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ICH Q8/Q9/Q10 Guidelines: Changing Paradigm in Pharmaceutical Development

Dissertação de Mestrado em Tecnologias do Medicamento, orientada pelo Professor Doutor Francisco Veiga e apresentada à Faculdade de Farmácia da Universidade de Coimbra

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ICH Q8/Q9/Q10 Guidelines: Changing Paradigm in Pharmaceutical Development

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I. Abstract

The conceptualization of quality within the pharmaceutical business has undergone maturation over the last decades. Evolution of the concept of quality has often been preceded by recognition of the existing problems and usually required a significant change in mind-set.

At the turn of the 20th century, the pharmaceutical sector presented signs of stagnation in drug development, lack of modernization and recurring quality issues. The ICH, backed by world leading regulatory agencies and pharmaceutical industry associations, recognised that changes were necessary and, on July 2003, its members agreed on a new quality paradigm. A novel regulatory landscape that could drive manufacturers towards an enhanced approach to quality, supported by science, knowledge, quality risk management and modern pharmaceutical quality systems was envisioned. The result was the publication of three new ICH guidelines: Q8 Pharmaceutical Development; Q9 Quality Risk Management; Q10 Pharmaceutical Quality System.

The objective of this thesis is to address the three ICH guidelines, focusing on the impact that the new quality vision will have in the product lifecycle management by the pharmaceutical industry, with special attention on the consequences of it in the future of pharmaceutical development.

The new principles, concepts and tools introduced by the ICH Q8, Q9 and Q10 guidelines are discussed and its integration is explored. This work also reflects on the benefits and limitations arising from the implementation of the enhanced approach to pharmaceutical development (Quality by Design) as well as future trends in this field.

2. List of Abbreviations

3.2.P.2 – CTD section “Pharmaceutical Development”

ANDA – Abbreviated New Drug Application

CAPA – Corrective Action, Preventive Action

CDER - Centre for Drug Evaluation and Research

cGMP – Current Good Manufacturing Practices

CMC – Chemistry, Manufacturing and Controls

CPP – Critical Process Parameter

CPV – Continuous Process Verification

CQA – Critical Quality Attribute

CTD – Common Technical Document

DoE – Design of Experiments

EBE – European Biopharmaceutical Enterprises

EC – European Commission

EFPIA – European Federation of Pharmaceutical Industries

EGA – European Generic Medicines Association

EMA – European Medicines Agency

EU – European Union

EVM – European Vaccine Manufacturers

FDA – United States Food and Drugs Administration

FMEA – Failure Mode Effects Analysis

FMECA – Failure Mode, Effects and Criticality Analysis

FTA – Fault Tree Analysis

GMP - Good Manufacturing Practices

HACCP – Hazard Analysis and Critical Control Points

HAZOP – Hazard Operability Analysis

ICH – International Conference on Harmonisation

IFPAC - International Foundation Process Analytical Chemistry

ISO - International Organization for Standardization

ISO 13485:2003 – Quality Management Standards for Medical Devices

ISO 9000, ISO 9001:2000, ISO 9004 – Quality Management Standards

IWG – Implementation Working Group

JPMA – Japan Pharmaceutical Manufacturers Association

MA – Marketing Authorisation

MAPP - Manual of Policies & Procedures

MHLW – Ministry of Health, Labour and Welfare, Japan

NDA – New Drug Application

ONDQA - The Office of New Drug Quality Assessment

PAT – Process Analytical Technology

PDA – Parenteral Drug Association

PHA – Preliminary Hazard Analysis

PhRMA – Pharmaceutical Research and Manufacturers of America

PQS – Pharmaceutical Quality System (=Quality Management System)

Q&As – Questions and Answers

QA/QC – Quality Assurance/Quality Control

QbD – Quality by Design

QC – Quality Control

Q-IWG – Quality-Implementation Working Group

QMS – Quality Management System

QRM – Quality Risk Management

QTPP – Quality Target Product Profile

R&D – Research and Development

RTRT – Real-Time Release Testing

SC – Steering Committee (ICH)

SOP – Standard Operating Procedure

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4. Introduction

The conceptualization of quality within the pharmaceutical business has undergone maturation over the last decades. At the beginning it was mainly based on finished product analysis. As more experience was gained, new opinions emerged and quality became to be focussed on manufacturing. A manufacturing process, backboneed by process validation, should be controlled to provide a consistent quality product. The 21st century brought a new thinking where quality not only should be reflected by the manufacturing process, but should be planned and revised throughout the product lifecycle.

The process of planning quality is known as Quality by Design and dates back to 1992 when Joseph Juran, expert and consultant in quality, described this concept under the belief that quality could be planned. Juran described three main processes as essential to manage quality: planning, control and improvement.¹

The new approach is that quality must be initially designed at product, process and control strategy level and extended throughout the product lifecycle.

This new quality vision was agreed within the ICH framework, during the ICH meeting held in Brussels in July, 2003: “a harmonized pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to risk management.”²

Following this agreement, ICH group members worked together to build up a new regulatory backbone that could drive manufacturers towards an enhanced approach to quality, supported by science, knowledge on product and processes, quality risk management and modern pharmaceutical quality systems. The result was the issuance of new ICH guidelines:

- Q8: Pharmaceutical Development;
- Q9: Quality Risk Management;
- Q10: Pharmaceutical Quality System.

The objective of this thesis is to address ICH Q8, Q9 and Q10 guidelines, focusing on the impact of these on the product lifecycle management by the pharmaceutical industry, with special attention on the consequences of such guidelines on the future of pharmaceutical development.

4.1. Background

The Pharmaceutical Industry plays a major role in making available therapeutic solutions and alternatives for the patients, however, it has been recognised that the pharmaceutical industry struggles to adopt innovative science and technology, whereas other industries manage to get their processes continuously optimized and modernized.

Drug shortages and quality metrics are two topics in today's pharmaceutical landscape that are leading the focus of both the industry and the regulators. These topics are related, and thus the discussion of one involves unavoidably the other.³

The process of building and measuring quality as well as the competence of manufacturers to reproducibly deliver quality product in a timely manner is, therefore, under special attention.

On the 3rd of September of 2003, a Wall Street Journal article urged⁴:

“The pharmaceutical industry has a little secret: Even as it invents futuristic new drugs, its manufacturing techniques lag far behind those of potato-chip and laundry-soap makers....”

“The FDA has concluded that the industry needs to adopt manufacturing innovations, partly to raise quality standards. The agency is overhauling its elaborate manufacturing regulations for the first time in 25 years. To begin with, the FDA plans to issue some guidance to the industry...”

“The FDA has challenged drug makers to do a better job. “You need to improve,” Dr. McClellan lectured the industry in March. “Other high-tech industries ... have achieved enormous productivity gains in manufacturing in the last 25 years. We should expect nothing less from the pharmaceutical industry,”

In the early 2000's this problem was already a major topic for discussion at the FDA, EMA and, consequently, at the ICH.

In the EU, a PAT team was formed in November 2003 to support PAT and quality-by-design activities in the EU. The PAT team served as a tool to harmonise as much as possible the assessment of applications that implement the ICH Q8, Q9 and Q10 principles and was seen as a key element in the implementation of QbD by encouraging process understanding.⁵ Similarly, FDA issued PAT guidance in 2004.⁶

In March 2004, FDA launched the “Critical Path Initiative” with the objective of driving innovation and scientific progress in the way how medicinal products are developed, evaluated and manufactured. “Critical Path” is understood as the period that encompasses drug development, after drug discovery, until effective marketing of the product. The “Critical Path Initiative” was launched after the release of the report “Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products”. This report provided an analysis of the “recent slowdown, instead of the expected acceleration, in innovative medical therapies reaching patients”.⁷ It also stated that slowdown was due to the fact that medicinal product development has become increasingly burdensome, costly and lacking efficiency. It was necessary to urgently accelerate and improve the efficiency of the critical path from laboratory research, throughout development to product commercialisation, to better meet urgent public health needs. Opportunities for improvement were identified, such as more modern technical methods, better predictive models, use of biomarkers for safety and effectiveness, and new clinical evaluation techniques.⁷ The report also recognised that pharmaceutical industry has been hesitant to introduce state-of-the-art science and technology into its manufacturing processes. Amongst the opportunities raised by this report, was the need to drive innovation and scientific approaches in the product’s development, evaluation and manufacture activities.⁷

Later on, on September 2004, FDA released the final report of the initiative “Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century”. This initiative, started in August 2002, was intended to promote the modernisation of the regulation of pharmaceutical manufacturing and product quality. Its intention was not to promote new GMPs, but to encourage innovation and modernization of the pharmaceutical industry interpretation of the cGMPs. The initiative goal to develop a modernized product quality regulatory system was driven by risk, science, integrated quality systems, international cooperation and public health protection.⁸ The FDA’s 21st Century cGMPs initiative would form the basis for discussions at ICH.

In May 2007, FDA released a report “Critical Path Opportunities for Generic Drugs” that identified some of the specific challenges in the development of generic drugs. The goal of this document was to bring these challenges to the attention of interested parties and identify opportunities for collaborative solutions.⁹

The effort of the FDA, EMA and MHLW, within the ICH framework cooperation scheme, combined with the participation of the PhRMA, EFPIA and JPMA, have led to the agreement on a new quality vision during the 2003 Brussels ICH meeting. New quality

guidelines would be developed to promote the implementation of the new vision. As ICH has no authority to impose regulatory requirements in any region, the developed and approved guidelines would have to be implemented by the three regions.

Table 1 – ICH procedure steps of the Q8, Q9 and Q10 guidelines

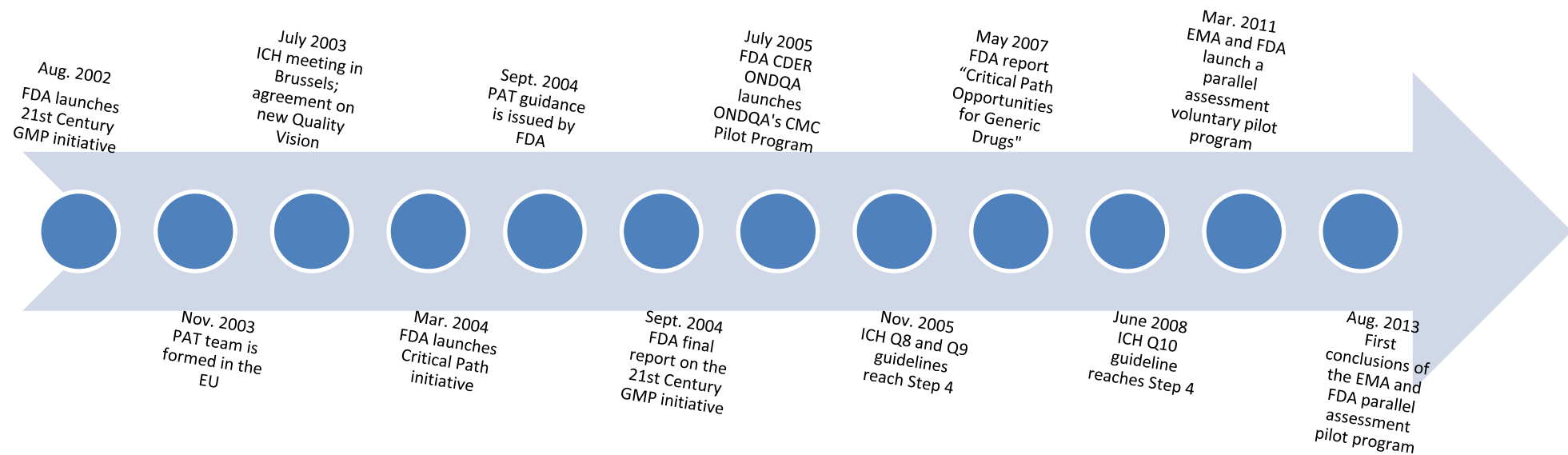
	Procedure Step	Q8	Q9	Q10
Initial guideline	Step 2	18 November 2004	22 March 2005	9 May 2007
	Confirmation of six-party consensus on the Technical Document/ Adoption of draft Guideline by Regulatory Parties.		Corrected on 15 June 2005	
	Step 4	10 November 2005	9 November 2005	4 June 2008
	Adoption of an ICH Harmonised Tripartite Guideline.			
	Step 5	EU: May 2006 MHLW: Sept. 2006 FDA: May 2006	EU: Jan. 2006 MHLW: Sept. 2006 FDA: June 2006	EU: July 2008 MHLW: Feb. 2010 FDA: April 2009
	Implementation			
Rev. 1	Step 4	13 November 2008	-	-
	Adoption of an ICH Harmonised Tripartite Guideline.			
	Step 5	EU: June 2009 MHLW: June 2010 FDA: Nov. 2009	-	-
	Implementation			
Rev. 2	-	2009 (corrections)	-	-

