International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2807-2822 www.ijprajournal.com ISSN: 2249-7781

Implementation of Question-Based Review In Support Of Quality by Design Streamlining the Us Fda's Review Process

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Submitted: 09-06-2023 Accepted: 19-06-2023

ABSTRACT

Question-based Review is a layout proposed by the US Food and Drug Administration (US FDA) that enhances the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use's Common Technical Document (ICH CTD) format to modernise the submission process. It's a question-answer format applied to the Quality Beat All Summary section of the submission. This format will put questions under every section, so the applicant can submit accurate data for acceptance of the actual application. The QbR arrangement is often applied to NDA, ANDA, and sort II DMF applications. The associated document available with Manual of Policy and Procedures 5015.10 (MaPP 5015.10) allows the reviewer to examine the critical information within the data provided. It encourages applicants to surround quality in their development process on purpose. QbR gives a structure through which the information collected by applying QbD is often presented. For effective application of the QbR format, the submission should be underwritten with thorough knowledge of the domain, risk assessment data, and data integrity. The questions asked drive the applicant to provide justification for the varied decisions made within the development phase. Also, questions regarding the quality target product profile, critical quality attributes, critical material attributes, critical process parameters, and style of experiment are balanced under the question-based review format. MaPP 5015.10, confirmed by the US FDA in 2014, clarifies the concept of QbR. There's MicroQbR available, which incorporates questions confirming the sterility of the merchandise. QbR is a step that can accelerate the review process with the intention of motivating the applicants to implement QbD in the project. [1]

Keywords: Question-based Review, Quality by Design, US-FDA, Quality Risk Management, ANDA, Design of experiment.

I. INTRODUCTION

Question-based review is a question-answer format intended to be incorporated in the Quality Overall Summary (QOS) section of the Common Technical Document (CTD), which includes the summary of data submitted to get the new drug approval. QbR may be a framework proposed by the Office of Generic Drugs (OGD) that focuses totally on critical pharmaceutical quality attributes.

QbR may be a podium for the application of the Centre for Drug Evaluation and Research's (CDER's) Pharmaceutical Current Good Manufacturing Practises (cGMPs) for the 21st century: A risk-based approach and an initiative to include Quality by Design (QbD) studies and process understanding in the drug approval applications. 1 QbR contains important scientific and regulatory review questions related to product and process design and understanding, product performance, analytical method validation, stability study, control strategy, etc. Recently, obstetrician topics also executed QbR successfully in clinical data handling in favour of branches of multiple choice questions of the respective category, viz., anaemia in pregnancy, screening of fatal chromosomal abnormalities, and vaginal birth after previous caesarean delivery.

QbR is additionally considered a development crossroad, promoting the inclusion of the Pharmaceutical Development Report (PDR). [1]

Historical background

In 2007, the FDA received an estimated 5,000 supplements, which was actually a striking increase in the number of manufacturing supplements to applications for new drug

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2807-2822 www.ijprajournal.com ISSN: 2249-7781

applications (NDAs), biological licence applications (BLAs), and abbreviated new drug applications (ANDAs). FDA recognised that there was an increase in lapses in NDA or ANDA submissions by the firms; a large number of supplemental applications for every manufacturing change were received. In both the original applications and supplements, the data mainly focused on chemistry. And the least attention was given to other important aspects of manufacturing, such as engineering and product development. Eventually, the FDA acknowledged that more and more controls were required for drug manufacturing processes for efficient drug products and, no doubt, for better regulatory decision-making. It resulted in a more stringent regulatory upbringing. To solve this issue in 2002, the FDA implemented changes through the pharmaceutical cGMP (good manufacturing practise) for the 21st century. Expectations were mentioned in Process Analytical Technology (PAT), which is a system for designing, analysing, and controlling manufacturing processes based on understanding science and factors that affect the quality of the final product. In 2005, it was time to implement QbD for a more systematic approach, and the USFDA asked some firms to submit their CMC in QbD format (Patricia, 2007). Question-base review (QbR) forms the platform of the QbD principle (Aloka and Robert, 2009). In a recent interview by Nick (2011) with Lawrence Yu, Deputy Director, Science and Chemistry, the FDA indicated that 2013 is the deadline for generics to implement QbD. [2]

REGULATORY ASPECTS TO QBD:[1,2,5,7]

The concept of quality by design (QbD) in the pharmaceutical industry has been introduced to enhance robust manufacturing processes, facilitate product quality, and manufacture products in terms of "six sigma." The PUCC (process of understanding control and capability) is a loop process implemented for continuous improvement. "Six Sigma" is a system of practises developed for systematic improvement of processes that eliminates defects with statistical significance. Since it was originally developed, six sigma has become an important element of many total quality management (TQM) initiatives. The significant number of reports on out-of-trend (OOT) results, out-of-specification (OOS) results, out-of-control (OOC), and out-of-statistical control (OOSC) indicate that the present system of the pharmaceutical industry is not immune to these issues. Hence, pharmaceutical industries are striving for new strategies and/or new elements that can add to or replace the existing elements of quality and risk management systems. [5] . For ensuring consistency of performance of pharmaceutical products and systems, the recent emphasis has been on building the "quality" instead of merely testing it. This philosophy forms the idea of "quality by design (QbD). ICH guidance Q8(R2) describes QbD as "a systematic approach to pharmaceutical development that begins with predefined objectives and emphasises product and process understanding and control, based on sound science and quality risk management." [1] The concept gravitates towards a "desired state" marked with "regulatory flexibility," focusing on scientific

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knowledge building, superior design, demonstration of performance, quality risk assessment (QRM), design of experiments (DoE), process analytical technology (PAT) tools, continuous improvement and learning, and life-cycle management [7].

