Cleaning Memo for April 2018
Dealing with Used and New Equipment

We generally know (at least we think we do) how to handle cleaning and cleaning validation for the manufacture of products we routinely make. We know what product is being cleaned and what potential next (also called subsequent or follow-on) products could be made in that cleaned equipment. So we can proceed to calculate carryover limits and then measure residues by appropriate sampling and analytical methods. On the other hand, what can or should be done for *used* equipment that I have purchased from another company or from a company specializing in used equipment? Or what can and should be done when I am purchasing *new* equipment? Remember my objective is to establish that the used (or new) equipment can be safely used for manufacture of my products.

We'll start with the situation of *used* equipment first. It is prudent (but not always possible) to obtain a history of products previously manufactured with that equipment. Questions include whether it is possible to identify specific products or product types that were processed. Were the products drug products? Were any of the products in the highly hazardous category (including beta lactams)? Were any non-drug products manufactured, such as cosmetics or agricultural products? That should be one of the first steps in terms of assessing whether the used equipment should be purchased, and may help direct steps to deal with potential contaminants left on the equipment.

If there are specific residues identified which should evaluated, then various steps are possible. For example, if identified highly hazardous active were processed, the equipment could be cleaned in a suitable cleaning process, and then those residues measured in a "cleaning verification" (one-time) study or protocol. Measuring those residues on the equipment *before* cleaning may also be done. The advantage of measuring residues before cleaning is that is tells us whether those actives of concern were actually present on the equipment at unacceptable levels. However, even if they were found acceptable before any cleaning, I would prefer to still clean and measure residues again *after* cleaning. The measurement techniques for highly hazardous active generally should be specific methods, and not non-specific methods like TOC. The reason is that TOC will pick up any organic carbon sources, and generally will not provide a good (or accurate) picture of the presence of highly hazardous actives.

Regardless of the type of residues identified (or because of the lack of information on possible residues), I highly recommend an initial "pre-use" cleaning first using an alkaline detergent cleaning agent followed by a rinse, and then cleaning with an acidic detergent cleaning agent followed by a more extensive rinse. The rationale for the alkaline detergent cleaning is to remove soils which may be removed (by dissolution, emulsification, dispersion, suspension or hydrolysis, for example) by a surfactant on the alkaline side. Once those soil types are removed, I then follow up with the acidic detergent cleaning agent to removed soils which may be removed by a surfactant on the acid side. If an *oxidant* may be of help, it is possible to use a peroxide additive to the alkaline detergent, or to follow up the acid detergent step with a peroxide *polishing* step.

Following this pre-use cleaning, the equipment should be sampled for residues of the detergents used, as well as for any specific analytical tests based on identified actives of concern. Furthermore, it is expected that the equipment be visually clean. In addition, I generally recommend use of TOC and conductivity for the final rinse to give me an overall picture of the cleanliness of the equipment, as well as possibly doing swab TOC measurements on expected worst-case locations. Finally, it may be possible to do non-specific testing by sampling with a suitable organic solvent and analyzing by FTIR or UV. What I would like to see is non-detectability by UV or a "flat line" by FTIR (insofar as a *flat* line is possible in FTIR) as a further confirmation of the effectiveness of the cleaning. Note that this latter technique may enable me to eliminate potential root causes if later I find "unknown peaks" in a subsequent study.

Once I have done this, my preference is then to clean the equipment with an already approved cleaning SOP in use in my facility, which hopefully will be the SOP I intend to use routinely on this "used equipment" going forward. This may also involve a "cleaning verification" to document removal of the cleaning agent from the equipment.

Now let's turn to the situation with newly purchased "new" equipment (equipment that I am purchasing directly from the equipment fabricator). In this situation, I (hopefully) don't have to worry about drug or other products made on the equipment. The major concerns are related to the fabricators processing materials (lubricants, cutting fluids, polishing agents, and the like) and to metal fines (which result from various fabricating steps).

Assuming that I don't have to worry about drug product (or other manufactured product) on the equipment, I would start with the alkaline/acid pre-use" cleaning discussed for used equipment. The rationale for the use of both for new equipment is that the alkaline detergent will be more effective at removing organic processing materials and the acid product will be more effective at removing metal fines. Note that the use of the acid product first will not likely be as effective in that metal fines may be *physically trapped* in organic residues and may not be adequately removed by the acid detergent.

I would still recommend the non-specific analysis by TOC and conductivity, as well as the visual assessment and the evaluation by FTIR or UV to document the effectiveness of the overall cleaning process. Once I have established the lack of unacceptable residues on the new equipment, I would do the same cleaning with the expected routine cleaning SOP to be used on the equipment (as suggested for "used" equipment).

The suggested relatively elaborate cleaning evaluation may be considered overkill in many situations. However, the objective of this one-time cleaning is to get it right the first time. This avoids situations either where I have to reclean and retest, or where I might have unforeseen problems come up in the future (potentially disrupting routine manufacture or potentially calling into question manufactured product quality).

The cleaning and evaluation process should be appropriately documented, both for regulatory inspection reasons as well as to provide a documented history of the equipment.

Note that in both situations (used equipment and new equipment), there are other activities that should occur (as part of IQ/OQ, for example) before I turn the equipment over for routine production use.

Furthermore, the examples discussed are generally relevant for stainless steel equipment cleaned with aqueous solutions. For other situations there may have to be some modifications to the suggested approach, but the principles behind the approach should be more or less the same.