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Teaser This article provides insights into the QbD-based development of nanopharmaceuticals with robust quality, efficacy, and safety features for their successful translation to the clinic.

Quality-by-design approach as a systematic tool for the development of nanopharmaceutical products

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In recent decades, extensive emphasis has been given on developing nanopharmaceutical products for improving the therapeutic performance of drugs, resulting in an increasing number of product approvals by drug regulatory agencies. Although nanopharmaceuticals are subjected to the same regulatory pathways as conventional pharmaceutical products, their biopharmaceutical characteristics at the nanoscale make them vulnerable to high variability in quality. Positive effects on drug quality assurance have resulted from adopting systematic quality-by-design (QbD) principles, boosting pharmaceutical manufacturing with improvements in the quality, safety, and efficacy of drugs.

Introduction

QbD is used in the global biopharmaceutical industry to develop a range of the products, including pharmaceuticals, biologicals, surgicals, along with additives and excipients [1]. However, given that these products are used in healthcare settings, they require rigorous quality assessments. Thus, global healthcare and federal regulatory agencies have prepared fixed norms for the industry to use to evaluate the quality of biopharmaceutical products. Despite the adoption of these stringent regulatory standards, gaps remain in monitoring the quality of the finished product. This has resulted in consequences including prolonged product review processes, delays to market launches, inconsistent product quality, poor patient acceptance, and an increasing number of product recalls and rejects [2].

As well as the regulatory agencies, the pharmaceutical industry is working hard to achieve robust, high-quality drug products by overcoming these challenges and issues. The concept of QbD has been extended to the systematic development of drug products by minimizing challenges including a lack of consistency in quality and product robustness [3]. QbD has a multifaceted role in the efficient development of complex drug products and processes, because it involves consideration and analysis of all the possible sources of variability relating to the end-product [4,5].

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Historical evolution of the concept of quality

Figure 1 portrays the historical events that resulted in the use of quality practices by science- and technology-driven manufacturing industries. The idea of quality was first initiated by Crosby during the 1950s, as the concept of 'zero defects', which was embraced as a crucial change in industrial quality control [6]. In 1982, Deming, an American statistician, also opined that, by embracing the principles of quality management, organizations could improve the quality of their products by concurrently reducing costs [7]. Further developments of the concept of quality based on Six Sigma principles [8] led to the concept of QbD being developed by Juran during the 1990s as a revolutionary approach for building desired quality into products [9].

Juran published his thinking on QbD philosophy in 1991 [10], and highlighted the 'quality trilogy', which principally described the key precepts and perspectives for implementing quality practices in product development (Fig. 2). Moreover, Juran also indicated that 'quality is a matter of conscious intent' and that it should be built into the product rather than the belief of testing quality into the products. The QbD concept has since been applied in diverse manufacturing industries to enhancing the quality of products and reduce associated costs [11].

Evolution of QbD and the pharma regulatory landscape

The evolution of the pharmaceutical regulatory landscape is closely linked to development and manufacturing practices adopted during the 1970s to 1990s. Although manufacturing industries were the first to implement quality practices into product development, the pharmaceutical industry lagged behind. The pharmaceutical industry had been developing drugs through traditional shot-gun approaches, such as one factor at a time (OFAT) or changing one separate variable at a time (COST), with little reliance on rational practices and scientific principles, resulting in limited knowledge and understanding of the resulting product and process behavior [12]. The use of QbD was initiated by the US Food and Drug Administration (FDA) in 1987 through its *Guideline on Process Validation* [13]. An article published in *The Wall Street Journal* in 2002 noted that 'although pharmaceutical industry involved in developing futuristic drugs has a little secret, yet their manufacturing techniques lag far behind potato chips and laundry soap makers', questioning the manufacturing standards of the pharmaceutical industry, including the role of regulatory agencies [14].

In August 2002, the FDA announced a new initiative, pharmaceutical current good manufacturing practices (CGMPs), to modernize pharmaceutical manufacturing and product quality. Subsequently, in November 2003, the International Conference on Harmonization (ICH) agreed to work on a harmonized plan to develop a pharmaceutical quality system based on science and a risk-based integrated approach. In 2004, the FDA published *Pharmaceutical cGMP for the 21st Century – A Risk-Based Approach*' to define expectations from industry on target product quality with ultimate robustness and efficacy for the benefit of patients [15]. In the same year, the FDA also published *Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations* and *PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*, to create a comprehensive quality system for drug development [16,17].