ICH Q8, Q9, Q10 GUIDELINES: THE FOUNDATION OF QbD2,3,6,18

ICH Guidelines Q8 for Pharmaceutical Development, Q9 for Quality Risk Management, Q10 for Quality systems are foundation of QbD.

Quality by Design relative to ICH20,21

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

Critical Concept: Design Space19-21

- 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[6]

STEPS INVOLVED IN QUALITY BY DESIGN PRODUCTS:

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[6]

Benefits of qbd:[6,8,9,10]

- 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

Opportunities:[6,11,12,14]

- 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.

This Figure. pictorially depicts the building blocks of a QbD-based progression [7].

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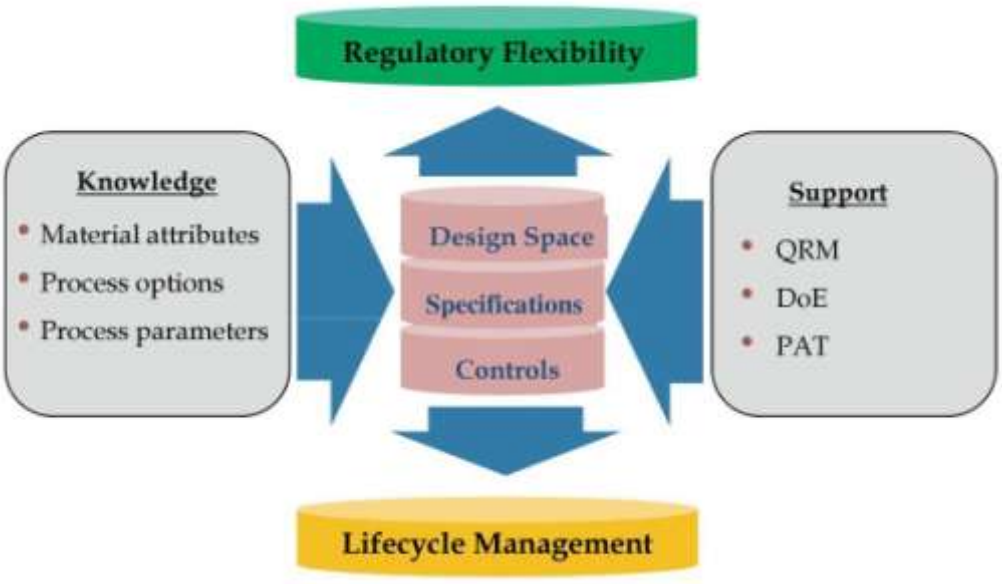

TOOLS FOR QBD:
Building blocks of Quality by Design (QbD); Key terms: QRM: Quality Risk Management; DoE: Design of Experiments; PAT: Process Analytical Technology.[7]

PAT as an important tool of QbD:

PAT is defined as "tools and systems that utilise real-time measurements, or rapid measurements during processing, of evolving quality and performance attributes of in-process materials to provide information to ensure optimal processing to produce a final product that consistently conforms to established quality and performance standards." [10]. ICH Q8 [9] identifies the use of PAT to ensure that the process remains within an established design space. The concept originates from the desire of the regulators to shift control of product quality towards a science-based approach that explicitly attempts to reduce the risk to patients by controlling the manufacturing process based on an understanding of the process. From a PAT standpoint, a process is considered well understood when [14, 15]

(1) All critical sources of variability are identified and explained; (2) variability is managed by the process; and (3) product quality attributes can be accurately and reliably predicted.

3.3.1. PAT steps With the combination of guidelines [10] and the literature of Read et al., there is a three-step process in the design and optimisation of drug formulations and manufacturing processes, namely design, analysis, and control. In the design step,experimentation is performed to understand which quality attributes are related to a given unit operation and which process parameters and raw material attributes have the most impact on the final product quality. This knowledge is then used to identify the QTPP, CPP, and CQA, which are needed for consideration in the design of an effective PAT-based control scheme for the process. [16]

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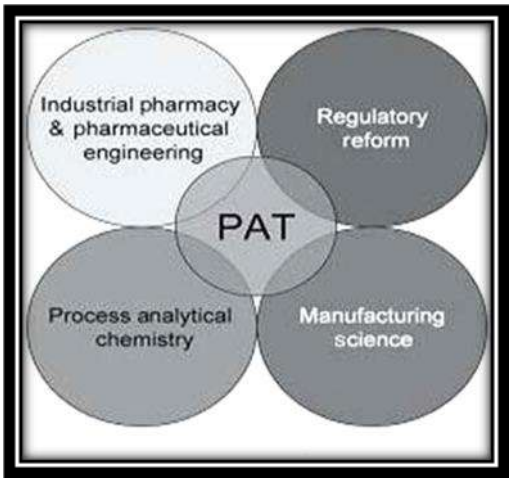

The objective for PAT implementation could be one or more of the following:

- Better process understanding
- Improved yield because of the prevention of scrap, rejects, and reprocessing
- Reduction in the production cycle time by using online, at-line, or in-line measurements and control
- A decrease in energy consumption and improved efficiency result from the conversion of the batch process into a continuous process.
- Cost reduction because of reduced waste and reduced energy consumption
- Real-time release of the batches

From an implementation perspective, perhaps PAT can be visualised as the three-step process illustrated in Fig. 1. The design phase starts early in process development when the given unit operation is being designed, optimised, and characterised. In this phase, the critical quality attributes (CQA) that are being affected by the process step are identified, along with the critical process parameters (CPP) that have been determined to affect the CQA. This process understanding is the essence of PAT and critical for the next two phases.

