International Journal of Advances in Pharmacy Medicine and Bioallied Sciences
International, Peer-reviewed, Indexed, Open Access, Biomedical Journal
www.biomedjournal.com
ISSN 2348-2109
International Journal of Advances in Pharmacy Medicine and Bioallied Sciences
www.biomedjournal.com
Indexed, Open Access, Peer-reviewed.

Review Article

Quality by design in pharmaceutical industries: a review.

Monali Bora*, Vishal Rasve, Poonam Ghorpade, Mahesh Kshirsagar, Kalpesh Tated.

SAJVPM ' s, College of Pharmaceutical Sciences and Research Center, Kada Ashti, Beed, M.S., India.

ARTICLE INFO

Article History

Received : 15-Oct-2022
Revised : 05-Nov-2022
Accepted : 10-Dec-2022

Key words

Quality by design,
Risk management,
ICH guidelines.

ABSTRACT

Quality by design (Qbd) is a modern approach to the quality of pharmaceuticals. It is describing the use of Qbd to ensure the quality of pharmaceuticals. In this review, Qbd is described as some elements. It is based on ICH Guidelines Q8 for pharmaceutical development, Q9 for quality risk management, Q10 for pharmaceutical quality systems. It also gives definitions, and applications, in Qbd in the pharmaceutical industry development and manufacturing of pharmaceutical products. Quality by design is a treading concept that is widely utilized for the optimization and development of pharmaceutical processes and product development worldwide. A large no.of industries are shifting towards risk-based approaches like Qbd as per their convenience and due to regulatory requirements these days .through along with complete knowledge about the process. This review has briefly described the elements of quality by design including basic terms like CPPs, CMAs, CQAs, QTPP, and design space along with advantages of regulatory bodies, regulatory challenges, and inspection & future perspective. It also includes prospects and current challenges and barriers associated with the acceptance of this concept among pharmaceutical industries.

*Author for Correspondence: chetanabora26@gmail.com

DOI: https://doi.org/10.5281/zenodo.7708999

INTRODUCTION

The concept of Quality of Design first erupted in the mind of the quality expert of products, and equipment. Qbd is a very scientific and very systematic approach that allows the building of quality for products from the very beginning and not just by testing it in the end [1]. The main purpose of Qbd in pharmaceutical companies is based on the manufacturing and innovation a quality product. Pharmaceutical companies are constantly working to empower and ensure the safety quality and efficiency of the products in traditional the finished products evaluation unit ensures products, quality, and performance, with a limited understanding of the process and critical process parameters (CPP's). Regulatory bodies are therefore focused on implementation through quality by design [2]. Quality by design can be shown as transparency as well as the accuracy of the product for the development process to understand reliability. We can be analysed efficiently and also; we can find and solve the basic problem quickly. The requirements of QbD are determining the extent to which any changes can impact the finished product quality. And also, the identification of all critical formulation attributes and related process parameters [3, 4]. The strategic flow of this concept involves identification of the consumer needs (QTPP), determination of critical quality attributes (CQA) and critical material attributes (CMA) understanding of critical parameters (CPP), Development of a design space, applications of control strategy and lifecycle management [5]. Qbd was printed as a modern approach to the development of critical methodology

and quality product-supported knowledge based throughout the event section [6].

History

The history of Qbd is important as it needs in the current pharmaceutical industry, and also understanding the conventional terms can lead to improvement in terms of present challenges.

According to one of the principal scientists, 'Jasmine' at Dr. reddy's laboratories SA," understanding the history of quality is very important if we want QbD to become entrenched in the pharmaceutical industry. History teaches perspective and proportion and I feel that both of these are lacking in the debate on how and why QbD provides better drugs and healthier lives. Besides, an awareness of quality history reduced the risk of mistakes being repeated in healthcare, mistakes can be fatal" [7]. In 2002 a new initiative by a federal agency for risk management (cGMP for the 21st century: a risk–based mostly approach). This began to modernize the regulation of FDA for pharmaceutical quality and to initiate a brand-new regulative framework supported Qbd management of risk and quality system This newer idea by FDA-cGMP initiative, two documents introduced by ICH for guiding the standard, that is lCH-Q8 (pharmaceutical development) & ICH-Q9 (QRM). The pharmaceutical business permits a lot of freedom to introduce new ideas, innovations, and enhancements which will enhance quality costing, or timing [8-10].

