Review Article

QUALITY BY DESIGN (QBD) : A COMPLETE REVIEW

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ABSTRACT

Quality by Design is the modern approach for quality of pharmaceuticals. This paper gives idea about the Pharmaceutical Quality by Design (QbD) and describes use of Quality by Design to ensure quality of Pharmaceuticals. The Quality by Design is described and some of its elements identified. Process parameters and quality attributes are identified for each unit operation. Benefits, opportunities and steps involved in Quality by Design of Pharmaceutical products are described. The aim of the pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. Quality cannot be tested into products but quality should be built in by design. It includes the Quality target product profile, critical quality attributes and key aspects of Quality by Design. It also gives comparison between product quality by end product testing and product quality by Quality by Design. The foundation of Quality by Design is ICH Guidelines. It is based on the ICH Guidelines Q8 for pharmaceutical development, Q9 for quality risk management, Q10 for pharmaceutical quality systems. It also gives application of Quality by Design in pharmaceutical development and manufacturing of pharmaceuticals.

Keywords: Quality by Design (QbD), Process Analytical Technology (PAT), Quality target product profile, Critical quality attributes.

INTRODUCTION

The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space, specifications, and manufacturing controls. Information from pharmaceutical development studies can be a basis for quality risk management. It is important to recognize that quality cannot be tested into products; i.e., quality should be built in by design. Changes in formulation and manufacturing processes during development and lifecycle management should be looked upon as opportunities to gain additional knowledge and further support establishment of the design space. Similarly, inclusion of relevant knowledge gained from experiments giving unexpected results can also be useful. Design space is proposed by the applicant and is subject to regulatory assessment and approval. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process.

In all cases, the product should be designed to meet patients' needs and the intended product performance. Strategies for product development vary from company to company and from product to product. The approach can also vary and should be outlined in the submission. An applicant might choose either an empirical approach or a more systematic approach to product development, or a combination of both. A more systematic approach to development (also defined as quality by design) can include, for example, incorporation of prior knowledge, results of studies using design of experiments, use of quality risk management, and use of knowledge management (ICH Q10) throughout the lifecycle of the product. Such a systematic approach can enhance achieving the desired quality of the product and help the regulators to better understand a company's strategy. Product and process understanding can be updated with the knowledge gained over the product lifecycle. [1-5]

Design[4, 5]

- Product is designed to meet patient needs and performance requirements.
- Process is designed to consistently meet product quality attributes.
- Impact of starting raw materials and process parameters on product quality is understood.
- Critical sources of process variability are identified and controlled.
- The process is continually monitored and updated to allow for consistent quality over time.

Definition [ICH Q 8(R1)]

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. [6]

Definition [FDA PAT Guidelines, Sept. 2004]

A system for designing, analyzing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes

of new and in-process materials and processes, with the goal of ensuring final product safety. [5, 6]

The concept of "Quality by Design" (QbD) was defined as an approach which covers a better scientific understanding of critical process and product qualities, designing controls and tests based on the scientific limits of understanding during the development phase and using the knowledge obtained during the life-cycle of the product to work on a constant improvement environment. QbD describes a pharmaceutical development approach referring to formulation design and development and manufacturing processes to maintain the prescribed product quality. Guidelines and mathematical models are used to ensure the establishment and use of the knowledge on the subject in an independent and integrated way.

Benefits of QBD [1,3,5,6]

- QbD is good Business
- Eliminate batch failures
- Minimize deviations and costly investigations
- Avoid regulatory compliance problems
- Organizational learning is an investment in the future
- QbD is good Science
- Better development decisions
- Empowerment of technical staff

Opportunities[7,8]

- Efficient, agile, flexible system
- Increase manufacturing efficiency, reduce costs and project rejections and waste
- Build scientific knowledge base for all products
- Better interact with industry on science issues
- Ensure consistent information
- Incorporate risk management

STEPS INVOLVED IN QUALITY BY DESIGN PRODUCTS[7-9]

1. Development of new molecular entity

- Preclinical study
- Nonclinical study
- Clinical Study
- Scale up
- Submission for market Approval

2. Manufacturing

- Design Space
- Process Analytical Technology
- Real time Quality Control

3. Control Strategy

- Risk based decision
- Continuous Improvement
- Product performance

Seven steps of quality by design start up plan

1. Hire an independent Quality by design expert.
2. Audit your organization and process with the expert conducting a gape analysis.
3. Hold a basic quality by design workshop with all your personal.
4. Review the expert's report and recommendation.
5. Draft an implementation plan, timelines and estimated costs.
6. Assign the resources (or contract out).
7. Retain the independent expert as your "Project Assurance" advisor.

