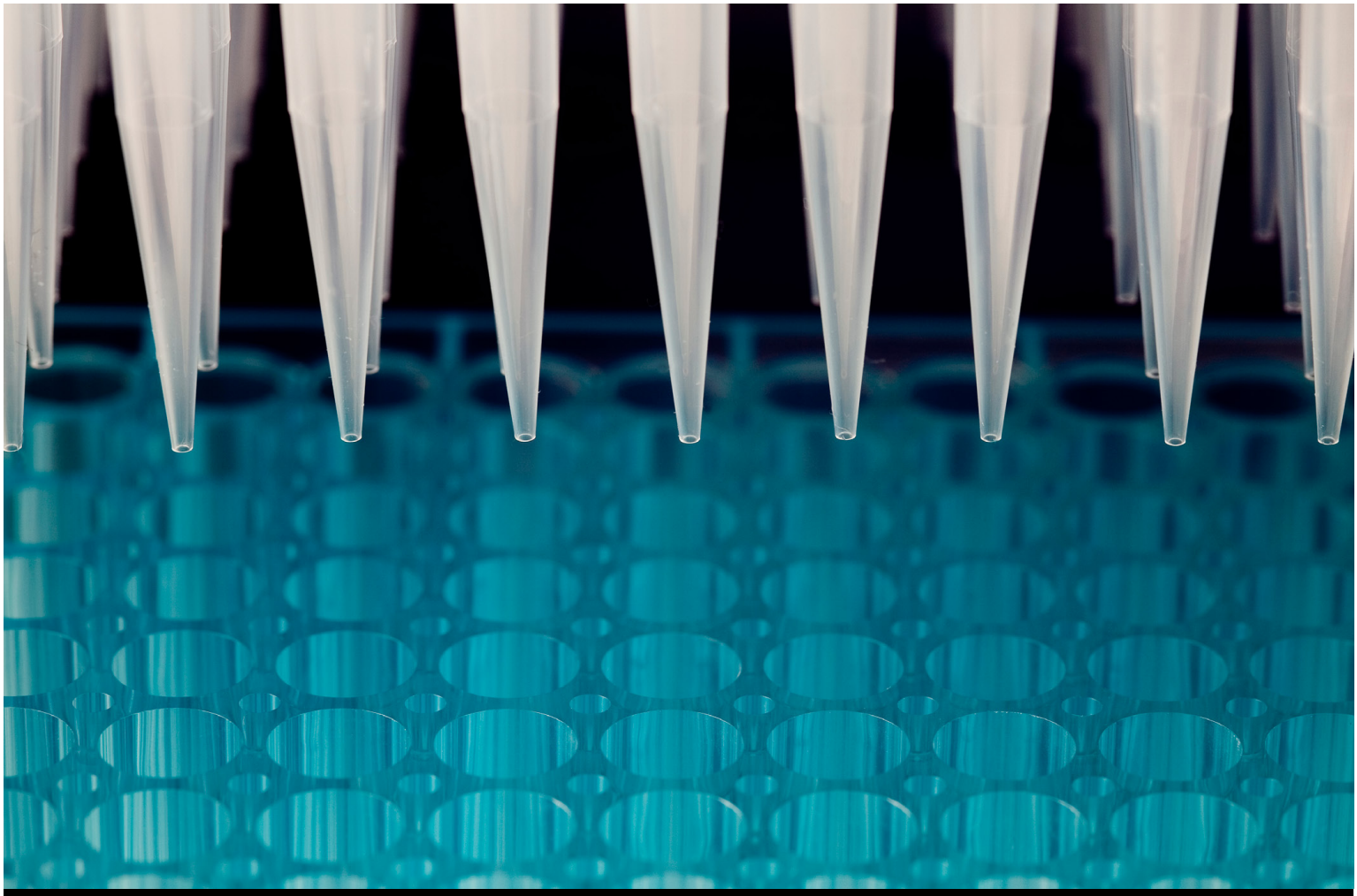

Value Paper

Are you PAT and QbD Ready? Get up to speed

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PAT and Quality-by-Design

As PAT and Quality -by-Design (QbD) become an integral part of the regulatory framework, automation group ABB argues more companies need to be up to speed.

