CHARACTERIZATION AND PROCESS VERIFICATION STUDIES IN A MINIATURE BIOREACTOR USED AS A PREDICTIVE TOOL TO SCALE-UP AN INDUSTRIAL PROCESS

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There is continuous pressure on the pharmaceutical industry to acquire a thorough understanding of their product and process, using a quality by design (QbD) approach, in order to speed up the timescales for approval of a therapy to market. One way to achieve this is to conduct detailed characterization studies using a miniature model, such as a bioreactor or a single-use micro-well plate system, in order to identify the key parameters which have an impact on the scale-up of a bioprocess. The design and development of such a representative miniature model, using integrated sensors for monitoring of process conditions on-line, is vital for scaling purposes and allows for parallelization and automation whereby multiple parameters can be tested in a high-throughput fashion.

This concept has been applied to a downstream process for the recovery of periplasmic Fab' from E.coli cells, a therapeutic recombinant protein used to treat autoimmune diseases. The aim of the research is to address the key challenges of scaling by characterizing a 20mL small scale model in terms of mixing performance and fluid dynamics and identifying which factors, such as shear stress, fluid velocity and spatial distribution of cells have the most impact on scaling. In the study, novel, advanced techniques, such as the dual pH indicator system for mixing time (DISMT) and particle image velocimetry (PIV), were used to characterise the fluid dynamics in the small scale bioreactor. The bioreactor was fitted with a miniature temperature and pH probe to observe conditions, and process verification studies were conducted in order to compare performance at different scales for a variety of operating conditions.

The results show that the small scale bioreactor was able to successfully mimic an industrially relevant heat extraction process up to 10,000 fold scale with good accuracy on the basis of constant volumetric power input. Assays were used to analyse the quantity and quality of the product and impurities, and scanning electron microscopy was used to examine the morphology of cells at different stages of the process. The study was further extended to 24 deep square micro-well plates and initial data suggests that the shaken system may also be used to scale-down 10,000 fold, and therefore indicates the feasibility and applicability of these single-use plates as a predictive tool for scaling up. The poster will discuss how fluid dynamic studies may be used to understand and improve scale-up and will additionally address alternative methods which may be used to minimise the variation observed in the feed material and hence its impact on subsequent unit operations.