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The Rationale for Rinse Sampling for Cleaning Agents

For CIP cleaning processes some companies that sample for active by both rinse sampling and swab sampling will only use rinse sampling for measuring residues of the cleaning agent. Why is this done, and is there a rationale for it?

I assume part of the reason it is done is because those companies believe that sampling only the rinse solution for cleaning agent is appropriate to establish that unacceptable levels of cleaning agent are not left behind on equipment surfaces so as to contaminate the next manufactured product. Why can this be a reasonable approach? Before I try to answer that question, I will try to answer why both swab and rinse samples are often used for measuring residues of active ingredient. One of the reasons is that when I take swab samples I can focus on locations which are most “difficult to clean”. How can I determine areas which are most difficult to clean? One issue is location where residues of the previous product have dried out or been baked onto equipment surfaces (such as the air/liquid interface in solution manufacture). Another issue is locations where there are higher amounts of manufactured product at the beginning of cleaning (such as the drain). A third issue might be locations where cleaning solution contact may be limited (such as in dead legs).

Now hopefully when the cleaning process is developed, I have taken into consideration these worst case locations (or, using the terminology of the new FDA process validation guidance, “sources of variation”). However, I want to swab sample these worst case locations and look for active because if the cleaning process is marginal, it is these locations where I would most likely detect active ingredient. (Note that these may also be locations where I specify that visual examination be focused – because generally if one can swab a location, one can also perform a visual examination on that location.) In other words, if the cleaning process is marginal, I would likely pick up failure in terms of high active ingredient at these locations. Rinse sampling is done because typically there are some worst-case locations (such as pipes) that not amenable to swab sampling. (Note for contrast that if I were disassembling all equipment for a manual cleaning process, I might only have to perform swab sampling to clearly establish that the cleaning is adequate.)

So, what is different about measuring residues of the cleaning agent? Let me make a critical (but reasonable) assumption here, which is that the cleaning agent used is readily water soluble and is readily rinseable. If the cleaning agent is not readily rinseable, then the rationale I am presenting does not apply. The rationale is just this – the assumption of worst case locations for residues of active ingredient does not necessarily apply to residues of cleaning agent.

For example, just because the air/liquid interface is a worst-case location where I am more likely to find residues of an active ingredient does not mean I am more likely to find residues of cleaning agent in that same location (as compared to other, easy-to-clean locations). Clearly if my rinsing is inadequate, I will find unacceptable residues of cleaning agent in a worst-case location (for the active), but it is also the case that I will likely find unacceptable residues of cleaning agent on various surface which are easy-to-clean (for the active). It is also the likely case that if rinsing is inadequate, I will also find unacceptable levels of active ingredient on equipment surfaces that are “easy-to-clean” (in the rinsing process, it is not the case that the active rinses away first and then the cleaning agent rinses away).

Let's examine the second example of worst-case locations – a location where there are higher levels of product left behind before cleaning starts. Again, using our assumption of a readily rinseable cleaning agent, if the cleaning process is inadequate it is not likely that I will have acceptable levels of active and unacceptable levels of cleaning agent. A possible objection to this is that perhaps there are some interactions between the cleaning agent and the active (or excipients) such that residues of active (or excipients) that are left behind complex in some way with cleaning agent. While that is a possible objection, hopefully if that is the case such interaction will be discovered in the design phase and a different cleaning agent can be chosen. If for some reason this were not identified in the design phase, then it is likely the case that there will be significant residue left on surfaces such that either (a) the surface will not be visibly clean and/or (b) high levels of active will be left behind such that swabbing for active will result in a failure of the validation protocol.

The third case of worst case location deals with a location where contact of the cleaning solution is limited (such as in a dead leg). In this case, it is not likely that I will have unacceptable residues of cleaning agent without also having unacceptable residues of active. Some of the same arguments used for the previous two situations also apply here.

The main thrust of all these arguments is that the idea of a worst-case location for residues of active are generally not going to apply equally to residues of cleaning agents. The only situation of the three discussed above where this could be true would be the third example (dead legs). But in that situation, it is most certainly the case that cleaning agent residues will only be unacceptable if residues of the active are also unacceptable.

For clarification, these rationales only apply if limits for residues of cleaning agent in the rinse solution are established appropriately. Calculating limits for grab rinse samples in a CIP process is covered in the January 2009 Cleaning Memo.

For further clarification, I am not advocating for CIP process that only rinse samples be taken for measuring residues of cleaning agent. What I am trying to provide is a rationale (perhaps used as part of a risk assessment) why some companies choose to only use rinse samples for cleaning agents in certain situations.