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Process analytical technology (PAT) in continuous bioprocessing

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INTRODUCTION

What to expect in the next 25 years?

"Right now, manufacturing experts from the 1950s would easily recognize the pharmaceutical manufacturing processes of today. It is predicted that manufacturing will change in the next 25 years as current manufacturing practices are abandoned in favor of cleaner, flexible, more efficient continuous manufacturing." Janet Woodcock, Director CDER, FDA (AAPS meeting, 2011)

Pall Life Sciences is assessing the needs process analytical technology (PAT) as an overall capability upgrade to be used in conjunction with our existing and planned continuous bioprocessing toolbox to enable on-line and at-line real time continuous monitoring and automation of the continuous products.

PAT paves the way of continuous manufacturing with the adoption of innovative technologies to perform timely measurements on critical quality attributes (CQAs) of raw and in-process materials, allowing better process understanding and control.

What is Continuous Bioprocessing?

Figure 1a

Current: Batch BioProcess* (individual unit operations)

Figure 1b

Future: Continuous BioProcess* (one piece flow)

USING PAT TO SET MONITORING AND CONTROL STRATEGIES

To implement a strategy in a continuous process, it is crucial to understand and minimize:

- incoming material variation,
- critical quality attributes (CQA) and critical process parameter (CPP) variations,
- perform timely in-process measurements,
- define representative sampling,
- develop chemometric models and set appropriate acceptance criteria, and
- characterize the propagation of changes and disturbances through the system.

In contrast to batch processing, in which local control of each piece of equipment is in many occasions considered sufficient, in continuous manufacturing not only is local control mandatory, but also the entire process flow must be coordinated and equipped with second-level control systems that supervise and align the work of individual unit operations.

The selection of appropriate PAT tools is a crucial step toward setting efficient monitoring and control strategies in continuous processes.

- easy-to-use instrumentation,
- measuring frequencies,
- ability to monitor multiple process parameters,
- directly measure CQAs,
- capturing the real-time process state, and
- eliminate traditional off-line techniques and increase efficiency.

IMPORTANT CQAs FOR CONTINUOUS OPERATIONS

An example of data obtained using off-line analytics; however this could be trended in real-time via PAT tools in the future.

Key critical quality attributes that could be measured on-line and/or at line are:

- Bioburden
- Product concentration
- Host cell protein (HCP)
- Aggregates
- Glycosylation profiles
- Metabiotics, etc…

Figure 2

Percent aggregation by size-exclusion HPLC*

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Percent Aggregation by Size-Exclusion HPLC

Figure 3

Protein concentration (mg/mL)*

Figure 4

Host Cell Protein per mg of mAb*

Figure 5

OUTLOOK

The ideal continuous controls platform combines automation, analytics and process control strategy; empowering users to execute advanced processes with excellence in quality, yield, and ROI

- True continuous tools (sensors, PAT, new data processing approaches)
- Data Management, Data Analysis, Data Insight and Automation
- Fill in the gaps using established platforms to meet new continuous requirements

Value of PAT implementation

- Ensure consistent product quality and increase robust overall manufacturing performance reducing heterogeneity
- Enable end-to-end continuous process by implementing lean, flexible and portable biomanufacturing
- Advanced computational tools enhance continuous monoclonal antibody production
- Integration of process analytical tools for monoclonal antibody toxilogogy measurement can be achieved
- Process time and cost savings can be achieved through automation and continuous integration in existing facilities