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THE APPLICABILITY OF CLEANING VALIDATION

Cleaning validation is primarily applicable to the cleaning of process manufacturing equipment in the pharmaceutical industry. Cleaning validation focuses on those cleaned equipment surfaces that, if inadequately cleaned, potentially could contaminate the product subsequently manufactured using that same equipment. This validation primarily covers product contact surfaces in the cleaned equipment (PIC/S, 2004), for these surfaces directly contact the next product. For clarification, the regulatory and scientific requirements for the cleaning of process equipment surfaces are different from those requirements for the cleaning of environmental cleanroom surfaces. While both involve aspects of cleaning, the focus of this book's cleaning validation is product contact surfaces of process equipment.

This includes the interior surfaces of vessels, agitators, piping, hoses, pumps, and other items that directly contact the manufactured product and thus can transfer residues directly to the next product. There are some applications where indirect residue transfer may occur. I like to call these surfaces "indirect product contact" surfaces. Some examples of indirect transfer are clear. The reflux condenser in the organic synthesis of an active ingredient may not directly contact the next manufactured product; however, the

refluxing solvent does contact the condenser surfaces and potentially could carry residues from the condenser surfaces to the solvent containing the active ingredient.

A more controversial example of indirect transfer involves the interior surfaces of a lyophilizer (or freeze dryer). Although debate about transfer from lyophilizer surfaces may be controversial, there is a fairly clear regulatory expectation that cleaning validation will be performed for lyophilizers (FDA, 1993). It is possible that residues left behind (on shelves, for example) potentially could transfer by an airborne route to the manufactured product. Such a transfer has not been demonstrated in real life cases. Such a transfer is more likely to occur with lyophilizing of bulk product on trays than it is with lyophilizing of product in vials. One possible rationale for cleaning validation for lyophilizers is that most companies that lyophilize parenterals will sterilize the lyophilizer surfaces prior to use. The ostensible reason is that bioburden from the lyophilizer surfaces somehow could be transferred to the lyophilized product. If it is possible that bioburden from the surfaces could be transferred, though, is it also not likely that product could be transferred? One interesting feature of residues in lyophilizers is that adherent residues (which are generally most difficult to clean) are least likely to transfer via an airborne route, whereas loosely adherent residues (which are more likely to be removed in cleaning) are more likely to transfer via an airborne route. Whatever the situation, because the products manufactured in a lyophilizer are usually parenteral products, some companies have been asked by regulatory authorities to validate the cleaning of lyophilizers, while others have chosen to pursue cleaning validation for other reasons.

Other types of cleaning cannot be validated because of the frequency of performing the identical cleaning procedure (SOP). For example, for clinical trial materials or for drugs made infrequently (every year or two, for example), it is doubtful that the exact same cleaning SOP would be used three successive times in order to obtain three PQ (performance qualification) runs. While three runs no longer are the regulatory expectation for process validation purposes (FDA, 2004a; FDA, 2004b), in most cases companies still require a minimum of three PQ runs unless a different number is justified. In such cases, the cleaning process cannot be validated; however, it is

still necessary to determine that the equipment is suitably cleaned for the manufacture of the next product. This calls for cleaning verification and involves performing tests similar to those done for the three PQ runs in cleaning validation, except that the tests are performed for each and every cleaning event. Although cleaning verification can be contrasted with cleaning validation, cleaning verification ordinarily should be defined in a cleaning validation policy or cleaning validation master plan.

Still other types of cleaning require neither validation nor verification. For example, cleaning of the outsides of tanks and the cleaning of walls and floors is required under GMPs. There should be SOPs defining those cleaning processes. However, those processes are not critical because the possibility of transfer to the product is remote, making validation unnecessary. When a significant possibility of transfer of residues from such surfaces to the next products exists, that situation should be rectified not by cleaning validation but rather by manufacturing controls. Furthermore, for extremely hazardous drug actives present on non-contact surfaces, there may be more of a concern related to personnel safety as compared to potential cross-contamination of the next manufactured product.

The applicability of cleaning validation should be written into a facility's Cleaning Validation Master Plan to define clear situations that require validation, but also to permit professional judgment in cases that may require considered reflection.

The above chapter is based on a *Cleaning Memo* originally published in October, 2000.

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WHAT'S A CONTAMINANT?