Definitions: As per ICH Q8 (R2) Pharmaceutical development 2009, QbD is defined as "A systematic approach to development that begins with predefined objectives and emphasizes products and process understanding and process control, based on sound science and quality risk management. It means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives. QbD identifies characteristics that are critical to quality from the perspective of patients and translates them into the attributes that the drug product should possess. And establish how the critical process parameters can be varied to consistently produce a drug product with the desired characteristics [11,12]. As per ICH Q8 (R1) A Systematic approach to development begins with predefined objectives and emphasizes products and methodology, understanding and methodology management, supported sound science, and quality risk management (QRM) [13].

Quality Design

1. Product is designed to meet patients' needs and performance requirements.
2. Process is designed to consistently meet product quality attributes.
3. Impact of starting raw materials and process parameters on product quality is understood.
4. Critical sources of process variability are identified and controlled.
5. The process is continuously monitored and updated to allow for consistent quality over time.

Step involved in quality by design products

1. Development of new molecular entity:
   - Preclinical study
   - Non-clinical 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. Here an independent quality by a design expert.
2. Audit your organization and process with the expert conducting a gap analysis
3. Hold basic quality by-design workshops with all your personal
4. Review the experts' reports and recommendations.
5. Draft an implementation plan, timelines, and estimated casts
6. Assign the resources (or contract out)
7. Retain the independent expert as your "project Assurance" advisor.

Benefits of QbD

Qbd could be a sensible business that eliminates batch failures and minimize deviations and expensive investigation. QbD additionally avoids regulative compliance issues and structure learning could be reasonably invested in the future.

Qbd is sweet science that offers higher development selections and management of technical employees. Qbd is an economical angle. it ensures consistent info and much better risk management a knowledge domain is made primarily for all merchandise [14-16].

- Build scientific knowledge for all cases of products.
- QbD is good business.
- Eliminate batch failures.
- Minimize deviations and costly investigation.
- Avoid regulatory compliance problems.
- Organizational learning is an investment in the future.
- QbD is good science.
- Better development decisions.
- Empowerment of technical staff.

Objectives of pharmaceutical quality by design

1. To achieve meaningful product quality specifications that are based on clinical performance.
2. To increases process capability and reduce product variability and defects by enhancing products and process design understanding and control.
3. To increase product development and manufacturing efficiencies.
4. To enhance root cause analysis and post-approval change management.
5. Performance-based quality specifications e.g. of FDA policies include tablet scoring and bead size in capsules labeled for sprinkling.
6. Pharmaceutical QbD is to increase process capability and reduce product variability that often leads to product defects, rejections, and recalls.
7. It enhances the manufacturer's ability to identify the root causes of manufacturing failures. Hence, increasing product development and manufacturing efficiencies.
8. To enhance root cause analysis and post-approval change management. Without good products and process understanding, the ability to efficiently scale- up and conduct root because the analysis is limited requires the generation of additional data sets on a proposed large scale.

Advantages of QbD

- It provides a higher level of assurance of drug product quality.
- It offers costs savings and efficiency for the pharmaceutical industry.
- It increases the transparency of the sponsor's understanding of the control strategy for the drug product to obtain approval and ultimately commercialize.
- It makes scale-up, validation, and commercialization transparent, rational, and predictable.
- It facilities innovations for unmet medical needs.
- It increases the efficiency of pharmaceutical manufacturing processes and reduces manufacturing costs and product rejects.
- It minimizes or eliminates potential compliance actions costly penalties, and drug recalls.
- It offers opportunities for continual improvement.
- It provides more efficiency for regulatory oversight.
- It streamlines post-approval Manufacturing changes and regulatory processes.
- It is more focused post the approval of CGMP inspections.
- It enhances opportunities for first-cycle approval.
- It facilitates continuous improvement and reduces the CMC supplement.
- It enhances the quality of CMC and reduces the CMC review time.
- QbD has significance over the traditional approach and it is already proven as of now.
- QbD approach uses systematic evaluation of individual variables & interactions over the limited understanding of analytical variables as in the traditional approach.
- QbD gives us the consistent quality of the product with less reprocessing and reworks and with reduced wastage. [17].

Pharmaceutical developments

Pharmaceutical developments are usually used in manufacturing. A system of 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.

