

Automated Process Control and Data Management for Cell Culture and Fermentation

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Taking a Cell Culture or Fermentation Process From “State of the Art” to “Ahead of the Curve”

Biopharmaceutical companies are facing major challenges and are “...compelled to incorporate tools that can improve their productivity and reduce R&D expenditures,” according to analyst Raghavendra Chitta of Frost & Sullivan in a July 2005 report. Life sciences trail behind the electronics and other manufacturing industries in adopting automated process control and data management systems, even though huge profit opportunities exist for those who can get higher-quality, higher-yield products to market faster. For example, Table 1 shows that Genentech’s drug Avastin brings in an average *daily* revenue of \$5.4 million. That’s a 5.4 million dollar opportunity cost for every additional day spent in its development.

Table 1: Opportunity Costs

DRUG	COMPANY	ANNUAL REVENUE	OPPORTUNITY COST
Avastin	Genentech	> \$2 Billion	\$5.4 M / Day
Synagis	MedImmune	> \$1 Million	\$2.7 M / Day
Aldurazyme	BioMarin	\$66 Million	\$181 K / Day

Table data calculated from public financial documents.

Most inefficiencies in the cell culture or fermentation process result from the use of manual methods of process control and data management, particularly in R&D, process development labs, and pilot plants. The products themselves are becoming increasingly complex, magnifying these inefficiencies. A “state-of-the-art” lab is pictured in Figure 1. “State of the art” is meant literally, as the true state, the “status quo,” of labs today. The current state of fermentation and cell culture labs is a loose collection of instruments, analyses, and measurements, brought together by clipboards and sneakers.



Figure 1: The “state of the art” is a loose collection of instruments, analyses, and measurements, brought together by clipboards and sneakers.

The “process” is the entire operation at a facility to make the desired product. The “methods” are the procedures, instruments, software and other tools used in the process. My colleagues and I have been studying both the process and the methods of a variety of industries for many years, and have focused specifically on the needs of the pharmaceutical industry for the past four years. WireWorks West makes process control easier for biopharmaceutical companies, by borrowing from our automation experience in other industries. We have worked with biopharmaceutical companies of all sizes, from an academic lab at MIT to a large pilot plant project at Genentech and have created a process control and data management software solution, FermWorks™, specifically designed to increase productivity and accelerate product development in cell culture and fermentation. After working with us, one Senior Process Development Scientist at a large West Coast biotech company told us, “FermWorks gives us profit maximization... We get products to market faster... if we’re one month faster to market, that is significant added value – as in *more revenue*.”

Manual methods have been used for years for good reasons. They are “tried and true,” and many businesses depend on established, “trusted” procedures rather than risk

introducing change. On the other hand, plenty of lab directors, researchers, and technicians would welcome automation, but they believe that manual process control and data collection are the only alternative available, given the equipment they have to use. Most comprehensive automation systems are large-scale, expensive systems with required hardware (such as PLCs) and fully custom software. These systems are just not practical in the process development lab or pilot plant, where automation rightfully takes a back seat to experimentation, innovation and cost-savings.

As development processes have become more complex, patent competition more intense, and time-to-market more critical, the inefficiency of manual methods is hurting biopharmaceutical companies. A case in point was BioMarin Pharmaceutical, in Novato, California. BioMarin researchers in Process Development collected data and managed recipe development for new drugs in the tried-and-true, old-fashioned way. To monitor the development process, they walked around the lab recording data on a clipboard from each instrument, and then manually entered all the data into an Excel spreadsheet. Based on their analysis of this aggregated data, they returned to each controller to adjust the recipe process by hand, in order to optimize the recipe for maximum effectiveness and best yield.

BioMarin's methods are not unusual; I see them all the time. So what's wrong with this typical day in a lab? A scientist takes cell culture samples and carries them to other instruments; records readings from a mass spec on a clipboard, eyeballs cell density through a microscope, calculates cell viability with pencil and paper, adjusts an media flow pump by hand... This approach is, "inefficient and error prone," according to Jim Michaels, Director of Cell Culture and Fermentation at BioMarin Pharmaceutical.

These manual methods:

- Are vulnerable to error (is that a 7 or a 1 on the clipboard?)
- Have slow response time (the nutrients came too late for some cells!)
- Are not tracked (who increased media flow?)
- Are not repeatable (how much did she adjust the pump? When?)
- Risk losing data (what was that cell density again?)
- Waste time (back and forth; gown on, gown off; my feet are tired)
- Limit resources (are you done with the microscope yet?)
- Reinvent the wheel (hey, ramping temp slowly is better! I knew that.)
- Require training on multiple interfaces (a new gas analyzer? Oh no.)

