



PAT MONITORING AND CONTROL

PAT monitoring and control roadmap



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About BioPhorum

BioPhorum's mission is to create environments where the global biopharmaceutical and device industry can collaborate and accelerate its rate of progress, for the benefit of all.

Since its inception in 2004, BioPhorum has become the open and trusted environment where senior leaders of the biopharmaceutical industry come together to openly share and discuss the emerging trends and challenges facing their industry.

Growing from an end-user group in 2008, BioPhorum's membership now comprises top leaders and subject matter experts from global biopharmaceutical manufacturers and suppliers, working in both long-established and new Phorums. They articulate the industry's technology roadmap, define the supply partner practices of the future, and develop and adopt best practices in drug substance, fill finish, process development and manufacturing IT.

In each of these Phorums, BioPhorum facilitators bring leaders together to create future visions, mobilize teams of experts on the opportunities, create partnerships that enable change and provide the quickest route to implementation, so that the industry shares, learns and builds the best solutions together.

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Abstract

BioPhorum's Development Group: Process Analytic Technology Monitoring and Control (PAT MC) workstream has created a roadmap for developing, validating, implementing process analytic technology (PAT) and navigating the path towards good manufacturing practice (GMP) application.

The roadmap has been generated to overcome the current organizational and regulatory challenges facing the biomanufacturing industry. It covers the following topics related to PAT application: building a business case, PAT technology development, deployment and engagement, qualification, validation, transfer, lifecycle management and the regulatory landscape.

The PAT MC roadmap aims to empower organizations with the best practices to enable PAT, which will lead to better process understanding and control, improved product quality and potentially improved productivity.

1.0

Introduction

In the International Council for Harmonisation (ICH) guideline Q8 (R2)¹, as well as in the Food and Drug Administration (FDA) *Guidance for Industry PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*², PAT is considered: “A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality”.

For example, one of the most widely adopted PATs is pH control in bioreactors. The bioreactor is fitted with a pH probe, that gives timely in-process analysis of the pH of the cell culture and automated controls make the necessary adjustments to maintain the pH within the operating range, which influences final product quality.

1.1 Scope

PAT MC is rapidly progressing as instruments shrink in size, have faster signal acquisition time, analyzers account for more variables and modeling becomes more machine-learning (ML) based. In this environment, it is challenging for pharmaceutical and biopharmaceutical companies to understand the ideal path to implement PAT. PAT enables advanced process controls, quality by design (QbD), and culminates in a well-understood process that ensures predefined quality attributes,

which is a precursor for real-time release testing (RTRT). Each organization, vendor and technology will have its own challenges regarding data management, organizational structure, internal support staff/ resources and funding.

Some organizations may find it prudent to implement PAT in conjunction with a product development and subsequent product commercial launch, as many of the considerations, activities and assessments will in general be the same.

This roadmap will serve to:

- Advise on the best practices to move from concept, through lifecycle management and/or regulatory approval of the PAT application
- Highlight use-cases for PAT MC and the benefits
- Enable effective decision-making and scalability.

Table 1 summarizes some of the objectives and outcomes which are addressed in the paper.

Table 1: Summary of objectives and outcomes addressed in the paper

Objective	Outcome
PAT monitoring Process monitoring—ensure process consistency and drive process understanding to improve process over product lifecycle	Enable decisions that optimize and achieve desired output
PAT ensures process under control and within control limits Process control—automate process decisions to increase process consistency and/or improve process yield, product quality and prevent batch loss	Increase yield, improve quality and avoid batch loss
Operations	Increase success rate or capacity throughput Process in control
Business	Reduce cost of goods Assurance of supply Product quality Return on investment Reduce time-to-market

This paper covers general concepts, definitions, common PAT techniques, method development and validation, instrument qualification, data engineering and data integrity requirements from development through clinical into commercial in a digital environment and typical lifecycle management concepts. In addition, it will briefly discuss related strategy on business case, regulatory and filing.

Appendix 1 is an outline of the PAT framework described in this paper.

2.0

Building a business case

The rationale for implementing PAT can be based on speed and efficiency, risk mitigation and ensuring process and product quality, which will be measured by return on investment (ROI). PAT MC will impact these business drivers by:

- Providing greater process understanding and control of each unit operation
- Increasing product output via real-time PAT MC, and enabling continuous manufacturing
- Eliminating human error via closed-loop control and electronic data capture
- Aligning to industry standard practices.

The initial steps to building a business case are to identify specific pain points from current practice and the potential benefits of PAT. Two major benefits offered by PAT are improvements to process design and control via real-time detection and/or feedback control, and supporting QbD to improve process understanding. Implementation of PAT could improve process development by providing additional data and control strategies resulting in improvements, e.g. increased titer or improved quality. In manufacturing, cost reductions are attainable via reduction of run failure, cost of goods and skilled operator costs.

However, a more prudent approach is to first gather some initial proof-of-concept data. This preliminary data can serve as a foundation for the business case and aid in the evaluation of both economical and operational advantages.

2.1 Implementation at development scale

The predevelopment stage starts from identification of a use-case and the associated user requirements of the system. Refining the problem statement will ensure that proper technologies are identified to suit the use-case. The technological solutions that meet these requirements can be compared or even evaluated in the lab against one another to determine a path forward. Section 3.0 of this paper details development activity considerations. Key evaluation criteria include maturity of

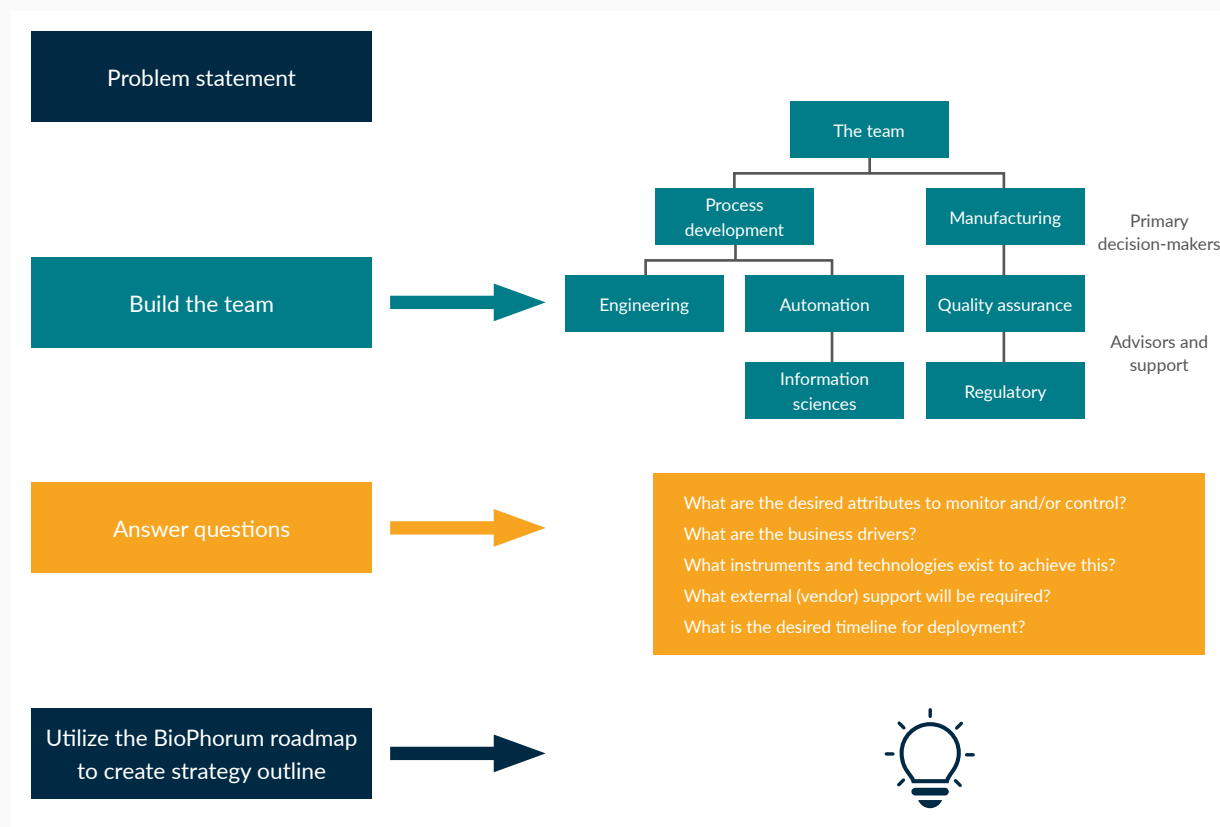
technology, fitness-for-purpose, cost of implementation, data management technologies, regulatory compliance, scalability, risk assessment, system lifecycle management and compatibility with current infrastructure.

Once a use-case has been identified, the business case can be built. If there are already case studies for the specific PAT implementation proposed, these can be used as a real-world reference. The business case should include an economic evaluation with estimated costs and a proposed timeline. PAT requires initial investment in equipment, as well as the costs of method development and update, or creation of new procedures to integrate with the existing quality system. PAT also requires training and resources to develop subject matter experts (SMEs). The potential returns of PAT are in preventing wasted runs, reducing cost of manufacturing, improving process robustness, reducing time-to-market and/or improving product quality.

Figure 1 shows the key stakeholders (primary decision-makers) engaged to build the business case are process development, manufacturing or a technology transfer sub-team and business strategy analysts.

