Next-Generation Monitoring of Bioprocessing to Enable Smart Data Management and Analysis

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The bioprocess lifecycle for any therapeutic protein includes a complex series of upstream and downstream activities starting with drug development followed by manufacturing, quality release and finally shipping the drug to the market. (Figure 1). These activities must adhere to strict regulatory guidelines and are designed, monitored and optimized through the use of several approaches including quality by design (QbD), process analytical technology (PAT) and continued process verification (CPV).
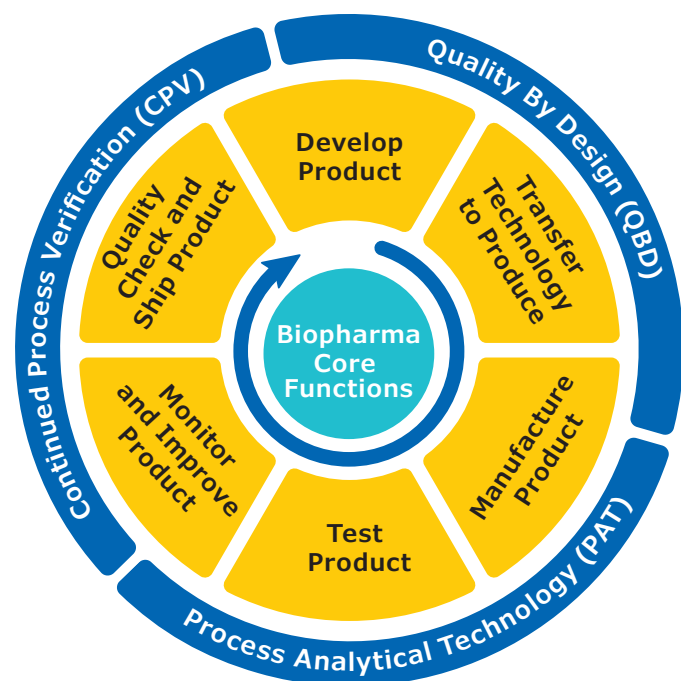

Figure 1. Overview of bioprocess life cycle

Every step of the process and each unit operation generate a massive amount of data at an incredibly fast rate. There is always uncertainty associated with the manufacturing batches due to the underlying biological processes; as such, it is paramount to understand these datasets to enable better decision-making. Adding to the challenge presented by the volume and velocity of the data is that it is typically stored in multiple, disparate systems. These disparate systems, which may not effectively communicate with each other, contribute to the difficulty in leveraging the data to inform and guide decision-making. Figure 2 provides a schematic of what the bioprocess data landscape often looks like, with many siloed data stores and information flowing to and from, but not converging in a truly integrated manner.

The enormous amount of data being housed in separate locations can present significant obstacles during investigations and quality deviation closures. In these cases, unified data sets must first be created, drawing input from multiple departments to pinpoint the root cause of the problem. In many cases, data are not readily available; some may exist only as paper-based, manual reports while others are housed in separate electronic systems. Data consolidation thus requires an enormous amount of time and labor, invariably slowing the manufacturing process and progress of the drug to the market and, ultimately, to patients in need.

Not surprisingly, regulatory agencies have put forth guidelines on bioprocess monitoring and data collection to ensure high product quality and process consistency. For example, the US FDA clearly states in its Process Validation: General Principles and Practices[1] – Stage 3 – Continued Process Verification – ensuring that the process remains in a state of control assures quality and is an integral part of process validation. Regulators also emphasize that drug sponsors must have a system for detecting unplanned deviation in routine processes.

MERCK

Process Development

eLN
- Process Development Experiments
- Development Reports
- Process Fitness

Engineering

Asset Mgmt.
- Work Order
- Maintenance Record
- Equipment Fitness

Manufacturing

BMS
- Facility Management
- Environment Fitness

Quality Control and Assurance

LMS
- Training Management
- People Fitness

Process Execution

Data Stores
- MES
- LES
- eLN
- eBR
- Custom DB Data
- Warehouse Data
- Historians

eBR
- Process Data
- Batch Report

QMS
- Process Excursions and events
- Non-conformance Management
- Investigation Reports

