REVIEW
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Proposal for implementing continuous process verification in medicines developed by Quality by Design using the 5W2H tool

Proposta de implementação da verificação continuada de processos em medicamentos desenvolvidos por *Quality by Design*, utilizando a ferramenta 5W2H

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ABSTRACT

Introduction: The inclusion of the Brazilian Health Regulatory Agency (Anvisa) in the International Coalition of Medicines Regulatory Authorities introduced the concept of the product lifecycle management into drug development. In this context, Continued Process Verification (CPV) plays a key role in ensuring continuous improvement and controlling batch-to-batch variability. However, detailed guidance on CPV remains limited in both national legislations and scientific literature. **Objective:** This study aimed to explore the theoretical aspects of CPV and outline the activities required for its implementation. Method: The research was conducted through a review of scientific articles and national and international regulatory guidelines. An action plan for CPV implementation was developed using the 5W2H tool. **Results:** Anvisa adopted the product lifecycle concept, with the Quality by Design (QbD) approach being recommended. QbD includes defining the Quality Target Product Profile (QTPP) and using experimental design to understand the relationships between formulation and process variables in the Critical Quality Attributes (CQAs). Risk management is essential within QbD framework and also plays a key role in process validation. CPV monitors process performance, detecting and correcting deviations to ensure product consistency. Tools such as statistical process control ensure controlled variability and continuous quality during manufacturing. Based on the information gathered, the 5W2H tool was applied to develop an action plan for CPV implementation. **Conclusions:** This study provided a theoretical and practical foundation for CPV implementation, helping pharmaceutical companies adopt better practices in lifecycle management.

KEYWORDS: Quality by Design; Critical Quality Attributes; Risk Analysis; Continued Process Verification; 5W2H

RESUMO

Introdução: A inclusão da Agência Nacional de Vigilância Sanitária (Anvisa) no Comitê Internacional de Cooperação Regulatória trouxe o conceito de ciclo de vida para o desenvolvimento de medicamentos. Nesse contexto, a verificação continuada de processo (VCP) garante a melhoria contínua e o controle da variabilidade nos lotes. No entanto, faltam detalhes sobre a implementação da VCP na legislação nacional e literatura científica. **Objetivo:** Aprofundar os aspectos teóricos da VCP e detalhar as atividades necessárias para sua implementação. **Método:** A pesquisa foi realizada por meio de revisão de artigos científicos e guias regulatórios nacionais e internacionais. Foi elaborado um plano de ação utilizando a ferramenta 5W2H para implementação da VCP. **Resultados:** A Anvisa passou a adotar o conceito de ciclo de vida do produto, sendo a abordagem de *Quality by Design* (QbD) recomendada. O

QbD inclui a definição do perfil-alvo de qualidade do produto e uso do delineamento experimental para o entendimento das relações entre variáveis da formulação e processo nos atributos de qualidade do medicamento. O gerenciamento de riscos é essencial no QbD, sendo também relevante na validação de processos. A VCP monitora o desempenho do processo, detectando e corrigindo desvios, garantindo a consistência do produto. Ferramentas como controle estatístico asseguram variabilidade controlada e qualidade contínua na produção. Considerando-se as informações levantadas aplicou-se a ferramenta 5W2H para a construção de um plano de ação para a implementação da VCP. **Conclusões:** Este trabalho forneceu uma base teórica e prática para a implementação da VCP, auxiliando as indústrias farmacêuticas a adotarem melhores práticas no gerenciamento do ciclo de vida.

PALAVRAS-CHAVE: *Quality by Design*; Atributos Críticos de Qualidade; Análise de Risco; Verificação Continuada de Processo; 5W2H

INTRODUCTION

The updating of pharmaceutical regulation in Brazil, driven by the entry of the Brazilian Health Regulatory Agency (Anvisa) into the Pharmaceutical Inspection Co-operation Scheme (PIC/S), has incorporated international concepts into national legislation. This has introduced a new regulatory approach, requiring a greater understanding of the manufacturing processes and characteristics of medicines produced in the country[1,2].

This regulatory transformation has been fundamental to the harmonization of national Good Manufacturing Practices (GMP) with international guidelines. This regulatory milestone, achieved with the publication of Collegiate Board Resolution (RDC) No. 658, of March 30, 2022, reflects the incorporation of process validation activities into the product life cycle concept, establishing a detailed format on how validation should be implemented in the context of pharmaceutical production.

The product life cycle, a concept that links product and process development to the qualification and continuous control of manufacturing processes, is centered on maintaining the production process in a state of control, as stipulated by the Food and Drug Administration (FDA)[3].

Regarding process validation, the FDA defines it as: the collection and analysis of data, from the process design phase through to commercial production, with the aim of providing evidence that the process is capable of consistently producing quality products[3]. Process validation covers three phases: phase 1, which consists of process design; phase 2, with process qualification; and phase 3, which corresponds to continued process verification (CPV)[4]. CPV is a control strategy implemented after the manufacturing process has been validated (monitoring at least three consecutive batches), the aim of which is to ensure that the process remains under control over time, consistently producing quality medicines and maintaining the validated status. In practice, CPV involves continuous collection and analysis of critical process and product quality data during commercial manufacture. This allows trends, deviations, and opportunities for improvement to be identified, promoting a more robust and dynamic control system, in line with the principles of pharmaceutical quality management. CPV is the final and continuous phase of the product life cycle and is directly related to the process validation phases, since using the knowledge acquired in phases 1 and 2 is fundamental to the effectiveness of CPV. Although Brazil has incorporated the concept of the product life cycle, details on how the different stages should be implemented in practice are still scarce in national legislation and scientific literature.

Normative Instruction (IN) No. 138 of March 30, 2022, for example, presents different approaches to process validation, including traditional, hybrid and continuous verification.

Considering the development of pharmaceutical products, the traditional approach to development is based mainly on observation and empirical experimentation, with a focus on quality control of raw materials and final products, using testing and sampling to ensure that products meet regulatory specifications[5]. Nasr et al.[6] mentioned that this approach, also known as Quality by Testing (QbT) or one factor at a time (OFAT), is limited by the lack of flexibility in the manufacturing stages and the difficulty in identifying and correcting the causes of failures. This can result in high costs, long development times and variations in products, compromising their safety and effectiveness.