The ICH Quality Implementation Working Group (Q-IWG) developed “Questions and Answers” and “Points to Consider” documents to provide clarification on the key issues and facilitate the implementation of the Q8, Q9 and Q10 Guidelines, available on the ICH website (<http://www.ich.org>). Several workshops were carried out in the three regions, led by experts from the ICH Q-IWG, with the participation of regulatory and industry representatives. Workshop, training material and case studies are also available and can be accessed on the ICH website.¹⁰

The Office of New Drug Quality Assessment (ONDQA) in the FDA’s Center for Drug Evaluation and Research (CDER) launched the ONDQA’s CMC Pilot Program in July 2005. Its objective was to provide participating firms an opportunity to submit CMC information incorporating QbD and enable FDA to implement the new enhanced approach concepts. The pilot program provided valuable experience for industry and FDA in implementing and assessing QbD. Submissions incorporating QbD elements and risk-based regulatory decisions took the first steps.¹¹ The outcome of this program and its conclusions were taken into consideration by the ICH.

Later, in 2011, EMA and FDA launched a three-year voluntary pilot program for the parallel assessment of sections of applications that are relevant to quality by design and to guarantee consistent implementation of ICH Q8, Q9 and Q10 at a global level.⁵ Biopharmaceuticals were not under the scope of this pilot program. The new quality paradigm presented numerous challenges to the established quality and regulatory culture, therefore it was necessary to provide further impulse and guidance to industry on this matter. The program consisted on the parallel assessment of specific quality sections of the CTD relevant to QbD, where both regulators could share regulatory decisions, harmonize approaches and set the necessary structures within the agencies. Industry expectations were that the program could lead to a more uniform policy between FDA and EMA. Experts from the Japanese Pharmaceuticals Medical Devices Agency contributed to this program as observers.¹²

Figure I **Timeline – Quality vision changing paradigm - major events**



5. Pharmaceutical Development Q8

5.1. History

In 2003, the EU had already in force a guideline (Note for Guidance on Development Pharmaceuticals) and FDA had issued a draft for its own guideline, each one adjusted according to the each region interpretation. The need for harmonisation regarding the pharmaceutical development information that regulators would like to see in 3.2.P.2 originated the proposal of a new guideline that could meet the expectations for the three ICH regions.¹³

On October 2003, the ICH Steering Committee endorsed the Q8 Concept paper. This document addressed the need for a new tripartite guideline that would describe the harmonised contents of the CTD section 3.2.P.2 and incorporate new concepts (quality by design and risk management). The guideline should describe, at high level, what is intended to see included in section 3.2.P.2 but does not define how such studies should be conducted. It also highlighted the benefits that a consistent approach for presenting and evaluating development information across the three regions could bring to both Regulators and Industry.¹³

The ICH Pharmaceutical Development guideline (Q8) was approved under Step 2 by the SC and released for public consultation on November 2004. The guideline was finally approved (Step 4) and recommended by the Steering Committee for adoption to the ICH regulatory bodies on November 2005 ¹⁴:

- EMA: Guideline “Note for guidance on pharmaceutical development” was issued as EMEA/CHMP/167068/2004-ICH. Date for coming into operation: May 2006.
- MHLW: Adopted on September 1, 2006 (PFSB/ELD Notification N° 0901001).
- FDA: Adopted on May 2006. Published in the Federal Register, Vol. 71, No 98, May 22, 2006.

In November 2007, the SC approved and released for consultation (Step 2) the Annex to Q8 which was finalised (Step 4) in November. It contained further insight into the new concepts and tools as well as the principles of quality by design, showing how these can be used by the applicant. The annex was included in the parent guideline which was recoded as Q8(R1).¹⁴

The Q8(R1) Guideline was revised in Summer 2009 (Q8(R2)) to include corrections to Example 2 on page 23:¹⁴

- EMA: Adopted by CHMP on June 2009: EMEA/CHMP/167068/2004-ICH.
- MHLW: Adopted on June 28, 2010 (PFSB/ELD Notification N° 0628-1).
- FDA: Published in the Federal Register, Vol. 71, No 98, Nov. 2009.

5.2. Objective

The ICH Q8 guideline objective is to provide the opportunity and guidance for the applicant to build a 3.2.P.2 section, applying new concepts and reaching an enhanced level of product and process knowledge. The development stage is clearly extended over the entire product lifecycle, creating room for continuous improvement. It also allows the applicant, regulators and inspectors to benefit from the new tools and concepts, as the gain of scientific knowledge may result in flexible regulatory approaches.¹⁴ The ultimate goal is to achieve more robust manufacturing processes than those that would result from the traditional approach to drug development.

5.3. Scope

The ICH Q8 guideline provides guidance on the contents of section 3.2.P.2 of the CTD.¹⁴ The Pharmaceutical Development section (3.2.P.2) of the CTD contains information on the development studies conducted to prove that the design of the product and its manufacturing process are appropriate for the intended performance of the product.¹⁵

This guideline (Q8) is applicable to new pharmaceuticals, including biotechnology-derived products^{14,15}. Even though this guideline scope does not cover submissions for drug products during the clinical research stages of drug development, it states the importance of considering the guideline principles during this early phase. The applicability of this guideline to other types of products is possible, depending on each particular case, and is subject to previous discussion with the appropriate regulatory authority.¹⁴

5.4. Structure

The ICH Q8 guideline is composed of Part I and Part II, where Part I constitutes the core guideline and Part II is the annex that provides deeper details about the key concepts and tools. ¹⁴

5.4.1. Part I:

The core guideline introduces the basis for the new ideals and concepts and presents the points what regulators expect to see being described in section 3.2.P.2 of the CTD. ¹⁴

Table 2 – Q8 Part I structure

Part I Structure			
Introduction	Objective of the guideline		
	Scope		
Pharmaceutical development	Fundamental principles and new concepts	Product and process understanding	
		Design space	
		Quality risk management	
		Quality by design	
		Lifecycle management	
		Flexible regulatory approaches	
		Formal experimental design (Design of experiments - DoE)	
		Process analytical technology	
		Continual improvement	
		Continuous process verification	
		Points to be considered in 3.2.P.2	Components of drug product
			Drug substance
			Excipients
	Drug product		
		Formulation development	
		Overages	

Part I Structure	
	Physicochemical and biological properties
	Manufacturing process development
	Container closure system
	Microbiological attributes
	Compatibility
Glossary	

5.4.2. Part II:

The Annex to the core guideline provides explanation of the principles and important concepts. It also shows different approaches and how to put into practice some of the concepts and tools, including some examples.¹⁴

Table 3 – Q8 Part II structure

Part II Structure		
Introduction	Approaches to pharmaceutical development	Empirical approach
		Systematic approach
		Combination of both
Elements of pharmaceutical development	Quality target product profile	Critical quality attributes
		Risk assessment: linking material attributes and process parameters to drug product CQAs
		Design space
		Control strategy
		Product lifecycle management and continual improvement
Pharmaceutical development information submitted in CTD	Quality risk management and product and process development	Design space
		Control strategy
		Drug substance related information
Glossary		

Part II Structure

Appendix 1	Differing approaches to pharmaceutical development
Appendix 2	Illustrative examples

5.5. Principles and Concepts

5.5.1. Two possible approaches

The Pharmaceutical Development guideline refers two possible strategies for product development. One more traditional and empiric approach (= Minimal approach) or a more systematic and enhanced approach (= Quality by design) can be followed. It is also possible to have a combination of both. This means that the use of an enhanced approach is optional and can be tailored according to the specificities of the product/process. The enhanced approach is presented as an advantageous alternative, in comparison to the traditional approach, from which the pharmaceutical industry could strongly benefit.¹⁴

The following table displays the differing aspects of each of the approaches.

Table 4 – Comparison of minimal vs. enhanced approach (adapted from Q8 appendix I)

Aspect	Minimal Approaches	Enhanced, Quality by Design Approaches
Overall Pharmaceutical Development	Mainly empirical Development research often conducted one variable at a time Focus on optimization	Systematic, relating mechanistic understanding of material attributes and process parameters to drug product CQAs Multivariate experiments to understand product and process Establishment of design space PAT tools utilised

Aspect	Minimal Approaches	Enhanced, Quality by Design Approaches
Manufacturing Process	Fixed Validation primarily based on initial full-scale batches Focus on optimisation and reproducibility	Adjustable within design space Lifecycle approach to validation and, ideally, continuous process verification Focus on control strategy and robustness Use of statistical process control methods
Process Controls	In-process tests primarily for go/no go decisions Off-line analysis	PAT tools utilised with appropriate feed forward and feedback controls Process operations tracked and trended to support continual improvement efforts post-approval
Product Specifications	Primary means of control Based on batch data available at time of registration	Part of the overall quality control strategy Based on desired product performance with relevant supportive data
Control Strategy	Drug product quality controlled primarily by intermediates (in-process materials) and end product testing	Drug product quality ensured by risk-based control strategy for well understood product and process Quality controls shifted upstream, with the possibility of real-time release testing or reduced end-product testing

Aspect	Minimal Approaches	Enhanced, Quality by Design Approaches
Lifecycle Management	Reactive (i.e., problem solving and corrective action)	Preventive action Continual improvement facilitated

Independently of which strategy is followed, the goal of pharmaceutical development is to ensure that the product will consistently meet the required quality, that the manufacturing process will be capable to produce a quality product and that commercial batches will link to clinical batches in all pertinent angles not only during shelf-life but throughout all product lifecycle.¹⁶

The development strategy must be adjusted to the product and process particularities. For this reason, companies are advised to contact authorities in advance and discuss the strategy and data to be presented in their application.

5.5.2. Product and process understanding

The ICH Q8 guideline strongly claims the importance of a deep product and process understanding as a vital component of the Pharmaceutical Development. The more knowledge is available, the easier it gets to establish an adequate control strategy and more flexibility can be obtained. The guideline addresses the tools that can be used and highlights the opportunity to present the knowledge collected during development in a regulatory submission and thus benefit from a facilitated review and approval from regulators¹⁴.

