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QUALITY BY DESIGN (QBD): MANUFACTURING AND PRODUCT QUALITY OF GENERICS DRUGS PERSPECTIVE

Nwoko valentine eziokwu*,
B.Pharm, M. Pharm, MBA

Formulation Pharmacist,
Pharmatex Industries, Lagos,
Nigeria

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ABSTRACT

Essentially, the QbD approach identifies 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 unit operation and provides the means of attempting to correlate how each unit operation affects the final product quality attributes. To apply QbD as a systemic approach, the company starts by understanding, step by step, the space design, the design of the dosage form, the manufacturing process, and the critical process parameters to be controlled in order to reach the new building block which is the expectation of variances within those critical process parameters that can be accepted. This approach allows the establishment of priorities and flexible boundaries in the process.

Key words: Quality by design, Generics, Regulatory.

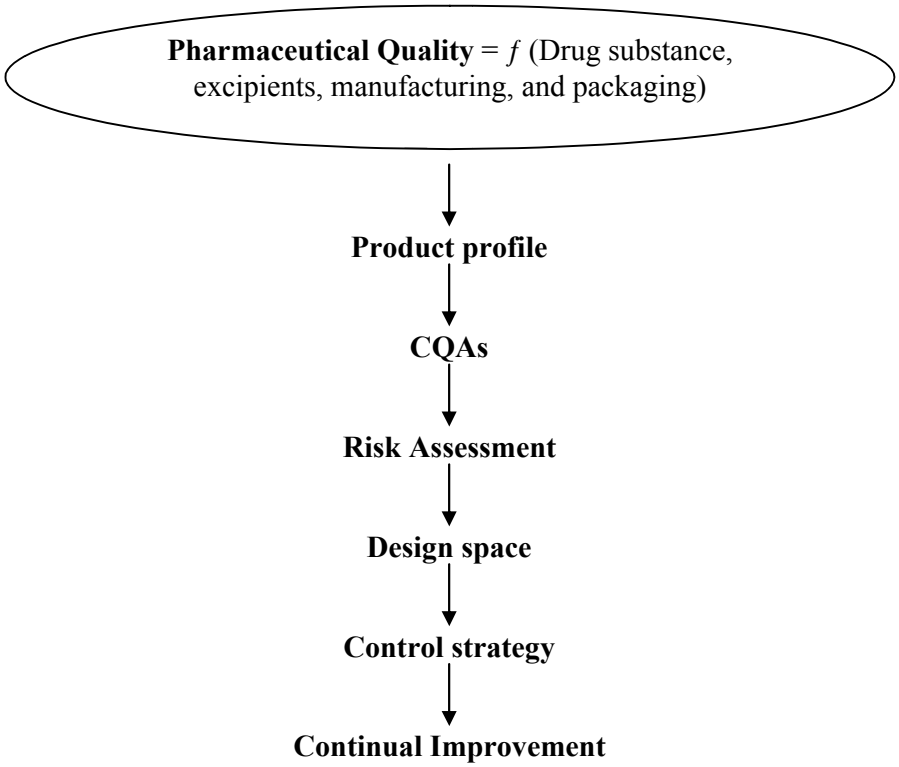
INTRODUCTION:

Quality by design (QbD) is a concept that promulgates a core message that quality should be built into a product based on knowledge of its characteristics and understanding of the process by which the product is manufactured. In a nutshell, QbD is about communicating meaningful and relevant science upfront to establish post regulatory approval opportunities that will guide subsequent manufacturing improvements. QbD speaks to real and significant changes in how industry and regulatory agencies approach the regulatory process. Quality by Design "means that product and process performance characteristics are scientifically designed to meet specific objectives... To achieve QbD objectives, product and process characteristics important to desired performance must be derived from a combination of prior knowledge and experimental assessment during product development." Quality by Design is a systemic approach that applies the scientific method to the process. QbD theory contains components of management, statistics, psychology and sociology. The FDA ' s new century has identified the QbD approach as its " key component " based on process quality control before industry end results. To apply QbD as a systemic approach, the company starts by understanding, step by step, the space design, the design of the dosage form, the manufacturing

Process and the critical process parameters to be controlled in order to reach the new building block which is the expectation of variances within those critical process parameters that can be accepted. This approach allows the establishment of priorities and flexible boundaries in the process. In order to initiate a successful QbD program, the first step is to identify those process parameters that are essential to product quality and develop well – validated analytical methodologies to monitor those parameters.