On the other hand, there are newer and more efficient approaches to drug development, such as Quality by Design (QbD). QbD is a quality paradigm based on scientific knowledge and risk management, seeking a deep understanding of the product and the process throughout the entire life cycle. By incorporating QbD into process validation, critical process parameters (CPPs) and critical quality attributes (CQAs) are defined, which is essential for ensuring continuous quality. CPV should be adopted for products developed with QbD, ensuring efficient and continuous control throughout the product's life cycle[8,9]. Therefore, the connection between QbD and CPV is direct, essential and strategic, as CPV is actually a practical and operational extension of QbD principles into the commercial production phase, through: continuous monitoring of CPPs and CQAs defined in QbD, use of in-line analytical tools (e.g. Process Analytical Technology - PAT), analysis of statistical data to ensure the state of control and the updating of process knowledge based on real data. In this way, CPV confirms and feeds back the knowledge generated by QbD,

strengthening the cycle of continuous improvement. Anvisa, through RDC No. 658/2022, recognizes the importance of QbD in the development phase, highlighting the need for a quality system that guarantees the consistent manufacture of products with appropriate quality attributes.

The CPV approach should be adopted for products developed using the QbD methodology, ensuring high quality assurance throughout the product's life cycle and for legacy products (those that are already registered with Anvisa but were developed using the traditional approach). Implementing CPV requires a detailed review of the process control strategy based on historical production data and critical events such as deviations and complaints[10].

The growing demand for medicines and processes developed with QbD is driving the adoption of CPV, since this approach allows for the control of variations in the process, based on the risk these variations pose to product quality. In addition to the lack of detail on process validation phases, many legacy products, which represent a significant segment of the portfolio of several pharmaceutical industries in Brazil, were developed using the traditional approach and lack the flexibility needed to implement an effective CPV.

The aim of this study is to propose the implementation of CPV in solid oral medicines developed using the QbD strategy.

The adoption of CPV, as a continuous process control technique, allows companies to act proactively in the face of quality risks, encourage continuous improvement, and reduce losses through failures and rework, ensuring that the medicines produced meet quality, efficacy, and safety standards for patients.

METHOD

An exploratory and descriptive study was conducted, characterized as a narrative review of scientific literature, both national and international, with the aiming to present and discuss topics related to process validation, CPV and QbD concepts applied to the development and manufacturing of medicines, from a theoretical and contextual perspective. As it did not follow a systematic review methodology, the study prioritized conceptual comprehensiveness and the interpretative flexibility of the researchers involved, which allowed for greater depth in the critical analysis.

The study was structured into three main phases: literature search, content selection and analysis, and data interpretation and synthesis.

The electronic searches were carried out up to February 14, 2025 using the Web of Science, PubMed, and Google Scholar databases, with the aim of covering indexed scientific sources accessible to the academic public. The descriptors and keyword combinations used included: process validation, continued process verification, QbD, pharmaceutical manufacturing, ICH guidelines, GMP, process control, among others. Boolean operators (AND, OR) and search filters were used when available, to refine the results and increase the relevance of the content retrieved. Scientific articles relevant to the topic in question were selected and the inclusion criteria established were: electronic availability of the text, pertinence to the topic addressed (process validation, CPV or QbD), Portuguese and English languages, no restrictions on the period of publication, to capture both the theoretical basis and recent advances, and acceptance of different types of scientific publications, such as original articles, reviews, regulatory guidelines, and technical documents from recognized bodies (for example: International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use - ICH, FDA, Anvisa). Exclusion criteria included publications that were irrelevant to the topic, duplicated, had merely opinionated or non-technical content, or did not directly address aspects related to process validation, ongoing verification or the practical application of QbD concepts in the pharmaceutical industry.

Based on this analysis, critical points were identified for the implementation of CPV in the life cycle of medicines, and it was possible to draw up a specific action plan for each of them by applying the 5W2H tool, allowing for a practical and structured approach to tackling the challenges identified.

RESULTS AND DISCUSSION

Life cycle of medicines

With the publication of RDC No. 658/2022, the national legislation regulating GMP for medicines, Anvisa adopted the product lifecycle as a guiding concep for ensuring product quality[11]. The product lifecycle is divided into stages that begin with the development of the product, continue with the validation of the process, and extend to the ongoing monitoring of commercial batches. This cycle remains active throughout the product's existence, until it is discontinued[1]. In addition to the resolutions published by Anvisa[1], several international guidelines and regulations are used by the pharmaceutical industry - particularly by multinational companies, to structure quality management system, implement GMP requirements, and apply the product lifecycle concept within process validation strategies.

The ICH Q10[12] guide provides a harmonized Pharmaceutical Quality System model that can be used for the different phases of the product lifecycle. It complements the ICH Q8[8] guide, which deals with pharmaceutical development, and the ICH Q9[13] guide, which deals with quality risk management. With the aim of integrating all the previous guides, the ICH Q12[14] guide covers the complete management of the product life cycle with the aim of harmonizing the management of changes to pharmaceutical products in the post-registration phase in all the member countries of the ICH management committee, in order to facilitate regulatory supervision and the continuous improvement of products.

ICH Q12[14]defines tools and approaches to facilitate change management as: established conditions (ECs), risk-based reporting categories, product lifecycle management document (PLCM) and post-approval change management protocol (PACMP).

According to ICH[14], the implementation of a knowledge management system in the lifecycle of a medicine aims to benefit the patient, the industry and the regulatory authorities, promote innovation and continuous improvement in the pharmaceutical sector to strengthen quality assurance and improve the supply of medicines. Increased product and process knowledge can contribute to a greater understanding of which post-registration changes require a regulatory submission, as well as a definition of the level of regulatory categories for these changes, i.e. a better understanding of the risk to product quality, providing an opportunity for greater flexibility in making changes after drug approval and more transparency between industries and regulatory authorities.

Within the process validation approach, the FDA Guidance for Industry - Process Validation: General Principles and Practices[9] already described the concept of the product life cycle linked to product and process development, the commercial qualification of the process and the maintenance of the process in a state of control during routine commercial production until its discontinuation.

Another guide that also addressed the product lifecycle according to the process validation strategy is the PDA Task Force on Technical Report No. 60 - Process Validation: A Lifecycle Approach, which provides a more comprehensive understanding of this concept. The PDA technical reports provide sufficient information on the application of statistical methods and approaches to process validation[15].

The life cycle of a product is a tool for monitoring and analyzing its behavior throughout its existence[11]. Understanding this cycle is fundamental for the industry to adjust its market strategies according to the different phases the product goes through. In other words, the life cycle allows companies to follow the product from its development to its eventual withdrawal or replacement on the market. For most pharmaceutical companies, the product life cycle begins with research and development, which is often a very long phase, and ends when the product is discontinued[11].

