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Review Article

Modern cGMP Approach for Process Validation

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Abstract

The US and European GMP regulation for process validation has been revised in these last years, introducing Quality Risk Management and Quality-by-Design concepts.

The old requisite of 3 repetitions of process validation runs has been substituted with a more robust risk and science-based approach.

In particular, the need of process knowledge has been emphasized and the concept that quality has to be guaranteed during all steps of the product life cycle, starting from the product design phase, up to the commercial production monitoring.

These concepts have now been implemented in the revised EU GMP Annex 15 for qualification and validation.

The article will cover these modern cGMP approaches for process validation activities, taking into account the recommendation of US, European and ICH guidelines.

Keywords: GMP; QTPP; FDA

Introduction

The US and European GMP regulation for process validation has been revised in these last years, introducing Quality Risk Management and Quality-by-Design concepts. The old requisite of 3 repetitions of process validation runs has been substituted with a more robust risk and science-based approach.

In particular, the need of process knowledge has been emphasized and the concept that quality has to be guaranteed during all steps of the product life cycle, starting from the product design phase, up to the commercial production monitoring.

As reported in the US FDA Guidance for Industry Process Validation: General Principles and Practices of January 2011, Process Validation (PV) is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. As described in detail in the document, Process Validation is approached based on the lifecycle of the product and process, according to the three different stages.

- Stage 1 – Process Design: the commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.
- Stage 2 – Process Qualification: during this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
- Stage 3 – Continued Process Verification: ongoing assurance is gained during routine production that the process remains in a state of control.

In comparison with the old version of the FDA Guidance on Process Validation issued in 1987, this new vision represents a more rational and scientific approach resulting in a better quality control and assurance for the product. The FDA 2011 Guidance describes activities typical of each stage.

The indications contained in the FDA guidance were furtherly detailed, modified and implemented in other guidelines: in Europe, EMA updated its process validation guideline and EU GMP Annex 15 according to the route indicated by FDA implementing in a specific way the new concepts.

The new approaches for Process Validation suggest a roadmap from process design up to the validation and maintenance of the state of control. According to these concepts, Process Validation is not anymore considered as a picture of a process, but as a continuous evidence of the quality and reliability of the process, and hence the quality of the corresponding product. Drug product quality is generated starting from the initial development phases, it has to be defined in the manufacturing process destined to validation, and continues throughout the life-cycle according to Quality by Design (QbD) and Quality Risk Management (QRM) principles.

Quality target product profile (QTPP)

The Target Product Profile (TPP) is a tool traditionally used in pharmaceutical companies for drug development, representing a plan defined at the beginning of the development stage with a clear final objective. From a development perspective, it is useful to refer to the Quality Target Product Profile (QTPP), which is the natural extension of the TPP for product quality.

The QTPP, as firstly described in the ICH Q8, includes the quality characteristics enabling the drug product to consistently deliver the therapeutic benefit reported in the label. As such, the QTPP is a strategic guide to the formulation scientists allowing the formulation activities to be focused on the development objectives. Therefore, the QTPP is strictly related to identity, strength, purity, and stability, which are the pillars of the Common Technical Document (CTD) quality section. QTTP elements should be based on the physico-chemical characteristics of the drug substance and the general quality attributes required for each drug product.

Critical quality attributes (CQA)

According to ICH Q8, the definition of the QTPP should be accompanied by the definition of the Critical Quality Attributes (CQA) of the drug product.

As defined in ICH Q8, a Critical Quality Attribute (CQA) is a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are generally associated with the API, excipients, intermediates, and drug product. During process design, Critical Quality Attributes should be firstly identified.

