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Review Article

Applications and Principles of Quality by Design in European Union Regulatory Dossiers for Medicinal Products from 2020 to 2023

Srihith R. Yaparla*, Koushik Yetukuri

Regulatory Affairs, Chalapathi Institute of Pharmaceutical Sciences, Lam, Andhra Pradesh, India.

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ABSTRACT

Dr. Joseph M. Juran introduced the quality by design (QbD) concept in the 1970s., represents a risk-based approach to drug development, emphasizing continuous risk management throughout a product's lifecycle and predefined objectives. Implementation guidelines are detailed in the International Council of Harmonization (ICH) standards Q8–11. About a decade ago, the European Medicines Agency (EMA) adopted QbD principles for the pharmaceutical regulatory framework in the European Union. Despite recognition as essential in 2014, the integration of QbD into European marketing authorization applications remains limited and is not standardized. Using information from EPARs, a recent four-year study (2020–2023) aimed to evaluate how QbD principles were applied in all EU-approved marketing applications. Approximately 33.13% (111) out of 335 pharmaceuticals were developed using quality by design (QbD) principles, and 37.01% of all permitted drugs (77 out of 208 under article 8(3)) used QbD. Remarkably, over four years, 30 to 40% of approved items presented as stand-alone documents adopted QbD. Interestingly, most approved fixed-dose combination medications (71% in 2020 and 100% from 2021-2023) were developed using a QbD strategy. Furthermore, the EMA denied four applications for market authorization incorporating QbD principles in the dossier. In conclusion, according to EPARs, regulatory dossiers lack complete QbD implementation, but the modest use of QbD components suggests a growing interest among businesses, potentially indicating a shift towards accepted development standards. Effective communication between regulatory bodies and companies is crucial for addressing challenges in QbD applications.

Introduction

Pharmaceutical companies have been investing resources for years to ensure that their products meet high quality standards comply with regulations and are cost effective. Their ultimate goal is to provide patients with the intended benefits. According to Woodcock's definition[1] a pharmaceutical product is considered of quality when it consistently provides the intended effectiveness mentioned on the label and is completely free, from any kind of contaminations. Even with the constant improvements that the pharmaceutical firms periodically introduce, product recalls, rejections and failures have been happening repeatedly due, to issues, with the quality and manufacturing standards not meeting the benchmarks. End product testing has long been relied upon to assess quality ensuring that products perform well and meet quality standards. However, this method falls short in understanding the processes involved the critical variables, at play and the necessary strategies to control these variables. A comprehensive understanding of these factors is essential to guaranteeing the quality of the product.[2,3]

The US Food and Drug Administration (FDA) introduced the pharmaceutical current good manufacturing practices (cGMPs) for the 21st Century project in 2002 in an effort to remove these barriers. This program aimed to improve FDA regulations related to the development and quality of pharmaceutical products. In January 2011, the FDA updated its industry-process validation: General principles and practices guidance, replacing its earlier

***Corresponding Author:** Mr. Srihith R Yaparla

Address: Regulatory Affairs, Chalapathi Institute of Pharmaceutical Sciences, Lam, Andhra Pradesh, India.

Email ✉**:** srihithroy24@gmail.com

Tel.: +91-7997027252

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recommendations on the core ideas of method validation.[4] Pharmaceutical QbD has changed over time as a result of the release of ICH guidelines pharmaceutical development [Q8 (R2)], quality risk management [Q9], & pharmaceutical quality system [Q10]. In addition, the results of the FDA-EMA parallel assessment of the QbD components for marketing applications and the development & manufacture of drug substance [Q11].[5-9] The concept of QbD was originally developed in the early 1970s by quality pioneer Prof. Joseph M. Juran.[10] According to Dr. Juran, a product's quality should be integrated, and the bulk of issues and complaints about quality originate from the product's initial design.[11]

QbD Concept

The ICH Q8 (R2) recommendations refer to the ideas of QbD which emphasize that quality cannot be added as an afterthought, to products, i.e., quality ought to be embedded in through design. It states that, quality-based (QbD) drug development is a systematic approach, to the development of pharmaceuticals begins by setting goals that prioritize understanding the process and product well as ensuring process control. The foundation of this approach will be based on research and thorough assessment of risk mitigation strategies, i.e., developing formulations and manufacture procedures that assure an appropriate quality level. Therefore, understanding how invention and development variables affect product quality is necessary for QbD.[12] Products such as efavirenz,[13] galantamine HBr,[14] tacrolimus,[15] liposome products,[16,17] dasatinib,[18] and linagliptin[19] have been developed incorporating QbD components.

