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Is Rinse Sampling Alone Acceptable?

In answer to a question during a recent conference, I presented a minority opinion on rinse sampling, namely that under certain circumstances rinse sampling *alone* can be an acceptable sampling technique for cleaning validation protocols. Objections were made that regulatory authorities do not find this acceptable. The next evening I arrived home to find a message that one of my clients had "survived" a regulatory inspection where the issue of using rinse sampling alone was a key question. This Cleaning Memo discusses what the regulatory documents say about rinse sampling, why rinse sampling has a bad reputation, and the conditions under which rinse sampling alone should be a defendable, science-based option for sampling in cleaning validation protocols.

What Do Regulatory Documents Say?

Here is what the **FDA 1993 guidance** says about rinse sampling:

> "There are two general types of sampling that have been found acceptable. The most desirable is the direct method of sampling the surface. Another method is the use of rinse solutions."

The FDA guidance then goes on to say that advantages of rinse samples are that "a larger surface area may be sampled" and that "unaccessible systems" can be sampled. A disadvantage of rinse sampling is given as "the residue or contaminant *may not* [emphasis added] be soluble or may be physically occluded in the equipment." Furthermore for rinse sampling, a "direct measurement of the residue or containment" should be made, because it is not acceptable that the rinse water just meet compendia tests.
What can we gather from these statements? Clearly rinse sampling is acceptable. And clearly there are certain things you should do (and certain things you should not do) if you use rinse sampling. Note that if the residue is soluble in the rinse solution, at least one disadvantage is removed.

Here is what the **PIC/S document (PI-006-2)** says about rinse sampling:

> "There are two acceptable methods of sampling that are considered to be acceptable, direct surface sampling (swab method) and indirect sampling (use of rinse solutions). A combination of the two methods is generally the most desirable, particularly where the accessibility of equipment parts can mitigate against direct surface sampling."

What can we gather from these statements? First, that rinse sampling is acceptable. Second, that a combination of the two is "generally the most desirable". From this latter phrase, are we to conclude that the two methods *must be* used together for all protocols? While using both methods may be appropriate in certain circumstances (particularly in cases portions of the equipment cannot be swabbed and other portions cannot be rinse sampled), can we conclude that this *categorically prohibits* the use of rinse sampling alone? If so, the same logic would seem to categorically prohibit the use of *swab sampling alone*. I believe a reasonable interpretation of this PIC/S statement is that "while both swab and rinse sampling are acceptable, other things being equal, the use of both can provide a better (more desirable) picture of residues in the equipment. However, this does not preclude the use of swab sampling alone or rinse sampling alone in a cleaning validation protocol."

Here is what the FDA says about rinse sampling in a **December 1998 Human Drug CGMP Note**:

> "While it is understood that rinse samples are capable of sampling larger surface areas, particularly ones which are difficult to access, for the purposes of cleaning validation, rinse samples *alone* [emphasis added] would not be acceptable unless a direct measurement of the residue or contaminant has been made. One disadvantage of rinse samples is that the residue or contaminant may not be soluble or may adhere to the equipment. Some firms use both swab samples, where feasible, and rinse samples during the course of their cleaning validation."

A possible inference in this statement is that under certain circumstances (namely, making sure you use a "direct measurement" of residues), rinse sampling *alone* would be acceptable. Furthermore, the last sentence does not state that "all firms must use rinse sampling and swab sampling where feasible", but rather that "some firms" use both.

Why Rinse Sampling Has a Negative Reputation

This is partly speculation on my part, but two possible reasons rinse sampling has a bad reputation is industry misinterpretation of the regulatory documents and industry misuse of rinse sampling. I believe the previous discussion (above) helps dispel the idea that regulators either don't like rinse sampling nor do they prohibit its sole use. In terms of industry misuse, this includes (1) the lack of sampling recovery studies for rinse sampling, (2) the use of the idea that "PW/WFI in, PW/WFI out, therefore my system is clean" (that is, not *directly* measuring the residue of concern), and (3) a confusion between the analysis of rinse water for validation protocol purposes and the analysis of rinse water for routine monitoring.

Why and How of Rinse Sampling Alone?

One reason for the use of rinse sampling alone is that it simplifies validation. Rather than doing recovery studies for both swab sampling and rinse sampling, only one recovery is needed. Furthermore, the number of samples requires may be reduced. However, the main reason for using rinse sampling alone is that it *minimizes interventions* into cleaned equipment. Particularly for new equipment that is better designed for cleanability and is hard piped, it make sense to utilize rinse sampling alone rather than risk opening the system up and then dealing with possible recontamination from the swab sampling process and from the reassembly process.

The basic conditions that should be met if rinse sampling alone is used include the following:

1. The rinse process covers all equipment surfaces.
2. The analytical method is a direct measure of the residue.
3. A rinse sampling recovery has been performed and is adequate.
4. Limits calculated for the rinse solution have to be adequately justified.

In general, consistency of the rinse process is critical for sampling recovery. For this reason, if a manual rinse is used, it must be carefully controlled to assure consistency of results (an example of a carefully controlled manual rinse sampling procedure could be a extraction of a filling needle in a fixed volume of water for a fixed time under specified agitation conditions). As a general rule, rinse sampling alone should be restricted to equipment where washing/rinsing is performed by an automated CIP process.

The purpose of this Cleaning Memo is to explore the issues in the use of rinse sampling alone (without swab sampling) in cleaning validation protocols.