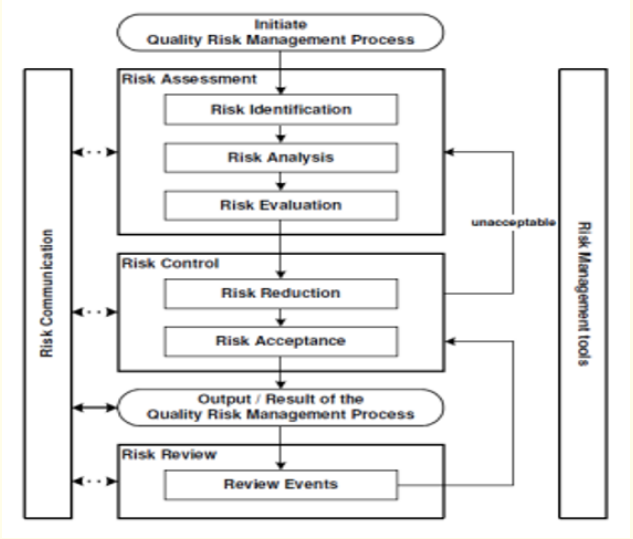
Quality risk management

Quality Risk Management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across its lifecycle.

An effective Quality Risk Management (QRM) can ensure the quality of the drug product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. QRM supports a scientific and practical approach to decision-making. The evaluation of the risk to quality should be based on the knowledge acquired and on the company quality system. The level of effort, formality and documentation of the quality risk management process should be commensurate to the level of risk. The implementation of a Quality Risk Management approach might occur starting from the very early stages of product development up to the entire life-cycle of the product.

The QRM approach is defined in ICH Q9 guideline that reports the overall process, a description of the QRM tools and the potential area of implementation.

The overall QRM process is represented by the following scheme (Picture 1).



Picture 1

Stage I: Process design

According to ICH Q8, "the aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space, specifications, and manufacturing controls".

Process design stage aims to create all this knowledge and experimental evidences generating the basis for further stages of the life-cycles. Comprehensive process design is vital to understand sources of variability and achieve process understanding.

Prior knowledge with similar processes and risk management can be used as the first step to identify a list of potential Critical Quality Attributes (CQAs). Prior knowledge can also be useful to identify a list of process parameters and material attributes potentially impacting the CQAs. Using risk management, the risk of these parameters and materials impacting the CQAs can be ranked. Based on these evaluations, experimental activities are prioritized, ultimately leading to a list of Critical Material Attribute (CMAs) and Critical Process Parameters (CPPs).

Process scale up and initial definition of the control strategy

Scale up could either be considered as the process of increasing the batch size or be intended as a procedure for applying the same process to different volumes. The increase of batch size, usually needed after early formulation stages, requires the definition of the right approach for scaling up a product from the laboratory to either the pilot or industrial plant. In this sense, a well-defined process should generate an adequate product in each situation by guaranteeing its starting quality attributes and relevant robustness.

As a first step, an accurate risk assessment should be carried out in order to evaluate all the differences between the starting process and the desired one. This helps defining the best scale up strategy based on the process equipment available and/or to be used. As highlighted in ICH Q10, another crucial aspect during scale-up activities is to perform a thorough monitoring of the process sub-steps which can provide a preliminary indication of process performance and the successful integration into the subsequent manufacturing development. In fact, the knowledge acquired during the scale up activities will be an important baseline for further process improvement or modifications necessary to the process.

After the production of a consistent and representative number of batches, exploring the critical fields of the process, it will be possible to evaluate the obtained data in order to potentially define a design space for product manufacturing, before starting the validation activities and define the control strategy for the product.

Design space

After the identification of critical input variables based on historical data analysis, the observation of the process and the preliminary experiments might be used design specific experiments, in order to create a model to define a design space.

The Design Space corresponds to the multi-dimensional combination and interaction of input variables (e.g. material attributes) and process parameters demonstrated to provide assurance of quality. In order to establish a Design Space, some key points should be evaluated: the effect of formulation-component properties should be studied with respect to process performance and product quality, multivariate interactions should be examined, supportive mathematical models should be used as appropriate, scale-up and equipment issues should be considered, the effect of operation or site change should be considered, and, uncertainty should be addressed with risk management.