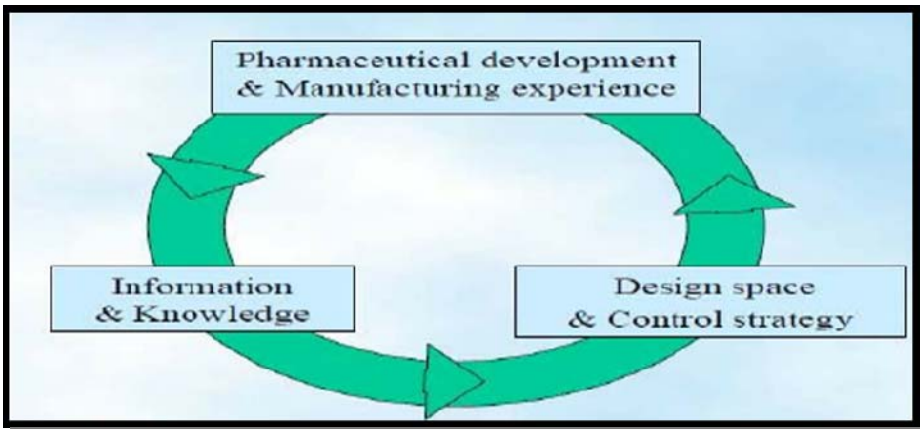

Figure 01: Pharmaceutical developments.

Pharmaceutical developments are usually used in manufacturing. A system of 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.

Key Elements of QbD

This part is an approach to development that is:

1. Shaping the Target product profile (TPP) because the correlation of quality, safety, and effectiveness is done. Identifies standards and characteristics of the merchandise as a basis of the planning and development of the merchandise.
2. Determine critical quality attributes (CQA).
3. Important Quality Attributes square measure the merchandise material properties that to be intervals their acceptable limits ranges or distributed to make sure the quality of the specified product.
4. Comparison of materials attributes and CPP to the CQA by Risk Assessment, Risk Assessment tools such as FMEA or bone diagram will determine the CPPs. ICH Q9 lists the tools which will be employed in the change management systems.
5. Institution of a space designed through the utilization of style of experiments (DOE's) a linkage and Important interactions between the CQA and CPP may be established and represented in a very stylistic area.
6. Management strategy Important sources of variability should be identified/ understood and managed or controlled.
7. Management of product lifecycle and continual improvement.

TPP

TPP outlines the required profile or characteristics of drug products that are geared toward drug labeling and drug development activities. TPP states are supposed to use and target the speed of administration, alternative essential attributes of the products, and quality designing for a drug [18].

CQAs (Critical Quality Attributes)

- If it is necessary to identify the quality attributes that are critical, I. e those defining purity, potency, and surrogate bioavailability critically, etc. It is based on the impact of quality attributes/parameters on the safety, efficiency, and quality (manufacturability) of the products.
- Manufacturability is also an attribute (important to business) that is critical to quality.
- The level of criticality may differ foray 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 continues critical, 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.
- CQA are physical, biological, microbiological, and chemical attributes to give assurance that the product obtained will attain the desired, quality, safety, efficiency, and efficiency and stability. And that can also be defined, measured, and continually monitored to ensure final product outputs remains within acceptable quality limits.
- Quality attributes include- clinical safety and efficiency, manufacturing an attribute, and parameters boundary approach edges of failure the critically may differ for the APT manufacturing process and level of critical increase in risk [19-20].

CMAs (Critical material attributes)

A parameter is important once a true modification there in parameters will cause the product to fail to fulfill the QTPP. Thus, whether a parameter is important or not depends on the however grant of an amendment one is willing to think about as well as different properties or characteristics of associates' input material. CMA ought to be inside associates' applicable limits range, or distribution to make sure the required quality of the drug substance, excipient, or in-process materials.

CPPs

CPP is outlined as any measurable input (input material attributes or operational parameters) or output (process state variables or output materials attributes) of a method step that has got to be controlled to attain the required product quality and method uniformity. During this read, each item would be a method parameter. Parameters are monitored before or in processes that influence the looks, impurity, and yield of the ultimate products considerably [21].

Risk assessment

Risk assessment is the combination of the chance of incidence of hurt and the severity of that hurt. Risk assessment helps to extend the quality of a technique or process. A risk assessment will acknowledge crucial attributes that affect the ultimate quality of the products. An assessment of Rick is useful for effective communication between FDA and trades research/development and producing and amongst multiple producing sites at intervals the corporate. Methods of risk assessment some strategies of risk assessment squares measures mentioned in ICH guidelines Q9 as follows [22].

