April 2007
Limits for Bulk Biotech Manufacture – Part 2

Last month we discussed the basic way limits are set for bulk biotech manufacture, and the rationale for an approach based on "industry standard practice". This month we will cover additional things to consider in justifying these limits. One item is that a carryover calculation for finished drug manufacture typically involves a carryover from the entire equipment train. ICH Q7 (GMPs for API manufacture) explicitly allows for the possibility that the cleaning after early manufacturing steps may not be critical (and hence may not require validation) if the residues left on equipment surfaces following those cleaning steps are removed by any final purification steps. In small molecule API synthesis, it is generally possible to document removal (much like what would be done for a "laboratory" viral clearance study). For small molecule API synthesis, we generally can identify those residues left after cleaning, and spike them into the purification process to demonstrate (possible) clearance. In biotech, we might believe that the residues left from earlier cleaning processes (following fermentation and harvesting, for example) are removed in the various subsequent purification processes, but it is difficult to identify those residues and demonstrate removal in downstream purification processes. Particularly if size exclusion chromatography is used, it is more likely that those degraded fragments could be separated from the native protein. Again we believe it occurs, although it either isn't or can't be demonstrated in the conventional way.

There may be alternative "experiments" that might demonstrate the clearance of cleaning residues from earlier processing steps. One possible approach is to "cook" the unprocessed bulk with sodium hydroxide or the alkaline cleaning agent used, to simulate the cleaning process. At the end of a specified time, the pH is neutralized and the temperature quenched. The simulated "residue" is then passed through the chromatographic purification column on a lab scale. Ideally the removal or separation of those degraded components can be demonstrated by something as simple as TOC analysis, with the TOC amount of the incoming feed being the same as TOC amount of the removed components. There may be other analytical options. This may be done on each chromatographic purification step individually, or on the cumulative purification process. (Note that I am not aware of any biotech company that has tried these clearance studies; however, I believe the principles behind the approach are sound.)

We can also fall back on the argument that I rejected earlier, namely that only a small portion of the TOC (particularly for upstream processes) is due to the protein itself, with a significant portion due to media and cell components. However, this is an argument that cannot be pushed too far.

While some might object to setting limits as discussed in Part 1 as arbitrary, it is the best alternative available in bulk biotech manufacture at this time. One study that biotech manufacturers might do to bolster their case is performing a simulated cleaning study to demonstrate degradation of the native protein by the cleaning solution. This is a (relatively) simple experiment, where the native protein is added to the cleaning solution at the temperature of the washing step for a time representative of the washing step. At the end of that time, the temperature and pH are quenched, and a sample of the mixture is then analyzed by the specific ELISA analytical procedure to demonstrate (hopefully) that the native protein cannot be detected in the cleaning solution. A control would be the native protein added to the neutralized cleaning agent at ambient temperature (to confirm no interference of the detergent solution with the ELISA technique). If the cleaning agent does interfere, then performing the same experiment with just KOH or NaOH in place of the detergent itself may be appropriate.

Some companies have done "carryover calculations" of a type for bulk biotech equipment. Sometimes this has involved carryover from only one equipment item (selected as a worst case among the equipment items). Such a calculation may demonstrate acceptable carryover (less than 0.001 dose carryover) to the next bulk active. Of course, this is the carryover from only one equipment item, not from the entire equipment train. Furthermore, there are inevitably cases for a certain combination of cleaned bulk active and subsequently manufactured bulk active where even this carryover calculation (for one equipment item) exceeds the 0.001 dose criterion. In those cases, it is necessary to do a further justification based on "softer" things, such as the degradation of the active during the cleaning process and the argument that the TOC is only partially due to protein fragments (and includes other sources of organic carbon).

Another type of "carryover calculation" I have seen is a "reverse" carryover calculation. In this calculation, the actual carryovers based on actual TOC results at each stage are summed up to calculate the actual cumulative carryover. In such a situation, one might find that the actual carryover is less than 0.001 dose. Note that this can be feasible because the actual TOC values measured are generally significantly less than the limits. It should be emphasized that this type of carryover calculation is not the same as setting limits based on carryover principles.

Note that this Cleaning Memo should be read in conjunction with March's Cleaning Memo (Part 1 of this topic) for a more complete picture of this issue.