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AUTOMATING INDUSTRIAL PROCESS DEVELOPMENT LABS

"Equipping a bioreactor process development lab with a modern networked automation system increases productivity, shortens the time required to produce optimum processes, and produces a wealth of statistically valid data."

Process development (PD) labs are used extensively in the life sciences industries to conduct experiments on various drug compounds. The goal of PD is to produce optimized, robust and reproducible processes that can be scaled up for manufacturing.

Better process understanding early in the drug product life-cycle leads to higher drug product yields and better product quality profiles. Favorable product quality attributes result in drug candidates that demonstrate better therapeutic effects and fewer safety concerns.

Currently, many PD labs are not fully automated. Many experiments are still run manually, with data recorded via pen and paper. Some labs have automated certain areas, but have yet to network their islands of automation into a coherent system, leading to poor productivity and other issues.

But some PD labs, particularly those with bench-top bioreactors, have upgraded to fully automated and networked control—dramatically improving lab productivity, increasing experimental run success rates, reducing labor and equipment resource requirements, and significantly enhancing the data packages used for tech transfer.

Enhancing data packages by obtaining more complete data in the PD lab can significantly reduce the required number of large scale engineering runs and conformance campaigns during pilot plant tech transfer and clinical/commercial manufacturing.

> “Obtaining more complete data in the PD lab can significantly reduce the required number of large scale engineering runs”

There are two main ways to automate a PD lab. The first and most common is to add an automation system to a lab’s existing bioreactors. With this method, the PD lab uses the current physical bioreactor vessels, head plates and associated hardware. In addition to the new automation system, additional sensors and analyzers are usually required in order to collect further data.

The second way to automate is to purchase new bioreactors, either individual bench-top reactors, or skid-mounted systems containing multiple reactors. Skid-mounted systems are assembled and thoroughly tested at the supplier’s facility, allowing for quick start-up once delivered to the lab.

With either option, investment in PD automation typically exhibits a very attractive return-on-investment (ROI), due to the benefits listed in Table 1 and explained in more detail below. Additionally, better data means the PD lab can be more easily aligned with regulatory agency such as the FDA and the EMA, and with initiatives such as Quality by Design (QbD) and Process Analytical Technologies (PAT).

Table 1: Reasons to Automate Process Development Labs

1. More experiments started and successfully completed
2. All experiments run under statistically similar conditions
3. More and better data collected
4. Greater statistical validity
5. Experiments can be monitored remotely
6. Labor productivity increases several-fold
7. Improved tech transfer for production scale-up
8. Improved relationships with CMOs and regulatory agencies
9. Enables integration of widely dispersed facilities
10. Significant cost savings and superior ROI

Automation Delivers Superior ROI

Across a host of industries worldwide, automation of manual processes has been found to deliver superior ROI as compared to most other manufacturing related investment. For this reason, investment in automation has grown faster than worldwide economic growth for decades, without signs of slowing.

Many processes were initially automated by necessity to increase throughput to mass production levels, to improve quality, and to ensure the safety of production personnel. But small scale processes like PD labs often lagged behind in terms of automation, as many of these leading reasons for automation didn't apply.

While it's possible to operate a bioreactor PD lab that's not fully automated and networked, it's not possible for such a lab to be competitive and world class. That's why leading life sciences firms are upgrading their bioreactor PD labs, realizing the benefits of fully networked automation.

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Automation allows a lab to start more experiments, because the process parameters and advanced control strategies for each experiment are stored in the automation system in a template, instead of being manually created, often from scratch. Prior run templates can be easily modified, quickly leading to a new experiment and corresponding data. Each run template can be automatically assigned to any number of bioreactor vessels on any bench in a lab.

Without a networked automation system, it's often necessary for data to be manually entered at each vessel. A 24-vessel run would thus require 24 manual data entry sessions, a time consuming process fraught with possibilities for error.