Address for correspondence

Nwoko Valentine Eziokwu
E-mail: valentinenwoko@yahoo.com
Mobile: 08026827847



EXAMPLE QBD APPROACH

1. Quality Target product profile (QTPP)
2. Determine critical quality attributes (CQAs)
3. Link raw material attributes and process parameters to CQAs and perform risk assessment
4. Develop a design space
5. Design and implement a control strategy
6. Manage product lifecycle, including continual improvement

Demystification of QbD (1)

1. QbD is a systematic approach to pharmaceutical development and 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 must be based on scientific and QRM principles
4. QbD doesn't 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. Public standards continue to have a role but some adaptation is needed
7. QbD doesn't have to be expensive .It can reduce manufacturing and regulatory cost
8. QbD doesn't change/reduce regulatory requirements. Opportunities for flexible regulatory approaches
9. QbD is important for all products including generics and biotech
10. Analytical testing is important and play a key role in the QbD (development and implementation)
11. End product testing is a component of the control strategy .Bioavailability and bioequivalence need to be demonstrated by dissolution testing and/or other means.

ORIGINS OF QBD

Any discussion of QbD should be framed in the context of the industry and regulatory climate at the time that FDA introduced the QbD concept as part of its two-year initiative, Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach Pharmaceutical cGMP initiative (also referred to as the Pharmaceutical cGMP Initiative or 21st Century Initiative) in 2002. QbD is not a new concept from a

pharmaceutical technology perspective. It is, however, a new concept relative to pharmaceutical regulatory review and submission. As a systematic and prospective approach to product design, process design and control, process performance, and continuous improvement, QbD designs quality into the manufacturing process. By doing so, QbD encourages innovation, continuous quality improvement, and science- and risk-based regulatory processes and ensures the availability of high quality medicines to the consumer.

Before the Pharmaceutical cGMP Initiative, the pharmaceutical industry already had begun moving toward conveying a more science-based approach through its emphasis on collaboration and risk-based regulation; the Pharmaceutical cGMP Initiative significantly hastened that process. Then, as now, the industry as a whole was doing a great deal of innovative work, but neither industry nor FDA were structured to encourage knowledge sharing. By focusing on what the regulatory agencies wanted, pharmaceutical companies limited their risk of regulatory exposure, but they also limited the vital, cross-industry knowledge sharing that advances industries and positions them for continued growth.

Because the orientation of regulatory authorities did not encourage quality to be built into the design of the pharmaceutical manufacturing process, multiple and repetitive inspections were the means by which quality was measured and demonstrated. This quality-by-analysis method of monitoring drug-product safety and efficacy brought reliable pharmaceuticals to market but required manufacturers to notify FDA of any change to quality or to the current manufacturing process. Depending on the change, time-consuming and costly requalification and subsequent regulatory approval might be required.

Focusing on the regulation of drug-product quality, the initiative, Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach (subsequently renamed Pharmaceutical Quality for the 21st Century) was intended to modernize FDA regulation of pharmaceutical quality for veterinary and human drugs and for human biological products such as vaccines. The goals of the initiative were to ensure that regulatory review, compliance, and inspection policies are based on pharmaceutical science and to foster the rapid adoption of technological advances throughout the pharmaceutical industry. Under any name, the ambitious initiative seeks to demonstrate and provide examples of enhanced quality.

Can we do without QbD in generics?
Do we want to get it right the first time every time?

How do we find the balance between speed and excellence?

By applying science efficiently and utilizing our prior knowledge effectively

Is QbD the only way to make quality products?