The combination of all this information starts in the process design stage, is developed during the following stages increasing the accuracy and robustness of the acquired data in order be presented in the Marketing Authorization dossier. According to ICH Q8, working within design space is not considered a change while movement out of the design space is considered a change and would normally initiate a regulatory post approval change process. The Design Space is proposed by the applicant and it is subject to Regulatory assessment and approval, different methods are used to present the chosen space.

The Control Space corresponds to the region within the Design Space where, given the Control Strategy, the process is run.

Different tools might be used to explore and define the different spaces according to the increasing process knowledge and understanding. The collection and analysis of experimental data is fundamental during process design stage: data should be optimized in order to gather the information and to increase the knowledge on the product. In this sense, the traditional approach of "change one setting at a time" has been substituted by the use more advanced statistical tools ranging from Design of Experiment up to multivariate analysis or modeling approaches.

Stage II: Process qualification

The new concept of the process qualification (also called stage II) starts with process design and continues for the entire lifecycle of the product (Stage III). During this stage, the process design is confirmed (with a PQ batches study) as being capable to confirm that the process is reproducible for commercial manufacturing.

The process qualification evaluates if the process design is reproducible based on: process knowledge, process understanding and control strategy.

Process performance qualification (PPQ)

Process Performance Qualification (PPQ) shows that the process, operated within established parameters, can be performed effectively and reproducibly to produce a medicinal product meeting its QTPP. Another aim is to provide evidence that the identified risks, as described in the risk analysis, are controlled by means of suitable actions. Risk assessment should be applied to establish the PPQ strategy. In particular, the chosen validation approach should be identified among Traditional, Continuous process verification or Hybrid Approach (refer to EMA guideline on PV).

In the traditional approach, a minimum of three consecutive batches, normally with the same batch size as the intended commercial batches, are manufactured under routine conditions to confirm reproducibility. The process validation protocol should be prepared and should define the critical process parameters, critical quality attributes and associated acceptance criteria.

In the Continuous Process Verification, the manufacturing process performance is continuously monitored and evaluated as being capable of providing the desired product quality. To use this kind of approach, a manufacturing process that uses Process Analytical Technology (PAT) and improved SW tools can be necessary. PAT processes are designed to measure in real time the attributes of an intermediate material and then adjust the process in a timely control loop, so the process maintains the desired quality of the output material.

In the Hybrid Approach, it may be necessary to use either the traditional process validation or the continuous process verification approach for different steps within the manufacturing process: the use of such criteria should be adequately justified and documented.

Stage III: Continued process verification (CPV)

The aim of this stage is to assure the control of CPP and CQA through the entire life-cycle. Several aspects must be assessed in order to establish an appropriate level of process control and detect unplanned deviations from the process as designed. CQA and CPP (including relevant process trends and quality of incoming materials or components, in-process material, and finished products) must be taken under control and periodically reviewed. The collection of this data will allow detection of undesired process variability.

If supported by appropriate SW tools, the review could be performed before releasing any batch: however, as this opportunity is not generally possible, criteria for frequency of the review must be established. Moreover, the frequency criteria must assure appropriate statistical population: number of batches must be suitable for the applied statistical tools. Acceptance criteria must be established and appropriate investigations and CAPAs must be generated in case of failure. Procedures should describe how trending and calculations are to be performed and should guard against overreaction to individual events as well as against failure to detect unintended process variability [1-15].

Conclusions

- The GMP regulation for process validation has been revised in these last years, introducing Quality Risk Management and Quality-by-Design concepts.
- The old requisite of 3 repetitions of process validation runs has been substituted with a more robust risk and science-based approach.

- In particular, the need of process knowledge has been emphasized and the concept that quality has to be guaranteed during all steps of the product life cycle, starting from the product design phase, up to the commercial production monitoring.
- These concepts have now been implemented in the revised EU GMP Annex 15 for qualification and validation and, in general, in the recommendation of US, European and ICH guidelines on process validation.

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