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# Table of Contents

# 1. Background, aim and scope

## 1.1. Background and scope

On 23th July 1991 Directive 91/42 / EEC entered into force, which gave legal status to the application of GMP as a global quality system in Europe. Pharmaceutical industry became a leader in the implementation of quality assurance systems in the production and quality control of its products.

As management systems matured, it was observed that, once achieved the GMP full implementation, countless resources were addressed for the formal compliance accreditation rather than focusing in areas that could provide significant improvements in the quality and efficiency of production processes. This leads to high compliance costs and caused delays in the implementation of innovations as well as the waste of resources.

In August 2002, the United States Food and Drug Administration (FDA) published the document "Pharmaceutical cGMPs for the 21st Century: A Risk - Based Approach" [1], in order to promote innovation within the pharmaceutical industry, changing the approach of a model based on pre-established compliance with standards ( prescriptive model ) to another one based on the creation of quality systems based on scientific evidence ( knowledge- centered model ).

The first result of this initiative was the publication in 2003 of the "Guidance for Industry Part 11, Electronic Records, Electronic Signatures - Scope and Application" [2], followed by other guidelines such as aseptic processing [3], and process analytical

[1] *FDA (2002): Pharmaceutical cGMPs for the 21st century: a RISK-BASED APPROACH.*

[2] *FDA (2003): Guidance for industry. Part 11, Electronic Records, Electronic Signatures — Scope and Application.*

[3] *FDA (2004): Guidance for Industry. Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice.*

technologies PAT [4] and comparability protocols to report changes in the registration of medicines.

In 2004, the FDA also published the guide "Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre- Market Approval" [5].

Also, in November 2005, the International Conference on Harmonization ( ICH ) published guidelines ICH Q8 [6] and Q9[7]. Both documents emphasize the increased knowledge of the process from the stage of development, the management of this knowledge so that it can be applied to the stage of industrial production and the risk management tools. These two documents propose a new approach to validate processes based on the recognition that initiatives to improve quality and productivity improvement have one thing in common: reducing variability. The aim is to exploit this synergy to improve the final quality of the drug.

The process is defined by the attributes of the raw materials and final product and by the process and equipment parameters. These two kinds of features should be monitored with intensity proportional to their influence on the final quality of the drug. Scientific knowledge about the intensity of this influence should be the goal of the development and scale up studies.

This knowledge should be taken into account when selecting Critical Quality Attributes (CQA) and Critical Process Parameters (CPP). These are evaluated when reviewing the quality of the product (PQR) and when process control strategies are applied. The

[4] *FDA (2004): Guidance for Industry. PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance.*

[5] *FDA (2004): Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval.*

[6] *ICH (2005): Q8 Pharmaceutical Development.*

[7] *ICH (2005): Q9 Quality Risk Management.*

objective of this exercise is to identify sources of variability unknown and / or uncontrolled, against which actions must be addressed to avoid negative impact on the quality of the product.

The ICH Q10 – guide [8] - pharmaceutical quality system – was published In June 2008, describing the elements of the new model that should ensure quality through continuous improvement tools.

On January 15th 2014, the European Medicine Agency (EMA) released the latest version of the "Guideline on Process Validation"[9], with the aim of promoting the implementation of quality systems based on scientific evidence. On January 31st, 2013 the new version of Chapter 1 of the EU - GMP came into force, and became a reference model for pharmaceutical quality system.

### 1.2. Objective

The purpose of this document is to guide the pharmaceutical drug manufacturers in the gradual incorporation of QbD systems to the manufacture of drugs. Specifically, it focuses on the area of manufacturing of industrial batches.

The paper is structured as follows:

• Chapter 1: Introduction.

• Chapter 2: Evaluation of the state of control of manufacturing processes, criteria and statistical tools to verify that the processes are stable and capable.

• Chapter 3: Assessment of deficiencies in the design, and in the understanding of the manufacturing processes as well as an improvement proposal; criteria and tools to

[8] *ICH (2008): Q10 Pharmaceutical Quality System.*

[9] *EMA (2014): EMA/CHMP/CVMP/QWP/70278/2012- Guideline on Process Validation.*

acquire the necessary knowledge of the process and to identify improvement actions and / or to redesign the process if necessary.

• Chapter 4: criteria for calculating the ROI of a project based on QbD; methodology to prioritize improvement projects and to calculate the necessary investment and savings estimations for each case.

• Chapter 5: Case Study, application of the previous chapters to a fictitious example: improvement project in tablet manufacturing.

• Glossary of Terms.