The regulatory landscape is currently undergoing a major shift and re-orientation brought about by the FDA's initiative 'Pharmaceutical cGMPs for the 21st Century' launched in 2002. This initiative gave birth to the Process Analytical Technology (PAT) framework for enhancing process understanding throughout the product lifecycle, which paves the way for process monitoring, verification and control and for real-time release in commercial manufacturing.[1]

Today, PAT is much discussed in manufacturing: however, to achieve the desired state of quality-by-design (QbD) the FDA expects PAT process monitoring at the commercial scale to reflect knowledge gained in pharmaceutical development and set out in the regulatory submission.

ICH Q8 (Pharmaceutical development) is one of three new guidelines 2, 3, 4 issued by the International Conference on Harmonisation (ICH), which facilitate PAT. These guidelines are in the process of being adopted by the US FDA and the EMEA.

Quality-by-design

ICH Q8 (Pharmaceutical Development) provides new options for the inclusion of various types of studies in the Common Technical D9ocument (CTD) format. The purpose of a QbD dossier is to allow the manufacturer to demonstrate an enhanced knowledge base and would expect to see evidence of the use of formal Design of Experiments (DoE) and PAT to gain this in-depth knowledge. Studies on the physicochemical and biological properties of the drug substance, on the characteristics of the excipient and how these affect drug performance and on formulation development are used to determine:

- Critical to quality attributes (CQA)
- The design space within which the process will operate
- Raw material, intermediary and end-product specifications

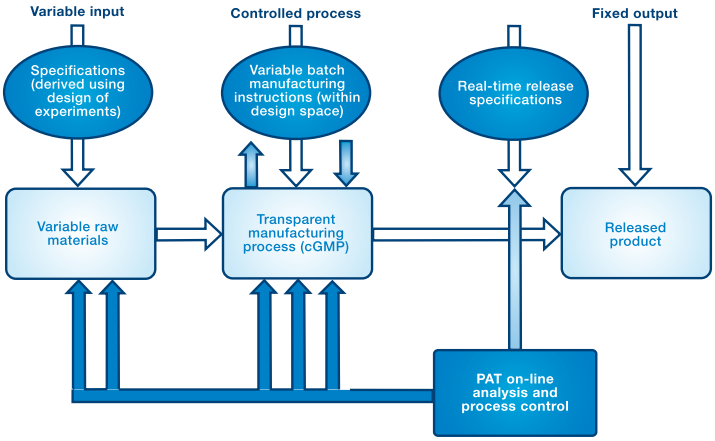

Figure 1 PAT - Science and risk - based approach to cGMP's

Pat approach:

- **Single or multi-dimensional material specifications as required.**
- **Variable process operations (controlled sequencing and automation with design space)**
- **Real-time monitoring and control of product quality using on-line analysis**
- **Continuous process verification**
- **Reduced or eliminated off-line product testing**

Process development studies allow the determination of process monitoring and control strategies for manufacturing and are used to determine:

- Critical process parameters (CPP)
- The robustness (against failure) of the processes within the defined process control limits
- The process validation strategy (3 batches no longer required, can be continuous process verification)
- Further studies that will form the basis of continuous process improvement during the product's lifecycle

Having submitted a QbD dossier based on ICH Q8 there is no change to compliance with the cGMP regulations in manufacturing, but there is in the way the regulations are met (see Figure 1).

Instant payback

The immediate benefits of QbD for the manufacturer are more predictable scale-up effects, the ability to bring new production sites on-line faster and to understand and avoid manufacturing failures. In addition, manufacturers who implement a risk-based quality management approach (ICH Q9) and an appropriate quality management system (ICH Q10)6 can expect further benefits from:

- Effective quality processes where the level of effort, formality and documentation is proportional to risk
- Process validation based on a product life-cycle approach 7 (see Figure 2)
- Efficient manufacturing optimized through continuous improvement
- Reduction in end-product testing and realization of real-time release

The FDA has undertaken a number of internal reorganizations and has changed significantly its own internal processes to ensure a risk-based approach to Chemistry and Manufacturing Controls (CMC) review and cGMP inspections, 3,8 Part of the rationale for these changes is to use limited agency personnel effectively, reduce delays and increase the speed of reviews and inspections. For example, the level of scrutiny of a submitted dossier will depend on the perceived risk against a number of criteria. Similarly, sites will be prioritized for inspections based on a risk assessment and the frequency of inspections will also take into account the identified risks.

Due to these new risk-based regulatory processes, manufacturers with a quality management system based on a risk-based quality management approach can also benefit from:

- Increased efficiency in regulatory review processes
- Being identified as a low risk manufacturer by the regulator (potentially fewer inspections)
- Facilitation of post-approval changes with reduced regulatory burden, e.g. changes allowed with QMS change process or category of changes down-graded on regulator's risk assessment

These benefits all translate into financial gains through decreased time to market for new drugs, increased throughput and yield and reduced waste and end product testing. In one case study, even a relatively simple PAT application in which a dryer monitor was used to analyse the moisture content and control drying time on a single unit operation delivered US$55m (38m) if savings for one company in the first year of operation.

