Large Scale process optimization using Bayesian modelling with Reduced Scale process priors

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Vaccine manufacturing processes are highly complex and involve a lot of steps from animal cell culture and purification towards formulation of the drug product. For each step, the process and its CPPs (Critical Process Parameters) need to be optimized to meet the specifications on CQAs (Critical Quality Attributes). Reduced scale models (RSM) aim to be representative of the regular large scale (LS) process, and are used to run optimization experiments at lower cost.

Here, an RSM has been developed to mimic the infection step of animal cell culture in bioreactor. The RSM consists of shaker-flasks. It is not meant to be completely similar to the LS (e.g. RSM agitation is performed by an orbital shaker instead by an impeller at LS or the pH regulation in bioreactor instead if the absence of pH regulation in RSM), but it has been chosen for its low cost and ease of manipulation, allowing the use of Design of Experiments (DoE).

Using DoE, experiments have been performed in RSM to screen the infection process step for CPPs. Several CPPs have been shown to impact the CQAs at the reduced scale. It is assumed that similar effects would be observed at large scale. A *D*-optimal DoE with 10 experiments has then been run at LS. The experiments have been designed to fully take into account the information gathered at RSM (using SAS PROC OPTEX and use of prior knowledge information). Uninformative Bayesian models have been fitted to the RSM data. The posterior distribution of the parameters has been used as prior information to fit an informative Bayesian model to the LS data. Prior sensitivity analysis aims to evaluate the impact of priors and likelihood on the posterior distribution. In order to take into account the dissimilarity between the RSM and the LS, the prior distributions based on the RSM data need to be weakened. Graphical comparison of priors and posteriors was critical for the prior sensitivity analysis.

The probabilities of success for the CQAs to meet the specifications for the LS, for different CPPs settings, have been derived from the output of the last model, thus closing the gap between early knowledge developed at reduced scale, and final process characterization obtained at large, regular scale, at controlled cost.