Once at a training session at the FDA's Basic Drug School, I was asked the question whether allowing a specified level of residue in a manufactured product (such as 0.001 of a therapeutic dose of a previous active) was, in fact, allowing manufacturers to produce and release drug products which were "contaminated." My answer at the time was related to the fact that with newer analytical methods, we were able to measure residues at even lower levels, so that it was not feasible to specify that "no residues" of previous products appear in any other product. In giving this matter more thought, my answer would be slightly different. Rather than concede that any measured residue is a "contaminant," I would now answer that question by stating that a contaminant is defined by both the presence of a "foreign" substance as well as the level of that substance in the drug.

This definition is related to the argument that "the dose makes the poison." For example, selenium is considered a poison (causing selenosis) at doses of 500 micrograms, but is necessary in human diets at levels of about 50 micrograms. In fact, selenium is included in some vitamin and dietary supplement formulations at around 100 micrograms (NIH, 2004). This analogy doesn't apply directly to residues in drugs because for the most part we are not considering substances that may have beneficial effects at extremely low levels.

However, consider situations where it is only certain levels of a given substance in a drug that render the substance to be classified

an “objectionable” contaminant. For example, bioburden in a non-sterile oral drug product can be present at certain levels, such as 75 CFU per gram, and not be considered objectionable. However, if those 75 CFU were *E. coli*, then one readily would conclude that the material was objectionably contaminated. It is both the nature of the substance and the level that are important.

This suggests that perhaps we should be more precise in our language as we discuss acceptable levels of residues. Thus, we should avoid phrases like “acceptable level of a given contaminant,” because in some cases it is the level that makes the “residue” a “contaminant.” Therefore, to say that a drug contains a residue of a previous drug at a given level is not to state that it is necessarily contaminated (or even adulterated). One way to look at this is to say that “a contaminant is an objectionable residue” (realizing, of course, that there may other types of contaminants).

This should not be used as an excuse to be sloppy in our cleaning efforts and say that any residue is okay as long as it is below the acceptance threshold. We should be conscientiously applying good manufacturing practices in our cleaning procedures so that any potentially contaminating residue is kept as low as practical. In a Human Drug CGMP Note, the FDA states that although equipment does not have to be absolutely clean as measured by the best available analytical technique, the equipment surfaces should be as clean as “reasonably achieved” by good cleaning procedures (FDA, 2001).

This is also not to be interpreted as saying that for any substance, some measurable amount may be acceptable. Consistent with the PIC/S cleaning validation guide (PIC/S, 2004), for certain allergens and cytotoxic substances, any residue should be below the limit of detection by the best available analytical technology. In such a case, one must still concede that a possibility exists that the drug will have a small, but not measurable (with current technology) residue of the allergen or cytotoxic material. If that unmeasured level of residue could still be objectionable, then in such a case it makes sense to use dedicated equipment.

Nor is it to ignore the fact that, with new information, levels that we regard acceptable today may become objectionable in the future. However, this is one of the tradeoffs we live with in trying to advance medical care.

The above chapter is based on a *Cleaning Memo* originally published in March, 2002.

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ADEQUATE “DOCUMENTED EVIDENCE” FOR CLEANING VALIDATION

A short definition of cleaning validation, consistent with a definition of process validation (FDA, 1987), is “documented evidence with a high degree of assurance that a cleaning process will consistently produce equipment and products meeting predetermined quality specifications.” In an internal audit or regulatory investigation, a key is reviewing that “documented evidence.” What could be included as part of that documented evidence?

One usually first thinks of the cleaning validation summary report. This is an important item. However, there is much more to the documented evidence than just this summary report. The consistency of the cleaning process is not demonstrated solely by the three (or whatever number is required) validation runs. It may be useful to think of the three validation runs as “confirming” the consistency of the cleaning process. The three validation runs are not experiments to determine if residues are acceptable. The experiments should be done earlier in the design of the cleaning SOP. At the point of cleaning validation, one should have a reasonable assurance that acceptable results will be the outcome. Therefore, other documents that could be considered part of the relevant “documented evidence” include the following:

- Cleaning validation master plan or high level policy
- Cleaning validation procedure
- Cleaning procedure or cleaning instruction
- Cleaning process development report or technology transfer report
- Cleaning validation protocol
- Analytical procedure
- Sampling procedure
- Report on rationale for selection of sampling locations
- Report on rationale for challenges (e.g., worst cases) to the cleaning process
- Analytical method validation
- Analytical/sampling method recovery
- Limits calculation report
- Deviation investigation report
- Training records
- Change control documents
- Monitoring records and/or trend reports
- Revalidation report and/or annual cleaning review report

Certainly under the new FDA investigation program (FDA, 2002), a key point to consider is the cleaning validation master plan or high level cleaning validation policy. This higher-level document—a practical necessity though not absolutely necessary—ties together most of the items listed above. One would question, for example, whether a cleaning process can still be considered validated (beyond the initial validation protocol) if it is not covered under a change control policy / procedure. Supporting the higher-level policy may be a more specific cleaning validation procedure document.

