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QbD: Improving Pharmaceutical Development and Manufacturing Workflows to Deliver Better Patient Outcomes

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Implementing quality by design in product design and formulation and manufacturing workflows can help improve efficiency and shorten development times.

Quality has always been a key focus for the pharmaceutical industry, with drug developers traditionally using late-stage quality testing to ensure medicines are safe, reliable, and effective for patients. However, there is a growing appreciation within the industry that this approach may not be the most effective or efficient to safeguard quality. After all, quality cannot be "tested into" a product—it should be there by design from the very beginning of product development right up to the manufacturing process.

The adoption of advanced process analytical technology (PAT) throughout the pharmaceutical value chain is now enabling forward-looking companies to move away from traditional quality testing methods and instead, use systematic, data-driven strategies to deliver quality outcomes. One such concept that is widely used in other industries and has been gaining traction within the pharmaceutical industry is quality by design (QbD).

In this article, the authors discuss the advantages of adopting a QbD approach, and how this concept can be applied throughout formulation and manufacturing workflows.

Moving away from traditional product development

QbD essentially involves designing quality into workflows upfront. The concept is aligned with the "Design for Six Sigma" paradigm, originally developed in the automotive industry. It represents a radical shift away from the empirical-based methods traditionally used in product development and manufacturing and has since been implemented across a variety of other manufacturing environments.

With a QbD approach, the product's essential attributes are first defined. Risk and data analysis are then used to understand how the processes affect the product characteristics. QbD provides a robust framework for the design and implementation of processes that achieve a consistent level of quality and meet predefined standards. PAT plays a crucial role in the implementation of QbD—it allows the development and manufacturing processes to be monitored and optimized through real-time controls.

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Using this data-driven approach to improve manufacturing and development workflows can save time and money in the long run.

The main issue with late-stage quality analysis is that it only detects and removes substandard products—it doesn't prevent them from being created in the first place. As pharmaceuticals become increasingly complex, it's more important than ever that quality is designed into the products from the initial concept to ensure patient safety.

In recent years, key regulatory authorities, including FDA and the European Medicines Agency (EMA), have actively encouraged QbD and PAT through a number of initiatives. FDA recently began updating existing regulations to encourage the adoption of new analytical technologies that facilitate risk-based processes, and in the past few years, the agency has also released two QbD case studies for abbreviated new drug applications. Recognizing that QbD offers significant improvements in quality, regulatory authorities are now beginning to insist that pharmaceutical developers and manufacturers adopt QbD throughout the value chain, especially given that the technology needed to implement this approach is widely available.

QbD provides the flexibility to operate within a broader design space when changes to the manufacturing process occur that are outside one's control.

Stages of a QbD-based product development

There are extra steps involved in the initial QbD-based product development. Additional upfront investment in terms of time, money, and resources will be required, but it protects against variability later on; it also minimizes risk, reduces waste, and saves time in the long run.

Through detailed characterization of materials such as APIs and excipients, the critical quality attributes (CQA) are defined. CQAs are the chemical, physical, biological, and microbiological attributes that may significantly affect the quality of the finished product. This information enables the identification of critical process parameters (CPPs), which are the key variables that affect the production process. CPPs can be monitored to detect any deviation in manufacturing processes, and active control of these CPPs can counteract these deviations in order to ensure product quality and that CQAs are met.

For example, Hermes Pharma was involved in developing an effervescent cough and cold formulation containing three APIs—acetaminophen, caffeine, and phenylephrine. Given the low concentration of phenylephrine, in the final product, a key challenge was to ensure content uniformity for all three APIs so that the product delivers reliable and reproducible efficacy when taken by patients. A QbD approach was adopted to improve the blend homogeneity of the APIs within the final product.

Figure 1: Near infrared spectrometer attached to a production scale blending container. The spectrometer wirelessly transmits data for real-time analysis.