- Failure Mode Effects Analysis (FMEA).
- Failure Mode, Effects and Critically Analysis (FMECA).
- Fault Tree Analysis (FTA).
- Hazard Analysis and critical control points (HACCP).
- Hazard operability Analysis.
- Preliminary Hazard Analysis.
- Risk ranking and filtering.
- Supporting applied mathematics tools.

Process analytical techniques (PAT)

PAT could be a term used for describing a border amendment in pharmaceutical production from static batch producing to a lot of dynamic approaches it involves processing the CPPs of the instrumentation accustomed, creating the products that have an effect on the CQA of the products and so dominant these CPPs at intervals outlined limits. This enables makers to supply merchandise with constituent quality and additionally helps to scale back waste and overall prices [23].

PAT has been printed by the U.S. FDA as a mechanism to vogue, analyze, and manage pharmaceutical manufacturing methods. Through the activity of vital process parameters (CPP) that have away on vital quality attributes (CQA). The thought very aims at understanding the processes of shaping their CPPs, and consequently observing them throughout a timely manner and so being plenty of economical in testing whereas the identical time reducing over-processing, enhancing consistency, and minimizing rejects. The authority has created public a restrictive framework for PAT implementation [24].

Quality risk management (QRM)

The FDA defines Risk Management as, a strategic safety program designed to decrease product risk by using one or more interventions or tools. It is a systematic process for the assessment, control, communication, and review of risks to the quality of the drug product across the product life cycle [17].

The ICH Q9 guideline: Quality Risk Management provides a structure to initiate and follow a risk management process. The relevant tools of QRM are as follows: [25]

According to lCH Q8 (R2), QTTP is a prospective summary of the quality characteristics of a drug's product that ideally will be achieved to ensure the desired quality taking into account the safety and efficiency of the drug product. It is a tool for setting the strategy for drug development. Recently QTTP is widely used in development planning, clinical and commercial decision-making, regulatory agency interactions, and risk management.

It is the quality characteristics that the drug product should possess to reproducible delivers the therapeutic benefit promised on the label. The QTTP guides formulation scientists to establish formulation strategies and keep the formulation effort focused and efficient. QTPP is related to identity, assay, dosage form, purity, and stability in the label. For example, a typical QTPP of an immediate-release solid oral dosage form would include:

Tablet Characteristics
Identity
Assay and Uniformity
Purity/ Impurity
Stability
Dissolution

It is important to acknowledge that QTPP should only include patient-relevant product performance elements. For example, tablet density or hardness may be included as a specification for process monitoring but may not be included in QTPP. Also, if the particle size is critical to the dissolution of a solid oral dosage product, then the QTTP should include dissolution but not particle size [26].

Challenges

Though Quality by design is an essential part of the modern approach to pharmaceutical quality, a lack of understanding regarding the pharmaceutical process is the cause and also the major limitation for QbD implementation. The end result has typically been of greater importance to pharmaceutical firms than the scientific understanding of the process involved. The majority of pharmaceutical firms believe that more straightforward instructions on how to actually adopt QbD are necessary. Companies sought clarification from FDA on QbD terminology, approved procedures, standards by which to appraise the sufficiency of controls, criteria for analytical method replacement, and criteria to select and deselect important quality attributes. [27-28]. The adoption of QbD is most adversely affected by ten major issues. These issues are assessed based on their applicability to various drug classes and adoption levels.

The first four challenges occur within companies

- Misalignment inside (Disconnect between cross functional areas, e.g., R&D and manufacturing or quality and regulatory)
- Lack of confidence in the business case, i.e., there is a lot of ambiguity around the timing and financial commitments necessary for QbD implementation.
- Lack of technology (e.g., challenges with data management and a limited grasp of the significance of Critical Quality Attributes [CQA])
- Third-party alignment (i.e., how to adopt QbD with a growing reliance on suppliers and contract manufacturers?)

The next six challenges are directly related to the regulatory authority

- The way promised regulatory benefits are currently being shared does not inspire confidence;
- The treatment of QbD across regulatory authorities is inconsistent;
- The industry lacks concrete guidance;
- The regulators are not prepared to handle QbD applications;
- The misalignment of international regulatory bodies;
- The interaction with businesses currently is not QbD-friendly.