Quality by design (QbD) and well understood product and processes[4,7,8]

- All critical sources of variability are identified and explained.
- Variability is controlled by the process.
- Product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, environmental and other conditions.
- To gain enhanced knowledge of product performance over a range of material attributes, manufacturing process options and process parameters considering appropriate use of quality risk management principles.

QbD BY PHARMACEUTICALS[8-10]

Even though the pharmaceutical industry has focus on quality, it has failed to keep up with other industries in terms of manufacturing efficiency and productivity.

Current scenario in the Pharmaceutical Industry:

- Cost of revalidation
- Off-line analysis for in-process - need based
- Product specifications as primary means of control
- Unpredictable Scale-up issues
- Inability to understand failures

Systematic approach to development:

- That begins with predefined objectives
- Emphasizes products and process understanding
- Process control (Figure 1)

Figure 1: Process, Quality, Design and PAT

QUALITY TARGET PRODUCT PROFILE[10,11]

A summary of the drug development program described in terms of labeling concepts and it mainly focus on the safety and efficacy.

- ✓ Description
- ✓ Clinical Pharmacology
- ✓ Indications and Usage
- ✓ Contraindications
- ✓ Warnings
- ✓ Precautions
- ✓ Adverse Reactions
- ✓ Drug Abuse and Dependence
- ✓ Over dosage
- ✓ Dosage and Administration
- ✓ How Supplied
- ✓ Animal Pharmacology and/or Animal Toxicology
- ✓ Clinical Studies

A natural extension of Target Product Profile for product quality – Quality characteristics (attributes) that the drug product should possess in order to reproducibly deliver the therapeutic benefit promised in the label guide to establish formulation strategy and keep the formulation effort focused and efficient .

It facilitates identification of what's needed/critical for the patient/consumer in the Quality Target Product Profile (such as Critical Quality Attributes, CQAs)

- Identifies risks and best approaches to manage.
- Uses tools/enablers in an optimized fashion (such as integration of QbD and biopharmaceutics)
- Generates and enables knowledge sharing.
- An iterative, learning, life-cycle process for optimizing decision-making and the therapeutic outcomes for the patient benefit.

A drug product designed, developed and manufactured according to **Quality Target Product Profile** with specification (such as dissolution/release acceptance criteria) consistent with the desired in vivo performance of the product.

CRITICAL QUALITY ATTRIBUTES[12-14]

- ➢ It is necessary to identify the quality attributes that are critical, i.e. those defining purity, potency and surrogate for Bioavailability Criticality etc. It is based on the impact of quality attribute/ parameter on the safety, efficacy & quality (manufacturability) of the product.
- ➢ Establish a link between CPP & CQAs: Identification of attribute or parameters that can be used as a surrogate for clinical safety & efficacy (important to patient) (Figure 2).
- ➢ Manufacturability is also an attribute (important to business) that is critical to quality.
- ➢ The level of criticality may differ for an API manufacturing process relative to a drug product manufacturing process
- ➢ API is one component of a drug product and one step further away from the patient continuum of Criticality. Several levels of criticality may be used to describe multiple levels of risk.
- ➢ As attribute or parameter boundaries approach edges of failure, the level of critically increased with the risk.

