Improving Data Management in Process Development

A WHITE PAPER

Productivity pressure and advances in instrument technology are creating the potential for a data bottleneck and inhibiting the value of process improvement.

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Introduction

Cost considerations and regulatory initiatives are persistent pressures driving change within the BioProcess industry as biotechnology companies strive to develop better drug candidates, more quickly and at lower cost[1]. Within the upstream process development environment, this means greater process efficiency in cell line selection and process development for downstream scale-up and manufacturing efforts. Process integration, device-to-device automation and higher throughput processes are the primary avenues for improvement but create the potential for increased data backlogs without matching methods for data collection, integration and archiving.

SCOPE

This White Paper describes the emergence of process automation and system integration within the Process Development Lab and the problem created when higher-throughput systems dramatically increase the pace of data generation.

This paper then describes the design and capabilities of One Hill Solution's SMARTLAB BioProcess Manager and its role in realizing process improvement in upstream & Downstream process development

[1] Bioprocess Control: Advantages and Challenges – Joseph S. Alford – Computers and Chemical Engineering Vol 30, Issues 10-12 – 12 September 2006 – Pages 1464-1475

Today's Process Development Environment

In a conventional process development lab, the infrastructure will have grown organically to meet demand, and will consist of a range of different sizes, types and manufacturers of bioreactors and analytical instruments to help monitor batch processes and a supporting array of common peripheral devices; each optimized to meet a specific purpose and each developed and supported independently by different device manufacturers. The result is a series of independent 'islands' of automation. Pressure on productivity is creating an opportunity for process integration, higher throughput and inter-device automation. Notable collaborations between device manufacturers are leading to encouraging synergies.

Each 'island' generates data; continuous process data from bioreactors and periodic data snapshots from analyzers which measure processes at different points in time. Process developers rely on this data to monitor batch runs and other groups use this data to make informed decisions on clone selection, scale-up and manufacturing considerations. Today, this data is managed manually. Different devices generate and output process data in different formats and with different degrees of accessibility. Process developers often must collect, migrate, transform and integrate data sources before process insight can be gained and informed decisions made. Today's data management is time-consuming, tedious and error-prone.

While integration efforts can reduce manual sample handling and process control, and higher throughput capabilities can improve speed, gains promised by these technologies are at risk if process developers are left with ever increasing amounts of data to manually process.

Towards a More Fully Integrated Lab

To achieve greater benefit from device integration and higher throughput capabilities consistent with comprehensive downstream PAT platform efforts, process development environments need a more holistic solution. An idealized vision of an integrated PD lab contains the following elements:

- Process integration beginning with batch preparation and ending with downstream purification
- Automated data collection, synchronization and integration of process data from bioreactors, analyzers and peripheral devices
- Seamless integration with downstream functions including product characterization, scale-up and manufacturing
- Accurate barcode tracking and accounting of media preparation and consumables use
- Integration of bioreactor and analyzer systems for feedback control and adjustment of batch processes in real time
- Elimination of tedious and error-prone manual manipulations of samples and data
- Real time process monitoring with flexible alarm capabilities for out-of-spec processes
- Automated report generation and information sharing of raw and analyzed process data

- Integrated statistical analysis capabilities
- Comprehensive batch record-keeping including media and consumables, vessel and analyzer data, alarm exceptions, notes and statistical analysis findings

Currently, gains are being made in device-to-device automation. Examples of this include collaborations between Vi-Cell XR and ambr15 systems for automated sample handling and feedback control, the Vi-Cell XR/Seg-Flow 4800 automated cell analysis system and between the ambr15 system and the Cedex BioHT system. Another significant step in the development of full integration is the development of One hill solution's SMARTLAB BioProcess Manager, which focuses on managing the integration of bioprocess data.

SMARTLAB BioProcess Manager – System Overview

One Hill solution has developed a data management solution designed to seamlessly connect, collate and synchronize data from standard upstream process development devices, eliminating the time consuming and error prone manual task common in all upstream process environments. Vessel data from all bioreactors is simultaneously monitored and at-line analyzer data, as it is generated, is automatically synchronized with vessel data. Data is historized and available to process developers via the SMARTLAB launcher which offers a series of practical utilities designed to meet the needs of the upstream bioprocess environment:

Real-Time Trending:	View critical vessel parameters in real-time, from desk or lab. React instantly to problems or review process data from overnight or weekend activity.
All-Batch Data:	Access and analyze all vessel and associated analyzer data of interest in different formats. Output is to an Excel file or .PDF.
Batch-to-Batch:	Analyze and display vessel and analyzer parameters and compare selected Batches. Data is displayed versus relative time, in scatter format, or in histogram format. Output is to an Excel file or in PDF format.
Batch Reports:	View current and/or average values of batch vessel data and/or batch analyzer data for a specified time period. The data can then be forwarded to a project team via automated report generator.
Alarm Notification:	Set process parameter limits from within the Real Time Trend utility. When the parameter limit is exceeded, an alarm notice is sent to selected users via text message and/or e-mail. The Alarm Dashboard allows the user to view and report on aggregate alarm activity to identify specific alarms, alarms on specific batches or alarms per vessel over time. Alarm set-up is highly customizable.