It is acknowledged that effective communication between the sector and the regulatory is necessary to address the difficulties and worries related to the implementation of QbD.

Control Strategy

A control strategy is described by ICH Q10 as "a planned set of controls that ensures process performance and product quality and is derived from current product and process understanding. The controls can be connected to facility and equipment operating conditions, process controls, finished

product specifications, associated techniques, and frequency of monitoring controls, as well as metrics and attributes related to drug substance and drug product ingredients and components. Controlling inputs and materials is typically part of a control approach. To guarantee consistent quality, process controls and monitoring, design space around single or multiple unit processes, and/or final product specifications are used [29–30]. The finished pharmaceutical product is examined for quality by determining if it adheres to requirements.

Different critical process parameters with potential quality attributes

Future perspective

Because it is currently frequently utilised in the development space, where we frequently incorporate event-based approaches into the process, QbD will be employed to a much greater extent in the future along with being applied to the production space. It happens frequently that the assembly stage stalls when we arrive, either because we have to travel to a facility that is already in operation for manufacturing purposes or because the facility is resistant to new improvements, especially in the PAT section. If we can keep the current production within the constraints of our instrumentation, everything will be good. However, it is here that we tend to run into significant opposition once we have reached the more advanced and significant portions of the conventional purposeful methods to PAT following controlled manner.

The application of the QbD concept can be jointly started by several regulatory authorities, such as the European Medicines Agency (EMA). Additionally, the EU has released a paper for "Real-Time Release." The EMA is happy to accept applications that intentionally embody quality. Intentionally, the (EMA) is only partially interested in applications that support the notion of quality (QbD). Using applied mathematics, analytical techniques, and risk management methodologies in conjunction with the design, development, and production of medicines, quality purposefully is a true abstract approach that seeks to ensure the standard of medicines. For the implementation of QbD, U.S. authority/EMA refers to ICH recommendations Q8, Q9, Q10, Q11, and Q12 [31]. Currently, "Q13-Continuous Manufacturing" and "Q14-Analytical Techniques Development" are the focus of ICH.

CONCLUSIONS

QbD is quickly becoming a significant and popular technology in the development of pharmaceutical goods. While applying QbD at the product/process designing level is where it is most effective, it should also be done in the manufacturing and quality assurance environments. By implementing the QbD concept in product development, patients will receive high-quality medications, manufacturing will experience production improvements with significantly fewer batch failures, and drug regulatory bodies will have more faith in the robust quality of products.

Currently, pharmaceutical companies are considerably more concerned with using past knowledge and a risk-based approach to benefit their clients through a consistent manufacturing process. The methodology of QbD, which has many benefits, has been able to successfully displace the conventional method of producing high-quality results. The adaption of QbD is further made necessary by the regulatory requirements Q8, Q9, and Q10. With QbD, modifications to the products and processes may be controlled more effectively. Manufacturing can make some adjustments without requesting regulatory approval in advance and can just inform them in annual reports. The use of QbD principles can transform the chemical, manufacturing, and regulatory control processes into ones that are based on science and risk analysis.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Beg S, Hasnain MS, Rahman M, Swain S. Chapter 1 - Introduction to Quality by Design (QbD): Fundamentals, Principles, and Applications, Pharmaceutical Quality by Design. Academic Press, New York, USA (2019), pp. 1-17.
2. United States, Rockville: 2006. ICH Expert Working Group, U.S. Department of Health and Human Services. Guidance for Industry, Q9 Quality Risk Management. International Conference of Technical Requirements for

Registration of Pharmaceuticals for Human Use; 2006 June.