Based on this marketing concept of the product life cycle, GMP guidelines can be extended to the life cycle phase of pharmaceutical development, just as they are already applied to the product production stage, always looking for ways to innovate and constantly identifying points for continuous improvement, making it possible to strengthen the link between pharmaceutical development and manufacturing activities. GMP therefore applies to all stages of the product life cycle, from the manufacture of experimental medicines, technology transfer, and commercial manufacture to product discontinuation.

According to the standard, which sets out GMP guidelines related to PIC/S qualification and validation activities, the concept of life cycle encompasses all phases of the useful life of a product, piece of equipment or installation, from initial development to discontinuation of use[2]. In this context, Anvisa, in accordance with RDC No. 658/2022, demonstrates the necessary direction for approaching validation studies of drug production processes by describing what each phase of the life cycle should correspond to:

a. linking product and process development - corresponds to Phase 1;

b. ensuring process validation in the commercial phase - corresponds to Phase 2;

c. maintaining the process in a state of control during commercial production - corresponds to Phase 3[1].

Quality by Design (QbD)

QbD is a systematic approach to development, with predefined objectives and based on knowledge of the product, the process, and quality control, based on science and quality risk management[8].

Although not mandatory from a national regulatory point of view, the use of an approach based on QbD concepts in the drug development phase is widely recommended because it emphasizes understanding the entire process and product. Anvisa recognizes the importance of applying the QbD approach in the product development phase by mentioning in RDC No. 658/2022: “Art. 6 - Good Manufacturing Practices apply to all stages of the product life cycle, from the manufacture of experimental drugs, technology transfer, commercial manufacture to product discontinuation”[1] and

> Art. 8 A Pharmaceutical Quality System suitable for the manufacture of medicinal products must ensure that:
>
> I - product conception is achieved through the design, planning, implementation, maintenance and continuous improvement of a system that enables the consistent manufacture of products with appropriate quality attributes;
>
> II - product and process knowledge is managed at all stages of the life cycle;
>
> III - medicines are designed and developed in such a way as to consider the requirements of Good Manufacturing Practice[1].

The criteria set out in the articles presented are met through the QbD approach during the product development phase. In this process, knowledge about product and process behavior is acquired through quality risk management and multivariate experiments, which allow for proper process design at all stages of the life cycle. This results in safer and more effective products

and facilitates continuous improvement when compared to the traditional method[13].

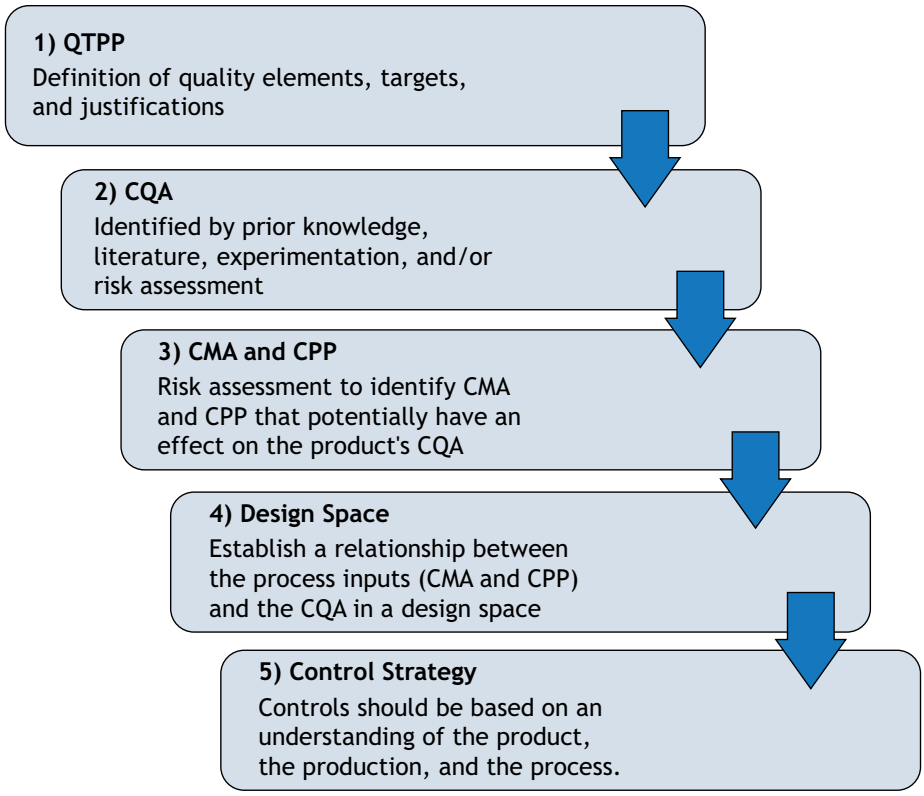
The elements of QbD assist in a more systematic and improved understanding of the product and process under development, but are not strictly regulatory requirements[16,17]. The QbD approach to drug development basically follows five stages, as shown in Figure.

The preparation of the Quality Target Product Profile (QTPP) is the first step in product development based on the QbD concept. It is a record that contains the prospective summary of the quality characteristics of a pharmaceutical product that must be achieved to guarantee safety and efficacy and is the ideal way to obtain the desired quality. QTPP is the basis of the product development project, as it contains the quality characteristics (quality attributes) with the necessary targets and justifications that support clinical and commercial decision-making, interactions with regulatory agencies and risk management[18,19].

Once the QTTP has been drawn up, the CQAs are identified, which are physical, chemical, biological, or microbiological properties or characteristics that must be within an adequate limit, range, or distribution to guarantee the quality of the product. The quality attribute is considered critical when there is a risk to the patient and can be identified using risk assessment tools. The criticality of the quality attribute is directly linked to the severity of the damage and does not change even with risk management[20,21].

In addition to the CQAs, critical material attributes (CMAs) are identified, which are physical, chemical and biological properties of the active pharmaceutical ingredient (API), intermediates and excipients that have a significant impact on the CQAs and must be within an appropriate limit, range or distribution. CPPs are process parameters, of a process step or unit operation (activity that involves physical or chemical changes, such as milling, mixing, granulating, drying, compressing, and coating) and impact on the CQAs and must be within an appropriate limit, range, or distribution. CPPs must also be identified after the preliminary definition of the production process. Both CMAs and CPPs can be defined based on prior knowledge and risk assessment[22,23].

The key to pharmaceutical product developing using the QbD approach is to define the relationships between the input variables (CMAs and CPPs) and the output variables (CQAs)[8,22]. The next step involves conducting Design of Experiments (DoE) studies based on the previously identified risks. DoE generally employs statistical models that evaluate the variables and



Source: Prepared by the authors, 2024.
QTPP: Target Product Quality Profile; CQA: Critical Quality Attribute; CMA: Critical Material Attribute; CPP: Critical Process Parameter.

