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BIOPROCESS MONITORING

STILL ON THE PATH TO DYNAMIC CONTROL

Brian Gazaille

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Bioprocess Monitoring

Still on the Path to Dynamic Control

Brian Gazaille

The biopharmaceutical industry agrees that process analytical technologies (PATs) and automation will improve process consistency, enhance biologic quality, reduce production costs, and accelerate workflows. However, technologies for on- and in-line bioprocess monitoring generally remain in process development laboratories. This eBook reports on scientific presentations and roundtables from recent industry events to show how drug makers are applying advanced sensor and automation technologies and what difficulties are hindering broad PAT implementation in commercial biologic manufacturing.

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The BioPhorum Operations Group (BPOG) queried member organizations in 2021 about the biopharmaceutical industry's adoption of process analytical technologies (PATs). In June 2022, the group published the first of several projected reports on the subject, the initial focus being adoption of solutions for *in-line monitoring* (ILM), by which "timely measurements" are taken from bioprocess samples without removing them from a process stream (**1**). The critical features of ILM are sample integrity and speed of analysis, the report suggests. Scientists want to use generated data to improve process control and thus product quality, ideally in real time, but certainly in time to identify when parameters begin to fall out of specifications.

Survey respondents agreed that PATs ultimately will raise several advantages for manufacturing processes and operations (**1**). Rapid data collection and analysis will improve process understanding and control, facilitating production of new biopharmaceuticals with similar manufacturing requirements. Data generated in real time will help companies hasten drug-product release and enable "proactive QA [quality assurance]" rather than "reactive investigations" into process deviations. Respondents often noted that ILM will enhance process robustness by increasing a drug maker's production capacity (because of accelerated testing), minimizing errors associated with manual sample handling, and reducing risks to product quality. Respondents also anticipated benefits for environmental sustainability and cost savings from reductions in requisite sampling and testing materials, decreases in capital investment in testing facilities, and prevention of process deviations and batch rejections.

Despite the considerable enthusiasm surrounding ILM, major biopharmaceutical companies have lagged in PAT development and adoption compared with the timelines listed in BPOG's 2019 technology road map (**2**). Nine of the 11 member organizations surveyed in 2021 confirmed that they have made plans for incorporating PATs (**1**). However, eight companies reported that they lacked a model by which to quantify implementation outcomes. That factor has hampered efforts to present clear business cases for investment in PAT infrastructure, which includes not only advanced probes and instrument formats, but also sophisticated software systems that interface with sampling mechanisms to collect, process, and analyze data. Some companies reported "change fatigue" in the wake of organizational restructuring — not to mention the COVID-19 pandemic, which compelled all manner of personal, personnel, and organizational adjustments. Lack of regulatory harmonization over testing requirements (e.g., for product release) represents another strike against the business case for advanced PATs by complicating plans to market products across multiple jurisdictions.

Technical and operational limitations abound, too. Biological products are much more complex than are small-molecule

pharmaceuticals, and current PAT offerings often are not sophisticated or robust enough to perform intricate product-characterization assays on, in, or even at line. Applying advanced instruments will necessitate new and sometimes complicated validation procedures, and companies have only started to consider how PATs will need to be validated over a biological product's life cycle, including additional comparability testing that might be prompted by postapproval changes. Compounding those concerns are anxieties about having enough qualified staff to implement and work with ILM systems (**3**).

Thus, PAT implementation remains a rough sketch rather than a fully painted picture, but the biopharmaceutical industry has begun to lay paint to the canvas. And the enthusiasm surrounding ILM remains palpable. I felt it when attending the January 2023 Well-Characterized Biological Products (WCBP) symposium in Washington, D.C. I vividly recall discussions from "Emerging Strategies on PAT, Modular Manufacturing, and Real-Time Release Testing (RTRT)," a roundtable session during which scientists from major pharmaceutical companies, developers of analytical instruments, and experts in data analytics described their companies' work with ILM systems and asked questions about next steps for implementation. Citing the BPOG survey, participants agreed that PATs largely remain confined to process-development laboratories, sometimes with applications for products that have reached clinical trials. One attendee explained that commercial biomanufacturing processes "have a different calculus" than those from process development because they work with larger volumes and with tighter specifications. To justify the expense, research, and effort, companies must have a "clear way forward and a clear value proposition to implement PATs and automate processes" that, in some cases, are becoming easy, fast, and inexpensive enough to perform off or at line.