3. Geneva, Switzerland: 2008. ICH Expert Working Group. ICH Harmonized Tripartite Guideline, Pharmaceutical Quality System Q10. International Conference of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2008 June.
4. Lionberger RA, Lee LS, Lee L, Raw A,Yu LX. Quality by design: Concepts for ANDAs. The AAPS Journal 2008; 10:268–276. https://doi.org/10.1208/s12248-008-9026-7
5. Dahmash EZ, Al-khattawi A, Iyire A, Al-Yami H, Dennison TJ, Mohammed AR. Quality by Design (QbD) based process optimisation to develop functionalised particles with modified release properties using novel dry particle coating technique. 2018. PLoS ONE 13(11): e0206651. https://doi.org/10.1371/journal.pone.0206651.
6. US Food and Drug Administration. Guidance for industry and review staff Target Product Profile – a strategic development process tool. 2007. https://www.fda.gov/media/72566/download. Accessed Sep 2022.
7. Jadhav JB, Girawale NN, Chaudhari RA. Quality by Design (QbD) Approach used in Development of Pharmaceuticals. Int J Pure Applied Biosci. 2014;2(5): 214- 223.
8. The Application of Quality by Design to Analytical Methods. Pharmaceut Tech. 2007; 31(10). https://www.pharmtech.com/view/application-quality-design-analytical-methods [Accessed in Sep 2022].
9. Aloka S, Robert I. Question base review (QbR) forms the platform of QbD principle. Technical. 2009;15:8-10.
10. Nick T. FDA mixed messages create QbD confusion; consultant. 2011. https://www.outsourcing-pharma.com/Article/2012/07/26/FDA-s-QbD-laws-are-confusing-consultant [Accessed in Sep 2022].
11. Food and Drug Administration. Department of Health and Human Services [Docket No. FDA–2008–N–0355]. https://www.govinfo.gov/content/pkg/FR-2009-09-17/pdf/E9-22378.pdf [Accessed in Sep 2022].
12. Nars MM. A new pharmaceutical quality assessment system (PQAS) for the 21st century, AAPS workshop October 2010.
13. Q8 (R1): Pharmaceutical Development, Revision 1, ICH Harmonized Tripartite Guidelines, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2007.
14. Callis JB, Lllman DL, Kowalski BR. Process analytical chemistry. Anal Chem. 1987;59: 624-637.
15. Yu, LX. Pharmaceutical quality by design: products & process development, understanding, & control. Pharmaceut Res. 2008;25:781- 791.
16. MUNSON J, Gujral B, Stanfield CF. A review of process analytical technology (PAT) in the US. Pharmaceutical industry. Current Pharmaceut Anal. 2006;2:405–414.
17. ICH. Draft consensus guideline: pharmaceutical development annex to Q8. Available at:, http://www.ich.org/LOB/media/MEDIA4349.pdf (Accessed Sept 2022).
18. Yu LX. Implementation of quality-by-design: OGD initiatives. FDA Advisory Committee for Pharmaceutical Science. Available at: http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4241s1_8.ppt (Accessed Sep 2022).
19. Food and Drug Administration CDER. https://www.fda.gov/media/70956/download [Accessed Sep 2022].
20. Nasr. M. Risk- based CMC Review paradigm, Advisory committee for pharmaceutical science meeting: 2004.
21. Rozet E, Marini RD, Ziemons E, Bollinger B, Hubert P. Advances in validation, risk and uncertainty assessment of bioanalytical methods. J Pharm Biomed Anal. 2011; 55(4):848-58.
22. FDA CDER. Guidance for industry: PAT-a framework for innovative pharmaceutical

development, manufacturing, and quality assurance. Sept. 2004.

23. Hinz DC. Process analytical technologies in the pharmaceutical industry: the FDA's PAT initiative. Anal Bioanal Chem. 2006;384(5):1036-42. doi: 10.1007/s00216-005-3394-y.
24. Bhattacharya J. Quality risk Management - Understanding and control the risk in pharmaceutical manufacturing industry. Int J Pharmaceut Sci Invention. 2015;4:29-41.
25. Yu LX, Lionberger R, Olson MC, Johnston G, Buehler G, Winkle H. Quality by Design for Generic Drugs. Pharmaceut Technol 2009;33:122-27.
26. Jain S. Quality by design (QBD): A comprehensive understanding of implementation and challenges in pharmaceuticals development. Int J Pharm Science. 2014;6(1):29-35.
27. Drakulich, A. Critical challenges to implementing QbD: A Q&A with FDA. Pharm. Technol. 2009; 33: 90–94.
28. Trivedi, B. (2012). Quality by desing (QbD) in pharmaceuticals. Int J Pharm Pharm Sci. 4:17-29.
29. Jain S. Quality by design (QbD): A comprehensive understanding of implementation and challenges in pharmaceuticaldevelopment. Int J Pharm Pharm Sci 2013;6:29-35.
30. Kadam VR, Patil MP, Pawar VV, Kshirsagar S. A review on: Quality by design (QbD). Asian J Res Pharm Sci. 2017;7:197-204.
31. Aksu B, Yeğen G. Global regulatory perspectives on quality by design in pharma manufacturing. Pharm Qual Des 2019;2019:19-41.