As an effort to harmonize quality standards worldwide, the ICH and FDA published a series of quality guidances: *ICH Q8-Pharmaceutical Development* in 2004, *ICH Q9-Quality Risk Management* in

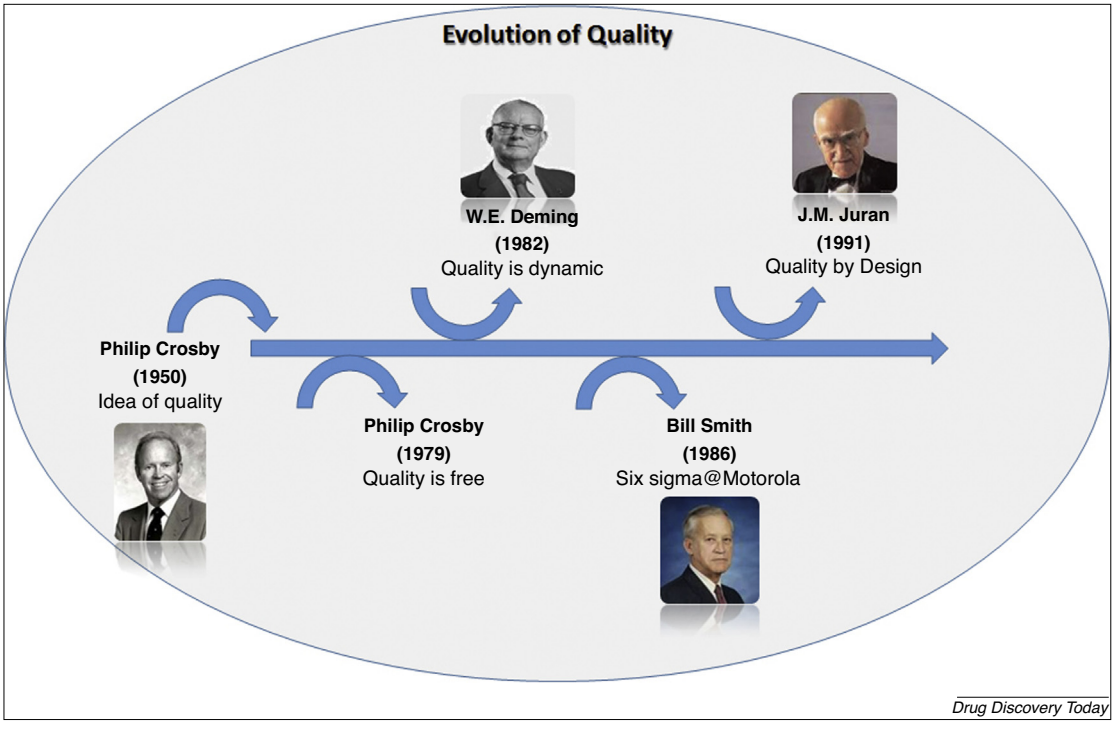


FIGURE 1

Evolution of the concept of quality over time.

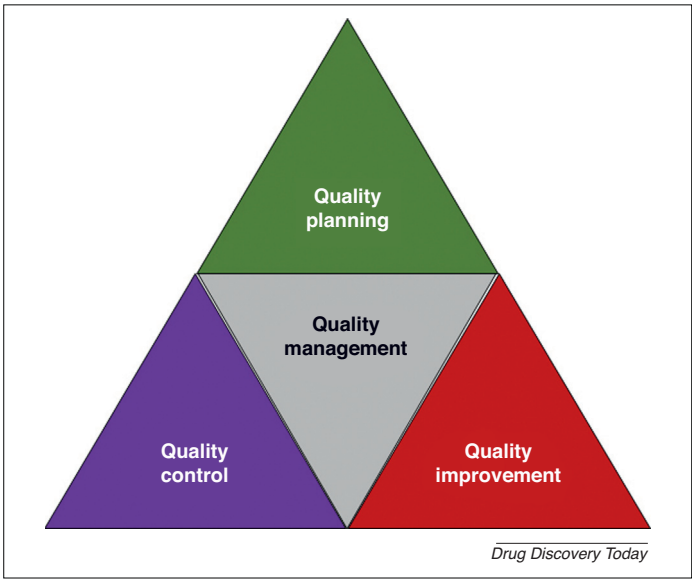


FIGURE 2

Juran's quality trilogy revolving around quality control, planning, and improvement.

2005, and *ICH Q10-Pharmaceutical Quality System,* in 2008 [18–20]. Based on these guidances, the FDA published a revised guideline entitled *Pharmaceutical Process Validation: General Principles and Practices* in 2011, in which the agency discussed the application of a risk-based experimental design approach for process development and optimization [21]. Figure 3 illustrates the chronological events relating to the landscape of regulatory events around QbD implementation for pharmaceutical development and manufacturing.

After publication of these guidelines, comments were invited from industry through a series of seminars and workshops for understating crucial aspects of QbD principles for practical implementation into pharmaceutical product development. In 2011, the FDA published *Questions and Answers on Q8, Q9 and Q10 Guidances* to provide solutions for ongoing discussions on the topic [22]. In addition to the FDA, the European Medicines Agency (EMA) also endorsed all ICH guidances (Q8-Q10), and a pilot program between the FDA and EMA began in 2011 for the parallel assessment of applications containing QbD elements [23]. The FDA also mandated the implementation of QbD in abbreviated new drug applications (ANDA) submitted from 2013 onwards [24].