Slowly and incrementally, biopharmaceutical companies are testing the utility of PATs in process-development settings and reporting about their experiences. Herein, I describe PAT applications that I learned about during presentations at the September 2022 BioProcess International Conference and Exhibition in Boston, MA, and the PAT roundtable discussion from the January 2023 WCBP event. I hope to show what kinds of parameters scientists are trying to measure, what they to hope to accomplish in their processes, and what difficulties they experienced during implementation. Close consideration of such examples could highlight what parts of the PAT painting need to be filled in for the industry to reach its goal of dynamic process control.

Notes from Biotech Week Boston (BWB) 2022

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The program for the 2022 BPI Boston event featured several case studies in PAT development and implementation. Upstream applications featured prominently, and presenters highlighted

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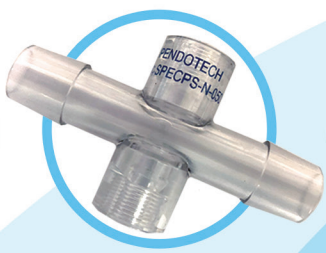

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multiple methods for rapid characterization of product quality attributes (PQAs).

Automating Bioreactor Sampling and Analysis: Letha Chemmalil (scientific associate director of global process analytical sciences and technology at Bristol Myers Squibb, BMS) began her presentation, titled "On-Line Measurements and Control of Product Titer, Critical Product Quality Attributes (CQAs), and Nutrients During Process Development," by describing emerging chromatographic technologies for analysis of upstream parameters. Those include high-performance (HPLC) and ultraperformance liquid chromatography (UPLC) systems equipped with in-line samplers, on-line systems for liquid chromatography–mass spectrometry (LC/MS), two-dimensional (2D) chromatography instruments, and technologies for microsequential-injection analysis (µSIA).

The BMS team implemented a Patrol UPLC system (Waters Corporation) for on-line measurement of protein-expression titers, size variants, and other CQAs. The instrument generated results comparable to those from BMS's standard at-line analyses but much more quickly. However, because the biologic in question generated wide peaks during elution from a protein A column, the team subsequently applied 2D LC, which enables collection of multiple fractions from eluate of the first-dimensional (1D) column. That step helped immensely with high-resolution peak cutting and parking, Chemmalil reported. Leveraging a 1:10 flow splitter further expedited the workflow.

She also demonstrated how the Patrol system could be programmed for automatic sampling during cell culture. Using that feature, her team has performed real-time amino-acid analysis (AAA) and profiling of peptides and *N*-glycans. BMS ultimately plans to leverage such capabilities for good manufacturing practice (GMP) biopharmaceutical production, although the technologies currently are applied in the company's process development laboratories only. Chemmalil highlighted that technology suppliers still need to improve mechanisms for automated sampling. That said, 2D LC systems hold much promise for reintegration of postflow effluent, and µSIA methods could help to fill gaps for particularly complex analyses.

Characterizing Complex PQAs During Perfusion Cell Culture: In "Automated On-line Monitoring of Glycosylation and Posttranslational Modifications from Perfusion Cell-Culture Material," Matthew Radle (a scientist at AstraZeneca, AZ) spoke about his team's efforts to enable in-process testing of bioreactor material harvested from a perfusion cell-culture process. In previous process-development workflows, AZ had used at-line sampling methods for off-line characterization of aggregation levels, posttranslational modifications (PTMs), and other relevant quality attributes. That process was time and resource intensive, Radle explained, which made it especially cumbersome for analysis of a continuously operating perfusion campaign. Thus, the

team needed to develop a rapid analytical method (in this case, for study of PTMs) and then to automate as much of the sampling and analysis as possible.

The best solution, Radle reflected, was to leverage peptide mapping, which would reduce the number of steps for sample preparation and analysis compared with AZ's original process. The group developed a workflow for in-line hydrophilic-interaction liquid chromatography (HILIC) based on separation of *N*-glycans labeled with 2-aminobenzamide (2AB). That step is followed by MS analysis of peptide content. Whereas off-line analysis using the original method took about 10 hours per sample, this on-line 2AB-HILIC-MS method could process a sample in 2.5 hours, saving significant time and resources. Radle added that the speed of the on-line method enabled data monitoring and trending for in-process samples rather than simply quantifying PTMs in discrete analyses. Thus, on-line 2AB-HILIC-MS fit well with the continuous nature of the perfusion-culture process.