Design of experiment (DoE):

To carry out the design of the experiment, the risk assessment should be taken into account first. A structured, organised method for determining the relationship between factors affecting a process and the output of that process is known as "Design of Experiments" (DoE). DoE is an excellent tool that allows pharmaceutical scientists to systematically manipulate factors according to a pre-specified design. A good design is based on sound cognition of the product and effective management of the whole process during manufacturing. DoE studies work together with mechanism-based studies to achieve better product and process understanding. DoE is a reasonable method to determine the relationship between the inputs and outputs of a process. It can help identify optimal conditions,CMAs,CPPs,and,ultimately,the design space. It is wise to establish a design space through DoE for multivariate experiments. ICH Q8 defines the design space as "the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality" [17].. It has been reported that there is no need to hand over supplements to revise (e.g., widen) the acceptance criteria to the FDA if the changes are within the design space. So far,a number of studies have been launched in the drug delivery systems after the QbD initiative was claimed,as summarised in Table 1. It has been demonstrated that DoE is effective in the design of different dosage forms and unit operations, and it can be used more broadly in the near future to guarantee high research efficiency with improved product quality. [18,19]

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Design:

Design: An experimental design consists of specifying the number of experiments, the factor level combinations for each experiment, and the number of replications.

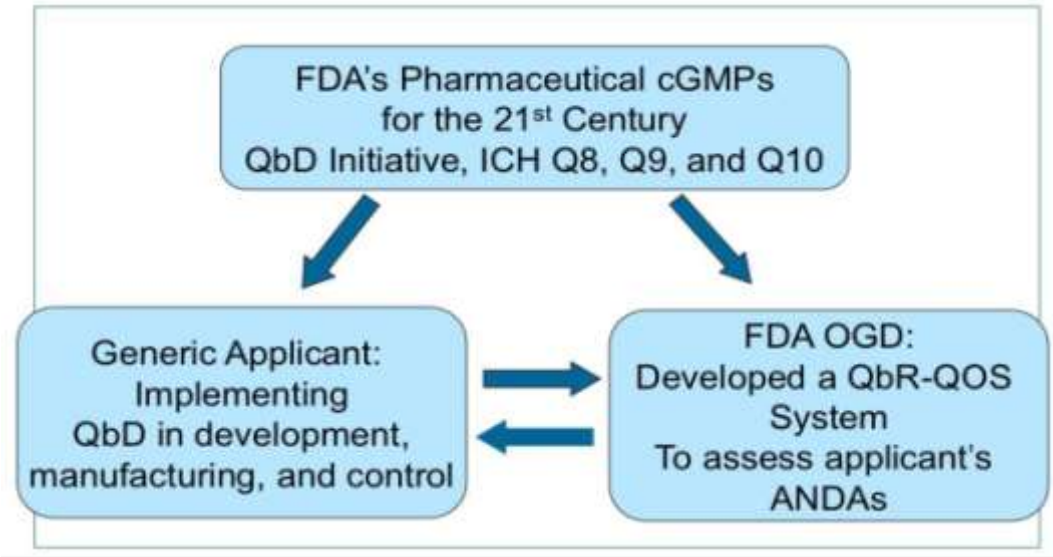
- In planning an experiment, you have to decide

1. what measurement to make (the response)
2. What conditions to study
3. what experimental material to use (the units). •

Example:

1. Measure the goodput and overhead of a routing protocol.
2. Network with n nodes in chain
3. Routing protocol, type of nodes, type of links, traffic [9]

GENESIS OF QBR:



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What is QbR-QOS?

- Uses a question-and-answer format
- Is a general framework for a science- and risk-based assessment of product quality.

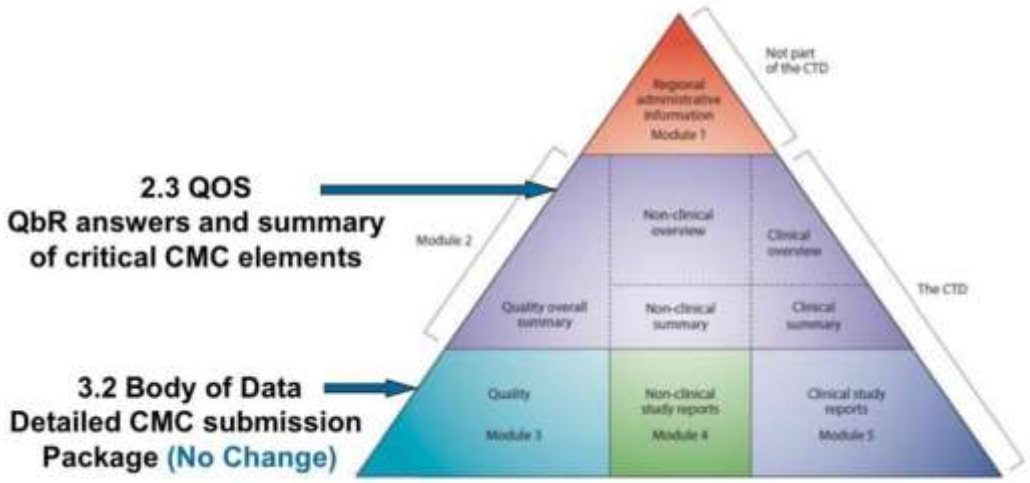
The QbR-QOS initiative started in 2005 in the Office of Generic Drugs (OGD).
fully implemented for the CMC evaluation of ANDAs (abbreviated new drug applications) in 2007.