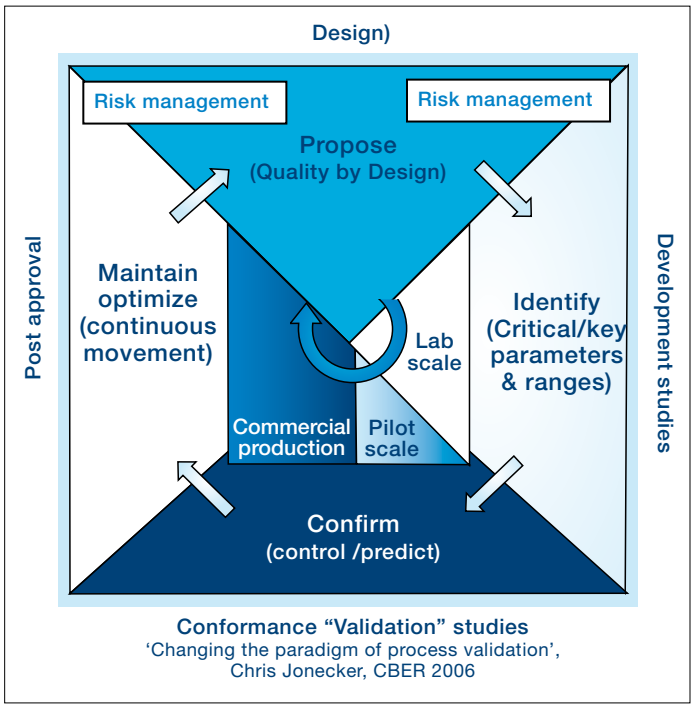

Figure 2 A lifecycle approach to process validation

Necessary changes

The PAT framework and the new ICH guidelines highlight the importance of pharmaceutical development as the foundation for all subsequent product lifecycle phases. PAT does not 'belong' to manufacturing but should be of equal interest to specialists working in the development environment. The demands of QbD and Pat will inevitably change the working environment for professionals in both areas and most critically for quality professionals (see Figure 3).

There are four key areas of change worth considering in detail: cultural change, changes to 'how things are done around here' (business processes), the introduction of new technologies and changes to the flow of data.

Any company planning to embrace QbD and PAT must be prepared for this to affect existing organizational culture across and within sites. PAT and QbD maybe seen by management as purely 'technical' issues, but failure to address cultural issues at an early stage is one of the major reasons for PAT project failure, or at best project delays, and lack of acceptance by staff.

No employee will enthusiastically embrace a programme, which they perceive may threaten their position or influence within the organization. Other consequences may be more subtle but also more damaging. Examples of the cultural changes that need to be actively addressed are:

- Interaction with the regulator no longer limited to regulatory affairs specialists
- Significant increase in dialogue between product development and manufacturing divisions and in multi-disciplinary team working
- Redefinition of roles and responsibilities, particularly for quality professionals, as end-product testing decreases in importance but other quality assurance activities become more important
- Need to learn and apply new skills and develop new competencies in new measurement technologies and multi-variate analysis and process modeling techniques

Business processes

The second area of change deals with the company's business processes. Typical areas where new business processes will need to be defined are:

- Planning and executing a QbD development programme, and compiling a QbD dossier
- The application of risk-based quality management principles in decision making processes
- Creating PAT-compatible specifications based on a multi dimensional design space
- Science and risk-based justification of novel analytical methods and process models and their verification as a process is scaled up
- Change control of analytical methods and process control algorithms that se models based on multi-variate statistics or other innovative techniques

There is much potential for wasted effort if new processes are not defined in preparation for the new QbD and PAT approach. For example, unspoken assumptions and gaps in documented responsibilities may lead to lack of clarity about the degree of rigour and level of scientific evidence (and raw data in electronic format), with needs to be provided and documented at each stage in the development project. This can be seen in particular as analytical methods based on statistical modeling techniques are transferred between development and manufacturing.

Clear procedures need to be in place specifying how, by whom and in what frequency such models need to be reviewed, revalidated and where appropriate updated.

