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Quality by design: A new approach to accelerate the technological development in health

Qualidade por concepção: uma nova abordagem para acelerar o desenvolvimento tecnológico e inovação na área da saúde

Camila Guindalini[I,*]

Martha Maria de Oliveira[I]

ABSTRACT

This article seeks to present a systematic and proactive quality management model based on scientific rigor, as well as on analysis and risk management, known as Quality by Design (QbD). Since 2012, regulatory agencies from the United States and the European Union have pressed the manufactures to speed the adoption of QbD principles for processes and products development. In Brazil, the new approach has received increasing attention from the pharmaceutical/biotechnological community, as well as from Anvisa, and it is now seen as a global regulatory initiative to assure the rational development of products, reducing the lead and launch time to market, incrementing the elaboration of clinical protocols, controlling costs and increasing success chances of the pharmaceutical sector. In this context, the adoption of the QbD concepts aims to add value to existing quality policies in organizations, providing not only more agility and assertiveness, but also more confidence in the new developed products.

KEYWORDS: Quality Management; Quality by Design; Innovation, Research and Development; Health Surveillance

RESUMO

O presente artigo pretende apresentar um modelo de gestão de qualidade sistemático e proativo, baseado no rigor científico e em análise e gerenciamento de risco, conhecido como Quality by Design (QbD) ou Qualidade por Concepção (QpC). Desde 2012, as agências reguladoras dos Estados Unidos e União Europeia têm sugerido a aplicação das diretrizes da QpC para o desenvolvimento de processos e produtos. No Brasil, a nova abordagem tem recebido atenção crescente da comunidade farmacêutica/biotecnológica, assim como da Anvisa, e é vista hoje como uma inciativa regulatória global que visa garantir o desenvolvimento racional dos produtos, reduzindo o tempo de disponibilização ao mercado, incrementando a elaboração de protocolos clínicos, controlando os custos e aumentando as chances de sucesso do setor farmacêutico. Nesse contexto, a adoção dos princípios da QpC pretende agregar valor à política de qualidade já existente nas organizações, propiciando não apenas mais agilidade e assertividade, como também mais confiança nos novos produtos desenvolvidos.

PALAVRAS-CHAVE: Gestão da Qualidade; Qualidade por Concepção; Inovação, Pesquisa e Desenvolvimento; Vigilância em Saúde

[I] Centro de Desenvolvimento Tecnológico em Saúde, Fundação Oswaldo Cruz (CDTS/Fiocruz), Rio de Janeiro, RJ, Brasil

* **E-mail:** cguindalini@cdts.fiocruz.br

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INTRODUCTION

At the same time as economic development, scientific and technological advances have brought innumerable benefits to human health, with direct impacts on the life expectancy and quality of life of the population. More recently, there has been a revolution in the development of new drugs with the advent of technologies in areas such as genomics, proteomics, large-scale analyses, imaging, and robotics. On the other hand, scientific progress does not equally consider all those who need it. Despite the numerous efforts of government agencies and entities and research institutes to reduce the gap in realizing the right to health, the challenge persists, especially for lower income countries[1-4].

Recently, the Lancet Commission on Investing in Health highlighted in its report *Global Health 2035: a world-wide convergence within a generation* that, if adequate health investments are made in low- and middle-income countries, approximately 10 million deaths could be avoided by 2035[5]. However, according to the survey of *G-Finder 2012*: *Neglected disease research and development: a five-year review*, only 1%–2% of the global total annually invested in research and development of new products is spent on the study of infectious diseases that disproportionately affect developing countries[6].

The field of public health is one of the most dynamic economic spaces for capital accumulation and innovation with a strong impact on the social dimension[3,7,8]. The stimulation of scientific and technological development at levels of excellence requires the creation and implementation of a systemic approach to innovation that fosters the expansion of research and production capacity. The need for public policies to be aligned with a national development strategy and with well-defined resource allocation priorities, together with instruments that generate synergy among research institutions, enterprises, and government entities, is becoming increasingly evident in order to optimize and boost results. In addition, it is critical that both development and regulatory agencies turn their attention to the structural gap that exists between what is discovered in the academic environment and what is made available as a solution to society[9]. Innovation systems must take into account both the findings and the new knowledge generated by research, as well as the demand for new products and interventions by industry and society.

