



Making a Difference

With pharma often reluctant to make use of innovation when it comes to manufacturing, it is necessary to implement regulatory policies to encourage industry-wide adoption of novel technology. Using a Quality by Design approach can provide an answer, resulting in lower costs and shorter project timelines

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The desire to move drugs from development to market as efficiently as possible is omnipresent. However, over the years, the pharmaceutical industry has often resisted taking up new and potentially beneficial systems that could reduce time to market. Much of this has been due to uncertainty over how regulators will respond to such innovations, and how this might make development and registration processes more lengthy and/or costly, rather than improving them.

The industry's reluctance to make use of novel approaches in pharmaceutical manufacturing is viewed negatively from a public health perspective – an area that is heavily dependent upon the availability of high-quality, effective and safe medicines. It is therefore necessary to implement regulatory policies to support and encourage companies to adopt new technology, to drive drug manufacturing towards embracing innovation and ensuring pharmaceutical quality.

In August 2002, the FDA took its first steps in modernising existing regulations, with a two-year initiative known as *Pharmaceutical quality for the 21st Century: A risk-based*

approach, which set out to encourage the early adoption of technological advances and facilitate risk-based processes (1). The new guidelines included information on the principles and benefits of implementing a Quality by Design (QbD) methodology. This concept represents a paradigm shift away from an empirical and experience-based manufacturing approach, and towards a more systematic one, drawing upon scientific and quality risk management (QRM) principles to ensure a predefined product quality (2,3).

Technological Support

The need to adopt new technologies and approaches is further highlighted in the FDA guidance, *Process analytical technology (PAT) – A framework for innovative pharmaceutical development, manufacturing and quality assurance*. This framework is a “system for designing, analysing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes” (4).

The goal of PAT is to enhance understanding and control of the manufacturing process, which is consistent with the idea that quality cannot be tested into products; it should be built-in or by design. This has led to the implementation of instruments such as near-infrared and Raman spectroscopy for in-line, on-line and at-line measurements. Evaluation of the frequently large datasets generated from these measurements can now be simplified with multivariate data analysis techniques, allowing for rapid determination of predefined process end-points. These extensive datasets can be used to reduce the testing of a finished product, thereby permitting real-time release testing, which results in faster batch release – positively affecting manufacturing times and costs.

The implementation of QbD has valuable repercussions for all of those involved, as the modernised regulations help to ensure that product quality is consistently high. Companies making use of QbD and PAT will see a decrease in non-compliant batches, leading to reduced timelines and expenses. Patients will also benefit from the enhanced level of quality surrounding the development and production of their medicines, which are constantly safe and efficacious.

The QbD process commonly encompasses a number of important steps (see Figure 1, page 54):

Product Profiling

The initial step when using a QbD approach involves product profiling: the quality target product profile (QTPP) describes the design criteria for the product, providing an understanding that ensures safety and quality are considered in advance of manufacture, as well as providing a starting point for identifying the critical quality attributes (CQAs) at a later date. These early steps will likely include extensive risk-based characterisation of any active pharmaceutical ingredients (API) and excipients beyond compendial requirements – for example, particle size distribution, morphology, polymorphism, processability, hygroscopicity, and batch-to-batch or supplier-to-supplier variation.

Risk Analysis

The CQAs for the drug product are clearly defined by performing risk analyses, so that anything deemed capable of impacting on product quality can be studied and controlled. The API and excipients – both individually and in their possible combinations during formulation – are also subject to rigorous study. Finally, risk analysis is extended across the process parameters, thereby defining critical process parameters (CPPs) and identifying any influence they may have on the CQAs.

Design of Experiments

The next stage involves the design of experiments (DoE): “A structured, organised method for determining the relationships

A Brief History of QbD

QbD emphasises the importance of truly understanding both the products and the processes involved in pharmaceutical development. As well as being supported by a number of FDA initiatives, this approach is also encouraged in guidelines released by the ICH:

- 2005: ICH Q9, *Quality risk management* – Describes a systematic process for the assessment, control, communication and review of quality risks (6)
- 2008: ICH Q10, *Pharmaceutical quality systems* – Describes systems that facilitate the establishment and maintenance of a state of control for process performance and product quality (7)
- 2009: ICH Q8(R2), *Pharmaceutical development* – Describes good practices for pharmaceutical product development (5)
- 2012: ICH Q11, *Development and manufacture of drug substances* – Lends support to the development and manufacture of drug substances, differentiating them from drug products (8)
- Presently in discussion: ICH Q12, *Technical and regulatory considerations for pharmaceutical product lifecycle* (9)

