Cleaning Memo for December 2020

Visual Residue Limits – Part 2

In this second of a two-part series, we will look at using Visual Residue Limits (VRLs) as part of *routine monitoring* to establish that a *quantitative* residue limit is being met. If you haven't read (and understood) last month's Cleaning Memo, please do so before considering this one.

Before I start, here is a little history about the use of VRLs in validation (qualification) protocols. The PIC/S Cleaning Validation Recommendations (1998) has a statement in its section on limits that the *most stringent* of three criteria should be used for limits *in a protocol*. Those three criteria are a dose-based calculation, 10 ppm in the next product, and visually clean. As this PIC/S document was written before the advent of HBELs, it is reasonable that a HBEL criterion could be substituted for (or added to) the dose-based criterion. The idea of visually clean *alone* has not commonly been used because many critical locations in equipment cannot be readily viewed (such as transfer pipes), as well as for other reasons (such as the variability of viewing conditions and the variability of the viewers). We should also clarify that in situations where an analytical method was *required* to confirm that residues of the active were acceptable, it was still a requirement that the equipment be visually clean. The reason for that is that residues of *other* materials (such as excipients) could also cause the equipment to not be visually clean, and it is considered a reasonable GMP interpretation that equipment be cleaned to the point that there are no visible residues. Now let's move to the issue of using a visually clean criterion in *routine monitoring*.

Again, some more history. It has always been an expectation following a validated cleaning process that equipment be visually clean. That is *not* new. (Note that for "minor cleaning" within a campaign there is *not necessarily* an expectation that the equipment be visually clean. While that "minor cleaning" is part of an overall validation program, it by itself is not a validated cleaning process.) However, the purpose of establishing that the equipment was visually clean for routine manufacture was *not* to provide "clear" evidence that the residue limits were being met. The evidence that residue limits were being met was the original validation protocols combined with the fact that the cleaning procedures (SOPs) were carried out correctly by trained operators. Verifying that the equipment was visually clean on a routine basis was done more for the reason that if the equipment was not visually clean, then something was wrong. The fact that the equipment was not visually clean does not tell us about the nature of the residue or about the cause of the residue. An investigation is needed as part of a CAPA program. One way to think of the traditional use of this requirement (that equipment be visually clean following routine cleaning) is that in such situations "visually clean" is a *necessary requirement* to say that the cleaning process was carried out correctly, but it (alone) is *not a sufficient reason* to say the cleaning process was carried out correctly. If the equipment is in fact visually soiled after the validated cleaning process, that (alone) is *sufficient*

reason to say something is wrong, but it doesn't tell us what is wrong (or provide the cause of the problem).

Now we get to the issue in Question #7 of the 2018 EMA Q&A document. That question and answer are as follows:

> "Q7. Is analytical testing required at product changeover, on equipment in shared facilities, following completion of cleaning validation?
> A: Analytical testing is expected at each changeover unless justified otherwise via a robust, documented Quality Risk Management (QRM) process. The QRM process should consider, at a minimum, each of the following:
> • the repeatability of the cleaning process (*manual cleaning is generally less repeatable than automated cleaning*);
> • the hazard posed by the product;
> • whether visual inspection can be relied upon to determine the cleanliness of the equipment at the residue limit justified by the HBEL."

Note that this clearly is in the context of *analytical* testing for *routine monitoring* ("following completion of cleaning validation"). The first bullet point suggests that this may be more critical for *manual cleaning* processes. The second bullet point suggests that is may be more critical for *low PDE actives*. The third bullet point suggests that the context might be residues (such as the active) for which an HBEL has been determined *for the validation protocol*. It further suggests that analytical testing is expected *unless* there is a risk assessment to justify *not* doing so. Different companies may have different approaches to address this issue for routine monitoring. Here are some possibilities:

1. For low PDE products, perform at least one chemical analytical test for the active as part of routine monitoring. This does not have to be with the same level of sampling as in the validation protocol. For example, for automated cleaning processes where a final rinse sample is a *reliable indicator* of possible residue levels, just a single final rinse sample for the low PDE active may be adequate. Of course, if this is an automated cleaning process, a final rinse conductivity is also still appropriate as an indicator of *process control*; and a visually clean requirement is also still appropriate. If this is manual cleaning for a low PDE active, a swab sample on one or more *critical* (worst-case) sampling locations may be adequate (still with the requirement that the equipment be visually clean).
2. For low PDE products, if the preference is not to perform a chemical analytical test for the low PDE active, then this is when it is *necessary* to do spiking studies (*as discussed in Part 1 last month*) to determine what the VRL is. If the VRL is the same or above the calculated carryover limit for that active, then a visual examination alone may establish that the residue is below the calculated limit. Note that depending on the active, it is entirely possible that this relationship between the VRL and the calculated limit would not hold; in which case using option #1 above should be considered.
3. For products with actives that do *not* have a low PDE (which I will call "traditional" actives), the same two options above can be considered. However, in

the case of "traditional" actives it is more likely that the VRL will be above the calculated limit (spiking studies could be used to determine the VRL). However, some companies may choose to come to this conclusion *without* performing spiking studies. For example, it is highly likely that a *calculated* L3 residue limit (amount per surface area) of 4 mcg/cm^2 would be readily visible on equipment surfaces. Some companies might want to use a more stringent criterion for the calculated limit, such as 1 mcg/cm^2, while others might want to use a less stringent criterion of 10 mcg/cm^2 (remembering that the lower the *calculated* limit, the less likely that "visually clean" will be suitable confirmation of meeting that residue limit).

An additional concern related to visual examination for *routine monitoring* is whether the equipment *must* be disassembled to the same extent as disassembly during the cleaning validation protocols (so that the identical surfaces can be observed). This may be possible; however, I would carefully consider whether product quality is being impacted more by the possibility of recontamination by the disassembly / visual assessment / reassembly process as compared to situation where visual examination is limited to what might be "practical". Each company will have to consider this as part of a risk assessment. For this consideration of extent of disassembly, the EMA's answer to Question #8 in the 2018 EMA Q&A document should also be consulted.

In exploring these options for your specific situation, please be aware that this discussion is in the context of VRLs as defined in Part 1. If you have a *different* definition of VRL (or a different means of establishing VRLs), then this discussion might not apply. In any case, these considerations may be addressed in appropriate risk assessments as part of a "life cycle" cleaning validation approach for routine monitoring.