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What's Really Different About Biotech?

There certainly are several things about pharmaceuticals produced by biotechnology processes that require them to be handled differently from traditional pharmaceutical manufacturing. As for cleaning and cleaning validation, one of the main differences is the type of analytical test used to measure residues following cleaning. While TOC is certainly an option for measuring residues for traditional "small molecule" pharmaceuticals, in the case of biotechnology-produced pharmaceuticals, it is almost mandatory. Why mandatory? Because in most cleaning situations involving biopharmaceuticals, the active (usually a protein) is readily degraded (denatured) by the cleaning process, particularly if (as is usually the case) cleaning involves hot alkaline solutions. If a specific analytical method (such as an ELISA method) were to be used for residue analysis, it is likely that no native protein could ever be detected except under conditions where the residue was never in contact with the cleaning solution. For this reason, for biotech manufacture, TOC is probably the best measure of potential residues. In measuring TOC, the carbon value is expressed as protein (as if all the carbon were due to active protein), and this worst-case active value is compared to the acceptance limit. One assumption in this type of calculation is the denatured protein fragments have a safety or medical concern no greater than the native protein (the active).

A second difference with biotechnology production is the need to separate out the finished drug manufacturing aspects of production from the upstream (or API) aspects of production, particularly in regard to setting acceptance limits. For finished drug production, setting limits is usually done in the same way as for traditional pharmaceuticals – using some kind of dose-based calculation to determine what is a medically safe level. However, on the "API side" of biotech production (beginning with cell culture or bacterial fermentation processes and ending with a final purification), if traditional dose-based criteria are used to calculate residue acceptance limits, the limits are usually so low that they can't be measured by TOC (and while a specific technique, such as ELISA, could measure them, the issue of degradation of the native protein clouds the issue of its use).

Why are residue levels calculated on dose-based principles so low on the "API side" of biotech production? Part of the reason is related to the relative ratio of the batch size of the active to the surface area involved in production. The smaller the batch size and the larger the equipment surface area, the lower the calculated limit. In considering the batch size of the biotech protein, it is necessary to consider the batch size of the active in the final API. In traditional drug manufacture, the API is usually prepared as a relatively pure solid (or liquid) material. A small amount of this API is then added to the finished drug to make a marketable product. For biotech, in many cases the final purified API is a relatively dilute "solution" of a protein. It is made this way because it may be impossible to produce a stable concentrated solution or a solid product. What this means is that if I have a traditional API with a potentially contaminating residue level of 5 ppm of the previous active, if it is formulated into a drug at a level of 0.1% of the API, then the level of that previous active drops to 0.005 ppm in the finished drug. On the other hand, if I have a biotech API with a potentially contaminating residue level of 5 ppm of the previous active, if it is formulated into a finished drug by diluting it by one half with WFI, then the level of that previous active drops to only 2.5 ppm in the finished drug.

Are there any aspects of biotech API production that make this acceptable? Well, one aspect comes from the ICH Q7A document. That document allows for the possibility of earlier phases of API production to be less

critical, and therefore not requiring cleaning validation, if those residues that are left by the earlier cleaning process are effectively removed by subsequent purification processes. For example, if the residues left after the cleaning step following fermentation are removed by subsequent purifications steps, that earlier cleaning step may not require validation. The trick, of course, is to demonstrate that those residues would be removed by subsequent purification. In biotech, this may be difficult because it may be difficult to characterize those residues so that removal is demonstrated. One would expect that removal would be accomplished by a chromatographic purification, but it may be difficult to prove conclusively.

That said, it also may be true that cleaning is critical following fermentation. The reason is not that residues left behind following cleaning might ultimately contaminate a finished drug. Rather, the issue is that residues left behind might affect the production efficiency of the next fermentation, such that yield is significantly reduced or the resultant batch contaminated. This is the same reasoning behind the criticality of microbial control in these earlier stages of biotech API production. The reason is not that microbes might survive through subsequent processes and ultimately contaminate a finished product. No, the reason is that microbes might survive and contaminate the next fermentation, causing a contaminated batch that has to be disposed of. The issue of "criticality' is not based on medical concerns, but a rather on production efficiency.

How are biotech companies to proceed, then, with setting residue limits for actives in API production? Realizing the less critical nature (because of the issues discussed above), the common biotech industry practice is to set limits for API production based on the capability of the cleaning process. By this I don't necessarily mean doing a formal process capability study; the number of production lots required to do a process capability study may be excessive for a new production process. On the other hand, many cleaning processes in biotech API are similar in that the primary components being removed in the cleaning process are not the active, but media, various buffers, and components other than the active. Usually the establishment of limits is based on practices such as requiring some "arbitrary" (but achievable) acceptance limits of samples, typically in the range of 1-10 ppm of TOC. Note that the limit is not necessarily set based on contamination of the next product, but rather on what can be achieved in rinse samples and/or desorbed swab samples. For these reasons, it is important to identify at what point in the manufacturing process the process changes from API manufacture to finished drug manufacture.

These are just two of the reasons of why biotechnology-produced pharmaceuticals are different from traditional "small molecule" drugs. It should be noted that this is not necessarily a hard-and-fast distinction. There may be (and are) traditional drugs that have actives which are degraded by the cleaning process, and which may require a technique such as TOC to adequately characterize residues of the active. There also may be biotech API manufacturing processes where traditional dose-based calculations can be effectively used. As with other aspects of cleaning validation, a careful review of the process is necessary to establish a balanced, effective, and achievable validation program.