Figure. Quality by Design (QbD) stages.

their interactions, enabling the identification of the process and product design space (DS). DoE is usually used in the QbD approach, although it is not mandatory, using previously identified CMAs and/or CPPs as factors[18]. As DoE responses, CQAs are conventionally selected.

The DS consists of a space where multidimensional combinations and/or interactions of process variables and their parameters are established, with the aim of guaranteeing product quality[20,24]. For the FDA, the DS must be determined from the combination of at least three variables, and experimental planning (DoE) is recommended to establish models that relate CPPs and/or CMAs to CQAs[3].

Finally, it is essential to define a control strategy to ensure that the production process is operating as expected and that the product maintains the desired quality. Derived from the DS, the stage of drawing up the control strategy must be based on an understanding of the formulation, the product and the production process. This strategy must be designed to ensure that the product with the required quality is consistently produced throughout its life cycle. The control strategy should include monitoring CMAs and CPPs based on the impact these factors have on product and process quality. Moreover, it should include product specifications, control of unit operations that influence quality, and real-time testing, rather than testing on the final product. The strategy should also include a monitoring program for checking multivariate models[25].

Based on the control strategy, the use of process analytical technology (PAT) tools is more frequent in the QbD approach. Although PAT was introduced to the pharmaceutical industry at the beginning of the 21st century, new PAT tools have been introduced over the last 20 years[26]. PAT is an important element of QbD with the aim of guaranteeing product quality at the process design stage. With a variety of methodologies and technologies used to design, analyze and control manufacturing processes in industries, the ultimate goal of PAT is to improve the safety and quality of products and processes. With the application of PAT, CPPs and key performance indicators (KPIs) are well defined, understood, and monitored on an ongoing basis to ensure that CQA targets are consistently achieved.

When applied to CPV, PAT tools guarantee product quality throughout the manufacturing process. Being used as a control strategy to monitor processes in real time, during the process and no longer in the final tests on the finished product, they make it possible to improve understanding and optimize processes, detect defects and quickly solve problems. According to Kim et al.[26], these tools are a trend that is gradually being adopted, as they contribute significantly to establishing process control.

Despite being widely recognized as a strategic tool in the context of QbD and CPV, the implementation of PAT in the pharmaceutical industry is still marked by important challenges, such as: technological - integration with legacy equipment incompatible with modern analytical sensors, validation, and qualification of PAT systems, lack of specific standards and practical guidelines, management and interpretation of large volumes of data and maintenance and technical support; organizational - conservative culture and aversion to change, lack of technical training, limited multidisciplinary integration, challenges in change management, difficulty in measuring return on investment, among others.

Risk management

In recent years, concern and discussion regarding the risks inherent in processes and activities in the pharmaceutical industry have increased in proportion to the growing importance of the subject. According to Lundin and Jönsson[27], risks within society are constantly envolving and are managed by industries, authorities, and organizations. Therefore, the development of effective techniques for risk analisis and management is essential. The Brazilian Association of Technical Standards (ABNT), in Guide 73:2009 (Risk Management - Vocabulary), addresses the fundamental concepts of risk management and defines risk as the combination of four elements: risk source, cause, event, and consequence. Moreover, the following terms are used in risk management: hazard is the potential source of harm, harm as injury or demage to property or the environment, and risk is the combination of the probability of an event and its consequences.

In Brazil, especially after the publication of the new GMP regulatory framework, Anvisa has improved the quality and safety requirements for medicines to ensure compliance with international standards. In this context, the risk management approach, integrated with quality management in the pharmaceutical industry, has been introduced as an essential component of an effective quality system[28]. Anvisa recently published Guide No. 62/2023 - version 1[29], called the Quality Risk Management Guide (GRQ). This guide, although regulatory, is not normative, and provides recommendations on best practices for procedures, routines and methods that involve risks in the pharmaceutical sector. The guide broadly defines risk as the combination of the probability of harm occurring and the severity of that harm. In addition, it is based on ICH Q9, which deals with quality risk management, and reflects the agency's understanding of quality risk management as a systematic process for assessing, controlling, communicating and reviewing risks to the quality of medicines throughout the product life cycle.

Guidance No. 62/2023[29] describes two basic principles for quality risk management. The first is that quality risk assessment should be based on scientific knowledge and ultimately linked to patient protection. Quality risk includes situations in which the availability of the product could be affected,

leading to possible harm to the patient. The second relates to the level of effort, formality, and documentation of the quality risk management process, which must be compatible with the level of risk.

Risk management is essential for identifying, preventing, and proposing mitigation actions against undesirable effects that may occur during a process or activity. It offers several benefits, including the optimizing of quality control activities, cost reduction, and improved process understanding and control, thereby promoting continuous improvement in pharmaceutical manufacturing. Risk assessment is an integrated process that involves identifying and analyzing the risks to which an organization is exposed, enabling the creation and implementation of strategies to mitigate or address these risks. In the pharmaceutical industry, this assessment is crucial to guaranteeing the quality, safety, and efficacy of medicines. Despite being a requirement of regulatory agencies, the way in which risk management is implemented in the pharmaceutical industry is still not fully standardized[30]. According to Kaleem et al.[31], risk assessment makes it possible to identify the sources of variation in a system and thus prioritize the critical points for investigation in a process.

To establish an effective risk management system, it is necessary to include systematic processes that coordinate, facilitate and improve scientifically-based decision-making in relation to risks. According to Guide No. 62/2023[29], there are specific steps to initiate and plan a quality risk management process, such as: defining the risk problem or issue, including relevant assumptions, and identifying the risk potential; collecting basic information or data about the hazard, harm, or potential impact on human health, which is essential for risk assessment; designating a leader and necessary resources; and drawing up a timeline, defining deliverables and the appropriate level of decision-making for the risk management process[29].

As part of risk management, risk analysis uses tools to analyze the risk associated with identified hazards. Risk analysis is the qualitative or quantitative process of linking the probability of occurrence and the severity of damage (severity). In some risk management tools, the ability to detect the damage (detectability) also influences the risk estimate. ICH Q9 describes a non-exhaustive list of known tools used for risk analysis:

a. Basic risk management facilitation methods (flowcharts, checklists, process mapping, cause and effect diagrams - Ishikawa/Fishbone);

b. Failure Mode Effects Analysis (FMEA);

c. Failure Mode, Effects and Criticality Analysis (FMECA);

d. Fault Tree Analysis (FTA).

e. Hazard Analysis and Critical Control Points (HACCP);

f. Hazard Analysis and Operability (HAZOP);

g. Preliminary Hazard Analysis (PHA);

h. Risk classification and filtering;

i. Statistical support tools (control charts, weighted moving average, design of experiments, histograms, Pareto charts, and process capability analysis).