In many ways, this status quo of manual process control and data management is dictated by the instrumentation. Instrument manufacturers certainly focus on excellence in function, accuracy, and speed of their devices. They are less concerned with acting as part of a larger whole, sharing and communicating with other instruments in "the big picture." The result is islands of data: isolated measurements and analyses, and isolated subsystems like scattered puzzle pieces. This is partly because of competitive, rather than cooperative, economics. Also, instrument manufacturers have specific expertise, and concentrate more on perfecting their own island, and less on building bridges. Lastly, a particular instrument could be a piece in many different puzzles, serving a variety of larger processes. It is a challenge to be a team player in those many different systems.

Would you prefer Los Angeles over Hawaii? As a metaphor for your process development lab, you would. You want a network of highly-connected subsystems, with data and control flowing seamlessly between them (and no rush hour). Isolated islands mean inefficiency and expense.

On the bright side, almost all modern instruments are designed with the *capability* to communicate and cooperate, to make the puzzle pieces fit together. What is lacking is the orchestra conductor who manages and controls all the individual instruments as a unified whole. This must be done by software that works at the *process* level, bridging gaps between disparate subsystems. Figure 2 shows the same lab, now well-connected and automated.

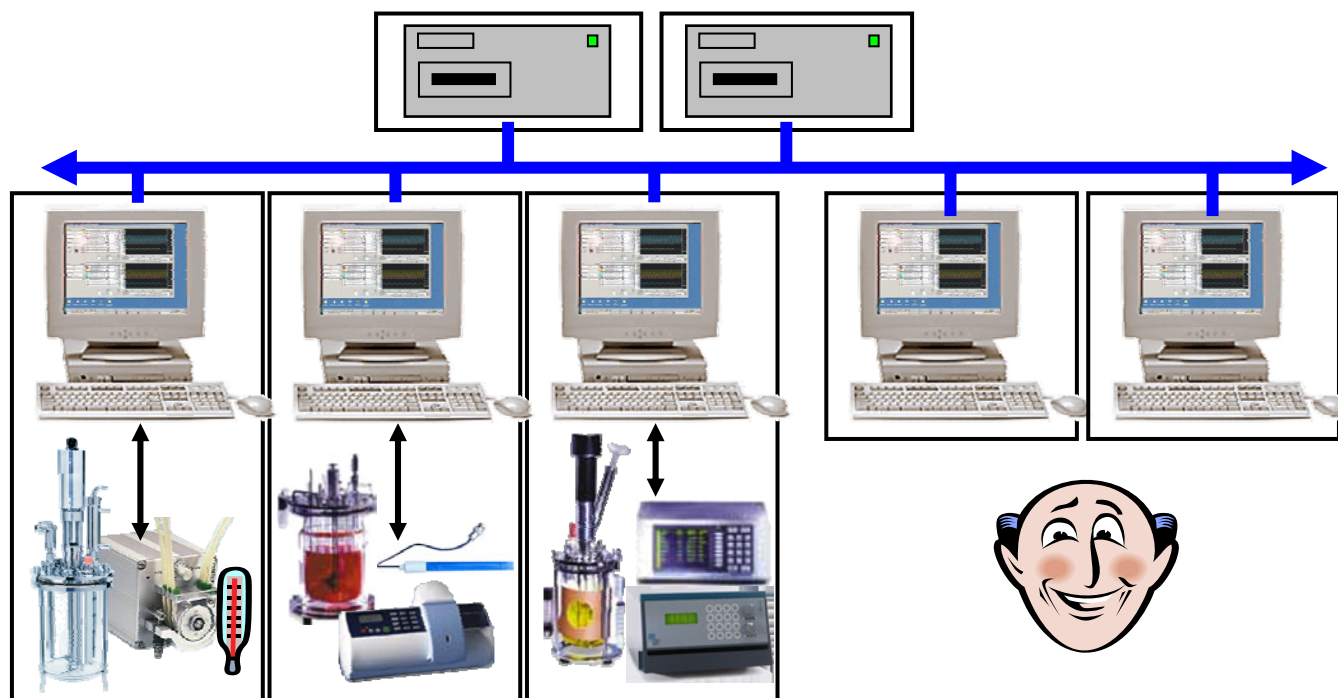


Figure 2: Automated Process Control and Data Management with FermWorks

Such automated process control and data management software must address the above shortcomings of the manual methods in these ways:

- Record and recall data accurately
- Make control decisions in real-time, continuous or batch
- Track all changes (who did what, and when? Allow notes for “why.”)
- Store automated steps for repeatability
- Keep data secure
- Save time by providing equal access from anywhere
- Share resources, such as an expensive mass spec, across the network
- Share knowledge as stored recipes and calculations
- Provide a single, unified interface, regardless of hardware

After we worked with BioMarin Pharmaceutical to install the comprehensive, automated software solution, FermWorks, Jim Michaels said, “BioMarin has realized a **30% savings** in time, resulting in substantial development cost reductions.” The methods they were using before are very common at biopharmaceutical companies, and generally accepted as “state of the art,” but now they are “ahead of the curve.”

Requirements of an Automated Process Control and Data Management System

There are some common requirements of any good process control and data logging software, such as archiving data securely, displaying and reporting data clearly, monitoring alarm conditions, providing real-time feedback control, etc. In this section, I will look more closely at less obvious requirements of an ideal automated process control and data management system for cell culture and fermentation labs, and describe the benefits to be gained. These requirements are:

- Be independent of instrument brands
- Be inclusive of ALL instrument brands
- Handle on-line, off-line, and calculated data equally well
- Maintain data history across instrument changes
- Unify facility and provide remote access across network
- Scale to accommodate larger volumes or growing facilities
- Add new instruments easily
- Extend to add more measurements, new analyses or control strategies
- Integrate upstream, downstream, and side subsystems, such as HPLC
- Facilitate GLP/GMP/PAT/FDA compliance

The process control and data management must be independent of the instrumentation. It must be “multi-lingual,” able to speak the language of each different island and communicate with instruments of all brands. Every R&D or process development lab has an eclectic collection of equipment. It is not economically possible to replace or upgrade them all, in order to achieve a unified system, and that would just be a waste of good equipment. Old devices, new devices, and future unknown devices need to be brought under one umbrella. Several years ago, BioMarin obtained a mixed set of very expensive cell culture and fermentation instrumentation as the result of a company acquisition. These acquired instruments, added to those already in the lab, resulted in an assorted mixture of instruments, of various ages and from various vendors. They included biocontrollers from New Brunswick, Sartorius (B.Braun), and Applikon. Each vendor’s instrument had its own proprietary control software and none of the instruments talked to the others. The data aggregation, integration, and analysis became even more cumbersome. Instrument-independent software cured these headaches and allowed BioMarin to save capital equipment budget by making full use of the legacy and acquired instruments.

To be “multi-lingual,” a system must support many types of physical connections: Ethernet, serial, analog & digital I/O, OPC, and other standard protocols. In addition, there must be open publication by instrument manufacturers of their command sets and data formats. Modern labs must avoid closed systems, often presented as “turn-key” or “complete,” that keep their communication protocol proprietary by bundling instrumentation hardware, a

PC, and some interface software. These become expensive “islands” that cannot be integrated with an automated system. Many such systems offer, at most, a token open interface through flat files (no real-time data availability). Or they might, for the small fee of several thousand dollars, offer additional OPC server software. Until the life sciences consumers understand the benefits of cooperative open instrumentation and demand that from vendors, these closed systems will persist.

Even with “multi-lingual,” unified data management software, there may still be some of these stubborn instruments or external analyses for which data must be collected by hand. It is important that this “off-line” data can be entered into the data management system and be treated as an equal citizen. It should be available for display, analysis, and feedback control, along with all the data from various instruments that were collected automatically. Also, any data analysis or calculated results must be equally available for display, further analysis, and feedback control.

A unified interface for all sources of data means the people in the labs don’t have to learn all the different systems. A Senior Process Development Scientist at a large West Coast biotech company pointed out the advantage of this, “Having a common data platform saves time and money in training and in the overhead of integrating different data sources and training on different systems.” Figure 3 shows data presented on a FermWorks Trends display.