In this context, this article aims to contextualize the importance of research and innovation processes in the health area, especially in Brazil, and to present a narrative review of the literature regarding the principles of quality as a foundation for technological development. More specifically, a new approach in the area, known as Quality by Design (QbD), is addressed, which aims to add value to the quality policy already existing in institutions and to increase innovation and production systems, making them more efficient, agile, and flexible. This new approach presents itself as an excellent opportunity to incorporate risk management into regulatory processes and to help build a stronger scientific knowledge base for all products developed, providing a better interaction between regulatory agencies, the scientific community, and the industry.

RESEARCH, DEVELOPMENT, AND INNOVATION IN BRAZIL

Research participates centrally in the framework of the general effort of science, technology, and innovation in Brazil, from the origin of ideas to the development of alternative ways to translate knowledge and implement new policies and types of regulation[10,11]. In fact, the number of scientific articles published by Brazilian researchers has steadily and progressively increased. According to the *SCImago database* (http://www.scimagojr.com), Brazil is today the 13th country in the world in the generation of scientific publications in all areas of science[12]. However, the emphasis reached in scientific production seems not to be largely translated into real products, as the number of patent applications, despite also showing relative growth, is still below that of other developing countries[13]. A recent survey by *Nature*, known as *Nature Index* (https://www.natureindex.com), places Brazil as one of the countries with the lowest efficiency scores for science spending, considering the number of articles published in high prestige international scientific journals and the total investments in research in the country. Although the prominence of Brazil in the scientific context cannot be ignored, the country still has a long way to go.

In other words, the urgency is clear for the elaboration and implementation of new research, development, and innovation strategies, as well as coordinated public policy actions that seek to overcome the gap between basic research and its practical application, increasing efficiency, ensuring quality, and reducing industry costs. It is a fact that the process used today in drug development is slow, inefficient, extremely risky, and increasingly costly for the pharmaceutical industry[14]. Kaitin[15] has proposed a new model of pharmaceutical development, a fully integrated network approach that engages key *stakeholders* in the drug development process and uses key competencies of each one to leverage prospects for success and speed up the process. In this proposed model, the academy would promote both basic research and translational medicine, working mainly on the training of human resources, on initial discovery processes, on preclinical studies, and on the initial phase of drug development. Small biotechnology and pharmaceutical companies would take part in the innovation process by working in partnership with large industries to develop new and emerging technologies. Large industries would participate in the initial processes of the chain only by coordinating and managing the activities, concentrating efforts and resources in the final stages of development, regulatory review and approval, and in Phase IV trials, analyzing the clinical and budgetary impact of the product on the health system. Contract research organizations would cover the entire process from preclinical studies. Contract research organizations are organizations that provide services and support to the pharmaceutical industry using outsourced contracts. By separating responsibilities and sharing risks and resources, the innovation network promotes an efficient mechanism to ensure the viability and economic success of all sectors of the pharmaceutical and biotechnology industry[15].

In a cooperative environment, the use of quality and risk management management tools are essential for all entities involved in the technological development process (academic, industrial, clinical and operational research sites), as they increase their perception of gains by working within an atmosphere that is concerned with seeking not only compliance with regulatory requirements, but also a culture of excellence capable of producing quality, reliable, and safe products and services.

QUALITY IN THE CONTEXT OF TECHNOLOGICAL DEVELOPMENT

Main quality management systems

In this context, quality can be defined, as: adequately meeting the needs and expectations of customers, doing it right for the first time ("zero defect")[16]. Furthermore, according to Juran, quality means compliance with specifications and it can be managed from three processes known as the Juran Trilogy: quality planning, quality control, and quality improvement[17]. According to Deming[18], quality is based on process control using the *Plan, Do, Check, Act* cycle and statistical methods, which should be the basis for continuous improvement..

The quality management system acts at all organizational levels, seeking to ensure the quality of the product or service. The *International Organization for Standardization* (ISO) is a nongovernmental organization whose objective is the development of international technical standards. The ISO 9001 standard set the format not only for quality management systems, but also for management systems in general, and it is the best internationally-established quality structure, being used by thousands of organizations in more than 170 countries (http://www.iso.org). In Brazil, the ISO is represented by the Brazilian Association of Technical Standards (ABNT).