- Included are examples, Q&A, and outreach.

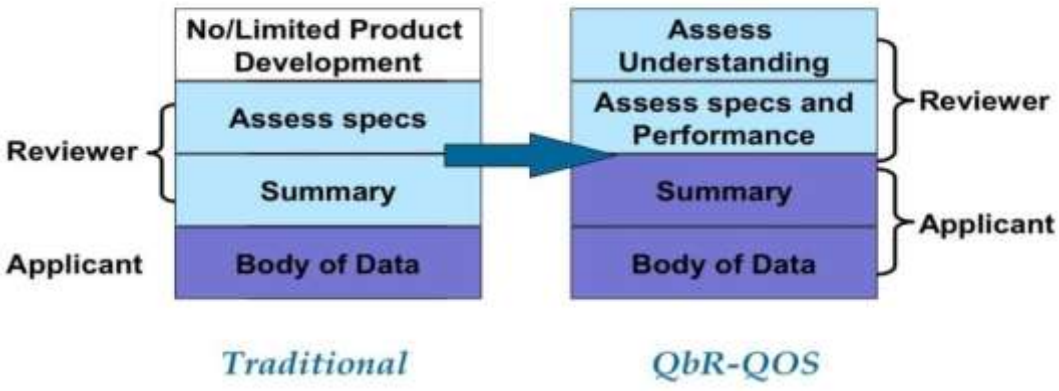
Currently, it is used by 100% of the generic industry for ANDA submissions.
A little more about QbR...

- Contains answers to important scientific and regulatory review questions.
  - Critical formulation and manufacturing variables
  - Specifications relevant to quality and performance
  - Risk of the design and manufacture
  - Control strategy[20]
- Expectation that ANDA applications be organised according to the Common Technical Document (CTD)
  - Builds upon CTD QOS
  - Results in minimal change for applicants generating multi-region submissions
  - Encourages electronic submissions [20].

ICH Common Technical Document:



Traditional vs. QbR-QOS ANDA Submissions



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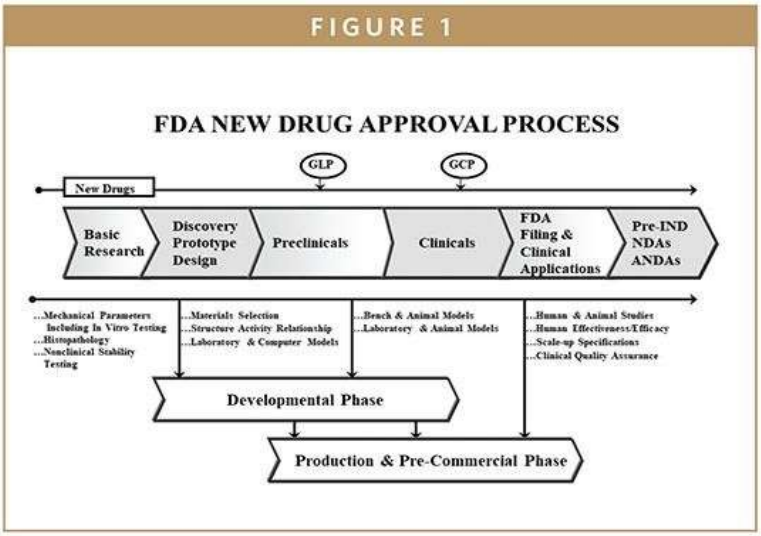
Positive Aspects of QbR-QOS

- Consistent with the current quality-by-design (QbD) paradigm
- Congruent with risk management approaches
- Seeks justification for choices made throughout the development and manufacture of generic products.
- Increases transparency in the thought processes of the applicants, which helps to reduce deficiencies and seek clarification.

QbR for Review of New Drug Applications (NDA)

FIGURE 1



- Explore the utilisation of the QbR approach for NDA review. To study:
  - Support the adoption of a science- and risk-based review.
  - Standardise the review approach for both NDAs and ANDAs.
  - Facilitate consistent communication with all quality stakeholders.
- Develop a QbR-based review template for both the NDA and the ANDA.
  - supports the implementation of integrated team-based review within the OPQ (Office of Pharmaceutical Quality).
- Initial Steps: The OPS TAG (Technical Advisory Group) team is set up.
- Included expert QbR users from Generic Drug Chemistry and review staff from ONDQA (Office of New Drug Quality Assessment) to explore the feasibility of implementation of QbR for NDA review.
- Develop one set of overarching QbR questions that apply to both new and generic drug products. [21,22]

QbR Review of NDAs:

- Led to a more focused, faster review.
- Proved useful as a standardised review tool
- Enhanced consistency
- Differentiated the applicant's response from the reviewer's evaluation
- The use of QbR questions that included risk assessment, QTPP, CQAs, critical properties of intermediates, etc. contributed to: enhanced product and process understanding; facilitation of patient-centric risk-based evaluation.
- Developed a single set of high-level questions that address the critical development aspects across various dosage forms and are applicable for new and generic drug substances and drug products.
- Additional review tools were developed:
  - A Quality Checklist
  - "flag" high-risk or noteworthy aspects of an application.
  - QbR Companion Documents: These documents contain additional details for each QbR question, e.g.,
  - What the applicant should provide for each question
  - Points of Consideration for Reviewers [21]

ANDA:

This guidance is intended to assist applicants in preparing abbreviated new drug applications (ANDAs) for submission to the FDA under Section 505(j) of the Federal Food, Drug,

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and Cosmetic Act (FD&C Act). This guidance details the information that should be provided in each section of the common technical document (CTD) format for human pharmaceutical product applications and identifies supporting guidance documents and recommendations issued by FDA to assist applicants in preparing their ANDA submission. This guidance identifies the information that an applicant should include to ensure that a complete, high-quality application is submitted to the FDA. FDA has previously published guidance documents on the filing process, including guidance for industry about refuse-to-receive standards and common, recurring deficiencies, which should be reviewed thoroughly prior to submission of an ANDA.

In general, the FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in agency guidance means that something is suggested or recommended but not required. **[23]**

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 the 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 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 in 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 and 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. [23,24]

Emergence of QbR:

The introduction of QbD required a platform to execute the same; QbR-QOS is the platform (Figure 1). It encourages the implementation of QbD. It makes the review process more efficient. Also, the bottlenecks with the previous review system necessitated the implementation of QbR. It uses QbR experiences from other CDER components (e.g., CDER MaPP 4000.4 Clinical Pharmacology and Biopharmaceutics Review Template), as well as other regulatory authorities (e.g., Health Canada) that use the QOS as a foundation for the primary chemistry review document. Before the introduction of the CTD format, the applicants would submit an expert report produced by an expert in the field, giving a summary of the documents. Later, with the introduction of CTD, QOS was submitted by applicants. Further, to streamline the application review process, the US FDA introduced QbR-QOS. A timeline depicting the development of QbR-QOS is given in Figure 2. [25]

Figure 1: Evolution of QbR-QOS.

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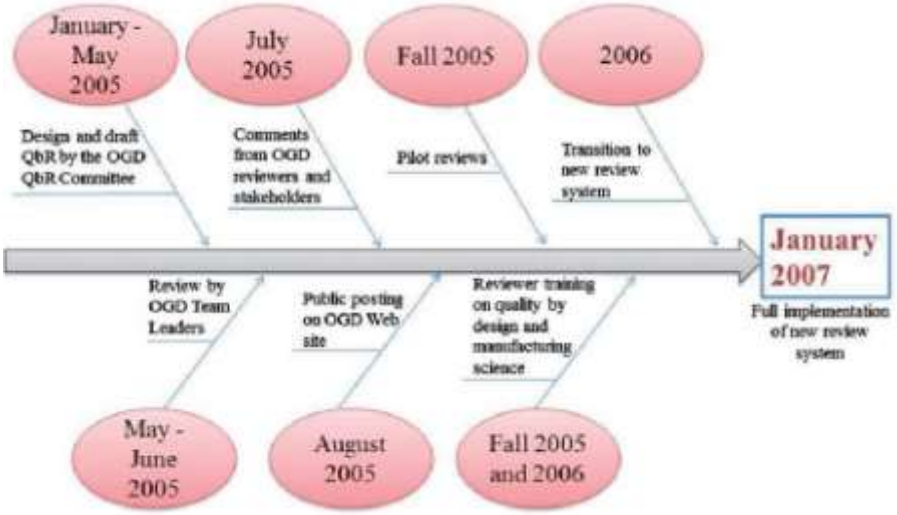

Figure:2 Chronological evaluation of QbR system.