5.5.3. Enablers of QbD

5.5.3.1. Prior Knowledge

Prior knowledge is an important source of knowledge and represents the first step for any further activity, including risk assessments. It may include knowledge from experience gained during development and manufacturing, but can also integrate external

information, such as scientific and technical literature and publications²⁵. Relevant prior knowledge used during product development stage, should be cited in the regulatory application dossier.²⁵

During the initial steps of the development, the available knowledge should be assessed, leading to the identification of knowledge gaps that need to be further studied. For this end, risk assessment methodologies are extremely useful.

5.5.3.2. Formal experimental design (Design of Experiments - DoE)

This concept is introduced in the Pharmaceutical Development guideline as a structured, science based experimental approach that can be used to evaluate the impact of identified variables and understand their possible interaction.

Design of experiments must derive from risk assessments and consider the objectives of the stakeholders.¹⁷ DoE consists in small-scale characterisation experiments with appropriate designs that allow multivariate analysis, analysis of interactions and statistical modelling.¹⁸

The use of this methodology provides a demonstrated understanding of the effects of CPPs and their interactions on CQAs, enhances product and process understanding thus creating the opportunity to propose a design space¹⁴. DoE results provide new and useful information that may lead to the review of previous risk assessments.

Multiple approaches for formal experimental design are possible. It also enables the development and implementation of predictive models. A model is a simplified mathematical representation of a system and can be used to predict the behaviour of a system under predefined conditions.¹⁹

The challenge of most development programs is to reach utmost understanding in the fewest number of studies, in an efficient and cost reduced way. In many cases, a multistep approach based on multiple studies is desirable.²⁰

Different study designs can be used, depending on the development stage and objectives. Screening study designs are normally used to identify which parameters have impact on a CQA or not. Refining study designs aim at understanding main effects and interactions and establishing relationships between parameters and CQAs. Optimization

study designs objective is to further understand relationships and establish mathematical models that grant the opportunity to find the most favourable set points for desired CQAs outcome.²⁰

This concept requires that companies change their current approach and it requires an understanding in DoE techniques. It also may implicate an investment in software and instrumentation to design and perform the experiments.

5.5.3.3. Quality risk management

Quality risk management is introduced by the ICH Q9 guideline and is referenced in ICH Q8 as a key element to Pharmaceutical Development. Knowledge about the product and manufacturing process can benefit from the employment of quality risk management processes. On the other hand, knowledge gained during pharmaceutical development can support future risk-based decisions. Risk assessment, a process used in quality risk management, can be highly useful during all the product lifecycle, from development phase throughout commercial manufacturing, by identifying critical material attributes and process parameters, establishing a control strategy and supporting risk-based decisions.¹⁴

In the context of the pharmaceutical development, quality risk assessment plays its major role in prioritizing and ranking material attributes and process parameters that can have an impact on drug product CQAs and finding relationships between these factors. It can be used during pharmaceutical development but can also help fine-tune the control strategy as more data becomes available, thus supporting continual improvement.¹⁴ Stakeholders are encouraged to use risk management proactively.

5.5.3.4. Process analytical technology

Process analytical technology (PAT) is the mechanism for systematic measurement of material attributes and process parameters in order to design, analyse or control the manufacturing process. It is presented in the ICH Q8 guideline as an important tool that can support the enhanced understanding of product and process and be an important component of the control strategy. It enables the use of feed-forward and feedback controls

in an adaptive manufacturing process.¹⁴ PAT, through online monitoring technologies, is fundamental to perform adjustments to a process in a timely and continuous manner and is already widely used in solid oral dosage forms manufacturing.²¹ To fully take advantage of PAT solutions, a step forward from simple process monitoring to effectively control the process using the data has to be taken.²¹

5.5.4. Quality by design

The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product.¹⁴ Quality is the suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength and purity.²²

QbD ensures that the elements of quality are understood and incorporated into the design of the process so that it can consistently yield a safe and efficacious product.¹⁸

It has been widely recognized that quality cannot be solely assured by testing and inspection. It must be designed and built into the product, supported by scientific knowledge and systematic practices.¹⁴ Quality by design is a concept that describes a more systematic approach to pharmaceutical development than the traditional approach recognised to be the dominant practice in the pharmaceutical industry. QbD pursues better process knowledge and refocuses pharmaceutical development in quality planning. Quality must be planned rather than tested.

The main steps for QbD include²³:

- the identification of the product attributes that are important to safety and efficacy;
- the linkage of those material attributes that can impact the desired product attributes;
- the design of the process to meet all critical attributes;
- the delineation of a proper control strategy to ensure consistent process performance;
- validation demonstrating the effectiveness of the control strategy;

- ongoing monitoring and review to ensure the desired process performance throughout the entire product lifecycle.

This approach is based on sound science and can make use of different information sources, concepts and tools, such as previous knowledge, design of experiments, design space, risk management and data gathered during the lifecycle of the product. It provides better understanding of the product which, ultimately, aids reaching the quality target and potentially eases and shortens the assessment process by the regulators.¹⁴ It also makes use of knowledge collected during the lifecycle of the product which can also be extremely useful to refine overall product and process understanding. A possible approach would be the identification of material characteristics and process parameters that have an effect on product CQAs, through prior knowledge, experimentation and risk assessment and the determination of its interactions and correlations followed up by the establishment of a control strategy that could consist on a design space and/or real-time release testing.¹⁴

Implementing a QbD approach to process development requires the formalisation of a commitment and its integration into a company's PQS. The result is a planned roadmap for development, the adoption of a lifecycle perspective and the search for further product and process understanding.

Although it is generally assumed that QbD represents a more complex and time/resource consuming approach to development, the enhanced approach is encouraged by the regulators. It has been described how a QbD approach, in comparison to a traditional approach, can lead to shorter development timelines and decreased costs, mainly because it reduces redundant and inefficient characterisation studies and allows reaching an appropriate level of product and process understanding early on.¹⁸

Quality by Design is expected to enhance safe and effective drug availability to the consumer and to significantly improve manufacturing quality performance.²⁴

The main elements that underpin QbD are¹⁴:

1. Quality Target Product Profile
2. Critical Quality Attributes
3. Risk Assessment: Linking material attributes and process parameters to product CQAs
4. Design Space
5. Control Strategy

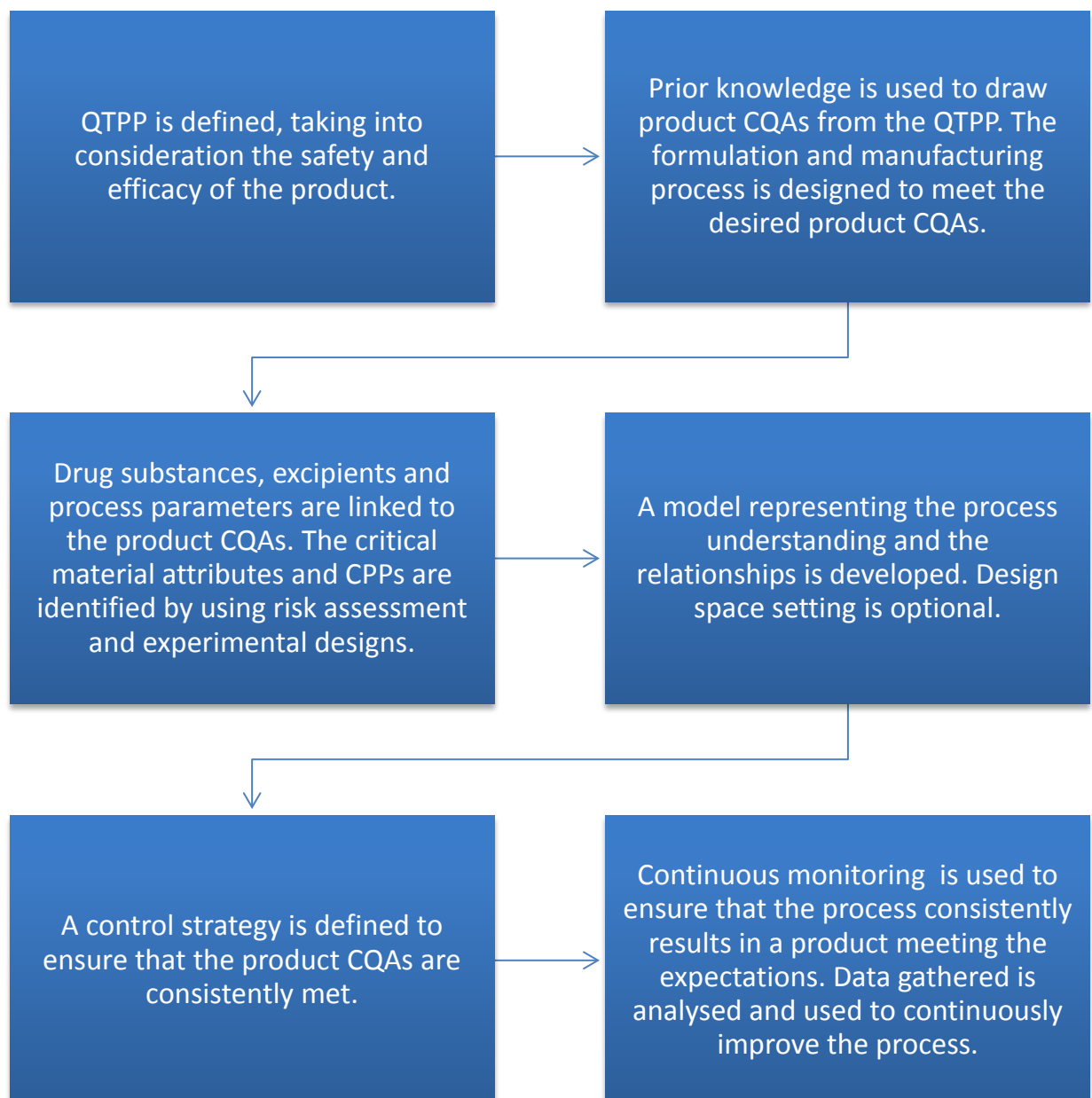
6. Product lifecycle management and Continual improvement

Amongst the available resources and tools that can support QbD, emphasis is made to the following¹⁴:

1. Prior knowledge
2. Experimentation (e.g. DoE)
3. Risk assessment
4. PAT

The following scheme represents a typical QbD approach to pharmaceutical development:

Figure 2 – Typical QbD approach to pharmaceutical development



Recapitulating, quality by design differentiates from the traditional approach as it encompasses further steps and aims to reach a higher level of product and manufacturing process understanding. The road to QbD is driven by systematic and scientific methodologies and tools, supported by prior knowledge and experience. The main goal is to master as many product and process aspects as possible so that an optimised control strategy is set, and thus assure that the intended quality is met.¹⁴

5.5.5. Quality target product profile

The quality target product profile provides the ground for the design of the pharmaceutical development activities¹⁴. The QTPP should describe prospectively the quality characteristics of a drug product that should be achieved to ensure the desired quality, safety and efficacy of the drug product. The elaboration of the QTPP is crucial as it will guarantee that the product will meet the needs of the patient.¹⁹ It is the first step where all ideal quality characteristics of the drug product are predefined and a starting point is set for the roll out of the pharmaceutical development. It will drive development activities for the definition of the critical quality attributes, the critical process parameters and the control strategy.