When QbD concepts are applied, designing high-quality products and evaluating them at every phase of their existence becomes easier, eventually benefiting patients significantly. To guarantee that the concepts of QbD are implemented, the ICH released the Q8 (R2) guideline in 2009 along with Q9 (R1), Q10, and Q11. These guiding concepts include the Critical Quality Attributes, Design Space, quality target product profile, quality risk management, and control strategies (see Table 1).[20,21]

Table 1: Elements of QbD[23,24]

QbD elements	*Definitions*
Quality target product profile	A hypothetical overview of the quality features of a medicinal product that preferably will be attained to assure the intended quality, considering into account safety and effectiveness of product.
Critical quality attributes	A quality of a product, whether physical, chemical, biological, or microbiological, that must be within a certain range, limit, or distribution, to achieve the desired quality level.
Quality risk management	A methodical procedure for identifying, managing, sharing, and reviewing risks to the drug's quality throughout that product's lifecycle.
Design space	The comprehensive combine and interrelation of process parameters & input considerations (material qualities) that shows to offer quality assurance
Control strategies	A thoroughly developed system of controls to ensure process efficiency and products quality, based on current knowledge about process and products.

Traditional and QbD technique comparison

Table 2 distinguishes between the existing technique and QbD approach. The QbD approaches were used to systemically establish and accomplish pharmaceutical development, manufacturing process control, and control strategy. Using QbD ensures that the finished product always fulfills the predefined standards, reducing the possibility for batch rejection because of failure to comply. There would be a greater chance of batch failure with a quality by end product testing method, and indicated noncompliance, the whole batch would have to be discarded, which would have serious repercussions.[22]

Steps for implementing QbD in pharmaceuticals

From the perspective of end-consumer health (patient health), QbD methodology typically recognizes numerous properties which were quality essentials and must be included in both drug material and excipient attributes. It also establishes how various process parameters can be changed and improved with extensive understanding on different variability sources and, by extension, adapting to implement a robust, adjustable, and dependable manufacturing process to produce a consistent product with desired characteristics over time. Six sections, or essential components, outline the QbD methodology's steps to achieve the quality enriched drug product. An outline of the essential QbD components were shown in Fig. 1.[26,27] In the pharmaceutical sector, improved process comprehension, improved production control, and the

Table 2: Traditional and QbD approach comparison[25]

Aspects	*Traditional approach*	*QbD approach*
Pharmaceutical Development	Theoretical	Multidimensional, systematic experiments
Manufacturing process	Inflexible	Adaptable, modifications are possible inside the design space
Process control	Through in-process examination	Process analytical technology (PAT) provides real-time feedback and feed forth
Product specification	Considering past performance and batch data	Product performance is included in quality control plan and audits
Control strategy	Through end-product testing and inspection or through in-process quality	Real-time release and a risk-based control strategy