LIMS
- Process Test Samples
- QC Methods
- Results

- QA Batch Fitness for Release
- Corrective Action Management
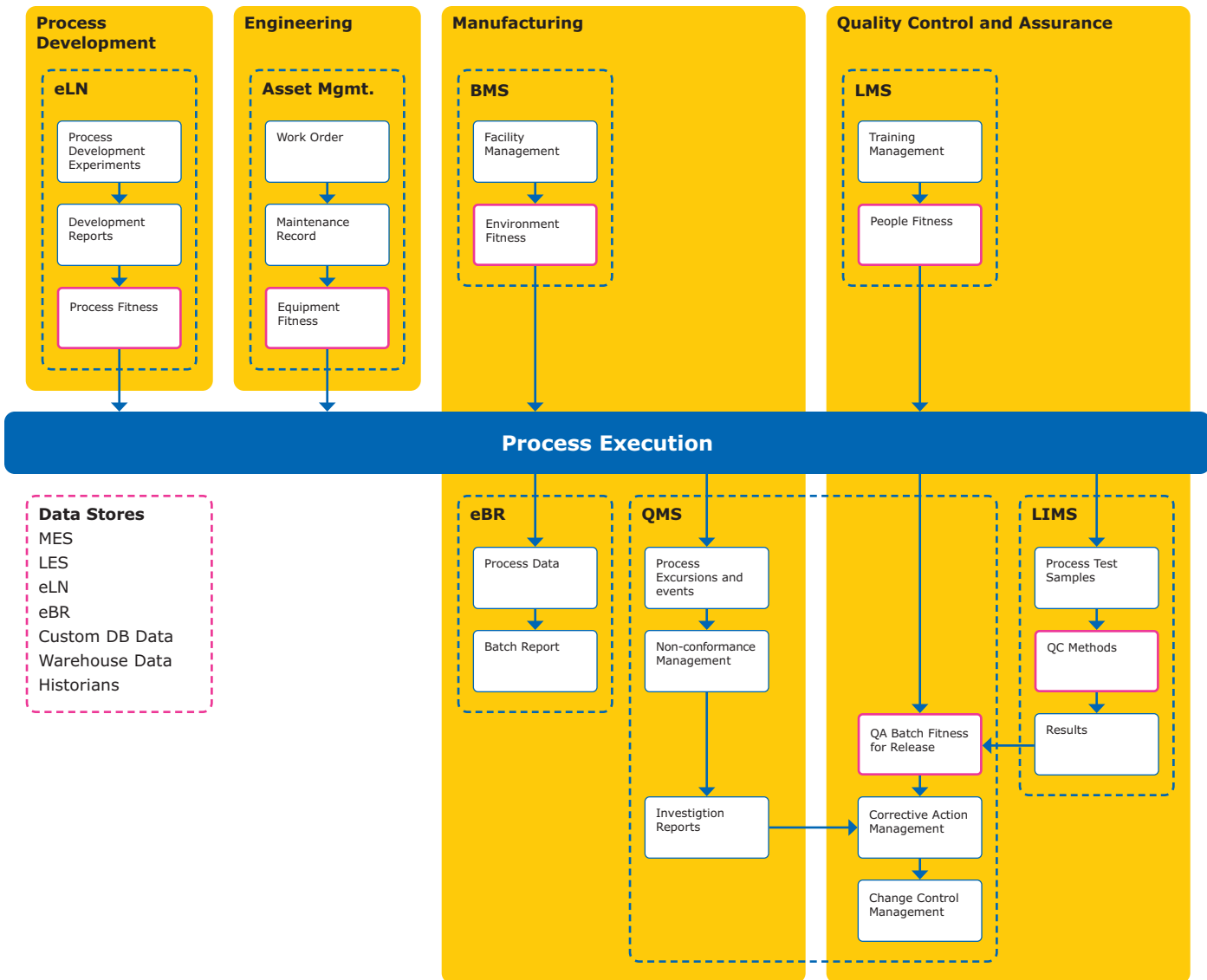- Change Control Management

Figure 2. Data are captured by disparate systems across the bioprocess lifecycle.

Given the need to collect and fluidly handle massive amounts of data being generated with tremendous velocity, a new approach to data management is essential.

Enabling Digital Transformation

In response to continued growth of the biopharmaceutical industry, the Biopharma Operation Group (BPOG) developed a technology roadmap and highlighted key market trends including significant growth in new product classes, regulatory uncertainties for new drug/therapy approvals, and rising cost pressures. BPOG also outlined key business drivers for the industry including the speed at which the drug must reach the patient in need, increasing manufacturing robustness by 10-fold, improving flexibility and reducing product changeover time by 90%, and significant reductions in the cost of the drug to the patient.