- Some will say: Definitely not!
  - Has the generic industry not provided quality products for many years?
  - Could the industry attain 72% market share without quality products?
  - Are the quality issues faced by generic companies any different from those faced by the brand companies?
- Are there supply interruptions? Product on short supply.

Why QBD should be on the executive team's agenda?

- Product and Process Development (PPD) –API, formulation, analytical, process development, validation, and preparation for commercial manufacture account for 15-30% of overall R&D expenditure.
  - Ineffective PPD is costing companies up to 20% of potential profits.
  - For the industry as a whole, PPD could represent an incremental $20-30 billion in profits
  - PPD can increase an individual compound's lifetime value by 30-50%.

If QbD can indeed be beneficial to the industry as pointed out by McKinsey, why is the QbD implementation not complete and why is there so much concern (or skepticism)?…

Challenges in adoption of QbD?

1. Using past success to predict the future.
2. We are doing just fine –no thanks.

3. Resistance to the change, "who moved my cheese" syndrome.
4. Difficulty to see the long term benefit and business-case.
5. QbD will slow us down and will impact ability to achieve FTF?
6. QbD will increase our development cost significantly.
7. The more we will tell the FDA, the more questions we will have, and more difficult it will be to gain approval.
8. Will the review be consistent from one application to another and from one reviewer to another

Despite the adoption challenges, it is clear to the Generics Industry that not implementing QbD is not an option

Can we do without QbD in generics?

- We do want to get it right the first time every time...
- We do want to reduce cost, shorten time to approval and launch, and provide uninterrupted supply of high quality and affordable medication to our patients...
- OGD has made it clear to the industry that not implementing QbD is not an option.

How do we apply QbD in generics?

1. Race to "First to File".
2. Frequently limited amount of API and the need to go to pivotal.
3. A balance between what parameters to fix and what to keep variable.
4. A balance between what to do before and what to do after submission.
5. A balance between risk and opportunity.
6. A balance between risk and budget

What is different in a QbD Dossier?

Submissions with enhanced and sound development studies that lead to increased Product and Process understanding

Systematic use of the following tools:

- Risk assessment
- Statistical tools
- Process Analytical Tools for monitoring the progress of the process "real time"
- Controls, for adjusting the process "real time"

Regulatory Assessment of Applications Containing QbD Elements - FDA Perspective

1. Industry feedback has focused on the use of prior knowledge and risk analysis
2. Intended to illustrate the types of development studies ANDA applicants may use as they implement QbD
3. Provide a concrete illustration of the QbD principles from ICH Q8 (R2) Both IR and MR illustrate QbD principles
4. Development of a real product may differ from the examples
5. Number of experiments may depend on the experience of the applicant

This should be explained in the submission

Pharmaceutical companies and QbD

The Pharmaceutical cGMP Initiative emphasizes scientific collaboration between FDA, academic institutions, and industry organizations. Pharmaceutical companies, collaborated with the FDA's Manufacturing Sciences Working Group, which was established at the launch of the 21st Century Initiative to identify efficient approaches for characterizing and controlling critical manufacturing process parameters and quality assurance.

CRADAs. Also in conjunction with the Pharmaceutical cGMP Initiative, Pharmaceutical companies established a cooperative research and development agreement (CRADA) with FDA to research chemical imaging applications in pharmaceutical manufacturing and quality assurance. Technologies resulting from such CRADA agreements are in the public domain and intended for usage industry wide.

CMC pilot. In 2005, Pfizer volunteered and was among 12 pharmaceutical companies selected to participate in FDA's CMC (Chemistry, Manufacturing, and Controls) pilot program under the auspices of FDA's Office of New Drug Quality Assessment. The pilot was conceived to develop guidance for a new approach and related system for pharmaceutical quality assessment (1). Participants submitted CMC and other control information demonstrative of their QbD approach, product knowledge, and process understanding of the

drug substance and drug product in a new drug application (NDA) or supplemental NDA. Pfizer's NDA for Chantix (varenicline) was the first candidate in the pilot program to achieve FDA approval.

