be some cases where the hold time will have no effect on the ease or difficulty of cleaning. In such a case, it would still make sense to establish a maximum DEHT, and to demonstrate effectiveness at that maximum time. In rare cases, one may find soils that are easier to clean the longer the DEHT. In such cases, one should establish a minimum DEHT (the worst case) as well as a maxi-mum DEHT, and demonstrate effectiveness at both extremes.

How does one establish a maximum or minimum DEHT? The most important considerations are that it be achievable and practical for one's manufacturing environment and capabilities. A good way to start for the maximum DEHT is to ask one's manufacturing/production department about the longest time the equipment would be dirty before the cleaning process would be started. One may want to be more conservative and add some additional time to what the manufacturing/production department specified. For example, if they stated a maximum time of four days, one might want to be conservative and specify a maximum DEHT of five days. Similarly, if a maximum time of 12 hours were specified, then one might want to expand that to 24 hours. The reason for this is that one wants to prevent manufacturing deviations, and any time the DEHT is exceeded, a deviation occurs. One wants a DEHT that will encompass all normal production.

For the minimum DEHT, a similar approach is used. Manufacturing/production is asked for the shortest time practical between the end of manufacturing and the beginning of cleaning. However, in this case, it does not make sense to be more conservative and specify an even shorter time. The reason is that if one establishes an even shorter time, and that time is the worst case, then one will have to include that time as one of the PQ (performance qualification) runs in the validation protocol. It may not be practical to do that. In addition, if a minimum DEHT of 2 hours is specified, and one is ready to start cleaning after 1.5 hours, it is a simple matter to delay cleaning for 30 minutes to prevent a situation in which a deviation would occur.

If such a DEHT were specified for a cleaning process, and if that DEHT is critical for control, then it is important to document that time. Documenting it means one needs to record the time of the end of manufacture and the time of the beginning of cleaning. The former should be defined based on one's manufacturing process, while the latter is defined based on one's cleaning process.

Examples of the "end of manufacturing" time include:

1. The time at which the discharge valve is closed.
2. The time at which no additional product is removed from the equipment for further processing.

Examples of the "beginning of cleaning" time include:

1. Time at which pre-rinse is initiated.
2. Time at which equipment is placed in sink for soaking.
3. Time at which cycle of automated parts washer is initiated.

The important point here is that, if it is important to control the DEHT, then it needs to be measured in some way, and that should be defined somehow for the cleaning procedure.

When the DEHT is specified, there are several ways to handle it in the validation protocol. One is to require that at least one of the PQ runs be performed at the worst case DEHT. The second is to require all three PQ runs to be at the worst case DEHT. Either option is acceptable. It is not a requirement that each PQ run be performed incorporating each and every worst-case condition. This can be difficult to accomplish. Provided one PQ run has been challenged under the worst case DEHT, the cleaning system has been appropriately challenged.

This Cleaning Memo is designed to present some basic information and to stimulate thought about the significance of the DEHT for validated pharmaceutical manufacturing. Application of these concepts should be based on both good scientific principles as well as what is practical and achievable in a given manufacturing environment.

Note: The acronym DEHT is not a standard abbreviation. It is used here solely so the words don't have to be written out each time.