Examples of aspects that can be addressed in the QTPP are¹⁴:

1. Proposed clinical use
2. Pharmaceutical form
3. Administration route
4. Target user
5. Dosage strength
6. Container closure system
7. Presentation
8. Delivery system
9. Attributes affecting drug release or delivery
10. Drug product appropriate quality parameters, according to the intended use

QTPP may suffer changes as product and process understanding evolves during development and manufacturing²⁵.

Differences in setting the QTPP can be found when developing a NDA or an ANDA product. In the case of an NDA, the QTPP needs to be developed, while for the ANDA product the QTPP is already known due to the existence of a reference product.

5.5.6. Critical quality attributes

A critical quality attribute is any property or characteristic of the active substance, excipient, intermediate or drug product that must be controlled to guarantee that the product will be adequate for its intended use, from a safety and efficacy perspective. CQAs can have a physical, chemical, biological or microbiological nature. The initial drug product CQAs derive from the QTPP and form the basis for the development roadmap. They can suffer modifications as more information is gathered and product and process understanding increases. Finally, by means of risk management and experimentation, the relevant CQAs are selected and prioritised, according to their possible impact on product quality¹⁴. The fact that a risk is mitigated by applying a robust control strategy does not mean that the attribute criticality is diminished.²⁶

Depending on the specificities of the drug product, the CQAs can cover different aspects. CQAs must be defined to materials (drug substance, excipients and intermediates) as well as to drug product. Materials CQAs also comprises the characteristics that can directly influence drug product CQAs¹⁴.

The process of identifying CQAs must be documented as regards to its link to the patient, severity of harm, relationships and information sources that support the identified CQAs, such as prior knowledge and experimental data. Explanation about how the drug substance and excipients CQAs relate to the finished drug product CQAs should be given.²⁷ The CQAs can change as a consequence of improvement decisions, based on business driven changes (new technology or new processes) or on knowledge acquired during product lifecycle.¹⁹ The definition of CQAs, supported by risk assessment, is an iterative process.

Figure 3 – Examples of CQAs for Solid dosage oral forms¹⁴

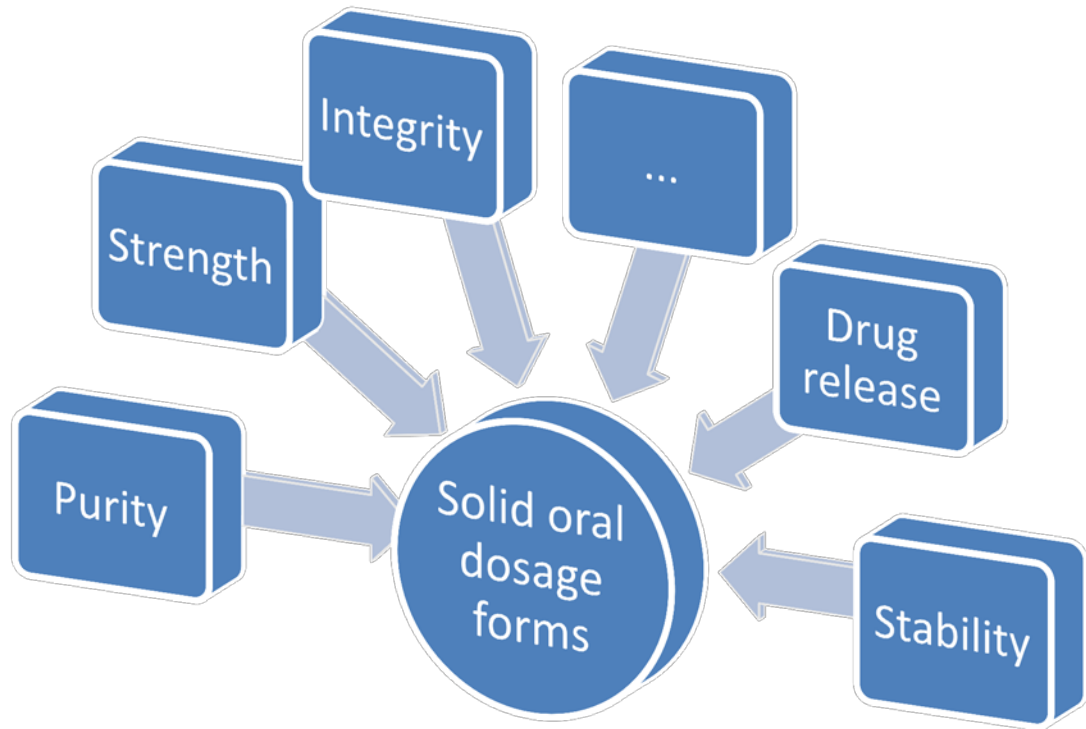


Figure 4 – Examples of CQAs for Transdermal patches¹⁴

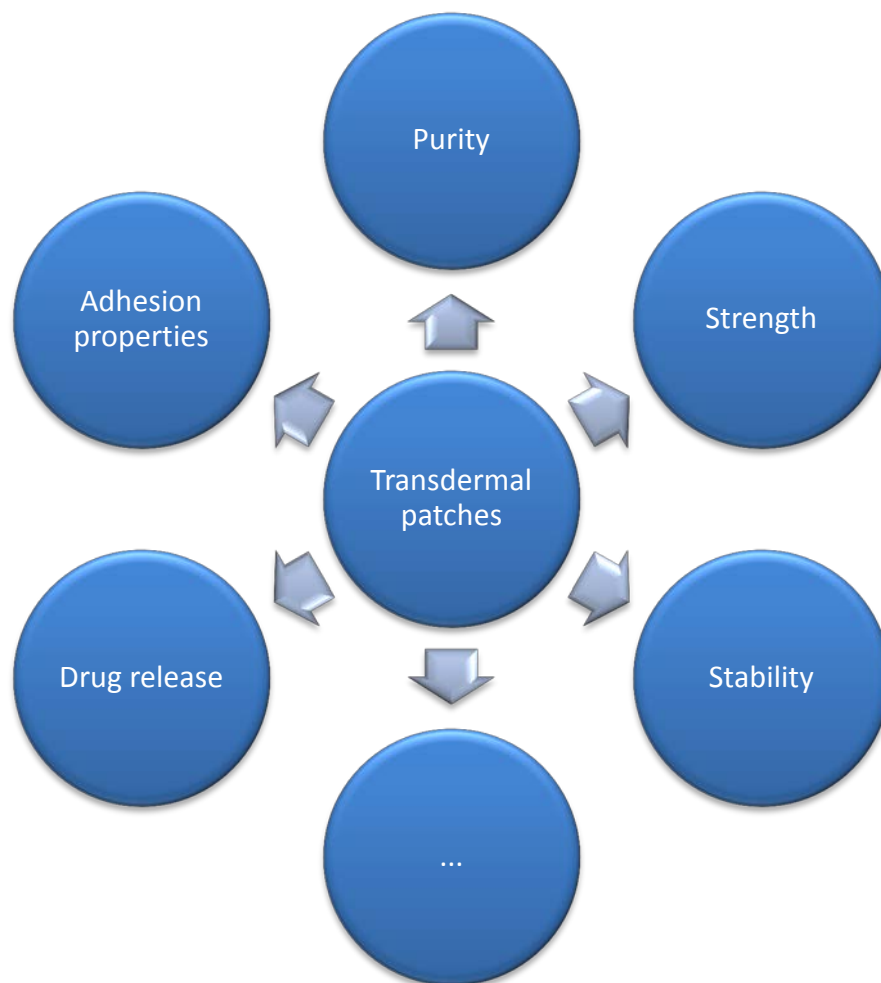


Figure 5 – Examples of CQAs for Parenterals¹⁴

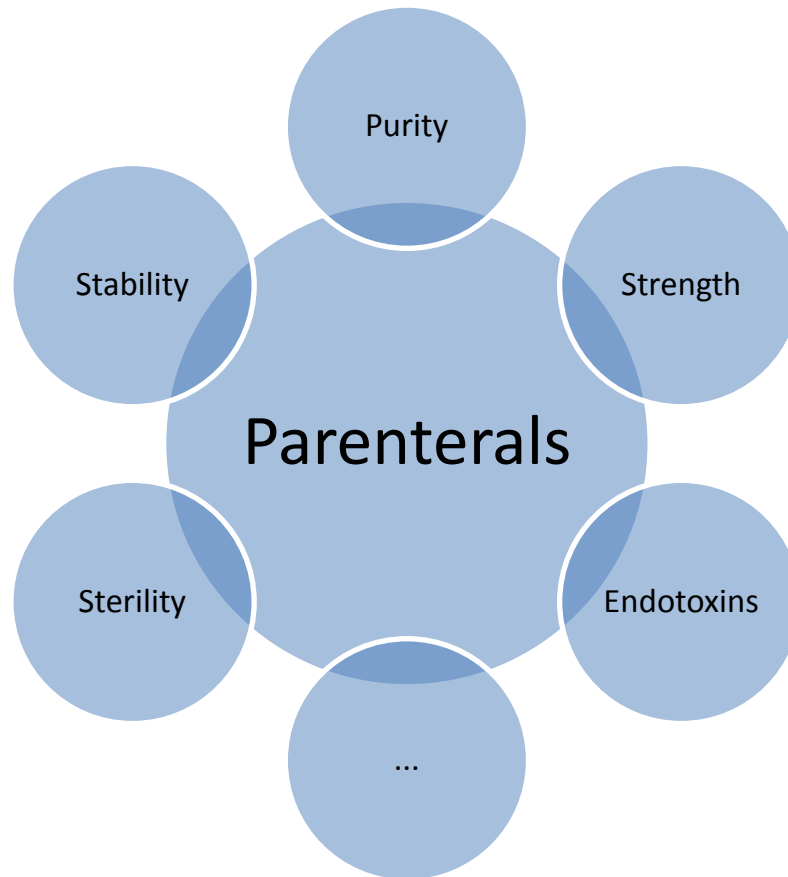
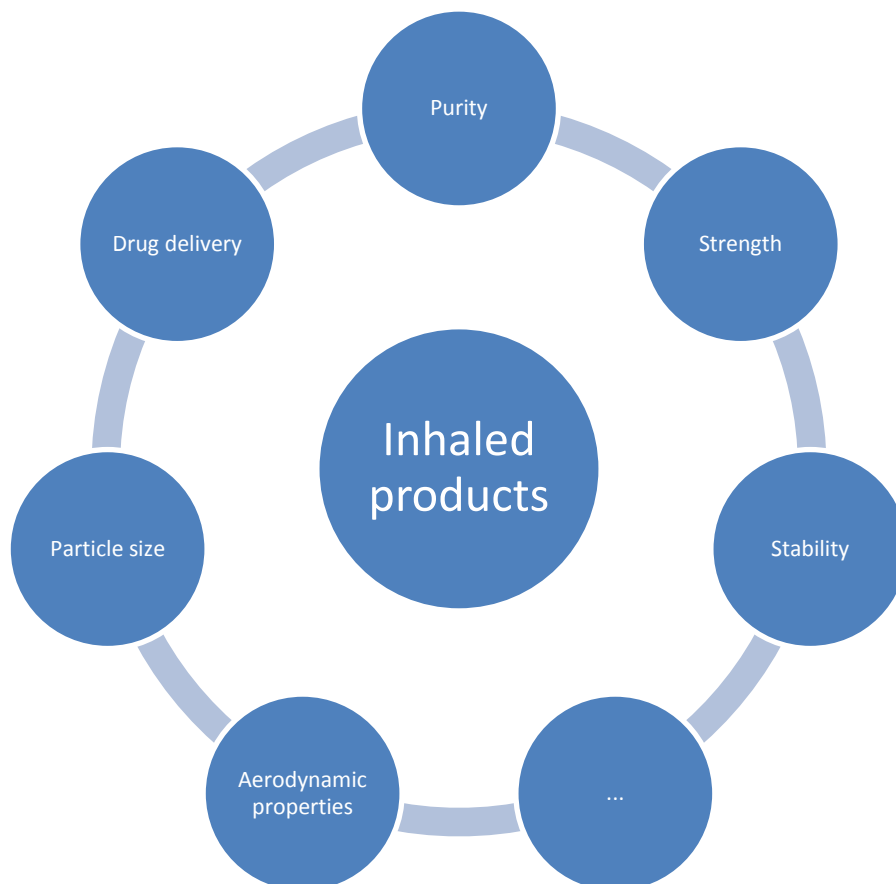


Figure 6 – Examples of CQAs for Inhaled products¹⁴



Notwithstanding the identification of the CQAs and the rationale being its designation, its acceptance limits should be defined. A control strategy should be designed and put in place to ensure that drug product CQAs are consistently within the acceptable limits.

