



## Bioprocessing Technology Overview

# Implementing CIMS for Process Operations

## Goal Is to Integrate Analytical Capabilities with Bioreactor or Fermentor Control Software

Gail Dutton

**F**or many bioprocessing professionals the proliferation of process monitoring and control solutions presents an immense opportunity to improve their knowledge of their mammalian cell cultivation or microbial fermentation processes.

Comprehensive information management systems (CIMS) are helping them manage this data, providing much needed efficiency boosts as scientists generate increasingly large datasets and companies implement quality by design as well as process analytic control standards.

The advantages of CIMS lie in their ability to seamlessly integrate information among a variety of analytic instruments and bioreactor control software to enhance and streamline bioprocessing workflow, according to scientists at Lonza Biologics ([www.lonza.com](http://www.lonza.com)) and Gevo ([www.gevo.com](http://www.gevo.com)).

Both Lonza, a supplier of active pharmaceutical ingredients, and Gevo, which provides renewable chemicals and advanced biofuels, needed real-time data to assess bioreactor run quality and to make control decisions. They also wanted to streamline and automate the information flow to eliminate as much manual data entry as possible.

"We wanted three main things: 24/7

information management during the whole fermentation process, better understanding and control of our processes, and better leverage of our process analytical technology," explains Peng Jiao, Ph.D., senior project leader for Lonza.

Gevo had similar goals. According to James Glenn, Ph.D., fermentation development specialist, "We needed better data management. Specifically, we wanted the fermentation off-gas data time-synchronized with our bioreactor operating parameters for post-run analysis, and we wanted this data available in a single file. We also wanted to increase throughput."

**CIMS automate the manually intensive work of pulling data into one report while providing real-time information that can be used for immediate process optimization.**

Automatic data aggregation was another objective. "CIMS eliminate copying and pasting mass spec raw data into Excel spreadsheets for calculations of oxygen transfer rate, carbon transfer rate, total volume of oxygen, and total volume of carbon. Previously, this data was copied for individual vessels and synchronized with fermentation time. This was labor-intensive and usually done after the fermentation was complete," Dr. Glenn adds.

When Lonza considered adopting a CIMS approach, it had three key concerns: "We were looking for easy integration with other systems, ease of use, and good technology support," Dr. Jiao notes.

"There can be problems when implementing data communication across products from multiple vendors," Dr.



Glenn explains, so customer support was very important. “Reliability and price were other important factors.”

### Technology

Lonza and Gevo both have used **Dasgip** ([www.dasgip.com](http://www.dasgip.com)) products for several years and chose the firm’s information-management system **DASware**. This system allows interconnectivity among bioreactors and external lab devices, with comprehensive data and information management, factorial design of experiments, and remote control of bioprocesses, according to Dasgip.

Karl Rix, Ph.D., CEO of Dasgip BioTools, explains that CIMS automate the manually intensive work of pulling data into one report while providing real-time information that can be used for immediate process optimization. Supporting Wi-Fi, intranet, virtual private networks or 3G connections, **DASware** also provides web-based or mobile device remote access to the bioreactor systems.

The technology is a modular addition to Dasgip Control, an integral part of Dasgip’s bioreactor control systems. **DASware** analyze, one of six available **DASware** modules, provides bidirectional interconnectivity to third party lab devices using established standards such as OPC and Modbus.

This let users establish control strategies driven by analytical results, such as feedback control loops for key nutrients, on-demand sampling strategies, or to select individual analyzer panels to investigate different process parameters at specific times.

Likewise, the **DASware** discover module allows users to retrieve historical process parameters and run-time data from an integrated SQL-server database using MS-Excel-style queries. The reports generated by one mouse click include recipe information, process information, and run-time data as well as an event log.

### Usage

“We mainly use Dasgip systems for our microbial fermentation processes, including bacterials and yeasts,” Dr. Jiao reports. “We set up the Dasgip with an autosampler, integrated with a YSI Life Science system. This allows us to moni-

tor the concentrations of substrates, such as glucose and methanol, so the system can control the feed rate based upon the feedback.” Manual data entry is possible, but, “we prefer the fully automated system, especially in the parallel small or mini-scales, from 100 mL to 1 L scales.”

Gevo uses **DASware** in fermentation process development to establish connectivity between a Thermo Fisher Scientific mass spectrometer and two Dasgip bioreactor systems of eight vessels each. The process produces isobutanol from corn mash.

“The Dasgip system is a complete package with software written specifically for their fermentation equipment. The system is modular, so it’s possible to add BioBlocks, pump modules, redox probes, etc. Also the software strikes a good balance between ease of use and freedom to fine-tune controls, such as using the trigger feature to add nutrients based on the carbon transfer rate,” Dr. Glenn says.

“To get the maximum benefit from the new technology, we needed Dasgip to write script calculations to replace our Excel spreadsheets for output of the oxygen transfer rate, carbon transfer rate, total volume of oxygen, and total volume of carbon.”

### Results

“CIMS has been helping us in many ways,” Dr. Jiao says. “For example, with monitoring the concentrations of methanol and then controlling the feed rate by YSI feedback data, we avoided the methanol accumulating during the *Pichia* fermentation process. The results speeded up the pace for process development and optimization.”

CIMS also eliminate errors inherent in manual entry, notes Dr. Glenn. Now, the mass spec data is transferred into the Dasgip control system, where script calculations determine the oxygen transfer rate, carbon transfer rate, total volume of oxygen, and total volume of carbon alongside other parameters, such as dissolved oxygenation, pH, and temperature.

“All the control data is synchronized with fermentation times and saved in one file.” That streamlines post-run analysis and also eliminates the need to synchronize and store multiple files. “The data is

available in real time, so we can monitor off-gas data and make control decisions to optimize fermentation performance.”

### Compatibility

CIMS integrated easily into both operations, according to the Lonza and Gevo researchers. The biggest issue, Dr. Glenn says, was finding time in the experiment schedule to actually stop the fermentors while the fermentor software was upgraded to support OPC communication with the mass spectrometer.

While that was under way, Gevo took the opportunity to perform preventive maintenance on the equipment. “We then spent about two weeks fine-tuning the script calculations.”

Neither Gevo nor Lonza reported any incompatibilities with other equipment. Gevo had Thermo Fisher Scientific mass spectrometers in place and worked closely with representatives from Thermo Fisher Scientific and Dasgip before the actual installation to ensure a trouble-free startup.

Although Dr. Jiao says CIMS is still a challenge for associates to use independently, that is mainly a matter of acceptance. “People like it, but it may take a little time for people to fully accept it.” He says any hesitation is being overcome with training.

Gevo users haven’t experienced any reluctance, according to Dr. Glenn. “Users embraced the new system because it avoided copying mass spec data files into Excel.”

Reliance on CIMS is reinforced by the knowledge that the information is accurate. “The fermentation group gave a presentation to management showing correlations between Excel calculations and the new Dasgip script calculations,” Dr. Glenn says. “Now we use the real-time data generated by Dasgip.”

Since real-time analysis of fermentor off-gas and insight into fermentor performance is readily available, Dr. Glenn reports, “Our group expects to have this data when discussing ongoing fermentations and making control decisions. It has become an important tool that our team uses to maximize fermentation process development for isobutanol production.”

**GEN**