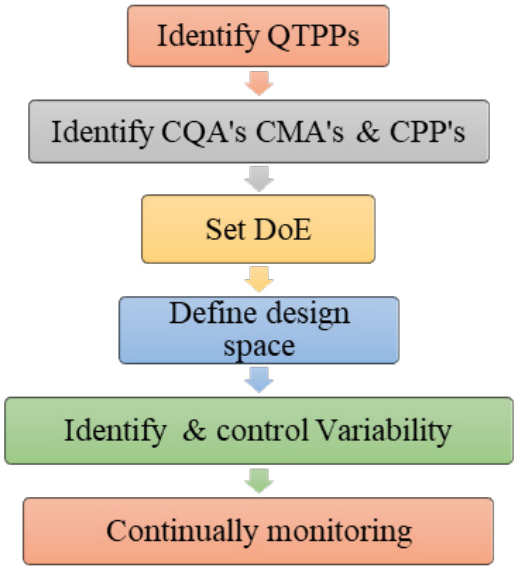

Fig. 1: Steps involved in QbD implementation

incorporation of targeted quality into the development of products are widely recognized as QbD's primary characteristics.[28] Higher upfront expenditures and a perceived lack of regulatory support are among the drawbacks for businesses that must begin using QbD.[29] Over a decade has passed since QbD was encompassed in the ICH Q8 - Q11 guidelines, which means pharmaceutical establishments would have had ample opportunity to incorporate it into their drug development processes. The EMA originally endorsed QbD concepts ten years ago, and the movement to incorporate QbD principles into the European Union's (EU's) pharmaceutical regulatory system has reached an important intersection. Nonetheless, in 2014, EMA recognized that, with just a minuscule percentage of market authorization applications (MAA) submissions in Europe including accompanying QbD data for support, application dossiers containing information on QbD are a long way off from becoming standard practice.[30] This research aimed to evaluate the QbD application data included in regulatory dossiers for pharmaceutical development that the EU has approved throughout the preceding four years (2020–2023).

Methodology

A review of all approved products over a span of four years (2020–2023) was performed through the EMA website. A medicine's evaluation by the EMA and other public information about it are available online in the form of the European Public Assessment Report (EPAR).[31] For this publication, the extent to which QbD concepts were applied to the preparation of each product's EPAR that was authorized and made available as the initial marketing report over the previously mentioned period was assessed.[32]

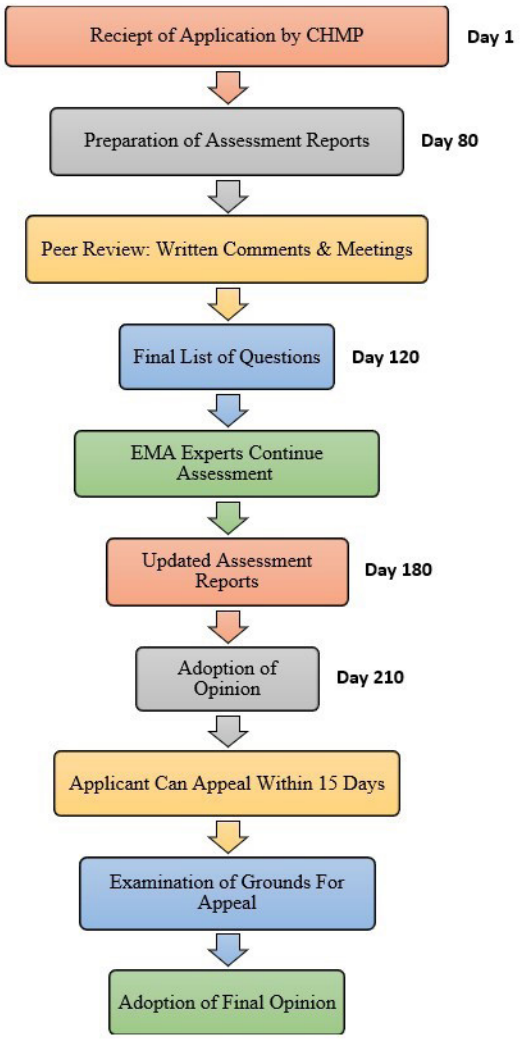

Fig. 2: Market authorization application review process

The term "Quality by Design," or QbD, were used to look through every EPAR. Applications containing this keyword were all categorized as QbD applications except EMA specifically stated otherwise. The regulatory body's decision and possibly the applicant's specific citation could determine whether a medication had been designated as "QbD." We searched for QbD components in every application that had QbD. Data of an additional category was gathered: submission type. The percentage of applications with QbD has been estimated for each category of statistical information that was collected.