5.5.7. Critical process parameters

A critical process parameter are those which can have an impact on a product CQA and, for that reason, must be evaluated and controlled to guarantee that the process results in a product meeting the quality expectations.

The process of identifying CPPs must be documented as regards to its link to the CQAs, interdependencies, control strategy, residual risk and information sources that support the identified CPPs, such as prior knowledge, quality risk management and experimental data (DoE). The CPPs can change as a consequence of improvement decisions, either originated from planned changes to the manufacturing process or from knowledge gained during commercial manufacturing and marketing period.¹⁹

5.5.8. Control strategy

The control strategy is referred in the guideline as a means to guarantee that the manufacturing process will consistently result in a product meeting the required quality. It is described as a planned set of controls that results from knowledge collected during pharmaceutical development. Those controls can include drug substance, materials or drug product attributes, facility and equipment parameters, and respective frequency of monitoring and control.¹⁴ The manufacturing process must be controlled to provide high probability that the product will consistently meet all specified requirements.

The strategy to control drug product quality must derive from product and process understanding and, at least, should focus on the identified critical process parameters and critical quality attributes and the linkage between the CQAs and CPPs must be considered. The objective is to find sources of variability, understand its impact and keep those variability sources under control. Understanding the impact of the source of variability on subsequent

stages provides the opportunity to target the control effort towards the critical steps, minimising the need for systematic final product testing. This will support the adaptability of the process to compensate for the variability and ensure a reproducible quality.¹⁴ The risk associated with CQAs is reduced by an adequate control strategy, however the criticality of the attributes is not changed.¹⁹

A suitable control strategy may allow a completely different approach to drug product manufacturing. The understanding of the variability sources turns them less limiting as it is possible to conceive an adjustable process step, supported by appropriate in-process controls, to provide the desired product quality¹⁴ and thus fulfil the QTTP.¹⁹

A high level of product and process understanding may also sustain the use of alternative means to ensure that quality is being met. It is the case of real-time release testing where surrogate attributes and the implementation of PAT may provide increased quality assurance, enabling the replacement of end product testing.¹⁴

Figure 7 - Examples of control strategy elements¹⁴



A control strategy must exist and its description and justification must be provided in the submission.¹⁴

Over the lifecycle of the product, the control strategy can be refined as more data and knowledge become available.¹⁹

5.5.9. Design space

Design space reflects an integrated multivariate range of critical input material attributes and process parameters, taking into account their interaction, that have proven to provide a drug product meeting the desired quality. It can be applied as part of the control strategy in the continuity of the implementation of an enhanced approach during pharmaceutical development¹⁴. Design space is not mandatory, but encouraged because its implementation can present advantages such as increased process robustness, better knowledge, post-approval regulatory flexibility, production flexibility and increased confidence by regulators.

The definition of a design space is only possible if an enhanced understanding over a wide range of material attributes, processes options and parameters can be demonstrated. This level of knowledge can be collected by means of formal experimental designs, PAT, risk assessment processes and prior knowledge¹⁴. The use of quality risk management approaches during the definition of a design space is fundamental and will contribute to its robustness.²⁵

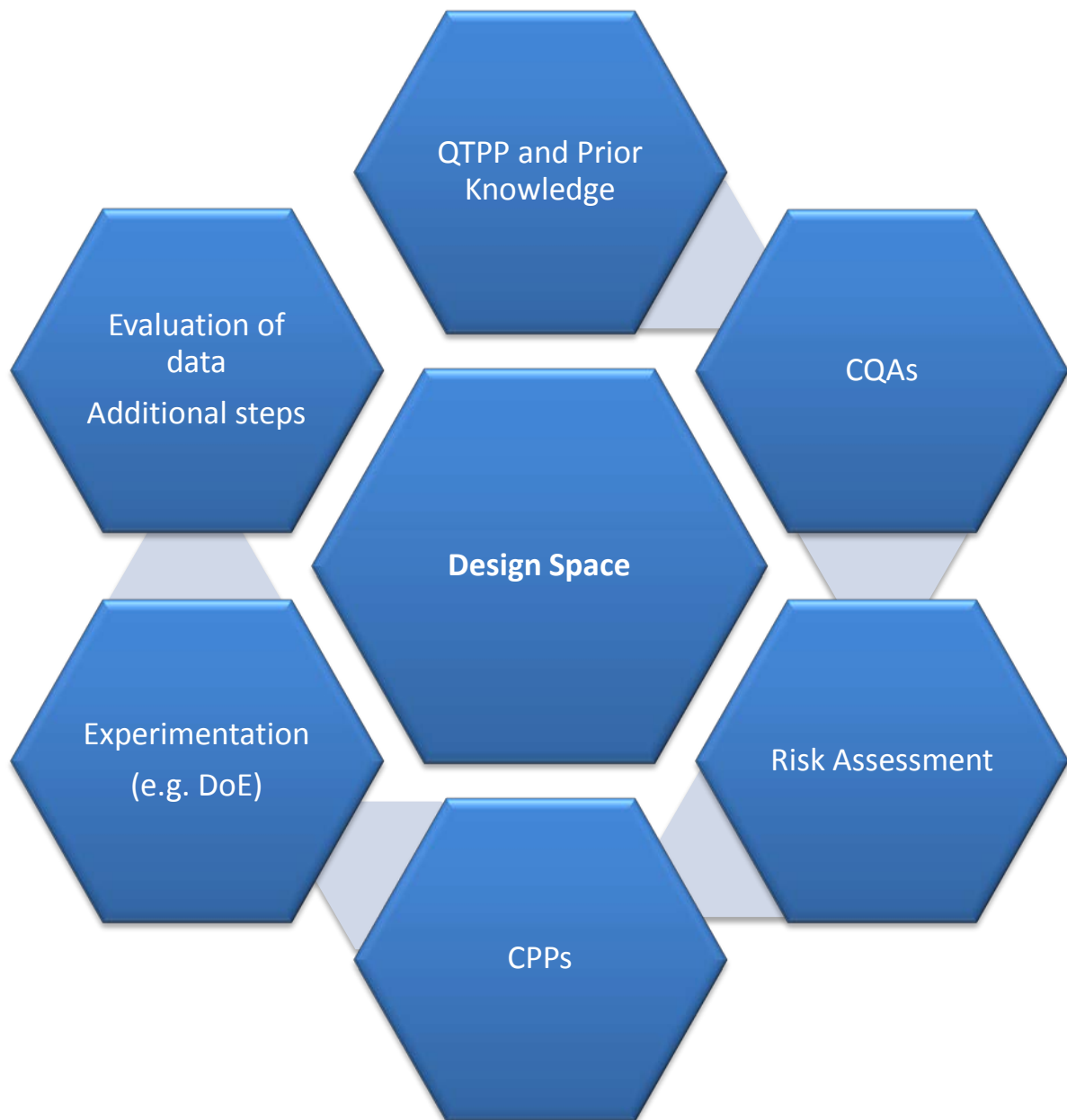
Knowing and understanding how several factors influence CQAs responses is fundamental to build knowledge about product and processes. Ultimately, this knowledge should be in the form of an equation so that it can be of practical use. These equations can be further converted into a design space.¹⁷

Different methods on how and when to implement a design space are possible and can be accepted.²⁵

In order to set a design space, the first stage involves the selection of variables, knowing their relationships and setting boundaries within which consistent quality can be accomplished.¹⁴ The design space is established after appropriate characterisation and is usually an extrapolation of the responses obtained.¹⁷

Design of experiments is commonly used as one of the possible methods to develop a design space.¹⁷

Figure 8 – Steps to achieve a Design space



The proposed design space is subject to regulatory appraisal and acceptance, though there is no regulatory requirement to have a design space. Moving within the established design space will not be considered to be a change, however shifting out of the design space will be considered to be a change and requires a regulatory post approval change process.¹⁴

The regulatory submission must clearly describe and justify the design space, enclose all relevant information about studied attributes and parameters to facilitate its complete understanding by regulatory agencies and inspectors.²⁵

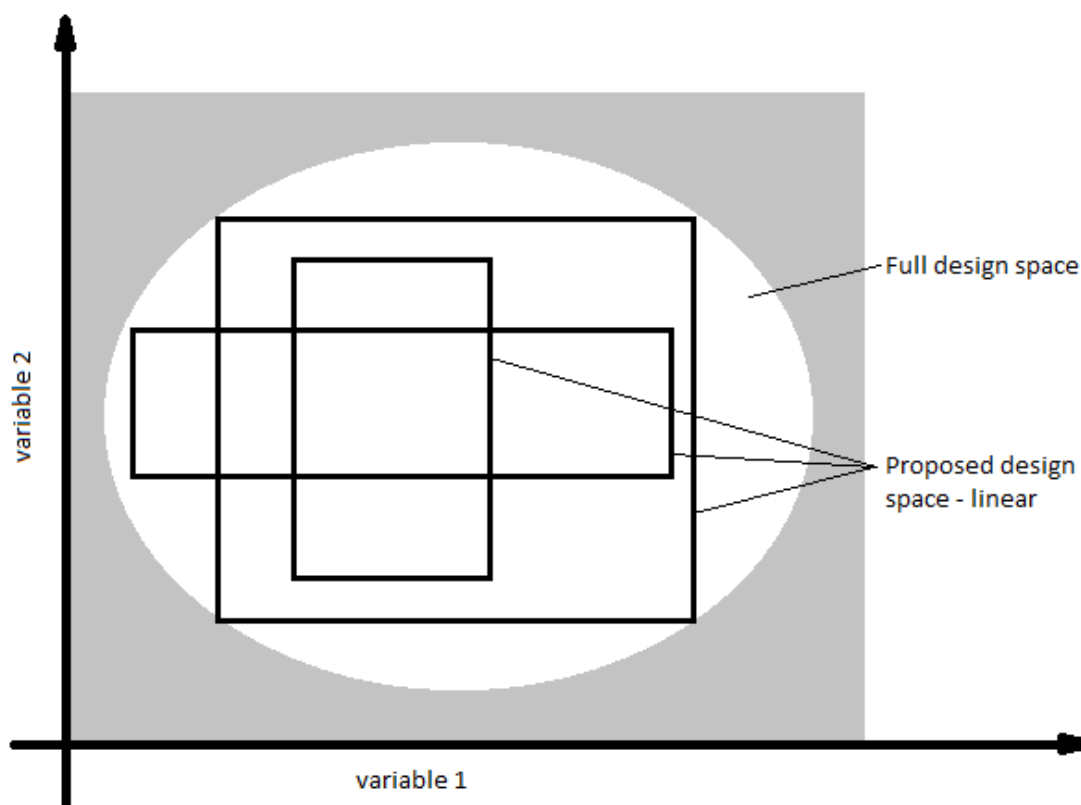
Rationale for including or excluding a variable in the design space should be given, as appropriate, as well as knowledge gained from experiments and studies. Details from design space should be included in the submission. It can be described from the perspective of multivariate ranges to complex mathematical interactions and may be established for single operations or multiple operations.