QbD fundamentals and benefits

The ICH and FDA define QbD in Q8 as 'a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management' [18]. The guideline also indicated that the aim of pharmaceutical development must be focused on designing quality products and manufacturing processes with conscious intent to consistently deliver the intended performance of the products. With integrated science and risk-based principles in place, QbD provides a proactive platform for end-to-end support and control on quality metrics at each stage of the product development cycle without relying on periodic end testing. By contrast, the traditional quality by testing (QbT) approach is considered to be time- and effort-consuming, and requires routine testing for quality monitoring throughout product development [25].

Thus, the QbD approach has significant merits in terms of improving scientific understanding of the product and process behavior, thus providing greater regulatory flexibility and control of the manufacturing process. Hence, the concept delivers enormous benefits to its stakeholders, including the manufacturing industry, regulators, and patients [26]. Other important merits of the QbD approach include augmentation in improving the effi-

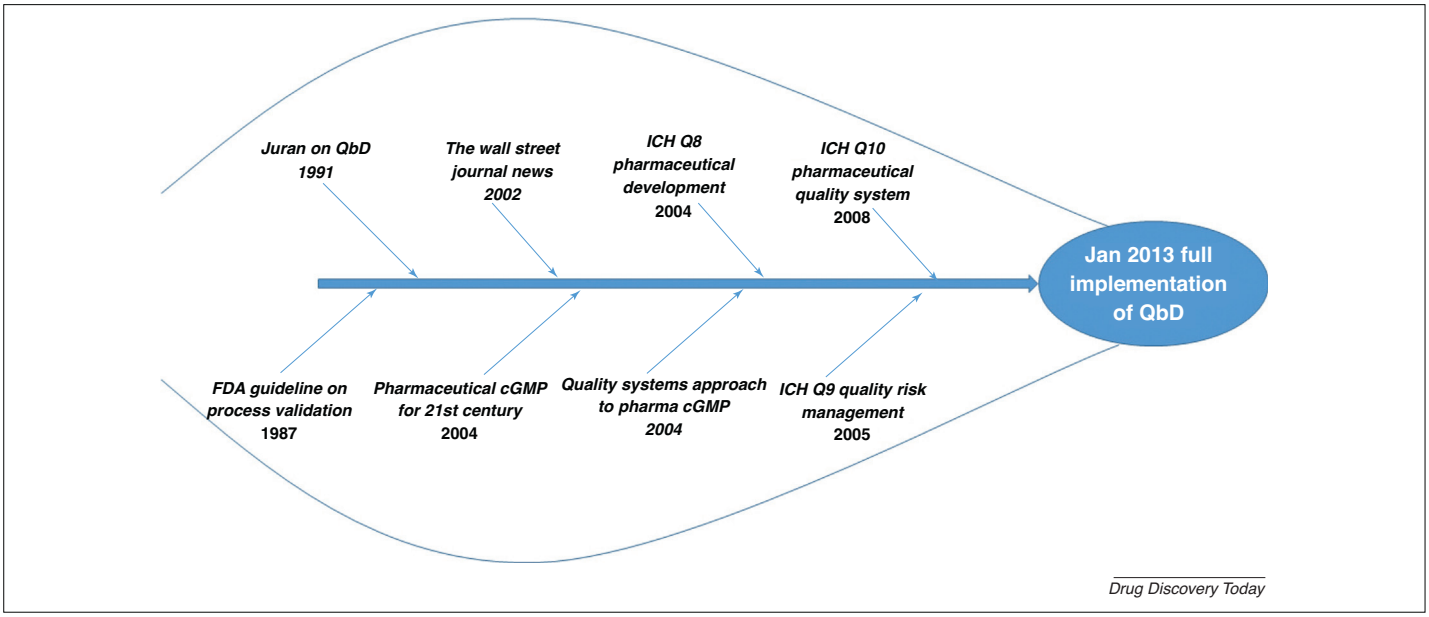


FIGURE 3

Chronological events indicating the pharma regulatory landscape adopted by regulatory agencies for quality-by-design (QbD) implementation.

ciency of the manufacturing process and minimization of potential compliance risks. It also enables continuous improvement, facilitates innovation and efficient regulatory oversight, reduces consumer generic skepticism, and streamlines postapproval changes throughout the drug development life-cycle.

QbD key elements

As per the ICH Q8-Q10, implementation of QbD methodology requires knowledge and understanding of the key elements. Figure 4 depicts the fundamental elements as building blocks of QbD for systematic development of product(s) and/or process(es).