Because of the particularities of the laboratory activities, the ISO initially created the *ISO/IEC Guide 25*, for the evaluation of the capability of testing and calibration laboratories. In 1999, the guide incorporated the experience gained from other standards, including the ISO 9000 family, and was renamed as the ISO/IEC 17025:1999, replacing the *ISO/IEC Guide 25*[19]. With the update of the ISO 9001, the second edition of the ISO/IEC 17025:2005 (ISO, 2005) was approved, or in Brazil known as: Brazilian Association of Technical Standards NBR ISO/IEC 17025:2005[20]. In the same context, considering the importance of laboratory activity, mainly in relation to analyses for product registrations, a quality management system entitled Good Laboratory Practices was developed by the Organization for Economic Cooperation and Development in 1978 [21]. Although both systems have different requirements and characteristics, they have common objectives: to ensure the quality of the activities performed within the laboratory and, consequently, of the product generated from these activities. In general terms, the ISO/IEC 17025 provides a system focused on the control of the laboratory at all levels (from the technical to the administrative area), and it works with audits of the quality system, having the advantage of being flexible to meet any type of activity that the laboratory proposes, be it testing or calibration. Its evaluation criteria are grouped into 25 requirements: 15 of them are management requirements ranging from contract review, document control, services and supplies acquisition, corrective and preventive actions, to the conduction of internal audits; and 10 are technical requirements, involving personnel, equipment, environment and facilities, analytical methods, quality assurance, and presentation of results. The focus of the Good Laboratory Practices is more specifically directed to the study being carried out, and it is used to ensure the quality and integrity of the submitted data in support of the approval of controlled products. Among the main requirements of the Good Laboratory Practices are organization and personnel of the test facility, quality assurance programs, materials, facilities and equipments, test systems, test and references substances , execution and reports of the study, storage and retention of records.

Quality assurance in the research and development environment

Research is a key part of the new drugs development chain . For this reason, scientific work must be conducted under controlled and verifiable conditions to ensure a sound basis for the decision to invest in the development of a strategy or in a specific product; otherwise valuable resources will be squandered in clinical studies with no real value for the population. There is growing recognition that the quality and reproducibility of both preclinical and clinical studies depend on the rigor with which researchers design and conduct their studies, how they control for potential experimental biases, and how they report essential methodological details[22-24]. A team of researchers at *Bayer HealthCare* in Germany recently reported that only about 25% of preclinical studies could be sufficiently validated, to allow pharmaceutical development projects to continue[23].

Placing quality processes as partners and creating opportunities for scientific discussions around the subject, rather than imprinting a perception of judgment and imposition, are essential to ensure the consent of researchers and other stakeholders involved in the process of implementing quality policies and to avoid interruptions and disruptions in the progress of the technological innovation chain[25]. More recently, many health research and organizations have recognized the need to establish sound quality standards to ensure the integrity and validity of the data they generate. There is a tendency of the scientific community to question the traditional peer review and to consider the need to incorporate the quality principles and quality assurance mechanisms to safeguard the recognition of the studies[25]. Basic research is not necessarily covered by any quality management system; in this way, aligned with growing concerns, the World Health Organization (WHO) published the document *Quality Practices in Basic Biomedical Research* in 2006[26], which has as its main scope the orientation of scientists in relation to the organization of research as a way of adding credibility to the data generated, facilitating their verification and stimulating the culture of transparency. The main elements that make up the guidelines of the manual include the implementation of the quality policy, employee training, project design, research protocol, standard operating procedures,

report of results, guidelines on publication practices, code of ethics and biosafety, storage and management of documents, quality supervision and assurance of both systems and procedures, scientific content, results, and final reports[27].

Other important initiatives in the area of quality management in basic research also deserve to be highlighted. The *British Association of Research Quality Assurance* published quality guidelines in 2006 for research laboratories that do not fall under the Good Laboratory Practices regulations[28]. The *American Society for Quality*, one of the largest quality organizations in the world, published a technical paper in 2012 entitled: *Best Quality Practices for Biomedical Research in Drug Development*[29]. The document discusses the need to implement quality standards for biomedical research and it presents what can be considered the first step towards the creation of an international ISO standard. These groups recognize that the implementation of good laboratory practices and good clinical practices has become essential so that the development of new health products can achieve higher success rates. Furthermore, a Brazilian standard, NBR 16501[30], was published in 2011, which describes the guidelines for applied research, development, and innovation. The standard is based on the *Plan, Do, Check, Act* cycle and it is divided into five sections: the research, development, and innovation management system, management responsibility, resource management, implementation, measurement, analysis, and improvement of research, development, and innovation system,

A NEW APPROACH: QUALITY BY DESIGN

Definition

Quality by Design *has* received increasing attention from the pharmaceutical community in recent years[31-33]. The term was initially introduced in 2004, as a result of the initiative of the *US Food and Drug Administration*: *Pharmaceutical Current Good Manufacturing Practice for the 21st Century Initiative*[34] and it was subsequently outlined in the *Process Analytical Technology Guidance for Industry* guidelines - *A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance*[35] and *International Conference on Harmonization* (ICH), ICH Q8, on Pharmaceutical Development, ICH Q9, on Risk Management for Quality, and ICH Q10, dedicated to the Pharmaceutical Quality System[36-38].