The wider the design space is in terms of operation coverage, the more complex it will be, however it will grant more flexibility.¹⁴ The design space can be based on different approaches (process ranges, mathematical relationships, or feedback-feed-forward controls to adjust parameters during manufacturing).¹⁹ The model of the design space, as a mathematical expression, can be represented graphically. Two-dimensional curve graphs or three-dimensional surface graphs are common and practical representations of the design space.¹⁷

The use of a design space requires understanding of parameters and attributes interactions. The demonstration of a single acceptable range is not considered a design space.²⁵ Despite the fact that the determination of a variable acceptable range and the determination of the edge of failure of a parameter or material attribute can be a useful knowledge source, these are not crucial for setting a design space.¹⁴ The proven acceptable range for one CQA only ensures it is met when all the other factors are not varied. On the other hand, the design space represents all combinations of factors values for which the CQAs meet acceptable range.

The edges of the full design space may or not be fully known. It may be more practical to propose a design space using a linear representation instead of the full design space. Furthermore, operating near the edges of failure of the design space can increase the risk of excursions outside the proven acceptable space, due to normal process variation.¹⁹ Design space is an extrapolated response surface model based on limited experimentation. Moving to unexplored areas of the design space carries risk.¹⁷ For this reason it might be appropriate to keep a safe margin when proposing a design space.

Figure 9 – Graphical representation of a design space



To ensure greater reliability of the process, further computational analysis may be applied. Diverse computational methods are available for analysis of process reliability, which require specialized statistical software solutions.²⁸

The design space can also provide flexibility in relation to scale and equipment. In this case it must be shown that the developed design space is valid for different scales, using relevant scale-independent parameters.¹⁴ It can also be generated for each process unit operation or across different unit operations.¹⁷

The design space and process models must be verified, confirmed and maintained at commercial scale, however it is not necessary to develop the design space at production scale.²⁵ Verification runs at scale allow comparing values to the model and ensuring its predictive capability.¹⁷

As a dynamic concept, design space should be reviewed periodically within a company's PQS. Risk management and increased knowledge collected during routine manufacturing activities and events such as failures and investigations should be used to reassess and improve the design space.²⁹

For legacy products, a design space can be developed using multivariate models to evaluate historical data. In this particular case, the design space will be dependent on the level of variability existing in the historical data. As a result, further studies may be necessary to refine the design space proposed.¹⁹

Ultimately, the design space proposed from materials, product and process characterisation studies is the result of the system design, selection of all materials, concentrations, equipment, process parameters and tolerances. Design space represents the level of process knowledge and understanding and its robustness is strictly dependent on the level of science and data that supported its generation. It must account for the inherent variability of different factors (raw materials, facilities, equipment, utilities and processing conditions) present during manufacturing operations, which can influence the product.²⁹

The documentation to be included in the submission will depend on the complexity and objective of the design space. A preliminary discussion with regulators is advised to fine-tune the development and submission logic as necessary.

The usage of the design space concept is introduced by the new ICH guidelines and is encouraged as it contributes to building up knowledge, reduce risk and post-approval regulatory activities.

5.5.10. Continuous process verification

The validation of the manufacturing process can also be achieved through continuous monitoring and evaluation, in replacement of the traditional approach.¹⁴ Continuous process verification provides the basis to ensure that the process is under control and that any deviation is detected and proactively addressed.¹⁸ It also constitutes a source for increased knowledge about the product and the process which may be used for taking improvement decisions.

5.5.11. Product lifecycle management and continual improvement

The development phase is not limited to the initial submission. The ICH Q8 guideline strongly underlines the continuous process of knowledge build-up, meaning that the

development section is not static and must be updated as more data is generated during commercial production. During product lifecycle, companies are encouraged to systematically monitor their manufacturing process and all aspects related to the product until its discontinuation. This monitoring can make use of statistical tools. It can serve to confirm that the process is delivering product meeting the anticipated quality level or to confirm design space mathematical models. The resulting increased understanding can be the basis for continual improvement through risk reassessment, modifications to control strategy, materials, manufacturing processes or redefinition of design space.¹⁴

It should be noted that development stage presents limitations. The models of the process that are constructed during development are intended to represent the process in the most efficient way, however, it depends only on risk analysis, prior knowledge, scientific principles and limited experimental data. It is not possible to experimentally evaluate all possible parameters and interactions. Only after commercial manufacturing of a significant number of batches, it is possible to provide confidence in the control strategy and explore a wider range of raw material and process variability.²⁸

The relationships between CPPs and CQAs should be refined as more data is collected from more batches. Commercial manufacturing is subjected to variability in all process parameters and not only on those considered critical during development and extensively studied. For this reason, higher potential for interactions is also expected during commercial manufacture.²⁸

Variability is detected and controlled using tools such as PAT and risk mitigation. The outcome is increased product and process understanding which leads to opportunities to implement effective improvements.²⁹

5.5.12. Real-time release testing

Real-time release testing is introduced in the ICH Q8 guideline as an element of the control strategy. It is derived from a high level understanding of product behaviour over the variability of material attributes and process parameters. Design space, modern technology and new control concepts as PAT are fundamental enablers of RTRT, which is based on extensive on-line or in-line measurements. With its application, there is an increased assurance of product quality and the product can be released based in real-time quality

control, in substitution of end-product release testing¹⁴, providing an opportunity for enhanced flexibility and efficiency.

Regulators point out that the RTRT is facilitated by an intense control of the single unit operations that lead to the final product. Despite RTRT is encouraged by regulators and convenient for industry, only a small number of companies so far have been successful at implementing it at commercial scale.³⁰

5.5.13. Flexible regulatory approaches

The level of regulatory flexibility is closely linked to the relevance of the knowledge collected during the development phase and presented in the submission. One of the major advantages from applying an enhanced approach to pharmaceutical development is that more information becomes available allowing the understanding of the impact of the materials and process variables in the quality of the drug product. The establishment of a design space is an enhancer of regulatory flexibility (e.g. moving within the established design space is not classified as a regulatory change¹⁴), an aspect from which companies can benefit from.

5.6. Content of the application dossier

The type and level of information to be presented in the application dossier must be compatible and support the chosen development approach.¹⁹

In general, the application must contain adequate and well organized information, to promote a facilitated assessment by the regulators. Reasonable information should be provided to support the rationale behind the studies performed and the proposed control strategy. A description of the studies and data evaluation methodologies, as well as results and conclusions must be included.¹⁹ Therefore, the dossier should contain information that can ensure to both company and regulator that decisions and conclusions are scientific and risk based, including risk management methodologies used during definition of QTTP, CQAs, CPPs, control strategy and experiments.¹⁹ In addition, information related to DoE must be sufficient and clear. Inclusion of full statistical data is not expected, but at least a summary of the followed rationale, methodology, factors, ranges and conclusions drawn should be presented in the dossier.¹⁹

6. Quality Risk Management Q9

6.1. History

The ICH reached a consensus vision in July 2003 that envisaged the development of a pharmaceutical quality system covering the entire product lifecycle and supported by two main pillars: scientific knowledge and risk management.³¹

On 11 November 2003 the final concept paper and business plan for a new guideline on quality risk management were endorsed and published.

The concept paper identified the need to³¹:

- provide terminology, definitions and principles of risk management;
- guidance on the application and operationalization of risk management and its linkage to decision-making;
- clarify the roles and responsibilities of industry and regulators;
- define communication channels and what information should be shared between industry and regulators;
- show how risk management can be used to prioritise allocation of resources;
- establish the association between risk management, pharmaceutical development and product lifecycle.

ICH members as well as its observers shared the common belief that such harmonized guideline could improve many quality aspects, providing a systematic, science based methodology to support decision making that ultimately would benefit the patients.³¹ Additionally, it was necessary to integrate risk management into the pharmaceutical quality system.³²

The ICH Quality Risk Management guideline (Q9) was approved under Step 2 by the SC and released for public consultation on March 2005. On June 2005, after a post Step 2 correction, it was republished for consultation. The guideline was finally approved (Step 4) and recommended by the Steering Committee for adoption to the ICH regulatory bodies on November 2005³³:

- EMA: Issued as EXT/24235/2006 on January 2006, with an explanatory note. On March 2008 it was included within the GMP Guide as Annex 20. Later it was relocated into Part III of the EU GMP guide.

- MHLW: Adopted on September 2006 (PFSB/ELD Notification N° 0901004).
- FDA: Adopted on June 2006. Published in the Federal Register, Vol. 71, No 106, June 2, 2006.

6.2. Objective

The inexistent application or misuse of risk management techniques by the pharmaceutical industry can be a cause for many undesired consequences: product unavailability, delays in marketing introduction, delays in the implementation of changes, release of noncompliant product to the market, unnecessary recalls, unnecessary product destruction, waste of resources, restriction of improvements to products and processes, and inadequate information to support risk-based decisions.³¹

Quality risk management can be useful to provide further assurance of product and process understanding and therefore, to ensure quality of the marketed products.²⁵

Although companies and regulators had already put in practice risk management methodologies, it was necessary to provide harmonized guidance on how they should apply its principles to quality of pharmaceutical products, interpret the results and use them to sustain quality decision-making. It was also essential to underline the added value that risk management brings to product lifecycle management and GMP processes and integrate it with the rest of the quality system. Risk management was not a new concept as there were programs already in place in other industries and agencies which could serve as a reference for the construction of the new ICH Q9 guideline.³¹

The guideline should be seen as an independent resource document that complements and articulates with other quality guidances. It does not pretend to set up any new expectations than the ones predicted by the existing regulatory requirements.³³

The availability of this guideline could hence enable the correct and systematic application of risk management allowing companies and regulators to take advantage of the full capabilities of this concept. It is also recognized the relevance of quality systems and that risk management is a key component for achieving a successful quality system.³³

The guideline addresses the risk related to quality of a drug product, which is only one part of the global risk.³³

6.3. Scope

The scope of the ICH Q9 guideline focuses on the application of quality risk management principles and tools to several points of the pharmaceutical process. It addresses the application of risk management to drug substances, drug products, biological and biotechnological products, including raw materials, packaging and labelling materials used in such products.³³

It also comprises the use of risk management in different phases of drug substance and drug product lifecycle, namely development, manufacturing, distribution, inspection and reviews.³³