Another important document is the cleaning process procedure or instruction (or whatever the detailed cleaning process followed by the cleaning operator is called in a facility). One may have excellent validation data (for example, with all the swab and rinse

samples meeting the properly calculated acceptance criteria), but the cleaning process may be inadequately detailed and controlled such that there is no reasonable assurance that the cleaning process will produce the same data if carried out in the future. Appropriate design of the cleaning procedure is equally as important as appropriate design of the cleaning validation protocol.

The rationale for a cleaning process development report (which sometimes is called a technology transfer report) is twofold. One function is to provide future scientists in your company with a good rationale on how the cleaning process and the various parameters (cleaning agent, cleaning agent concentration, times, temperature, hold times, etc.) were selected. Furthermore, although such reports may not be critical to the validation investigation by regulatory authorities, those regulatory authorities may ask for this information. It is part of the emphasis of the FDA in asking pharmaceutical manufacturers to understand their manufacturing processes (FDA, 2004). A second reason is to provide assurance that the cleaning validation will be successful once the protocol is executed. As mentioned previously, the execution of the cleaning validation protocol should not be viewed as an experiment to test whether the cleaning process is effective; rather the "experiments" should be performed before the execution of the protocol in order to have a high degree of assurance that the cleaning process will be successfully validated when the cleaning validation protocol is carried out.

Other protocol related documents, such as the cleaning validation protocol itself, analytical procedure(s), sampling procedure(s), a report on the rationale for selection of sampling locations, a report on rationale for challenges (e.g., worst cases) to the cleaning process, analytical method validation, sampling/sampling method recovery, limits calculation report, training records, and any protocol deviation investigation report may exist as "stand alone" documents (e.g., analytical method validation), but some may also just be incorporated into the cleaning validation protocol (e.g., justification for sampling locations).

Other documents related to demonstrating consistency after initial validation is complete include the training records (particularly for any retraining on process clarifications and for operators

in manual cleaning processes), monitoring/trending after protocol execution, process-related deviations/investigations, change control, and revalidation.

The purpose of this chapter is not to proscribe certain ways to document cleaning validation but rather to consider all the evidence that can be part of the assurance of consistency of a cleaning process. This chapter should serve as a reminder that any of these documents may be requested as part of an audit or investigation of cleaning validation for a process or a facility.

The above chapter is based on a *Cleaning Memo* originally published in July, 2003.

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WATER QUALITY FOR VALIDATED CLEANING PROCESSES

The quality of the water used for aqueous cleaning is critical for performance. This includes the water quality for any pre-rinse, for the washing step itself, and for any rinses. Quality includes chemical properties—pH, conductivity, hardness, Total Organic Carbon (TOC), etc.—and biological properties, including bioburden and endotoxin. Unfortunately, there are few regulatory guidelines that deal with this subject. (One guidance will be covered later.) However, there are a number of good scientific principles to apply. We'll start with water quality for washing, then cover rinsing, and finally cover pre-rinsing.

Water for Washing

For the washing process, perhaps the most critical element to control is the water hardness (calcium and magnesium ions). Hardness ions are well known to affect the efficacy of cleaning of aqueous surfactant solutions (LeBlanc, 2000). If tap (potable) water is used for cleaning, hardness can be accounted for by using chelants in the cleaning formulation. It can also be a problem if the hardness in the water varies, either seasonally or by source. For example, some municipalities obtain their water both from surface waters and from deep wells. The deep-well water is more likely to have

an elevated degree of hardness. If a cleaning process were designed using the surface water, that cleaning process might not be effective if the deep-well water (with higher hardness) were used. A second concern with hardness ions in any tap water source is that, if alkaline cleaning agents are used (for example, those with potassium or sodium hydroxide), hardness ions may precipitate as calcium carbonate at high pHs. Depending on the conditions of precipitation, the result may cause a white residue on surfaces. That white residue may cause a surface to fail a “visually clean” criterion. This can be minimized by utilizing a cleaning agent with chelants, or by using an acidic post-rinse. The later approach is a common one and a carryover from cleaning processes in the dairy industry where the precipitation of “milk stone” (from the calcium in the milk) in the alkaline cleaning step is a routine feature.

