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CEHT for Sterilized Equipment

A question that sometimes comes up is "How should I handle a Cleaned Equipment Hold Time (CEHT) if my next step is to perform a SIP cycle on the cleaned equipment?" Does it make sense to evaluate the CEHT in such a situation? If so, why?

In trying to address the issues in such questions, it is important to separate out two aspects of the hold time. One aspect is the hold time from the end of cleaning until the beginning of the SIP cycle. The second aspect is the hold time from the end of the SIP cycle until the equipment is actually used for product manufacture.

For the first aspect, one might argue that hold time is irrelevant since the major concern in a CEHT study is bioburden proliferation. Since we will be "sterilizing" the equipment, a small bioburden population will not be a challenge for the SIP cycle. However, that argument is not entirely valid. How would one know that the bioburden proliferation during the hold time was insignificant unless one performed a hold time study and measured bioburden at the end of cleaning and at the end of the hold time (immediately before the SIP cycle)? Furthermore, if the bioburden proliferation was due to gram negative bacteria, while the SIP cycle might be effective in killing microorganisms, it will also release endotoxin onto the equipment surfaces. Therefore, it still makes sense to consider performing some kind of evaluation of any bioburden change in the time between cleaning and the SIP cycle.

Of course, some of the same issues that are normally considered in conventional CEHT studies may be evaluated. For example, for equipment cleaned with hot aqueous alkaline solutions which is subsequently rinsed with hot purified water and then closed to external contamination, I am an advocate of not requiring a formal CEHT study provided the CEHT is 24 hours or less. The rationale is that there is not likely to be significant proliferation under those conditions. This same rationale may be applied to the specific situation of this paragraph, namely the hold time from the end of cleaning until the beginning of the SIP cycle. Some may also extend this by saying that provided the bioburden is low at the end of cleaning and provided that the equipment is dry and closed to external contamination, then the time between cleaning and the SIP cycle can be several days without a formal study. There is certainly a scientific rationale for that approach.

The second aspect is the hold time after the SIP cycle. In one sense we might argue that this is not really part of cleaning validation, and that it really belongs as part of sterilization (or SIP) validation. However, wherever it belongs, the issue still has to be addressed. Clearly it makes sense to set a time limit for use of the equipment in the "sterile" state. Yes, I realize that loss of sterility is an event-related phenomenon and not a time-related phenomenon. As a practical matter, we will generally set some kind of time limit. Does it make sense to check for the sterility of the equipment after storage for so many days? And if we must, what technique do we use? My contention is that it makes no sense to test the equipment for sterility. Any test for sterility would be subject to false failures due to contaminated samples. Certainly it makes no sense to open the equipment up and then sample surfaces for sterility. Which surfaces would one sample (that is, which would most likely be points of failure)? Sampling in such a way is just too problematic. Well, perhaps we can sample by introducing a sterile medium into equipment and processing it much like we would process a product? Does this make sense? Again, the key is opening up a sterile system to introduce the sterile medium. While there are ways around this, the value it adds is minimal.

A better procedure to qualify a hold time after a SIP cycle would be require that the equipment be kept under positive pressure and that that positive pressure be continuously monitored. If the SIP cycle has been validated, and if the equipment is maintained closed in an overpressure situation, then loss of sterility will not happen. However, it is still prudent to set some kind of reasonable time limit on this hold time. Note that in this case, one cannot say that the hold time is validated. I believe this is truly as case of verification, because the continuous pressure monitoring for each event stands on its own. Doing the continuous pressure monitoring successfully for three runs is not adequate to say that the system is validated and that there is no need to do further pressure monitoring on subsequent runs.

As one addresses these issues for equipment that is sterilized, it is important to also consider in advance those steps that will be taken if the hold times are exceeded. For exceeding the first hold time (between cleaning and the SIP cycle), some companies may choose to do a complete cleaning, while other may choose to perform a hot WFI rinse. For exceeding the second hold time (from the end of the SIP cycle until use), some companies will just repeat the SIP cycle. Note that this applies to exceeding the time as long as the overpressure is maintained. If the overpressure is not maintained, then this clearly calls for an investigation and subsequent CAPA.

The purpose of this Cleaning Memo is to explore some of the issues that need to be considered in the establishment of hold times for sterilized equipment. Practices that are adopted will depend on the specifics of the individual situation. Quality Risk Management principles certainly come into play in selecting appropriate practices.