My New Dishwasher and Cleaning Validation

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I really like my new stainless steel dishwasher. It has lots of cool blue lights and many buttons and different cycles and it's fun to use and watch. It's like magic--I put the dirty dishes in and they come out clean a few hours later! Technology has changed a lot since when I was a kid and had to wash everything by hand. (Although I still enjoy the Zen of hand dishwashing.)

Pharmaceutical cleaning processes are a lot like the dishwasher and washing dishes--clean the plate, knife, or pot with some detergent, then rinse off the detergent/cleaning agent. Whether hand cleaning or machine cleaning, the objective is the same-- clean the surface, then clean off the detergent. Both the manual and automatic cleaning processes are controlled: the manual home process by experience, training and a method remembered; and the home dishwasher process by the program made by the manufacturer. Both pharma processes are also controlled: manual cleaning by SOP and training, and automated processes by computer and/or Programmable Logic Controller.

We have to verify or validate cleaning in the pharmaceutical industry using analytical chemistry, but what do we do at home? How do we know what clean is?

When you teach a child how to wash dishes (for those who still wash by hand!), I bet you say something like "OK now, clean the dish until it looks clean, then rinse it off." It is much the same in our industry, when we use the "visually clean" standard, except that we would typically use one more test just to be sure. "Visually clean" is still a great standard in the pharma industry today, and our excellent eyes can see residual product, on stainless steel, in some cases down to the ppm level.

Just like when we learned how to clean dishes, manual cleaning process require training and consistency to be effective. For me, I learned how to clean dishes by hand early, about 7 years old, but I was trusted only with the rinsing part of the sink, which of course, is pretty easy compared to the cleaning/scrubbing part. It took a few years until I was allowed to graduate to the washing side of the sink (and QC was the rinse side sibling who occasionally kicked back a dirty dish!).

For the dishwasher, most of us use the "visually clean" standard as our only means of knowing that the dishes are clean. If not clean, we usually just put them back in the dishwasher for another round, or possibly change the cycle next time.

If we look at modern dishwasher cycles, there are all kinds of them, with heated wash cycles, sani-rinse cycles, eco-clean, soil sensing cycles, heated dry, eco-dry, and the list goes on. Lots of buttons and lights—what fun! How do we choose which one works? Most people just guess and see which one works; very few read the manual. Are we that disorganized in our industry? I would say no, but in some sense we do experiment--we figure out which pot is "worst case" and experiment with an acid, base, surfactant or blend of cleaning agents, time, temperature of the cleaning solution, etc. to find out

which one works best.

Getting the right dishwasher cycle is easy, right? We toss everything in the dishwasher, put some soap in (no suds please!) and press the button. But wait, some people insist on rinsing first, some people use gel soap, some dry soap, some use the new pods. And all those buttons! who knows which one to press; oh well, no time, just press "normal wash" and I'm done. Well it was easier when I was a kid, or for those of you that have no dishwasher. Just fill up the first sink with warm soapy water, and the second one with warm clear rinse water. Let the silverware soak, wash everything. But we need some training, right? and good eyes help too. I would argue that yes, we can come up with both a manual and an automated cleaning process, but it seems to have a "trial and error" approach.

Once the dishes in our dishwasher are clean, then we have to rinse them. Hmmmm, sani-rinse or regular? "Sani-rinse" sounds good, but it takes more energy. Decisions, decisions. Regular rinse today; default choices are easier! For manual dishwashing at home, we usually just rinse until there are no suds, which is like rinsing until there is little or no detergent left in the rinse water. On the industry side, rinses can be tough. We have to make sure the full surface of the tank or part to be cleaned is covered with rinse water, and we have to rinse off the cleaning agent fully. If we are using purified water, we would like to switch to WFI for the final rinse, to reduce microbial and other contaminants to the minimal level. The number of rinses must be determined also. In the dishwasher, this is typically pre-programmed, but on the industry side, we often have to experiment. Sometimes, tanks must be rinsed many times to get the cleaning solution fully out of the rinse water.

For the dishwasher cycle, I am relying on the dishwasher manufacturer for that, and hopefully they are talking or experimenting with the different detergent manufacturers as well! Even though there are lots of different combinations of cycles, over time, I can figure out which one works for my type of cooking, soil level, detergent choice, water temperature and the like. So, over time, I can get a combination that works. It's really the same with cleaning validation, in that we have to experiment with the cleaning cycle to figure out what works with the surface we are using, the soilent or residual drug/biologic and rinsing of the detergent.