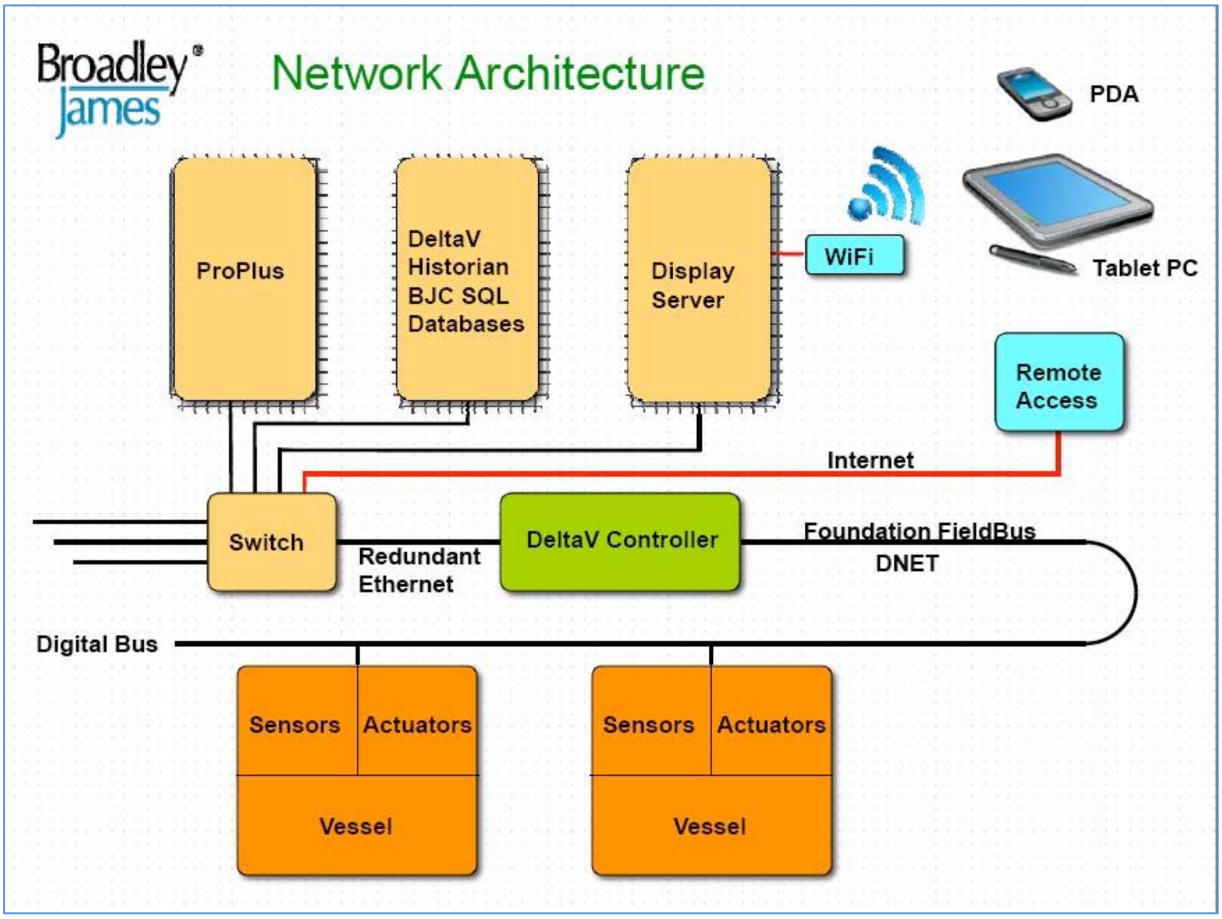

Fig (1) Schematic of a BioNet multi-vessel control system. Includes the continuous DeltaV Historian and BioNet SQL database for control strategy templates and for capture, tagging, and integration of data from NovaFlex auto-grab sample analysis.

Once an experiment is started, automation enables scientists and other lab personnel to easily and continuously monitor progress, leading to a much higher percentage of successfully completed experiments.

A typically experiment in a mammalian cell culture bioreactor PD lab runs about 15 days and must be closely monitored. Automation can provide local and remote access and control to the experiment while it's in progress, allowing scientists to make adjustments as required. These adjustments can be made while an experiment is in progress, a crucial feature that can often be the difference between a successful and a failed run. It's also possible to switch from one control strategy to another mid-run, simply by selecting a new template in a drop-down menu.

With manual experiments, it can be difficult to ascertain the status of an experiment due to insufficient data points, and impossible to monitor or adjust experiment parameters remotely. This inevitably leads to a relatively high percentage of failed experiments.