Target product profile

A target product profile (TPP) is a planning tool used to describe the fundamental characteristics of the intended therapeutic drug product. It is the fundamental element for initiating QbD-based activities in development and is defined at an early stage based on the available prior art (i.e., knowledge, know-how, and past experience) and prior literature reports [27]. The FDA Guidance *Target Product Profile – A Strategic Development Process Tool*, published in 2007, provides detailed insights into the applicability of TPP and its usage for the development of products such as pre-investigational new drug (pre-IND) applications, IND, new drug applications (NDA), and biologics license applications (BLA) [28]. In this guidance, the agency described the advantages of defining TPP for these products, where an applicant or sponsor must 'begin with the end goal in mind' or target objectives in mind. Moreover, TPP is a dynamic summary that changes as knowledge of the drug product increases. Hence, for dynamic improvement in quality, TPP should be updated regularly during the product development life cycle.

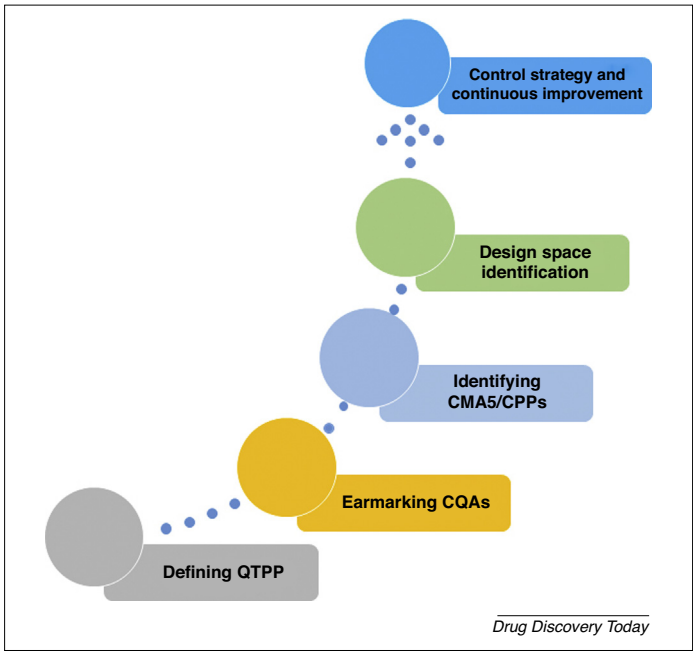


FIGURE 4

Fundamental building blocks of quality-by-design (QbD) required for the efficient development of drug products. For definitions of abbreviations, please see the main text.

Quality target product profile

Using TPP as the predefined measure, the quality TPP (QTPP) is defined as 'a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product' [18]. QTPP is considered a pivotal element of the QbD approach, and has a crucial role in defining the objectives of developing a drug product. An ideal QTPP should contain properties of the drug substance, functional traits, and clinical perspectives of the target product for the intended patient population. The successful execution of a product development exercise meeting the end objectives always depends on holistically defining the QTPP.

Critical quality attributes

Critical quality attributes (CQAs) are integral components of a drug product, and describe the functional quality traits of a product. CQAs are also an essential part of a manufacturing control strategy and must be identified during the early stages of development. They constitute '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' [18]. The consistency in product performance and process robustness can be easily accessed by monitoring the CQAs. Initially, the QAs are identified from QTPP on the basis of their direct and/or indirect influence on the safety and efficacy of the product and, ultimately, on the severity of harm to the patients. Use of prior experience and literature support can help sponsors and manufacturers to better understand the CQAs. Subsequently, out of the many possible QAs, only a vital few are demarcated as CQAs. With the use of sound science and a good quality management system, the acceptable ranges of CQAs are defined and monitored throughout the product life cycle to monitor the performance of both the product and process [29]. From a development perspective, it is always better to investigate the linking of the CQAs of the drug product with the formulation and/or process variables. Given that multiple functional and nonfunctional elements of a drug product tend to influence the CQAs, drug product CQAs can be of various types, including CQAs associated with drug substance(s), excipient(s), and packaging materials. Thus, while identifying drug product CQAs, one should also analyze the possible impact of the CQAs of the drug substance, active raw materials, and/or excipients.

Critical material attributes

Critical material attributes (CMAs) are also considered pivotal elements, and regulate drug product quality by their direct influence on the CQAs. CMAs are defined as the physical, chemical, biological, or microbiological property or characteristic of an input material that should be within an appropriate limit, range, or distribution to ensure the desired quality of the resulting drug products [30]. Initially, the Mas that might influence the CQAs are screened on the basis of their criticality, where only a few vital material attributes will be identified as CMAs. These primarily include active and inactive input raw materials or excipients, which have direct links with the drug product CQAs.