AZ introduced automated technologies to facilitate sampling and analysis. The most difficult part of implementation was to create bridges across natural process gaps — e.g., between the bioreactor and chiller, then from the chiller to an HILIC column. Radle's group was able to create such interfaces using on-line microfluidic devices and a compatible LC/MS system. He explained that although obstacles remain in automating analytical processes, continued research and development (R&D) into PATs soon will help to accelerate difficult and time-consuming activities such as clone selection during cell-line development. The ability to monitor and trend data from in-process material also will be a boon for product quality.

Investigating Cell Viability and Demise: Michael Butler (principal investigator at Ireland's National Institute of

Biomass-Based Feeding in Shake Flasks: A New World of Applications

Bioprocess automation has become more important amid a growing number of marketed products and the need to accelerate transitions from development stages to commercial production. Whereas large-scale biologic production mostly is carried out in bioreactors, experiments for process development are carried out preferably in shake flasks. This vessel type holds several advantages over bioreactors, including lower cost per experiment, faster setup, flexible scalability, and easier laboratory integration.

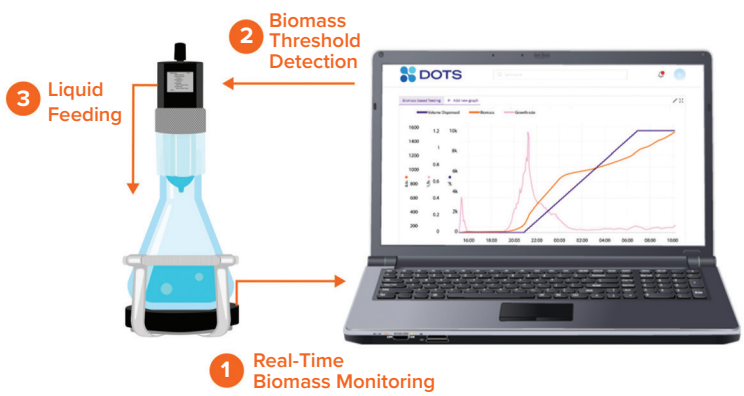
A major disadvantage is the limited number of sensing and control options. Automated feeding of substrates, an operation that has been common in bioreactor-based cultures for many years already, is only now being applied in shake flasks because of advancing technologies.

Recent developments have brought forth a new application called *biomass-based feeding*, in which the feeding to a growing microbial culture is initiated when it reaches a specified biomass level or cell density. Enabled by the interconnectivity of a biomass monitoring system, an automated feeding system, and powerful software (e.g., the DOTS platform from Scientific Bioprocessing Inc.), automated substance release provides novel control options for shake flasks.

Many less-studied processes will benefit from the application. By using biomass as the determinator of substrate injection, feeding can be fine-tuned to a culture's requirements without having to know its growth pattern. Biomass-based feeding enables simulation of bioreactor-like conditions, improving transferability of results from shake flasks to larger vessels. The application also furthers efforts to automate shake-flask experiments.

Biomass-based feeding marks a milestone in laboratory automation in a high-impact vessel type and is an important step toward the smart shake flask of the future. To learn more about biomass-based feeding, visit https://www.scientificbio.com/biomass-based-feeding-in-shake-flasks.

—Sina Schmidl, PhD, product marketer, Scientific Bioprocessing Inc.



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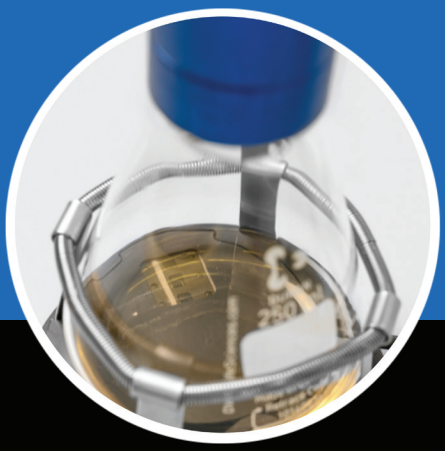