Our BioContinuum™ Platform is designed to enable a step change in business drivers through technologies that will drive next generation bioprocessing. The scope of our platform includes digital technologies/ data management, process analytical technologies and intensified processing.

As a part of digital technologies/data management, we have launched the Bio4C™ Software Suite which focuses on digital 4Cs – control, connect, collect and collaborate and is a key component of the facility of the future. Specifically conceived and designed by our bioprocess experts for bioprocess experts, the Bio4C™ Software Suite is comprised of stand-alone, but seamlessly compatible software products. Intuitive interfaces and easy access enable a broad user base to collaborate with global teams across geographies and organizational silos to control, monitor and analyze equipment, processes, results and data in near real-time.

The Bio4C™ Suite offers a convergent, open digital environment, adaptable to changing productivity, process and regulatory needs (Figure 3). Control software ensures control and management of all unit operations while connect software allows centralized unit operation and efficient workflow management. Collect software, described in detail below, supports aggregation of data sets from multiple sources enabling rapid process analysis, as well as automation and insight. Finally, we have the collaborate layer where we collaborate and partner with our customers to support them with integrated solutions such as cloud connectivity.

Overall, the Bio4C™ Software Suite allows for data transparency and manufacturing intelligence leading to quick and efficient data-driven decisions for mastery at the process and plant level.
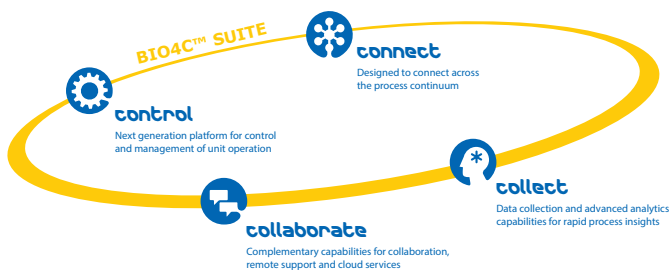

Figure 3. Bio4C™ software enables digital transformation of bioprocesses.

Bio4C™ ProcessPad Software: Enabling Data Acquisition, Aggregation and Process Analytics

Bio4C™ ProcessPad is a browser-based platform for data acquisition, aggregation and process analytics. The software enables collection and use of process information from multiple, complex and disjointed data sources across the process and product lifecycle in near real-time.

This approach to data management and process monitoring delivers a range of important benefits:

- Streamlines and accelerates data aggregation and reporting

- Provides a single, validated source of aggregated analytics for process troubleshooting

- Accelerates closure of investigations and supports the ability to meet quality metrics

- Enables faster movement of quarantined lots

- Ensures product consistency and quality compliance

Bio4C™ ProcessPad collects data sets from three major sources: manual records, which are transcribed into an electronic format via webforms; machine data via data historians; and connectivity to external databases such as QMS,LIMS etc. (Figure 4).