Critical process parameters

Similar to CMAs, critical process parameters (CPPs) are related to the intended process(es) used for manufacturing of drug products

and directly influence the CQAs. These are also the key variables that can affect the process performance and variability in product quality. A formal risk assessment approach is used to identify the criticality of process parameters. With the screening approach in place, only a few vital process parameters will be identified as CPPs from the possible process parameters. Apart from CPPs, the process parameters without any variability in their impact on CQAs are discriminated as noncritical process parameters (non-CPPs) [30]. CPPs should be monitored and controlled to ensure the consistency in process performance and product quality without any unacceptable variability. Unlike CPPs, non-CPPs are further fixed throughout the product development cycle.

Design space considerations

Design space (also referred to as the proven acceptable range) is a function of a multidimensional combination of CMAs and CPPs. When a design space is established between CMAs and CQAs, it is considered to be the product design space, whereas a design space established between CPPs and CQAs is referred to as the process design space [31]. Risk assessments, prior experimentations, and multivariate factor screening methods are used to identify the criticality of factors and their ranges to establish a design space. There could be more than one design space in a pharmaceutical product. Ideally, design space is generated using experimental design on a laboratory and/or pilot scale, and extrapolated to the exhibit and/or commercial scale by establishing a correlation with the help of scale-independent parameters [32]. Design space is a multidimensional space between the investigated ranges of CMAs, CPPs, and CQAs. It is proposed by the applicant and is subjected to regulatory approval. Working within the design space is considered ideal to keep the product and/or process variability negligible, whereas movement outside the approved design space is considered as a change and requires regulatory approval.

Control strategy and continuous improvement

A control strategy is designed to ensure consistency in product quality, which is a function of the criticality associated with the input parameters with the output parameters. The elements of the control strategy should describe and justify how in-process control of input materials (drug substance and excipients), intermediates (in-process materials), and container closure systems impact the final product quality. These controls should be clearly defined at the end of product development and should be based on a risk-based scientific understanding of the formulation and process parameters, thereby leading to continuous improvement.

QbD implementation roadmap

The QbD implementation in the product development life cycle involve a five-step approach, which has been described below [1,26].

Step I: define the product development objectives

At the start of the product development cycle, the underlying objectives are defined by the sponsor or manufacturer in terms of the current need for the target product in terms of providing therapeutic efficacy against a particular unmet therapeutic need. Based on prior literature support and prior experience, the objectives are outlined in the form of a TPP. Using the information described in the TPP, key elements summarizing the quality characteristics of the drug product are defined in the form of a QTPP. Furthermore, the patient-centric CQAs of the drug product are identified from the QTPP and have direct linkage with the safety and efficacy of the product [33,34].

Step II: identify the CMAs and/or CPPS, and link them with CQAs

This step involves identifying the CMAs associated with the product and CPPs associated with the processes involved in drug product development. A meaningful link is then established between the CMAs, CPPs, and CQAs based on cause-and-effect relationships. Selection of right CMAs/CPPs is essential, because these directly influence the CQAs. Ishikawa fish-bone diagrams are usually preferred for building cause-and-effect relationships. Moreover, the use of quality risk management (QRM) tools, such as Risk Estimation Matrix (REM) and Failure Mode Effect Analysis (FMEA), are also suitable alternatives [19,35]. Besides risk assessment, factor-screening studies based on experimental designs are also useful. Low-resolution (III–V) designs are suitable for factor screening, and require minimal experimental trials to perform the screening study. Examples of commonly used screening designs include fractional factorial design (FFD), Taguchi design (TD), Plackett-Burman design (PBD), and Minimum-Run Resolution IV design [36].

Step III: establish the design and control spaces

Based on the CMAs and/or CPPs identified, experimental designs are used for factor optimization. High-resolution (V–VIII) response surface designs are used for performing optimization of the product and/or process parameters. Examples of the most commonly used response surface designs include FD, Central composite design (CCD), Box-Behnken design (BBD), D-optimal design (D-OD), and mixture design (MD) [36]. Selection of a suitable experimental design with adequate resolution and optimal number of experimental runs is vital for achieving the desired outcomes along with the necessary understanding of product and process parameters.

DoE execution involves the optimization of CMAs and/or CPPs with one or more response surface design(s), followed by modeling of the response values of the CQAs by using polynomial mathematical equations. With the help of numerical optimization involving desirability function and graphical optimization procedures, the optimal solutions for the intended product(s) and/or process(es) are identified [37]. Moreover, based on the target product development objectives, a suitable 'design space' is demarcated in the overlay plot. The design space has immense regulatory importance for the flexibility regulatory review process and ease of regulatory oversight. Regulatory approval is a mandatory requirement and, after approval, the design space is also referred to as the 'Proven Acceptable Range (PAR)'. Post regulatory approval of the design space, there is a narrower working region also referred as the 'control space' or 'Normal Operating Range (NOR)'. Control space has no regulatory importance and is generally used as an in-house specification for developing a more stringent region for smooth functioning within the design space [38]. Movement within the design space is acceptable and considered as 'no change', and, thus, does not require any further regulatory supplement and approval.