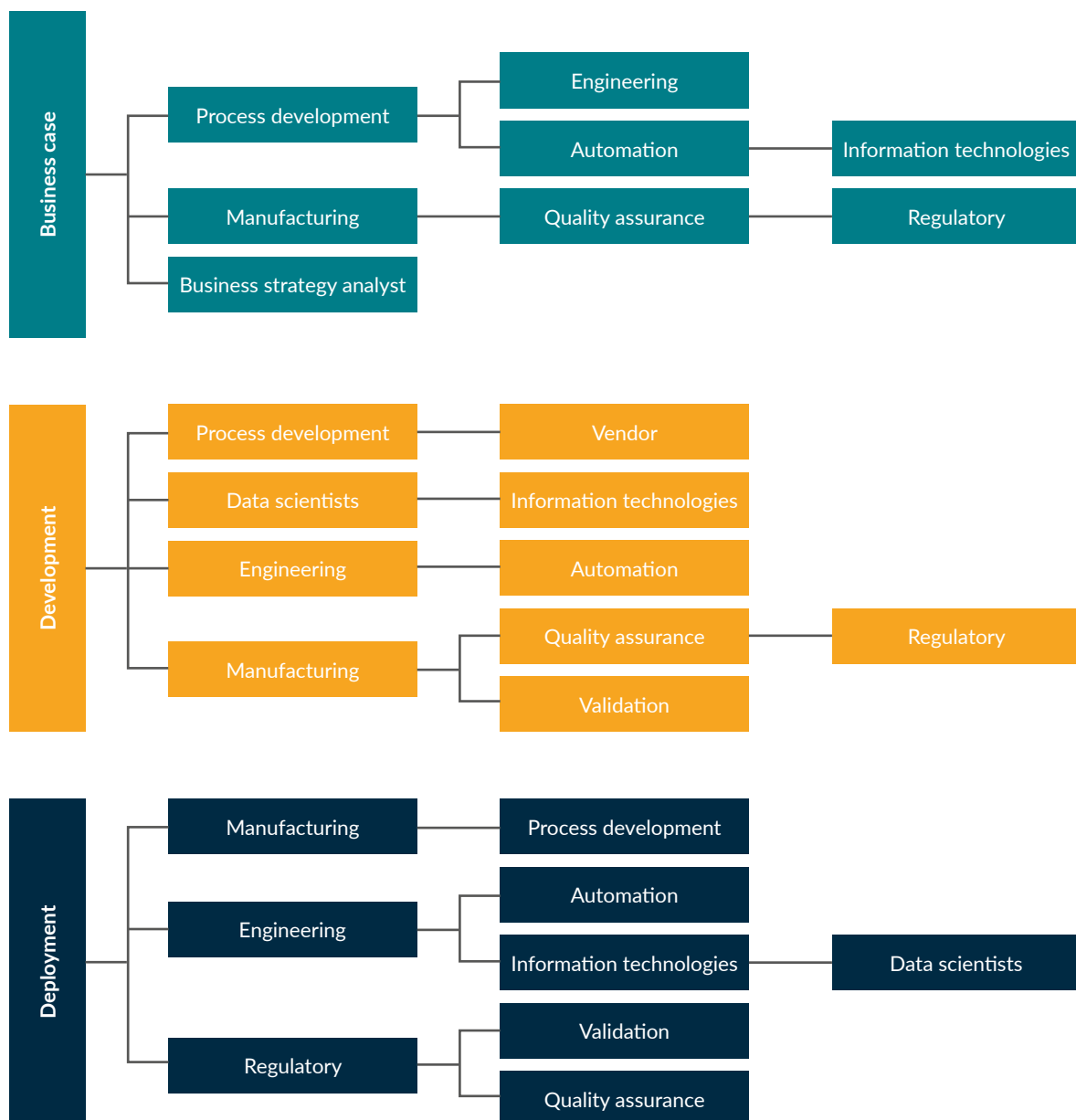
- The primary decision-makers and advisor/support organizations should have representation on the project team
- The primary decision-makers will be experts in their relevant areas and be tasked with leading this phase of the project, deciding on how to conduct required activities, and requesting input from supporting organizations
- The advisors will have direct input or activities tied to the phase
- Support organizations will assist as needed
- Initial discussions should define the project scope and identify impacts to each stakeholder and allocation of resources.

Figure 1: Building a business case is a cross-functional exercise that requires a team



Each organization will classify or structure these functions in various ways. The stakeholders may be within the organization or in a parallel organization. Regardless, it is best to involve primary teams and decision-makers from the start. This will enable streamlined and holistic decision-making which will avoid implementation obstacles later in process characterization, manufacturing or regulatory approval. As a reference, Figure 2 shows the functions required at the different stages of the PAT framework.

Figure 2: Functions required across stages of the PAT framework



2.2 Implementation at scale

When process development feels that a PAT method is sufficiently mature to migrate into a manufacturing space, a new cost/benefit guide should be built. This should consider the compatibility of the technology at a larger scale. It should also provide detailed insight into the comparability of the bench scale model to current quality data to ensure consistency of the process. A risk assessment (RA) generated by manufacturing SMEs may provide insight which the development group has not yet considered. A ranked list of mitigations in the RA may help with the cost/benefit analysis. Finally, the cost of the core technology and the related costs associated with its operation in a highly regulated space should be forecast. Details in the model should include:

- Justification for initial cost of the equipment to be procured, including the expense associated with software licensing, installation qualification/operational qualification (IQ/OQ), validation documentation, training and ongoing preventative maintenance costs
- Level of scalability achieved in development labs prior to at-scale implementation
- Whether the technology has proven to be compatible from the bench to a pilot or engineering lab space
- Whether an engineering assessment has been performed to identify spatial constraints, utility requirements, scaled equipment, integration with single-use technology as needed, etc.
- Whether an IT assessment has been performed to identify security risks to data, compatibility with current systems, alignment with company policies, hardware or infrastructure requirements
- Whether technology meets the requirements of local regulatory bodies and aligns with the guidance of ICH Q8¹

- Requirements for additional technical expertise around the instrument:
 - Whether the technology requires regular on-the-floor support
 - Any additional SMEs in quality control (QC) or quality assurance (QA)
- Waste considerations or environmental impacts coming from implementation
- Potential consideration for instrument redundancy is on a case-by-case basis based on risk to process and business continuity.

Aside from outlining a cost model, a benefits analysis also needs to be performed. This benefit analysis should be based on the project development strategy and possible incentives be data driven to invest in a new platform. Key questions to ask in the analysis include:

- Will PAT provide a competitive advantage or improve the marketability of a product or service?
- Does the technology lead to a reduction of deviations or batch losses?
- Is there potential to drive up yield of a product line?
- Can critical quality attribute (CQA) testing performed by a quality division be replaced by on-the-floor documentation?
- Will product quality be improved by real-time testing or dynamic system control?
- Is there a reduction in sampling and sample handling that can be accounted for?
- Does data integrity or the availability of data being collected improve?
- Will implementation lower environmental impact (reduce water consumption or waste output)?

3.0

Development

PAT MC has proven to be an asset for defining and developing biopharma processes and will effectively reveal insights in a timelier and more cost-effective manner, as well as add to the robustness of the process, process characterization and data packages. For example, a sufficiently characterized, monitored and controlled process may not require additional testing for each lot to demonstrate successful process control.

The organization can anticipate more efficient execution of process design and tech transfer activities:

- Development of process-related calculations and *in silico* models
- Tabulation of process parameters with targets, set points, operating ranges, acceptable ranges including process control action and rejection limits, and parameter classifications
- Determination of performance indicators (PIs) with expected values or ranges for process monitoring program
- Developing in-process control (IPC) strategy and acceptance criteria.

Additionally, process development is defined by the FDA as stage 1 of the process validation lifecycle. Process development integrates data and knowledge from various sources to develop, justify and improve the commercial process and come up with a process control strategy to ensure product quality expectations are met consistently. The following section on the development phase advises on structuring and categorizing process development testing to meet regulatory expectations.

In the development phase, key stakeholders (primary decision-makers) who will engage at this stage are process development, data scientists, manufacturing and engineering.

- The primary decision-makers and advisor/support organizations should have representation on the project team
- The primary decision-makers will be experts in their relevant areas and be tasked with leading the phase of the project, deciding on how to conduct required activities and requesting input from supporting organizations
- The advisors will have direct input or activities tied to the phase:
 - Vendor, information sciences (IS), automation, validation, QA
- Support organizations will assist as needed:
 - Regulatory.

Each organization will classify or structure these functions in various ways. The stakeholders may be within the organization or in a parallel organization.

3.1 Technology comparison

Technology comparison will be conducted via investigation of available PAT and the business drivers. The organization will want to answer:

- What are the desired attributes to monitor and/or control?
- What are the business or strategy drivers?
 - Speed to market, cost of goods, continuous operations, unit operations, etc.
 - Matrix components of the unit operation
- What instruments and technologies exist to achieve this?
 - How will the technology interface with the process?
 - What type of model?
 - What are the infrastructure requirements?
- Is the analytical technique appropriate for what needs to be monitored?
 - What are the method requirements?
 - What is the impact level of the method?
 - What is the current reference method for the target attribute and is there any precision data for it?
- What external (vendor) support will be required?
- What is the desired timeline for deployment?

Given the number of variables to consider when scoping potential PAT, the organization must pursue those instruments and technologies that align best with their needs, while understanding how support from internal resources and the vendor will coalesce to progress the program¹. Refer to the BioPhorum PAT comparison paper¹⁹.

PAT technologies are to be assessed against traditional non-PAT technologies for cost-effectiveness. System and data requirements, as well as vendor support, should be captured and communicated during deployment (Section 4.0) to the tech transfer team.

3.2 Early phase

The first step in developing a PAT is to define the application of the technology. Prior to developing a PAT, a comparison of similar PATs of different models or from different vendors should be conducted to assess technical feasibility and demonstrate business case benefit. This initial scoping may include preliminary tests in a scale-down environment to better understand performance capability and/or limitations. Once the specific vendor, maker and model of PAT have been selected, the method should be clearly defined and developed further in scale-down models to provide a robust basis for proof-of-concept studies. Comparability studies between the existing/reference method and the PAT are necessary at this phase; such studies should include an assessment and evaluation of robustness, frequency of measurement and assessment of CQAs. All early phase assessments can be done with the PAT operating as a standalone system, not necessarily integrated into site data-system infrastructure. However, in the early phase it is important to establish the system's capability to integrate with an automated data acquisition strategy to collect and process the data generated by the analytical techniques in real time.

3.2.1 Developing the IPC strategy and acceptance criteria

The PAT MC program should improve the robustness of the process. When developing the IPC strategy, it is important to keep in mind the validation approach (Section 5.0). In some cases, it can be validated during development using a qualified scale-down model. Alternatively, this validation may require a validation at full scale.

Ideally, the program will bridge gaps in process understanding, assist with operation troubleshooting, highlight areas for process improvements and tighten control parameters. Inherent assay and measurement variability should be understood and considered when determining acceptance criteria. If the assay or technology variability is greater than the process variability, the method (technology) may not be the best indicator of overall process performance. In addition, the number of batches or the amount of data will depend on the degree of PAT method development and/or implementation.

The following are recommendations for assessment and evaluation of the program technology:

- Design and optimize the experimental protocol
- Ensure an adequate number of runs to procure data to support claims
- Confirm that PAT MC does not affect growth or product quality via an analysis of variance (ANOVA) and forward processing
- If unsure of the affected quality attributes, analyze more PIs so that the data are available.

To define success of the PAT monitoring/control method, the CQAs and critical process parameters (CPPs) need to be monitored to ensure the quality and consistency of the biopharmaceutical product and demonstrate efficient feedback control of the same parameters. The assessment data package should target equivalency of means using a 90% confidence interval on the difference in means. Equivalency of means is determined using the two one-sided t-tests (TOST) procedure and is demonstrated when the bounds of the two-sided 90% confidence interval of average difference falls entirely within the equivalence acceptance criteria range. A two-sided 90% confidence interval can be replaced with two one-sided 95% confidence intervals. Section 5.1 includes further details that address the qualification and validation of the analysis.

