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Is Pre-cleaning Allowed?

Occasionally when I review regulatory documents, something jumps out at me that I had not fully thought about before. In a review of the FDA's Human Drug CGMP Note of the second quarter 2001, I noticed the following FDA question and FDA answer:

> Question: "Must a firm quantify the amount of residue on equipment surfaces in support of validating the cleaning procedure?"
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> Answer: "In validating the original cleaning procedure, a firm need not quantify the level of chemical contamination remaining after manufacturing a product and before cleaning during validation exercises. The firm must, however, ensure that they validate the proposed cleaning procedure as for routine use, and not pre-clean or otherwise attempt to make it easier for the procedure being validated to meet its cleaning objectives."

In this Cleaning Memo, I am not addressing the question of quantifying the amount of residue before cleaning is performed (but you can read the FDA answer yourself). The focus is the statement about "pre-cleaning".

As we are all aware, "pre-cleaning" of some type is used in many cleaning procedures. For example, in automated CIP processes, it is typical to have an ambient water flush prior to cleaning with a detergent or caustic solution. In some manual cleaning processes, the equipment may be pre-soaked prior to scrubbing in a sink with a brush. In lyophilizer cleaning, an initial action may be physically removing (such as manually) any broken glass fragments prior to an automated WFI flush.

So, the question is, are these initial steps described above a type of pre-cleaning that is not allowed under this FDA CGMP Note? If the answer is "Yes", then we are in a lot of trouble. However, I think what the FDA is getting at is doing some kind of pre-cleaning in the validation protocols that is not ordinarily done. I think that as long as the pre-cleaning is part of the written procedure, as long as it is adequately specified/defined, and as long as it is challenged in the validation protocol, pre-cleaning should be acceptable.

By "part of the written procedure", what I mean is that is documented somewhere. Usually this is in the written SOP, although it might be part of the PLC program for an automated process. It might be part of the manufacturing process for the drug product. For example, a firm might state that at the end of the manufacturing process, the equipment is immediately (or at least within a short time) flushed with ambient water. In this case, the equipment may be allowed to sit uncleaned for a period (this period is the dirty hold time) until it is cleaned by a standard cleaning process. And in this case the "pre-cleaning" may not be in the cleaning procedure, but in the manufacturing procedure.

By "adequately defined", what I mean is that it is not just a general statement like "Flush with ambient Purified Water", or like "Presoak in hot water". More specificity is required, such as "Flush with ambient Purified Water for X minutes" or "Presoak equipment in a solution of 1% Detergent XYZ at ambient temperature for a minimum of M hours but no longer than N hours". There may be a different level of specificity involved in certain situations. For example, in a lyophilizer pre-cleaning of broken vials, the procedure may specify to "remove the glass fragments until there are no glass fragments visible on the shelves". In pre-cleaning for an ointment, the procedure may say "Using a plastic scraper, remove gross soil"; but, since what is "gross soil" is subjective, there might be digital photographs of what represent adequate pre-

cleaning and what represent inadequate pre-cleaning.

By “challenged in the validation protocol”, I mean that worst cases (if such worst cases are possible) should be considered in the validation protocol. For example, in the manual cleaning pre-soak example, if the pre-soak time is “a minimum of M hours”, then it would be preferable to make sure that each of the protocol runs was performed at exactly M hours. For clarification of what “exactly” means, I am not suggesting that if the minimum time is one hour, you have a stopwatch and time it to precisely 60 minutes. Specifying a challenge time of 60 to 80 minutes should be acceptable in this situation. Note also that I recommend that each of the protocol runs be at this challenge condition. The reason is that for the most part the challenge conditions will be conditions that are less stringent (such as shorter time) in terms of pre-cleaning effectiveness; in such cases, there should not be a concern about interfering with scheduling on commercial equipment, so having all runs at the least stringent cleaning process condition should be practical.

The bottom line is that I think what the FDA is referring to in the Human Drug CGMP Note is pre-cleaning done in a protocol that is not routinely done as part of overall cleaning process. However, that should remind us that pre-cleaning should be a standard procedure, which is adequately specified, and which is challenged in the validation protocol.