June 2008
Still More on Floors and Walls

Last month's Cleaning Memo elicited more responses than usual. Therefore, I am taking the liberty to wait until July to talk about "revalidation", and will continue to discuss the issue of setting limits for and measuring residues on floors and walls.

Two basic assumptions in last month's Cleaning Memo were (a) that floors and walls could be a concern for cross-contamination, but that they are better addressed as part of a containment program, and (2) any residue on floors and walls that could contaminate the next manufactured batch were relatively loosely adherent residues (because of the need for airborne transfer from floors and walls into the manufactured product), and hence would be readily removed by general "housekeeping" cleaning procedure used for floors and walls.

Some people suggested that it is appropriate to measure residues on floors and walls in other industries, and therefore it may be appropriate for pharmaceutical manufacture. Measuring bioburden and checking for listeria in fish processing was one example given. Another example cited was bioburden on surfaces for clean rooms. Those are all valid concerns for those specific situations. However, I'm not sure they apply to previous product actives in either sterile or non-sterile manufacturing (although certainly the measuring of bioburden on surfaces applies to situations where manufacturing is in a cleanroom). Even on that issue it is important to make a distinction between what we should do for cleaning validation for process equipment and what we do for validation of cleaning (sanitizing) processes within a cleanroom. In fact, what is done for cleanroom cleaning is not ordinarily referred to as "cleaning validation". Whereas the cleaning (sanitizing) products may be validated to be effective against certain organisms, the overall cleaning program is generally called an "environmental monitoring" (EM) program. It is not the same as cleaning validation for process equipment, where once the cleaning process is validated, and the extent of analytical testing is reduced for routine monitoring. For an EM program for cleanrooms, the same sampling is continued routinely on a fixed schedule. I might also note that another difference between process equipment cleaning validation and cleanroom environmental monitoring is that cleaning validation has residue limits (above which the cleaning g process fails), whereas environmental monitoring has action and alert levels (above which I will do an investigation, but not necessary reject all product made during the time that levels were exceeded).

Another issue was whether I was confusing occupational exposure with active cross-contamination. I do realize there is a difference, but what I was trying to suggest was to leverage occupational exposure data (which may have already been performed) to support a low risk of cross-contamination. If such cross-contamination can be modeled and if such models (which are clearly a worst case) can indicate a low risk, then it would not be necessary to perform the air sampling during the subsequent placebo run, nor necessary to measure residues of the prior active in the subsequent placebo product (as I suggested last month).

A further issue was whether I was trying to make this a cGMP requirement. That was certainly not my intent. As I suggested in the last paragraph, this should not be something that every company should do. However, if several companies published data supporting the minimal probability of cross-contamination by an airborne route from floors and walls to subsequently manufactured product, this may be an issue that can be "put to rest" as not a significant concern. I believe that such studies, if performed, will actually demonstrate the lack of such transfer.

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A last issue relates to a possible cause of this concern over floors and walls. Annex 15 of the EU's GMP's states (paragraph 38) that "Normally only cleaning procedures for product contact surfaces of the equipment need to be validated." That sounds good enough – we focus on equipment and we focus on product-contact parts. What follows is something that may be causing some confusion: "Consideration should be given to non-contact parts." What does "non-contact parts" refer to? Could it conceivably apply to floors? Perhaps, but perhaps not, because it refers to "non-contact parts", which sounds like equipment parts. The source for this paragraph in Annex 15 is paragraph 7.3.1 of PIC/S PI 006-3. In that document, the full paragraph reads, "Normally only cleaning procedures for product contact surfaces of the equipment need to be validated. Consideration should be given to non-contact parts into which product may migrate. For example, seals, flanges, mixing shaft, fans of ovens, heating elements, etc." Certainly the list of "non-contact parts" in the PIC/s document are merely examples, but there is no suggestion in that more detailed document that cleaning validation for floors and walls is an expectation. The upshot is that the origin of concern about floors and walls in a cleaning validation program is a mystery to me.

I believe that cross-contamination from floors and walls is not a significant risk. However, right now it is my belief. It would nice to have some supporting studies that back this up. That is why I suggested (last month) the types of studies that can put this concern to rest.

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