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Biomass-based Feeding

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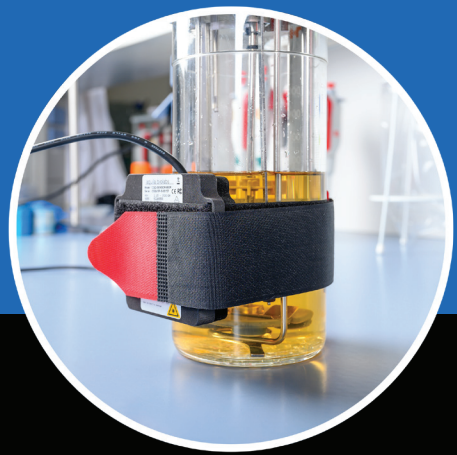

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Bioprocessing Research and Training (NIBRT), adjunct full professor at University College Dublin, and a distinguished professor emeritus from the University of Manitoba in Canada) spoke about the value of technologies for continuous monitoring of cell health during culture. Historically, scientists have applied hemocytometry using Trypan blue dye to quantify dead and viable cells in bioreactor samples, but as Butler and colleagues explained in a 2019 article for BPI, that method has significant limitations (**4**). Dead cells lack membrane integrity, so Trypan blue dye easily enters and saturates them. However, cells can have intact membranes and exhibit some metabolic activity yet be nonviable for expression of therapeutic proteins. Dye exclusion cannot identify such cells. Since publication of that article, NIBRT has worked with analytical-instrument suppliers to develop advanced optical and dielectric-spectroscopic methods for label-free detection of cell nonviability.

Using a high-resolution flow-imaging microscope from J.M. Canty, NIBRT scientists analyzed Chinese hamster ovary (CHO) cells at different developmental stages. Cells that had reached the point of nonviability for protein expression exhibited a distinctive vacuole formation that might serve to initiate cell death.

NIBRT also has worked with ABER Instruments to investigate the dielectric properties of viable and nonviable cells. As Butler and his team explained in their 2019 publication,

> Dielectric measurements of cells rely on the principle that their intracellular ionic content is separated from surrounding aqueous media by an electrically insulating membrane. So cells can create a dipole of charge when exposed to an electromagnetic field. If that field is created from an alternating current, then the dipole formation depends on the current's frequency: A low frequency creates a permanent dipole in the cell membrane; at high frequencies, no dipole might form. A "sweet spot" radiofrequency range provides for a characteristic beta-dispersion response profile. That response can be different for each cell type and depend on membrane permittivity and the conductivity of intracellular fluids. (**4**)

Performing a "sweep" from high to low frequencies during a bioreactor run enables measurement of physiologically relevant features such as total biomass, cell volume, and cytoplasmic conductivity.

NIBRT has applied on-line biocapacitance probes from ABER to study CHO cell volumes and cytoplasmic conductivities as indirect measurements of cell demise. During his presentation, Butler reported that the method identified early signs of nonviability that would have gone undetected by dye-exclusion assays. The NIBRT team still is determining whether cytoplasmic conductivity is a reliable indicator of cellular demise, and results from initial testing have raised intriguing questions about whether living-but-nonviable cells can be brought back into their exponential growth phases through media supplementation and other such

interventions. Further investigation could be useful for optimizing culture conditions and media-feeding strategies. Butler added that biocapacitance measurements even could help to prevent expression and fragmentation of host-cell proteins (HCPs).

Modeling Lentivirus Production: Several BWB talks addressed mathematical models used to analyze process data. For instance, Erin Masucci (a technical operations scientist at Janssen) delivered a presentation titled "Enhanced Process Understanding of Lentiviral Manufacturing By Real-Time Raman Spectroscopy." Janssen sought to use in-line Raman spectroscopy to help monitor lentivirus production and prevent deviations in specifications. Raman spectra can be analyzed over time using chemometric models based on partial least squares (PLS) regression, Masucci explained. But such models are notoriously difficult to create. The Janssen team explored how equipment size, production volumes, probe placement, and other practical parameters influenced chemometric model creation. Masucci also described how her team trained candidate models for measurement of glucose and lactate, pH, viable cell density (VCD), total cell viability, dissolved oxygen (DO), and viral titer.

