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Hold Time Issues

There are several types of "hold times" that may need to be addressed for cleaning validation. They include:

Dirty Hold time (DHT) – the time from the end of manufacture until the beginning of the cleaning process (also called things like "soiled hold time")

Clean Hold Time (CHT) – the time from the end of cleaning until subsequent use of the equipment (subsequent use includes product manufacture or a SIP cycle)

Sampling Delay Time (SDT) – the time from the end of cleaning until samples are taken for measuring residues (hey, this is a new acronym that I think I'm inventing)

I have written previous Cleaning Memos relating to the first two (DHT and CHT). This Cleaning Memo will try to make some distinctions and clarifications about the three hold times.

Sampling Delay Time

Let me cover the SDT first, since I have not formally covered this in a Cleaning Memo in the past. The SDT is a reflection of the fact that it is possible that residues on cleaned surfaces may change over time. Certainly we are aware of this possible change for bioburden testing (it's the primary concern for CHT studies). So, what else can change? One possibility is the degradation of the drug active on the cleaned surface. Degradation may be due to such effects as light, air, and/or temperature. In other words, if I set a limit for my active and have a specific analytical method for measuring that active, I might get one result if I measure immediately after cleaning, but a lower result after a time of (for example) 24 hours.

You might say that the equipment is not used for at least 24 hours, so the analytical results at 24 hours are more reflective of residues on the surface. Which is partly true, the results after 24 hours using a specific analytical method for the active are reflective of residues of that active on the surface. But should I not also be concerned about residues of those degradation products? Let's take a look at a situation where the active degrades during the cleaning process itself (and not during the SDT). In such a case, would it be acceptable to say (having a specific analytical method for the drug active) that if it were not detectable I passed my acceptance criterion for residue of the drug active? In that case, the more typical approach is to say that my main concern is residues of the degradant. And, the approach is either to have a specific method for the degradant, or else to use a method like TOC and assume (as a worst case) that all the TOC is due to the undegraded drug active. Should I not do the same thing (measuring residues using a specific method for the drug active or using TOC) if the active degrades during the SDT?

Note that this is important when either swab sampling or a separate sampling rinse is used. For a grab sample of the final process rinse, the SDT is not applicable. The sampling delay time should be specified in the protocol by requiring that the sampling of surface should be done within a specified time after the end of cleaning. That acceptable time can be addressed during sampling recovery studies. For example, I might just swab a spiked surface at a specified time after spiking. This is already generally done because there is usually a delay between spiking and swabbing to allow the spiked material to dry.

There is no relationship in terms of time between a SDT and a DHT. The SDT focuses on sampling of residues on equipment surfaces after completion of the cleaning process. The DHT focuses on soils on equipment surfaces at the time of initiation of the cleaning process. For emphasis, for a SDT the residue level on the surface is generally much lower than the soil level for the DHT. Furthermore, the SDT focuses on the effectiveness of the sampling and analytical methods, while the DHT is focused on the effectiveness of the cleaning process.

Dirty Hold Time

The DHT is a part of every cleaning protocol where I evaluate the effectiveness of a cleaning process. Sometimes I hear people say that they initially do a cleaning validation protocol (to evaluate the effectiveness of the cleaning process) and then follow that up with a DHT protocol (to evaluate the effectiveness of the cleaning process after the DHT). In fact, every cleaning process protocol has a DHT. That DHT may be very short (a few minutes), but it still technically is a DHT. In other words, if my initial three protocols involve situations where the cleaning process is started five minutes after the end of manufacture, then I have effectively validated a cleaning process with a DHT of five minutes. If I then repeat those protocols later using a longer DHT of 24 hours, then I have effectively validated the cleaning process with a DHT of 24 hours. The important point I trying to make here is that every protocol that measures effectiveness of the cleaning process has a DHT of some sort.

My next point on DHT is something I have covered before, but it bears repeating here. There are some cases where the DHT has no effect on the effectiveness of a cleaning process. For example, the time after the end of manufacture may have no effect on the difficulty of cleaning of a solid oral dose product on a tablet press. If that is the case, a DHT may be specified, but the DHT does not represent a worst case. There certainly may be exceptions, such as a solid that contains hygroscopic ingredients; this should emphasize the important of understanding the factors involved in a cleaning process.

There may be other situations where the cleaning becomes more difficult up to a certain time, and then difficulty of cleaning does not change. For example, if I have a liquid on a surface, as it dries it may become more difficult to clean. However, once it dries, the difficulty of cleaning does not change with additional time. In that case, I might set my DHT as 96 hours, but any time after 24 hours might represent a worst case if the drying time is 24 hours. I can also think of situations where cleaning might become easier with time. For example, suppose I have a liquid that becomes a friable powder on drying. The bulk of that friable powder may be easily removed by vacuuming or brushing, prior to a manual washing step. In this case, I may want to specify in my cleaning procedure to wait a fixed time before cleaning begins.

Clean Hold Time

The emphasis for CHT is possible microbiological proliferation after the equipment has been cleaned. The major concern here is that the equipment is stored wet, in which case microbiological proliferation is a possibility. A secondary (but also important) concern is that the equipment remains visually clean during the CHT. This later concern I typically deal with by protecting the equipment from external contamination by closing it and/or wrapping it in some way to prevent ingress of external contamination. (I suppose that appropriate protected equipment could be visually dirty by microbiological proliferation; however, if the microbiological proliferation is such that the equipment is visually dirty, then you really have a problem.)

An important consideration for CHT is that CHT protocols or studies may be done independently of a protocol to measure effectiveness of the cleaning procedure. For example, I can choose to write two protocols, one for the cleaning procedure (which includes a DHT and evaluation of residues after cleaning) and a second protocol just to evaluate residues after the CHT. If I have two protocols, they may be performed on the same cleaning event. That is, I clean the equipment and measure residues on a given cleaning event for my cleaning validation protocol. And then for that same cleaning event, I evaluate the residues after the CHT in a separate protocol (I might call it my CHT protocol). The bioburden data measured at the end of my cleaning procedure in the first protocol also becomes the baseline data for microbiological proliferation in the second protocol. Of course, it is also possible to separate these two protocols in time, and perform the cleaning validation protocol on one cleaning event and the CHT protocol on a different cleaning event.

This is not to say that I can't write one protocol, in which both types of residues (after cleaning and after the CHT) are measured. One rationale for two separate protocols is documentation in case the cleaning evaluation passes and the CHT evaluation fails. It also may make things simpler in the future if one or the other evaluations has to be redone. For example, in a manual cleaning process, if there are changes in the future, I might (depending on the circumstances) just repeat the cleaning evaluation and not have to repeat the CHT evaluation.

The purpose of this Cleaning Memo is to present considerations in understanding these different hold times. As covered in my Cleaning Memo of January 2005, understanding the cleaning process is a key to making sure cleaning validation is both effective and efficient.