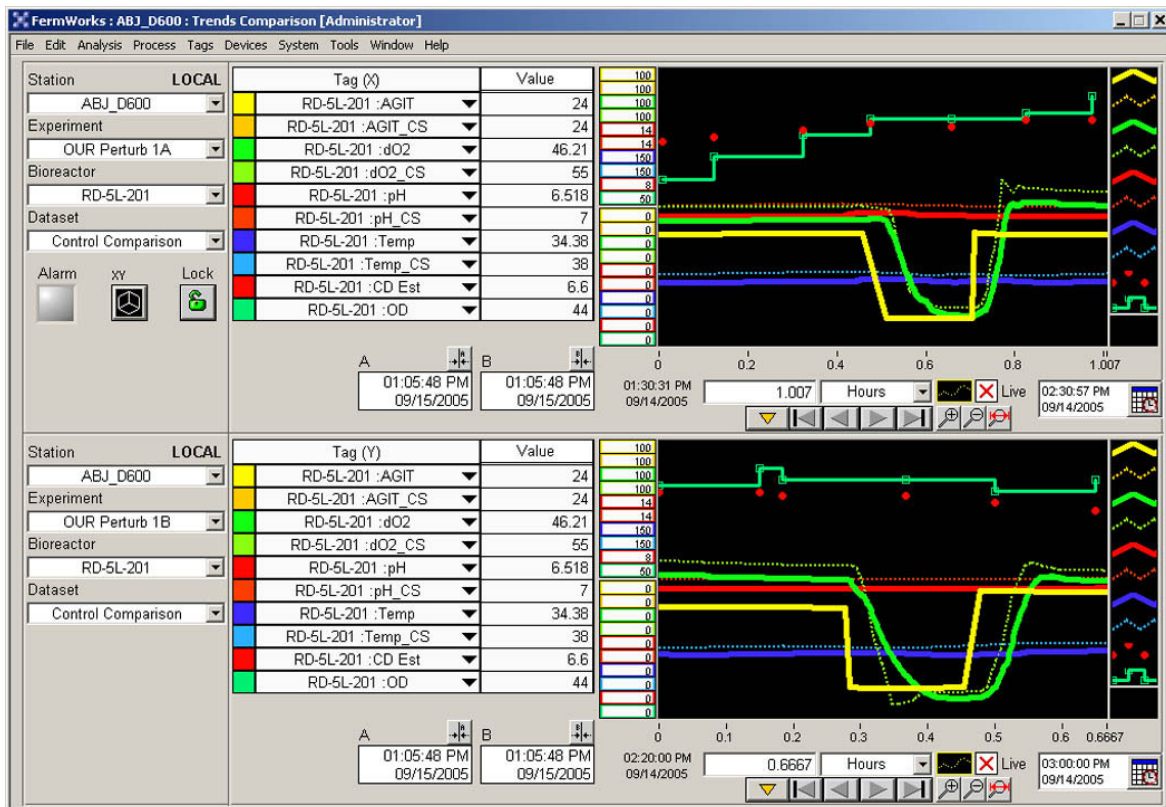


Figure 3: A FermWorks Trends Display

Real-time feedback control, using data from all sources for decision-making, gives faster, more accurate response to changing conditions in the process. This response reduces waste and improves product quality. Unlike manual adjustments, automatic control decisions happen in real-time, are tracked, and can be repeated exactly in another run. One Research Scientist at a mid-sized biopharmaceutical company said, "We've been able to reduce the time between experiments on our reactors from two weeks to just a few days. We're now performing more experiments each year on the same set of equipment."

Another data management goal requires device-independence: one method of measurement should be able to be replaced with a new one, with no interruption to the history of the process value. Here, the phone companies set a good example. A customer can buy a new phone (instrument), but his phone number doesn't change; his identity stays the same. Likewise, when an old mass spectrometer is replaced with a new kind of gas analyzer, the nitrogen measurement should have a seamless history across the two.

Besides being able to communicate with each different data island, there need to be bridges between the islands. This requires a *distributed* process control and data management system. A distributed system requires a robust network to be in place, linking all computers, instruments, data servers and archives. A company's IT group has to be an active player here, and should be involved early in the planning.

The advantages of a distributed system are many. First, all aspects of the process control and data management can be available from any site on the network. A technician can monitor many reactors from one station, or respond to alarms remotely; a researcher can check on and adjust experiments from his office, create reports, and be automatically notified by email or pager when problems arise. Second, instrument resources can be shared. One expensive gas analyzer can serve many reactors. Third, know-how and results can be shared. A recipe or control strategy developed by one scientist can be used by others, for scale-up or for other runs. Process data and results can be shared and compared on a live system, even from a meeting room. The Operations Manager of a San Francisco Bay Area biotechnology firm said, "I have immediate access to all the reactors I manage in three separate facilities, and this has streamlined our post-experiment data analysis."

