SUCCESS STORY

CHASE
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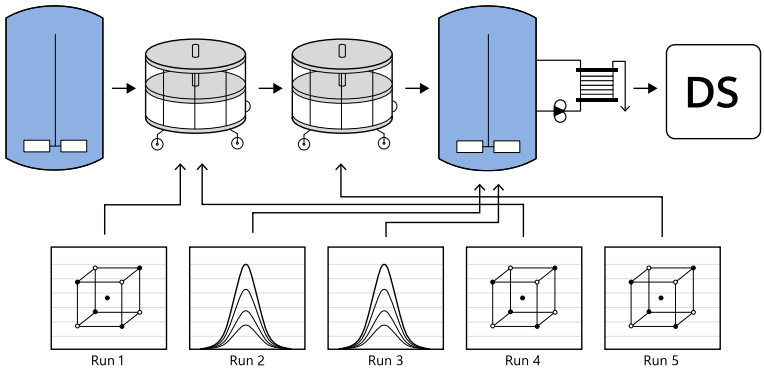

Holistic Experimental Design (© CHASE/Oberleitner)

HOLISTIC DESIGN OF EXPERIMENTS FOR BIOPHARMACEUTICAL CONTROL STRATEGIES

USING INTEGRATED PROCESS MODELS TO CALCULATE EFFICIENT DESIGNS FOR A MANUFACTURING PROCESS

The first stage in the FDA's process validation lifecycle encompasses the creation of a control strategy that ensures that a biopharmaceutical production process is capable of consistently delivering quality product. This is done by investigating the effects of process parameters (PP) on critical quality attributes (CQA). The FDA recommends Design of Experiment (DoE) approaches followed by multivariate regression analysis of the results, which is considered the state of the art in the process characterization phase. Experimental design approaches such as factorial, fractional factorial or optimal designs are generally applied to each unit operation (UO) of the process individually. This method, however, does not take into account that UOs are connected within a process and that these connections could be exploited for a more efficient design procedure. In other words, the holistic nature of such a process is neglected. By employing an Integrated Process Model (IPM), the interplay between UOs can be leveraged and the effects of PP changes downstream investigated.

Here we introduce a novel approach to experimental design for biopharmaceutical process characterization, called holistic Design of Experiments (hDoE) that uses an IPM at its core to accelerate process development. The primary objective of hDoE is to provide scientific evidence for process robustness in an efficient manner while using conservative, statistical methods to ensure patient safety. It is a recommender system that identifies the

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most efficient set of experimental runs at specific UOs in an iterative cycle of design and evaluation.

In the initial step of the procedure, each UO is allocated a minimal set of optimal runs to roughly identify relations between PPs and CQAs using regression models. The number of runs used to fit this first iteration of models is generally substantially smaller than that of the state-of-the-art approach. These models are then integrated into an IPM to facilitate the simulation of out-of-specification (OOS) events for the process. Here, the OOS rate is used as the single metric expressing process robustness as it is a function of CQA distributions over all UOs as well as the predefined specification limits for the produced drug substance. The experimental effort recommended by hDoE contains the specific runs that would result in the largest reduction of the OOS rate. These runs can either be optimal DoE experiments used to augment existing designs per UO or spiking runs that challenge the clearance capabilities of a UO. While the former reduces model uncertainty, the latter improves knowledge about the link between UOs. The recommended set of experiments is then performed, and results are fed back into the IPM to improve the quality of OOS predictions for the next cycle. This is done until the OOS rate falls below the desired threshold, and the process satisfies the required robustness criteria.

The efficiency of the hDoE approach was validated through a set of simulation studies representing different process conditions set up in-silico. Results demonstrate significantly reduced experimental effort for process characterization compared to traditional methods while providing evidence for robustness based on sound, statistical methods.

In conclusion, holistic Design of Experiments presents a comprehensive and innovative approach to gaining process understanding in biopharmaceutical development. By integrating DoE and spiking studies in an iterative manner, hDoE optimizes parameter estimates and minimizes the occurrence of out-of-specification events. This not only improves product quality but also contributes to substantial cost savings in the development process. Overall, hDoE can be viewed as viable and in many cases a more efficient alternative to the biopharmaceutical industry's current approach to process characterization.

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