Cleaning Memo for August 2016
What is Placebo Sampling?

Placebo sampling (also called a "placebo run") is a procedure in which I process a placebo product (with no active) in my manufacturing equipment. After processing that placebo product, I measure a residue of a prior active (the residue of the prior active left after the cleaning of that prior product) in the placebo product. I then compare the concentration of the measured residue to the calculated limit in the next product (what I commonly call the L1 limit). Of course, I will do sampling at various points in the processing to deal with any preferential transfer issue (transfer of residues to a small portion of the next processed product). A good (but not perfect) analogy for placebo sampling is a media fill. In a media fill I might process media on my aseptic vial filling line much like I would for product manufacture. I then incubate all filled vials to determine the suitability of my aseptic line and associated procedures to adequately protect filled product from microbiological contamination.

Placebo sampling is not something new. The first reference I am aware of is from 1989 in a paper by D W Mendenhall ("Cleaning Validation", *Drug Development and Industrial Pharmacy* 15(13), pp. 2105-2114). Mendenhall referred to a type of sampling he called "Pseudo-Product Samples", which is what is commonly now called "placebo sampling".

The next reference is the 1993 FDA Cleaning Validation Guidance. In Section VI of that guidance is a paragraph on "Placebo Product". The FDA guidance reads: "In order to evaluate and validate cleaning processes some manufacturers have processed a placebo batch in the equipment under essentially the same operating parameters used for processing product. A sample of the placebo batch is then tested for residual contamination." The FDA then goes on to give some concerns about this type of sampling, and finally states "Because of such problems, rinse and/or swab samples should be used in conjunction with the placebo method."

It is for this reason cited by the FDA that placebo sampling is not commonly used for product contact surfaces of equipment. If I can do swab and/or rinse sampling appropriately, why go to the effort of placebo sampling? In addition to the problems pointed out by the FDA, a major concern is having an analytical method that can measure the target residue in the placebo product itself (I may have to do more analytical method development if I am trying to measure an active in a matrix of excipients, as compared to doing so in pure solvent).

This brings me to my May 2008 Cleaning Memo titled "More on Floors and Walls". In that Cleaning Memo, I discuss the issue of possible transfer from *non-product contact surfaces*, specifically floors and walls, into processed product. The route of such contamination is typically airborne, although it could be by other vectors such as operator's gowns or gloves. One way to assess possible transfer from floors or walls is to measure airborne residues during processing of a product. That is, if I am concerned about transfer of the active of Product A into Product B, I might have previously

measured airborne residues of the active in Product A during the manufacture of Product A (done primarily for operator safety reasons). Low levels may suggest the low risk of potential transfer to room surfaces, and hence low risk of transfer from those surfaces to Product B. It should be noted, however, that although airborne transfer *from product to floors/walls* is one possibility, others such as product spillage and poor operator practices may also be involved.

Another option is to measure airborne residues of the active of Product A *during the manufacture of Product B*. Low airborne residues in that situation would give me more confidence in the low likelihood of transfer *from floors/walls* into Product B (although it is at least theoretically possible, but not at all likely, that residues of the prior active were still in the air from the previous manufacture).

A third option is to do placebo sampling after manufacture of Product A. That is, I manufacture Product A, and then clean the equipment and optionally the room as is ordinarily done. Then I process a placebo of Product B, and look for residues of the active of Product A in the samples of that placebo. One difference between placebo sampling and airborne sampling is that, if done correctly, the placebo sampling collects *all* possible residues that could transfer into the manufactured placebo. That includes residues from direct product contact surfaces (such as process equipment interior surfaces), indirect product contact surfaces (such as interiors of isolators) and non-product contact surfaces (such as floors and walls), as well as (theoretically) any possible residues in the air itself (independent of transfer from room surfaces).

So while a placebo study may allow one to determine whether transfer of residues from prior manufacture is acceptable or not, it doesn't tell the full story. If the residues are unacceptable, you don't know what the source of residues is unless you have previous process equipment cleaning validation data (which deals with the direct product transfer). However, even with that help I still am not able to separate out indirect and non-product surface contributions to transfer. If the residues in the placebo are acceptable, there may be some unknowns (I still don't know the relative contributions of various sources), but at least I have demonstrated an *overall* acceptability.

If a placebo study is performed, I generally don't recommend that placebo sampling be done as a validation study. I generally like it to be done as a study that is part of an overall risk assessment to deal with residue sources other than direct product contact surfaces.

One possible variation of a placebo run is to actually measure residues of the previously processed product in an *actual* product. There are several complications here. One is the need to measure residues of the previous active *not only in excipients* of the next product, but also in the presence of the *active* in that next product. There may also be financial issues, depending on the cost of the active in that next product. Finally, there is always the problem of getting overall unacceptable residues transferred to an *actual* product. The good news (or should I say bad news) in that situation is that regardless of whether I get

unacceptable residues in a placebo or unacceptable residues in an actual product, I am not going to be happy and will spend significant effort in a suitable investigation.

There may be other situations where a placebo run might be suitable. For example, in situations where a facility is being converted to a different use (but still for pharmaceutical manufacturing) and I have concerns about non-product contact surfaces, in addition to sampling and measuring residues directly on room surfaces, I might also consider the value of a placebo run in providing assurance about suitable decontamination for the room itself.

The purpose of this Cleaning Memo is *not to require* placebo sampling in any specific situation. Rather the purpose is to show the possible value of such a procedure in certain situations.