In addition to collecting data from multiple sources, the software contextualizes the data, making it readily available for process monitoring through data visualization and analysis. The software also facilitates 21 CFR Part 11 compliance with a full audit trail and fulfillment of the validation set of activities.
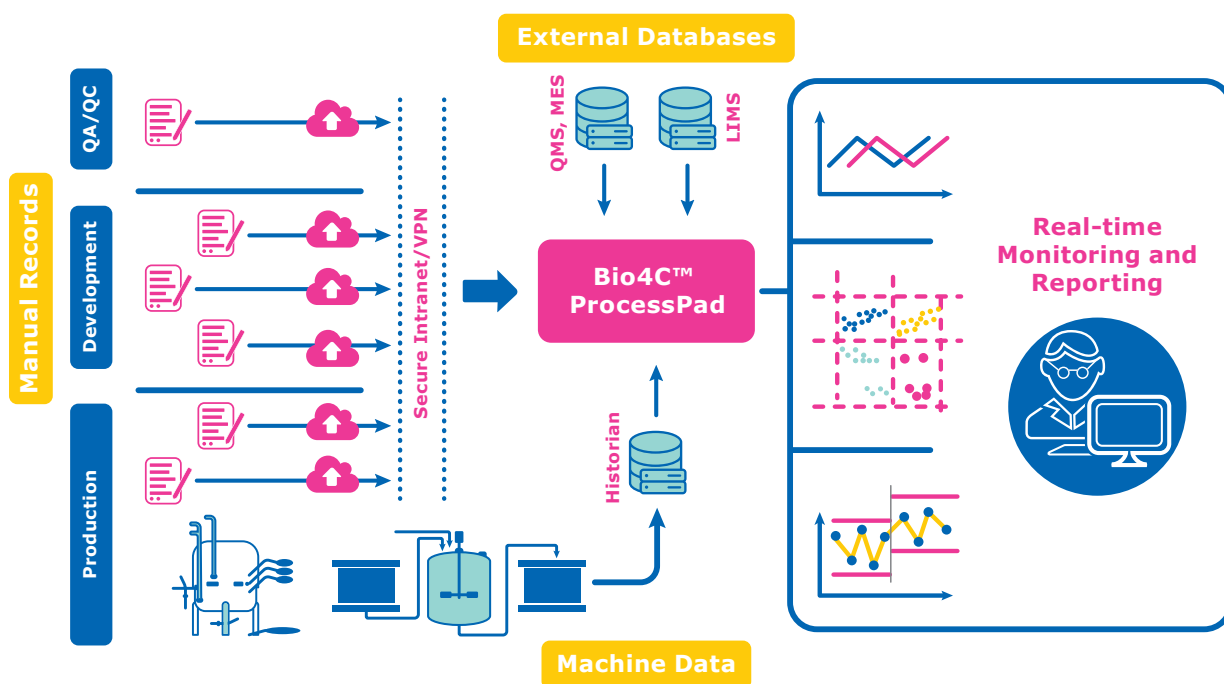

Figure 4. Overview of Bio4C™ ProcessPad

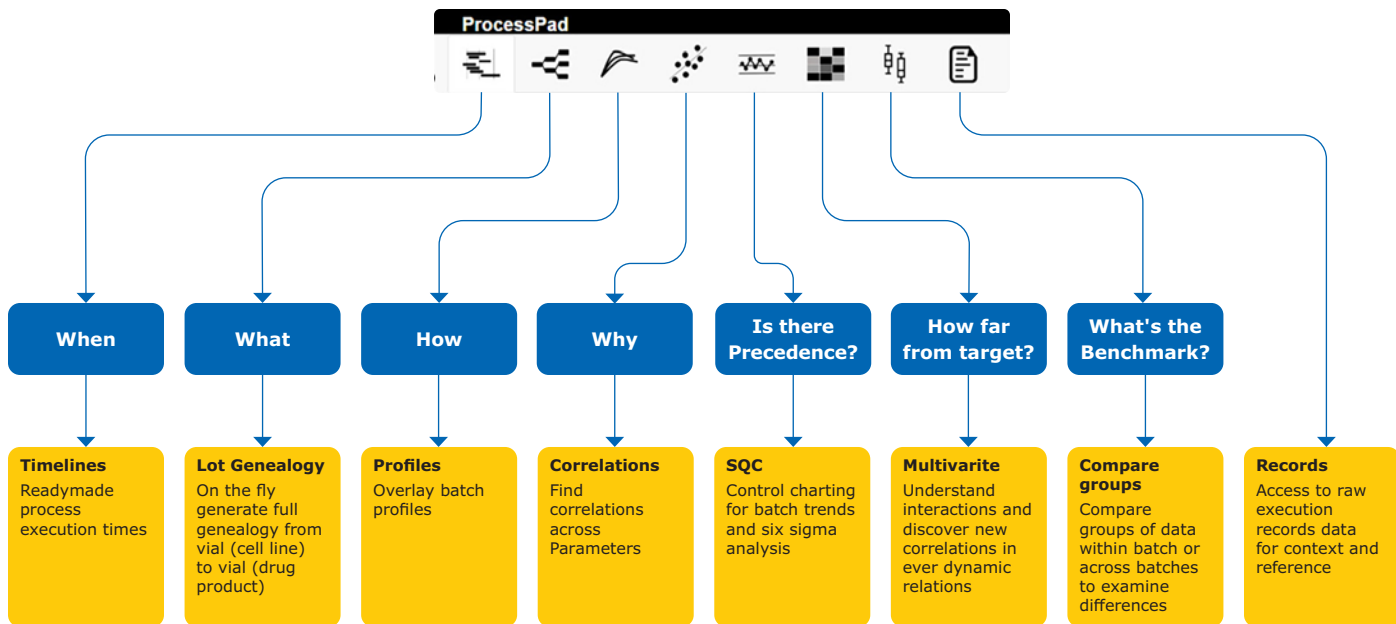| When	What	How	Why	Is there Precedence?	How far from target?	What's the Benchmark?	
Timelines Readymade process execution times	**Lot Genealogy** On the fly generate full genealogy from vial (cell line) to vial (drug product)	**Profiles** Overlay batch profiles	**Correlations** Find correlations across Parameters	**SQC** Control charting for batch trends and six sigma analysis	**Multivarite** Understand interactions and discover new correlations in ever dynamic relations	**Compare groups** Compare groups of data within batch or across batches to examine differences	**Records** Access to raw execution records data for context and reference

