FOCUS ON QBD

New processes with parallel bioreactors

Claudia M. Huether and Dr. Falk Schneider, DASGIP AG, Jülich

The pharmaceutical industry and regulatory authorities are facing new challenges in the development of new drugs that have complex interdependencies. Even at the early stage of process development, a number of detailed parameters have to be captured and large amounts of data must be analysed systematically. The following provides some insights into the more notable advantages of using process-integrated data management in tandem with parallel bioreactor systems.

A decade ago, the typical bioreactor fermentation process generally involved less than 15 process parameters, most of which were manually defined. Ten years on, bioreactor systems can easily capture more than 40 parameters automatically. This translates into more work for both the pharmaceutical industry and regulatory authorities when it comes to analysing and interpreting data.

A good example is the development and manufacture of monoclonal antibodies. The A-Mab study demonstrates how the "Quality by Design" (QbD) concept can be implemented (see below)[1]. It also reveals that improved product understanding – as well as a precise knowledge of the critical quality characteristics of the target product – are essential requirements for the development of modern pharmaceuticals. The identification of these characteristics and monitoring them during the manufacturing process is an important requirement in the US Food and Drug Administration's process analytical technology initiative (PAT). This requires defining, among other things, a large number of cultivation process parameters found in the bioreactor. These critical process parameters (CPP) are systematically defined with methods such as design of experiment (DoE). DoE ensures efficient planning of the experiments that are to be carried out, and helps to identify interdependencies between the individual factors. Parallel bioreactor systems are ideal for use in process development in accordance with PAT (see Fig. 1). They support the DoE approach, enable the integration of external laboratory analysis and feature powerful and flexible integration management.

Tab. 1: Methods for carrying out the concept of *Quality by Design* (QbD).

QbD requirements	Methods
Better understanding of the product and process	Process analytical technology (PAT), such as OD, exhaust gas analysis, HPLC, (N)IR spectroscopy
Knowledge of the critical quality attributes (CQA), use of prior knowledge	Data mining, improved information infrastructure
Exchange of process information between process development and production	Archive (historian), control system integration, exchange of recipes
Optimised process execution, adherence to design space	Improved control strategies such as feedback control
Systematic search for critical process parameters (CPP)	Statistical experimental planning such as design of experiments (DoE)

Expanded bioreactor analysis

The typical parameters that are captured in a bioreactor when cultivating bacteria, animal or human cells include temperature, pH, dissolved oxygen and the actual values of key actuators such as pumps, stirrers or gassing conditions. In addition, data such as viable cell density and nutrient or metabolite concentrations are determined with external analysis equipment using primarily manual methods.

When integrating externally-determined data into the bioprocess or long-term archive, manual or analogue data transmission from laboratory equipment to the bioreactor control system is increasingly being replaced by network connections and standards like "OLE for process control" (OPC). The DASGIP Control 4.0 OPC Software for example collects the data from an integrated autosampler and analytical equipment, then visualises and saves it together with the primary process data in its built-in data historian. That means the analysis data is available within the control process – particularly for process development – and can be used in monitoring and process control for operations such as the online feedback control of analytes or metabolites.

Integration of autosamplers and analysis equipment

At the University of Delaware, Babatunde A. Ogunnaike and his team combined an autosampler from Nova Biomedical with a DASGIP Parallel Bioreactor System. This approach established the foundation for effective real-time online control of glycosylation patterns on monoclonal antibodies (mAbs) produced with Chinese hamster ovary cells (Fig. 2).

For establishing base regulatory control of key process variables known to effect glycosylation, the researchers designed a bioreactor system with nutrient control and cellular metabolite monitoring in addition to the common bioreactor measurements. Within this system, parameters including

BIOMANUFACTURING

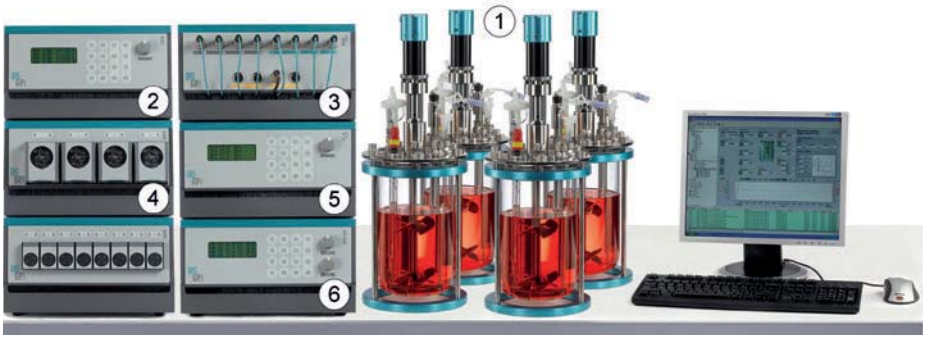

Fig. 1: Parallel bioreactor systems for statistical experiment planning (DoE): this parallel DASGIP bioreactor system consists of four 2.7 liter reactors (1), the DASGIP OD4 module (2) for measuring optical density and the PH4PO4 module (3) for measuring pH, dissolved oxygen, redox potential and level. The system also features the MP4 and MP8 pump (4) modules, the TC4SC4 temperature and agitation system (5) and the MX 4/4 (6) module for individual gassing.