Following QbD principles, an early RA should be conducted to confirm development early phase findings and future potential adherence to regulatory standards. Regulations can have a significant impact on the development, implementation and use of PAT methods by setting standards and guidelines for their implementation and use. Regulatory agencies typically have established guidelines and requirements for the use of PAT in pharmaceutical manufacturing. These regulations can determine the frequency, quality and general approach to PAT methods in several ways, such as required PAT implementation, quality standards, data frequency and reporting requirements. Compliance with these regulations is important to ensure product quality, safety and consistency, and to avoid regulatory non-compliance issues. Refer to initial registration in Section 7.1 for an understanding of the regulatory standards that must be met by the end of development.

3.3 Mid phase

As part of the PAT MC development, the design of experiment (DoE) should incorporate studies to determine statistical significance of the program, including:

- Demonstration of the PAT MC capabilities, including impacts, identifying and mitigating adverse events, while establishing or demonstrating:
 - Ranges and limits for process parameters and IPCs
 - Time limits and hold times for operations
 - Removal or control of impurities or reagents based on RAs
 - Chromatography resin and membrane lifetimes and long-term storage
 - Viral clearance and microbial bioburden and endotoxin reduction
- Assessment of PAT MC effect on process parameters, product quality and PI.

Development data will be used to classify process parameters and IPCs, and establish the respective PAT MC effect. The development team will document the justification for parameter and control classifications, such as critical or non-critical. A summary of the control strategy, reflecting inputs, procedural, statistical and model-based assumptions will be created. These classifications will be made by advisors and support resources, and endorsed by stakeholders.

3.3.1 In-process control and monitoring

Small-scale and/or *in silico* models should represent the planned commercial process and scale-dependent differences should be understood. Comparable performance will be based on evaluation criteria relating the small-scale model to the representative pilot, clinical and/or commercial-scale data.

Once data have been collected, a data analysis method is developed that can be used to analyze the data and identify any deviations from the target CPPs and CQAs. This is a complex process that requires careful planning, implementation and validation. The data analysis method should be validated and verified to ensure that it is accurate, reliable and consistent (Section 6.0).

The data analysis, monitoring and control will take place in an established IS network to allow for remote access and control, real-time monitoring and democratization of the data. These data could be leveraged in future system validation following a risk-based approach and a computer system assurance model. It should be further leveraged allowing the overall projects to move faster and have reduced testing at scale.

The process of developing a data analysis method typically involves several key steps:

- **Select appropriate statistical techniques:**
It is crucial to select the appropriate statistical techniques that will be used to analyze the data. The choice of statistical techniques will depend on the type of data being collected, the objectives of the analysis and the requirements of the manufacturing process. Some common statistical techniques used in PAT include multivariate analysis, control charts and DoEs
- **Define variables and data pre-processing:**
The data need to be organized into meaningful categories, removing outliers and errors, and transforming the data into a format that can be easily analyzed using statistical techniques
- **Perform exploratory data analysis:**
In exploratory data analysis, the data are visualized to identify patterns, trends and relationships between variables. Exploratory data analysis helps identify potential outliers or data quality issues and provides insights into the underlying data structure
- **Develop a predictive model:** A predictive model is a statistical model that makes predictions and provides insights into the manufacturing process. Developing a predictive model involves selecting appropriate variables, defining the model structure and training the model using the collected data to predict
- **Test and validate the model:** The developed predictive model should be tested and validated to ensure that it is accurate, reliable and consistent. The performance of the model is evaluated by comparing the predicted values with actual values using different metrics. The model should be continuously monitored and updated to ensure that it remains relevant and effective.

3.4 Final phase

The final phase of development is to support deployment (Section 4.0) and prepare an initial technology transfer package to manufacturing facilities. Standard tech transfer documents include:

- Bill of material (BOM): a brief narrative description of each unit operation, including step purpose and how the unit operation is to be run
- Media, buffer and solution preparation information including lists of raw materials, related concentrations, preparation methodology and storage details
- Chromatography column packing and membrane installation information with any associated process parameters and Pls
- Membrane and resin cleaning, re-use and storage information
- Raw materials and active product ingredient (API) starting materials
- Tabulated process parameters with targets, set points, operating ranges, acceptable ranges including process control action and rejection limits and parameter classifications.

The deployment of PAT techniques will require additional information to the process including:

- Pls with expected values or ranges for the process monitoring program
- Process-related calculations and *in silico* models
- IPC strategy and acceptance criteria
- Implementation of the method:
 - Demonstration and testing of the method (model) should be conducted prior to moving into deployment (Section 4.0)
 - Qualification and validation plan of the PAT method/models (Section 5.0).

The analytical methods and data collection systems should be well established (vetted) and integrated with the process control system and procedures for data collection, storage and analysis. This may involve training personnel on how to use the method, integrating the data acquisition system into the manufacturing process and establishing protocols for addressing any deviations from the target CPPs and CQAs. As part of the PAT MC program lifecycle management, the entire approach (including statistical models and methods) should be continuously monitored and updated to ensure that it remains relevant and effective.

4.0

Deployment and engagement

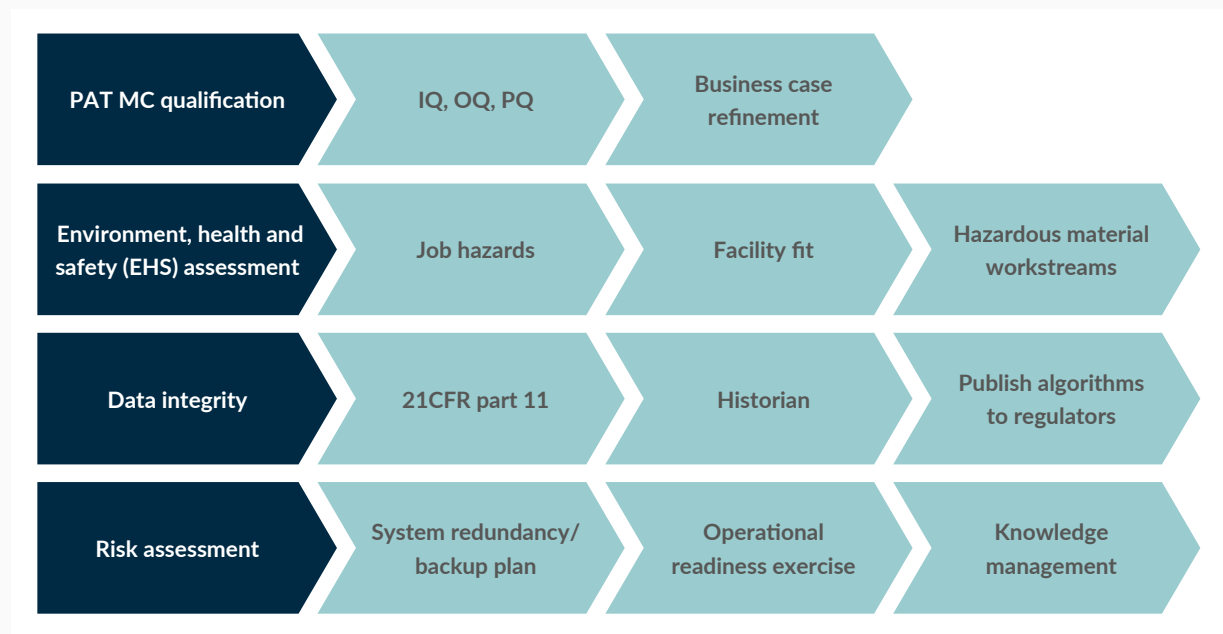
The PAT MC program development will have assessed the in-scope PI, which are a direct or indirect measurement of a product quality attribute (PQA), product quality indicator or process consistency measurement.

The PI and PAT MC action limits should align and specify if:

- The PAT MC program will reduce the risks of specification failures and provide important information for process consistency
- The IPC testing is required per regulatory expectations.

As this information becomes available during development, it should be discussed and analyzed extensively with the primary decision-makers on the project team. The business case (project charter) should also mature as the project advances, accounting for the time, costs and labor associated with the offline analytics that the PAT MC will replace. The result will be a well-vetted PAT MC platform that is nearly ready for implementation. Figure 3 summarizes the activities required for deployment and engagement.

Figure 3: Examples of development and deployment activities



4.1 Tech transfer from pilot lab

Development phase activities typically occur in a less rigorously controlled environment than at commercial scale. These activities may be conducted utilizing vendor SMEs, company development staff and vendor or temporary infrastructure, such as a local server. In this way, the resulting networking and digital robustness of the PAT MC will need to be shored up to allow for scaling up and regulatory scrutiny.

Tech transfer stage activities will be targeted to begin when pivotal studies are initiated if tied to a process or product, or, if progressed as an independent change control (CC), once development activities have completed, such as determining data requirements, acceptable fit for facility, and data package and method acceptance. The activities and requirements outlined in this section can be applied while: maturing the PAT MC from development and pilot scale to commercial scales, as well as transfer to external partners, contract manufacturers or laboratories, or to another commercial site. The activities will be discussed further in Section 4.3.

To bring a new piece of an instrument to a GMP environment, it must be qualified, and the associated manufacturing process validated. Equipment qualification includes IQOQ and performance qualification (PQ). The protocols for these qualifications should be in place before the initial deployment of the instrument. In addition, safety assessment including electrical or laser hazards, instrument footprint and how it fits into the facility space, as well as cleaning validation protocol, should also be discussed during the engagement with the intended GMP facility. If consumables are needed for an inline instrument, risk for extractables and leachables should also be assessed.

4.2 Digital considerations

Another important aspect of a PAT MC program in GMP manufacturing is data integrity. Software or the interface of the instrument must comply with 21 CFR Part 11¹⁴. The system can be integrated into an existing control system or operate by itself. However, data should be accessible to users during operation and saved as well as backed up appropriately with traceability.

Developing a PAT infrastructure and governance will enhance the commercial and lifecycle management digital ecosystem. A foundational layer of any digital initiative, such as PAT MC, is the semantic layer. Standardization of what data are called or referred to is imperative, as these descriptors will be inputs and outputs of a PAT MC program. (For example, a bioreactor may be referred to as a vessel, fermenter, production vessel, etc.) Standardization of terminology should span the data environment, such as batch records, development laboratories, analytical sciences, etc. As a PAT MC program grows, more sophisticated ML-based algorithms will utilize data that are properly assigned to reference data ontology in the semantic layer. Data analysts in less developed digital organizations will also benefit, as less time will be needed for data wrangling and polishing. To improve the semantic layer, the following need to be considered:

- Establish standard vocabularies
- Standardize synonyms
- Eliminate free text fields.