Figure 5. Bio4C™ ProcessPad software provides the toolset needed for efficient process troubleshooting.

By consolidating process-related data, Bio4C™ ProcessPad software accelerates investigations and process troubleshooting (Figure 5). The software helps answer key questions such as what, when and how a process deviation occurred, leveraging built-in statistical methodologies such as correlations, group comparisons, bivariate and multivariate data analysis.

In addition to aggregating multiple, disparate data sets, Bio4C™ ProcessPad software delivers important benefits for near real-time process monitoring/data analysis as well as reporting and sharing data.

Near Real-time Process Monitoring and Data Analysis

Bio4C™ ProcessPad helps in process lifecycle management by capturing datasets from development, scale-up and commercial manufacturing in one platform and provides access to the process map. This involves tracking of critical process parameters (CPPs) and critical quality attributes (CQAs) and helps in understanding how the process has evolved over time with full traceability of changing parameters and control limits applied over the lifecycle of the product.

Reporting and Data Sharing

Generation of reports is streamlined, from process summary and product quality reports, to ad hoc reports required for root cause investigation, batch excursion reports and equipment utilization. With all data sets consolidated in advance there is no need to invest a significant amount of time and labor gathering information from disparate sources. Reports are then easily shared with stakeholders throughout the organization via the software.

Conclusion

The biopharmaceutical industry is witnessing significant growth as well as pressure to improve productivity and reduce costs. The ability to more effectively capture and leverage large and disparate data sets will be essential to addressing these challenges. Breaking down silos among data sets and unleashing powerful information and insights will improve productivity and process economics.

The new Bio4C™ Software Suite allows biopharmaceutical teams to control, connect, collect and collaborate more effectively and efficiently. Bio4C™ ProcessPad enables data acquisition, aggregation and process analytics as never before. This approach to data management creates a central, validated source of information for process analytics, facilitating key activities such as monitoring, investigations, troubleshooting, reporting, data sharing and regulatory compliance.

Bio4C™ ProcessPad Software Modules

Bio4C™ ProcessPad Software is available in
three modules to address your specific needs.

ProcessPad RT

Trending, Reporting and Analytics on Machine Data

- Bioreactors
- Chromatography Systems
- CIP Skids
- Buffer Systems

ProcessPad *offline*

Capture, Trending, Analysis and Reporting of offline data

- Offline Batch/Run data
- Analytical Test Results data
- SQC, Out-of-trend and continued process verification

ProcessPad *stab*

Capture, Trending, Analysis and Reporting of Stability data

- Profile Trending
- Reporting
- Shelf life prediction

[1] **https://www.fda.gov/files/drugs/published/Process-Validation--
General-Principles-and-Practices.pdf**

BioContinuum™ Platform
Converge, Intensify and Evolve. Together.

An expanding environment of advanced processing,
software, automation and analytic technologies,
unlocking the potential of Bioprocessing 4.0 and
empowering biomanufacturers to achieve greater
speed, flexibility and quality.

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For additional information, please visit **MerckMillipore.com/Bio4CProcessPad**
To place an order or receive technical assistance, please visit **MerckMillipore.com/contactPS**

We provide information and advice to our customers on application technologies and regulatory
matters to the best of our knowledge and ability, but without obligation or liability. Existing laws
and regulations are to be observed in all cases by our customers. This also applies in respect to
any rights of third parties. Our information and advice do not relieve our customers of their own
responsibility for checking the suitability of our products for the envisaged purpose.