Step IV: scale-up and validation of design space

Given that regulatory agencies require full-scale commercial design space for product and/or process development, design space usually generated on the laboratory scale requires extension to demonstrate the impact of variation in scale on the ranges of CMAs and CPPs, and the fulfilling of regulatory needs [39]. In this regard, the lab-scale design space is subject to validation studies through checkpoint trials during exhibit and/or commercial-scale manufacturing. Any point that goes outside the established design space is considered an 'edge-of-failure'. This approach helps to assess the robustness of the design space and to establish a control strategy at the commercial scale.

Step V: control strategy and continuous improvement

The control strategy is framed at the end of the QbD-based product development exercise and is a mandatory regulatory requirement. It constitutes key enablers responsible for variability in product CQAs and process controls and helps to maintain the consistency in the quality of the end product. The crucial input parameters noted during the product development exercise are recorded in the form of quality control strategies and monitored during each batch operation [18]. Negligence in identifying an appropriate control strategy can influence the quality and efficacy of the product, and safety to patients. Moreover, the control strategy also helps to reduce risk and control needs to enable researchers to consider these parameters and their impact on product quality for changes both within and outside the design space.

QbD application to pharmaceutical product development

With huge manufacturing and regulatory advantages, QbD can be applied for diverse products. To improve the product quality and robust performance, science should be put into practice using new ideas and innovations during product development [34]. The application of QbD paradigms in pharmaceutical development is becoming routine practice. QbD is applicable for variety of products, including solid-dosage forms (tablets, capsules, pellets, granules, and dry powders), liquid-dosage forms (solutions, suspensions, and emulsions), semisolid-dosage forms (ointments, lotions, suppositories, and gels), and sterile-dosage forms (injectable, ophthalmic, nasal, and otic), along with processes involved in the manufacturing of such preparations. Several reports have been published on the utility of QbD for these dosage forms, which have demonstrated unparalleled potential in multifold enhancement of product and/or process performance.

QbD application to nanopharmaceutical product development

QbD has been adopted by most parts of the drug product development pipeline for pharmaceutical applications. However, there is still room to extrapolate the applications of QbD to complex products, including nanopharmaceuticals (nanomedicines). The current era of disease treatment has paved the way for the use of therapeutically effective and efficient nanomedicines. The application of QbD to nanopharmaceutical products has several benefits for optimizing product performance in terms of complex design, dynamic material properties, and stringent regulatory

TABLE 1

Commonly encountered CMAs, CPPs, and CQAs during the development of nanostructured drug delivery systems

Type of delivery system	CMAs	CPPs	CQAs
Nanostructured lipidic carriers	Lipid concentration, drug:lipid ratio, surfactant concentration, volume of aqueous to oily phase	Stirring speed, time, rate, temperature of water bath, homogenization speed, number of cycles	Particle size, zeta potential, surface charge, encapsulation efficiency, drug release profile
Nanoemulsions	Amount of oils, surfactants, cosurfactants, cosolvents	Type of mixing, mixing speed, temperature, homogenization speed, number of cycles	Drug permeation flux, refractive index, viscosity, globule size, zeta potential, polydispersity index
Self-nanoemulsifying systems	Amount of lipids, surfactants, cosurfactants, cosolvents, polymeric precipitation inhibitors, charge inducers	Type of mixing, mixing speed, temperature	Emulsification time, globule size, zeta potential, polydispersity index, drug release profile, *ex vivo* permeation, turbidimetry
Nanovesicular systems	Molar concentration of phospholipids, cholesterol, surfactants, stabilizers, lipid charge, organic solvents	Temperature, stirring rate, shaking time, hydration time, sonication time	Percent encapsulation, entrapment efficiency, vesicle size, dug pay load, drug leakage, stabilization ratio, percentage drug content
Nanosuspensions	Drug:surfactant ratio, concentration of surfactant, stabilizer	Mill speed, milling time, type of beads	Particle size, entrapment efficiency, drug release
Polymeric nanomicelles	Concentrations of drug and block-copolymers, surfactant amount, surfactant type	Stirring type, speed, rate, time, hydration temperature	Entrapment efficiency, drug loading, particle size, rheology, refractive index
Polymeric nanoparticles	Monomer concentration, concentration of polymer, surfactant, molecular weight of polymer, initiator, stabilizer, concentration drug: polymer ratio, volume of oil phase, pH	Manufacturing method, stirrer type, stirring speed and time, temperature, homogenizer speed	Percentage yield, entrapment efficiency, drug loading, drug release profile, polydispersity index, particle size, zeta potential
Metallic nanoparticles	Concentration of metal ions, concentration of ligand, volume of aqueous phase		Percent yield, drug loading, drug release profile, polydispersity index, particle size, zeta potential