By tackling the semantic layer, ability to aggregate and explore data within and across systems will open to support critical decision-making. PAT instruments must be connected as a raw data source with information stored in historians, which are accessible by data analysts, who in turn utilize historical data to create multivariate models for modeling. The model is deployed to servers with connections to operational instrument data, as well as additional sources if available (analytical sciences, development, etc.). Software or independently sourced code on the server monitors real-time processes, with the trends available for staff or management. An ideal monitoring platform will also include a notification system to alert of statistical abnormalities, or mitigation via automated control loops.

The infrastructure needed to implement and unlock the data PAT provides in a MC program is costly. In addition to instrument procurement, automation and data analyst skills, an IS partnership, as well as persuasive and persistent leadership, is also required. Many PAT MC programs stall after development due to:

- The complexity of expanding the program
- The time needed to implement
- Quality risk avoidance
- Budget.

However, once the digital infrastructure is created and PAT MC is implemented, the initial investment costs are recovered via increased output, market capitalization, scalability, process robustness and other factors.

4.3 Organizational and operational readiness

Due to the cost and duration of ROI, PAT MC projects are challenging. Project momentum can be maintained via strategic organizational roles and responsibilities. A team of scientists and engineers would ideally work with vendors to test PAT and develop its use-case. As the technology matures, these SMEs could move with the technology to ensure continuity of knowledge, enabling a way for SMEs to grow professionally. This is regardless of whether the PAT is being implemented in development labs or commercial manufacturing. If the PAT is not matured, the team of SMEs are offered a new PAT to develop. The greatest impediments to the implementation of PAT MC programs include insufficient organizational support, limited resources and lack of perseverance. These programs take time and significant skill to implement. Continuity of the team of SMEs ensuring aggregated skill sets are not lost, and do not need to be relearned by new team members, is paramount.

Instead of an organizational structure that symbiotically progresses technology and personnel, roles and responsibilities of key stakeholders will need to be established as part of the tech transfer operational readiness team:

- Technology development lead:
 - Lead activities while under development (Section 3.0)
 - Provide technical, troubleshooting and issue resolution to manufacturing
 - Assess gaps.
- Technology transfer receiving organization lead (Manufacturing):
 - Partner with stakeholders to drive overall strategy of RAs, characterization, validation, regulatory and filing
 - Lead lessons-learned exercises
 - Communicate issues and risks associated with the project
 - Ensure compilation of consumables, material numbers, BOM and sample plans
 - Ensure completion of commercial documentation, including GMP training materials
 - Facilitate and own the RA.
- Technology validation lead:
 - Lead activities during qualification and validation (Section 5.0) at the direction of regulatory
 - Define the criteria for model maintenance and performance.
- Technology automation lead:
 - Perform/create equipment recipe changes/authoring
 - Perform testing at the direction of engineering
- Technology engineering lead
 - Equipment and system upgrades, installation and drawing updates
 - Issue necessary work orders
 - Assess facility fit
 - Enable automation and IS workstreams.

- Regulatory:
 - Direct quality for GMP documentation strategy and oversight
 - Support regulatory document generation and submission
 - Define PQAs
 - Empower Quality to lead RA activities
 - Ensure analytical methods for in-process and product testing are approved, qualified and validated as needed.

The goals of the technology transfer team include:

- Establish a project plan and scope of the transfer
- Identify and plan for items and tasks requiring long lead times, which may include but are not restricted to:
 - Components
 - Capital projects
 - Change controls
 - Equipment
 - Import/export licensing
 - Filter validation
 - Inspection method
 - Quality RA
 - Software
 - Raw materials
 - Single-use systems
- Establish a regulatory strategy in alignment with Section 7.0 of this paper
- Establish a governance strategy
- Evaluate PAT MC program requirements and receive capabilities for alignment and gap assessment.

Gap assessment exercises help ensure success by identifying risks and building on the implementation strategy. All rationale and limitations are to be discussed, resolved, documented and included in the tech transfer plan.

An operational readiness exercise (ORE) is one such analysis. In the ORE, the PAT MC program fit into the receiving facility capabilities, operations and organizational structure is assessed. All aspects of the PAT MC program are to be assessed in the ORE, for example: material receipt, application licensing, maintenance, completion of the affected unit operations, all/any components, including digital.

Additional topics covered in the ORE include:

- BOMs
- Material and component specifications
- Pls
- Control strategy
- Parameter classification
- Process parameters.

A testing readiness exercise (TRE) will be conducted to evaluate analytical methods, attributes to be measured, method invalid rates and typical failure modes, sampling strategy, sample stability and method capabilities. For PAT MC programs utilizing inline instruments, perform a cleaning, sanitization and cross-contamination evaluation and validation (Section 5.0).

Additional assessments can be added if needed to ensure the successful transfer and implementation of the PAT MC program. Prior to utilization in commercial batches, all assessments and deliverables should be completed. Executive stakeholders may abort, resize or delay the program if the assessments reveal unattainable goals/timelines, scope expansion or cost during the assessment period. Additionally, the tech transfer team may decide that the change control governing the PAT MC implementation will include a change effectiveness review to allow for vetting of any new issues that arise at commercial scale. During this time, both the new PAT MC program and the pre-existing operation will be available.

5.0

Qualification, validation and transfer of method/models

During initial development of a PAT method the data generated are for understanding and used for information and monitoring purposes only. This helps build an initial understanding including potential challenges and roadblocks toward the development of a PAT method.

An important step during the implementation of a PAT method is a comparison of the technology against the existing reference method. This requires data from qualified methods to validate the corresponding PAT methods.

It is generally recognized that analytical methods used during clinical development, such as those that support investigational new drug application (IND) and clinical trial application (CTA) filings and amendments, are evolutionary (phase-appropriate validation) and require less extensive validations (method qualification) than methods that support new drug application (NDA)/ biologics license application (BLA) and marketing authorization application (MAA) filings for control of commercialized products (method validation).

General requirements for method validations based on risk are (as applicable):

- Qualified equipment/instruments
- Trained personnel
- Appropriate system suitability tests (SSTs)
- Proper storage and traceability of analytical data.

The complexity of the technology should be considered. Additionally, official references such as ICH Q8¹, ICH Q9¹⁰ (relating process robustness into the method) and ICH Q14 (PAT method)⁶ should be considered and aligned with. Overall, to use data generated from PAT for various applications from research to manufacturing, phase-appropriate methods must be developed or qualified or validated according to the corresponding development/qualification or validation strategies (see Table 2).

Table 2: Strategy of method qualification, validation and transfer

Method strategy	Description	Scope	Requirements
Development	See Section 3.2 Development method for initial testing or application in research for first data collection	Non-GMP, process monitoring during developmental stages	N/A
Qualification (phase-appropriate validation)	In the clinical space/before process performance qualification (PPQ); objective evidence that equipment or system and its ancillary system are correctly installed, work as expected and are fit for the intended use	Non-GMP or GMP (clinical stages: tox to pre-PPQs), IPC, RTRT, process monitoring	Five elements of ICH Q2 (R1) ³ with robustness and intermediate precision
Validation	At-scale validation; establishes objective evidence that a process can consistently deliver a quality product	GMP testing from PPQ onwards, IPC, RTRT and process monitoring, replacement of (offline) CQA testing	Five elements of ICH Q2 (R1) ³ with robustness (including data from all scales) and repeatability
Transfer (co-validation)	Qualification of labs for the use of an analytical method. Can be part of validation (precision, co-validation)	Primary and secondary transfers; range from non-GMP to GMP testing	Precision (inter-lab)
Verification for routine use	Lifecycle management of PAT		

5.1 Qualification and validation method

This section includes guidance and best practices on how to qualify or validate methods that have been developed once identified and required in either a clinical or commercial manufacturing site. The main objective of the validation runs (e.g. PPQ) is to successfully execute the required number of lots as specified by validation, stability, comparability, local qualification/validation procedures and/or regulatory requirements, while demonstrating a robust control strategy and CQAs within the required ranges. See Section 6.1.1 for more detail on RA considerations. Change control assessments should be considered where relevant. PPQ is where you need the methods validated, although there may be some exceptions (e.g. for inline products, depending on filing strategy).

There are three steps to consider during validation of a method:

1. Writing the validation protocol
2. Executing the validation of the method
3. Completing the validation summary report.

5.1.1 Writing qualification/validation protocol

When writing a qualification or validation protocol, consider the scope of the method in terms of stage and intention. A local project leader should be appointed to guide the project and evaluate who should be included or consulted in the implementation team. Some groups to include are local quality organizations, area management from impacted organizations, authors of documentation and the analytical development team (including technology/PAT SMEs). Other teams that should be consulted are technical operations (IT, automation, engineering), manufacturing or those running the methods and those using data outputs. Once the team is determined, decisions should be made on the scope of the validation, the roles and responsibilities of team members and a project charter or other supporting documentation.

The protocol should include the scope of validation and the intended validated use of the method (monitoring, IPC testing replacement), as well as any acceptance criteria and/or expected outcomes. It should include information on the site or process area at which the method is being validated and other details on instrument type, equipment, method, materials and any other relevant information. Information on how the method is set up should be documented for reproducibility. Information on the sampling plans needed for the method validation should be included. The number of manufacturing batches/runs, number of samples or sampling frequency should be determined by statisticians or per local guidance. The protocol should provide guidance on the data that should be collected as part of the validation, how they will be collected and instructions on how to perform data analysis. The rationale and justification for decisions regarding acceptance criteria, sample size and how data analysis is performed should be documented in the protocol.

Acceptance criteria are a continuation of the information discovered during development of the method and documented in the development report. Information learned during development, deployment and along the way should inform the acceptance criteria for the method being validated. Acceptance criteria/expected outcomes are generally presented in a table for criteria versus method. For example, Table 3 compares glucose Raman prediction results versus the offline method with must-pass acceptance criteria as per the instructions in the protocol. Information on how the acceptance criteria are generated and justified should be included in the protocol. Instructions on how to perform data analysis should also be specified in the protocol. Some types of analysis that can be performed in the protocol include range, linearity, reproducibility, accuracy/standard error of prediction, specificity and robustness at-line. Multiple analyses can be used as needed for the method that is being validated.

For other PAT methods that do not have the absolute value of the attribute of interest, the acceptance criteria may be different.

