



A smart path for novel biologics

Use Case

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Pawel Linke, Specialist for lab automation, Roche Pharma Research and Early Development (pRED)

Introduction

Cell culture is at the heart of the production process for many biopharmaceuticals, but finding the optimal conditions to maximize yield can be a complex and time-consuming process. Traditional process development relies on costly and labor-intensive set-ups, significantly limiting throughput and the range of experimental conditions that can be assessed. Scientists in Roche Pharma Research and Early Development (pRED) have adopted an alternative approach, combining single-use microbioreactors with advanced automation and analytical platforms to streamline the workflow.

Optimizing fermentation takes time; and people

The production of large biological molecules for therapeutic use is complex, requiring expression of the target peptide, protein or antibody in suitable host systems, followed by extraction and purification to yield the final drug. Efficient expression requires not just the right host organism and clone, but also the right physical conditions and chemical environment to promote production. Exploring these numerous parameters to optimize biotherapeutic production is a very time-consuming complex process, requiring cell expansions in the seed train to subsequently run numerous fermentations in parallel to

identify the best candidate and its conditions for expression. With more data points being obtained for each variable it's more likely to establish a highly productive final process. Fermentation development has historically relied on performing parallel experiments using a number of shake flasks or 2 l bioreactors, with continuous monitoring via an array of samples from each of these bioreactors to enable analytics. Unfortunately, this approach is both time consuming and labor intensive, with one researcher able to handle only a few 2 l bioreactors simultaneously.

A microbioreactor farm – Miniaturized, parallelized condition testing

When the Bioprocess Research Department at the Roche site in Penzberg Germany was challenged with significantly increasing numbers of proteins to be produced, the team realized they needed to look for an alternative solution. Pawel Linke, specialist for lab automation, explained: "We were asked by the management to look for a way to do even more process development for the more complex bio-therapeutic candidates, as well as double the number of projects we performed per year. This clearly wasn't going to be possible with our existing workflow – a very hands-on process – without significantly increasing headcount, which wasn't an option."

“We looked at the possible solutions on the market and chose a system of high-throughput single-use microbioreactors. We now have two different types of microbioreactors: four that can run up to 48 parallel fermentations of up to 15 ml, and five larger vessels that allow us to run 12 x 250 ml fermentations simultaneously. This shift represented a huge increase in capacity, allowing us to run four or five times as many fermentations with the same number of staff. However, it also created new challenges, as we significantly decreased the culture volume while at the same time increase the number of samples to be analyzed. We therefore needed a way of efficiently processing up to 250 samples every day, before analyzing them on a Cedex Bio HT Analyzer from our sister division Roche Diagnostics.”

Streamlined data collection with custom lab automation

“We have a huge number of laboratory automation systems here in Penzberg and, based on this experience, we decided that a Tecan liquid handling platform would be the best fit for our needs. A key requirement for our workflow was the ability to integrate a large centrifuge to spin down the samples before analytics, and the Fluent® Automation Workstation’s ability to mount a robotic centrifuge below the worktable was a real benefit. We simply place the samples from the bioreactors on the workdeck, and the system is able to automatically load them into the centrifuge using its Robotic Gripper Arm™ (RGA). Once spun down, the Fluent platform splits the supernatant into several aliquots in different labware formats, depending on the downstream application.”



“We now have two different sized Fluent systems with slightly different configurations, giving us more than enough capacity to process samples for every microbioreactor every day, although we have this many experiments running in parallel at present. The smaller system is equipped with an RGA for lab ware movements and an 8-channel Liquid Handling Arm™ (LiHa) for pipetting, while the larger system has a third arm equipped with a Multiple Channel Arm™, allowing entire 96-well microplates to be duplicated or transferred simultaneously. Each platform also has on deck integrated Tecan microplate readers for some onboard analytics. Although both have cooling modules, we have now developed for mass spectrometry analytics a workflow based on sealed, pre-pierced plates that can be accessed by the LiHa. This avoids evaporation without the need for cooling, further simplifying the workflow.”

Joint efforts to let components interact the most efficient way

„When we first implemented this set-up, the Cedex Bio HT Analyzer required 15 samples to be loaded into a rack for processing, but we have worked with our Roche Diagnostics CustomBiotech colleagues to develop a 96-well microplatebased sampling system, allowing us to more efficiently and accurately transfer the high number of samples between the devices. Peter Hloch, Director International Product Management, Roche CustomBiotech, highlighted: „Automation is key in the future of bioprocessing, and joint efforts are needed to let components interact in the most efficient way. It was our pleasure to support the colleagues in pRED. Finally we developed an optimal solution in record time that is now ready for all our Cedex Bio HT users.“

Furthermore, we implemented Sm@rtline Data Cockpit (SDC), a middleware from AGU GmbH to streamline the flow of online-, atline- and metadata between all devices. This solution is able to take the sample IDs from each microbioreactor and provide that information to Tecan’s FluentControl™ software.

The Fluent platform uses an integrated barcode scanner to confirm the identity of each sample, associates that ID to all aliquots it generates for the analysis, and exports the information back to SDC. The middleware then provides the relevant information to the Cedex Bio HT Analyzer. This means that, although each platform is effectively a standalone instrument, the software environment is as automated as the physical process – it’s a very smooth work flow finally allowing a feedback loop to the bioreactor.



We developed this approach also because we have many different researchers in the lab, working on a number of different projects. The touchscreen user interface on the Fluent workstations makes it very easy for people to walk up and use the systems with only minimal training – we have around 30 users – with a couple of ,key users‘ to handle protocol development and maintenance tasks. All together it’s a great fit to our needs.“



Cedex Bio HT Analyzer

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