Increase efficiency with a powerful Process Analytical Technology solution for the biopharmaceutical industry

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Biotechnology-derived pharmaceuticals are a major and rapidly growing sector of the overall pharmaceutical market, with annual sales of recombinant protein products alone expected to exceed $50 billion in the next few years.[1] More than 90 biopharmaceuticals have been approved for use by the US FDA since 2000,[2,3] including vaccines, monoclonal antibodies (mAbs) and recombinant proteins other than antibodies. The development pipeline behind these approved pharmaceutical products is extensive with more than 200 therapeutic recombinant and mAb agents now in clinical trials. These demonstrated technical and market successes have been tempered in part by high development costs and correspondingly high patient costs. This aspect of the biopharmaceutical industry has drawn a sharp technical, financial, regulatory, and political focus. The industry must improve production efficiencies, quality, and yield in order to expand product supply and availability while reducing product cost.

A call for innovation and efficiency: the PAT Initiative

The US FDA has encouraged biopharmaceutical producers to implement innovative technologies for process control and management of product quality. These technologies are now routinely employed with great success in other process industries, such as petrochemical, food, and semiconductor processing. Innovative examples also exist in small-molecule pharmaceutical production. This initiative is the Process Analytical Technology (PAT) Initiative[4] and seeks to provide a framework to blend statistical process control with on-line physical and molecular sensors to fully parameterize all facets of the biological production process. This strategy will naturally increase process knowledge, process and product quality, yield, and throughput, which will drive down production cost.

Most implementations of PAT systems in biopharmaceutical production have been limited to simple on-line physicochemical sensors such as pH, dissolved oxygen, and agitation rate, or simple molecular measurements such as UV absorbance at a single wavelength. Groton Biosystems currently markets PAT solutions to permit on-line classic small molecule nutrient and other simple measurements of active fermentation and cell culture systems. Groton Biosystems and Agilent have now joined forces to implement on-line monitoring of complex reactor nutrients by HPLC. This system consists of the Groton ARS™ Automatic Reactor Sampling System coupled to an Agilent 1200 Series LC system (Figure 1).

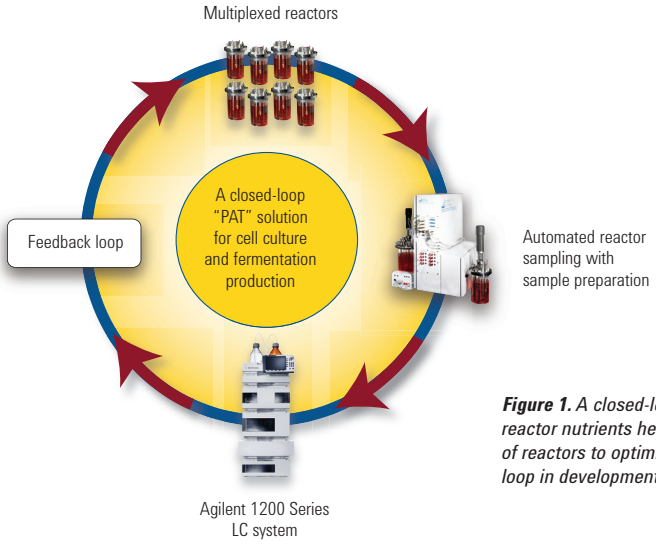
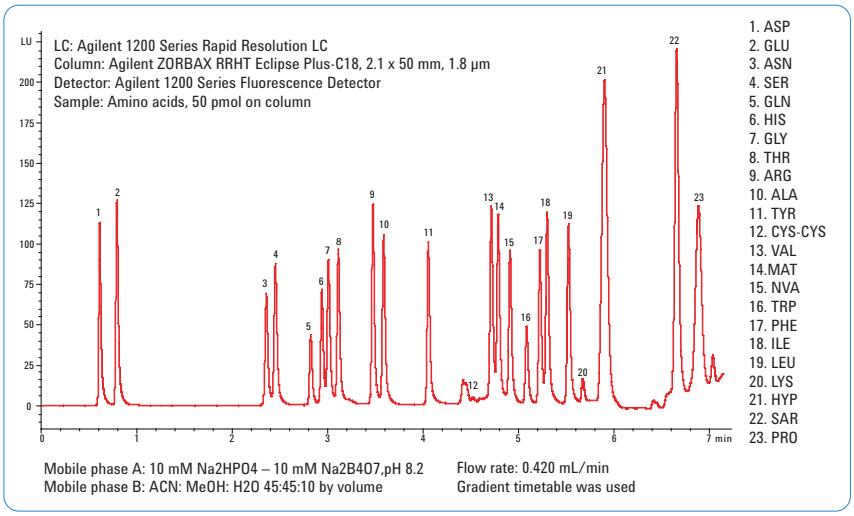