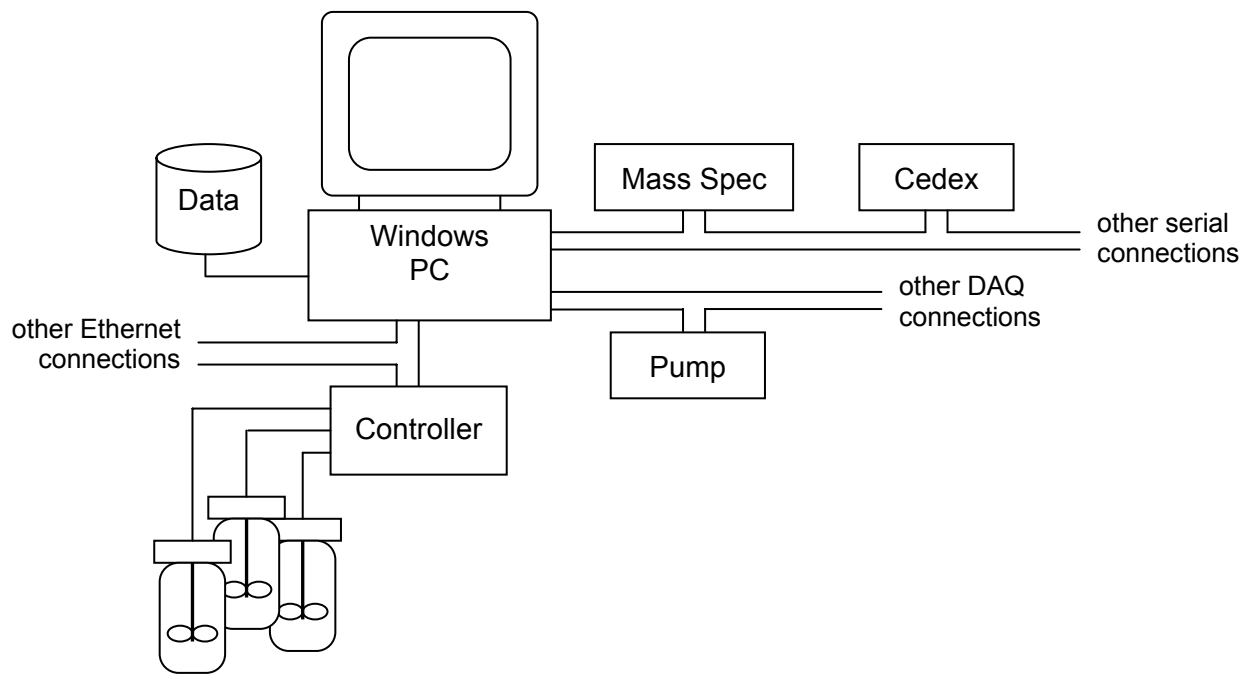


Figure 4: Architecture Diagram of one FermWorks Station on a Network

Deploying a recipe for larger volumes is one important requirement for scale-up. The process control and data management system must also scale in other ways. You must be able to add more instrumentation, more computers, or additional users, with no inherent limits. Also, you must be able to extend the system to add new control strategies, new result calculations, or new report or display formats. These abilities will minimize the cost of expansion for companies that want to unify their facilities and plan for the future. Expansion includes scaling up production, increasing process volumes, adding more bioreactors and other instrumentation, developing new control strategies or analyses, training personnel, and integrating with other parts of the business enterprise.

It is extremely valuable to have these instrument replacements and scale-up, expansion, and customization capabilities without having to shut down the system. Live additions and changes, without system downtime or software upgrades, save a lot of trouble, time and money. Also, the ability to customize in-house avoids waiting for version upgrades from a supplier and protects proprietary algorithms.

As Director of Cell Culture and Fermentation, Jim Michaels can testify first-hand to how valuable the automated process control and data management system is to BioMarin Pharmaceutical. He said, "FermWorks provides flexibility, customization, data analysis, and data review that are very accessible and very well done."