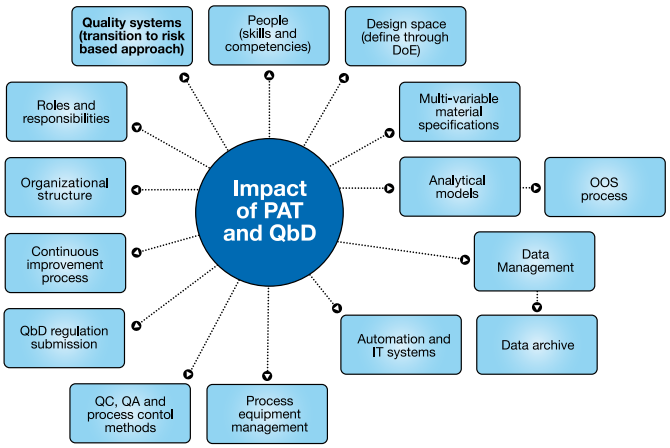

Figure 3 PAT and QbD are not business as usual.

The roles and responsibilities for processes affecting quality should clearly set out when quality professionals need to be involved. Examples of critical processes are Continuous Process Verification, Change control and Corrective & Preventative Action.

The aim is to avoid the bureaucratic deadlock caused by a 'one size fits all' approach to quality but at the same time ensuring unjustifiable project short cuts are not made due to time pressures and finance constraints.

Another pitfall commonly made is inadvertently to fail to take into account information held by other groups when making decisions affecting quality. It would be highly inappropriate, for example, for engineering decisions with a possible effect on the process performance (e.g. affecting the physicochemical attributes of the end product), or on on-line measurement technologies, their associated analytical models and any related process control mechanisms to be taken without reviews taking place with relevant experts in these areas.

New technologies

The third area of chance is the introduction of new technologies – one of the central ideas behind PAT. Different approaches will suit different organizations, depending on their goals and whether PAT is being introduces for existing or new products. Following a QbD approach, the type of on-line analytical measurement required is determined based on the CQAs and CPPs

identified during pharmaceutical development; the analytical equipment tested during this phase and moves with the process into pilot production and into commercial manufacturing.

The analytical technologies being introduced on-line may be familiar or may be innovative new technologies. In both cases questions need to be asked about the number and competency of resources available to support the analytical technology and associated models.

Is there more than one employee who understands the technology and can use the modeling package to create the analytical models? How will a peer review of analytical method development take place? How are precision, accuracy and specificity defined for this analytical technology? What factors can influence the measurement (e.g. the change to technical components or process interfaces, caking of optical windows, temperature variations) and what response does the analytical system give to such changes? Is a robust contract in place with the supplier for support if there is insufficient in-house expertise? Are the quality units able to review results and make science-based judgements on validity?

These issues are critical when the analytical model is being used to control process in real time or for real-time release.

Data systems have typically grown as islands in R&D manufacturing, filling a specific niche for which they were designed. Companies hold a significant amount of 'forgotten' data about their existing products in disparate systems such as LIMS, ERP, EBR and MES but also in proprietary IT solutions. Looking to the future it is critical to the success of QbD and the concept of continuous improvement to be able to access all data linked to a particular product and process to identify the root causes of product and process performance deviations.

Any PAT and QbD initiative must therefore address the current data landscape and set out a data strategy for the future. Questions to be answered include what data to store, in what format, where, what metadata (date, time etc.) is required and how the data will be retrieved and/or archived. A single unified data system is not required but interfaces between systems are crucial and an information management tool that makes visible all related data sets is desirable.

Managing change

One tried and tested approach to reducing the threats and risks posed by a QbD and PAT initiative is to make an assessment of the 'readiness' of the organization for the changes that will follow before any technical projects are initiated.

Where the current status quo is not compatible with the proposed changes, then a series of actions are put in place that move the organization into a 'ready' state to smooth the way for technical project success. A PAT Readiness assessment typically consists of a series of workshops at senior management and at operational level. These workshops ensure that the programme's business goals are clearly defined and understood and a number of audits are carried out to determine the organization's capability when it comes to receiving the technical project and using the technology effectively.

The audits typically look at such areas as people, quality management systems, validation and change management practices, analytics, automation, data systems (R&D data systems, LIMS, ERP, MES etc.) and IT infrastructure and highlight medium and high risk areas for further action.

There is no mandatory requirement to follow a QbD or PAT approach and the cGMP regulations remain the same. However, the FDA is strongly encouraging companies to embrace these concepts with the indication that there will be both regulatory and business benefits for those bold enough to make the required changes.

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