Automation allows the lab to start and complete more experiments in a given time frame, as a single person can operate up to 24 bioreactor vessels, as opposed to about 8 vessels with manual operation and data collection.

Another benefit of a modern bioreactor automation system is superior process control. These systems feature not only PID control, but also other more advanced loop control methodologies such as model-based control. Superior process control means that experiment parameters are controlled closer to setpoint, resulting in better data resolution and confidence levels, while yielding greater experimental success and improved process understanding.

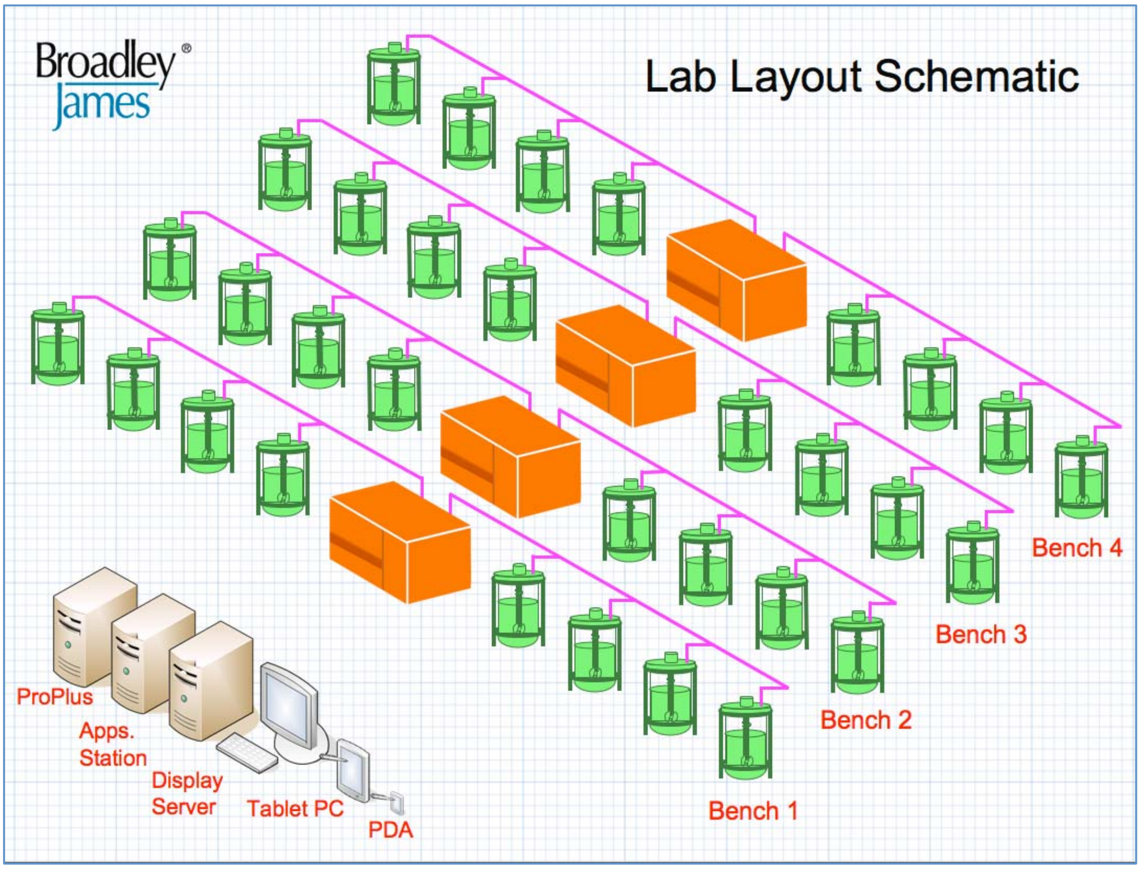

Fig (2) A schematic of 4 NovaFlex bioanalyzers networked with sample lines to 32 benchtop bioreactors for auto grab-sample analysis and data integration with the DeltaV continuous Historian data. NovaFlex's and DeltaV communicate via OPC.

Increasing the number of experiments is important, but experiments without statistically valid data have limited value. This is where an automated system really excels, particularly as compared to manual methods of data collection and recording.