Applying a formal risk management process may not be necessary or appropriate on every occasion. In certain cases empirical risk assessment may be acceptable.³³

Despite the benefits from the employment of risk management, companies still must at all times comply with regulatory requirements and communicate appropriately with its regulators.³³

6.4. Structure

The ICH Q9 guideline is composed of the core guideline that describes concepts, principles, methodologies and the integration with other activities and two annexes which delineate methods, tools and its applications.³³

Table 5 – Q9 structure

ICH Q9 Quality Risk Management	
Introduction	
Scope	
Principles of quality risk management	
General quality risk management process	Responsibilities
	Initiating a quality risk management process
	Risk assessment
	Risk control
	Risk communication
	Risk review
Risk management methodology	
Integration of quality risk management into industry and regulatory operations	
Definitions	
References	
Annex I: Risk management methods and tools	Basic risk management facilitation methods
	Failure mode effects analysis (FMEA)
	Failure mode, effects and criticality analysis (FMECA)
	Fault tree analysis (FTA)
	Hazard analysis and critical control points (HACCP)
	Hazard operability analysis (HAZOP)
	Preliminary hazard analysis (PHA)
	Risk ranking and filtering
	Supporting statistical tools
Annex II: Potential applications for	Quality risk management as part of integrated quality management
	Quality risk management as part of regulatory operations
	Quality risk management as part of development

ICH Q9 Quality Risk Management

quality risk	Quality risk management for facilities, equipment and utilities
management	Quality risk management as part of materials management
	Quality risk management as part of production
	Quality risk management as part of laboratory control and stability studies
	Quality risk management as part of packaging and labelling

6.5. Principles and Concepts

6.5.1. Risk

It is described as the combination of the probability of an adverse occurrence and its severity. In some cases, detectability is also considered for the risk characterisation.³³

6.5.2. Quality risk management

Risk management is a well-defined process that when performed correctly allows to identify and understand risks and consequently provides consistent information for taking quality decisions. It involves the systematic assessment, control, communication and review of the quality related risks during the entire product lifecycle.³³

The essence of quality risk management is scientific knowledge and the safeguard of the patient.

Figure 10 – Application of quality risk management during the product lifecycle



Not all single detail of the product can be studied during development or commercial manufacturing. Risk management provides the basis to prioritise and allocate resources according to the potential risks.³⁴

The dedicated work, rigour and associated documentation must be proportionate to the risk grade.³³

Quality risk management is essential for decision making processes either during development, technology transfer, commercial manufacturing, post approval change, lifecycle management and product discontinuation. It should not be a one-time effort, but a repetitive process, because risks must be constantly reviewed. Risk control contributes to a greater assurance of quality.²⁵

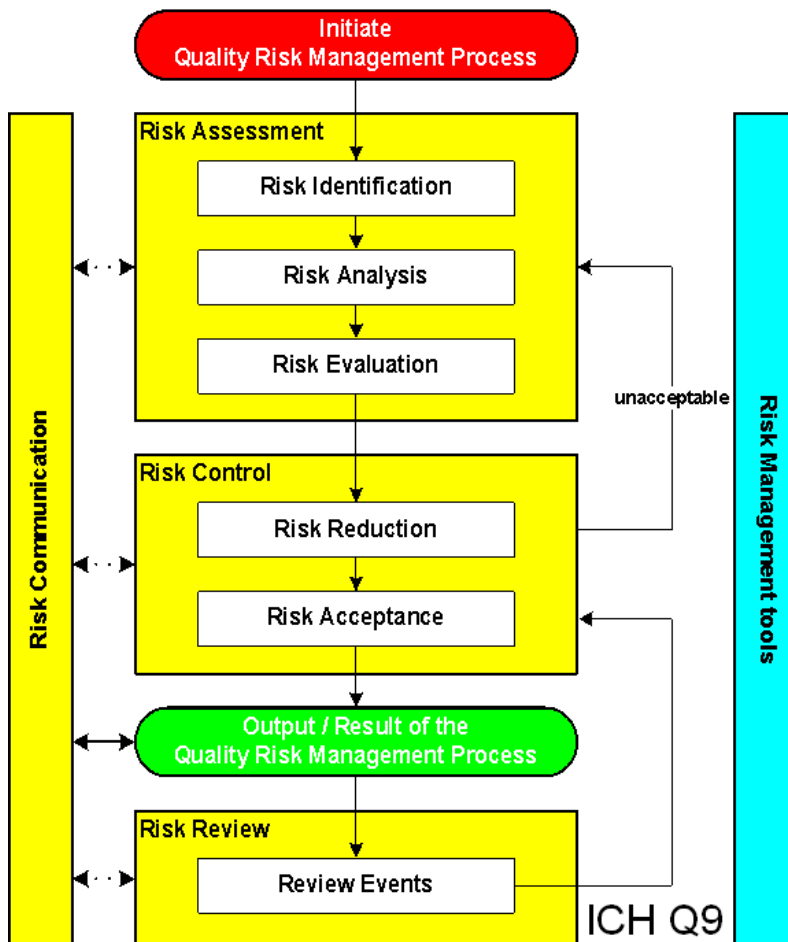
QRM is not an excuse to doing things with insufficient time and resources, to avoid doing things the right way, or deciding what to do depending on what might be under the focus of inspections. It neither serves as an excuse to being out of compliance with the regulations.³⁵

The higher the focus on scientific principles, experiments, prior knowledge, and experience, the better the science brought into the quality risk management process.

6.5.3. Quality risk management models

The ICH Q9 provides an example of a general model that can be used, but other models can be used if adequate.

Figure 11 – Quality risk management model (ICH Q9)



The devotement to each phase of this model and the level of depth may vary and should be consistent with the associated risks. Decisions can be taken at any level and decisions may originate a move to a preceding stage, an adjustment to the model or the ending of the process, depending on the information at disposal.³³

6.5.4. Risk management teams

The task of performing risk management activities usually implies the summoning of a team of experts from different areas. Ensuring the right people are involved will result in reduced subjectivity. The selection of the team members is closely linked to the nature of

the process under evaluation. Notwithstanding, the team is always composed of a member who is acquainted with the risk management process. Members responsible and empowered to take decisions should coordinate the process across the different functions and departments within the organization and guarantee that all necessary resources are assigned and that the risk management process is outlined, set up and reviewed accordingly.³³

6.5.5. Risk management process

The general process of risk management involves a series of steps. The beginning of this process is characterised by the definition of the problem or eventual risk. Any presumptions that may be relevant for the initiation of the process are also considered at this stage.³³

A leader is named and the necessary resources must be allocated. Additionally, a timeline is set and a delineation of the desired outputs and level of decision making is performed.³³

Pertinent data and circumstantial information related to the potential risk are gathered for the risk management activities.³³

6.5.6. Risk assessment

The risk assessment purpose is to identify hazards and assess the risks associated to those hazards. It starts with a specific problem or risk issue. If the issue in question is well characterised, the identification of an adequate tool and the necessary set of information is more promptly achieved.³³

The identification and characterisation of the risk is, as discussed above, a fundamental step to initiate the risk assessment. Three questions can usually aid when defining the risk.³³

- What can go wrong?
- What is the probability that it goes wrong?
- What would be the severity of its consequences?

Risk assessment is generally conducted by a team that goes through the product or process step-by-step to identify, analyse and evaluate each potential risk. Outcome of the assessment should be a list of prioritized risks and a rationale whether they are either considered acceptable or requiring action.

Risk identification, as a component of risk assessment, is the methodical use of information to identify sources of failure, related to the risk or problem in question, and forms the basis for subsequent steps. This stage comprehends the use of historical data, theoretical analysis, informed opinions and stakeholder's interest, with the aim to find possible sources of risk and respective consequences.³³

Risk analysis is the next step where the objective is to rate the risk by linking probability and severity. In some cases an additional factor – detectability – may be considered.³³

The third step consists in the evaluation of the risk. A comparison against criteria is performed and the level of evidence obtained is analysed.³³

The quality and validity of the data used for the risk assessment will impact the quality of the outcome. The correct use of suppositions and adequate definition of sources of uncertainty will potentiate the output. Uncertainty can derive from gaps of knowledge, process understanding or science, sources of hazard and detectability of problems.³³

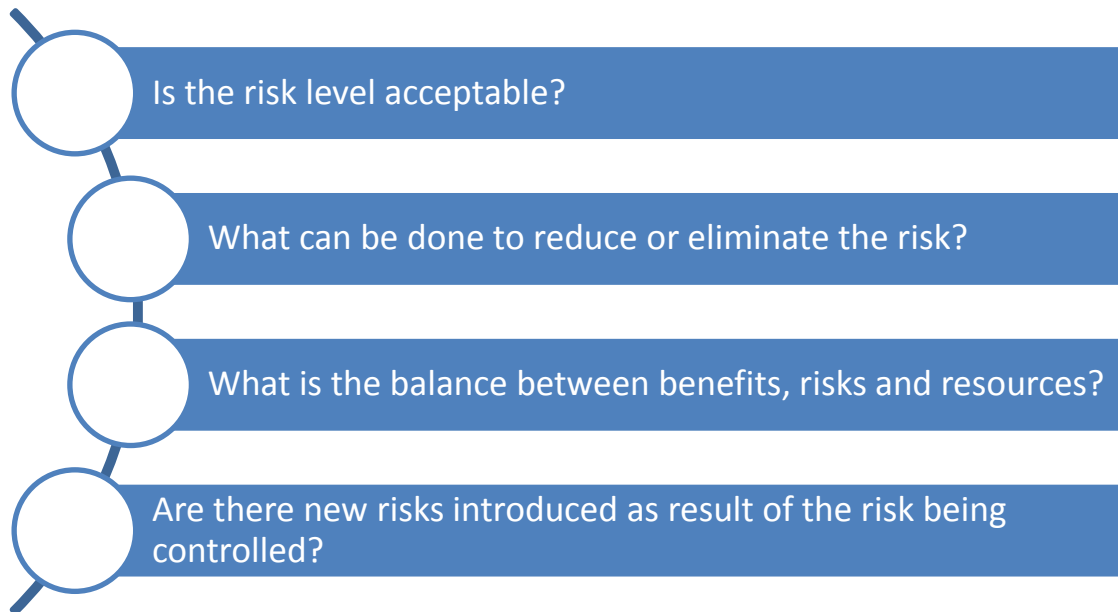
The result may be a quantitative rate, when expressed numerically, or a qualitative rate if given as a descriptive category (e.g. “no risk”, “low risk”, “medium risk” or “high risk”). These categories may sometimes be determined by the use of a “risk score”.

Quantitative risk rating provides the probability for the occurrence of an event under specific circumstances and thus can be applied to a given consequence one-by-one. Sometimes, in order to perform an estimation of the overall relative risk, a combination of multiple severity and probability analysis is carried out, using “risk score” in the process or a quantitative rating.³³

6.5.7. Risk control

Control of risks involves taking decision to minimize and/or tolerate the risk. The aim of risk control is to minimize the risk to tolerable levels. The dedication to this activity should be proportionate to the particular risk rating and focus mainly on the answers to four questions.³³

Figure 12 – Risk control – 4 essential questions³³



Decision-making process during this stage is usually supported by the evaluation of the benefit-cost correlation of control measures.³³

6.5.8. Risk reduction

If a risk is above an acceptable level, then action must be taken to reduce such risk. The reduction of the risk may be achieved through minimization of severity and probability or through enhancement of its detectability. The implementation of any measure may impact other identified risks or introduce new ones, therefore the overall risk assessment must be revised accordingly.³³

6.5.9. Risk acceptance

Risk acceptance consists in decision to accept risk. It can be a formal decision where the stated risk is accepted or a passive decision if the risk is not stated.³³

In specific cases, the risk is not possible to eliminate even when implementing the most adequate measures. Consequently it can be considered that an appropriate strategy was applied and that the risk was mitigated to an acceptable level. This approach depends on many factors and is applied case-by-case.³³

A scientific rationale to why a risk is considered acceptable must always be provided.

