A COMPREHENSIVE STUDY IN PAT- APPLICATIONS FOR A QBD-COMPLIANT DEVELOPMENT OF CONTINUOUS BIOPHARMACEUTICAL PRODUCTION

Reiner Luttmann Hamburg University of Applied Sciences
reiner.luttmann@haw-hamburg.de
Jens Fricke, Sven-Oliver Borchert, Jan-Patrick Voss Hamburg University of Applied Sciences

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The development of continuously operated integrated pharmaceutical production processes needs a tremendous expenditure. Beside the installation of a full-scale production, scale-down concepts are essential to meet the QbD-specifications of the FDA.

In this presentation the surrounding PAT-field of such a plant for production of potential Malaria vaccines (shown in ICB I and ICB II) is discussed in order to create model based QbD-compliant strategies. This includes fully automated processing, global process monitoring with additional classical and spectroscopic measurement procedures including enhanced data processing and MVDA. A full-scope model of the plant allows an in-silico development of process control.

The two-stage upstream line is scaled-down in a sixfold sequential/parallel operated bioreactor plant including flow analysis at-line measurements for substrates- and target protein-detection. This plant allows a fully automated simultaneous DoE-process optimization and identification of CPP-Critical Process Parameters. The DoE-model and Monte Carlo simulations create also the Design Space and the Control Space of QbD-production.

Similar methods are used in the down-stream area for optimization of cyclic protein purification. These methods are applied with an AEKTA^T avant which is developed especially for DoE.

The main focus of the work lies on the development of a global MVDA-based monitoring system for biotechnological variables like cell mass, glycerol-, ammonium-, total secreted-, and target protein-concentration but also on the evaluation of process quality (reproducibility) of the running processes.

Applications of NIR-, Raman-, and 2D-Fluorescence-Spectroscopy and the appropriate PLSR-modeling leads to a partly success. This was improved by using the nonlinear SVR-Support Vector-machine Regression. However, a MVDA-application with only classical process variables from agitation, aeration, temperature, feeding, pH, pO_2, and process balances creates astonishing results in a satisfying bio-monitoring up to the on-line detection of the secreted target protein concentration.

The quality of running processes was evaluated with a GB-Golden Batch approach. The GB-tunnel was created with data from QbD-conformed process courses and then used for an on-line observation and prediction of actual first principal components. A MPC-Model Predictive Control was also implemented in order to avoid a leaving of the GB-tunnel by correction of process set-points. These methods open the way to an on-line release of pharmaceutical products.