

## DEVELOPMENT OF A SCALE DOWN TOOLBOX FOR PERFUSION PROCESS DEVELOPMENT

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### Background and novelty

Merck KGaA has a legacy of perfusion manufacturing processes with several commercial products that were developed in the 90s. These processes were developed for adherent cell systems. Since then, with the advances in media design and the monoclonal antibody driven portfolio, development efforts have been focusing on fed-batch with suspended cells. Recently and as many players in the biomanufacturing industry, Merck is working on the development of an integrated continuous process. To support this effort a process development platform for perfusion cell culture needs to be developed.

Process development for fed-batch is clearly defined and scale down tools are well defined. Similar capabilities are needed for the development of perfusion processes but technical limitations (continuous flow, cell retention) complicate the scale-down process. Because of the duration of perfusion runs and the lack of small scale models, the experimental throughput for perfusion process development is generally considered as very low. The present study proposes a scale down toolbox for perfusion process development and optimization.

### Experimental approach

To support perfusion process development, an experimental toolbox is proposed to address the need for higher experimental throughput. In the presented study, existing small scale systems were used to mimic perfusion conditions. Ideas on how to use these systems for media development and/or clone screening will be presented here. The generated data will help to understand how the proposed scale down experiments for perfusion are aligned to a bench scale continuous perfusion model data set. This work should also help to define clone selection criteria specific for perfusion process development.

### Results and discussion

First a methodology for the screening of 470 clones in fed-batch mode was established. From this initial screening, 12 clones were selected and tested in a series of small scale models ranging from microliters to several liters. This extensive screening was performed to assess relative clone performance in each model by comparing the ranking obtained in the different scale down systems based on a number of process criteria and/or quality attributes [1].

A selection of the clones mentioned above with different growth and productivity characteristics were tested in 3.5L continuous perfusion cell cultures. The proposed scale down toolbox and screening methodology was then applied to the same clones. The benefit of this experimental approach is two-fold. First, the generated data helped to understand how the toolbox can be used to predict different process conditions (CSPR, productivity...) and thus evaluate the performance of different media and/or cell lines. Second, this study should help to define the key clone specific parameters needed to assess the ranking during clone screening for perfusion.

[1] A. Y. Rouiller, J-M. Bielser, D. Brühlmann, M. Jordan, and H. Broly, "Screening and assessment of performance and molecule quality attributes of industrial cell lines across different fed-batch systems," *Biotechnol. Prog.*, vol. 32, no. 1, pp. 160–170, 2015.