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Specificity of Analytical Methods

A somewhat controversial issue in cleaning validation is the nature of the analytical method used to measure residues (such as the drug active or the cleaning agent) in the validation protocol. The crucial issue is whether the analytical method should be (or preferably should be) a specific method. Furthermore, if non-specific methods are allowed, what is their appropriate use? Many people express a belief that only specific methods should be used. It is important to distinguish between a specific method for a target residue and a method that is a direct measure of the target residue.

A specific method is a method that unequivocally measures the target residue in light of potential interferences. For example, it is possible to devise an HPLC procedure that is specific for methyl cellulose, provided that potentially interfering substances were accounted for. Such a procedure would also be a direct measure of methyl cellulose. A direct measure is one where there is a direct correlation between the presence of the target residue and a quantitative response in the analytical procedure. For example, TOC (Total Organic Carbon) would be a direct measure of methyl cellulose, although it would not be a specific method. In contrast, conductivity (also a non-specific method) would not be a direct measure of methyl cellulose (methyl cellulose is not an ionized species and therefore doesn't contribute to conductivity). This distinction is important because, in the early days of cleaning validation, some companies tried to use compendial specifications for Purified Water as the acceptance criteria. This was unacceptable because, in many cases, there was no correlation between the analytical methods used in the Purified Water specification and the presence of the target residue. (Note: an additional problem was that there was no expressed correlation between the level of contaminant found in the rinse water and the possible level of the contaminant in the subsequently produced product—but that's a different issue.)

Here's what some regulatory documents say about the subject. The FDA's cleaning validation guidance document states that companies should "determine the specificity…of the analytical method" used for residue analysis. This clearly does not call for a specific method, but rather requires that the specificity be evaluated. Proposed Annex 15 to the EU GMP's states that "the analytical method must be specific for the target residue". This can be interpreted in one of two ways. One is to say that a specific method is required. The other is to say that this phrase ("specific for the target residue") is really just another way of saying that the procedure must be a directly related to (or a direct measurement of) the target residue. PDA's Technical Report #29, while not a regulatory document, states that "specific tests are generally required for validation of cleaning for dosage form manufacturing", while non-specific tests can be used in the "early stages of bulk drug production…." However, that document continues to discuss the various uses of TOC.

Needless to say, this issue is not as simple as "only use specific methods". The almost universal use of TOC in biotechnology facilities should be a clear indication that specific methods are not absolutely necessary. What then are the scientific principles behind the appropriate selection of an analytical method (at least in regard to its specificity). The first principle is that the analytical method should be a direct measure of the target residue. As discussed above, the target residue has to give a quantitative response in the analytical procedure. The second principle is that "specific" methods should be demonstrated to be specific in light of potentially interfering substances (such as cleaning agents, cleaning process by-products, excipients, processing aids, and sampling materials). The third principle is that for non-specific methods there have to be no negative

interferences. What this means is that any potentially interfering substances should contribute positively to the response. For example, TOC qualifies under this criterion because (as a practical matter) any interfering substance contributes positively to the measure of organic carbon. [In contrast, if conductivity were used to measure a cationic specifies, there may be interfering substances that would neutralize the cationic species, such that the cationic species could be present and yet not contribute to conductivity.]

The objection may be given that TOC "doesn't give you an exact measure of the target residue". However, in one sense it is not relevant. The important thing for residue analysis is to determine that the actual amount measured is at or below the calculated acceptance limit. If I measure a certain organic drug active by TOC, and then treat that carbon as if it were all active drug, I can arrive at a number, not of the exact amount of drug active present in the analytical sample, but rather of a upper limit of what might be present. If that upper limit value is compared to the acceptance limit and if it is lower than the acceptance limit, then that target residue is at an acceptable level.

It is, of course, the responsibility of each pharmaceutical manufacturer to demonstrate that the analytical methods utilized are appropriate for the intended use. It is not a simple matter of saying one type of method is appropriate. It is possible to correctly use both specific and non-specific methods, and it is also possible to misuse both specific and nonspecific methods. Care in selection, as well as appropriate analytical method validation, is necessary to help insure that the goals of the cleaning validation protocol are achieved.