Networked Automation Provides Statistically Valid Data

With an automated system, complete data from each experiment is collected and stored in a central database. In a typical bioreactor lab, data is generated from three main sources.

The first and primary data source is the bioreactor automation system. Inputs to the automation system from field instruments include all relevant experiment parameters including but not limited to temperature, pressure, pH, dissolved oxygen, and volume of gasses delivered to a bioreactor. Other pertinent data residing in the bioreactor automation system include all manually entered information such as batch times, run parameter templates and various control strategies. This is commonly referred to as on-line data.

Data is also gathered from other automation systems that are networked to the bioreactor automation system, often referred to as at-line data. An example of at-line data is information gathered from an automated system that periodically samples and analyzes material from in-process experiments. This information is typically transmitted to the bioreactor system through a high-speed digital data link.

> … data are easily accessible to all corporate personnel, whether at the lab or at some remote location.”

The third data source consists of information manually entered by lab personnel, referred to as off-line data. Common off-line data include product analysis information from a liquid chromatography lab, most importantly protein content of drug compounds measured in-process or post-production.

All three sources of data—on-line, at-line and off-line—reside in one central database. These data are easily accessible to all corporate personnel, whether at the lab or at some remote location. Accessible data include not only real-time information from current experiments, but also historical information from prior experiments. Comparing data from current to past experiments is often an excellent way to analyze experiments in order to improve process understanding and expedite optimization.

Local data access is typically through the bioreactor automation system Human Machine Interface (HMI), which in most systems consists of one or more PCs running software that can display data in a variety of forms including numerically and graphically. Local data access can also be provided by handheld operator interface devices connected to the bioreactor automation system through a secure wireless network.

Remote data access can be provided in a variety of ways. Thin client PCs can be connected to the bioreactor automation system HMIs, typically through an Ethernet-based corporate local area network. These PCs can be installed in offices throughout a facility, allowing personnel to analyze experimental data using Microsoft Excel and other tools. The HMIs can also be connected to a corporate-wide ERP system and/or a data historian, providing data to all company personnel with access to these systems.

For off-site personnel, secure thin client access can be provided through a corporate VPN. Most modern automation systems also provide browser-based access, allowing any device that supports Internet access to view data.

Reviewing and analyzing experimental data can lead to quicker understanding and optimization of each experimental condition. Once an optimum condition is determined, multiple experiments can be quickly run with this condition to generate statistically valid data, crucial for tech transfer.

In a typical lab, experiments involve the testing of many different conditions and parameters over several blocks of runs. Automation allows many more of these experiments to be run, increasing the quality of the data.

With automation, it becomes feasible to test each condition in duplicate or triplicate, which adds to the data's statistical confidence level, often generating results with a 95% confidence level.

Better Data Leads to Quicker Tech Transfer

The purpose of PD is to quickly determine the most optimum process condition for a particular drug compound for full-scale production. Without the statistically valid data generated by a fully networked automation system, tech transfer and scale-up can be more of an art than a science, with often extremely costly consequences.

For example, a typical contract manufacturer might charge $2.5 million for a 5,000 liter engineering run, and take six weeks to set up and complete the run. If the run isn’t successful, costs can quickly escalate, as can time-to-market. In addition, many CMOs add a surcharge of about 10% if they are required to become unduly involved in troubleshooting proposed process parameters.

A fully automated and networked bioreactor PD lab can be expected to reduce the number of required engineering runs, often to just one. In many cases, the savings from one less engineering run can exceed the cost of the entire networked automation system, leading to a dramatic ROI.

As a CMO becomes more confident in the data produced by a fully automated and networked bioreactor PD lab, the relationship between the lab and the CMO improves, leading to a host of intangible but important benefits. Better data also leads to improved relationships with regulatory agencies, another hard to quantify but very significant benefit.

Another reason to automate and network a bioreactor PD lab is to allow two or more labs in widely dispersed geographic locations to work together as one. Because each experiment is automated, it’s possible to run statistically similar experiments at different facilities, no matter the distance between the labs.

Once an experiment is started, scientists at all facilities can view its progress, allowing the next experiment to be improved based on actual process data. When an experiment is completed, experimental data is immediately available at each facility.