pH, glucose, glutamate, glutamine, lactate, Na^+, K^+, and NH_4^+ were measured using a Bioprofile 100+ bioanalyzer with an autosampler that was integrated with the DASGIP Parallel Bioreactor Control Software via OPC. The validated bioreactor-analyser system allowed for closed loop control of glucose concentrations in the media, leading to improved quality and yield of the target product[2]. A multi-scale model using process variables (glucose and glutamine media concentrations, DO, pH, temperature and agitation rate) to predict glycosylation patterns is currently under development, and will be used as the basis of a model for predictive control strategy of glycosylation.

Data and information management

The measured process data, profiles and recipes for each reactor are stored by control modules. Additional information must frequently be incorporated to conduct enhanced analyses; for example, for comparing individual approaches from a parallel cultivation or with existing process runs.

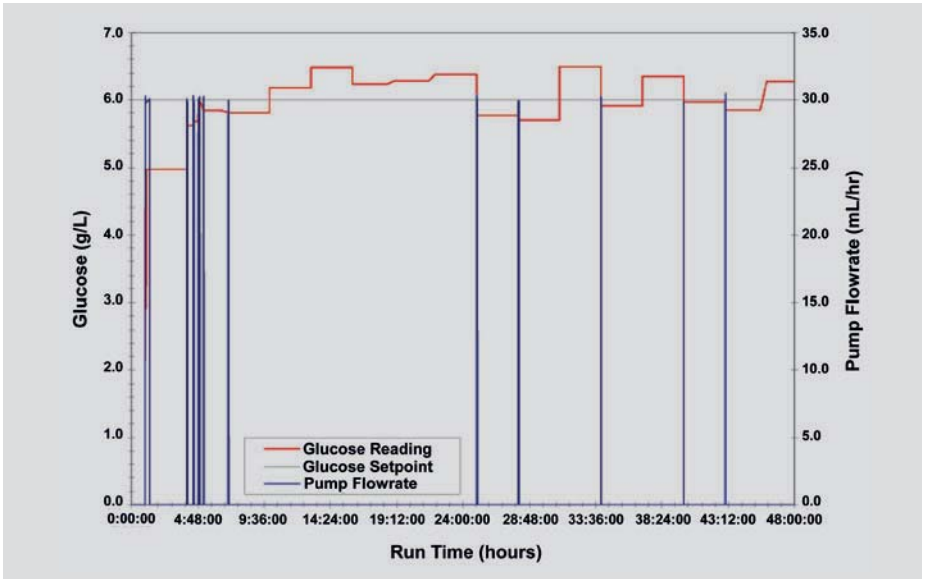

Fig. 2: Controlling the glycosylation of monoclonal antibodies in Chinese hamster ovary (CHO) cells[2]. At-line glucose measuring (red) over an analyser and autosampler and the resulting glucose feed (blue) form a closed-loop regulated feeding delivery with a defined set point. After automated sampling, the externally-measured glucose concentration is forwarded to the control software. This allows the glucose concentration in the reactor to be regulated via the glucose feed at a specific set point. (Carried out with an autosampler from Nova Biomedical, combined with a DASGIP parallel bioreactor system and the DASGIP Control 4.0 OPC control software.)

The type of organism used within the process, the composition of the culture media, nutrient supplements and defined set points or feeding strategies all flow into the analysis, as do analysis results such as product yield or living cell density.

This supplemental information is often saved separately and administered individually by each user. However, this particular information is also the key to any targeted information retrieval – also known as "data-mining". Software properties like the DASGIP information management option, combined with the integrated archive system, ensure that all of the process-relevant information is collected, stored in a central database and intuitively available to the user based on self-defined criteria[3]. Through targeted queries of historical and current data, the process data can be compared in various ways, and thus enables a comprehensive process analysis. Besides OPC, connectivity opens integration into supervisory control systems and corporate histories. This allows for data access not only across different workplaces, but also between different sites.

Handling maximum complexity

Strict regulations for the processing of biopharmaceuticals has lead to the need for detailed control of operational processes and comprehensive information management for the large amount of data generated through bioprocesses. When working with parallel bioreactors, automating processes by integrating autosamplers and analysers – and combining that with intelligent data management – ensures that the resulting data will conform to PAT.

References

[1] CMC Biotech Working Group (2009): A-Mab: a Case Study in Bioprocess Development, Version 2.1. www.ispe.org/PQLI_A_Mab_Case_Study_Version_2.1.pdf

[2] Rix K and Grolms M (2010) BioPharm International Suppl June, p. 22-28

[3] Huether CM and Schneider F (2009) BioTech International Feb/Mar, 6-10.

Contact

Claudia M. Huether
DASGIP AG
Rudolf-Schulten-Str. 5, 52428 Jülich, Germany
Tel./ Fax: +49-2461-980-121/ - 100
c.huether@dasgip.de, www.dasgip.com