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Cleaning Validation for Medical Devices

I recently suggested to a large medical device trade organization that I could offer a one-day seminar on cleaning validation for medical devices through their educational arm. The answer I received was something to the effect that there is not enough interest in the medical device community for such a subject. Certainly the emphasis now in the medical device arena is more on the cleaning that occurs during reprocessing of devices. However, the issue still is of significant import to medical device manufacturers in the cleaning of devices during initial manufacture. This Cleaning Memo will address two issues related to validation of cleaning processes of medical devices during the manufacturing process. The first is the regulatory basis of such validation. The second issue is related to one of the primary differences between cleaning validation during the manufacture of pharmaceuticals and cleaning validation during the manufacture of medical devices -- namely the issue of what is tested and how residue limits are set. Please note here that the emphasis is on cleaning of the device itself or of equipment product-contact surfaces used to manufacture the device, and not on general room environmental controls (which is a separate subject).

Regulatory basis
The FDA medical device regulations in 21 CFR 820.70 deal with several aspects of cleaning. One section calls for "…procedures to prevent contamination of equipment or product that could be reasonably expected to have an adverse effect on product quality." Another section calls for procedures to remove manufacturing materials to an amount "…that does not adversely affect the device's quality", and the "…removal or reduction of such manufacturing material shall be documented…." Furthermore, 21 CFR 820.75, dealing with process validation, states "…where the results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated." This logically applies to cleaning processes.

This is further elaborated in the Global Harmonization Task Force (GHTF) document GHTF SG3.N99-10, entitled "Process Validation Guidance". The GHTF document states that "process validation is part of the integrated requirements of a quality system". It echoes the FDA requirements in stating that if the output of a process is fully verifiable, then process validation is not required. It adds a slight nuance to the requirement if the process is not fully verifiable. In such a case, if the risk to the patient is low, then process validation may not be required. If the risk to the patient is high, then the process should be validated (or the product redesigned to reduce that risk). Needless to say, there is also some compliance/regulatory risk as well as patient risk if a decision is made not to validate a process that is not fully verifiable. The GHTF document then goes on to list several process for which this decision tree model may be applicable, and "cleaning processes" is one of those items.

Residue and limits
One similarity between cleaning validation for pharmaceutical and medical device manufacturing is that in each case, the ultimate concern is potentially unacceptable residues in or on the product (medical device or drug product) if the product is used by a patient. With pharmaceutical products, however, what is actually measured is the residue on cleaned manufacturing equipment surfaces. This is done on the assumption that residues on the equipment surfaces could be transferred to the product manufactured next in the cleaned equipment. Residue limits are based on pharmacological (dosed-based) or safety (toxicity-based) effects of that residue in the next product.

With medical devices, on the other hand, the main concern with residues is not the residue on the manufacturing equipment (although that might be a factor), but rather the residue on the surfaces of the medical device itself. The nature of those residues may differ depending on the manufacturing (including cleaning) methods utilized. As an example, for metallic implants the main issue is not residue on the manufacturing equipment itself, but rather residue on the cleaned metallic implant. Rather than test the manufacturing equipment itself for residues (as is typically done for pharmaceutical cleaning validation), in this case a better measure of the effects of those residues is testing the surfaces of the cleaned metallic implant itself.

In pharmaceutical manufacturing, the acceptance limit for residues depends on the pharmacological or safety effects as well as the dosing of the next product manufactured in the cleaned equipment. If the residues for medical device manufacturing are measured directly on the medical device itself, then it follows that the main concern is the effect of those residues if that specific medical device is used in or on a patient. What effects should one consider from those residues? While the effects may be numerous, one starting approach is to consider the various biocompatibility tests in AAMI/ISO 10993. These tests include cytotoxicity, systemic toxicity, irritation, sensitization, and the like.

If these are the test procedures for determining acceptability, how are residue limits established? Here are two approaches, based on whether the cleaning validation is being done on a new device or on an established device. [Note: This is not to imply that these are the only ways to accomplish this.] For new devices the approach to residue limits is to establish what can be achieved in the cleaning process, approximate this level (or slightly higher residue levels) in test devices, and then perform biocompatibility testing to establish that those levels of residues are safe. In such a strategy, it should be emphasized that the attempt is not to show how dirty the device can be and still be acceptable; rather the strategy is to determine that a well-cleaned device has residue levels that do not affect the quality of the device. For cleaning validation the residue acceptance criterion (the upper limit) should be that level of residue used for the biocompatibility study. One might ask, if biocompatibility is the ultimate concern, why not just use biocompatibility testing as the acceptance criterion? The reply should be that biocompatibility is not discriminating enough for a validated cleaning method to show consistency in the process. There could be wide variability in the cleaning process and the biocompatibility testing could still show the same results. As pointed out before, the objective is NOT to show how dirty the device is and still be acceptable.

For established medical devices, an alternative strategy can be used. That strategy involves establishing the residue levels of past production, which already has satisfactory biocompatibility testing completed, and then validating the new cleaning process based on those levels as the acceptance criteria.

The residues selected for testing will depend on the potential residues that could be left on the medical device following cleaning and on the intended use of the device. It may include various device processing aids, by-products of manufacturing, cleaning agents, bioburden, and endotoxin. And, as with pharmaceutical cleaning validation, issues related to various worst-case conditions, including raw materials, processing conditions, cleaning conditions, and storage issues, should be addressed.