Making Do Without Cutting-Edge Equipment: Whereas many BWB presenters spoke about uses of advanced PATs, Cindy Chelius (a senior scientist in upstream bioprocess development for global product development and supply at BMS) provided a valuable lesson in resourcefulness in "Controlling Product Quality Using In-Process Control Strategies." Her group was tasked — under difficult extenuating circumstances — with translating a perfusion cell-culture process into a fed-batch workflow. Doing so required considerable changes to $N - 1$ bioreactor conditions and feeding strategies. The team also needed to account for differences in the VCDs that are attainable in perfusion and fed-batch modes. Considering the circumstances and the kinds of equipment that were readily available, the BMS group needed to devise strategies for maintaining in-process control using off-line analyses.

Chelius focused on data generated for glycation and acidity levels in the fed-batch process. Instead of using a method such as on-line Raman spectroscopy, her unit decided to use a glucose-targeting approach based on off-line measurements analyses that could be conducted quickly enough for in-process intervention. The strategy succeeded, keeping the fed-batch process in control with results comparable with those obtained in the original, perfusion-mode process. After further experimentation, the team discovered that a glucose-targeting approach could serve as a reliable indicator for in-process control across process-development scales and perhaps even for fast analyses of commercial-scale processes.

Although the presentation was not about advanced tools for ILM, it stands as a reminder that in-process control is possible without cutting-edge solutions. In fact, biopharmaceutical manufacturers might find it increasingly difficult to justify investment in elaborate (yet necessary) PAT infrastructure as some off-line assays become easier, faster, and less expensive to perform.

Impressions from WCBP 2023

The PAT roundtable discussion at WCBP 2023 featured lively conversations among scientists working in analytical-method development, data science, process development, regulatory CMC, quality assurance and control (QA/QC), and other functional groups from biopharmaceutical companies and industry suppliers. In addition to concerns described above, roundtable participants identified other key considerations for PAT implementation based on their companies' experiences in adopting such solutions into their workflows. On the organization's website, CASSS members can find complete session notes compiled by facilitator Jennifer Rea (a staff scientist at Genentech/Roche) and scribe Srujana Govindarajulu (a principal process engineer at Pfizer) (**5**). Below, I share my impressions of the discussion, highlighting key topics and unresolved questions about PAT implementation.

Emerging Methods: Although multiple methods are being formatted for on-/in-line application, most such technologies have been designed to measure upstream parameters. Participants highlighted uses of biocapacitance and Raman probes for real-time measurement of glucose levels in a bioreactor. Some such solutions can be integrated with bioprocess control systems, enabling dynamic adjustment of glucose supplementation based on the collected data. Raman probes can be applied for real-time metabolite monitoring, AAA, and other complex bioreactor parameters. Some companies have begun using automated LC-MS systems for in-line multiattribute monitoring (MAM), especially for analysis of glycosylation patterns and other PTMs.

Downstream applications received less discussion, perhaps because such advances have tended historically to lag behind upstream innovations. However, some companies are using in-line Raman spectroscopy to monitor polysorbate levels in finished drug products. And Flow VPX systems (Repligen) have been applied during downstream process development for in-line measurement of protein concentration. For instance, the technology can be used in continuous manufacturing to perform in-line analysis as material passes from a bioreactor to a chromatography column for purification. Other possibilities include analysis of protein concentration during product recovery by ultrafiltration/diafiltration (UF/DF).

When To Implement PAT: Considering the industry's generally favorable impression of ILM, the major question is not whether to invest in PATs, but when it might be most advantageous to implement them.

Most companies are still years away from incorporating ILM into commercial production processes. As one participant noted, application of PATs at such scales will require significant investment, so users will feel incentivized to use ILM tools only when they are close to guaranteeing improvements in yield, product quality, and speed. Current analytical instruments already meet many of today's biomanufacturing needs, and they are

becoming easier, faster, and less expensive to use.

Another participant pointed out that drug makers have little incentive to incorporate PATs for processes involving marketed drug products. Regulators would classify introduction of novel sensors and analytical instrumentation as process changes, which would compel companies to dedicate effort, resources, and funding to demonstrate comparability with originally approved methods.

For such reasons, ILM is likely to remain in process-development laboratories for some time. There it be advantageous for gathering product and process knowledge that ultimately can be leveraged during commercial manufacturing. Some participants added that significant implementation of PAT and associated automation might be most effective when establishing new facilities.

