ULTRA SCALE-DOWN CONCEPTS TO ADDRESS EARLY STAGE PROCESS DEVELOPMENT CHALLENGES IN INTEGRATED CONTINUOUS BIOPROCESSING

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The benefits of continuous bioprocessing, e.g. accelerated process development and scale-up, reduced capital costs, and standardisation, could be achieved through facility automation, universal process architecture, and the alignment of operational structures for the development and manufacturing organisations [1]. Both control strategy and rational design of universal process architecture demand an understanding of the limits and interdependence of these unit operations, and knowledge on how these could be controlled to sustain desired product quality over long periods of time. For example, to effectively implement global process control, which coordinate feed flowrates, will require information as to the impact on product quality and operational efficiency of the range of flowrates on individual process equipment.

One of the advantages of continuous processing is the potential for operating plants to serve clinical development by shortening plant operation. Could the same be used in early stage process development? How does this scale match process development goals which, apart from producing material to demonstrate feasibility of the process, have broader goals such as generating envelopes of performance and experimental data for process understanding? This presentation will initiate discussion on early stage bioprocess development needs when facilities are running integrated continuous processes and envisage how the process of technology transfer from development scale to operating scale might look. We will provide insights into the challenges encountered in designing scale-down mimics of continuous unit operations such as tangential flow filtration or TFF [2] and will illustrate ultra scale-down concepts [3] which could be used to understand unit operations within a continuous platform.

TFF is a key unit operation that has been cited as having potential for upstream cell separation or clarification. In a previous work [2], we successfully demonstrated a microscale TFF platform which mimicked a typical bench-scale TFF, Pellicon 2™ (Merck Millipore) based on operating conditions. We obtained similar fluxes, transmissions of antibody fragments, total protein and DNA (unpublished). This was achieved with membrane area that is smaller by 100-fold and reduced feed material by at least 10-fold. We identified that fluid transfer is a key limitation in the reduction of feed since pump requirements for continuous flow dictate the minimum volume of material needed to run the equipment efficiently. Without compatible fluid transfer technologies, material requirement for scale-down, continuous equipment will still be in the litre-scale per experiment. For investigative studies, important to identify key process parameters and quality attributes, these amounts would be prohibitive and would require more resources and time. This highlights the need to re-consider the typical use of geometrical scale-down models to evaluate continuous unit operations and requires more thought on early stage development. Otherwise, we may only be moving the cost and risk of biomanufacturing from industrial scale to the bench scale of process development.

The USD approach endeavors to understand the complex engineering environment within an individual unit operation by identifying key engineering parameters and determining the critical flow regime. This insight is then developed into USD technologies and techniques to mimic larger scale operation. The approach suits the requirements during the early stages of product development when the amount of material is scarce and information about the product or process is limited. First applied to continuous centrifugation with the USD centrifugation technique, the USD concept has been extended for other unit operations. The USD techniques were powerful in revealing process interactions. They facilitate Quality by Design and help define process control strategy by determining and quantifying critical processing parameters which control the critical process attributes.

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