Water for Rinsing

A general principle involving the manufacture of finished drugs utilizing water in the formulation is that the quality of the water for the final rinse should be at least as good as the quality of the water added in the next manufacturing process. For example, if a parenteral drug product is formulated with Water for Injection (WFI), then the final rinse of the previous cleaning process should be with WFI. If an oral drug product is formulated with Purified Water (PW), then the final rinse of the previous cleaning process should be with PW. The rationale for this is that any residues left behind from the final rinse are residues that would be added in the next product anyway. In this way, concerns about residues from the final rinse water itself are minimized. If water is used for rinsing, and the subsequently manufactured product does not have water in the manufacturing process, then additional information is required. For example, if the product is a non-sterile oral, solid dose product, PW clearly would be acceptable for a final rinse. If the aqueous cleaning process involves cleaning an active pharmaceutical ingredient (API) made by an organic synthesis route (in which no water is used in the synthesis), the most common approach is to use deionized water as the final rinse (such facilities rarely have a validated

Purified Water system). Of course, in that specific situation, some solvent rinse would be used after the water rinse to remove any water from the equipment, being that water would interfere with the organic synthesis.

One additional concern about the final rinse quality is that one also should be aware that using a lower quality water for the final rinse may leave behind mineral deposits, which in and of itself would not be a problem; however, those mineral deposits may be visible when the rinse water dries, and therefore would cause the equipment to fail any “visually clean” criterion.

Water for Pre-rinsing

In most cases, the quality of the water for pre-rinsing is the least critical of the three cases. After all, why be scrupulous about the quality of the water for this step when the greater issue is removing all the previous product? Water for pre-rinsing is solely used to flush residue out of the system prior to the washing step itself. Some companies will choose to recycle their water, and use for the pre-rinse the water from the previous final rinse (*not* from the initial post-rinses, for these will be highly contaminated with residues and cleaning agent). Choices of water quality to use for the pre-rinse sometimes are based on practical issues, such as using the same water as was used for the washing step.

Regulatory Guidance

One useful regulatory guidance on water quality for cleaning processes is the EMEA’s “Note for Guidance on Quality of Water for Pharmaceutical Use.” (EMEA, 2002). The relevant comments regarding water for cleaning are given in Table 5 of that document. That table is summarized as follows—

Cleaning step	Product type	Minimum acceptable water quality
Initial rinse	Intermediates and APIs	Potable water
	Non-sterile drug products	Potable water
	Sterile drug products	Purified water
Final rinse	API	Same quality of water used in API manufacture
	Non-sterile drug product	Purified water, or same quality of water used in API manufacture if higher quality than Purified Water
	Sterile non-parenteral drug products	Purified water, or same quality of water used in API manufacture if higher quality than Purified Water
	Sterile parenteral drug products	Water for Injection

Note that this guidance does not address the quality of water used for the washing step.

Although not regulatory documents per se, FDA 483's have been sent to some companies if they have used potable (tap) water for cleaning. However, the main issue was not the use of potable water but rather the lack of a monitoring program to measure and control the quality of the water. Such a monitoring program generally includes both chemical and microbiological quality of the water. Although records from testing at the water source by the municipality may help, it is best to have an onsite monitoring program in place in the individual pharmaceutical facility. This is a better measure of the water quality *as it is used by the facility*.

Overall Choices

It should be acknowledged that in any cleaning operation there may have to be some adjustments to deal with what can be achieved practically. Though it may be possible to justify the use of tap water as a pre-rinse, PW for the washing step, and WFI for the rinses, the engineering and quality concerns involved in having all three water sources piped for appropriate use may be a challenge. In addition, if tap water were chosen for any process step, assuring consistency of that water would be critical. That scenario usually would include a comprehensive chemical and microbiological monitoring program.

The discussion in this chapter is not meant to prescribe certain water qualities that must always be used. Rather, this discussion is meant to explore how water quality might affect the various steps in the cleaning process. Such information can be critical in selecting the appropriate water quality for a given step or a given process.

The above chapter is based on a *Cleaning Memo* originally published in June, 2001.

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