Review Process for Medicinal Products Approval in EU

The EMA carries out a comprehensive scientific assessment procedure for centralized marketing authorizations throughout the EU. This enables pharmaceutical firms to apply to the EMA with just one application and market their products throughout the European economic area. Reviewing a new medicine's application for marketing authorization may require up to 210 "active" days. Experts

from EMA examine the applicant's evidence throughout this time. Each applicant responds to any inquiries from the Committee on Medicinal Products for Human Use (CHMP) throughout the duration of one or two "clock-stops." Subject to CHMP authorization, the applicant's expected response time determines the duration of these clock stops, which are normally three to six months for the first and one to two months for the second. Fig. 2 contains comprehensive details regarding the review process employed by EU for approving pharmaceutical products.[33]

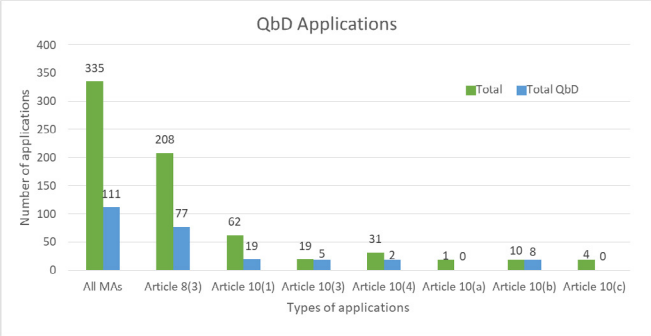

Fig. 3: Statistical representation of number of MA's approved in EU during 2020-2023

Table 3: EU submissions and QbD development[34]

Types	*Total*	*Total QbD (n)*	*%*
All MAs	335	111	33.13
Article 8 (3)	208	77	37.01
Article 10 (1)	62	19	30.64
Article 10 (3)	19	5	26.32
Article 10 (4)	31	2	6.45
Article 10 (a)	1	0	0
Article 10 (b)	10	8	80
Article 10 (c)	4	0	0

n – QbD applications number; % - percentage; MAs – Marketing Authorizations

Statistical Findings and Discussion[34,35]

Initially, the 335 marketing authorizations (MA's) for pharmaceutical products that were approved during 2020 – 2023 were systematically classified corresponding to the nature of submission: stand-alone applications, well-established use, fixed-dose combinations, abridged applications (generic, hybrid, and biosimilars); informed consent in accordance with the EU application law; and stand-alone applications. Table 3 lists the various submission options for pharmaceuticals between 2020 and 2023, with total number of applications approved during those periods. Table 4 represents QbD employed applications approved during 2020–2023. All out of 335 pharmaceutical products, 111 (33.13%) were manufactured utilizing QbD. 77 (37.01%) out of a total of 335 authorized pharmaceutical products were produced utilizing QbD (see Table 3), of which 208 were submitted with a stand-alone document (refer to article 8(3)). Between 30 and 40% of the medicinal products developed throughout this four-year period were approved upon a complete dossier was submitted. It is intriguing to observe that the majority of authorized fixed dose combination products 71% in 2020 and 100% from 2021 to 2023 were QbD implemented. Figs 3 and 4 illustrate significant statistical assessment of the applications with QbD principles.

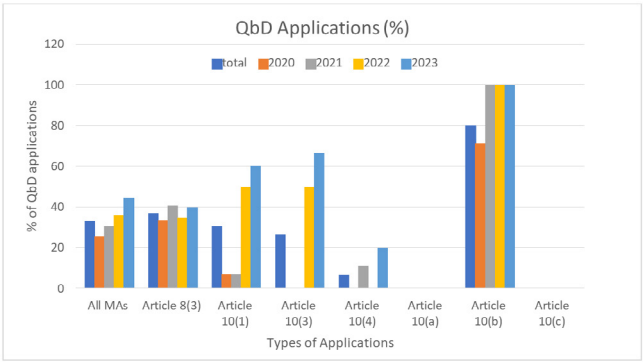

Fig. 4: Percentage of QbD implemented medicinal products approved in EU (2020-2023)