This can lead to huge gains in productivity and much quicker time-to-market. In situations where two labs are located in widely disparate time zones, for example one facility in the United States and one in Europe, experiments can be run simultaneously sharing workloads and potentially cutting time-to-market in half.

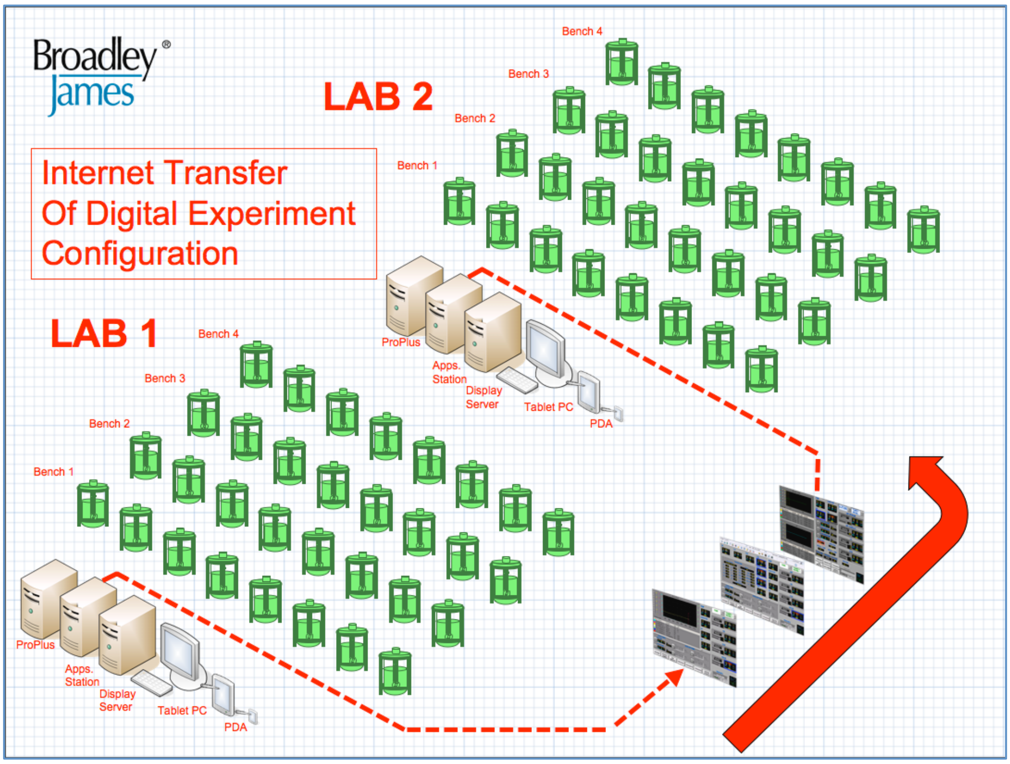

Fig (3) Experiment setup and control strategy templates can be quickly loaded onto two vessels or a group of 16 or more vessels all at one time. These same templates can also be transferred to another lab for identical bioreactor setup if additional bioreactors are needed for the experiment.

Improved Productivity and Quicker Time-to-Market

When a bioreactor lab upgrades to a fully networked automation system, concrete operational and tech transfer benefits are quickly realized. With the same number of personnel, a lab can expect a several-fold increase in the number of successfully completed runs.

> … a lab can expect a several-fold increase in the number of successfully completed runs"

This higher lab throughput will significantly cut cost and improve time-to-market. Labs will realize a substantial reduction in data variance from vessel-to-vessel, from bench-to-bench, from operator-to operator, and from facility-to-facility.

These and other benefits will produce more runs and create more data with less variance, leading to better statistical significance of experiment and project results, and better tech transfer data packages.

Better data packages from the PD lab results in fewer campaign engineering runs with CMOs and/or internal scale-up facilities, resulting in major cost savings. Fewer engineering runs also result in significant improvement in time-to-market, a crucial factor in today's fast-paced pharmaceutical market.

Production in most PD labs is limited by a lack of qualified personnel. With costs for a full time employee in the life sciences industries approaching $250,000/year, investments in automation that allow existing personnel to run more successful and statistically valid experiments will produce a quick ROI.