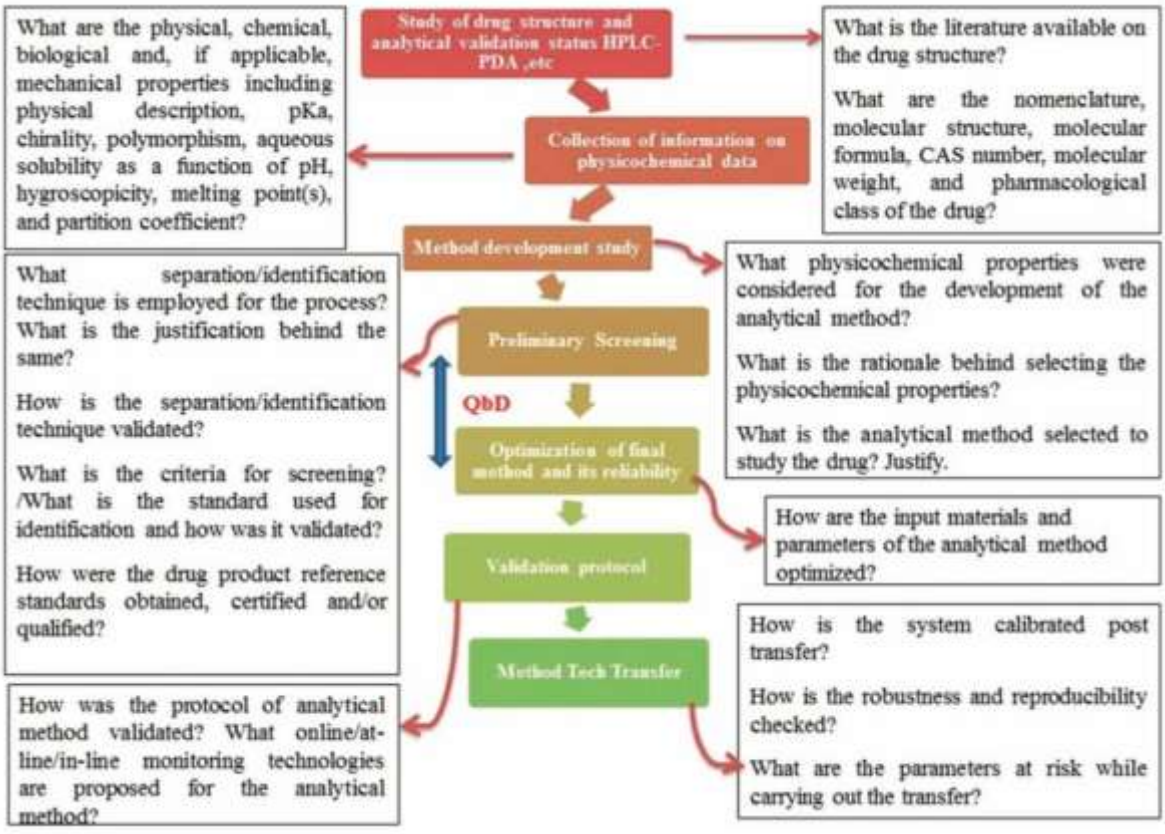

Figure 3. Hypothetical schematic case study (analytical method development) on QbR-QbD environment.

Why is QbR necessary?

The bottlenecks of the previous review system were: (a) quality by end-product testing; (b) little or no scrutiny on product and process design; (c) little or no mechanistic understanding; (d) overly conservative specifications; and (e) it did not adjust the review to the level of scientific understanding. [25]

Benefits of QbR5 [25, 26]

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The QbR format benefits applicants in the following ways:

- helps execute QbD,
- better inter-departmental communication,
- reveals what information the FDA considers critical,
- reduced supplements. The QbR has come in handy for reviewers as it has encouraged:
  - consistent evaluation,
  - assess critical information,
  - reduced supplements,
  - concise data,
  - smooth preparation of the primary review report

Micro QbR6

The QbR framed for terminal sterilisation and/or aseptic processing covers the following aspects:

- Overall manufacturing operation
- Microbiological monitoring of the environment
- Container closure integrity
- Sterilisation/depyrogenation processes
- Specifications for product release and product stability.

Methodology for applying QbR approach adjoined with QbD:

QbR incorporates a list of questions that intend to cover the multiple sections under QOS with a focus on the implications of QbD and risk-based knowledge. The various questions addressing the elements of QbD are categorised in this review article. Quality by Design (QbD) is an approach to incorporating quality into the product process from the very beginning. It focuses primarily on product and process understanding and quality risk management. Approval of the QbD design reduces the number of supplements usually required to be filed post-approval. Hence, an updated and thorough review summarising the QbR for application of the adjoining QbD in the regulatory window in detail is presented here. [25]

Step 1: Quality Target Product Profile

- What is the quality target product profile (QTPP) of the finished product based on the proposed indication and patient population? How is the QTPP justified?
- What are the quality attributes of the finished product?

Step 2: Critical quality attributes

- What are the quality attributes of the finished product? Which quality attributes are considered critical quality attributes (CQAs)? For each CQA, what is the target, and how is it justified?
- What is the approach for meeting the CQAs related to clinical performance? If applicable, what in vitro bio-performance evaluations (i.e., dissolution method, flux assay, etc.) were used during pharmaceutical development to ensure clinical performance?

Step 3: Identification of critical material attributes and critical process parameters

- What attributes of the drug substance, excipients, and in-process materials were identified as critical, and how do they impact the drug product CQAs?
- What input material attributes and process parameters were selected for study, and what were the justifications for the selection?
- What process parameters and material attributes were identified as critical, and how do they impact the drug product CQAs?

Step 4: Understanding the development process

- What formulation development studies were conducted?
- What biopharmaceutics evaluations (comparative dissolution, bioequivalence studies, biowaivers, etc.) support the formulation changes and link the development formulations to the proposed commercial formulation?
- What process development studies were conducted? Provide a summary table listing batch size, process parameter ranges, equipment type, and estimated use of capacity.

Step 5: Control strategy, including justifications

- For 505(b)(1) applications, what is the rationale for selecting the proposed dosage form for the drug product?
- What is the rationale for the excipient selections?
- What is the rationale for selecting this manufacturing process for the drug product?
- How were the process parameters adjusted across lab, pilot/registration, and commercial scales? What are the justifications for any changes?
- If applicable, what online, at-line, or in-line monitoring technologies are proposed for routine commercial production that allow for real-time process monitoring and control? Provide a summary of how each technology was developed.

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- If applicable, what supportive data demonstrate the compatibility of the drug product with the means of administration (e.g., additives and/or diluents, other co-administered drugs, dosing device)? • What is the commercial batch formula and how does it differ from the registration batch formula? Provide justifications for any differences.
- What is the flow diagram of the manufacturing process that shows all incoming materials, processing steps, unit operations, and in-process controls?
- What are the in-process test results for each process step of the registration batch(es)? What are the differences, if any, in the in-process controls for the registration batch(es) and the intended commercial batches? What are the justifications for these differences?

