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Can Protocols Use Limit Tests?

A general practice in cleaning validation protocols is to use analytical methods that can effectively measure a certain residue over a defined range. In the analytical method validation, it is generally the practice to establish that measurement of the residue is linear over that defined range. This applies whether the analytical method is a specific analytical procedure (such as HPLC) or a non-specific analytical method (such as TOC). Is it possible to use a limit test for protocol purposes? That is, can I use an analytical method which is essentially a "go" or "no go" test? Such a procedure would not specify how much of the residue is actually present, but could tell me that I was below a certain level (the "limit" of the test method). If the limit of the test method were at or below the calculated (or otherwise established) residue limit for cleaning validation, then any test sample below the limit of the "go/no go" test would be adequate evidence that I had met my acceptance criterion.

Before we discuss the use of such a method, it should be clear that other things being equal, I as a manufacturer would want a test method that could tell me exactly how much residue was present, or at least how much was present in the range of 10% to 100% of the residue limit. The reason I might prefer this is that I would want to know how robust my cleaning procedure was. If my cleaning limit for my active were 1.3 mcg/mL, in one sense I would not care if the my actual test samples were 0.9 mcg/mL or 0.2 mcg/mL. Both meet my acceptance criterion. However, in designing a cleaning procedure, if I could assure (with slight revisions) that my results would be closer to 0.2 mcg/mL as opposed to 0.9 mcg/mL, I would probably try to achieve the lower result. In the design of my cleaning process, with the lower result I would have much more confidence that I would meet my acceptance criterion in a validation protocol. In contrast, if I had an analytical method that could only tell me whether my result was above or below 1.3 mcg/mL, I would not have any idea of how robust my cleaning procedure was.

That said, is there a serious compliance reason for not using a limit test? After all, a limit test is one of the three methods listed in ICH Q2. Furthermore, isn't the main objective of cleaning validation to assure that the residue is below the established acceptance criterion? Do we really want to get into a discussion about whether a value of 20% of the residue limit produces a safer product than a value of 70% of the residue limit? Assuming our limit calculation was correct, both produce safe products.

In one sense, there is already a test procedure which is essentially a limit test. That procedure is using visually clean as the sole acceptance criteria (see the April 2002 Cleaning Memo). Of course, if that is done, I must clearly do spiking studies to determine at what level residues are visible. Furthermore, those spiking studies must take into consideration things like viewing distance, viewing angle, lighting, and the viewer's visual acuity. However, when all is done, I am essentially using a "go/no go" test procedure. If the surface is visually clean, I can safely say the residue is below the "visual limit", and if the visual limit is at or below my established acceptance criterion, then I have passed that criterion. If the surface is visually dirty, I can safely say the residue not below the "visual limit", and if the visual limit is at or below my established acceptance criterion, then I have not passed that criterion. While use of "visibly clean" itself is somewhat controversial, if properly used I believe it passes muster from a scientific perspective and a compliance perspective. If this procedure can be used as a limit test, then limit tests based on analytical procedures (such as HPLC, UV, or TOC) should also be acceptable if properly controlled.

Are there specific situations where I might prefer such a limit test? At least one case would be in a cleaning verification mode. In a cleaning verification mode I am essentially doing a "one-off" evaluation. In such a situation, I do not want to do a lot of pre-verification studies to determine what would be a good cleaning process. Neither do I want to spend a lot of effort on analytical method development and validation. Therefore, if I can establish a limit test, it might be appropriate. In such a limit test I would generally want to carry along a 100% standard. That is, if my limit was 1.7 mcg/mL, in addition to my test sample I would run a standard prepared at 1.7 mcg/mL. If the response in the analytical procedure for the test sample was the same or less than the response in my standard, I would have confidence that my test sample did not exceed my residue limit criterion. In most cases, I would probably want to run a standard at a value somewhat below my acceptance limit. In other words, if my confidence in my analytical method was ± 10%, then I might run a standard that was 75% of my acceptance limit. This would provide additional assurance that if the response of the test sample was below the response of the standard, I was clearly below my acceptance criterion. This situation is not unlike the situation with establishing a visual limit. In using visual detection alone, I generally would like my visual limit to be significantly below my acceptance criterion, such as by a factor of 50%, to account for variations in an observer looking at a surface and deciding whether it is visually clean or not.

Of course, this also means I must perform a recovery study at the acceptance limit, and put that factor into my standard. For example, if my acceptance limit in a swab sample was 1.8 mcg/mL, and my swab sampling recovery was 60%, then running a standard at 1.8 mcg/mL would not be adequate to say I was meeting my acceptance criterion. If my test sample had a response below the standard, I could only say the corrected test sample (corrected for sampling recovery) was below 3.0 mcg/mL (1.8 divided by 60%). I would have to run a standard at 1.08 mcg/mL to claim (at a 60% recovery) that my test sample met the acceptance criterion of 1.8 mcg/mL. And as discussed in the previous paragraph, I would probably want to be run the standard at an even lower level (such as 0.75 mcg/mL) to have an assurance that the test sample had a value below my acceptance criterion.

The purpose of this Cleaning Memo is not to advocate nor discourage any type of analytical test or method validation. Its purpose is to explore the correct use of a limit test, and to discuss how such a method might be applied in practical situations.