Since 2012, the *Food and Drug Administration* has encouraged the adoption of QbD principles in the development, manufacture, and regulation of pharmaceutical products. Currently, QbD is a global regulatory initiative that can be defined as a systematic, scientific, risk-based, holistic, and proactive approach. The principles of this new concept emphasize the importance of rational development in order to achieve the expected quality and minimize errors that add higher costs to processes[32].

The traditional approach for product development and manufacturing generally involves the use of empirical methods, especially with regard to the relationship between processes and product, and between product and its clinical aspects. On the other hand, QbD is defined by the ICH Q8 guidelines 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"[38]. The QbD promotes the deep understanding of the product and the production process and encourages quality building during the process, not just testing it at the end.

Implementation

The principles of QbD implementation can be summarized as: identification of attributes that can be of significant importance in the effectiveness and safety of the product, process design to achieve the specified attributes, robust control strategy to ensure consistency of process performance, process validation mechanisms to demonstrate the efficiency of the control strategy and, finally, constant monitoring to ensure the consistency of the process throughout the product life cycle. Risk analysis and management, management of materials, statistical tools, and analytical process technology are the basis for these activities[31]. We present a more detailed description of each step below:

1) Identification of product attributes that are of significant importance for its safety and/or effectiveness

Identification of the Target Product Profile

The identification of the *target product profile* consists in the establishment of a prospective summary of the product quality characteristics that should ideally be achieved in order to ensure the desired quality. This may include, for example, the type of administration, dose, pharmacokinetic characteristics, among other specifications that should be established as soon as the product is identified as a potential candidate, and which should be reviewed as the product development progresses.

Identification of the Critical Quality Attributes of the Product

After identifying the product profile, the next step is to identify the critical quality attributes, that is, the physicochemical, biological, and microbiological properties of the product and excipients that must be within pre-established limits to ensure product quality. Because biotechnological products have a number of quality attributes that can potentially influence their efficacy and safety, the identification of the product profile should initially be performed using a risk analysis, according to the ICH Q9 *Guideline*. The risk is considered low when there are specific clinical data about the product that demonstrate the absence of adverse effects on safety and efficacy; the risk is considered high if data show otherwise, and it is intermediate if there is no data in the literature about the product.

2) Definition of the design space

As defined in the ICH Q8 guidelines, the design space can be defined as the multidimensional combination and interaction of input variables and process parameters that have been shown to ensure quality. The purpose of establishing a design space is to

integrate all the available information into a space in which all critical quality attributes are fulfilled, making the process more robust and ensuring the quality of the result. Proper design and characterization of the product may influence its entire development chain up to manufacturing. Working within the design space means maintaining specifications and ensuring quality. The design space is wider than the operating space, so any change outside the space established requires a review of the study in development. These specifications are based on a number of sources of information that link attributes to product efficacy and safety, such as previous clinical trials with similar products, non-clinical studies with the product (*in vivo* and *in vitro* experiments), and prior scientific literature.

Once the acceptable variability for the critical quality attributes has been established within the product design space, process characterization studies should be conducted to define the acceptable variability in the process parameters, that is, they should define the critical control points and the parameters of the process whose variability affects the critical quality attributes of the product. This characterization should consider: 1) risk analysis to identify parameters used in the characterization of the process, and 2) results of the designed studies using the concept of *Design of Experiments*, which is an approach that organizes the experiments in a rational way and calculates the acceptable range of variation for the parameters identified as key ones in the processes.

3) Definition of a control strategy

A control strategy can be defined as a set of controls established from the understanding of the characteristics of the product and the processes that ensure performance and quality. In a traditional control strategy, any variability in the input components results in variability in product quality, as production controls are fixed. On the other hand, in a dynamic strategy, production controls can be changed within the design space, and the variabilities of the input components can be removed or reduced, resulting in a greater consistency of the product quality. Controls may include: internal process controls, raw material controls, inputs, stability studies, process validation tests, real-time monitoring, and comparative studies.

