Cleaning Memo for September 2016
What is Placebo Cleaning?

Placebo sampling was discussed in the August 2016 Cleaning Memo. Sometimes "placebo *sampling*" is confused with "placebo *cleaning*". This Cleaning Memo will address what placebo cleaning is, and its relationship to placebo sampling.

Just to refresh our memories, placebo *sampling* is done after a cleaning process; it involves manufacturing a placebo product on the cleaned equipment, and then measuring the residues left over from the cleaning process in that manufactured placebo. Placebo *cleaning* is where I "manufacture" a placebo product on the "soiled" equipment in order to effectively clean that equipment.

Here is a simple example of placebo cleaning. I manufacture a petrolatum ointment on my equipment (a screw blender, for example). Then, rather than clean the equipment with an organic solvent or an aqueous detergent (or a combination of the two), I clean the equipment by passing a placebo through the equipment on a *continuous* basis. That placebo may be a true placebo of the next petrolatum product to be manufactured on that equipment, or it may be just pure petrolatum (I'll cover another option shortly).

How do I know that the cleaning process is effective and complete? One way is to measure the concentration of the previous active in the placebo product as a function of time. Hopefully what I would see is an initial high concentration of that previous active in the placebo. That initial high concentration would gradually decrease until such time that the concentration in the placebo was at a predetermined acceptable level (based on the potential contamination of a "next" product).

I'm sure you can already see some potential issues with this type of cleaning. One issue is whether there are locations in the equipment where material could "hang up" and be released at a later time (think of this as a type of "dead leg"). The best way to deal with this issue is to have equipment designed to prevent these types of hold-up volumes. It may also be possible in the placebo cleaning process is have several "pauses" in the placebo cleaning processing. If there are issues with hold-up locations, I might see a "blip" up in the concentration of the previous active each time I stop and start the process again. Also, just for clarification, this type of placebo *cleaning* also inherently involves placebo *sampling* (although the reverse is not true; I can do placebo sampling *without* doing placebo cleaning).

A second issue with this type of placebo cleaning is that once the placebo cleaning is completed, and I start manufacturing the next product, I just process that next product for a given time to clear the placebo out of the equipment. I can do something similar to what I did for placebo cleaning in reverse. That is, as I start manufacturing the "next" drug product, I measure the concentration of the desired active in that drug product as a function of time. I may initially see a very low concentration until it finally reaches the specification value for that active in that new product. If I have adequately dealt with

potential hold-up locations in my placebo cleaning, the concern for that "hold up" problem occurring is minimized as I manufacture the drug product and flush out the placebo.

Note that in this type of placebo cleaning, there may be some initial "precleaning" where I open the equipment and physically remove (using a plastic scraper, for example) the bulk of the previous petrolatum product before I close up the equipment and start my placebo cleaning.

I said there is one other possible option to consider. That third option is to clean the equipment not with a true placebo, but to clean it with the *actual* next product. Using the same example of a petrolatum ointment, for cleaning I start processing the next petrolatum drug product. As a function of time, I measure *both* the concentration of the *previous* drug active and the concentration of the drug active in the *second* product. Hopefully what I see is a gradual decline in the concentration of the previous drug active and a gradual increase in the concentration of the active in the second drug product. I design my cleaning process until I reach a condition whereby both the concentration of the prior active is at an acceptably low value and concentration of the active in the second product is in specification.

The advantage of this third option is that it simplifies my overall process (reducing the time to clean, for example). The disadvantage of the process is that I have to have an analytical method that measures each active in the presence of the other active. Note also if there an unusual interaction between the two actives, I may not want to use this option.

I mentioned measuring the concentrations of the two actives as a function of time in all three situations. This is generally done in the design/development stage of the cleaning process. If I pick a time which provides adequate assurance that the concentration of the prior active is acceptably low and the concentration of the next active is consistently in specification, I should not have to perform analyses *as a function of time* on a *routine* basis. Note that this design/development study is probably not something that I can do on small scale equipment and then apply to larger scale equipment. These studies probably have to be done on commercial scale equipment (unless extensive work is done to correlate performance on the two sizes).

While this general approach of placebo cleaning may seem strange to most of us, it is something that may companies may have used (but haven't called it placebo cleaning). For example, let's say I have vial filler for liquids. One of the concerns of this situation is that filling needles and a part of the filling equipment may be situations where residues on those cleaned surfaces transfer to a *small portion* of the next manufactured product. That small portion is generally the first vials that are filled on the equipment. This is generally not a problem because the first X vials that are filled are discarded as the filling process "lines out" and/or as initial vials are used for things like weight checks. In essence, what is being done in this situation is using the next product to flush out any residues which could preferentially transfer to the initial portion of the next product vials (in essence, a *type* of placebo cleaning).

This approach of doing placebo cleaning may also be a *possible* option on small scale *continuous* manufacturing equipment. For example, suppose I have small scale continuous liquid manufacturing line, composed of an inline mixer/blender, an intermediate storage vessel, and a bottle/vial filler. After processing one product for multiple months, I then want to switch to a different liquid product. Rather than clean the equipment with a detergent (for example), I clean the equipment by immediately starting manufacture of the next product and processing it until the previous product is adequately removed. The initial portion of the manufactured product for the inline mixer and for the vial/bottle filler is discarded until each is producing acceptable product.

Obviously, in this example the storage vessel between the mixer and filler requires special attention. If it is small enough, perhaps I can process on a continuous basis and address all three equipment items by placebo cleaning using the actual next product. Otherwise, I might have to separately clean that large storage vessel. Another option is to use a single-use vessel for that intermediate storage vessel.

The main advantage of using placebo cleaning in this continuous manufacturing situation is that the equipment (almost) never shuts down. While I might lose some of the second product by using it to flush out the previous product, I would do the same if following a conventional cleaning process I started manufacturing without drying the equipment after a conventional aqueous cleaning. And, if I were to dry the equipment in that situation, I might lose some advantage of keeping the continuous manufacture operating continuously.

It should be clear that placebo cleaning, while appropriate in some cases, is not appropriate for many situations. Placebo cleaning does require a *different paradigm* for "cleaning validation", so be prepared to think outside the box (but still using good scientific and logical principles). The purpose of this Cleaning Memo is not to recommend or to discourage the possible use of placebo cleaning. Rather the purpose is to start a dialogue about its possible use.