EXPLORE A PROBABILISTIC NETWORK MODEL APPLICATION FOR BIOPHARMA MANUFACTURING PROCESS

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Process and product knowledge are cumulated through the bioprocess validation lifecycle to ensure consistent process performance and product quality. With accelerating development timelines, the accumulation of process knowledge during the continued process verification (CPV) stage of process validation is becoming increasingly important. However, there are several common challenges in accumulation of data driven bioprocess knowledge, including but not limited to the small sample size and lack of statistical models for the end to end processes.

Sample sizes of data in Bio-manufacturing drug substance processes are frequently quite small due to time, economic, and physical constraints. There are increasing numbers of empirical studies that have demonstrated Bayesian methods are explicitly selected to better accommodate small sample sizes because they incorporate both the observed data information and the prior knowledge via Bayes' theorem.

In contrast to a statistical model that focuses on a single unit operation, a network model includes reasonable connections between the unit operation models (e.g., the output of the previous step becomes the input for the next unit operation) and corresponding data transfer in terms of process parameter and product quality distribution. A framework that combines cause and effect diagrams with Bayesian belief networks (BBNs) can be leveraged to increase the process understanding.

Vacaville is a commercial manufacturing site using CHO cells and fed batch processes for products launched from Genentech/Roche during the last decade. Variability of raw materials (e.g. trace element content) is a known challenge for bioprocess, which could lead to process performance and product quality variation. Through commercial manufacturing, it is observed the operation variability will also contribute to the process variation. As the key focus of commercial manufacturing is on product quality and process performance consistency through improved raw material, process and product understanding, the need to build a network model is rising. The feasibility of using a probabilistic network model is explored using a case study for the upstream process. All potential factors (raw material, operator, operation, instrument, etc) are considered to build a network model between process inputs and outputs. The model simulation leverages both product specific and site specific knowledge. The construction of the model, model simulation outcome, and potential application for this method will be discussed.