Cleaning Memo for February 2020
Highly Hazardous Products in Shared Facilities

This is a continuation of a discussion on products with highly hazardous actives, and deals with the question of manufacturing highly hazardous products in the same equipment or in the same facility as products that are not highly hazardous. The obvious answer to that question is “Yes”, that certainly can be done from a regulatory compliance perspective. After all, isn’t that the whole point of ISPE’s Risk MaPP and the EMA’s 2014 guideline on limits in shared facilities. The idea behind both those documents is “the dose makes the poison” principle. So, if we can establish that the dose (that is, the residue limit) is low enough by a comprehensive toxicological assessment, then with appropriate cleaning validation we make a highly hazardous product in the same equipment with products that are not highly hazardous. By doing so we can clearly avoid dedicated equipment.

The next question is whether that is a good business practice. Some may say it is, because it allows pharmaceutical manufacturers to make product more efficiently, thus saving costs (and depending on what planet you live on, passing those savings on to patients). However, there are other compliance and business reasons to may lead to the opposite conclusion. The first reason is that the risk to patients, and therefore the business risks to a pharmaceutical manufacturer, is much higher if any pharmaceutical product becomes cross-contaminated with a highly hazardous active. So, there are probably some things that I as a manufacturer should consider to minimize that risk.

Certainly having solid cleaning validation is one of those things. But, we all know that things don’t always go right; so we want to set up practices and procedures to assure consistency after cleaning validation is completed. For example, we may want to increase what we do for routine monitoring for highly hazardous actives as compared to non-highly hazardous actives. That routine monitoring may include rinse or swab sample testing solely for the highly hazardous active (preferably by a specific analytical method). And it may include enhanced visual inspection, either a more extensive visual inspection or perhaps even visual inspection with a documented visual residue limit for the highly hazardous active.

Other practices may include more elaborate cleaning procedures as compared to what is ordinarily done for non-highly hazardous actives. This may include longer washing times and/or rinsing times, higher concentrations of detergents, and use of a oxidizing treatment (either before detergent cleaning or after detergent cleaning) to provide a higher assurance of molecule degradation (thus reducing the inherent toxicity of the residue). It may also include just repeating the cleaning process (that is performing it again from “start to finish” as opposed just extending the wash/rinse times). Some companies have also manufactured a placebo batch (which is then discarded) between batches of different highly hazardous products.

Other practices utilized for highly hazardous actives may be present not to protect patients, but to protect cleaning operators. Certainly personal protective equipment (PPE)
may be different, and this includes the extent and type of gowning, type of gloves used, and types of eye, breathing and other fascial protection. In addition, the use of some PPE items may involve a decontamination step as the cleaning operators leave the cleaning area or leave the manufacturing suite.

Finally, with highly hazardous actives there may more concerns about transfer of residue from one product to another from *indirect product contact surfaces* or from non-product contact surfaces. These may be from floors, walls, outsides of equipment, or even the manufacturing operators’ PPE.

With all these concerns, I may be tempted to throw my hands up and just say I don’t want to manufacture highly hazardous actives at all. But that is not the point of this Cleaning Memo. Most of the issues discussed above are applicable to highly hazardous active even if they are not made in equipment shared with non-highly hazardous actives. For companies that can’t (or don’t want to) provide those added safeguards, avoiding highly hazardous actives sounds like a good decision. But that still brings us back to the question of manufacturing highly hazardous active and non-highly active in the same equipment. And my main concern is a practical one. If I manufacture both in the same facility and treat both the same, I have a better assurance of making sure things are done correctly. But if I have certain procedure for highly hazardous actives and a different (typically less stringent) set of procedures for non-highly hazardous actives, I run the risk of the procedures being use incorrectly. Now if I “accidently” use a more stringent procedure for non-highly hazardous product, from a scientititie perspective I may have little concern (although from a CGMP perspective I am NOT following the approved procedure). In the opposite situation of using less stringent procedures for highly hazardous products, clearly I not only have a CGMP issue of using the wrong procedure, but I may face a significant risk of patient safety, product quality, and/or operator safety.

It is for these reasons that I may want to pursue and do a more comprehensive risk assessment (including business risks) before I make highly hazardous products and non-highly hazardous products in the same equipment, suite or facility.

Note that this is not exactly the same issue discussed in EMA’s 2018 Q&A document. Question #9 in that that document seems to be addressing the question of thinking that if I place all highly hazardous product in one facility, then I don’t have to worry about implementation of health based exposure limits. EMA’s answer is clear; if you make multiple highly hazardous products in a given equipment, then you should definitely be concerned about getting the active of one highly hazardous product in a different highly hazardous product. Of course, that concern is mitigated if the active of the first product is present in the second product at a level below the health based exposure limit, which is the *same* concern where all products are not highly hazardous, where both product are highly hazardous, and where only one of the products is highly hazardous.

Let me close by stating that I am not saying that both highly hazardous and non-highly hazardous product should be made in separate equipment, suites and/or facilities. What I am saying is to pay more attention to all the risks if you do so.

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