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# APPLICATION OF MULTIVARIATE DATA ANALYSIS IN THE MONITORING AND CONTROL OF MAMMALIAN CELL PROCESSES

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High throughput (HT) methodologies are increasingly being adopted for bioprocess development activities. However, often the large quantities of data generated from such studies as well as from historical batch records are not fully harnessed for their potential insights. Multivariate data analysis (MVDA) is a well-known technique that can reduce the dimensionality of large data sets and help generate useful correlations of typical process behaviour and determine root causes of process deviations.

This work focuses on the application of various MVDA techniques and data mining tools to investigate the impact of process variations on the critical quality attributes (CQAs) of mammalian cell processes. Three separate projects investigating the application of these techniques were explored. The first focuses on understanding the impact of cell culture operation, generation number and initial conditions on final titre and impurity levels. A systematic methodology was applied to analyse HT data generated in a Design of Experiment (DOE) study using the ambr® 48 (advanced micro-bioreactor) system. The project applied multiple MVDA techniques including Principle Component Analysis (PCA) and Partial Least Squares (PLS) to successfully identify the key critical process measurements impacting on the target antibody concentration and host cell protein (HCP) levels at harvest. A similar approach was adopted in the second project that investigated the influence of manufacturing beyond standard operating conditions on the product-related CQAs of a mammalian cell process. The insights from the MVDA allowed the modification of the control limits of key process parameters to be redefined with confidence. The final project focuses on the development of an advanced glucose control strategy for a high titre mammalian cell line. The project aims to predict the on-line glucose concentration through correlations developed between the available on-line process measurements and the off-line metabolic profiles. The predicted glucose concentration is then used to manipulate the substrate feed rate to control the glucose concentration at a desired set-point. Better control of the glucose concentration aims to further increase titre production as well as potentially reducing unwanted post-translation modifications (PTMs) in susceptible cell lines. These techniques can be combined with the application of Process Analytical Technologies (PAT) and Quality by Design (QbD) allowing for the development of more efficient and better controlled processes.