Step 6: Design the space.

- What evidence supports excipient-drug substance compatibility and, if applicable, excipient-excipient compatibility?
- What are the excipient specifications, and how are they justified? How do the proposed acceptance criteria for the material attributes of the excipients ensure the quality of the final drug product?

Step 7: Risk evaluation

- What aspects of the formulation were identified as potentially high-risk to the drug product's performance?
- What is the potential risk of each process step impacting the drug product CQAs, and how is the risk level justified?
- What are the residual risks upon implementation of the control strategy at commercial scale?

Literature on QbR using QbD approach in Pharmaceutical field :

In the current picture, regulatory bodies are focusing more on the implementation of a QbR-based QbD approach for method development, quality assessment, product improvement for the period of production, product quality control, PAT application, control strategy, risk evaluation, etc. Several reports have been published on the QbR-QbD approach, as detailed in Table 1. Manzural et al.8 reported a road map in the context of generic solid dosage formulation with three important categories, i.e., product, process understanding, and control strategy, along with critical attributes, respectively, with regard to the QbR-QbD approach. They also briefly explained how to control the risk of bioequivalence studies, scale-up, validation, and stability studies. Yu et al.9 well explained the US FDA QbR system for quality assessment of generic drugs and covered up to promote QbR four important beneficial points, viz., assure product quality through design and performance-based specification, continuous improvement along with reduced CMC supplement through risk assessment, quality of review on behalf of standardised review questions, and reduce CMC review time by submitting QOS followed by QbR. Jinag et al. reported QbR in context on behalf of modern pharmaceutical quality regulations. They incorporated QbD (various design of experiments selecting process variables) to influence the product quality by process performance, except for the previously taken documentation in a mechanistic way, viz. manufacturing process, testing result of raw materials, in-process product, and finished product. [25]

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Study no	Research envisaged	Specific Discipline	Remark	References
1	Mitigating the risks of generic drug product Development: an application of quality by design and QbR approaches	Generic formulation and manufacturing process	Control risk, reduce time	Manjurul[8]
2	US FDA QbR for generic drugs: a new pharmaceutical quality assessment system	Quality assessment	Implementation and benefits of QbR	Yu et al.[9]
3	Modern pharmaceutical quality regulations: QbR. In developing solid oral dosage forms	Solid oral dosage form		Jiang and Lawrence[7]
4	FDA Office of Generic Drugs QbR Initiative: an update-past, present, and next steps	QbR	Origin, benefits and challenges faced by QbR	Aloka and Iser[10]
5	FDA Perspectives: common deficiencies in Abbreviated New Drug Applications: part 1: drug substance	Regulatory affairs	Importance of QbR and content expected while answering the questions	Aloka and Iser[11]
6	QbR for generic drugs: an enhanced pharmaceutical quality assessment system (FDA White Paper)	QbR	QbR overview	Food and Drug Administration[12]
7	Advancing product quality: a summary of the inaugural FDA/PQRI Conference	Quality by design	Scope of QbR	Yu et al.[13]
8	QbR: an FDA Reviewer's perspective	QbR	Reviewer's perspective of QbR	Skanchy[14]
9	FDA perspectives: common deficiencies in Abbreviated New Drug Applications: part 2: description, composition, and excipients	FDA perspective	Application of QbR	Aloka et al.[15]
10	FDA perspectives: common deficiencies in Abbreviated New Drug Applications: part 3 – control of the drug product and stability	FDA perspective	Contibution of QbR in reducing deficiencies	Aloka et al.[16]

QUESTION BASED REVIEW TO REVAMP CMC SUBMISSION REVIEW :

Pharma R&D investment has increased 62 percent in the last decade, but the number of new drugs approved is 22 percent lower than the previous decade. The failure rate in phase III, the most expensive part of pharma R&D, is 40 percent. A Data Monitor study of 346 NDAs found that 42 percent of submissions received a complete response letter, resulting in a median delay in approval of 13 months. Cost cutting and the retirement of baby boomers with deep expertise have resulted in a shortage of in-house experts with the savvy to drive innovation and gain regulatory approvals.

The registration dossier for medicines is an important document that is submitted for review to regulatory agencies by pharma companies for approval to market their medicines. Utmost care should be taken during its compilation and filing, as it plays a direct role in the earliest possible availability of medicines in the market, which in turn translates into business for the company.

Global chemistry, manufacturing, and control (CMC) dossiers are critical to a successful regulatory submission. The creation and subsequent assembly of the CMC dossier require orchestrated cooperation between R&D, clinical, regulatory, sales and marketing, and other groups that will have input into this important document. Managing the construction of a clear, concise dossier can be a daunting task, but it doesn't have to be. A simple understanding of best practises surrounding the creation and presentation of the CMC section will make for a successful submission.

QbR is an enhanced pharmaceutical quality assessment system. It is a general framework for CMC assessment of the ANDA. A successful dossier submission can prevent a delay

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 2807-2822 www.ijprajournal.com ISSN: 2249-7781

in product registration. Effective documentation and CMC submission prevent noncompliance; more than 50% of the dossier comprises CMC documentation of substances (API) and product parts (FPP). CMC regulatory compliance is seen as a process of governance that ensures CMC practises are carried out in accordance with regulatory agencies requirements and expectations. Since such requirements and expectations change with time, a function of CMC regulatory compliance is to ensure that all CMC practises are updated accordingly. [26]

Principles for CMC Review:

- Ensure that applications contain the following:

Quality target product profile (QTPP)
Critical quality attributes (CQAs)
Identification of those aspects of drug substances, excipients, container closure systems, and manufacturing processes that are critical to product quality and support the safety and efficacy of the drug product
An understanding of the development of the drug product and its manufacturing process
Control strategy, including justifications

- Evaluate each risk assessment.
- Take a scientific and risk-based approach [26].

