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Revisiting Cleaning Validation for Medical Devices

I recently presented at an ASTM conference on cleanliness of medical device implants. An expanded paper based on that presentation will hopefully be published shortly in ASTM's online Journal of Testing and Evaluation. The industry seems to be heading in the direction of the ASTM testing procedure being adopted. My position is slightly different. While the ASTM procedure may be a good procedure, it probably is NOT a good procedure for measuring the cleanliness of implants for cleaning validation purposes. Why is that the case?

I recognize that the ASTM procedure states nothing about using it for cleaning validation purposes, nor does it have acceptance criteria for residues measured by that procedure. However, there does not seem to be adequate discussion (through published papers or symposia) within the medical device community of what tests may be appropriate for cleaning validation purposes. I see two major concerns as the medical device industry goes forward. First, we should remember what put the industry in this situation in the first place. The issue with the Sulzer recall was not that they had used inappropriate techniques for measuring residues (indeed, we are still unclear about exactly what the problem was with the Sulzer implants). The key factor was that they failed to evaluate the effect of a change in their manufacturing process. Perhaps that was partly because they didn't know how to address such changes. Which brings me to the second issue, namely that an evaluation technique for cleaning validation purposes should be able to detect changes in the cleaning process (and also changes in the manufacturing process that would show up as a "cleaning problem").

How does this impact the ASTM test method. First, my belief (and this is strictly my belief -- I admit I have no hard data) is that the proposed ASTM method is a sledgehammer that, if used for cleaning validation purposes, will not be able to provide useful information about the effectiveness of a cleaning process. Remember that the purpose of cleaning validation is to address the effectiveness of the cleaning process. An extreme extraction procedure and a gravimetric weighing technique are not likely to be a useful tool for evaluating a cleaning process.

This can be illustrated by some of the comments I heard at the ASTM conference. In discussing the evaluation technique involving spiking model surfaces with residues and determining percent recoveries, one person stated (or asked) how this reflected situations where residues were ground into the surface. Well, that may be a valid question in certain contexts. However, if those "ground in" residues are not capable of being removed by a cleaning process, what is the relevance to cleaning validation (at least for most of the cleaning processes used for metallic implants)? If those "ground in" residues are a problem, then an appropriate way to measure them should be used (perhaps in a two-step process involving measuring readily removed residues first, followed by a procedure to measure "ground in" residues). Alternatively, manufacturing methods could be investigated which did not involve processes which could "grind in" residues. The upshot is that normal cleaning processes are not designed to remove "ground in" residues, so what is the relevance if the sampling/analytical technique actually measures them?

If my argument is valid, then what techniques are available for evaluating the effectiveness of a cleaning process for medical device implants? Basically, there are five relatively straightforward techniques that can be

adopted, each of which addresses a certain aspect of possible residues that could be removed (to an extent) by conventional cleaning processes. Those methods are:

- 1.Total Organic Carbon (TOC), for organic residues
- 2.Particulates (such as USP <788>), for particles
- 3.Conductivity, for ionized species
- 4.Bioburden, for microbiological contamination
- 5.Endotoxin, for pyrogens

All of these may not be applicable in certain situations, but these measurements can provide an overall assessment of the effectiveness of a cleaning process. I must admit I'm not sure endotoxin is a requirement, but I have included it because of (unproven) concerns that the Sulzer recall may have been due to endotoxin.

All these methods are relatively standard "off-the-shelf" techniques. The most common objection about these is that TOC doesn't measure insoluble organic residues. While this is true, we must be careful to define what "insoluble" means. The key for TOC analysis is that the organic material be soluble at levels of around 5-30 ppm. If something is water soluble at that level, then it is a good candidate for TOC analysis. This is not generally information one can get from a MSDS sheet or a specification sheet. It generally has to be determined experimentally (see my Cleaning Memo of December 2004 for techniques to demonstrate adequate water solubility for TOC purposes). Even for materials that are water insoluble below these levels, if solubility is greater in acids or bases, those can be used for extraction. There are even techniques for measuring TOC using glass wool wipers and direct combustion.

For clarification, I am not suggesting that the ASTM efforts are not useful. A test method measures what it measures. However, the proposed ASTM method is probably not a good technique to use for cleaning validation purposes. My contention is that other techniques are more readily suitable for measuring the effectiveness of a cleaning process, as well as for evaluating any possible changes in that cleaning process.