Organizational approaches to QbD. Today, QbD is part of the pharmaceutical industry's acronym-laden lexicon, as reflected by its prominence as a topic at trade association meetings, symposia, and the steady up-tick in QbD training and similar initiatives in place at pharmaceutical companies. Recognizing the criticality of new quality paradigms in the development of future medicines, in 2006, Pharmaceutical companies established an internal Quality by Design Limited Duration Team (QbD LDT). Charged with developing guidelines for the implementation of QbD , the team developed a Quality by Design Toolkit for roll out to co development teams and sites. Conceived as a "living document," the QbD Toolkit provides development and manufacturing organizations with a list of agreed-upon QbD definitions for use within Pfizer and in its regulatory submissions. Knowledge gains are incorporated as the company extends its application of QbD approaches, and results are evaluated. Updated regularly, the most current definitions are posted to the QbD section of Pharmaceutical companies' intranet for easy access.

Another focus of Pharmaceutical companies QbD is the work of the International Conference on Harmonization (ICH). Closely aligned with many of the high level concepts found in ICH guidelines Q8 Pharmaceutical Development, Q9 Quality Risk Management, and Q10 Pharmaceutical Quality Systems, QbD is a beneficial for the pharmaceutical industry, regulators, and patients (2–4)

How will industry assess that QbD has worked?

- Faster approval
- Meaningful regulatory flexibility
- Less regulatory question

How will the FDA assess that QbD has worked?

- Reduction in product failures
- Reduction in product withdrawals
- Reduction in customer complaint

BENEFITS OF QBD

Strongly focused on collaboration between research and manufacturing, QbD advances process understanding for increased effectiveness and efficiency. The "real time, real data" sharing of industry knowledge optimizes front-end design to more fully support the product life cycle. The science- and risk-based approach boosts regulator confidence by minimizing regulator risk. Because QbD brings medicines to patients in a better-understood and fundamentally more reliable way, consumers benefit as well.

QbD reduces post approval regulatory submissions, minimizes risk around manufacturing failures and product recalls, trims non-value-added regulatory and compliance activities, and facilitates novel approaches to process validation. At the same time, QbD improves regulatory flexibility, process understanding, and application of technology. QbD hones regulatory-review criteria, capitalizes on experience to leverages industry wide expertise, and fosters global harmonization that will benefit the global pharmaceutical industry, its consumers, and other stakeholders.

QbD concepts coincide with a burgeoning global industry movement toward building quality into pharmaceuticals from development through manufacturing by bridging gaps between pharmaceutical development and manufacturing and using sound science to demonstrate and assure the product's safety, quality, and efficacy throughout its entire life cycle. Launched in 2007, the Product Quality Lifecycle Implementation (PQLI) initiative is a global, industry-led effort led by International Society for Pharmaceutical Engineering to facilitate the implementation of ICH standards.

Pharmaceutical companies are actively engaged in the PQLI initiatives. In collaboration with the European Federation of Pharmaceutical Industries and Associations, the European Medicines Agency conducted a regulator/industry event around ICH Q8, Q9 and Q10. Pharmaceuticals companies played a key role in facilitating this collaborative initiative. Activities included mock regulatory inspections that were conducted at

manufacturers' sites and seminars on topics that included product life-cycle management, forward-thinking action steps, and criticality.

CURRENT CHALLENGES

It is important to note that QbD didn't and was not expected to solve ALL pre-QbD quality challenges

CONCLUSION

The examples cited in this article are just some ways of how QbD is affecting the pharmaceutical industry and its regulatory agencies on a global scale. To facilitate continuous improvement and technical innovation, the global pharmaceutical industry needs a global quality and regulatory framework for postapproval changes. Trying to develop increasingly complicated technologies with fewer resources than were available in the past is an ongoing challenge for the pharmaceutical industry. By enabling pharmaceutical companies to focus on critical and promising products and process areas, QbD and other global harmonization efforts will help the industry meet such challenges. The QbD initiatives in place throughout Pfizer are fostering the vital co development, collaboration, and innovation that position the company to meet 21st century global industry challenges. In harmony with First Time and other continuous improvement programs and initiatives, QbD will support global transformation and drive its forward growth.

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