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More on Limits for API Manufacture

A group of European pharmaceutical scientists representing small molecule API manufacturers has published recommendations on setting limits for API's in cleaning validation. They advocate some good things, but there are also things that should cause concern.

Here is the web link to the document, which is entitled "Justification of Limits for Cleaning Validation in the Manufacture of Active Pharmaceutical Ingredients": http://www.gmp-compliance.org/eca_news_928.html.

First the good news. In addressing what I typically call the "default" limit (it is called the "absolute criterion" in the document I am discussing) for the API in API manufacture, the authors advocate using a value of 100 ppm API in the next API. This is in contrast to the typical default value (or "absolute criterion") of 10 ppm used in finished drug product manufacture. The rationale used by the authors is related to the fact that during a final crystallization, residues are more likely to remain in the solvent than in the API itself. The authors refer to a "statistical distribution" of 10% of the residue in the API and 90% in the solvent. If only 10% of the residue makes it to the next product, then an added factor of 10 can be used in the drug product limit of 10 ppm; hence the "absolute criterion" is 100 ppm (which is used if it is more stringent than a dose-based carryover calculation). While I like their conclusion (default limits or absolute criterion of 100 ppm), I'm not sure the rationale provided is adequate, and there certainly is a simpler rationale for the higher default limit in API manufacture.

The reason I would be concerned about the rationale is that it may be true, but is not always true, that residues are removed by a crystallization step. One recent case where it was not true was in the Viracept recall issue. In this case, an impurity (a genotoxic material) was created in the manufacturing process at a fairly early step, but apparently the final crystallization (if there was such a step) did not remove that residue. In other words, there may be great clearance in a crystallization step, but to assume it is true in all cases is perhaps overly optimistic.

A better rationale for a higher default limit is the fact that any residue in the API will result in a lower concentration of that residue in any drug product made with that API. In other words, an API containing 100 ppm of a residue, if formulated into a finished drug product at a level of 10% API in the finished drug product, will result in a finished drug product containing 10 ppm of the result. And 10 ppm is precisely the default value for finished drug product manufacture. So, the key is to set a default limit at 100 ppm for API manufacture as long as the concentration of that API in a finished drug product is 10% or less (obviously this rationale would not apply for aspirin manufacture where the API is essentially 100% of the finished drug product). [Note that in my training seminars for API manufacture I typically recommend default limits of 50-100 ppm in the next API.]

The issue of greater concern is that the authors recommend setting a carryover dose for API manufacture at 1/100 (or 0.01) of a dose in the maximum dose of the next API. The rationale is essentially similar to the rationale given for the default limit. If the carryover limit for finished drug product manufacture is 1/1000, then because of the "statistical distribution" issue (10% residue in the API and 90% residue in the solvent in the crystallization step), then API manufacturers should be able to use an additional factor of 10 and only be required to set limits at 1/100 of a dose in the a dose of the next API.

The good news is that the authors recognize that there is something different about API manufacture in terms of setting limits. The bad news is that there is no scientific rationale for saying we should allow 1/100 carryover of the cleaned API into the next API. If that were the actual fact, we would be violating the principle of 1/1000 of a dose being a safe level. The authors were on the right track in talking about removal of residues in a final crystallization step. However, there is a better way of dealing with this issue, and that is to appeal to section 12.70 in ICH Q7A, which states "For example, in early production it may be unnecessary to validate equipment cleaning procedures where residues are removed by subsequent purification steps". Although the authors cited ICH Q7A, there is no indication in their document that they appreciated the impact of this statement in Section 12.70. The impact is that if residues of early cleaning steps are removed by a final purification step (such as crystallization from a solvent), then those earlier cleaning steps are not critical and do not require validation. What this means is that in calculating dose-based limits, I don't have to include the surface area of the earlier equipment, and only have to consider equipment from that purification process onward. This reduction in the total surface area will result in residue limits per surface area that are significantly higher, as compared to calculating a dose-based limit based on the entire equipment train (as is the practice in finished drug manufacture). It is in this way that cleaning validation is less stringent in API manufacture. However, in no case would I maintain that I was allowing 1/100 of a dose carryover into a dose of the next active. Perhaps the end result will be the same between using (a) 1/1000 dose on the equipment surface area beginning with the purification step, and (b) 1/100 dose based on the surface area of the entire equipment train. However, the former has a basis in good science and in regulatory documents, while the latter does not.

The purpose of this Cleaning Memo is to focus on the scientific rationale for why cleaning validation may be less stringent for API manufacture. Note that while the discussion focused on small molecule API synthesis, the principles apply equally to large molecule biotech bulk active manufacture where the various purification processes may remove residues from earlier cleaning steps. Also note that the key for this purification process is that the purification process of the next manufactured API must be considered. Furthermore, this determination of the effect of the purification process is not a theoretical consideration. The effect must be demonstrated. A possible demonstration is performing lab clearance studies, much like viral clearance studies, to demonstrate removal of residues by the purification process.