Quality risk management is essential throughout all stages of the product lifecycle, including development and validation. It contributes to building process knowledge and understanding risk scenarios, enabling informed decisions regarding the controls to be applied during commercial pharmaceutical manufacturing. The aim is to make assertive decisions, promote continuous reassessment and encourage ongoing process improvement[29]. According to ICH Q9[13], quality risk management should be integrated into product development, with the aim of creating high-quality medicine and an effective manufacturing process. Improving knowledge about process performance and the characteristics of the desired product makes it possible to evaluate quality attributes, material attributes and establish processing options and process parameters. This makes it possible to identify which of these attributes and parameters are critical to the process and need to be controlled throughout the product's life cycle. Furthermore, it is essential to carry out continuous reviews of risk assessments and mitigation plans to ensure that the control strategy is appropriate, based on the product's manufacturing history[32].

As part of the QbD approach, risk assessment is used to identify CQA, CMA, and CPP. Based on the relationship established between the elements described in the QTPP, the next step is to identify the CQAs, the criticality of which is based mainly on their influence on the efficacy and safety of the product. The identification of CQAs is an important part of pharmaceutical development and various tools can be used, for example: understanding the QTPP, reviewing the literature and historical data, experimentation, and development studies, advanced statistical tools, and risk analysis. Subsequently, critical material attributes and process parameters are identified and investigated in depth to keep them under control throughout the product lifecycle.

Different studies show the application of different risk analysis tools, especially in the identification of CMA and CPP. After drawing up the QTPP, Charoo et al.[33] used the PHA tool to identify CMA and CPP with a risk to the CQAs in their study on the application of QbD to the development of dispersible tablets. Han et al.[34] studied the mutual interaction between the CMA of intermediates and CPP of telmisartan tablets based on the QbD approach. The authors applied FMEA to quantify the risk related to the CPP of the high shear wet granulation step to investigate the robustness of the manufacturing process by means of multivariate analysis. To do this,

knowledge and experience with similar processes and the QTPP were considered.

Claycamp et al.[35] sequentially used qualitative and quantitative risk assessment tools in the formulation of ciprofloxacin tablets. The authors built on a previous study, in which first an Ishikawa diagram and an FMEA were used to identify the most likely material and process variables that could affect QTPP for granulation and tableting. Dissolution, disintegration, and uniformity of tablet content were identified as CQAs. For the CMAs, the level and source of the binder, the level of disintegrant and the type of magnesium stearate used as a lubricant were identified as the highest risk variables. The CPPs considered were roller pressure and granulator speed, as well as the compression speed of the ciprofloxacin tablets.

Corroborating the combined application of tools, Costa et al.[36] stated that it is important to understand that there is no appropriate risk management tool for all cases and that it is possible to adapt a tool to meet specific needs. It is not always possible to assess specific risks using the same tool and more than one tool can be used in a single risk assessment. ICH Q9[13] confirms this understanding when it describes that the combined use of tools provides flexibility that can facilitate the application of risk management principles to quality, since many tools complement each other.

Process Validation

Process validation has been carried out in the pharmaceutical industry since the 1990s. But only in the last four years have there been really important changes. According to Anvisa, process validation is: "Documented evidence that a process, operated within pre-established parameters, can perform its functions effectively and reproducibly for the production of a medicinal product within its pre-established specifications and quality attributes" (Anvisa, 2022, p.4)[2].

Other equivalent definitions can be found in both Brazilian and international legislation, as shown in Chart 1.

Despite the different definitions of process validation, they all converge on a common concept: validation aims to ensure that the process, when operated under the predetermined conditions, consistently produces a safe and effective product that complies with established specifications and quality attributes. According to Aleem et al.[37], process validation was developed and implemented as a tool to ensure final product quality. Therefore, validation is essential to achieving this objective and constitutes a regulatory requirement for drug approval. Process validation requirements are part of the quality system regulation, the aim of which is to consistently produce products that are suitable for their intended use and to ensure that the products meet the required quality standards to be used for their intended purpose. Process validation is therefore a key element in ensuring that these principles and objectives are met[38].

The current resolution, in the light of the new regulatory requirement, has brought about some changes to the way in which it is conducted and what is no longer accepted in process validation studies, but the biggest of these is in relation to the rationale, which is now based on the life cycle strategy. As a result, all the knowledge acquired during the development phase becomes part of phase 1 of the validation approach, so risk management, life cycle, statistical control and continuous improvement must be closely related to process validation. Therefore, according to Pazhayattil et al.[39], process validation is no longer a singular and finite activity, it is a continuous activity that starts in the development phase, covers phase 2 (process qualification) and continues into phase 3 (continued process verification - CPV) which can

Chart 1. Regulatory bodies' definitions of process validation.

Anvisa RDC No. 658/2022	Anvisa IN no. 138/2022	WHO TR - 32th WHO, 1992	PIC/S, 2004	FDA, 1987	EMEA, 2021
Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity, or system actually leads to the expected results.	Documented evidence that a process, operated within pre-established parameters, can perform its functions effectively and reproducibly for the production of a medicinal product within its pre-established specifications and quality attributes.	It is the documented act that certifies that any procedure, process, equipment, material, operation, or system actually leads to the expected results.	A means of ensuring and providing evidence that processes are capable of repeatedly and reliably producing a final product of the required quality.	Documented evidence that provides a high degree of confidence that a specific process can consistently produce a product meeting its predetermined specifications and quality characteristics.	A means of ensuring and providing evidence that processes are capable of consistently producing a final product of the required quality.

Source: Prepared by the authors, 2024.
Anvisa: National Health Surveillance Agency; RDC: Collegiate Board Resolution; IN: Normative Instruction; WHO: World Health Organization; FDA: Food and Drug Administration; EMEA: European Medicines Agency.

include sampling during routine monitoring and returning to phase 1 as changes are introduced.

Similar to Anvisa, other international guidelines also emphasize the importance of process knowledge by defining risk management and change control as fundamental pillars of validation studies, extending throughout the three stages of the process validation approach that comprise the product lifecycle.