Table 4: QbD development during 2020 – 2023[35]

Types	*2020*			*2021*			*2022*			*2023*		
	Total	*(n)*	*%*	*Total*	*(n)*	*%*	*Total*	*(n)*	*%*	*total*	*(n)*	*%*
All MAs	90	23	25.6	88	27	30.7	103	37	35.9	54	24	44.4
Art. 8 (3)	51	17	33.3	59	24	40.7	63	22	34.9	35	14	40
Art. 10 (1)	15	1	6.67	15	1	6.67	22	11	50	10	6	60
Art. 10 (3)	6	0	0	4	0	0	6	3	50	3	2	66.6
Art, 10 (4)	10	0	0	9	1	11.1	7	0	0	5	1	20
Art. 10 (a)	0	0	0	0	0	0	1	0	0	0	0	0
Art. 10 (b)	7	5	71.4	1	1	100	1	1	100	1	1	100
Art. 10 (c)	1	0	0	0	0	0	3	0	0	0	0	0

Art. – article; MAs – Marketing Authorizations; (n) – QbD applications; % - percentage

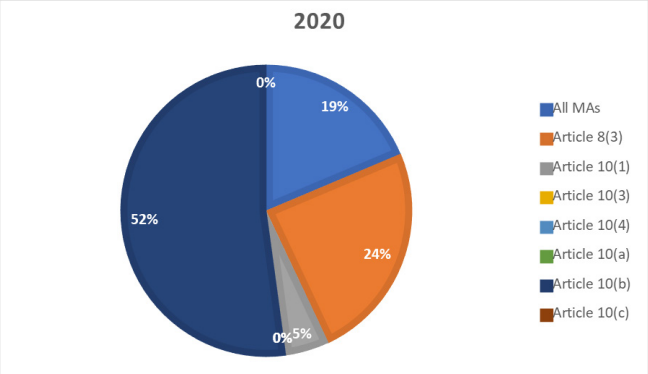

Fig. 5: Percentage of QbD implemented applications approved by EMA during the year 2020

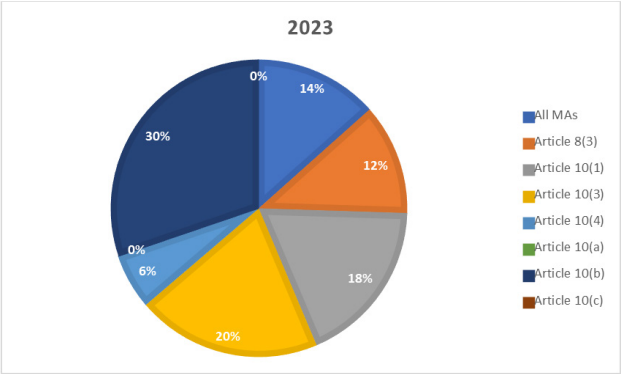

Fig. 8: Percentage of QbD implemented applications approved by EMA during the year 2023

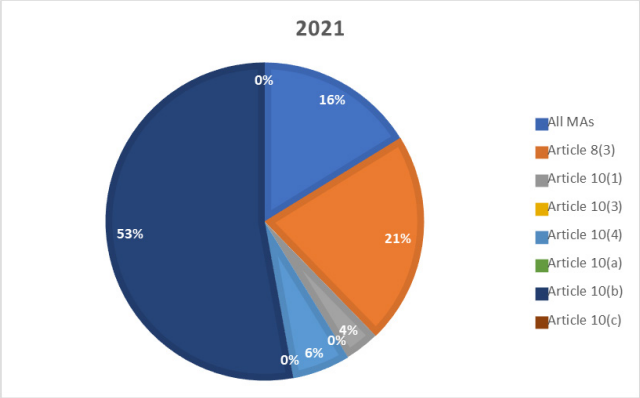

Fig. 6: Percentage of QbD implemented applications approved by EMA during the year 2021

