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Dealing with Deviations in the CEHT

This month's topic is how to handle situations in which the clean equipment hold time (CEHT) is exceeded in ordinary cleaning processes (after a specific CEHT is validated in a cleaning validation protocol). Two types of CEHT will be covered. One type is the CEHT from the end of cleaning until subsequent use or sterilization. The second is the CEHT after a steaming process for either sterilization or bioburden reduction.

In the situations described, the time of exceeding the CEHT is typically going to be a relatively short time, for example, a few days or maybe even a week. If the deviation is for a month or more, clearly a more comprehensive cleaning of the equipment is usually required.

Let's start with a situation where a validated CEHT of, for example, seven days, is exceeded by a few days. What action should be taken? In order to address that, we have to consider how the equipment can be recontaminated during that extra time. If the equipment is sealed (or wrapped for small parts), it is not likely that bioburden proliferation will occur. Why? Bioburden proliferation is only likely to occur if the equipment is stored wet. If bioburden proliferation has not occurred at the end of seven days (the validated CEHT), it is not likely to occur on days 8, 9 or 10 unless the equipment has somehow become wet. Therefore, in that situation, I might just pass hot WFI or Purified Water (the water quality is dependent on the final rinse used in the cleaning process) through the equipment to deal with any extraneous contamination. I realize that extraneous contamination (such as dust) is not likely to enter the system if it is closed or wrapped, but it is still prudent to include such a corrective action. Note here that if a company decided to clean the equipment again with a validated cleaning process, that would also be acceptable (but probably not necessary).

This first example was with a situation where the validated CEHT was 7 days. What if the validated CEHT is relatively short, for example, 24 hours, and I exceeded that time by 72 hours. Can I apply the same corrective action? I would argue that I probably can't. With a validated CEHT of only 24 hours, I might have acceptable bioburden after 24 hours but not after 96 hours. In that case, I would probably not just want to pass hot WFI or Purified Water through the equipment, but to clean the equipment with a validated cleaning process, particularly one that utilized a hot aqueous alkaline cleaning agent.

In these two cases, would I have to sample and not release the equipment until the results are evaluated? If the only sampling were "Is it visually clean?", then it would be prudent to do that. On the other hand, if I performed bioburden sampling (for example, a final rinse water bioburden sample), it doesn't make sense to hold the equipment pending results, because I have just added another hold time concern to the situation. Certainly it may be beneficial to do such testing, but not to quarantine the equipment until bioburden results are available. On the other hand, if I performed bioburden sampling, and the results were unusually high, I certainly would want to do an investigation before I released product that was made in that equipment.

In both these situations, immediately (within 24 hours) following the corrective action, I should begin the next process step, whether that is manufacture of a batch or steaming the equipment for sterilization.

Okay, let's switch to the situation where I have cleaned the equipment, and within the CEHT I have steamed the equipment. I have another CEHT (if I were in the acronym business, I would call it the SEHT - Steamed or

Sterilized Equipment Hold Time), which is the hold time after steaming up until the time the equipment is used for processing the next product or batch. With this situation there are two examples to consider. The first example involves equipment that is truly validated sterile, and is closed and maintained under positive pressure continuously. As I have discussed previously (September 2006 Cleaning Memo), a formal study to document the SEHT is not required here. If I set an arbitrary SEHT of seven days, then what action should I take if I exceed that hold time by a few days? Assuming that the system has been maintained closed and under positive pressure, the minimum should be to perform a sterilization cycle again. Only if I were concerned with a compromise in system integrity (loss of the positive pressure) would I consider cleaning again in addition to the sterilization process.

A second situation involves a case where the equipment is steamed and is not validated sterile, but rather the steaming is for “bioburden reduction” only. Typically, this may be done in cases where the equipment is not closed and not maintained under positive pressure. In that case, during my SEHT following steaming, I should have bioburden data to support that hold time. Since this is an open system, I would be more concerned about external contamination if I exceeded the hold time. Therefore, in this situation I would first rinse the equipment with hot WFI or Purified Water (the water quality is dependent on the final rinse used in the cleaning process), followed by the steaming process for bioburden reduction. Some companies would choose to clean again (by a validated process), followed by the steaming step. Clearly this is also acceptable.

In the examples given, the additional process would restart the CEHT or SEHT clock. In the example given there have been no extraordinary events to recontaminate the equipment. In such cases, those specific events need to be considered in taking corrective action. Furthermore, the examples given do not cover all possibilities. There may be specific circumstances which would cause me to consider additional corrective actions. There is no single corrective action that would apply to any deviation of the CEHT (or SEHT). Variations on the actions given may be considered based on the specifics of the situation.

One other option to consider is to avoid exceeding the CEHT. If I know in advance that I am going to exceed the CEHT, then before expiration I can reclean the equipment using the previously validated cleaning process. In this situation, I am cleaning “clean” equipment with a validated process, so I am merely restarting the CEHT clock. The advantage of doing this (as compared to exceeding the CEHT and then perhaps using a hot water rinse) is that I am not in a deviation situation. Therefore I can avoid the investigation and paperwork that is associated with a deviation. A similar approach can be used for resteamming prior to exceeding the SEHT.

One additional option is to validate a longer CEHT or SEHT than I actually specify in my SOP. In other words, the SOP has a CEHT of 72 hours, but I have actually validated a time of 120 hours. Therefore, if I exceed the SOP time by 24 hours (for example), I am still within my validated time of 120 hours. Note that in this case, the situation is still a deviation and needs to be handled accordingly. I am not a big advocate of such an approach, because of the concern about manufacturing people believing that in all cases any SOP specification is actually broader than that listed in the SOP. However, it is a defensible approach from a compliance viewpoint.