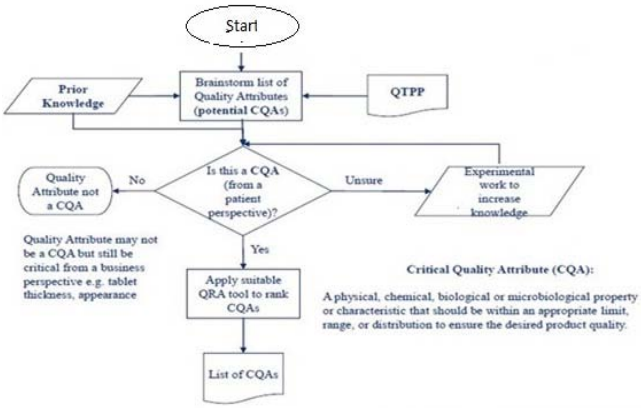

Figure 2: Decision Tree to Decide CQAs

Certain Key Aspects of QBD[15-17]

➢ **The Target Product Quality Profile (TPQP)**

Target Product Quality Profile (TPQP) is a tool for setting the strategic foundation for drug development — "planning with the end in mind." More recently an expanded use of the TPP in development planning, clinical and commercial decision making, regulatory agency interactions, and risk management has started to evolve.

➢ **Drug Substance and Excipient Properties**

To consistently achieve the drug-product quality specified in the label, the drug substance needs to be thoroughly characterized with respect to its physical, chemical, biological, and mechanical properties such as solubility, polymorphism, stability, particle size, and flow properties.

➢ **Formulation Design and Development**

Not all prototype formulations can be evaluated in human subjects, which mean that developing sensitive *in vitro* dissolution methods is crucial to an effective development program.

➢ **Manufacturing Process Design and Development**

Process development and formulation design cannot be separated because a formulation cannot become a product without a prescribed process. Process design is the initial stage of process development, in which an outline of the commercial manufacturing processes is documented, including the intended scales of manufacturing. The outline should include all the factors that need to be considered for the design of the process, including facility, equipment, material transfer, and manufacturing variables. Other factors to consider during process development are the QTPP and CQAs.

Product quality by end product testing vs QbD[17,18]

➢ Comparison is shown between product qualities by end product testing vs. quality by design (Figure 3, 4).

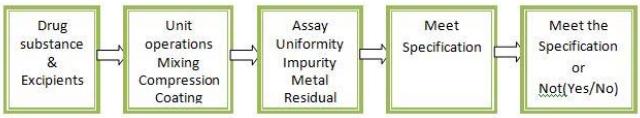

Figure 3: Flow-chart for Product Quality by End Product Testing

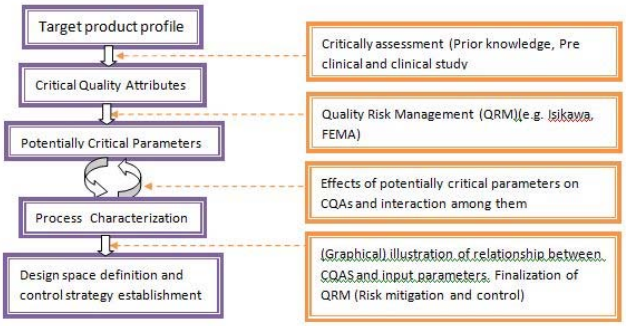

Figure 4: Simplified flow-chart of QBD process

Successful adoption[17,18]

- Regulatory flexibility to accommodate quality by design submissions
- Common dossier accepted worldwide by regulatory agencies
- Post-approval changes within pre-defined design space can be implemented with regulatory flexibility
- Laws and processes in place to protect intellectual property (IP)

Designed to consistently meet desired product quality[17-19]

- Design space concept
- Experimentally defined process operating space based on scientific principles.
- Critical process parameters identified.
- Critical - impact product quality.
- Space - operating range yielding acceptable product Space.
- Critical process parameters are consistently controlled.
- Product of process is always desired quality Product.
- End product testing might be reduced.

Designed to facilitate continuous improvement[17,18]

- Process control strategy: control of the process.
- Performance and continuous process improvement.
- Real-time process feedback Process improvements within design space Knowledge builds with experience Leverage information/new technologies to improve process efficiency Key opportunity to continuously improve the process. E.g. increased supply, more efficiency.