What about batch to batch cleaning? I have several iron skillets and I love cooking in them with my induction cooktop. But when I first started using them, the cleaning process bugged me a bit--everyone said not to use soap because it will harm the non-stick surface. "No soap? I thought; hmmmm, it doesn't seem real clean..." Over time, I learned that cleaning with just hot water was enough, but you also have to wipe the pan out with some oil and heat it a bit. The hot water, oil and heat of the stove is enough. There still may be some residual bacon grease, but it's so small it does not matter. This reminds me of my microbiology major professor who always told me "Don't take this microbiology lab stuff home with you, John!!"

So far, we have been talking about cleaning processes, but what about Cleaning Validation? Cleaning validation is done for shared equipment (different products) or to minimize carryover (batch to batch). Why do we have to do cleaning validation in industry? We must complete cleaning validation because regulators require it, but also because we want a high confidence that that our cleaning procedures

work day in and day out. Cleaning validation is the formal process for scientifically demonstrating that the chosen cleaning procedure works repeatedly. Cleaning validation is documented evidence that the cleaning procedure results in equipment that is ready for the next batch or product, each and every time we clean it. Cleaning Validation also allows us to use indirect methods, like pH and conductivity in routine production, rather than taking swab or rinse samples each time (cleaning verification), which can be a lot of work. Validation is just proving that it works consistently, and writing it all down formally with a protocol and report (both reviewed and signed).

What about Cleaning Verification? Some manufacturers, particularly those involved with clinical trial phase production, use cleaning verification for shared equipment (different products or batches). Cleaning verification involves checking the product-contact surfaces each time by sampling rinse water or doing swab samples and using indirect methods such as pH or conductivity and by using the "visually clean" criteria. Cleaning verification is done each time, rather than using cleaning validation.

Cleaning processes vary across our industry when we consider batch to batch cleaning. All the way from strict full cleaning processes after each batch for separations processes in biologics, to continuous processes for small molecule drugs, where the unit operations are never cleaned until shutdown. The point in controlling batch to batch carryover is risk control: what is the risk of batch to batch carryover for this unit operation? Can we prove that it is less than 1/1000 or so carryover so that we can separate one batch from the next?

For my iron pan, I've convinced myself that batch to batch, the bit of grease carryover is fine. The hot water, oil wipe and heat are enough to control the possible carryover. For the pharma industry, we would need some data to prove that the batch to batch carryover is at an acceptable low level. So, there are some similarities; while in the kitchen we use processes given to us by good cooks or dishwasher companies combined with our experience, in our industry we do the same thing, but now we need to prove it with data and cleaning validation (as a standard set by regulatory authorities and consensus standards).

Cleaning validation typically starts with a cleaning process, then moves to proving the process, then documenting the protocol once we find a cleaning process that works, performing the cleaning process at least three times in the commercial process, then documenting the results of the cleaning validation study.

An example of a simple cleaning validation from industry is a shared buffer tank. Cleaning is very easy, using Purified Water and a WFI rinse, since only salts are in the tank, and they can easily be rinsed with water alone. No detergent is needed in this case. Validation proves that the automated CIP cleaning sequence can clean all the product contact surfaces like pipes, valves, pumps, and the tank itself.

A more difficult example from industry is an affinity column used for downstream purification of a biologic. Column resins are typically sensitive to cleaning agents, and thus the cleaning cycle is typically a sanitization cycle with a weak base so as not to harm the resin. In this case, we would like to clean the column of the active drug substance and other impurities, sanitize the column, packing and associated tubing/valves etc., then restore the column to a "ready to use" state by flowing buffer or

possibly a storage solution into the column and associated tubing/valves, etc. This can all be done manually with pumps, or automatically by a column chromatography skid and Programmable Logic Controller/computer combination.

Remember that good cleaning validation is a lot like using your dishwasher: use good equipment, good detergent, proven processes, and check to make sure the dishes are clean! (and write it all down for the auditors). Use of a recognized consensus standard is also helpful. Good references for cleaning validation include the FDA Guide to Inspections Validation of Cleaning Processes (7/93), and PDA Tech Report No. 29.

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