Both the EMA and FDA have been actively supporting the implementation of QbD and PAT:

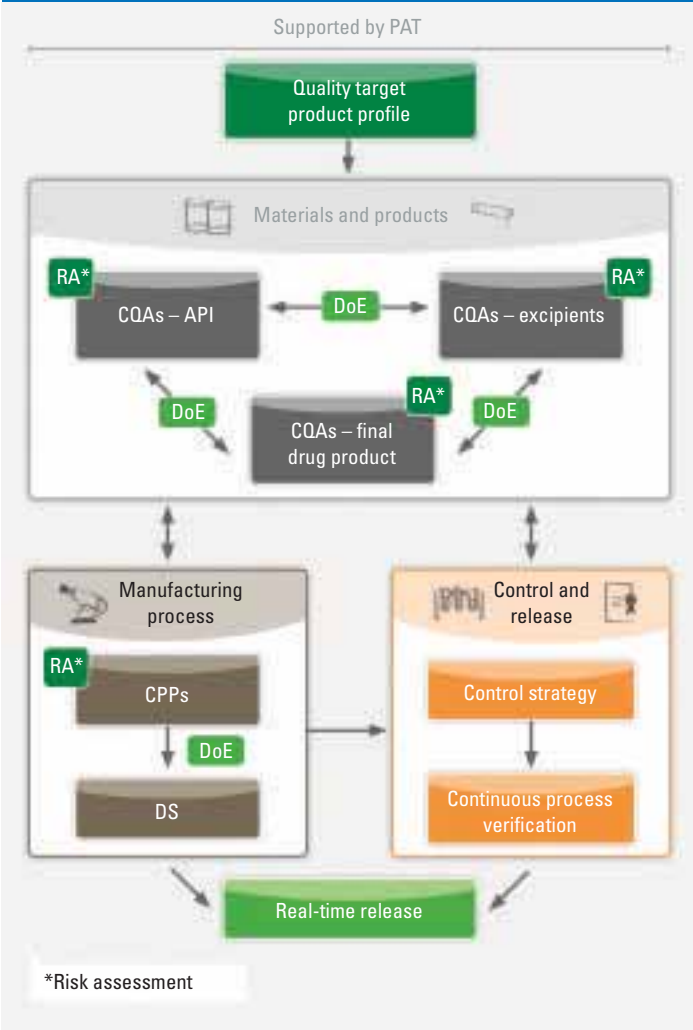
- August 2002: FDA releases *Pharmaceutical cGMPs for the 21st century – A risk-based approach* (1)
- January 2004: The EMA-PAT team is formed to ensure that the European framework and authorities are adequately prepared to conduct thorough and effective evaluation of PAT-based submissions
- March 2011: FDA and EMA initiate a joint pilot programme for QbD parallel assessment
- FDA releases QbD study examples for abbreviated new drug applications (ANDA):
 - December 2011: Quality by Design for ANDAs: An example for modified release dosage forms
 - April 2012: Quality by Design for ANDAs: An example for immediate-release dosage forms
 - March 2012: EMA releases *Guideline on real time release testing (formerly Guideline on parametric release)*
 - January 2013: The FDA Office of Generic Drugs states that it expects full QbD implementation
 - April 2014: FDA and EMA extend their pilot programme of QbD parallel assessment by two years

among factors affecting a process and its output” (5). The DoE is important for formulation development, and typically covers parameters such as compatibility studies between the API and excipients, as well as the type and ratio of excipients that help define the product composition. In addition to these, the DoE will often include planning for combinations of different dosages and product flavours in a single development. A comprehensive DoE will also evaluate the processability of the constituents to detect and minimise potential problems during later scale-up.

Design Space

The design space (DS) is the multi-dimensional combination of input variables and process parameters that have been demonstrated to provide assurance of quality. It is often considered an optional step in a QbD approach according to ICH Q8(R2), but establishing a DS can be useful in demonstrating an understanding of the product and

Figure 1: An overview of the QbD process within a manufacturing environment



process, as well as providing manufacturing and regulatory flexibility (5). An approved DS can similarly aid in avoiding the need to register any subsequent variations to the authorities.

