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What's Happening to Worst-case Process Conditions?

Past practice for cleaning validation has been to perform cleaning validation protocols under "worst-case" process conditions. The idea of *worst-case* conditions comes from the 1987 FDA process validation guidance, which states "Parts of the process which may vary so as to affect important product quality should be challenged. In challenging a process to assess its adequacy, it is important that challenge conditions simulate those that will be encountered during actual production, including "worst case" conditions." It should be noted that worst-case conditions have usually been considered worst-case within normal processing parameters or process parameters. The place to stress a process *outside* the normal process parameters or process specifications has generally been in prevalidation studies (that is, during the cleaning process design/ development phase).

The FDA's new (2008) draft guidance on process validation does not mention worst-case process conditions. In fact, that new guidance states that the validation performance qualification lots "should be manufactured under normal conditions by personnel expected to routinely perform each step of each unit operation in the process. Normal operating conditions should cover the utility systems (e.g., air handling and water purification), material, personnel, environment, and manufacturing procedures." This is a significant shift, from *worst-case* conditions to *normal* conditions.

Let me state upfront that this change formally applies to process validation, but I believe conceptually it also applies to cleaning validation. I can see no reason for not applying what is in this draft process validation guidance (or at least what survives to the final guidance) to cleaning validation, and if it is appropriate, adopting it for cleaning validation. If that is the case, does this mean we can simplify cleaning validation by forgetting about worst-case conditions? I'm sure you know that the answer is definitely "No".

Why is that the case? What has happened (or at least my interpretation of what has happened) is that the idea of "worst-case" conditions has migrated from the validation runs themselves to the various design and development portions of validation. Under the new draft process validation guidance, process design and development become part of the *overall* validation process. A key part of the design phase is to identify and control sources of *variation*. Key items for process variation are listed in that document as follows:

- Understand the *sources* of variation
- Detect the *presence* and *degree* of variation
- Understand the *impact* of variation on the process and on product attributes
- *Control* the variation in a manner commensurate with the risk it represents

How does this deal with "worst-case" conditions? Well, let's take a common "worst-case" condition for cleaning validation, the dirty equipment hold time (DEHT). We can apply the four things that the FDA wants us to consider in cleaning process design. First, we understand that DEHT might vary, and that a longer time might mean cleaning is more difficult under that circumstance. Note here that we might also come to the conclusion that for certain dry product manufacturing steps that DEHT has no effect on difficulty of cleaning (nor on the nature of residues), and therefore it is NOT a significant source of variation that we must address in the design. If our conclusion is that it can be a source of variation, the next step is to address "detection" of the

presence and degree of variation. In other words, if the manufactured product stays on the surface and is not cleaned for a defined time, how difficult can it be to clean? The third step is to understand the impact of the longer DEHT, which generally is an unacceptable residue if the cleaning is not robust enough. The final step is to control the variation. This is done typically by defining a maximum DEHT and then designing the cleaning process to be effective under that condition. I've listed these as four steps, consistent with the four bullet points in the FDA draft guidance. However, in the case of DEHT it is fairly straightforward and one could just simplify the process by saying "If the DEHT affects difficulty of cleaning, design the cleaning process to be effective under the worst-case condition (which might be the maximum time)."

You might say, "You can't just do this in the process design stage; doesn't this maximum DEHT have to be challenged in the cleaning validation runs (that is, the protocol)?" Certainly the answer is "If you want to or need to, you can do it." However, if appropriate control of variation can be shown in the process design phase, either through laboratory or scale up studies, then there is no need to challenge the worst-case in the validation protocol. The new FDA draft guidance is explicit about relying on laboratory and pilot-scale studies, provided they are demonstrative of what happens in commercial manufacture: "*Before* any batch from the process is commercially distributed for use by consumers, a manufacturer should have gained *a high degree of assurance* in the performance of the manufacturing process such that it will consistently produce APIs and drug products meeting those attributes relating to identity, strength, quality, purity, and potency. The assurance should be obtained from objective information and data from laboratory-, pilot-, and/or commercial- scale studies. Information and data should demonstrate that the commercial manufacturing process is capable of consistently producing acceptable quality products within commercial manufacturing conditions, including those conditions that pose a high risk of process failure."

Now those of you paying careful attention already have noted in this last quote that the FDA mentions "those conditions that pose a high risk of process failure". Isn't this just another way of referring to "worst-case" conditions? Perhaps, in one sense. However, the shift in emphasis is important. It is one thing to say that the validation runs must include worst-case conditions. It is quite another thing to say that that those worst-case conditions (or conditions that pose a high risk of process failure) must be addressed, and can be addressed by studies at the laboratory, pilot and/or commercial manufacture stage. This change in emphasis is not insignificant, and it is a change consistent with the "life-cycle" validation approach and "quality by design". It is also a change which, if embraced by the industry, should make cleaning validation easier to implement.

Before I conclude, let me also state that while this shift from requiring "worst case" conditions in protocols is something that is consistent with the FDA's latest documents, it may still conflict with other regulatory or advisory documents. For example, the PIC/S PI 006-3 document mentions "worst case" process conditions. It should be clear to all that as changes are made in approaches to validation, global harmonization needs careful attention.