Cleaning Memo for October 2017
Meaning of "Dedicated"?

I often get questions about how to handle cleaning validation for dedicated equipment. As I mentioned in a recent Cleaning Memo, words and wording are very important when we read regulatory documents or ask questions about what we should do. What "dedicated' means is a good example of this.

I generally see the word "dedicated" to be used in at least one of three ways:

> In one case, "dedicated" means I am only making a certain *type of product* on my equipment. For example, the equipment is dedicated to making only dermatologicals. Or it is dedicated to biotech. Or it is dedicated to making to only making products with highly hazardous actives. Or it is dedicated to materials for clinical trials (investigational medicinal products, or IMPs).
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> A second case is "dedicated" means I am only making *one active* on this equipment, albeit *at different strengths*.
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> A third case is when "dedicated" means I am only making *one formulation* (same active and same excipients, but perhaps with different batch sizes) on this equipment.

I'm sure you can see how each of these may be handled different for cleaning validation programs. I'm not sure how the first use helps a lot. However, it is a valid use of the term "dedicated". Certainly knowing that only a certain type or class of products is made on my equipment can help me restrict what I have to do for cleaning validation. In all cases I am still going to set acceptance limits, determine appropriate sampling, decide on appropriate analytical methods, and the like. However, key issues for dealing with acceptable practices will typically be different in biotech facilities, in dermatological facilities, in highly hazardous facilities and in clinical trial material facilities. While we can discuss what is appropriate in each of those dedicated situations, the fact that it is "dedicated" does not come into play as such when I am trying to set up a cleaning validation program. What is more critical is what it is dedicated *to*.

So, let's move on to the second case, where only one active is made on my equipment. Is this is a case of "dedication" that is meaningful for cleaning validation. Does this fit into the FDA statements on "dedication"? Well, to be perfectly clear the 1993 FDA cleaning validation guidance only uses the term "dedicate" or "dedicated" for two situations where the cleaning is difficult. The first situation involves the following specific sentences in Section III:

> "Bulk pharmaceutical firms may decide to dedicate certain equipment for certain chemical manufacturing process steps that produce tarry or gummy residues that are difficult to remove from the equipment. Fluid bed dryer bags are another example of equipment that is difficult to clean and is often dedicated to a specific product."

The second situation involves bulk manufacture where there may be by-products from the manufacture of "potent" actives. The specific wording in Section V is:

> "In a bulk process, particularly for very potent chemicals such as some steroids, the issue of by-products needs to be considered if equipment is not dedicated."

Other phrases in that 1993 guidance that may be interpreted (or perhaps misinterpreted) as "dedication" deal with *different batches of the same product*. The specific wording in Section III is:

> "If firms have one cleaning process for cleaning between different batches of the same product and use a different process for cleaning between product changes, we expect the written procedures to address these different scenario."

The specific wording in Section IV is:

> "Determine the number of cleaning processes for each piece of equipment. Ideally, a piece of equipment or system will have one process for cleaning, however this will depend on the products being produced and whether the cleanup occurs between batches of the same product (as in a large campaign) or between batches of different products. When the cleaning process is used only between batches of the same product (or different lots of the same intermediate in a bulk process) the firm need only meet a criteria of, 'visibly clean' for the equipment. Such between batch cleaning processes do not require validation."

The important issue here is what "batches of the same product" means. If I have a drug product with a level of 100 mg active and a second one with 200 mg of the same active, are those two products the *same* product? I suspect it is a stretch to make that claim, when the formulations are different. Yes, there may be ways to simplify cleaning validation in that situation where only those two formulations (different active levels) are the *only* products made on that equipment. However, I would not consider that situation as "dedicated" equipment for cleaning validation purposes. One simplification in this case may be to use a grouping (matrixing) approach, selecting the higher strength as the "most difficult to clean" product (based on the expectation that it is more likely to leave higher residue levels of the active on cleaned equipment surfaces).

This brings us to the third case, where dedication is one formulation only. Clearly in this case, the concerns for cleaning validation are reduced. This may be a situation where, between batches of the same formulation, I *may* only do what is sometimes referred to as "minor cleaning". Minor cleaning may involve vacuuming between batches of the same formulation in solid oral drug product processing, or a water flush between batches of the same formulation in liquid oral drug product manufacture (or as mentioned in last month's Cleaning Memo, a solvent flush between batches of the same intermediate or active in small molecule API synthesis).

In this last case, the minor cleaning is *not* generally a validated cleaning process. There is not necessarily an expectation that the equipment will be visually clean after that "minor cleaning". The goal in minor cleaning is to minimize batch intermingling and/or to improve process efficiency (such as being able to produce more batches in solid oral dose

manufacturing before buildup of product on equipment surfaces interferes with product *physical* properties). While that minor cleaning does not require validation itself, that minor cleaning should be considered as *part* of my overall validation strategy at the end of a fixed number of batches in a campaign. That is, does the "difficulty of cleaning" of that final batch change as I increase the number of batches in a campaign, even though the next campaign may be the same formulation? If the next product in the next campaign is the same formulation, I may also be able to only set limits for my cleaning agent and for bioburden (in non-sterile manufacturing), and strictly rely on visually clean for carryover of the active. This also assumes that there is no buildup of degradation products as the campaign proceeds.

As has been suggested, this concept of "between batches of the same product" may also apply to campaigns where campaigns of different products are made on the same equipment (note that this is taking us outside the concept of equipment dedicated to one formulation). For example, I make eight batches of Product A on equipment, with minor cleaning between batches and a full, validated cleaning after the eighth batch. I then make ten batches of Product B on that cleaned equipment, with minor cleaning between batches and a full, validated cleaning process after the tenth batch. While not strictly "dedicated" equipment, it appears to fall within the constraints given by the FDA of "between batches of the same product".

As a side issue, I will address another issue along this line because the question will inevitably come up. The FDA 1993 guidance also states that "When the cleaning process is used only between batches of the same product (or different lots of the same intermediate in a bulk process) the firm need only meet a criteria of 'visibly clean' for the equipment. Such between batch cleaning processes do not require validation." I must admit I have never fully understood the intent of this wording. As ordinarily done in the industry there is generally no expectation that minor cleaning between batches of the same product be validated. For example, in solid oral dose manufacture, it generally is not an expectation that equipment be visually clean after minor cleaning. Furthermore, for liquid oral dose manufacture using a water rinse between batches, the equipment may appear to be visually clean when viewed in the wet state (it may be viewed in the wet state if drying is not done). However, it is likely in some cases that equipment viewed in the wet state and noted as visually clean would *not* be visually clean if viewed in a dry state. Perhaps the intent of the FDA is that this requirement for visually clean only applies if a full cleaning process (and not a minor cleaning process) is performed between batches. In that case, visually clean may be adequate to demonstrate lack of cross-contamination of the active between batches (in this case, contamination refers to changing the concentration of the active in the next processed batch). If that is the case, it would still seem that in many cases, validation would be required if cleaning agents were used or if there were bioburden concerns. So, I am still not entirely clear about the FDA's intent.

Whatever their intent, my intent here is just to help clarify different uses of the terms "dedicated" and "dedication" so we understand their different uses, making sure all involved in a discussion are on the "same page".