Notes and Comments:	Add comments/notes to any process, identify a process anomaly on a graph and tag it with a comment or note which becomes a permanent record. This utility is very useful to keep records of certain incidents, addition, tests, observations and changes occurring on the vessel within the Batch timeframe.
Batch Notes:	Tag any batch with user specified notes and number such as Lot #, area etc.. These tags / notes become a permanent record and forms part of the batch report.
Audit Trail:	Keep track of all changes and additions. Track user's sign on and sign off. SMARTLAB complies with 21CFR part 11.
Connectivity Diagnostics:	Check the network connection status of of vessels and analyzers on the SMARTLAB network. The vessel and analyzer node PC's function as data buffers that can hold 1 Gb of data.

Most Process Development environments have developed highly customized and purpose-built Excel tools for data management, analysis and visualization. The SMARTLAB system works with these existing tools by simplifying the data collection and import function and reducing the chance of input errors.

Case Study

A test of the SMARTLAB system was conducted in the upstream process development laboratory of a large contract biotechnology research and manufacturing organization. The test ran for approximately ten weeks and was designed to test the SMARTLAB system in a realistic environment; to identify user-specific requirements and improvements and to quantify and characterize potential advantages of the system compared to current data management practices. Specific test criteria included:

a) *reduction in data management effort*
b) *ability to change user behavior (forego conventional methods in favor or SMARTLAB system)*
c) *ability of Alarm Notification capability to prevent or reduce batch failure.*

The site laboratory consisted of a staff of approximately 15 researchers, 25 bench-top bioreactors and controllers from different manufacturers as well as five Nova 400, two Nova pHOx, five Vi-Cell XR, two Cedex HiRes analyzers all considered 'at-line' or co-located with the bioreactor systems as well as a conventional range of associated laboratory and analytical tools. All bioreactor and at-line analyzer devices were previously connected to the site's laboratory network

Working with the support of the site's IT group, a SMARTLAB server was connected to the laboratory network and linked to the site's SMPT server to enable outgoing e-mail messaging for the SMARTLAB alarm notification function. Four Xcellerex[2] XDR-10 bioreactor controllers operating single 10l single-use bag assemblies were connected to the SMARTLAB system. One Nova Biomedical[3] 400 multi-function analyzer and one Beckman-Coulter[4] Vi-Cell XR cell analyzer were also connected to the SMARTLAB system.

Prior to the SMARTLAB set-up, site researchers would manually retrieve bioreactor .csv data via a network connection to a lab-based laptop for data integration. Data from the Nova 400 was retrieved via print-out and manually transcribed into the lab-based laptop. Data from the Vi-Cell XR was manually retrieved from a text file via network connection to the lab-based laptop. At periodic intervals, researchers aggregated all data into a master Excel spreadsheet and manually synchronized it based on batch ID numbers and date/time codes prior to visualization and analysis.

Following set-up of the SMARTLAB system, five site researchers were provided with User ID's and provided with basic orientation and training and familiarized themselves with the system, using existing reactor runs. Following this, approximately 14 batches were completed and all vessel and analyzer data was automatically saved to the SMARTLAB historian and archived. During this period, no concurrent manual data processing was conducted and researchers relied solely on the SMARTLAB system for data capture, integration, visualization and analysis.

[2] GE Healthcare Life Sciences – Data File 29-0929-27 AA
[3] http://www.novabiomedical.com/products/bioprofile-analyzer/
[4] http://www.beckmancoulter.com/wsrportal/wsr/research-and-discovery/products-and-services/flow-cytometry/cell-counters/vi-cell-series/index.htm#2/10//0/25/1/0/asc/2/731050///0/1//0/

Findings

Data Integrity: No loss of data was recorded. A software upgrade to the Nova analyzer necessitated the replication of several analyses

Time and Effort: Researchers reported an estimated 10%-15% reduction in time required for data management

User Behavior: Users reported a preference for SMARTLAB's automated data collection and integration feature; citing time savings and convenience as primary advantages. All users reported a preference for SMARTLAB data management vs. prior manual data management. Users described the ability to view SMARTLAB process data from their desks, rather than just in the lab, as very advantageous

Batch Rescue: Users had the ability to adjust alarm upper and lower limits. No alarms were observed during the test as bioreactor processes never went above or below limits so no evidence to support batch 'rescue' was obtained. During the final few weeks of the trial, selected upper and lower alarm limits were adjusted to test the alarm notification system. Approximately ten alarm notices were sent via e-mail, and all were received within 15 seconds of process variation. E-mail notices included a text description of the variation, batch ID, time stamp and a screen capture of the monitored processes including the variation.

Cost Justification

The following are cost savings when using SMARTLAB over manual data gathering.

No. of Hours per Year	**2080**
Lost Production - Manual Data Entry	**2.0 hrs./ day**
Total Lost Production	**520 hrs. / Yr.**
Fully Burdened Hourly Rate – Lab personnel	**$55.00 /hr.**
Total cost of Inefficacies	**$28,600.00**
Assumption: Personnel / Lab	**3**
Total	**$85,800.00 / Year**

Couple the above with the financial impact of human error – depending on when it occurs in the production / research cycle and the impact can be in the 100's of thousands of dollars

Conclusions:

In response to competitive pressure for lower cost, faster and more efficient process development, the emergence of laboratory device-integration between different device manufacturers and the development of balanced high throughput low volume instruments are leading initiatives towards a comprehensive PAT goal. To complement these initiatives and to provide corresponding automation capabilities with increasing amounts of process data, One Hill Solutions SMARTLAB BioProcess Manager represents a viable option. The SMARTLAB system is easily installed on existing lab networks, works will all common bioreactor and analyzer systems and is proven to reduce time and effort, improve process insight and control and has the potential to reduce batch loss through automated alarm notification.