

DoE bioprocess development

Eppendorf DASware is the effective route to design of experiments (DoE) in early-stage bioprocess development. Claudia M Huether-Franken and Sebastian Kleebank explain how the design software applies DoE to DASGIP parallel bioreactor systems.

Many different industries apply quality by design (QbD) principles to ensure product quality and efficient manufacturing. For at least the last decade, ever since the US FDA launched its pharmaceutical cGMP initiative in 2004, QbD has been driving the pharmaceutical industry as well. Since the ICH Guidelines Q8–Q11 (2009–2012) were finalised, there has been increasing regulatory emphasis on QbD for pharmaceutical manufacturing processes.

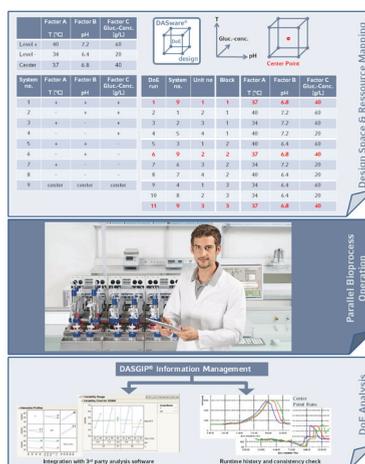
State-of-the-art pharmaceutical development follows the QbD guidelines even in early process development. Risk analysis is used to identify the critical process parameters considered to have an impact on product quality. Design of experiments (DoE) and multivariate analysis (MVA) are structured approaches to the development and optimisation of processes. Compared with a one-factor-at-a-time method, they offer a reliable and meaningful way to determine a proper design space for the manufacturing process. Designed for simultaneous operation of multiple bioreactors, the Eppendorf DASbox and DASGIP parallel bioreactor systems are adequate tools for the easy implementation of DoE in bioprocess development processes.

Design of experiments – the efficient way

DoE is a structured method for investigating the influence of various critical process parameters, and interactions and dependencies of specific values. It increases the efficiency of development processes on the one hand and enables the streamlining of post-approval changes and regulatory processes in later manufacturing processes on the other. In early product development, DoE can be used as a time and cost-effective way for clone and cell-line screening or media optimisation, for example. Parallel cultivation systems fully support seamless DoE approaches. Set points such as pH, dissolved oxygen, temperature, induction time stamps and feed profiles can be automatically varied. Parallel operations save time compared with sequential ones and eliminate reproducibility issues. Using advanced parallel systems reduces manual operations, which are error prone and usually hard to track.

Application to parallel bioreactor systems

DASGIP parallel bioreactor systems ensure defined and controlled process conditions to facilitate the screening of bacteria or cell cultures, and the optimisation of media or substrate quantities on a small scale. For example, the



Eppendorf DASware design software.

easily extendable modular DASbox system with four mini bioreactors per unit offers controlled and reproducible cultivation results.

All processes can be precisely defined, optimised and adapted. In addition, all results are accurately and precisely documented. The comprehensive Eppendorf DASware design software easily applies DoE to DASGIP parallel bioreactor systems.

The following example gives an overview of how easily such an experiment can be set up using DASware design. A full-factorial three-factor (pH, temperature, feed-stock concentration) design was chosen for an *E. coli* batch fermentation using a single fourfold DASbox mini bioreactor system. The biomass production (OD_{600}) served as response value.

Setting the design space

Upper and lower levels for each factor were defined as values that appreciably differed from the centre point while remaining biologically reasonable. The DASware DoE builder was used to create a full-factorial design chart. Alternatively, the design can be created using common third-party DoE software and later imported into DASware with a single mouse click. Resource mapping automatically compiles individual, process-specific instructions with DoE information and available hardware resources. Using the fourfold DASbox, three parallel runs were needed to carry out the 11 process runs in total. All critical process values were monitored and documented throughout.

Analysis and a consistency check were performed using the comprehensive DASGIP information manager, along with user-friendly chart displays. Via simple exports, the data can also be analysed with renowned third-party DoE tools.

Gathering full process understanding, and tracking any interfering factors and interacting parameters at an early stage of product/process development are the keys to short time to market. The Eppendorf DASware design software and DASGIP line of parallel bioreactor systems ease DoE approaches and support user-friendly and comprehensive documentation, data analysis and information management. ■

Further information

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