

Why the FDA and EMA want you to implement QbD

Quality by Design – 9 basics and what’s in it for sponsors

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Quality by Design (QbD) is not a new concept. For more than a decade, QbD principles – which, according to a [presentation to ICH](#), is the “integration of patient needs, science and quality requirements during the development of a pharmaceutical product and its manufacturing process” – have been used to improve the quality of products and processes in the automobile industry and others.

Given the success of QbD in industry, the [U.S. Food and Drug Administration \(FDA\)](#) decided to get into the act, and has been nudging QbD implementation for the discovery, development, and manufacture of drugs. The FDA began these efforts more than a decade ago, citing these reasons:

- Pharmaceutical manufacturing is not state-of-the-art compared to other industries.
- Reasonable product quality is achieved by pharma – but at a great effort and cost.
- Little emphasis on drug manufacturing – mainly on development—although manufacturing accounts for approximately 25% of expenses.
- For some products, waste as high as 50%.
- Inability to predict effects of scale-up on final product.
- Inability to analyze or understand reasons for manufacturing failures.
- Drug shortages due to manufacturing problems.
- Lack of improvements based on new technologies.
- Need for intensive regulatory oversight.
- Global fragmentation.

More recently, the [FDA provided more detailed guidance](#) on implementing QbD for pharmaceutical product design, process understanding, and lifecycle management. A major focus is on performing in-process testing in order for adjustments to be made prior to any failures. As well, confirmation – of product quality and process changes--is deemed important.

Similarly, the [European Medicines Agency](#) (EMA) promotes QbD as an approach that aims to ensure the quality of medicines by employing statistical, analytical and risk-management methodology in the design, development and manufacturing of medicines.

Reducing variability

One of the goals of Quality by Design initiatives is to ensure that all sources of variability affecting a process are identified, explained and managed appropriately. This enables the finished drug product to consistently meet its predefined characteristics from the start - so that it is “right first time.”

The core message from regulatory bodies is that quality should be built into a pharmaceutical product from the beginning based on knowledge of its characteristics and a thorough understanding of the process by which the product is manufactured.

The thinking is that QbD will produce a high quality drug product that is free from contamination and that reliably delivers the therapeutic benefit promised in the label to the patient. This article provides an overview of QbD and how PCI Synthesis uses QbD.

Speeding regulatory approval

In a nutshell, QbD is about communicating meaningful and relevant science up front to establish post-regulatory approval opportunities that will also guide subsequent manufacturing improvements.

Why implement? There are numerous benefits for industry. Chief among them is that indicating QbD principles in regulatory submissions ensures less hassle during review. Fewer deficiencies can result in quicker approvals.

Other benefits include fewer manufacturing problems, reduced number of post-market manufacturing supplements, and the ability to implement new technology that improves manufacturing without regulatory scrutiny.

QbD challenges

QbD, despite its many benefits all around – for sponsors as well as regulatory bodies --is not a bed of roses. It still presents challenges. According to the FDA, the devil is in the details:

- Need agreement on terminology.
- Need to determine what relevant data is needed in applications.
- Need to determine next steps for global implementation.
- Need to determine how best to handle legacy products in line with those products issued under QbD
- Need a “regulatory agreement” or post-market management plan.
- Need to assure collaboration and coordination between inspectors, compliance and review.
- Need training and more training.

How PCI Synthesis employs QbD

At [PCI Synthesis](#), QbD is a systemic approach that begins by identifying the quality attributes of the product based on scientific rationale, as opposed to attempting to fit the proverbial square peg into a round hole through a trial-and-error approach.

This rational design approach goes further to identify the limiting factors of each step in a synthesis process and provides the means of attempting to correlate how each step of the process affects the final product quality attributes.

In other words, QbD principles are applied at every step of the development of a synthesis process.

To apply QbD as a systemic approach, the company starts by understanding, step by step:

- The space design (more below)
- The design of the dosage form
- The manufacturing process
- The critical process parameters to be controlled in order to reach the next new building block
- The variances within critical process parameters—are they acceptable?

This approach allows the establishment of priorities and flexible boundaries in the process.

The basics of QbD in pharmaceutical development and manufacture

1. QbD is a systematic approach to pharmaceutical development and API manufacturing using:
 - Modern scientific and quality risk management (QRM) principles.
 - Quality control strategies based on product and process understanding.
2. Sufficient details of development and manufacturing information to be included in regulatory submissions.
3. Regulatory decisions are based on scientific and QRM principles.
4. QbD does not equal Design Space (DS) and/or Design of Experiments (DOEs).
5. DS is not required, but establishing a DS is useful to show product and process understanding and to provide manufacturing and regulatory flexibility.
6. QbD doesn't have to be expensive. It can reduce manufacturing and regulatory cost.

7. QbD doesn't change/reduce regulatory requirements. Rather, it provides opportunities for flexible regulatory approaches.

8. QbD is important for all products including generics and new pharmaceutical products.

9. Analytical testing is important and plays a key role in development and implementation of QbD.

QbD is one of the behind-the-scenes approaches that we use to improve our processes to meet our sponsors' needs and FDA's requirements. Please also check out other related articles, including "[Internal Auditing: A Sound Business Practice to Ensure Successful Outcomes in cGMP Manufacturing](#)" and "[Shedding Light on Quality Investigations in Chemical Manufacturing: Getting to the Root Cause of Process Deviations and Quality Excursions to Ensure cGMP Compliance.](#)"