Phase 1, which corresponds to the development and characterization of the process, is the stage in which the process is designed and knowledge is acquired, based on an understanding of the possible sources of variation in the process. It is in this phase that all the knowledge about the product and the assessment of process risks are used to define the CQA, CMA, and CPP. Phase 2, which corresponds to process performance qualification, involves confirming the process design carried out in the previous phase during the manufacture of the product on a commercial scale, with the aim of verifying the reproducibility of the process against the established parameters. To do this, it is necessary to develop a sampling plan that challenges the compliance and reproducibility of the defined CQA, CMA, and CPP, to validate the control strategies. Phase 3, which corresponds to the continuous verification of the process, consists of assessing the ability of the process to remain within its control state during routine commercial production. To do this, the same sampling plan applied in phase 2 should be used, to verify statistical safety by means of process capacity and performance indices.[4,40,41].

All new processes must be validated, and, in theory, the studies should be completed before the final product is marketed. When it is not possible to wait for the studies to be completed, it is necessary to validate the process during routine production. Processes for legacy products that have been produced for some time should also be validated. Finally, processes that are significantly modified (inclusion or exchange of equipment, inputs, packaging materials, among others), which may affect the quality of the product and/or the reproducibility of the process causing the validated status to change, need to be validated again, since the process is no longer the same as the initial validation[42,43,44].

As established by IN No. 138/2022[2], three types of process validation are defined in its subsections:

a. Prospective validation - refers to validation carried out during product development, usually during pilot batches, before production on a commercial scale. This validation can also be applied strategically in situations of change, for example: changing the manufacturing site. It is important to note that the batches used for process validation will only be marketed once the studies have been successfully completed.

b. Concurrent validation - validation that takes place during the routine production of products. It should only be applied in exceptional situations, where the risk-benefit ratio is clearly favorable to the patient. The decision to carry out this validation must be duly recorded and approved by qualified personnel.

c. Retrospective validation - although it is no longer commonly used by Anvisa, this validation is based on the analysis of documentation from batches that have already been produced, with the aim of evaluating previous production experience. The purpose is to verify that the process has not been altered and that all procedures have been carried out in accordance with established standards.

The process validation approaches to be used have also been updated since the publication of IN No. 138/2022[2]. The current legislation includes the following types of approaches in its subsections: traditional and continuous verification. The traditional approach is used in the product development phase in which a defined batch number is used for follow-up during the process validation study. Processes developed using this approach must follow the prospective validation type before the process can be certified as validated[1]. Continuous verification is an approach that monitors batch by batch over a defined period. It can be used as an alternative approach to traditional process validation for products developed by QbD, in which process performance is continuously monitored and evaluated using process analytical technologies[1].

Unlike continuous verification, continuous process verification is an alternative approach to process validation in which the performance of the manufacturing process is continuously monitored and evaluated. According to the FDA, continuous process verification is not a part of process validation but is carried out batch by batch over a defined period instead of process validation with conventional concepts. PAT and multivariate statistical process control can be used as tools to verify in real time that quality attributes are being met to detect deviations or variations that could affect the quality of the final product. This makes continuous process verification a recommended practice by regulatory agencies and is seen as a more efficient and effective approach than spot process validation. CPV, in turn, is an integral part of process validation. Specifically, it represents the third stage of the process validation lifecycle, following process development (the first stage) and process qualification (the second stage). In this phase, activities are implemented to provide continuous assurance that the process remains in a state of control. Therefore, the primary objective of CPV is to ensure that the process operates under statistical control, consistently producing high-quality products.

In addition, RDC No. 658/2022[1], in its Art. 75, describes the hybrid approach, which is an approach between traditional

and continuous process verification that can be used when there is a substantial amount of knowledge and understanding of the product and process obtained from manufacturing experience and historical batch data. Another possibility is to use the grouping approach, in which it is possible to draw up a matrix for validation studies justifying not monitoring all batch sizes and presentations (except new molecules), all production routes (as long as the volume of equipment occupancy is proportional) and identical formulations (which are proportional)[1].

Regardless of the approach used, the processes must be robust and guarantee consistent product quality before any release to the market.

Continuous Process Verification (CPV)

CPV consists of a set of activities and techniques aimed at ensuring that a process is operating according to the established specifications and within the state of control. Its main objective is to continuously monitor and evaluate process performance in real time, identifying problems or deviations and implementing corrective actions. It is a proactive quality tool that allows trends in the process to be observed, promoting continuous improvements and preventive actions to avoid the occurrence of deviations. Moreover, CPV aims to ensure that the process maintains its validated status, guaranteeing the robustness and reproducibility of the data throughout the drug's life cycle. This approach enables early detection of problems, allowing immediate adjustments to the process to avoid producing batches that are out of specification[45].

According to Anvisa, CPV is defined as "documented evidence that the process is maintained in a state of control during commercial manufacturing"[1]. The regulatory agency also states that pharmaceutical manufacturers must monitor production process to ensure that the state of control is maintained throughout the product lifecycle. Relevant process trends should be evaluated and the potential causes investigated and addressed, and the scope and frequency of CPV activities periodically reviewed.

FDA[3] describes that the objective of phase 3 "is the continuous assurance that the process remains in a state of control (the validated state) during commercial manufacture", and recommends that monitoring of process parameters and quality attributes be continuous, with sampling during the process qualification stage until sufficient data is available to generate real estimates of variability.

Collecting and evaluating the data obtained and the information acquired about process performance in phase 3 makes it possible to detect unwanted instabilities in the process, as well as preventing future nonconformities and implementing continuous improvement so that the process maintains its state of control[46].

Boyer et al.[47] suggested that the implementation of CPV should be carried out in two stages due to the importance of initially gaining an understanding of the CPPs and CQAs established based on the risk assessment of the process and product in order to subsequently define the control strategy and monitoring to be carried out through statistical analysis of the data obtained to verify the stability of the process, confirming its state of control.

CPV activities can be implemented in two stages: phase 3A and 3B[47]. For each stage, supporting documentation must be prepared according to the specific requirements of the planned activities, including the monitoring strategy, the definition of the parameters and attributes to be monitored, the assignment of responsibilities, and the statistical methods to be applied to the study. Once the documentation has been prepared and approved, the data collecting phase begins, enabling the generation of process performance information.

Based on the suggestion by Boyer et al.[47], phase 3A comprises defining the control plan considering the CQA and CPP to be monitored in several batches to establish control limits that will be applied in phase 3B for these attributes and parameters. In phase 3B, batch monitoring continues to assess the occurrence of rule violations and take action when they occur.

According to the results of phase 3B, it is possible to identify the state of control or verify the need for a process revalidation. In some cases, it is possible to identify the need to return to phase 1 of the product life cycle for further product development and/or process improvements, or simply to send the statistical data for the annual product quality review (PQR) documentation[10].