Table 3: Performance summary of Raman method validation for glucose

Parameter	Acceptance criterion	Result	Pass/Fail
Specificity	Using spectral regions specific to glucose will result in model specific to glucose	Glucose model uses the spectral regions of glucose	
Accuracy	Root-mean square error of prediction (RMSEP) ≤ 0.50 g/L (arbitrary value) (RMSEP is the ability to obtain results that are close to those by reference methods)	RMSEP = 0.xx g/L	
	Equivalence: TOST with 90% confidence interval lower/upper control limit (LCL/UCL) which is within (-0.50; 0.50) (optional, arbitrary value)	(LCL: -0.xxx; UCL: 0.yyy)	
Linearity	The linear regression of the predicted glucose and the accepted reference value should generate $R^2 \geq 0.90$ (arbitrary value)	$R^2 = 0.xx$	
Range	The range of the method will be reported as the lowest and highest glucose value that are within the calibration range of the model and where acceptable accuracy and linearity has been demonstrated	Range of calibration: 1.0–8.0 g/L (arbitrary value) contains validation range: x.x–y.y g/L	
Reproducibility	Glucose concentration predictions must have a relative standard deviation (RSD) $\leq 10.0\%$ (arbitrary value)	RSD = x.xx%	
Robustness	Passing the RMSEP criterion for the independent validation (or else) ≤ 0.50 g/L (arbitrary value)	RMSEP = 0.xx g/L	

Before proceeding with qualification/validation, instrumentation, and data infrastructure and management considerations need to be taken into account. These should be addressed by local procedures on instrument qualification and data management/infrastructure for intended use.

Data infrastructure should be designed according to the needs of the PAT methods and considerations for the data and systems such as formatting, frequency, archiving, backups and controls, network, redundancy/uptime and hardware/software. This should be designed and documented in parallel with the method during the business case, development and implementation steps. The details and requirements for the data should be included in the design specifications of the infrastructure

documents. Data management and infrastructure must be qualified or validated via local procedures and guidance before the qualified PAT method can be used for good practice (GXP) purposes.

Training needs to be considered before executing the qualification/validation stages. Operators or those using the method, may need additional training on standard operating procedures (SOPs), work instructions (WIs) or relevant operational procedures. Media simulations or engineering runs can be used as additional training opportunities and ways to verify method procedures before GXP use. Those executing the method qualification/validation may need training on the data capture, archiving or analysis system and should complete a dry run or smoke test prior to executing.

5.1.2 Execution of qualification/validation

Once the validation protocol is approved, validation starts with predefined batches as defined in the protocol:

- Mitigate any unexpected events such as a power interruption or instrument failure according to local quality guidance
- Ensure both PAT analyzers and reference methods are followed under GMP during execution
- Use qualified instruments (if not mentioned) and IT infrastructure
- Ensure IT data integrity and archiving are as per the method requirements
- Follow protocol instructions to collect and analyze data
- Record and keep all relevant data, printouts, original supporting documentation, etc. required to complete analysis or include in the summary report
- Record all data transformations, edits, omissions, calculations, types of analysis etc. for reproducibility of the analysis.

5.1.3 Qualification/validation summary report

After completion of the execution of the validation protocol, a qualification/validation summary report should be issued to summarize all the activities, data and outcomes per the protocol.

Data collection and other information should be performed as specified in the protocol. This includes the offline and method values or predictions from the PAT analyzer or other information as specified. The data analysis and comparison should be completed as outlined in the protocol. Comparison against the acceptance criteria should be performed and documented in the summary report. Analysis should include but is not limited to specificity, range, linearity, reproducibility, accuracy/standard error of prediction and robustness. All data and analysis should be included in the summary report as evidence that the method meets the acceptance criteria defined in the protocol.

Potential risk factors or unexpected issues uncovered during validation should be documented and addressed during the issuance of the summary report. A cross-functional team (CFT) including quality risk management should review the risks and summarize any potential harm or mitigations in the conclusion of the summary report.

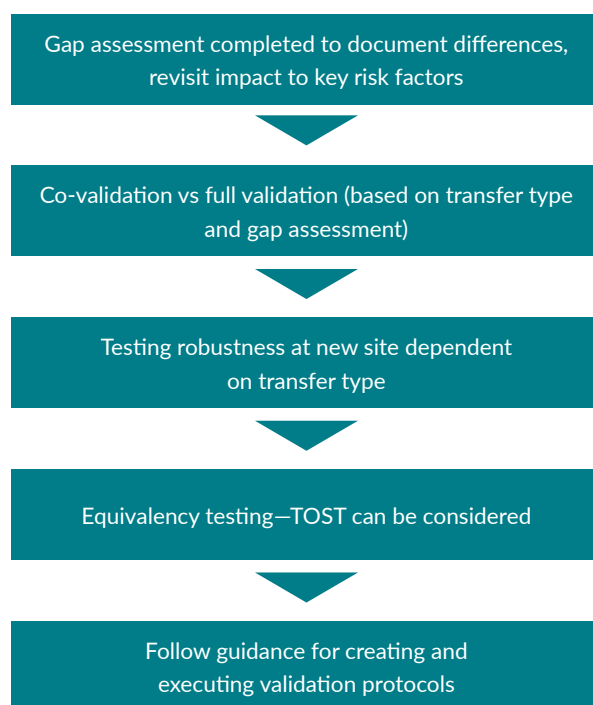
The outcome of the summary report should inform and help define the lifecycle management strategy for the method for future use. Data from the summary report can also be used to define the outline detection limit as a safeguard for the method implementation. The summary report can also inform other organizations such as chemistry, manufacturing and controls (CMC) and QA for regulatory impact or filing.

The summary report should be reviewed by all groups that informed the protocol and should be approved by local quality organizations, CMC/regulatory submission and filing teams, area management and any impacted analytical or data consumption teams, as necessary.

5.2 Transfer of methods/models

If a method needs to be qualified or validated at another site, processing area, lab, etc. (see flow chart in Figure 4 of steps for consideration), a supplementary validation should be performed to ensure the method can be used in the new space. The section below defines the different scenarios for qualifying the method to new spaces and gives guidance on how to perform those activities. Methods transferring to different scopes (e.g. at-line to online) are not covered in this section and should be qualified and considered separate methods.

Figure 4: Flow chart of potential steps considered during method transfer



A gap assessment should be completed documenting the differences to develop test cases and informing how to assess and document these gaps. A CFT should be consulted to review and justify the information gathered during the gap assessment. Information from the gap assessment will help to define the best way to approach a new qualification, if needed, as per the risk. Examples of areas to investigate and document include materials,

software, unit operating systems, instruments, procedure and process. Certain validation for elements does not need to be repeated, such as specificity as it is intrinsically tied to the sample matrix/process and remains unaffected by alterations in the instrument. A risk-based approach to what can be leveraged from previous qualification/validation should be included in the validation plan.

As part of the gap assessment, consideration should be given to assessing additional risks as part of the transfer process—revisiting the key factors identified as part of the lifecycle maintenance, the completed RAs, implementation strategies and lifecycle summary report. Impact to key risk factors may include:

- Could lead to mitigation studies or additional testing during method transfer
- Consider ‘where/when’ RAs are performed and how these are documented (Section 6.1.1)

- RAs should be revisited after the method completes (e.g. at PPQ)
- RAs occur on a periodic basis based on impact of risk factor.

The way the method is being transferred should be defined and reviewed to identify how much validation should be performed. Robustness testing should be linked to the precision of the method from most to least challenging. Information from the gap assessment should be considered alongside information in Table 4 by a CFT to determine the required level of validation.

Table 4: Overview of validation requirements and considerations depending on transfer type

Transfer type	Validation necessary	Additional considerations/ best practices
Clinical to commercial	Yes	Accuracy, precision and robustness
Site to site	Yes	Accuracy, precision and robustness
Lab to lab	Yes	Accuracy, precision
Instrument to instrument	Conditional	Accuracy or precision (if needed)
Operator to operator	No	Accuracy or precision (if needed)
Day to day	No	Accuracy or precision (if needed)

Lifecycle management

After completion of validation/qualification activities, a lifecycle management process is put into place to ensure integrity and availability of the PAT method over time and to address potential risk factors that could impact the product quality and/or the product control strategy. Lifecycle management for PAT is considered continued process verification (CPV) for the method/model that was validated. An implementation strategy documents the potential mitigation steps for the identified risk factors, as well as the method acceptance criteria and how to detect and respond to outliers.

All these initiatives have inputs from CFTs which include but are not limited to members of the engagement, project implementation and validation teams, support teams such as engineering, calibration and maintenance operators, IT and local quality oversight (QA/QC). Other inputs from PAT SMEs, manufacturing and end-users are valuable in identifying and mitigating potential risk factors and developing a robust PAT lifecycle management process.

This section outlines the steps needed to make updates over time to validated/qualified methods and models as well as removal and sunseting considerations for existing documents, processes, etc.

6.1 Implementation strategy and risk assessment

Before implementation or transfer of a PAT method/model a formal RA or other RA tool such as failure mode and effects analysis (FMEA) should be completed following guidance from quality risk management and local quality organizations^{2, 12}. This RA is a key activity to review potential risk factors associated with the PAT method/model and to document a potential mitigation strategy. The RA and mitigations are documented as part of the overall lifecycle management process in the implementation strategy summary report as described in Section 6.1.3. The RA is a continuous process but should be initiated or performed before or around the same time as validation or transfer activities. It may need to be revisited after some experience/knowledge is gained from use of the method.

6.1.1 Risk assessment and addressing key risk factors

During the RA, a list of potential risk factors should be documented. Potential risk factors and mitigations are listed in Table 5, not as a complete list of potential risks that could occur and potential mitigations, but as examples. Including the appropriate teams in the RA will help ensure all risks are documented and reviewed for potential harm. Mitigation of potential risk factors should also be discussed cross-functionally with local quality and regulatory organizations making the final decision on how to proceed.

Some potential risk factors should be addressed before intended use. The instruments used for measurements should be set up with calibration/maintenance schedules appropriate to the risk, as defined in the instrument or PAT method RAs.

6.1.1.1 Addressing key risk factors

- Outlier detection set-up: safeguarding data from the instrument before it can be used by the PAT method/model
- Safeguard: periodic method verification—the cycle time of the verification is dependent upon intended use and confidence in the method (versus the offline method)
- Instrument maintenance: performance management and spare parts
- Strategy: reference method for defaults
- Other risks can be mitigated as per the information gathered in the PAT RA.

Table 5: Examples of PAT method potential risk factors and mitigation

Potential key risk factor	Potential mitigation
Training (people)	More detailed written instructions or hands-on training; include periodic training or additional advanced SME training
Instrument maintenance and calibrations (equipment)	Implement maintenance/calibration schedule, include information on activities in local instructions (SOP, WI, JA); implement software scheduler, spare parts stocking, etc.
Process/method changes	Include triggers to revisit method-validated state in implementation and lifecycle management plan
Raw material/supplier changes	Include triggers to revisit method-validated state in implementation and lifecycle management plan. Manage in CC process or CFT review for impact
Instrument variability and drift	Include outlier detection methodology and triggers in the implementation and lifecycle management plan
Reference PAT method changes	Demonstrate equivalency to replacement reference analytical method
Modeling software changes	Demonstrate equivalency to replacement software method
Change to acceptance criteria	Include triggers to revisit method-validated state in implementation and lifecycle management plan
Changes to data used in model creation/validation	Include triggers to revisit method-validated state in implementation and lifecycle management plan
Changes to model diagnostics/monitoring thresholds	Include triggers to revisit method-validated state in implementation and lifecycle management plan

6.1.2 Defining outlier detection limit and acceptance criteria

Potential risk factors and their mitigation strategies have an impact on the lifecycle management of the PAT method/model and help inform acceptance criteria limits (wide or narrow) and defining outlier detection limits and responses.