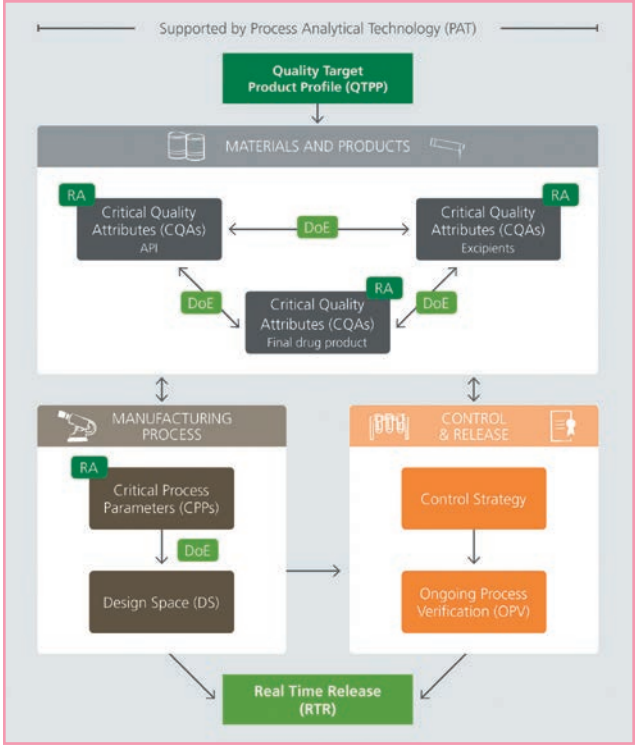
The formulation involved three separate blending steps. Prior to adopting QbD, the blending time and speed would have been based on the formulator's experience, rather than being verified by experimental investigation. With the QbD approach, monitoring of the mixture at various locations within the container was carried out using high performance liquid chromatography (HPLC) for the initial blending steps and near infrared (NIR) spectrometry for the final blending process (see **Figure 1**). This data-driven approach meant that only when acceptable levels of blend homogeneity had been reached would the blending process continue to the subsequent step, resulting in more consistent levels of product quality.

Easier scale-up

In most cases, transitioning from laboratory scale to mass production is rarely straightforward. However, scaling up is often significantly easier when QbD is employed, because the manufacturing process is better understood. It reduces the risk of encountering unexpected problems that negatively impact on production throughput and timescales.

FIGURES ARE COURTESY OF HERMES PHARMA.

Figure 2: The potential approaches for quality-by-design (QbD) implementation within a pharmaceutical development and manufacturing environment. RA is risk assessment; DoE is design of experiments; API is active pharmaceutical ingredient.



In the effervescent cough and cold remedy example mentioned earlier, the adoption of QbD significantly reduced the time required to optimize the scale-up process. By monitoring the CPPs throughout the multi-step process, the formulators were able to gain an understanding of the main contributions towards blend inhomogeneity. And by pinpointing issues specific to a particular step in the process, attention could be given to the factors involved, which helped overcome the challenges during scale-up. Without QbD, scaling up would have been based on a trial-and-error approach and would have likely taken considerably longer to optimize.

Simplifying regulatory compliance

Another benefit of having a good understanding of the CQAs and CPPs is the ability to easily establish a formulation and process design space that ensures compliance with the quality target product profile. Essentially, the need to register later adjustments with regulatory bodies after large-scale production has begun can be avoided, which is important as such revisions can lead to significant delays when it comes to bringing a product to market. Moreover, by using QbD, risk can be managed more effectively and it will be easier to determine exactly which product changes will require additional regulatory submissions.

QbD also provides the flexibility to operate within a broader design space when changes to the manufacturing process occur that are outside one's control. For example, at Hermes Pharma, hot melt coating is used to mask the unpleasant metallic taste of acetylcysteine in the production of a mucolytic product. However, it was discovered that the particle size distribution of the API varied between batches of the raw material—a situation that often occurs, because in many cases, suppliers do not fully specify the particle size distribution of their APIs. As a result, if the same amount of coating was applied to each particle, the coating thickness would vary and the unpleasant taste could come through. However, because QbD was applied together with PAT, the formulators were able to screen the particle size distribution of the incoming API and categorize these into distinct classes with an associated coating method. This approach provided a more consistent coating layer irrespective of particle size.

QbD approaches based on process analytical technologies facilitate real-time release testing.

If only one process was designed for a very narrow particle size range, the unsuitable particle size fractions would have to be discarded by sieving, which is of course not cost efficient. Alternatively, the formulator would have had to agree upon a very specific particle size with the supplier, which would incur additional costs. Working within a predefined and regulatory-approved design space avoids the need to apply for additional regulatory approval when changes in raw material specifications are encountered.

Other benefits of QbD

QbD approaches based on PAT also facilitate real-time release testing. This approach gives manufacturers more timely information on product quality and means that any manufacturing problems can be dealt with faster, in a more informed manner.

QbD also puts in place the quality assurance framework necessary for continuous process improvement. Compared to traditional batch testing, continuous process verification is much more able to push the processes towards optimization and maintain manufacturing parameters within acceptable limits. It also reduces the sampling effort, further boosting process efficiency.