Control Strategy

Based on the enhanced product and process understanding offered by the steps above, and in combination with QRM (CQAs and CPPs), a control strategy can be established to ensure the product is consistently produced at the desired level of quality. The control strategy can be improved with the implementation of PAT solutions, which permit the monitoring and active real-time control of the processes within the predefined limits (the DS). The identified “controls should be based on product, formulation, and process understanding and should include, at a minimum, control of the CPPs and material attributes” (5).

Validation and Verification

In an attempt to ensure product quality is maintained during all manufacturing batches without exception, it is recommended to employ continuous process verification. This is instead of traditional validation approaches, such as the

‘three golden batches’ approach, which involves the extensive analysis of the first three batches, after which the process is deemed sufficiently validated. Continuous process verification moves away from validation as a discrete exercise and instead provides an “alternative approach to validation in which manufacturing process performance is continuously monitored and evaluated” (5).

Cutting Costs

With a large number of steps and parameters, there may be some that are discouraged by the QbD approach, especially when they are likely to add time or cost penalties (or possibly both). However, this does not have to be the case, and the approach frequently reduces manufacturing and regulatory expenses throughout the production process.

Development

In the development phases, it is true that the initial workload introduced by QbD is higher than for traditional approaches, mostly due to the extensive characterisation of the API and excipients (in order to define CQAs). There is also the potential need to test more batches of API and excipients from multiple suppliers in order to screen for overall variability, minimising the risk of basing analyses on a one-off excellent batch. However, this analysis can help protect against batch-to-batch and supplier-to-supplier variability over the entire product lifecycle, adding value to the process in the long run.

While the development stage workload of a QbD approach is higher, exploring, understanding and defining the CQAs enables a science-based development process and more accurate identification of CPPs. This approach can help to minimise dead ends due to the production of unfavourable batches, and thus helps to reduce time and cost – something that is especially relevant when the API is expensive and only available in very limited quantities.

Upscale

Upscaling from the laboratory to a pilot manufacturing programme, and through to production scale, is always a major endeavour. The QbD approach is particularly valuable as it frequently results in fewer delays, a reduced need for large trial batches and fewer adjustments to the process, since the CQAs and their dependence upon CPPs are well understood. The extensive QRM performed early on also means that any potential risks associated with the manufacturing process are minimised.

Ensure Compliance

Sound knowledge of CQAs and CPPs, along with their interactions, provides vital information for successfully

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establishing a formulation and process DS that ensures compliance with the QTPP. Establishing a QTPP-compliant DS can be especially useful for avoiding the need to register later adjustments – a bureaucratic procedure that can be both time-consuming and costly. It is important to be aware of this as, depending on the type of variation, it is possible that batches will need to be quarantined until the authorities approve such a change.

Real-Time Release

The combination of DS, PAT solutions, the enhanced understanding of product and process, and the use of QRM creates a platform for making use of real-time release (RTR) testing strategies. Process and PAT data from manufacturing can be used for batch release in preference to lab analysis, while giving assurances that the product is of the intended quality. For commercial production, RTR testing can reduce the throughput time – for example, the duration between the delivery of the raw materials to the dispatch of the finished product to the customer.

Continuous Improvement

With the ability to perform continuous process verification rather than the traditional approach of assessing a number of discrete batches, not only is product quality assured, but there is also a subsequent reduction in time and effort. Additionally, continuous improvement ensures that processes tend towards optimisation and that manufacturing parameters are within acceptable limits.

Becoming the Norm

QbD is gaining importance among pharmaceutical manufacturers, for both regulatory and product quality reasons. Although the initial steps of a QbD approach require greater effort than traditional ones, this concept offers a more targeted, systematic and traceable way of product and process development. Once QbD is in place, synergies arise between existing and subsequent developments due to the ability to adopt CQAs and CPPs from comparable products. Such synergies, coupled with increasing experience of working within a QbD framework, will result in decreased development times, and thus reduce the overall time to market.

By infusing QbD – supported by PAT – into the product development process, it becomes possible to significantly

reduce manufacturing times and costs, while ensuring that products are of a quality and consistency required by regulatory bodies, healthcare practitioners and patients alike. Put simply, by adopting this approach, every stakeholder benefits – which is why it is expected that QbD will become the norm in the years ahead.

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Note

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