Quality Target Product Profile (QTPP)

Drug product? For 505b(2) and 505(j) applications, what are the characteristics of the listed or referenced drug product? [27]
proposed indication and patient population? How is the QTPP justified?
505b(1): scientific and clinical rationale for the selected dosage formcharacterization of the RLD product
–Patient population
-Dosage form and strength(s)route of administration and alternative methods of administration
–Delivery system
Container closure system
Release or delivery of therapeutic moiety and attributes affecting pharmacokinetic characteristics
–Quality attributes

Question-Based Review and the Future of Regulatory Submissions:

The Question-Based Review (QbR) framework, utilised in CDER and CVM, integrates important scientific and regulatory review questions into regulatory submissions. The QbR framework facilitates the communication of risk assessment activities, engenders a comprehensive description of product and process development, and envisages an overall control strategy for drug products assessed by the FDA. Industry professionals and regulators benefit reciprocally from the risk-based evaluation of applications and the integration of risk management into development, communication, and management plans.

QbR questions, which can be integrated into the Quality Overall Summary (QOS), should be asked and addressed internally, in real time, during pharmaceutical development activities, rather than writing answers after the fact for the purposes of submission. QbR creates a framework for the applicant to provide a concise knowledge base for review and lifecycle activities, as opposed to the detail-rich Module 3 of the Common Technical Document (CTD). The QbR framework, moreover, incorporates QbD principles.

QbR questions are meant to be flexible; irrelevant questions may be omitted, and related questions may be grouped together to provide a concise overview. The FDA has taken efforts to ensure that quality assessments using QbR do not exclude critical information from the submission. A CDER MaPP on QbR has been issued (21). 21. The FDA Centre for Drug Evaluation and Research (CDER) issued a QbR MAPP for chemistry review. [27]

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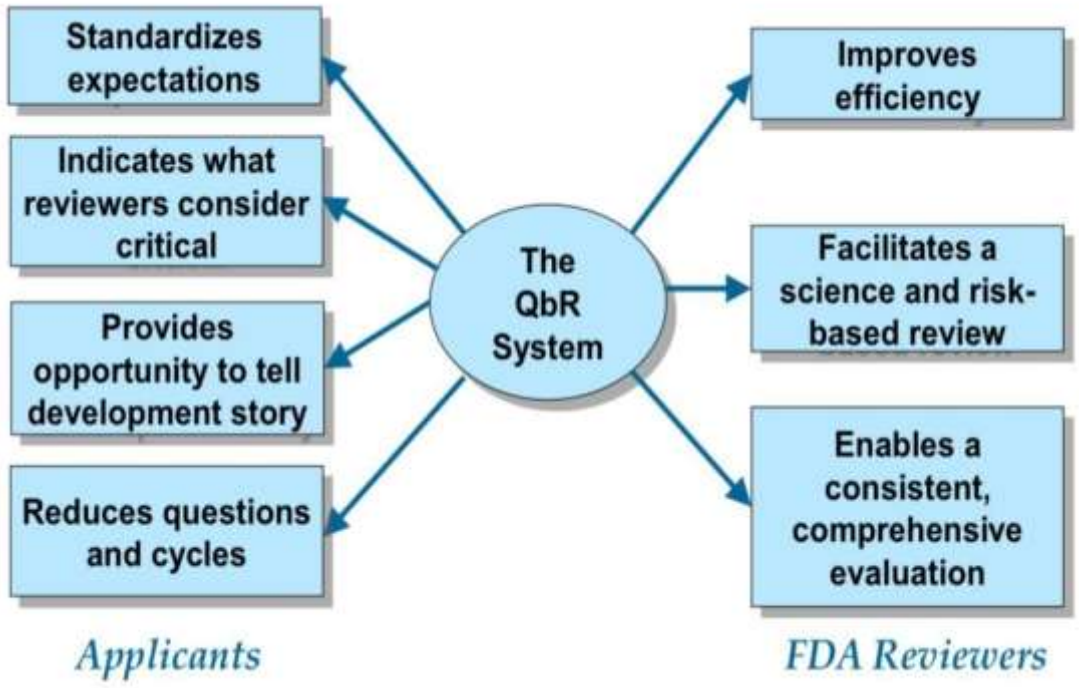
Volume 8, Issue 3 May-June 2023, pp: 2807-2822 www.ijprajournal.com ISSN: 2249-7781

Benefits of QbR:



II. CONCLUSION:

The goal of a well-characterised 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.

This review article illustrates the concept of QbRQOS and its execution in generic drug development, along with QbD, and offers a better knowledge presentation of raw materials and manufacturing parameters (with critical quality attributes) impacting finished product quality. This will result in a more robust process for the US-FDA review system in various complicated situations (production, manufacturing, quality control, pharmacovigilance) under the QbR advance scheme. Therefore, we conclude that QbR-QOS is a dynamic model that will give better prospects for ANDA sponsors to make generic drugs available to the market faster and also be helpful in maintaining the quality of drug products through relevant document submission in regulatory compliance. [28]

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