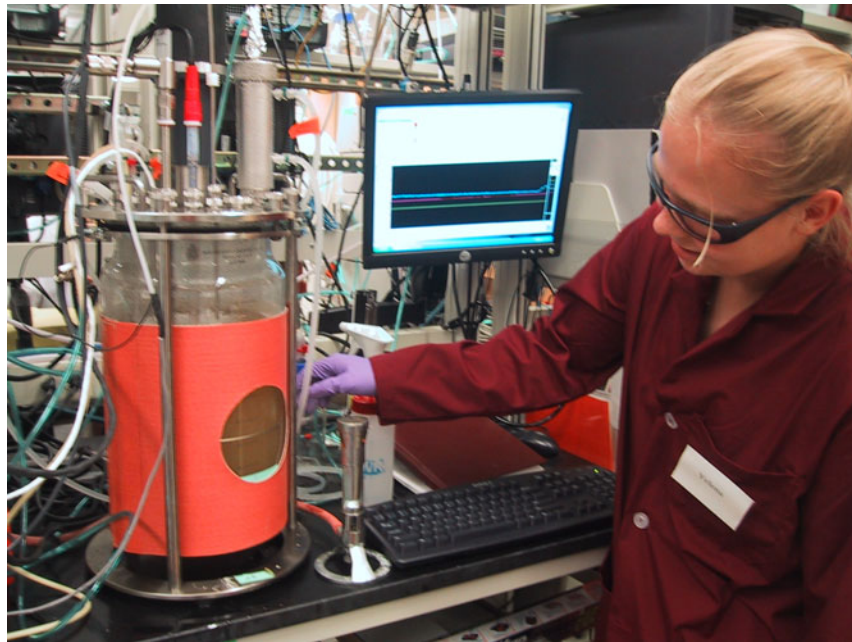


Figure 5: FermWorks in a Fermentation Lab at MIT

It is often essential to bridge the gaps between different subsystems within the bigger process picture. Not only to share and communicate with the reactors and other instruments directly involved in fermentation and cell culture experiments, but also to bring the upstream, downstream, and side subsystems into the picture. When a sample from a reactor is taken to a microscope or an HPLC, valuable analysis will be carried out there. The results of that analysis say something about the success of the process and quality of the product, and those results should be integrated into the records and control decisions for the on-going process. If the sampling, analysis, and results of the various subsystems can be automatically integrated, you have a more efficient process and a higher-quality product.

Once the entire process is linked and unified, bridges can be built to other parts of the business enterprise, such as LIMS systems. Whenever data from one system must be manually entered into another, there's an opportunity for automation. Of course, it is best to focus first on building bridges across gaps in the system that must be crossed on an hourly or daily basis, then address the more infrequent data transfers.

Biopharmaceutical companies also struggle to comply with FDA regulations, GLP, GMP, and PAT standards at an earlier stage. Manual methods make this much more difficult, because changes can't be recorded and tracked, procedures can't be repeated exactly, and systems are less secure. The system security and tracking commonly found in FDA 21 CFR Part 11-compliant manufacturing facilities would be great in process development, but the high cost and inflexibility of the systems usually selected for manufacturing makes them impractical. However, FermWorks implements FDA-compliant systems for labs and pilot plants, with full security and tracking features, without sacrificing the flexibility and openness required during process development.

Benefits of an Automated Process Control and Data Management System

There are many benefits of an automated process control and comprehensive data management system in cell culture and fermentation labs and pilot plants, and they all lead directly to the main point of greater efficiency and shorter time-to-market.

In particular, the benefits are:

- Reduce operating costs
- Avoid lost opportunity costs
- Develop higher-quality products
- Reach better yields
- Reproduce results reliably
- Ensure data security and reduce risk of data loss
- Meet higher safety standards, be FDA compliant
- Unify all sources of data and calculated results
- Integrate subsystems into the larger process
- Run more experiments with the same resources
- Share instrument resources
- Share know-how and results
- Extend useful life of hardware and software investments
- Add custom, novel analyses and control strategies
- Minimize cost of expansion

As pressure on biopharmaceutical companies to accelerate the commercialization of life-saving biotherapeutics and comply with government regulation increases, incorporating advanced process control and data management is essential. An additional benefit is that incorporating a comprehensive software system, like FermWorks, frees laboratory scientists from the mundane manual data collection and process control methods, and allows them to focus on essential research and development.

Ms. Meg Kay is Director of Process Control Products at WireWorks West, Inc. WireWorks West has provided its FermWorks™ system, since 2000, and other process control and analysis applications to Genentech, Bayer, Stanford Genome Technology Center, BioMarin, Centocor, NexBio, Novozymes, Flextronics, The University of Victoria, and others.

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