4) Validation and monitoring of the process

After establishing the control strategies and defining the product and process design spaces, the validation and subsequent continuous monitoring should be conducted to ensure that the established process will, in fact, deliver a product of acceptable quality within the established design space. Following the product life cycle and implementing continuous improvement in processes is essential to maintain the consistency of the product quality.

5) Quality risk management

Quality risk management can be defined as a systematic process to access, control, communicate, and review the risks to product quality throughout its life cycle, that is, from the initial development, throughout commercialization, up to the discontinuation of the product[39].

Assessing risk throughout the development of a product provides data to enhance its development and manufacturing process, as it allows for the anticipation of potential problems that can be mitigated or even excluded from the process, thus ensuring the achievement of the expected performance. In this way, the variability of product or process quality attributes tends to decrease, reducing expenses and increasing production efficiency[39]. The guidelines of ICH 09: *Quality Risk Management*[36] provide guidance on *quality risk management* principles and tools that extend throughout the product life cycle. It is postulated that quality risk assessment should be based on scientific knowledge, giving priority to patient protection. The steps in *quality risk management* can be summarized as: 1) Risk assessment: identification, analysis, and classification; 2) Risk control: reduction, mitigation, or acceptance; 3) Risk communication: sharing of information between the parties involved throughout the process; 4) Risk review: implementation of mechanisms for ongoing review and monitoring, since risk models are highly changeable.

For risk analysis, several tools are available, among them: basic tools (flowchart, checklist), *failure mode effects analysis*, *failure mode, effects, and criticality analysis*, *fault tree analysis*, *hazard analysis and critical control points*, *risk ranking and filtering*[39].

6) Management of materials

The materials used in biotechnological processes tend to be complex and exhibit intra-batch variability in relation to their impact on the process. Thus, a robust material management must be defined to ensure the successful implementation of QbD. First, risk management tools should be used to assess the risk associated with materials in relation to their impact on process consistency and product quality. From this analysis, materials are classified according to their criticality to guide the actions of characterization, control, and monitoring.

7) Statistical approach to the design of experiments

The use of statistical approaches in the elaboration of experimental studies, as well as in the evaluation of the data and results obtained, is considered an essential activity for the implementation of QbD since a great amount of materials and parameters in the processes have potential to impact operations in biotechnology. Statistical analyses such as multivariate analysis and *principal component analysis* can be extremely useful as diagnostic tools for identifying root causes and increasing knowledge and understanding of the process[33].

8) Process analytical technology

Process analytical technology can be defined as a system for production design, analysis, and control by measuring the critical quality and performance attributes in real time, that is, during processing, to ensure the quality and consistency of the final product[35].

CONCLUSIONS

Fortunately, the advancement of science, the greater knowledge about the characteristics of pharmaceutical inputs and excipients, and the technological advances in equipment have allowed product development to no longer be merely experimental, but starting to contemplate more scientific and controlled approaches. In this context, the QbD concept appears as a potentially useful tool to reduce the development time of products and make them available to the market, increase the development of clinical protocols, control the costs, and increase the chances of success in the development sector and in the innovation chain.

The adequacy of the QbD concept to the reality of companies, industries, and research institutions will facilitate the control of processes in real time, ensuring the quality of the final product. This is due to the detailed establishment of the relationships between the critical quality attributes of the products under development and the desired clinical properties, as well as the relationships between the processes and the attributes of quality and materials, which allow a thorough knowledge of what is being produced, thus mitigating or eliminating potential risks that may arise. By defining the design spaces of the products and processes under development, the possibility of creating barrier mechanisms to move outside these spaces becomes very broad, which confers to the company a competitive advantage and agility in the technological development process.

Finally, the implementation of the QbD concept will allow the improvement of processes and not just their control. The successful implementation of the QbD will bring numerous benefits to the entire development and production chain of new medical supplies, drugs, and vaccines, as well as their regulation. In practice, the benefits of adopting QbD are numerous and include: reduction of nonconformities, costs, and volume of documentation and regulatory burden; optimization of time and resources dedicated to the development and scheduling of the process; minimization of post-registration changes and submissions; and, the introduction and implementation of practices and concepts in the institution from the latest global standardization. In short, an organization that adopts the QbD concept from the beginning of the project and dedicates more time to the planning and execution of the product development ensures a greater efficiency in its processes, by obtaining the final product according to its use, reducing cost with waste from quality flaws and deviations.

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Conflict of interest

The authors report that there is no potential conflict of interest with peers and institutions, political or financial, in this study.