CPV can be applied to all the products in the company's portfolio, both new products developed using the QbD concept and those already in the marketing phase, known as legacy products. What differentiates the applicability of CPV for each is the phases that the product has been through previously and the data available for the implementation of phase 3.

The main objective of CPV is to assess whether the process of the batches produced routinely for commercialization maintains a state of control, and statistical analysis tools are used for this verification. With a controlled production process, it is possible to control the quality of the product as it is being built/manufactured instead of inspecting it at the end, when all the costs are inserted into the product and, consequently, the loss is greater[48].

Despite the conceptual and regulatory advances in CPV, many companies are unable to demonstrate, in a structured way, the concrete results obtained from the actions implemented throughout the product's life cycle. This manifests itself in three main points: a lack of clear quantitative indicators (KPIs) to prove the reduction in deviations following parameter adjustments or process improvements, a reduction in inter-batch variability, based on statistical analysis, and an increase in product conformity, translated into fewer failed or reworked batches.

The lack of detail on the concrete impacts of CPV prevents it from being perceived as an instrument of strategic and measurable value. Without this evidence-based approach, the technical and organizational challenges of its implementation are magnified, and there is a risk that the VCP will be treated as a mere formality — rather than as a tool for continuous improvement.

Connecting actions to real results is what transforms CPV from a regulatory concept into a practice of operational excellence.

As a practical example for reducing deviations related to table average weight nonconformities (out-of-specification variations) during the compression process, statistical process control (SPC) can be applied with CPV through the implementation of control charts to monitor table weight in real time, identify sources of variation through statistical analysis, and support adjustments to the CPV protocol by proposing improvement actions. This approach resulted in a reduction of weight-related deviation, decreased rework and batch rejection, and improved KPI performance, with average table weight maintained within the revised control limits.

SPC is a set of quality monitoring tools. Using these tools, information is obtained on the behavior of the process, identifying its variability and allowing control over time, through continuous data collection and the investigation and mitigation of possible special causes responsible for the instabilities of the process under study[49,50].

Technical Report no. 60[10]: Process Validation: A Lifecycle Approach of 2013 presents some analytical tools that can be used in phase 3:

a. Descriptive statistics;

b. Statistical process control charts;

c. Statistical power and sample size determination;

d. Process Capability Study and Capability Index;

e. Analysis of variance (ANOVA);

f. Hypothesis testing/confidence intervals;

g. Pareto analysis or graph;

h. Acceptable sampling plan;

i. Normal and non-parametric tolerance intervals.

Almaya et al.[50] addressed SPC strategies for the manufacture of direct compression drugs by using tools such as statistical control charts and process capability and capability index studies (Cpk and Ppk) to statistically monitor and predict process variability, ensuring that the process remains capable and in a state of predictive control. In this study, we present simulated graphs, obtained using statistical software for data processing, of the control chart and capability index for dosing as a CQA of a tablet by direct compression as an illustration of the different types of processes: one in a state of statistical control but unable (Cpk and Ppk < 1.00) to consistently deliver a product within specifications, a highly capable process (Cpk and Ppk > 1.33) but outside the state of control and finally a process within the state of control and able (Cpk and Ppk ≥ 1.33) to ensure current quality and predict future product quality.

For this type of process, the authors presented the lower control limit (LCL) and upper control limit (UCL) established for the product dosage, which can be applied during the CPV phase to monitor this critical quality attribute (CQA). The authors also describe that rigorous monitoring and the use of statistical and technological tools enable the ability to identify and react only to significant variations, reducing losses and ensuring consistent product quality.

Kharbach et al.[51] addressed the application of multivariate SPC in product quality review (PQR) to monitor and improve the manufacturing processes of an oral powder mixture containing six active ingredients (ascorbic acid, pseudoephedrine hydrochloride, caffeine, chlorpheniramine maleate, paracetamol and ibuprofen) based on historical data from 164 batches produced over a one-year period. The study aimed to compare the effectiveness of univariate and multivariate statistical process control (MSPC) methods in monitoring batch quality using Shewhart charts (control chart) and capacity indices (Cp and Cpk) to evaluate the variables individually and the application of principal component analysis (PCA) and charts based on Hotelling's T2 statistic using classical scaling (autoscaling) and robust scaling to consider the interaction between the variables. Different results were observed by the authors, since the SPC indicated that all 164 batches were within the control limits specified in the Shewhart charts, indicating that the process was apparently stable. However, the capacity indices showed sub-optimal values for some APIs, suggesting limitations of the univariate method. On the other hand, the MSPC identified four batches outside the control limit with autoscaled data and seven batches after robust scaling. These batches showed subtle variations associated with interactions

between active ingredients that SPC CEP did not detect. By removing the extreme batches, the capability indices (Cp and CPK) improved significantly, showing that MSPC is more sensitive and effective at detecting subtle deviations and improving quality control.

Although SPC is a powerful tool for ensuring the robustness of pharmaceutical processes, its effective implementation depends on structural and cultural changes. Overcoming the technological (need for reliable, standardized and continuous data, lack of integration between systems, limitations in IT infrastructure and difficulty in defining control limits) and organizational challenges (reactive organizational culture, lack of statistical knowledge in teams, lack of knowledge about the benefits of SPC, fragmentation between technical areas, and regulatory pressure and aversion to change) requires strategic vision, investment in training and integration between areas, as well as a strong commitment to data-driven quality, as advocated by ICH Q10 and the CPV guidelines[12].

5W2H action plan for implementing CPV

The purpose of developing the 5W2H action plan is to organize, guide, and monitor the actions required for CPV implementation based on the QbD approach. The 5W2H tool is an action-planning method designed to support the execution of activities through a structured checklist, enabling more accurate planning and decision-making regarding the actions to be implemented[52]. Due to its versatility and dynamic nature, this tool is widely applied in situations such as: quality planning; merger and acquisition planning; human resources management; product development planning, and risk management, among others, making it an extremely useful and flexible tool[53]. Furthermore, using 5W2H as an action plan offers a structured approach to risk assessment, providing an organized way of identifying, analyzing and mitigating threats in the implementation of CPV activities. The spreadsheet is also extremely useful in the context of SPC during CPV studies as it allows variations to be identified to ensure that the process remains within the established control limits. It facilitates the planning, execution, and follow-up of corrective or preventive actions, as well as optimizing communication between the teams involved in the process. This is essential for maintaining the quality and efficiency of production processes.

