



## Integrated Equipment to Offer 24\*7 Sampling and Analysis Solutions for Liquid Processes

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The biopharmaceutical industry has significantly advanced over the last few years with a number of products ranging from vaccines and monoclonal antibodies to recombinant protein products being approved by the FDA for human therapeutic use. Yet, there are an extensive number of products still in the development phase or in clinical trials. The products that reach the market are expensive due to their high cost of development. It is thus absolutely essential to improve production efficiency and expedite development to reduce product cost and their time to market, without compromising on product quality and yield.

The US FDA PAT initiative encourages biopharmaceutical industries to embrace innovative technologies in their process development and subsequently implement them in production, ultimately leading to a better process understanding, control, and management of final product quality. Most of the PAT systems implemented today in the biopharmaceutical production are limited to simple, online physiochemical sensors to measure basic process parameters such as pH, agitation rate or dissolved oxygen, molecular measurements such as ultraviolet absorbance at a single wavelength.

Groton Biosystems, headquartered in Boxborough, Massachusetts, is focused on developing innovative, online solutions for liquid process challenges. Its proprietary automated reactor sampling system (ARS) is an automated, PAT-compliant, online sampling system used in reactors/fermenters for biopharmaceutical process applications such as cell culture and fermentation.

To engender a completely automated reactor sampling and complex nutrient analysis, Groton has enabled coupling of its ARS system with laboratory analytical equipment such as HPLC. Groton has collaborated with a leading analytical industry partner such as Agilent Technologies, to offer a total closed-loop monitoring solution by coupling the ARS system with the Agilent 1200 Series LC system.

The most significant aspect of this collaboration from a PAT perspective is that such integration has enabled bringing bench top lab analytical systems, such as HPLC, close to the process to connect it real time with a system such as ARS, to provide online data. Thus, through this integration, increased data

points are obtained, which is a key aspect in PAT to fine-tune process control, increase yield and quality of the product, and reduce cycle time.

The ARS system, a stand-alone system, offers several benefits in which it enables automated, hands-free sampling of reactor components. Through automated sampling, Groton's ARS has reduced the risk of contamination and the risk of human error factor that could result from conventional manual sampling. The integration of the ARS with the Agilent 1200 series LC has overcome the typical concerns and barriers associated with conventional manual sampling and yielded an effective tool that supports automated sampling at any desired frequency and additionally, operation of the Agilent 1200 series LC is not compromised on interfacing it with the ARS system. The ARS also includes unique sample preparation operations, which facilitate delivery of a completely prepared sample, directly from the reactor to the HPLC injection valve. On the whole, the ARS system allows interfacing to four analytical instruments and up to eight input multiplexed lines, which enables sampling from up to eight reactors at a time.

One of the key challenges associated with a bioreactor sampling system is to maintain the sterility of the system. The ARS system achieves this through a combination of proprietary isolation valves and an on-board clean-in-place (CIP) system or steam-in-place (SIP), for large-scale systems. The entire sample system from reactor interface to the assay instrument (HPLC) interface after and between each sample acquisition is exhaustively cleaned by these systems.

The primarily targeted biopharmaceutical application for the ARS-1200 is to perform on-line amino acid analysis in complex bioreactor media formulations. This ARS system is extremely scalable and could be employed in process development areas to pilot and production reactor systems. The primarily targeted biopharmaceutical application for the ARS-1200 is to perform online amino acid analysis in complex bioreactor media formulations at the pilot level.

This system is currently being used extensively in method's development applications and is capable of being used as a validated system in the manufacturing environment. At this point, Groton is looking forward to expand the number of analytical instruments that could be integrated with the ARS system, to make it an extremely powerful PAT tool. For instance, Groton is planning to develop a closed-loop system by integrating the ARS system to the reactor control system through OPC (OLE for process control, where OLE is object-linking and embedding) to obtain data from the analytical instrument to send it back to the reactor control system, to perform predictive feeds and controls.