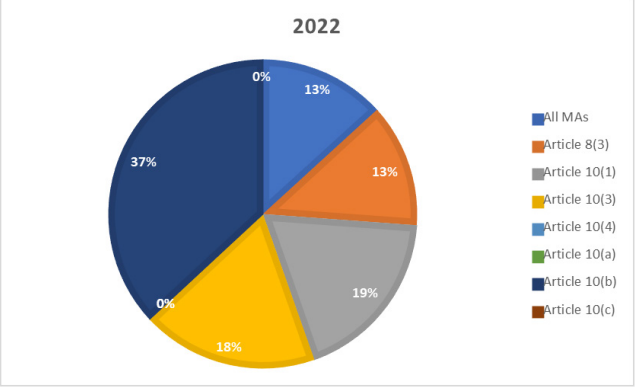

Fig. 7: Percentage of QbD implemented applications approved by EMA during the year 2022

Subsequently, the proportion of applicants that have applied QbD concepts was evaluated yearly for the previous four years (2020–2023). Out of 90 MAAs, 23 (25.56%) were determined that they used QbD concepts in the development of their products for the year 2020. Similar to this, 27 (30.7%), 37 (35.9%), and 24 (44.4%) of the applications for the years 2021, 2022, and 2023 adopted QbD principles (see Table 4). The Figs 5 - 8 demonstrated the statistical evidence on the yearly analysis for the MAA's in EU between 2020–2023. Furthermore, based on the statistical evidence described previously, the EMA refused a total of four applications for market authorization, which had QbD principles included in the dossier.

EMA recognized in 2014 that employment of QbD is still several years from becoming an established process because there were just an insignificant number of MAAs with supportive QbD information submitted in Europe. Rendering to EMA, the total number of applications with QbD increased to 8 during 2013 from a median of five a year later 2008. The current analysis has demonstrated that, irrespective of what type of submission, approximately 111 of the 335 pharmaceutical products authorized in Europe between 2020 and 2023 included a description within their medicinal record regarding the application of QbD for the production of the products. The majority of approved QbD-developed pharmaceuticals were submitted with full submissions and dossiers (n = 77). As of 2020, approximately 23–37 QbD applications have been approved annually, or about 35% of total applications, contrary to the 8 QbD submissions that were submitted in 2013. Products with fixed dose combinations are an acceptable example, too. It is stimulating to observe that more businesses are beginning to indicate at least a few QbD aspects in their dossier as stated in ICH Q8 – 11 guidelines, which include claiming a design space even if the majority of European regulatory papers rarely address full QbD advancement, as defined by the EPARs, indicating that applications were not rejected due to their quality. Development through QbD should result in a general improvement of product quality, ultimately improving the business's reputation and public perception. Moreover, regulatory authorities feel more at ease approving the medicine application because the quality has been incorporated into every process steps. For pharmaceutical businesses, however, comprehending QbD's scientific basis and method of execution is important. It is imperative for the regulatory bodies to standardize respective departments regulatory requirements and comprehension. It is acknowledged that

efficient interaction between the private sector and the regulatory agencies is necessary to address the challenges and concerns related to QbD implementation.

With the purpose to conduct this study, EPARs that the EMA had prepared and made available were evaluated. The information in this article depends on what EMA had published and what the firm has chosen to include in the regulatory dossier, as access to the entire dossier is unavailable. As such, this evaluation may not accurately reflect the application of QbD concept in the medicinal products development, but rather the process in which this data was supplied in European dossiers.

CONCLUSION

In conclusion, according to the EPARs, regulatory dossiers do not frequently reflect the use of complete QbD during pharmaceuticals development. Yet, as observed by the inclusion of a few QbD components in the development, more businesses are beginning to investigate the concept and establishing the necessary facilities for supporting it, which is reassuring and likely indicates that QbD developing into an accepted development standards in the further and it is recognized that effective communication between the regulatory bodies and companies is required to address the problems and concerns regarding the QbD implementation in product development.

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