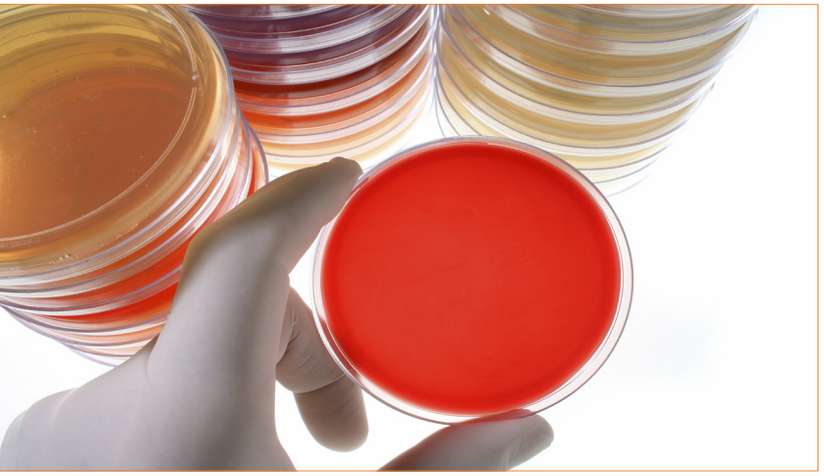
Square pegs in round holes

Understanding bioprocess variation ensures facility fit during technology transfer

The scale-up and transfer of manufacturing processes is common during the lifecycle of biopharmaceutical molecules. A lack of understanding of process variations can lead to poor process performance and even failures during such transfers.

During R&D phases only small quantities of biopharmaceutical product are needed but the requirements increase as the product enters clinical trials. Non-GMP pilot plant studies can be used to assess how the process will perform at larger scales and mitigate the risk of process failures during cGMP manufacture. Subsequent increases in cGMP production-scale are likely to be required as the molecule progresses through clinical trials and into commercial manufacture. ››



Increases in scale may involve transferring products between a sponsor's manufacturing sites while a significant proportion will choose to transfer the process to a contract manufacturing organization (CMO). Additional transfers will be required should the product sponsor change their CMO or bring the process back in-house which can happen depending on their experiences and changes in manufacturing strategy.

The biopharmaceutical industry strives for consistency between production runs no matter what the scale or location of the process. The continued difficulty in linking the molecular structure of large proteins to their efficacy and safety means the industry must maintain that the "process is the product". A change in the process implies that the resultant product cannot be assumed to be the same as that for which data was generated during clinical trials. It should be recognized, however, that within defined limits process variability is a fact of bioprocessing life.

Despite the fact that many well defined scaling criteria and models exist it is not unusual to see some differences in process outputs between processes operated at different scales and in different locations. The pH of a chromatography elution pool at the process scale may differ from the laboratory and pilot scales due to differences in systems designs and hold-up volumes. An ultrafiltration step may take more or less time for the retentate to reach specifications limits. We may be able to assess the risk and conclude that these changes are within design limits and therefore will not impact patient safety but this lack of complete certainty when products are scaled or transferred creates problems for engineers attempting to fit an existing process to a new facility or scale of operation.

A typical approach to modelling processes and predicting facility fit uses average values derived from historical datasets. This is then considered to be the most likely scenario. However, that a given bioprocess with its inherent variation conforms perfectly to typical values is actually a relatively unlikely outcome. The impact of this is that individual process steps developed for the 'average process' may not be well designed for the actual process.

Consider a cell culture process producing a recombinant protein with seven recovery and purification steps and each step giving a 90% yield. Should each step including the cell culture give as little as a 2% deviation from the expected yield, the difference in overall process yield can deviate from the predicted value by around ±15%. Imagine the impact of having this additional volume of product. If the normal and cross flow filtrations are sized on protein mass or volume per square metre of membrane we can add in contingent area, however, if these turn out to be unexpectedly low we run the risk of exacerbating the problem by having excess area which contributes to product losses through hold-up volumes and non-specific binding.

'The Process is the Product'

How then should we design those unit operations towards the end of our process such as formulating cross flow filtration or final bulk filtration steps? It is common to build safety factors into design calculations without trying to cover every processing eventuality yet relatively little consideration is given to how these safety factors are derived and the impact of these on process costs versus the risk of poor process fit, disruption or even failure.

The solution is to develop more sophisticated decision-support tools to enable the process variability within process limits that we are able to measure and understand, to be factored into calculations for facility fit models. Such tools have been developed by collaborators working with the Department of Biochemical Engineering at University College London in the UK and have integrated stochastic simulation with multivariate analysis to detail how sub-optimal facility fit can be alleviated by alternative process configurations. The objective, therefore, is to allow managerial decisions to be made between the risk of process disruption due to poor process fits and the implications on Cost of Goods of mitigating against every eventuality.