# Pharmaceutical “Quality by Design” (QbD): An Introduction, Process Development and Applications

**Quality means fitness for intended use. Pharmaceutical quality refers to product free of contamination and reproducibly delivers the therapeutic benefit promised in the label to the consumer. The Quality of the pharmaceutical product can be evaluated by in vivo or in vitro performance tests. Quality by design assures in vitro product performance and In vitro product performance provides assurance of in vivo product performance. “Hence Quality by design relate to Product Performance”.**

# Definition

The pharmaceutical Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. Quality by Design (QbD) is emerging to enhance the assurance of safe, effective drug supply to the consumer, and also offers promise to significantly improve manufacturing quality performance.

# QbD development process include:

* Begin with a target product profile that describes the use, safety and efficacy of the product
* Define a target product quality profile that will be used by formulators and process engineers as a quantitative surrogate for aspects of clinical safety and efficacy during product development
* Gather relevant prior knowledge about the drug substance, potential excipients and process operations into a knowledge space. Use risk assessment to prioritize knowledge gaps for further investigation
* Design a formulation and identify the critical material (quality) attributes of the final product that must be controlled to meet the target product quality profile.
* Design a manufacturing process to produce a final product having these critical material attributes.
* Identify the critical process parameters and input (raw) material attributes that must be controlled to achieve these critical material attributes of the final product. Use risk assessment to prioritize process parameters and material attributes for experimental verification. Combine prior knowledge with experiments to establish a design space or other representation of process understanding.
* Establish a control strategy for the entire process that may include input material controls, process controls and monitors, design spaces around individual or multiple unit operations, and/or final product tests. The control strategy should encompass expected changes in scale and can be guided by a risk assessment.
* Continually monitor and update the process to assure consistent quality.

Design of experiments (DOE), risk assessment, and process analytical technology (PAT) are tools that may be used in the QbD process when appropriate. They are not check-box requirements.

# Traditional approach & Enhanced QbD approach

| **Aspects** | **Current** | **QbD** |
| --- | --- | --- |
| Pharmaceutical Development | Empirical, Random, Focus on optimization | Systematic, Multivariate experiments, Focus on control strategy and robustness |
| Manufacturing Process | Fixed | Adjustable within design space, managed by company’s quality systems |
| Process Control | Some in-process testing | PAT utilized, Process operations tracked and trended |
| Product Specification | Primary means of quality control, based on batch data | Part of the overall quality control strategy, based on desired product performance |
| Control Strategy | By testing and inspection | Risk-based control strategy , real-time release possible |

# Advantages of QbD

**Benefits for Industry:**

* Better understanding of the process.
* Less batch failure.
* More efficient and effective control of change.
* Return on investment / cost savings.

**Additional opportunities:**

* + An enhance QbD approach to pharmaceutical development provides opportunities for more flexible regulatory approaches.

**Ex: Manufacturing changes within the approved design space without further regulatory review.**

* Reduction of post-approval submissions.
* Better innovation due to the ability to improve processes without resubmission to the FDA when remaining in the Design Space.
* More efficient technology transfer to manufacturing.
* Greater regulator confidence of robust products.
* Risk-based approach and identification.
* Innovative process validation approaches.
* Less intense regulatory oversight and less post-approval submissions.
* For the consumer, greater drug consistency.
* More drug availability and less recall.
* Improved yields, lower cost, less investigations, reduced testing, etc.
* Time to market reductions: from 12 to 6 years realized by amongst others.
* First time right: lean assets management.
* Continuous improvement over the total product life cycle (i.e. controlled, patient guided variability).
* Absence of design freeze (no variation issues).
* Less validation burden.
* Real time controls (less batch controls).
* Realistic risk perceptions.
* Contributes substantially to realize the better, cheaper and safer mandate.

# QbD activities within FDA

Specifically, the following activities are guiding the overall implementation of QbD:

* In FDA’s Office of New Drug Quality Assessment (ONDQA), a new risk-based pharmaceutical quality assessment system (PQAS) was established based on the application of product and process understanding.
* Implementation of a pilot program to allow manufacturers in the pharmaceutical industry to submit information for a new drug application demonstrating use of QbD principles, product knowledge, and process understanding. In 2006, Merck & Co.’s Januvia became the first product approved based upon such an application.
* Implementation of a Question-based Review (QbR) Process has occurred in CDER’s Office of Generic Drugs.
* CDER’s Office of Compliance has played an active role in complementing the QbD initiative by optimizing pre-approval inspectional processes to evaluate commercial process feasibility and determining if a state of process control is maintained throughout the lifecycle, in accord with the ICH Q10 lifecycle Quality System.
* Implementation of QbD for a Biologic License Application (BLA) is progressing.

While QbD will provide better design predictions, there is also a strong recognition that industrial scale-up and comercial manufacturing experience provides new and very important knowledge about the process and the raw materials used therein. FDA is aware that knowledge is not static and builds throughout the manufacturing lifecycle.

FDA’s release of the Process Validation guidance in January 2011 notes the need for companies to continue benefiting from knowledge gained, and continually improve throughout the process lifecycle by making adaptations to assure root causes of manufacturing problems are quickly corrected. This vigilant and nimble approach is explained by FDA to be essential to best protect the consumer (patient).

# International Conference on Harmonization. (ICH)

Relevant documents from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. (ICH)

* Pharmaceutical Development Q8 (R2)
* Quality Risk Management Q9
* Pharmaceutical Quality System Q10

The difference between QbD for NDA and ANDA products is most apparent at the first step of the process. For an NDA, the target product profile is under development while for the ANDA product the target product profile is well established by the labeling and clinical studies conducted to support the approval of the reference product.

# Conclusion

* Ensures robust commercial manufacturing methods for consistent production of quality drugs.
* Ensures the consumers that therapeutic equivalent generics are manufactured every single time.
* Offers the agency that quality applications are submitted to improve the review efficiency and to reduce the application approval times.
* QbD methodology helps in identifying and justifying target product profiles, product and process understanding.
* Helps in continuous improvement.
* There is a need for vigorous and well funded research programs to develop new pharmaceutical manufacturing platforms.