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Equipment Grouping Strategies for Cleaning Validation

The purpose of "equipment grouping" for cleaning validation is to simplify validation in cases where there are multiples of either "similar" or "identical" pieces of equipment or equipment trains. The objective in equipment grouping is to classify the different pieces of equipment as "identical" for cleaning validation purposes so that it is not necessary to perform three PQ cleaning runs on each individual piece of equipment. Just as for product grouping, there are a number of conditions that must be met before one can appropriately group together different pieces of equipment for cleaning validation purposes. For now, just the simplest case of one drug product that can be made in any number of "identical" manufacturing equipment or trains will be considered. In this case, for each piece of equipment, there must be the same manufacturing procedure. Furthermore, each piece of equipment must be cleaned with the identical cleaning SOP.

One key is to verify that the different pieces of equipment are, in fact, identical for cleaning validation purposes. For example, it usually would be inappropriate to try to group together a double cone blender and a V-blender. They may be cleaned with the same SOP, but the "geometry" of cleaning would be different. If one were considering two V-blenders from different manufacturers, there may be problems demonstrating they were identical for cleaning validation purposes. Even with the same model of V-blender from one supplier, the FDA has suggested in a Human Drug CGMP Notes (September 1999) that one should really depend, not on the manufacturer's assertion, but rather on the IQ/OQ evaluation to demonstrate that two pieces of equipment are truly identical. It may be the same model, but some engineering details or materials of construction may be different.

However, if the different pieces of equipment can be documented to be "identical", then grouping them together for cleaning validation purposes is straightforward. For the total number of pieces of equipment, three PQ runs should be performed. Usually it is best to not perform all the three cleaning PQ runs on only one item. If there are two identical V-blenders, for example, one PQ run should be performed on one blender and two PQ runs on the other blender. With three identical blenders, it is preferable (but not absolutely necessary) to perform one PQ run on each of the three blenders. For four or more blenders, one could either perform one PQ runs on each of three blenders, or else choose the more conservative route of doing one PQ run on each blender (in other words, do more than three PQ runs). If the former is chosen, then at any revalidation, those blenders for which a PQ run was not performed initially should be targeted for the revalidation.

A second case for equipment grouping involves items that are similar in every way except for size. This usually involves grouping together simple equipment, such as utensils or storage vessels. Why should this be limited to simple equipment? What is different about complex equipment that might disqualify it from an equipment grouping strategy? A key feature for equipment grouping is that the items be identical **for cleaning purposes**. The more complex the equipment is, the more difficult it becomes to say the equipment will be cleaned the same. One can certainly imagine very large equipment, which may be more difficult to clean because with the distances involved, the impingement force from a spray device is less than in the case of a smaller item. With a smaller item, one can also argue that the ratio of surface area to product batch size is much larger, and therefore residue limits will be significantly lower. One can also argue that as equipment gets smaller, geometry because more significant and cleaning may be more difficult. For that reason, equipment grouping for items of different sizes should generally be limited to very simple items, such as utensils of

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different size or to simple storage tanks. [This said, it should be noted it is at least **theoretically** possible that if one can conclusively document that one size (the largest or the smallest) is the most difficult to clean, then it would be possible just to run three PQ runs on that most-difficult-to-clean size, and have the validation apply to all sizes.]

When items of different sizes are grouped together, there are two options for handling PQ runs. The more conservative option is to perform three PQ runs with the largest size and three PQ runs with the smallest size. If those two sizes are successfully cleaned, then it is a reasonable assumption that all intermediate sizes should also be cleaned. The less conservative option is to perform a total of three PQ runs, with one run being on the largest size, one run being on the smallest size, and the third run being on any size. In either case, a successful validation would result in the conclusion that the cleaning of all sizes within the range from the largest to the smallest were also validated.

There are a number of items that make grouping strategies for equipment more difficult. One is that in many cases the cleaning processes for the largest and smallest sizes are somewhat different. Even though the cleaning agent, cleaning agent concentration, temperature, etc. in the two SOPs are identical, not everything in the cleaning situation remains the same. Things that may be different include the amount of cleaning solution used and the ratio of cleaning solution to surface area and/or to residual product (to be cleaned). In certain cases where impingement is a major factor in cleaning, it may be necessary to say that the cleaning processes are not identical (or perhaps that the lower impingement in one case makes it the worst case). In cases where factors such as impingement are not crucial, the key to say the cleaning process is the same is to confirm that contact time with the surfaces is the same.
A second factor in dealing with different sizes is residue limits. In dealing with the same target residue, the amount allowed per surface area (in units such as $\mu g/cm^2$) will generally be lower with smaller vessel sizes. This is due to the fact that in calculating such limits, the limit is directly proportional to the batch size and inversely proportional to the product contact surface area. In most cases, one will find the that the ratio of batch size to surface area will be smaller with smaller equipment sizes. Therefore, one can perform three PQ runs on the largest size at its calculated residue limit and three PQ runs on the smallest size at its residue limit. However, if one does a total three PQ runs, but mixes together the largest and smallest to achieve a total of three PQ runs, it is probably preferable to select the lowest residue limit for all PQ runs (which will usually be the residue limit for the smallest size equipment).

It should be obvious that unless the equipment is identical from an IQ/OQ perspective, equipment grouping can be very complex. As with product grouping, one can reach a point where it is actually simpler to validate items separately rather than to do the work to justify an equipment grouping strategy. This will have to be evaluated on a case-by-case basis at each facility. And, as with product grouping, the procedures and criteria for equipment grouping should be explicitly stated in a policy or procedure for that facility.

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