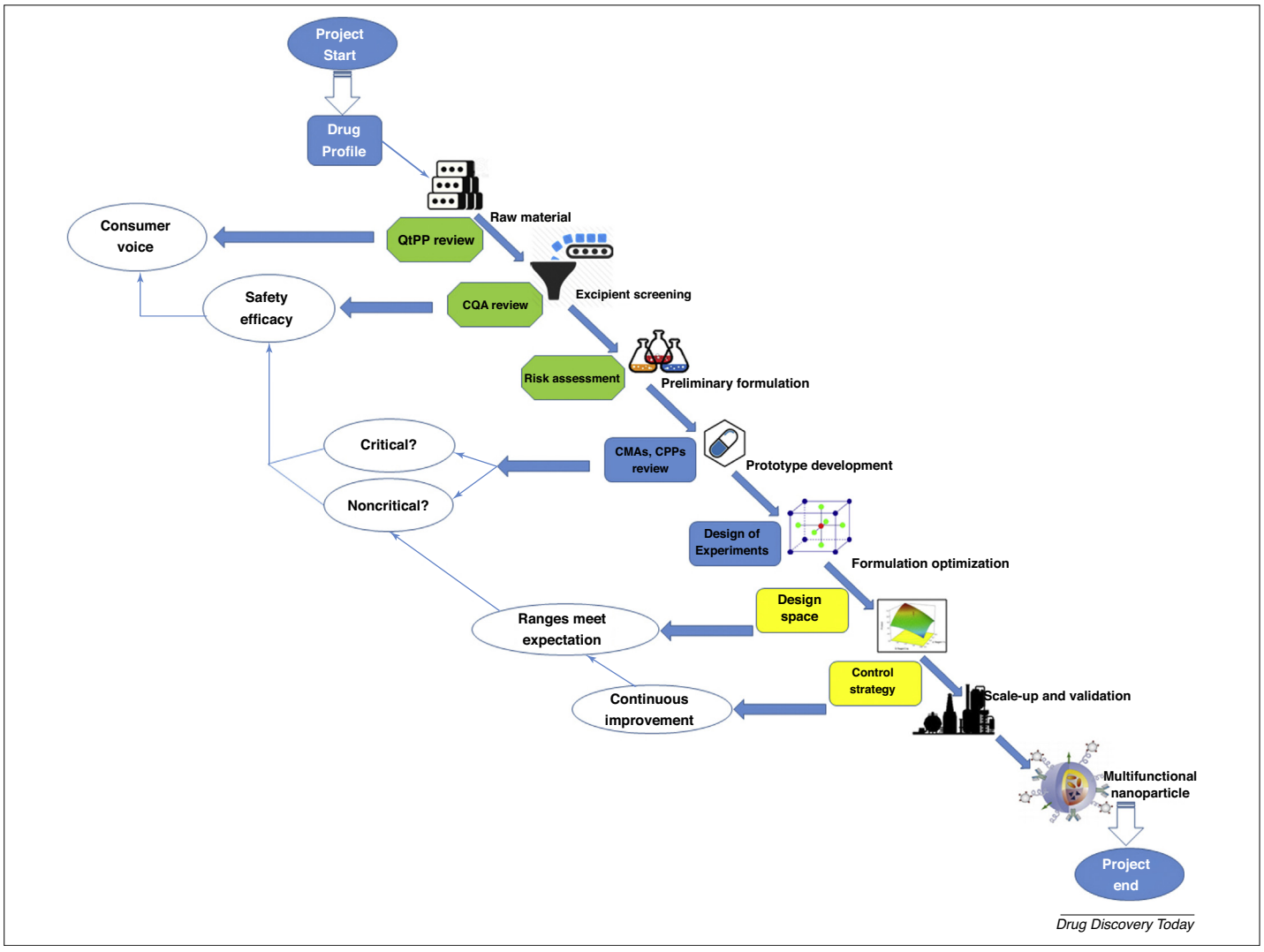


FIGURE 5

Key milestones associated with the quality-by-design (QbD)-based development of nanostructured drug products.

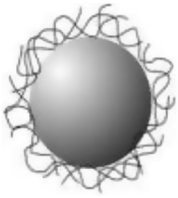
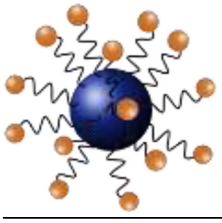
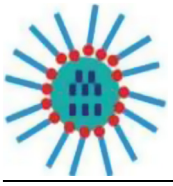
requirements for CAs, including particle size, zeta potential, drug loading, *in vitro* drug release profile, surface morphology characteristics, pharmacokinetic performance, drug stability, and impurity profiling [40,41]. Table 1 provides information on commonly used CMAs, CPPs, and CQAs in nanopharmaceutical products. Figure 5 provides a schematic view of the development of nanopharmaceuticals, which involves critical consideration of their QAs, identification of material attributes and process parameters, and understanding of the variability in, and selection of, optimum conditions in the design space. The continuous flow of research publications on the regulatory approval of nanopharmaceutical products by FDA and EMA is a testimony to the application of QbD. Diverse nanotechnology products, especially liposomes, niosomes, nanoparticulate systems (polymeric, lipidic, metallic, and hybrid), micro/nanoemulsions, nanosuspensions, and nanogels for oral, inhalational, parenteral, topical, transdermal, and ophthalmic applications have been discussed in the literature in terms of the application of QbD tools for systematic development with immense benefits coupled with robust quality and performance [42,43]. Table 2 provides examples of the QbD-based development of various nanotechnology products.