Figure 1. *A closed-loop system for monitoring reactor nutrients helps to ensure proper feeding of reactors to optimize product yields (feedback loop in development).*

A solution: the ARS-1200 Series On-Line HPLC System

Sampling of active bioreactors requires that the sampling method preserve the sterility of the system. The ARS system accomplishes this through a combination of isolation valves and an on-board Clean-in-Place (CIP) system that exhaustively cleans the entire sample system from reactor interface to the assay instrument (HPLC) interface after and between each sample acquisition. The CIP process parameters can be easily managed by the user to ensure consistent and complete operation whether one is sampling mammalian reactors or microbial fermentor systems. The ARS also includes sample preparation operations that permit delivery of a completely prepared sample aliquot directly from the reactor to the HPLC injection valve. Control of the ARS is integrated seamlessly into the method programming for the Agilent 1200 Series LC. Operation of the 1200 Series LC is neither compromised nor modified by the addition of an ARS system.

Rapid Amino Acid Analysis



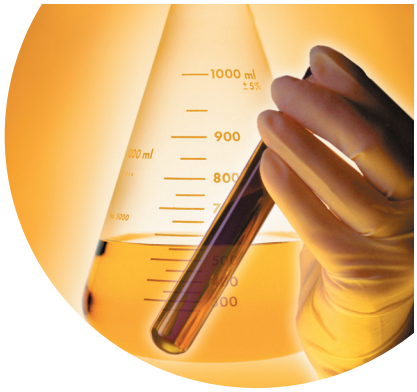


Figure 2. *Fast analyses such as this one are the key to real-time monitoring and optimization of production processes.*

Rapid PAT amino acid analysis

The first target biopharmaceutical application for the ARS-1200 is amino acid determination in bioreactor media systems. For this application, the ARS sample preparation steps will include filtration to remove cells and debris and to remove protein, a typical interference in amino acid determinations.

Defined media formulations are the most common media formulations for both fermentation and cell culture. They are precise mixtures of chemical compounds at precise concentrations and always include amino acids, the essential building blocks for protein synthesis by the active organism in the bioreactor. Successful monitoring of amino acid concentration in real time by the ARS-1200 will permit process development teams to monitor essential amino acid consumption and to formulate appropriate feeding strategies to optimize each amino acid in the media over the course of the reactor cycle. The fast separation times and high resolution achieved by the Agilent 1200 Series LC utilizing state-of-the-art column technologies will enable total assay cycle times in the 10- to 15-minute range for most reactor conditions (Figure 2).

It is expected that use of the ARS-1200 system for on-line amino acid analysis will significantly compress Design of Experiment (DOE) optimization in late-stage development by streamlining and automating collection of relevant data. Subsequent real-time monitoring of production processes will permit timely feeding of reactors to optimize product yields and to reduce reactor cycle time by maintaining protein expression at optimum levels at all times.

Automation increases productivity

The ARS-1200 system will provide a high level of automation for development, scale-up, and production within biopharmaceutical facilities. This automation product will ensure sterility of the reactors it samples while enabling complete amino acid assays in near real time without compromise. Users will enjoy labor savings and productivity gains in sampling and assay of reactors.

The rugged, automated Agilent 1200 Series LC system is ideal for process monitoring. Find out how its flexible, modular design can fit your laboratory and production needs.

Learn more at
www.agilent.com/chem/1200rr
and **www.grotonbiosystems.com**

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