Data, Data Everywhere, Yet Timelines Did Not Shrink: Some participants emphasized the insufficiency of mere data collection. In-line PATs take multitudes of measurements over the course of a process. Such information is highly valuable, but questions remain about how — or to what extent — it might enable dynamic process control. One attendee said that real-time monitoring must provide actionable insights, but how much action can be taken considering the deluge of incoming data? Another participant noted that real-time monitoring often does not occur instantaneously; data are collected rapidly, but performing a complex analysis can take time — perhaps too much time, in the case of a clear process deviation.

Some participants mentioned that artificial intelligence/machine learning (AI/ML) could play a role in transforming droves of data into triggers for bioprocess control.

From Data to Control: Process Analytics in Bioprocessing

Reproducibility is highly needed in biologics production. That is why understanding interdependencies among process parameters and establishing control strategies are so important in upstream bioprocess development. Thorough process analytics is a prerequisite.

Scientists have to monitor numerous parameters to gain sufficient process understanding. Those include not only pH, temperature, and dissolved oxygen (DO) levels, but also expression-system growth kinetics, ratios between total and viable cell densities, cell-specific productivity, and metabolite concentrations. Furthermore, the resulting product requires characterization: Has the process at hand produced the intended target, or did it generate undesirable by-products that can diminish product quality significantly? Monitoring for all such parameters is quite a complex task.

Measurements can be taken off line with automated sampling devices presenting materials to external analyzers. But automating sampling steps can raise other difficulties, including need for additional manual work in the absence of automated feedback loops. Online analyzers enable automated feedback loops by providing data almost instantaneously and eliminating manual sampling steps.

Such systems require bioprocess control software, which receives sensor signals and accordingly adjusts the acting units inside a bioprocess control system — e.g., an aeration unit or pump. Both analog and digital options are commercially available to ensure communication between control software and analyzer hardware. One communication standard is *open-platform communication* (OPC).

Online solutions for automated feedback control are becoming increasingly attractive because they hold much promise for reducing workloads and speeding up processes. In the coming years, technologies for data acquisition, analytics, and process automation will become faster, more precise, and more powerful than they are now. Such advances will receive support from predictive analyses (e.g., design-of-experiment approaches) and artificial intelligence, both of which will provide significant opportunities to simulate processes, predict where obstacles might occur, and determine strategies for bypassing them — all of which will contribute to time and cost savings and to patient safety.

—David Solbach, global marketing manager for bioprocessing, Eppendorf Bioprocess Center

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Current AI-based solutions are sophisticated enough to help with data curation, given sufficient model training.

Novel Validation Requirements: Thinking ahead to implementation in commercial biomanufacturing processes, a few participants highlighted that regulatory agencies probably will expect to receive data from "dual" analytical-testing regimes (e.g., from a standard off-line measurement and an automated/on-line analysis) to establish comparability of the new PAT methods. ILM algorithms are likely to require validation as well, especially as a drugs move through their product life cycles and other data are obtained.

The Reality of RTRT: RTRT remains the least advanced of PAT applications, participants agreed. RTRT could be advantageous, but key assays for batch release, such as those for mycoplasma and sterility testing, will continue to be rate-limiting steps, diminishing the utility of — and incentive to implement — RTRT. In special cases, batch release requires closing investigations, which also would reduce the benefit of instruments for RTRT.

However, participants identified workarounds that could make RTRT more productive. One attendee noted that a polymerase chain reaction (PCR) assay could be applied for accelerated mycoplasma testing. Another possibility is to use drug-substance rather than drug-product samples to perform some assays. Doing so could save time during subsequent batch-release testing. RTRT also could be applied in select cases — e.g., in place of visual inspections of particles in vials and for batch release of cell therapies and other time-sensitive biopharmaceuticals.

The Next Steps in PAT Implementation

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Although ILM and dynamic control of commercial-scale biomanufacturing processes are largely aspirational today, significant advances are in the works. Presenters at BPI Boston 2022 and WCBP 2023 expressed great enthusiasm for the future of PATs, and they agreed that, to reach the next development stage, biopharmaceutical manufacturers will need to work with industry suppliers to enhance automation capabilities, especially for interfaces between sampling mechanisms and analytical instruments. Data analytics also need to improve substantially to enable truly real-time monitoring and generate actionable insights from the considerable stores of process data that will be collected.

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