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More Uses for Visual Limit Determination

Last month I discussed that in a cleaning validation protocol, it is only required that one determines a Visual Limit (VL) by performing a spiking study if one is exclusively using visual examination as the acceptance criterion for defined equipment surfaces. However, there are other situations broadly under the category of cleaning validation, but not part of a cleaning validation (or qualification) protocol, where determining a Visual Limit may add value.

The first situation is where I am in the early stages of cleaning process development, and I want to know how effective my cleaning process is. In that situation I may not have an analytical method (and associated sampling recovery studies) developed and validated. However, if I can determine the carryover limit (in µg/ cm^2), I could readily either determine the lowest practical Visual Limit or else determine whether the residue spiked at the calculated limit was readily visible on spiked surfaces. In this way, I could determine whether the cleaning process was effective in terms of meeting the required residue acceptance limit. Note in this case, I would prefer to either determine the lowest VL or a VL at least 50% of the calculated limit in order to be convinced that the cleaning process was robust.

A second situation is using visual examination as a primary routine monitoring tool for the cleaning process after it has been validated. In this case, I would want to establish the VL at either the acceptance limit or the lowest possible Visual Limit. The purpose here is just to use this as a confirmation that the cleaning process is continuing to be effective after completion of the validation protocols. Of course, the assumption here is that all critical surfaces during the monitoring process can be inspected visually. Particularly for equipment cleaned by a CIP process, the level of visual inspection for routine monitoring may not be to the same degree as visual inspection during the validation protocols (where there may be significant disassembly and/or tank entry for visual inspection). In addition, if this monitoring is to be comprehensive, areas like pipes (that may not be inspected visually) should be sampled by rinse water testing to confirm acceptable monitoring results. Where this second situation may have particular value is in manual cleaning, where in many cases all critical surfaces are readily accessible for visual inspection.

It is important to understand what is being said here. I am not saying that a VL needs to be established for routine monitoring purposes. What I am saying is that if a VL is determined experimentally, then routine visual monitoring of equipment on every cleaning event contains a higher level of assurance that the cleaning process is acceptable. However, it may not have the same high level of confidence that may be present in the validation runs unless all critical surfaces are visually examined during the routine monitoring process.

A third situation for the use of visual limits is in an investigation where I have identified a possible cleaning process problem, but done so only after the cleaned equipment has been used for manufacture of another product. The key assumption for this use is that the equipment was visually examined after the problematic cleaning process. One way to check for the effect of the problematic cleaning process on the subsequently manufactured product is to take samples of that subsequent product and analyze it for residues that might have been left on equipment surfaces. This is possible, but not necessarily an easy task, because analyzing for residues of the prior active (and of the cleaning agent) in the subsequently manufactured product may require significant analytical method development. Assuming the validated methods are HPLC methods, these

methods will have to take into consideration possible new interfering substances from that subsequently manufactured product. If the validated method is TOC, then it will be impossible to measure residues in the next product (assuming the next product is not just inorganics).

In this situation, if (as assumed) I have a visually examined the equipment after the problematic run and if I have a VL for a given residue, I can determine whether that residue was at an acceptable level. Note that I might want to do this for both the active ingredient (API) and the cleaning agent. In this case, however, I am allowed to recalculate the residue limit with the actual cleaned product ("Product A") and the *actual subsequent product* as the next product ("Product B") in the carryover calculation. I do not necessarily have to use the carryover calculation based on any worst case assumptions; using the actual two products is acceptable, and may result in a higher limit (thus making it more likely that the residues would be acceptable). In this situation, I would still treat this as a process deviation; however, the visual examination may help provide assurance that the subsequently manufactured product was acceptable. This would be part of my corrective action; I would still have to deal with preventive actions to keep whatever might have gone wrong from happening again.

These are just three possible used of visual examination apart from use in cleaning validation protocols. They certainly are not mandatory uses, but rather can be considered as part of risk assessment in designing and implementing an overall program.