Outlier detection limits are used to identify where the model is not performing as expected or some lots/measurements are not representative (some statistical examples: Hotelling T Square (HT2), DModx and X_Residuals). The outlier detection limits are based on validation results as well as the competence and robustness or validity of the offline data. Defined by the performance of the methods and knowledge gained from the development through validation and use, these limits are used to refine the applicability of the model. Outlier detection limits can be updated over time as the method is used and as more experience is gained with the data. It should be documented in qualification/validation reports, implementation strategy and any lifecycle management documents for the method. A justification should be included if the outlier detection limit is updated. The outlier detection method should also be reviewed over time based on

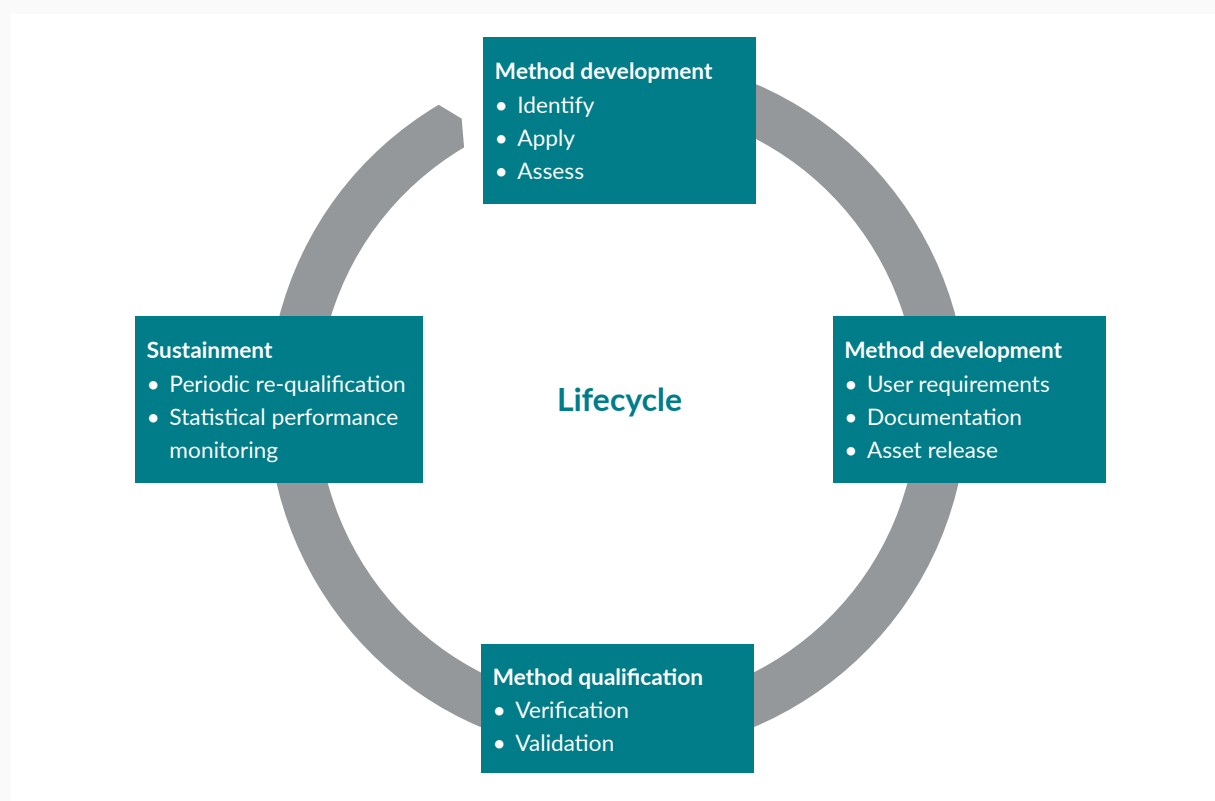
the frequency of the implementation strategy and can include any CPV or statistical process control (SPC). The responses to an outlier should be documented in the implementation strategy based on criticality of the measurement. Deviations, retesting or other strategies can be considered as part of the response to the outlier detection limit being exceeded. Consider the frequency of events as part of your response strategy, many events that continue to trigger a control action and preventative actions (CAPA) or other procedural update to consider if the limits are appropriate or if the manufacturing process may have changed. Experience with outliers can also be used to justify any system for removing outliers from your data set. There should be instructions if your method is not performing as expected based on outlier detection and how to revert to other tests/methods.

Acceptance criteria for models are used to measure against a known set point/value for an offline analysis performed at a defined frequency to monitor the performance of the model. This occurs after the operation timeframe defined in the implementation strategy. For example, this could be set to verify the online data against offline samples every three months for a method used weekly to biweekly and the acceptance criteria could be set to two to three times the PAT accuracy close to the reference method or reviewed more frequently for a

continuous process. They should be set with information on the reference method and agreed by the operations team. Acceptance criteria are not used for ongoing online review of methods but should be considered during discussions on continuous verification of the model and justification documented. Some at-line methods may not be applicable for acceptance criteria verification and outlier detections should still be used to monitor the method.

If acceptance criteria have failed, more data should be collected to verify the failure. The default method (offline or other) should be used, the online/at-line method will monitor and collect data for an additional one to two batches to update the model. The updated model will be verified as per Section 6.2 or other procedures in the implementation strategy document. Then, it can be put back into use once qualified or validated.

Figure 5: Lifecycle management



6.1.3 Method implementation strategy summary report

After the method validation is completed, a method implementation strategy summary report is issued that should include information/reference from the RA, the method development report, the method validation execution and the lifecycle maintenance of the PAT method. This report can be used to interface

with regulatory agencies and can include or reference different GMP documents such as PPQ summary reports, validation summary reports, depending on local procedures. The method implementation strategy summary report can include reference to the equipment qualification or other information needed for use of instruments and methods after validation is completed. The mitigation of key risk factors

for long-term utilization of the method should be included in the summary report. The summary report can be re-used over time for the same technology or referenced for method transfers. Considerations regarding differences in the gap assessment can be consulted to see if the existing information can be used for method transfers. It could be rolled up to a larger technology implementation strategy if there are enough commonalities or technologies used.

Lifecycle maintenance and strategy should be included in the implementation strategy summary report including outlier detection limits and acceptance criteria, and how they are being monitored and reacted to.

6.2 Updates to validated methods/models

6.2.1 Considerations for model-based methods

It is not necessary to perform a full validation/qualification for model-based methods. Instead, a local site-agreeable method qualification can be performed closer to the verification. The extent of validation/qualification/verification should be defined within procedures for the PAT method and determined by quality or the RA. It can be different depending on the company or sites dependent on regulations or internal quality systems and procedures. Some triggers that can prompt a method/model update are given in Table 5.

6.2.2 Considerations for non-model-based methods

A non-model-based PAT lifecycle needs to be managed in accordance with the product maturity. A risk-based approach should be used to assess comparability based on the lifecycle stage. During development and pre-commercialization, in alignment with ICH Q8¹ and ICH Q11⁴, there should be sufficient understanding of the technology to ensure that any product may be manufactured consistently and of the required quality. As no model is required for characterization, a bracketing approach may be used to demonstrate the ability of the technology to provide consistent results across the established design space. In a post-approval or commercialized phase, focus should be given to maintenance and control of established conditions (ECs) as defined in ICH Q12⁵. Use of a parameter-based approach versus a performance-based approach is based on the technology in question.

6.2.3 Method/model maintenance strategy

Based on the method verification results during routine operation use, if data analysis leads to method update, the method should then go through a qualification. During this time, the backup/offline method should be used to monitor the interim batches being manufactured. The online/at-line method should still collect data and the interim data should be used to update the method. An additional batch should be used for verification of the updated method. This verification should include the information for outlier detection and acceptance criteria as previously validated and documented in the summary report. Depending on the implementation and lifecycle management strategy a verification, qualification or validation will be required.

If passed, the model can be put into routine use. If failed, the model will need to be assessed further. There should be an investigation into the model and method including review of data, equipment, software and other factors that could cause the model to fail. After the investigation and any necessary remediation, the model can be reverified with another confirmatory batch.

A quality RA is in place that should be revisited at a frequency identified by local QA, regulatory or other guidance as per the implementation strategy. During the lifecycle of the method or model any additional risks identified or new information should be included in updates to the original RA. Key risk factors should always be considered when making changes to models and methods, including validating new methods, method transfer and any updates to qualified methods.

6.2.4 Other considerations for method lifecycle management

There are additional considerations to be taken into account if relevant to the model/method. Lessons learned can be performed to pass valuable knowledge from older methods to newer technologies. If an iterative phase approach is used, other information can be included in the summary report as triggers to move to a next phase or implementation.

6.2.5 Retirement of methods/models

If methods/models need to be retired, a written justification should be provided to impacted groups and local guidance should be followed. If an online method is being removed, an alternative PAT or offline method needs to be put into place before retirement. Consideration must be given to the impact of removing methods/models to the process, data, documentation, etc. before the final sunset.

7.0

Regulatory landscape

Implementation of PAT tools should be encouraged during the development phase of the product as it helps collect critical data during the early phases of the product lifecycle prior to commercialization.

Important guidelines include ICH Q8 *Pharmaceutical Development*¹, ICH Q11 *Development and Manufacture of Drug Substances*⁴ and ICH Q14 *Analytical Procedure Development*⁶. The ICH Q14 is intended to complement ICH Q2 *Validation of Analytical Procedures*³. Guideline ICH Q2 discusses the characteristics for consideration (e.g. accuracy, precision, specificity) during the validation of analytical procedures as part of registration applications submitted within the

European Commission, Japan and the US. The objective of validation is to demonstrate that the analytical procedure is suitable for its intended purpose. On the other hand, ICH Q14 describes science- and risk-based approaches for developing and maintaining analytical procedures suitable for the assessment of the quality of drug substance and drug product. ICH Q14 also defines the minimal and enhanced approaches to analytical procedure development (Table 6).

