ACCELERATING BIOPROCESS DEVELOPMENT BY ANALYSIS OF ALL AVAILABLE DATA: A USP CASE STUDY

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Bioprocess development generates extensive data from different unit operations and it generally includes large datasets (e.g. time series, quality measurements). By analyzing all available data, bioprocess development can be accelerated. This can only be achieved by having a clearly defined data logging and analysis strategy. Here, we present a case study using available data from the development and optimization of the upstream process (USP) of Sabin inactivated polio vaccine (IPV) using animal component free medium.

IPV production using attenuated Sabin strains instead of wild type polio viruses is an initiative supported by the World Health Organization. This change is favorable to reduce the risk of outbreaks during IPV production. Optimizing this process using only animal free components reduces operational costs and lowers the risk of adverse effects related to animal derived compounds.

During the process development, 40 bioreactors at scales ranging from 2.3 to 16 L were run. For optimization and robustness studies, design of experiments (DoE) was performed and several USP operational parameters were varied. These included operational mode (batch vs semi-batch), multiplicity of infection (MOI) and time of infection (TOI). This data was routinely analyzed using factors based on DoE methodology.

With the new strategy, it became possible to scrutinize all data from the 40 USP development runs in a single data study. The total data package that was analyzed; this included the DoE response parameters, all offline data (e.g. cell, substrate and product concentrations), all data generated by the bioreactor control systems (T, pH, DO, DOCO), and derived calculations (specific rates like μ and q_{glu}). This analysis showed which parameters were most important regarding the bioreactor performance. This USP case study showed that with the new strategy a more detailed, reliable and exact view on the most important parameters regarding bioreactor performance could be obtained.

In order to do this, a feature based approach supported by the inCyght® software was utilized. It consisted of logging all data into a database, which was used to determine data integrity for all variables and batches. Exact phase information (cell growth, virus production phase) and other meta information are transferred into the database for each batch. This allowed outliers to be visually determined and certain variables to be excluded from the analysis (i.e. those that did not fluctuate). Univariate outlier detection technique was used to further determine outliers. Principal component analysis (PCA) was used to gain a multivariate process understanding and partial least squares (PLS) regression was performed to identify correlations. This result determined the best subset of variables to be fitted by using multiple linear regression (MLR). Future experiments will focus on the relevant parameters highlighted by this approach.

This strategy was applied for the analysis of previously produced data. Further development will use this data analysis methodology for continuous accelerated process development, intensified DoE and integrated process modelling.