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Limits for Drugs with Multiple Actives

One thing that is almost always done for cleaning validation of finished drug products is to set residue limits for the active and to then measure residues of that active in the validation protocol. This is a relatively straightforward process (at least conceptually) if there is only one active in the drug product. If there are two (or more) actives in a drug product, how are measuring residues of the "active" handled?

Certainly one option is to set limits for each active independently, and then to measure each active in the protocol execution. This can mean using different analytical methods for each active. Note that "measuring each active" can also mean just measuring TOC, and in independent calculations assuming worst-cases in which that TOC is due solely to each of the actives present. That worst-case calculation is then compared to the appropriate limit for each active to determine whether all the actives are below their respective residue limits.

Another option for finished drugs with multiple actives is to establish a grouping strategy, in which a "worst-case" among the different actives is established. How is a worst-case established? Well, some of the same principles used for selecting worst case products (discussed in previous Cleaning Memos) can be used for selecting worst-case actives. However, there are also some significant differences for establishing a grouping for actives in the same drug product. One major difference is that, in selecting the most difficult-to-clean active, the effect of the excipients can usually be ignored. Why? Because in this case, each active is being cleaned using the same matrix (the excipients); therefore, in this case a simple evaluation of relative solubilities of the different actives in the cleaning solution is adequate to determine which product active is more difficult-to-clean. Therefore, other things being equal, one should consider choosing the active that is least soluble in the cleaning solution.

One may also be tempted to select as a "worst case" the active that is the largest percentage in the formula or the active with the lowest residue limit. Unfortunately, one cannot select an active satisfying both the highest formula concentration and the lowest residue limit. Because the multiple actives are present in the formula at a fixed ratio, and because the dosing of the drug product is the same (for each active), the active with the highest concentration in the drug product is necessarily the active with the highest residue limit, and vice versa, that active with the lowest concentration in the drug product is necessarily the active with the lowest residue limit. In other words, including worst-case criteria of highest formula concentration and lowest residue limit does not allow one to select one active as a worst-case. Therefore the only meaningful basis for selecting the worst case (for finished drug products with multiple actives) is based on difficulty of cleaning, which in most cases will be based on solubility in the cleaning solution. The principle behind this is that if the least soluble active is reduced to 0.001 of its dose in the next product, any more soluble active should also be reduced to 0.001 of its corresponding dose in the next product.

There is at least one exception to this approach. That exception applies to drug products containing multiple actives in which the different actives are present in the different excipients. An example would be a tablet with two layers, with one active in one layer and another active in the other layer. In such a case, the worst-case for cleaning should take into consideration the different excipients present in each layer. In the example cited, the approach to handling multiple actives essentially becomes a case of grouping for different drug products, and

would use the principles for drug product modified for the "two" drug products being together in one finished product.

The purpose of this Cleaning Memo is not to proscribe certain ways to handle cleaning validation for finished drug products with multiple actives. Rather the purpose is to present the options and considerations in using those different options.