June 2012
Regulatory Guidances I'd Like to See Changed – Part 2

This Cleaning Memo is a continuation of last month's Cleaning Memo dealing with statements and issues in guidance documents that I think only serve to confuse what is appropriate for cleaning validation. Here is my second set of statements and recommended changes.

1. The following statement is in the PIC/S Recommendation PI 006-03:

> "For certain allergenic ingredients, penicillins, cephalosporins or potent steroids and cytotoxics, the limit should be below the limit of detection by best available analytical methods. In practice this may mean that dedicated plants are used for these products." (Section 7.11.3(d))

While readers of my Cleaning Memos know my concerns about Risk-MaPP, the basic principle of performing a toxicological evaluation for highly hazardous actives is sound. A suggested revision of this is as follows:

> "For certain highly hazardous actives, such as cephalosporins, reproductive (sex) hormones, cytotoxics, mutagens, and teratogens, including those actives where the primary safety concern is not due to the therapeutic effect of the drug, the limit should be established based on a toxicological assessment of safety issues. If that limit is not achievable or not measureable by available analytical methods, segregated and/or dedicated equipment should be utilized."

Note that I took the category of "penicillins" out of the changed statement. The reason for this is that (as a practical matter, because it is written into the USA CFR) penicillins will be made in segregated areas.

2. The following statements are in the PIC/S Recommendation PI 006-03:

> "The period and when appropriate, conditions of storage of equipment before cleaning and the time between cleaning and equipment reuse, should form part of the validation of cleaning procedures. This is to provide confidence that routine cleaning and storage of equipment does not allow microbial proliferation." (Section 7.7.2)

> "In general, equipment should be stored dry, and under no circumstances should stagnant water be allowed to remain in equipment subsequent to cleaning operations." (Sections 7.7.3)

These statements are referring to the "clean hold time" (although it should be noted that the reference to "before cleaning" in 7.7.2 is talking about the "dirty hold time"). Section 7.7.2 is fine. What concerns me is the phrase "under no circumstances" in Section 7.7.3. While the concern is microbiological proliferation if the equipment is stored wet (with water), there certainly could be a time period between the end of cleaning and subsequent use whereby the equipment is wet with water (even "stagnant water") where the concern over microbiological proliferation is not significant. Certainly microbes can reproduce very rapidly under certain conditions. However, it is typically the case that the conditions which might exist in pharmaceutical equipment following cleaning are generally not ideal conditions, particularly in terms of nutrients available for microbial reproduction. It is reasonable that there is a time period, whether it be a few hours, an 8-hour shift, or 24 hours, where there could be stagnant water remaining in equipment and microbial reproduction might not rise to the

level of “significant” proliferation.

Of course, I could also mention the fact that if equipment is stored dry, what is the chance of microbial proliferation? And what is the point of a formal study to document the clean hold time (other than demonstrating it is dry both at the end of cleaning and at the beginning of manufacture of the next product). However, for now I will not pursue that line of argument.

Here is my proposed change to Section 7.7.3:

> “In general, it is preferable to store equipment dry, so as to avoid issues of microbial proliferation during storage.”

Note that this issue of stagnant water also is present in the FDA Cleaning Validation guidance.

3. The following statement is in the FDA guidance:

> “For example, sanitary type piping without ball valves should be used. When such nonsanitary ball valves are used, as is common in the bulk drug industry, the cleaning process is more difficult.” (Section 1)

The issue here is whether “ball valves” should be used. Obviously, if I were designing a new system, I would try to avoid ball valves (or at least utilize so-called "sanitary” ball valves). But am I going to retrofit existing equipment based on this statement in the FDA guidance? Probably not. However, what that means is that I will use extraordinary means to clean those ball valves (such as cycling them open and closed multiple times in the washing and rinsing steps). Furthermore, these ball valves would be “worst-case” locations; disassembly for visual examination and sampling for residues in the cleaning validation protocol should be considered. Here is my proposed revision:

> “For example, sanitary type piping and sanitary ball valves are preferred. If sanitary types are not utilized, they represent a worst case situation, and special attention should be devoted to them in the cleaning procedure and in the cleaning validation protocol.”

My proposed revisions might require some wordsmithing to have them more easily fit into the applicable document(s). However, they would be steps in the right direction in clarifying issues that can result in industry confusion.

For balance, I should add a statement here in support of regulatory guidance documents. And that statement is to encourage pharmaceutical manufacturers to actually read the guidance documents. All too often I get questions from manufacturers and the answers are clearly addressed in guidance documents (the most frequent question of this nature is “Why can’t I set my limits solely based on TOC and conductivity specifications for Purified Water or WFI?”).