Table 6: The minimal approach and enhanced approach for analytical procedure development according to ICH Q14

Minimal approach for analytical procedure development	Enhanced approach for analytical procedure development
• Identifying attributes to be tested • Selecting an appropriate analytical technology • Performing development studies to evaluate analytical procedure performance characteristics (e.g. specificity, accuracy) over the reportable range (including the calibration model, limits at lower and/or higher range end) and robustness • Defining and documenting the analytical procedure description and the analytical procedure control strategy (e.g. parameter settings and system suitability).	All steps of the minimal approach including one or more of the elements below: • Evaluation of the sample properties and expected variability of the sample • Defining the anticipated performance criteria and documenting them in an analytical target profile (ATP) • Conducting RA and evaluating prior knowledge to identify the critical analytical procedure parameters • Conducting uni- or multivariate experiments to explore ranges and interactions between identified analytical procedure parameters • Defining an analytical procedure control strategy based on enhanced procedure understanding including set points and/or ranges for relevant analytical procedure parameters ensuring adherence to performance criteria.

The near-infrared spectroscopy (NIRS) guidance of the FDA and the European Medicines Agency (EMA) can be applied to similar PAT, for example, Raman^{15, 16}. The guidance of the FDA on NIRS applies to PAT applications in manufacturing and analysis of pharmaceuticals. This may include raw materials, in-process materials and intermediates and finished products¹⁵. According to the FDA guidance on NIRS, an applicant must provide information about every NIR analytical procedure that is included in its commercial control strategy, as well as information about the development and validation of these procedures. In addition, for the lifecycle maintenance of models associated with NIR analytical procedures, applicants should provide high-level summaries of their plans¹⁵.

The qualification and validation of PAT should be conducted in accordance with ICH Q2(R1)³, as with traditional analytical equipment qualification and validation. The ICH Q2(R2)⁷ provides recommendations on how to derive and evaluate the diverse validation tests, and contains a collection of terms with definitions to bridge the differences between various compendia and documents of the ICH member regulatory agencies.

For validation, any issues during incorporation of PAT into the manufacturing process, such as probe fouling and cleaning validation for complex continuous manufacturing, should be addressed. The American Society for Testing and Materials (ASTM) standard E2898-20a⁸, covers the validation of at-line, online or inline PAT methods for both drug substance and drug product measurements, and gives examples on how to incorporate these aspects of PAT method validation into a documented RA. In ASTM standard E2476-22⁹, additionally, the application of this risk-based approach for PAT method validation is described with regards to the impact to product quality.

7.1 Initial registration

ICH Q8(R2)¹ and ICH Q11⁴ recommend using enhanced QbD approaches with PAT as enabling technology during drug substance and drug product development. Use of statistical process control methods during the manufacturing process is also recommended. PAT tools should be considered with appropriate feedforward and/or feedback controls. It is recommended that manufacturers developing a PAT-enabled process consider a scientific, risk-based approach relevant to the intended use of an analyzer for a specific process and its utility for understanding and controlling the process².

ICH Q8 (R2)¹ suggests knowledge gained through the application of scientific approaches and quality risk management (ICH Q9 (R1), ICH Q10)^{10, 11} during the development of a product and its manufacturing process should be presented during filing in the Pharmaceutical Development section 3.2.P.2 of a regulatory submission in the ICH M4 Common Technical Document (CTD) format (ICH M4 and ICH M4 (R4))^{12, 13}. This section is first prepared for the initial marketing application (IMA) which can then be updated to support new knowledge gained over the lifecycle of a product⁵. The Pharmaceutical Development section is intended to provide a comprehensive understanding of the product and manufacturing process for reviewers and inspectors. The guidance states that demonstration of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches. Based on the level of relevant scientific knowledge provided, the degree of regulatory flexibility will be predicated.

The analytical procedure description should be included in the ICH M4 Quality (M4Q) CTD section 3.2.S.4.2 for drug substance or section 3.2.P.5.2 for drug product⁶. Validation data and supportive information needed to justify the analytical procedure control strategy should be included in the CTD section 3.2.S.4.3 for drug substance or section 3.2.P.5.3 for drug product. The process development section of the dossier (e.g. 3.2.S.2.6 or 3.2.P.2) should include the model development information for multivariate models used as part of manufacturing development studies or for IPCs or tests⁶.

PAT used in a control strategy for drug substance CQAs can be implemented to ensure quality of the drug substance through upstream controls. A control strategy is defined as a planned set of controls, derived from current product and process understanding, that assures process performance and product quality¹¹. A control strategy using PAT can include, for example, in-process testing or use of measurements of process parameters and/or in-process material attributes that are predictive of a drug substance CQA. PAT can also be used to enhance control of the process and maintain output quality⁴. Analytical procedures used as part of the control strategy should be included in relevant CTD sections (e.g. 3.2.S.2, 3.2.P.3 and 3.2.P.4). In addition, for submission, a summary of the overall control strategy should ideally explain how the individual elements of the control strategy work together to assure drug substance quality^{4, 12}. In the ICH M4Q, it is recommended that the individual elements of the reported control strategy are provided in a marketing application in the appropriate sections of a submission, as for example:

- Description of Manufacturing Process and Process Controls (3.2.S.2.2); or
- Control of Materials (3.2.S.2.3).

To design a quality product and its manufacturing process to consistently deliver the intended performance of the product should be the purpose of pharmaceutical development. The establishment of the design space, specifications and manufacturing controls should be supported by scientific understanding from

information and knowledge gained from pharmaceutical development studies and manufacturing experience. The applicant can choose to propose the design space which will be subject to regulatory assessment and approval. It will not be a change when working within the design space. However, movement out of the design space will be a change and would normally initiate a regulatory post-approval change process¹.

Additionally, the applicant can choose to conduct pharmaceutical development studies that can lead to an enhanced knowledge of product performance over a wider range of material attributes, processing options and process parameters. Demonstration of a higher degree of understanding of material attributes, manufacturing processes and their controls by inclusion of this additional information in the Pharmaceutical Development section will facilitate establishment of an expanded design space. In these situations, opportunities exist to develop more flexible regulatory approaches, for example, to facilitate:

- Risk-based regulatory decisions (reviews and inspections)
- Manufacturing process improvements, within the approved design space described in the dossier, without further regulatory review
- Reduction of post-approval submissions
- Real-time QC, leading to end product release testing.

This expanded understanding can be gained by application of, for example, formal experimental designs, PAT and/or prior knowledge¹.

7.2 Registration of a PAT model

A strategy for regulatory submission and lifecycle management of the PAT models will depend on the impact of the model on the product control strategy and the impact of the model changes on product quality and/or the ECs as defined in ICH Q12⁵.

The regulatory expectation on validation and documentation increases as the potential impact of the model on quality increases (Table 7). Based on long-term intent of a model and to facilitate its end use, a company can decide to increase the validation and documentation requirements at an earlier phase of analytical development. Similarly, qualification activities may be performed earlier for CMC deliverables.

Table 7: Model validation and documentation expectations

Category	Impact level		
	Low	Medium	High
Model use	Product or process development	Ensure consistent product quality, but model predictions are not the sole indicator of product quality	Prediction of product quality, where model predictions are significant indicators of product quality
Examples	Process optimization, process scale-up and formulation	IPC models, design space models; PAT is used for process control, but is not part of the commercial control strategy	Chemometric models for pharmaceutical product assay; PAT is used for process control which is part of the registered control strategy
Validation	No formal validation; method development will not include all variability expected in commercial manufacturing	Limited validation may be appropriate	Full model validation is done following relevant guidelines
Documentation	History of how models were developed and used to guide process development	Capture of model assumptions; summary of model inputs and outputs; relevant model equations (e.g. for mechanistic models) either in the submission or via a reference; statistical analysis where appropriate; a comparison of model predictions with measured data; and a discussion of how the other elements in the control strategy help mitigate uncertainty in the model, if appropriate	Data and prior knowledge (e.g. for established first-principles-driven models), such as model assumptions; appropriateness of the sample size, number and distribution of samples; data pretreatment; justification for variable selection; model inputs and outputs; model equations; statistical analysis of data showing fit and prediction ability; rationale for setting of model acceptance criteria; model validation (internal and external); and a general discussion of approaches for model verification during the lifecycle

PAT methods including the key aspects (parameters), validation outcome and performance should be included as part of the PAT methods submission (Section 5.0). Lifecycle management should be in place in the local implementation plan to ensure reliable and robust application of PAT methods for routine use.

Based on regulatory guidance, low- and medium-impact models are not registered with the national regulatory agencies (NRAs) but are fully managed through the license holder's pharmaceutical quality system (PQS). However, high-impact models are validated and registered, and changes are reported based on the impact of the change on the product quality and/or the ECs²⁰.

7.3 Regulatory filing strategy

Submission strategy

The submission strategy will vary based on the timing of introduction of the technology. If PAT is being introduced during the early phases as an additional method, validation of the technology will suffice. When existing methodology needs to be replaced by PAT, comparability of the PAT methodology against the existing analytical method will be required in addition to validation of the PAT method.

Early phase—PAT will be introduced as an additional method in the IND or investigational medicinal product dossier (IMPD) in the analytical sections. This would need limited validation data as the product is in the early development phase. Comparability data will be generated by comparing the analytical data with the

PAT-generated data. Once comparability is completed, the existing analytical method can be replaced once the submission is approved.

IND/IMPD application—It is standard practice to use three batches for comparability. Three batches of product analyzed via PAT technology are compared to the same batches analyzed via the standard analytical methodology. Comparability data captured along with the validation of the PAT technology is required.

Agency guidance—Contact health authorities for advice before proceeding with submission, especially when clarification is required on the approach to take:

- Type C meetings—FDA¹⁷
- Scientific advice—EMA¹⁸
- Rest of the world—local affiliates will communicate via emails, telecommunication or meeting.

Discussion and conclusions

The adoption of PAT is a collective journey that necessitates a broad spectrum of expertise within an organization. It is essential to involve QA, regulatory and other advisory teams from the outset and maintain regular engagement to avoid potential roadblocks, unnecessary reiterations and delays. The implementation of PAT should be driven by a clear business case or a specific problem, rather than the appeal of new technology. Knowledge management plays a pivotal role, spanning from the initial problem statement to lifecycle management.

The landscape of PAT is evolving rapidly with the miniaturization of instruments, analyzers accounting for more variables and the increasing use of ML and artificial intelligence (AI) in modeling. In this context, it can be challenging for pharmaceutical and biopharmaceutical companies to discern the optimal path for PAT implementation. PAT is a system for designing, analyzing and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes. It represents the medium for digitization, continuous improvement and operational excellence within the industry. This system facilitates advanced process controls, QbD and results in a well-understood process that can increase throughput, utilization, efficiency, risk mitigation, process and product quality, and data integrity. It ensures control and monitoring of quality attributes, a prerequisite for RTRT, and is a critical step on the digital transformation roadmap toward pharma 4.0. Each organization, vendor and technology will face unique challenges related to data management, organizational structure, internal support staff/resources and funding.