ICH Q8, Q9, Q10 GUIDELINES: THE FOUNDATION OF QbD[2,3,6,18]

ICH Guidelines Q8 for Pharmaceutical Development, Q9 for Quality Risk Management, Q10 for Quality systems are foundation of QbD (Figure: 5)

Figure 5: The Foundation of QbD

Quality by Design relative to ICH[20,21]

- Concepts aligned
- Design Space - Key to understanding
- Process robustness
- Design of Experiments (DOE)
- Quality management Quality management

Critical Concept: Design Space[19-21]

- Multidimensional combination with interactions Multidimensional interactions put variables (e.g. raw material attributes) and process parameters
- Demonstrated to provide assurance of quality
- Defined by applicant and reviewed by regulator Defined regulator
- Once design space is approved, regulatory post approval change requirements will be simplified approval Inside vs. outside design space Inside space
- Regulatory flexibility to operate within the design space Regulatory space

MERCK EXPERIENCE[19-21]

Development of Design Space: **Science based Product and Process Design in Development**

- Enhance process understanding to support science based approach
- Integration of drug substance and drug product process development at the interface.
- Drug substance properties designed for downstream manufacturing process

Utilization of Design Space: **Effective Process Control and Quality System**

- Use of extensive monitoring during development to enhance process understanding.
- Use science based control during manufacturing.
- However, process control may be limited by time needed for biological assays.

Process Analytical Technology (PAT) is an integral part of Quality by Design

- Used in development to gain process understanding
- Implemented in routine manufacturing to monitor process, control product quality and reduce release testing control
- PAT testing can replace additional laboratory testing

APPLICATIONS OF QUALITY BY DESIGN (QbD)[7,8,10,22-29]

Quality by design (QbD) – a comprehensive systematic approach to pharmaceutical development and manufacturing

Advancement in the pharmaceutical development and manufacturing by Qbd can be explained against traditional approach (Table:1).

Table 1: Pharmaceutical aspects: Traditional versus QbD.

Aspects	Traditional	QbD
Pharmaceutical Development	Empirical	Systematic; Multivariate experiments
Manufacturing Process	Fixed	Adjustable within design space; opportunities for innovation
Process Control	In process testing for go/on-go; offline analysis wide or slow response	PAT utilized for feedback and feed forward at real time
Product Specification	Primary means of quality control; based on batch data	Part of the overall control strategy, based on the desired product performance
Control Strategy	Mainly by intermediate product and end product testing	Risk based; controlled shifted up stream, real time release
Lifecycle Management	Reactive time problem and OOS; Post approval changes needed	Continual improvement enabled within design space

In Pharmaceutical Development

To design a quality product and a manufacturing process to consistently deliver the intended performance of the product

QbD IN CMC REVIEW OFFICES

- Science-based assessment
- Restructured organization and reorganized staff – premarket staff and postmarket
- CMC Pilot
- A number of applications submitted
- Lessons learned
- Evaluation of information
- Implementation of PMP

Office of New Drug Quality Assessment (ONDQA)

- Science-based assessment
- Restructured organization and reorganized staff – premarket staff and post market
- CMC Pilot
- A number of applications submitted
- Lessons learned
- Evaluation of information
- Implementation of PMP

Office of Generic Drugs (OGD)

- QbR contains the important scientific and regulatory review questions
- Evaluate whether a product is of high quality
- Determine the level of risk associated with the manufacture and design of this product.
- 416 applications received using QbR by June 2007
- Successful in ensuring that questions address issues regarding QbD

Office of Biotechnology Products

- Have more complex products
- Already doing some aspects of QbD
- In process of preparing to accept applications using QbD
- Beginning a pilot for biotech products for QbD –using mainly comparability protocols
- Also implementing Q8, Q9 and Q10

BENEFITS OF IMPLEMENTING QbD FOR FDA

- Enhances scientific foundation for review

- Provides for better coordination across review, compliance and inspection
- Improves information in regulatory submissions
- Provides for better consistency
- Improves quality of review (establishing a QMS for CMC)
- Provides for more flexibility in decision making
- Ensures decisions made on science and not on empirical information
- Involves various disciplines in decision making
- Uses resources to address higher risks

Benefits to Industry

- Ensures better design of products with less problems in manufacturing
- Reduces number of manufacturing supplements required for post market changes –rely on process and risk understanding and risk mitigation
- Allows for implementation of new technology to improve manufacturing without regulatory scrutiny
- Allows for possible reduction in overall costs of manufacturing –less waste
- Ensures less hassle during review –reduced deficiencies –quicker approvals
- Improves interaction with FDA –deal on a science level instead of on a process level
- Allows for continuous improvements in products and manufacturing process.

Pharmaceutical Development

Widely used in pharmaceutical development and manufacturing (Figure: 6).

