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Validation of Analytical Methods

Last month we discussed one element – specificity – of analytical procedures used for cleaning validation protocols. This month we'll cover issues related to method validation. This subject is one that the FDA is paying more attention to in evaluating cleaning validation. In the proposed European guidelines and in the Canadian Guidelines, this topic is specifically mentioned. What is appropriate for the validation of an analytical method used for cleaning validation? The basis for most discussion of analytical method validation is ICH Q2A and Q2B. We'll use the points in these documents as the starting point.

Before discussing these issues, it is important to remember that these ICH documents were written for analytical procedures for drug products and drug actives, and not necessarily for residues for cleaning validation purposes. Rather than have a "one size fits all" SOP for method validation, it may be preferable to evaluate the ICH criteria and the specific situations you as a manufacturer face, and write a separate SOP on analytical method validation for cleaning validation. This can also be handled by having options within one "global" SOP.

Typically, the SOP for method validation would cover the following items:

- Accuracy
- Precision
- Linearity
- Specificity
- Range
- LOQ/LOD
- Intermediate precision

Accuracy is an evaluation of how close the measured values using the technique come to the correct value. This is usually done by measuring three standards over the selected range (one at the lower end of the range, one at the upper end of the range, and one in the middle of the range).

Precision is the closeness of the results. It involves doing multiple measurements on the same sample and determining the RSD (relative standard deviation). The sample is usually in the mid-point of the range, and a minimum of six measurements is made on the same sample.

Specificity is the ability of the method to unequivocally measure the target analyte in the presence of other species that might be present. This can be accomplished by spiking standards with potential contaminants and showing no effect on the resulting measurement. For certain methods, such as TOC (Total Organic Carbon), there is no need to perform this test since it is well known that TOC is non-specific. The key, of course, is to handle the data appropriately for a non-specific test (see January 2001 Cleaning Memo).

Range is the set of values over which the procedure is validated. Range is involved in the selection of standards for precision and accuracy, for example. If the procedure is linear over the range, that should be demonstrated by appropriate procedures (such as the method of least squares). The range should be a useful range, such as 25-100% of the acceptance limit in the analytical sample, or 50-200% of the expected analytical value.

The LOQ is simply the lower end of the validated range. LOD is not absolutely necessary. It is significant, however, if the method LOD is below the acceptance limit in the analytical sample. (It is assumed, however, that you have not arrived at the point of doing method validation if the LOD is above the acceptance limit in the analytical sample). LOD can also be important if there are problems in the future; knowing that data was below the detection limit may help you solve a future potential contamination issue.

Intermediate precision is performing the accuracy and precision experiments under different conditions, such as on different days, with different analysts, with different lots of reagents, with independently prepared standards, and using different pieces of equipment.

It is also expected that method validation be performed on qualified (through system suitability testing) equipment.

If a validated method is to be transferred into a manufacturer's lab from another lab, then a defined procedure for method transfer should be followed. This amount of work to be done in this transfer procedure will depend on the specific circumstances, such as whether the equipment is identical. At a minimum this may include analyses of samples by both laboratories. It is up to the new laboratory to demonstrate that the previously validated method is appropriate to use in their laboratory.

A final topic related to method validation is recovery. This can be handled as part of the analytical method validation package, or it can be handled separately. However, since this is really an evaluation of the sampling procedure, my preference is to treat it separately. Evaluation of recovery will be handled in a future Cleaning Memo.