Historically, PAT was introduced by development scientists and engineers, but this approach has seen its challenges. It is critical that a validated business case with a specific problem statement should be developed with input from key business stakeholders including process development, manufacturing, engineering, automation, QA, IS, regulatory and business analysts. Ideally, the problem statement will address an operational issue such as gaps in process knowledge, inconsistent quality attributes, process consistency and robustness, and will be supported by a CFT with executive sponsorship. This CFT will enable a better understanding of the full scope, benefit and process to circumvent future obstacles in project implementation by leveraging the BioPhorum roadmap.

The adoption of real-time data acquisition, as enabled by PAT, has numerous benefits. The rich data sets provided as early as proof-of-concept and development stages improve the quality of process design by revealing process changes as they occur and aiding in the identification of factors affecting PQAs. This, in turn, allows for more precise IPC, acceptance criteria and parameter classifications. PAT adoption also assists statisticians and modelers in creating *in silico* models and streamlines a risk-based process validation approach.

While in development, the CFT will be able to assess data integrity, training and knowledge base requirements, and determine digital infrastructure needs to prepare for deployment to GMP operations. The business case and regulatory strategy will be revisited and refined as the program costs and technology capabilities become clearer. Before moving into deployment, demonstration and testing of the method (model) should be conducted. The analytical methods and data collection systems should be integrated with the process control system, and procedures for data collection, storage and analysis should be well established. This may involve training personnel on how to use the method, integrating the data acquisition system into the manufacturing process and establishing protocols for addressing any deviations from the target CPPs and CQAs.

PAT adoption can also lead to more efficient execution of process design and tech transfer activities, including the development of process-related calculations and *in silico* models, tabulation of process parameters with targets, set points, operating ranges, acceptable ranges including process control action and rejection limits, and parameter classifications.

Development phase activities occur in a less rigorously controlled environment and should include a framework considering risk understanding, data integrity assessments and migration planning holistically. The handoff to commercial-facing teams culminates in an ORE to identify any remaining gaps or changes that may be required. This exercise and the inclusion of vendor SMEs, company development staff and temporary infrastructure deployments result in networking and digital robustness of the PAT MC plan and create a comprehensive package. Decision points and knowledge management should be maintained throughout the process to facilitate scaling and regulatory alignment. The framework establishes long-term maintenance of the digital packages (models), method validation, data governance/integrity and lifecycle management of the program. The established methodology is iterated at each phase containing touch points for continuous improvement and allows for QA, regulatory and peripheral/secondary/tertiary team members to properly steer the primary stakeholders and decision-makers.

The implementation of PAT is not a solitary endeavor, but rather a collaborative effort that requires a diverse range of expertise across an organization. It is crucial to engage with QA, regulatory and other advisory teams early and frequently throughout the process to circumvent potential obstacles, unnecessary rework and delays. PAT should be implemented with a clear business case or to address a specific problem, rather than being driven by the allure of new technology. Knowledge management is a key component, extending from the initial problem statement through to lifecycle management.

Risk identification, mitigation and documentation are essential aspects of the process, and these risks should be revisited at each stage and when circumstances change. Lifecycle management is necessary to ensure the compliance and performance of the method over time. This involves developing an implementation strategy and defining how it will be implemented and maintained before deployment.

It is important not to let the pursuit of perfection hinder progress. A phased implementation approach may be considered, starting with using the tool for information only, and gradually moving into more complex or automated use.

The implementation of PAT tools is highly encouraged during the early and development phase of a product as it aids in the collection of critical data prior to commercialization. The submission strategy for PAT varies based on the timing of the technology's introduction. If introduced during the early phases as an additional method, validation of the technology will suffice. However, if PAT is to replace an existing methodology, comparability of the PAT methodology against the existing analytical method will be required in addition to validation. These comparability data are generated by comparing the analytical data with the PAT-generated data. The registration and lifecycle management of PAT models depend on their impact on the product control strategy and the impact of model changes on product quality and/or the ECs. High-impact models are validated and registered, and changes are reported based on the impact of the change on the product quality and/or the ECs.

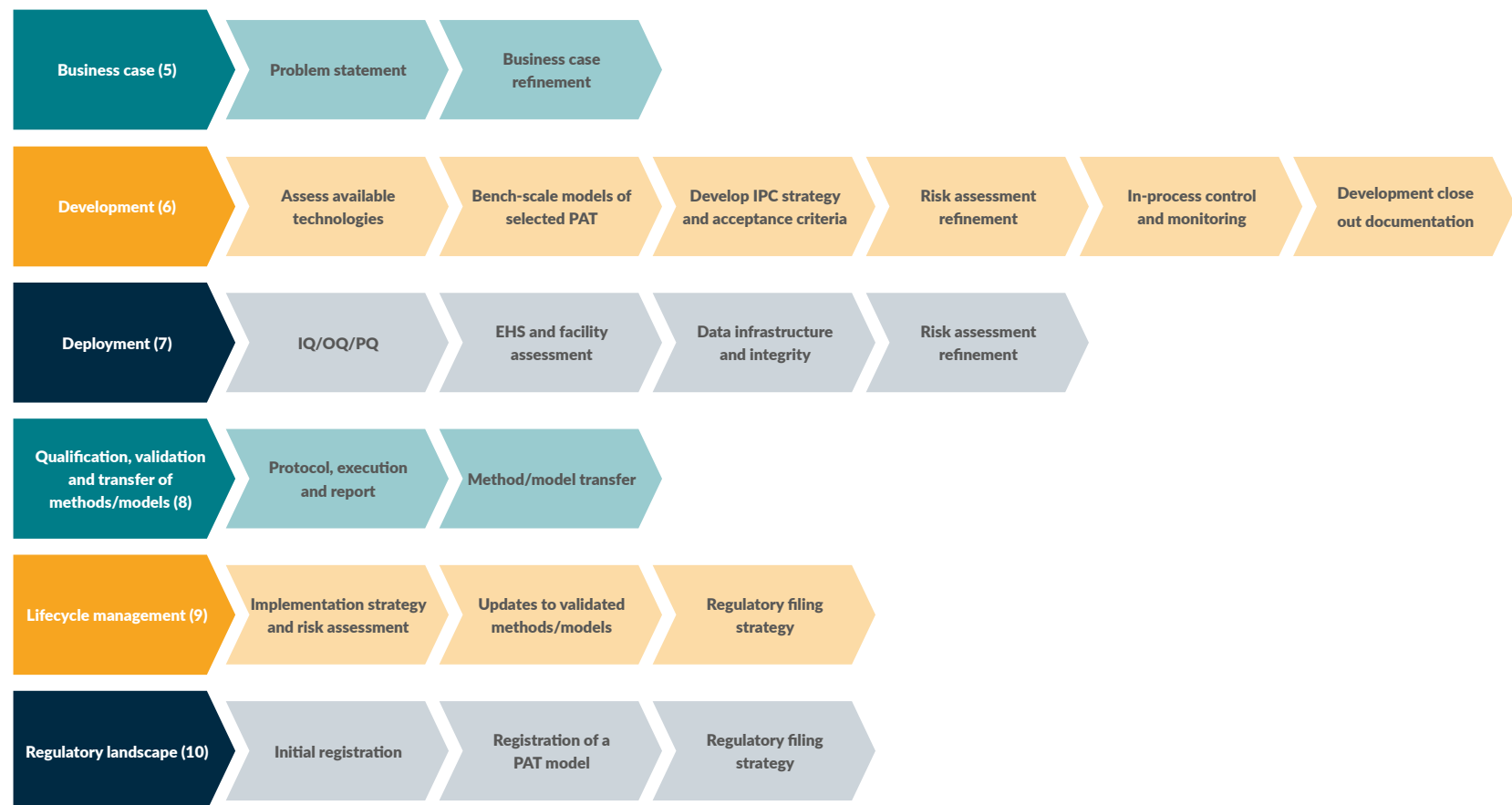
In line with the ICH Q2³, ICH Q8 (R2)¹, ICH Q11⁴, ICH Q14⁶ and the FDA guidance for industry document *PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*², PAT is viewed as a system for designing, analyzing and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes, with the aim of ensuring final product quality. These guidelines recommend the use of enhanced QbD approaches enabled by PAT technology during drug substance and drug product development, and the use of statistical process control methods during the manufacturing process. They also provide recommendations on how to derive and evaluate diverse validation tests and bridge the differences between various compendia and documents of the ICH member regulatory agencies.

Manufacturers developing a PAT-enabled process should consider a scientific, risk-based approach relevant to the intended use of an analyzer for a specific process and its utility for understanding and controlling of the process. ASTM standards E2898-20a⁸ and E2476-22⁹ cover the validation of at-line, online or inline PAT methods for both drug substance and drug product measurements, and describe the application of a risk-based approach for PAT method validation with regards to the impact on product quality.

In conclusion, the adoption of PAT is a strategic move that can bring significant benefits to the pharmaceutical industry. However, it requires careful planning, cross-functional collaboration and a clear business case to ensure its successful implementation.

Appendix

PAT framework



Glossary

Term	Definition
AI	Artificial intelligence
ANOVA	Analysis of variance
API	Active product ingredient
ASTM	American Society for Testing and Materials
ATP	Analytical target profile
BLA	Biologics license application
BOM	Bill of material
CAPA	Control actions and preventative actions
CC	Change control
CFT	Cross-functional team
CMC	Chemistry, manufacturing and controls
CPP	Critical process parameter
CPV	Continued process verification
CQA	Critical quality attribute
CTA	Clinical trial application
CTD	Common technical document
DoE	Design of experiment
ECs	Established conditions
EMA	European Medicines Agency
FDA	Food and Drug Administration
FMEA	Failure mode and effects analysis
GMP	Good manufacturing practice
g/L	Grams per liter
GXP	Good practice
HT2	Hotelling T Square
ICH	International Council for Harmonisation
IMA	Initial marketing authorization
IMPD	Investigational medicinal product dossier
IND	Investigational new drug application
IPC	In-process control
IQOQ	Installation qualification/operational qualification
IS	Information sciences

Term	Definition
IT	Information technologies
JA	Job aid
LCL/UCL	Lower/upper control limit
MAA	Marketing authorization application
ML	Machine learning
MSAT	Manufacturing science and analytical technology
NDA	New drug application
NIRS	Near-infrared spectroscopy
NRA	National regulatory agencies
ORE	Operational readiness exercise
PAT	Process analytic technology
PAT MC	Process analytic technology monitoring and control
PI	Performance indicator
PPQ	Process performance qualification
PQ	Performance qualification
PQA	Product quality attribute
PQS	Pharmaceutical quality system
QA	Quality assurance
QC	Quality control
QbD	Quality by design
RA	Risk assessment
RMSEP	Root-mean square error of prediction
ROI	Return on investment
RSD	Relative standard deviation
RTRT	Real-time release testing
SME	Subject matter expert
SPC	Statistical process control
SOPs	Standard operating procedures
SSTs	System suitability tests
TOST	Two one-sided t-tests
TRE	Testing readiness exercise
WIs	Work instructions

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