Regulatory milestones in the application of QbD to nanopharmaceuticals

The crucial path initiatives for the approval of any drug product involve compliance of the sponsor to the mandatory requirements of the regulatory agency. These include detailed evaluation of the chemistry, manufacturing, and control of the drug substance, and the formulation and stability characteristics of a new drug product and/or a gene drug product. Similarly, the development and manufacturing of nanopharmaceutical products involve a series of steps associated with diverse factors and variables. This leads to difficulty in monitoring product quality and in reducing the variability and performance throughout the life cycle. Thus, QbD could have application in the monitoring of product performance with the target objectives and end goals in mind to provide consistency in product quality and robustness. Moreover, as a systematized approach, the appli-

TABLE 2

Select literature instances on QbD-based development of nanostructured drug products

Delivery system	Drug	CMAs/CPPs	Design	Refs
Liposomes 	Paclitaxel	Concentration of phospholipid and cholesterol	CCD	[44]
	Hyaluronidase	Phosphatidylcholine and speed of rotation	CCD	[45]
	Sirolimus	Molar ratio of DPPC:cholesterol and of DOPE:DPPC	CCD	[46]
	Dithranol	Concentration of compritol 888 and phospholipon 90G	CCD	[47]
	Paeonol	DC-Cholesterol concentration, molar ratio of lipid/drug, polymer concentration	BBD	[48]
Polymeric nanoparticles 	Hydrocortisone butyrate	PLGA, PVA, stirring speed and time, sonication time	PBD	[49]
	Glibenclamide	Amount of poloxamer 188, amount of PVP S 630 D, solvent: antisolvent volume ratio	PBD	[50]
	Pyridostigmine bromide	Concentration of poly(lactic acid) and PVA	CCD	[51]
Metallic nanoparticles 	Gold	Stirring rate, sodium citrate concentration and ionic strength	BBD	[52]
	Silver	Amount of precursor (AgNO3), stabilizer (Daxad), reducing agent (Asc), and pH controller (HNO_3)	FFD	[53]
Nanoemulsion 	Raloxifene	Amount of Capryol 90, Cremophor RH 40, and Transcutol HP	D-OD	[54]
	Olmesartan	Amount of oleic acid, Tween 40, and transcutol	D-OD	[55]
	Carvedilol	Amount of Capmul MCM and Nikkol HCO 50	CCD	[56]
	Ezetimibe	Amount of lipid and surfactant	CCD	[57]
Nanosuspension 	Carvedilol	Concentration of drug and alpha-tocopherol succinate, level of sodium lauryl sulfate	CCD	[58]
	Rebamipide	Concentration of drug, Lutrol F127, and Kollidon 90F	CCD	[59]
	Simvastatin	Amount of compritol, poloxamer; volume of acetone	FD	[60]
Nanogels 	Tamoxifen	Concentration of lecithin, Span 80, and water	D-OD	[61]
	Estradiol	Concentration of lecithin, *N*-methyl-2-pyrrolidinone, and *N*-Lauroyl L-lysine methyl ester	CCD	[62]

cation of QbD principles results in significant resource savings. Although there are no regulatory requirements for the application of QbD to nanotechnology products, the adoption of such paradigms into their development would be welcome. As per the current thinking of regulatory agencies, as reflected through discussions at public forums, white papers, and news articles, it is clear that the agencies are more interested in considering new drug applications with QbD elements, emphasizing the multiple facets of end-consumer needs, such as quality, safety, and efficacy. Several studies have already evaluated the importance of QbD in the development of nanotechnology products. Given the complexities involved in the development and manufacturing of nanopharmaceutical products, regulatory agencies should also develop specific regulatory guidances for such products to harmonize the requirements for a particular level of product and process quality.

Concluding remarks

The application of QbD tools to the development of nanopharmaceutical products is considered as 'the best' approach to confirming product quality for the benefit of patients. Whether for new products or generic nanopharmaceutical products (also referred to as nanosimilars), QbD enables the acceleration of product development with minimal efforts to produce maximal performance. This should provide greater flexibility to formulation scientists monitoring product CQAs during batch manufacturing by avoiding any deviation in the form of out of specifications (OOSs). In addition, QbD tools provide an overview of product quality throughout the product life cycle.

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