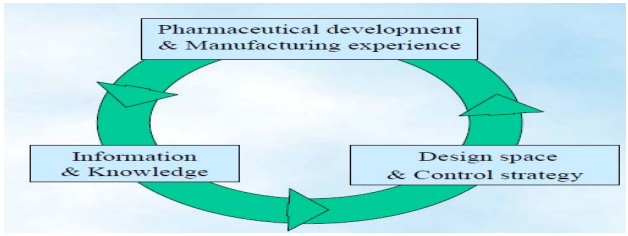

Figure 6: pharmaceutical developments

Used in PAT

A system for designing, analyzing and controlling manufacturing through timely measurement of critical quality performance attributes of raw and in process materials and processes with the goal of ensuring final product quality (Figure : 7).

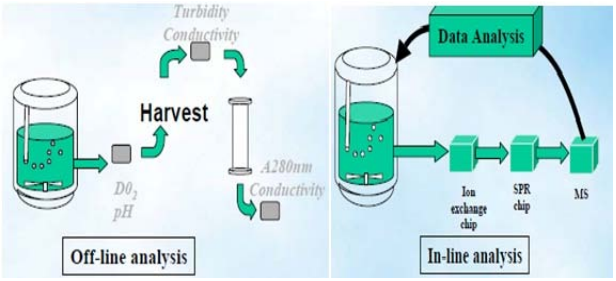

Figure 7: Off-line & On-line Analysis

For experimental design

A structured organized method for determining the relationship between factors affecting a process and the output of that process (Figure: 8).

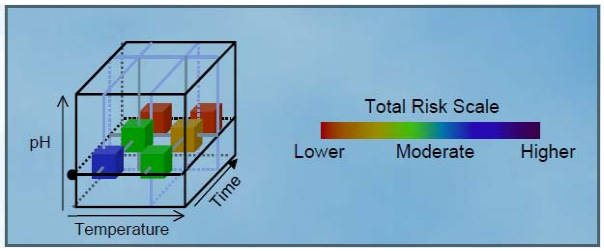

Figure 8: For experimental design

Design Space

Multidimensional combination of and interaction of input variables and process parameters that have been demonstrated to provide Quality Assurance (Figure: 9)

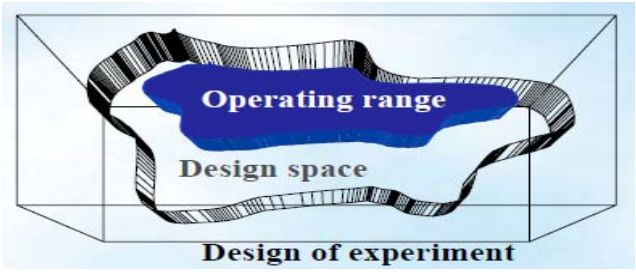

Figure 9: Design space

- Linkage between process inputs (inputs variables and process parameters) and critical quality attributes
- Proposed by Applicant
- Subject to regulatory assessment and approval
- Implementation before or after MA
- Established for one or more unit operation(s) or up to complete process
- Working within the design space: not considered as a change

HPV vaccine manufacturing process by using QbD

Manufacturing process of HPV vaccine can be performed by using QbD (Figure: 10)

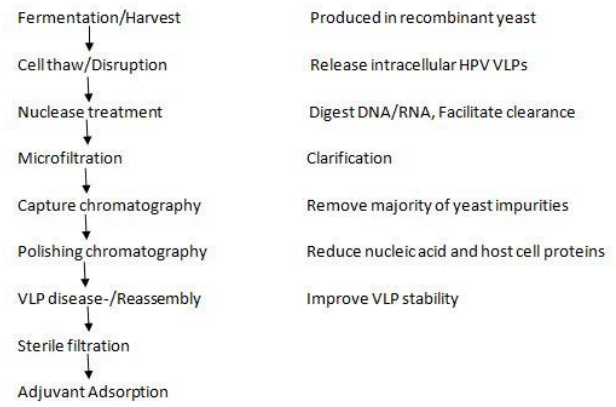

Figure 10: Manufacturing Process of HPV vaccine

Quality by design approach in coating process

Quality cannot be tested into product but it should be built in product. Parameters that affect the coating process are given below (Figure: 11). Traditional and Quality by Design approach can be explained for the coating process (Figure: 12).

