January 2006
Acceptance Criteria for Dedicated Equipment

This Cleaning Memo addresses the question of what residue limits should be set for manufacture of one product in dedicated equipment. Before we get into those details, it is necessary to restate some important issues related to dedicated equipment so that it is clear that residue limit must be set for dedicated equipment, and that cleaning validation ordinarily must be done.

The 1993 FDA cleaning validation guidance states that "When the cleaning process is used only between batches of the same product … the firm need only meet a criteria of 'visibly clean' for the equipment. Such between batch cleaning processes do not require validation." Since "between batches of the same product" could refer to dedicated equipment, some have interpreted this (understandably so) to mean that cleaning validation is not required. Furthermore, the interpretation could be that the only requirement for such cleaning in a validation protocol is that the equipment be visually clean. What this ignores is that in dedicated equipment using a detergent as a cleaning agent, one should be concerned about the carryover of the detergent to the next batch of product. It also ignores any possible concern about contribution of bioburden and/or endotoxin to the next manufactured batch.

For the most part, industry has realized these issues and has conducted cleansing validation for dedicated equipment. This issue has also been "corrected" by the FDA in 2002 in its Compliance Guidance Manual 7356_002, which states that a "lack of demonstration of effectiveness of cleaning" for dedicated equipment warrants a warning letter. What is a "demonstration of effectiveness of cleaning" except cleaning validation (although it could be cleaning verification, which I usually consider as part of an overall cleaning validation program)?

So, if cleaning validation should be done for dedicated equipment, what should the acceptance limits be? Criteria for dedicated equipment for detergent, bioburden and endotoxin should be determined no differently for dedicated equipment than they are for non-dedicated equipment. The limit for detergent will be set based on toxicity, with the next product being a batch of the same product (since it's dedicated equipment). Limits for bioburden will be set typically on industry standard practices, such as 1-2 CFU/cm2. Limits for endotoxin will be set based on WFI specification.

This brings us to the issue of setting limits for the active. How exactly is that done? There are at least three options to consider. The first is to say that the equipment must be visually clean. If the same active carries over to the next product, my main concern is that the carryover not affect the level of active in the next product. This can be readily estimated assuming a visually clean level of 4 µg/cm2. The only other concern is the issue of lot integrity. Yes, I may carryover some active to the next batch, and it may not significantly affect the active level in that batch, but can I treat these as separate lots if a recall is necessitated based on a problem with the active in the first batch? It is for this reason that some companies choose to actually set limits for the active and measure it in a cleaning validation protocol.

The other two options are to set specific values for limits. One way to set a specific value is to say that if 0.001 of the dose of a different active is acceptable in the next product, then 0.001 of a dose of the same active should also be acceptable. Therefore, set limits using the same formula for non-dedicated equipment, just

using the same product as the next product. Another way to set a specific value is to establish a default limit, such as 10 ppm of the active in the next batch. If this default limit were used, it would be used as a default independent of the dose-based (MAC) calculation (although it conceivably could also be used as an "either/or, whichever is lower" with the dose-based limit). If this option is chosen, it is helpful to perform a "reality check" to confirm that 10 ppm is an acceptable level in terms of effect on the strength of the active in the next batch as well as in terms of lot integrity. Note that there is no need to be concerned about issues like allergenic effects, cytotoxicity, and reproductive hazards of the active, since any carryover of the active should not contribute to any change in these properties (in dedicated equipment, the next batch has the same active).

The purpose of this Cleaning Memo is to clarify the need to generally perform cleaning validation for dedicated equipment. Note that there may be specific exceptions to this requirement. For example, if I were making a bulk API, and cleaning it with a volatile solvent such as methanol, I may not have to measure detergent residue or bioburden. However, even if I were to choose to use a requirement of only visually clean for the active, I would still perform a cleaning validation protocol. The only acceptance criterion may be visually clean, but I would still execute it as a formal protocol.