The proposed action plan for implementing CPV is shown in Chart 2 and considers “what” needs to be done, stage by stage. For each of the proposed stages, the activities related to the elements of QbD and process validation were considered. It should be noted that in the 5W2H plan, “how much it costs” was defined based on time, i.e. how much it costs in time for each stage. Chart 2 shows the importance of deepening knowledge of QbD and risk management, so that the CQAs, CMAs, and CPPs are described, as well as knowledge related to the SPC for monitoring the process in the life cycle.

The plan covers everything from drawing up the CPV Standard Operating Procedure (SOP), selecting the products to be monitored, classifying them by criticality, defining and carrying out phases 3A and 3B of the CPV, to statistical monitoring and holding meetings with multidisciplinary teams. Each stage has been designed to ensure that the principles of QbD are applied correctly, with a focus on understanding and controlling the process throughout the product’s life cycle.

For example, the stage of identifying the products to be included in CPV uses a decision tree to separate products monitored via CPV from those monitored by other strategies, such as product quality review. Next, the definition of the criticality matrix makes it possible to prioritize products with the greatest risk or impact, such as those with the greatest number of deviations or the greatest production volume.

In phase 3A, data is collected from at least 30 batches for each product selected, to establish the statistical control limits for the critical attributes and parameters (CQAs, CMAs, and CPPs). The plan details how this collection should take place - including variations such as different shifts, raw materials and seasonality - and how the data will be handled (for example: use of control charts and capability indices such as Cp, Cpk, Pp, Ppk).

In phase 3B, continuous monitoring of the established parameters begins, with the collection of data from all manufactured batches. Monthly meetings with the areas involved (validation, production, QC, and QA) are scheduled to discuss the results, investigate special causes and define corrective actions or continuous improvements.

CONCLUSIONS

CPV should be regarded as a strategic tool for continuous improvement, capable of identifying trends and special causes of variation before they impact final product quality. In addition to its regulatory role, CPV aims to confirm the validated state of processes, ensuring their robustness, reproducibility, and reliability throughout the product lifecycle.

However, its implementation may present challenges, especially regarding the organization and execution of the activities required to initiate and maintain continuous monitoring. The absence of clear operational guidelines may hider both the implementation and maintenance of CPV activities. In this context, the present study proposed the application of the 5W2H tool as methodological support for planning CPV – related actions within the QbD framework, offering a practical and effective alternative for managing these activities in pharmaceutical organizations.

Chart 2. 5W2H action plan for implementing CPV.

5W					2H	
What?	**Why?**	**Where?**	**Who?**	**When?**	**How?**	**How much?**
Drawing up CPV SOPs	Directing CPV activities	Validation sector	Validation analysts	Start of CPV studies	Filling in the company's SOP mask with the CPV step-by-step process	1 month
Identify the products that will be part of the CPV	Separate the products that will be monitored by CPV from the products that will be monitored in another way (e.g. by RQP)	Validation sector	Validation analysts/ PCP analyst	After approval of the CPV procedure	By drawing up a decision tree for each product	The timeframe may vary depending on the number of products in the company
Create a priority matrix of the most critical product(s) for the start of CPV studies	Products considered most critical need to be monitored first	Validation sector	Validation analysts/ Quality assurance analysts	After completion of decision tree	Draw up criteria for classifying the criticality of products (for example: product with > number of batches/year x > number of deviations)	The deadline may vary according to the number of products in the company
Draw up a protocol for CPV phase 3A by product	Description of the product's CQA, CMA and CPP that will be monitored and direction of CPV activities	Validation sector	Validation analysts/ Development analyst	Once the criticality matrix has been completed	Use standard validation protocol template for detailed description of CPV activities	15 days per product
Collect data from batches selected for CPV phase 3A (Minimum 30 batches)	Establishment of control limits for CQA, CMA and CPP	Validation sector	Validation analysts	After approval of the phase 3A protocol	Data on the attributes and parameters considered critical from at least 30 batches already produced, following the order of criticality established in the priority matrix - 1st study = product in 1st place matrix, then successively	Time needed to evaluate the largest number of variables - production shifts, batches of different raw materials, longer seasonal periods, and different equipment
Draw up CPV phase 3A report to establish control limits for CQA, CMA and CPP	Evaluation of the results obtained to establish the control limits for the CQA, CMA and CPP	Validation sector	Validation Analyst	After completion of the statistical evaluation of the results obtained	Collection of results for statistical evaluation of process capability indices (Cp and CpK), control charts and performance indices (Pp and PpK)	1 month
Hold a meeting with the areas directly involved in CPV studies	Share the control limits established for the CQA, CMA and CPP, investigate outliers and disseminate next steps in the CPV	Meeting room or online	Multidisciplinary team (Validation, production, QC and QA)	After drawing up the phase 3A report	Call a meeting to present and discuss the results obtained	1 day
Draw up protocol for CPV phase 3B by product	Monitoring of the control limits established in phase 3A for the QC, WAC and PPC of all manufactured batches of the products chosen for CPV	Validation sector	Validation analyst	After satisfactory completion of phase 3A	Use standard validation protocol template for detailed description of CPV activities	15 days per product
Monitoring of the CQA, CMA, CPP of all batches of products selected for CPV manufactured s in the company	Collection of in-process control data, analytical and operational results of the production process	Validation sector QC Production	Validation analyst, QC, and Production	After approval of the phase 3B protocol	Data extraction from the ERP system (e.g. SAP) or feeding into a spreadsheet prepared by Validation to compile the data	Throughout the product's life cycle, until it is discontinued
Prepare CPV phase 3B report for each product	Check that the process remains stable and capable and propose improvements if necessary	Validation sector	Validation analyst	Monthly	Survey results for statistical evaluation (control chart and capability)	1 month
Meeting with multidisciplinary team	Discuss results of CPV reports and investigate special causes	Validation sector	Multidisciplinary team (Validation sector, Production, QC and QA)	Monthly	Call meeting to present and discuss results	1 day

Source: Prepared by the authors, 2024.
POP: Standard Operating Procedure; CPV: Continuous Process Verification; PCP: Production Control Plan; RQP: Product Quality Review; CQA: Critical Quality Attribute; CMA: Critical Material Attribute; CPP: Critical Process Parameter; QC: Quality Control;
QA: Quality Assurance; ERP: Enterprise Resource Planning; SAP: Systems Applications & Products.

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Authors' Contribution

Barros RS - Design, acquisition, analysis, data interpretation, and writing of the paper. Prado LD - Conception, planning (study design), and writing of the paper. All the authors approved the final version of the paper.

Conflict of Interest

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

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