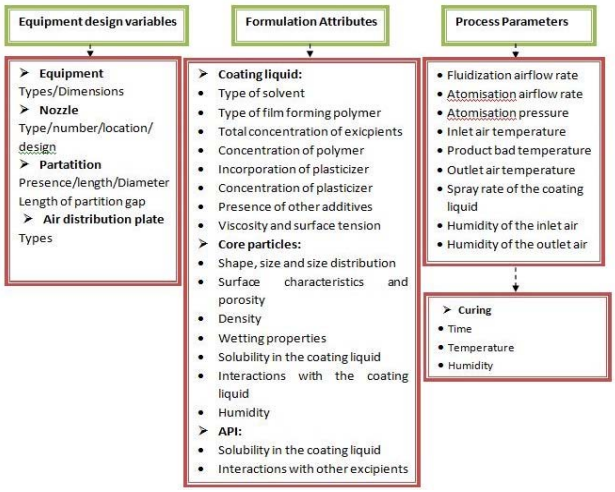

Figure 11: Parameters that affects coating process

Figure 12: Traditional and Quality by Design approach in coating process.

Quality target product profile for the ANDA product

The Quality Target Product Profile (QTPP) is "a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product."1 The QTPP is an essential element of a QbD approach and forms the basis of design for the development of the product. For ANDAs, the target should be defined early in development based on the properties of the drug substance (DS), characterization of the RLD product and consideration of the RLD label and intended patient population. By beginning with the end in mind, the result of development is a robust formulation and manufacturing process with an acceptable control strategy that ensures the performance of the drug product.

A critical quality attribute (CQA) is "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality."1 The identification of a CQA from the QTPP is based on the severity of harm to a patient should the product fall outside the acceptable range for that attribute.

All quality attributes are target elements of the drug product and should be achieved through a good quality management system, appropriate formulation/process design and development. From the perspective of pharmaceutical development, we only investigate the subset of CQAs of the drug product that also have a high potential to be impacted by the formulation or process variables. Our investigation culminates in an appropriate control strategy.

CONCLUSION

The goal of a well-characterized method development effort is to develop a reliable method that can be demonstrated with a high degree of assurance to consistently produce data meeting predefined criteria when operated within defined boundaries. QbD can be applied to the development and evaluation of analytical methods.

During method development, all potential factors (the inputs) and all critical analytical responses (the outputs) are studied to determine the relationships. Critical analytical factors are identified in an approach that parallels what is described for process development in ICH Q8 and Q9. The QbD process on an active partnership of analytical scientists at both the development and operational laboratories as methods are developed and as factors that lead to potential method failures are identified and controlled. A corporate knowledge repository is required throughout the process to ensure critical information is captured that can be reviewed and added to in the future such that lessons learned can be applied to the specific method under consideration and also to other similar methods being applied to other products. Such a repository (in line with concepts described in the draft ICH Q10) will enable continuous improvement and change control of the method to take place throughout its lifecycle.

Rather than continuing to perform analytical technology transfer exercises and ICH validation, a QbD approach

based on a risk-assessed change control procedure should be adopted. Each time a method is changed, a risk assessment should be performed. Where the change is identified as having a potential to take the method outside its known design space, a method evaluation and, if appropriate, an equivalency exercise should be performed to ensure method performance criteria are still met. This will allow for method improvements to be made via internal change control procedures, and even switches between different techniques (e.g., HPLC versus NIR) may become much easier to implement.

A QbD approach for analytical methods that includes risk assessment, robustness testing, and ruggedness testing is much more rigorous than ICH validation requirements (Q2(R1)). It also includes an assessment of method variability compared with the specification limits, which is one of the most important method attributes to test when deciding whether the method is fit for its purpose. The approach described herein suggests that ICH Q2(R1), while adding some value, must be substantially rewritten to take account of the QbD risk-based approaches described in this article.

This new QbD process offers the opportunity for much greater regulatory flexibility in the future. The method performance criteria could potentially be registered instead of the method itself. The method used could be referred to as an example of how to attain the required method performance criteria. Any changes to this method would be covered by internal change control procedures.

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