All of these process improvements mean that patients will benefit from an enhanced level of quality in their medicines, ensuring that the medicines are consistently safe and effective. As a result, customers benefit from a more reliable supply capability, preventing out of stock situa-

tions where product batches need to be destroyed due to poor quality.

A stepwise approach to implementing QbD

There are three key stages in implementing a QbD approach to pharmaceutical development and production (see **Figure 2**):

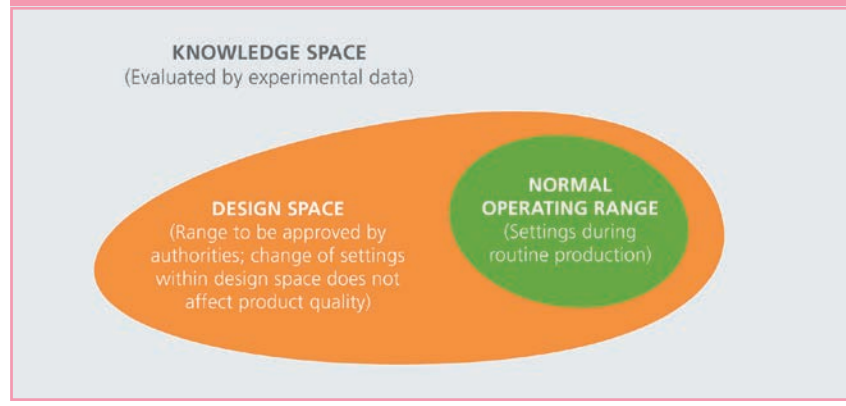
- Initial product profiling, risk analysis, and CQA/CPP determination during early development
- The design of experiments and the definition of possible and meaningful design spaces during the formulation/manufacturing development phase
- The establishment of a manufacturing and control strategy during scale-up and routine production. Manufacturing is also supported by ongoing process verification to ensure continued operation within the defined parameters.

At Hermes Pharma, the first step in our development programs is to establish the quality target product profile (QTPP) for the product. The pharmacological and patient requirements as well as quality are considered in advance of manufacture, hence, providing a starting point for identifying CQAs in the next step. This is followed by risk-based characterization of APIs and excipients, including an assessment of factors such as particle size distribution, morphology, processability, and batch-to-batch or supplier-to-supplier variation.

Risk analyses are also performed to determine CQAs for the pharmaceutical product. The goal is to study and control any factor—be it physical, chemical, or microbiological—that could affect the quality of the product. It's important to study APIs and excipients both in isolation and in combination to define their characteristics in as much detail as possible. Failure to keep these factors within the set boundaries creates the risk of manufacturing substandard products that can lead to manufacturing downtime or increased costs, and potentially harm supplier relationships. CPPs are variables contributed by the manufacturing process with the potential to impact the CQAs, resulting in a low-quality product. The greater the potential CQA impact, the more closely the CPP has to be controlled.

Next, the design space is defined. For example, the design space could be the relationship between specific process inputs and the CQAs. If the design space is developed accurately and all essential aspects of the process are within the design space, then the CQAs must be acceptable. The design space enables manufacturers to demonstrate to regulatory bodies a comprehensive understanding of their process. The regulatory body then approves the design space as an operational range, giving manufacturers the flexibility to operate provided the workflow remains within that range (see **Figure 3**) and avoid having to submit revised information to the regulatory authorities.

Figure 3: The relationships between normal operating range, the design space, and the knowledge space that evolves during the product development process.



Then, using the knowledge gained from the previous steps, together with the CQAs and CPPs, a control strategy is established. This control strategy must be defined in order to determine which analytical methods are required and where in the process they will be employed. PAT enables the control strategy to be further improved, as it facilitates the monitoring and control of the production processes in real-time.

To maintain product quality across all batches, ongoing process verification should be performed. Unlike traditional verification approaches, such as the "three golden batches" method, which focuses on analyzing the first three batches only, continuous process verification does not treat validation as a discrete exercise. This way, the manufacturing processes are operating at the very highest levels of quality for the industry.

Conclusion

QbD looks set to become increasingly important for the pharmaceutical industry as more and more companies are looking to boost production output, reduce throughput times, and lower costs by shifting from batch production to continuous manufacturing. However, for these "always on" processes, it just isn't possible to perform quality testing within a series of continuous process steps in the same way as it is following each operation of a batch process.

Additionally, as FDA, EMA, and other regulatory bodies further scrutinize production processes to ensure the highest levels of safety, QbD will make it easier for companies to demonstrate that they are operating within acceptable limits. As regulatory authorities start to insist that companies design quality into products at every stage of the pharmaceutical value chain, the use of QbD will become ever more important. **PT**