6.5.10. Risk communication

Information about existing risks and its management should be documented and provided to all interested parties, especially to action owners, at any stage, including its results. Interested parties may include people or departments within the company, regulators and patients.³³

The content of this communication can cover any aspect of the risk management activities towards quality. Communication with authorities pertaining quality decisions might be performed as preconized by regulations and guidances.³³

6.5.11. Risk review

Risk management should be a continuous process, as part of quality management, therefore a procedure should exist to review and supervise activities.³³

Revision of the risk management process outputs should be made as new knowledge and experience is gained. The risk management process should be revised whenever a change occur, planned or unplanned, namely changes originated by change controls or failure investigations. Frequency of risk reviews is dependent on the level of risk and may result in the reassessment of previous decisions.³³

Effective documentation of all risk management activities is necessary.

6.5.12. Methodologies and tools

Different methodologies and tools may be used to perform risk management activities. The objective is to provide a documented, systematic and reproducible means to assess the probability, severity and detectability of undesirable events.³³

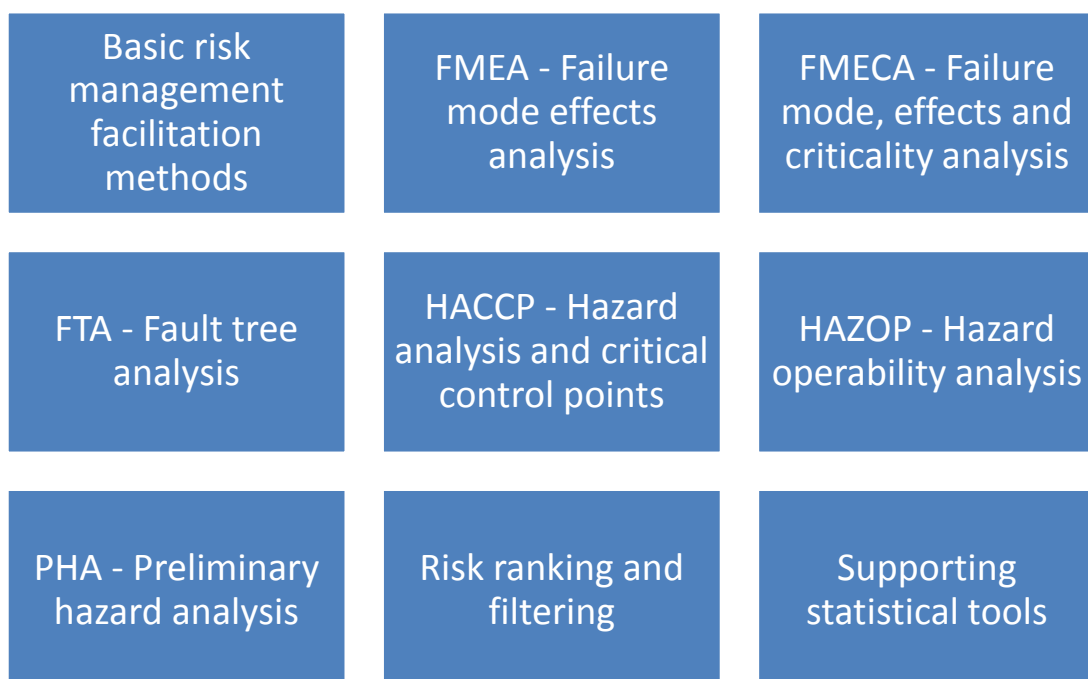
Despite the usefulness of older existing methodologies to informally assess and manage risks, there are now more systematic and recognized tools for formal risk management at the disposition of pharmaceutical industry and regulators.³³

Quality risk management tools are primarily used in risk identification, risk analysis, risk evaluation and risk control.

The tools can include two types: risk assessment and control tools, and statistical and analytical tools. The former relate to risk identification, control and communication and the latter relate to variation analysis, identification of risk areas, and determination of probability or frequency of risks.

The tools are extremely useful over the lifecycle of the product and ultimately contribute to the decision-making processes within the many PQS activities. The most used tools within PQS common activities are FMEA and Cause and Effect Diagrams.²⁹

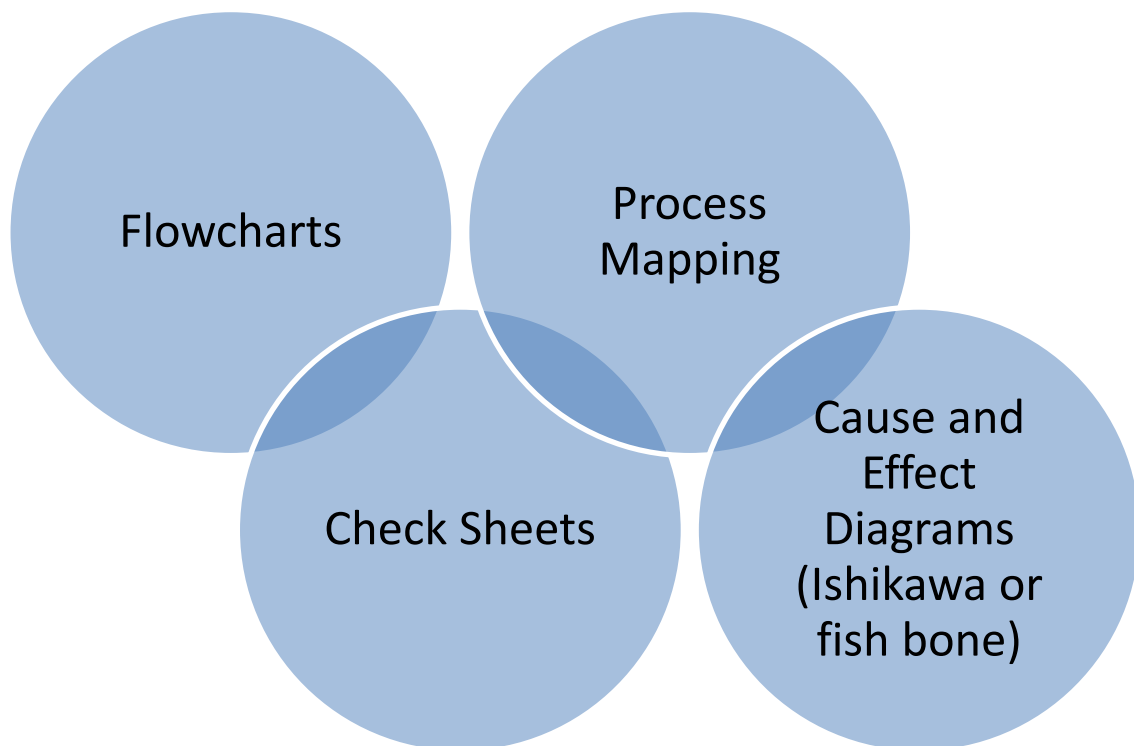
Figure 13 – Quality risk management tools³³



6.5.12.1. *Basic risk management facilitation methods*

Set of simple and common techniques used to gather, structure and organize data and facilitate decision-making. Usually used to scope and evaluate the fault modes of a specific process, can be used to feed other advanced tools. Combination of different tools can provide a powerful methodology for risk assessment.

Figure 14 – Basic risk management facilitation methods



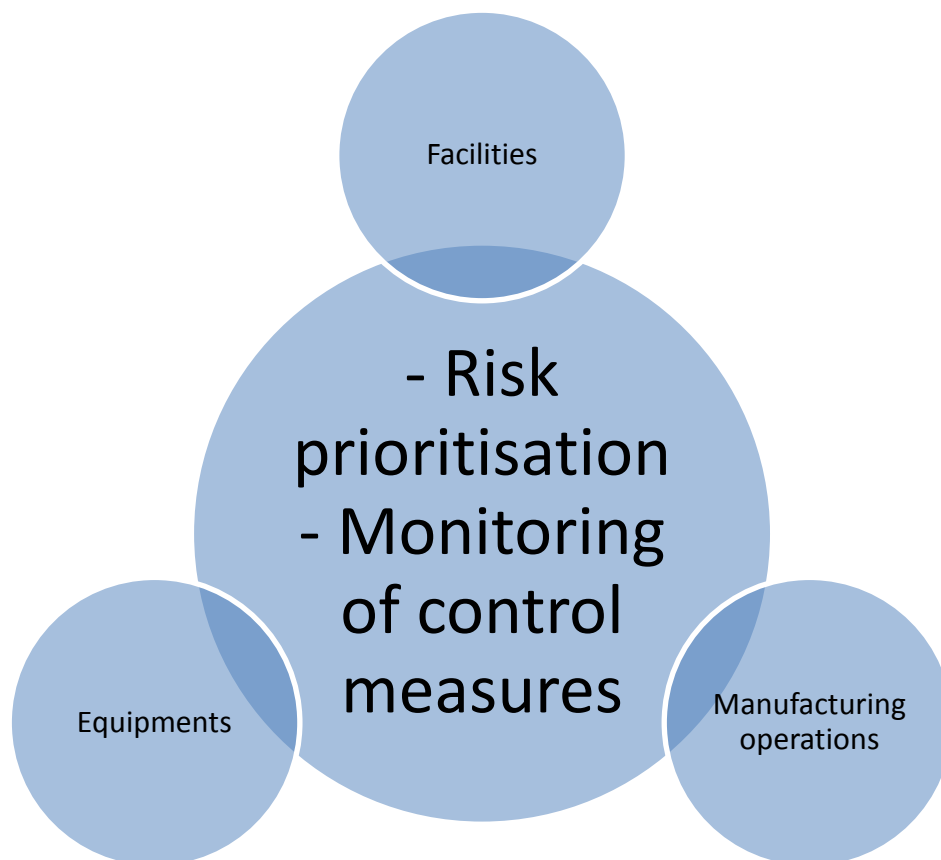
6.5.12.2. FMEA – Failure Mode Effects Analysis

FMEA is the risk-evaluation method most widely used across risk-intensive industries.

This tool addresses the potential failure modes of a process and its effect on outcomes and/or product. After establishing failure modes, risk reduction is used to minimize, control or eliminate them. The use of this tool is supported by product and process understanding. FMEA allows the analysis of complex processes by breaking it down to simple steps. FMEA is a useful and robust tool for identifying important potential failures, its causes and possible effects.³³

Due to its flexibility, it is a tool that can be adapted according to the specific procedure needs.

Figure 15 – Application of FMEA



The results of this tool may be useful for further risk management activities.

6.5.12.3. FMECA – Failure Mode, Effects and Criticality Analysis

This tool consists in an extension of FMEA to include the analysis of effects severity, probability and detectability. The use of this tool implies that process or product specifications are already defined and permits the identification of cases where preventive action is necessary to further reduce risks.³³

Figure 16 – Application of FMECA

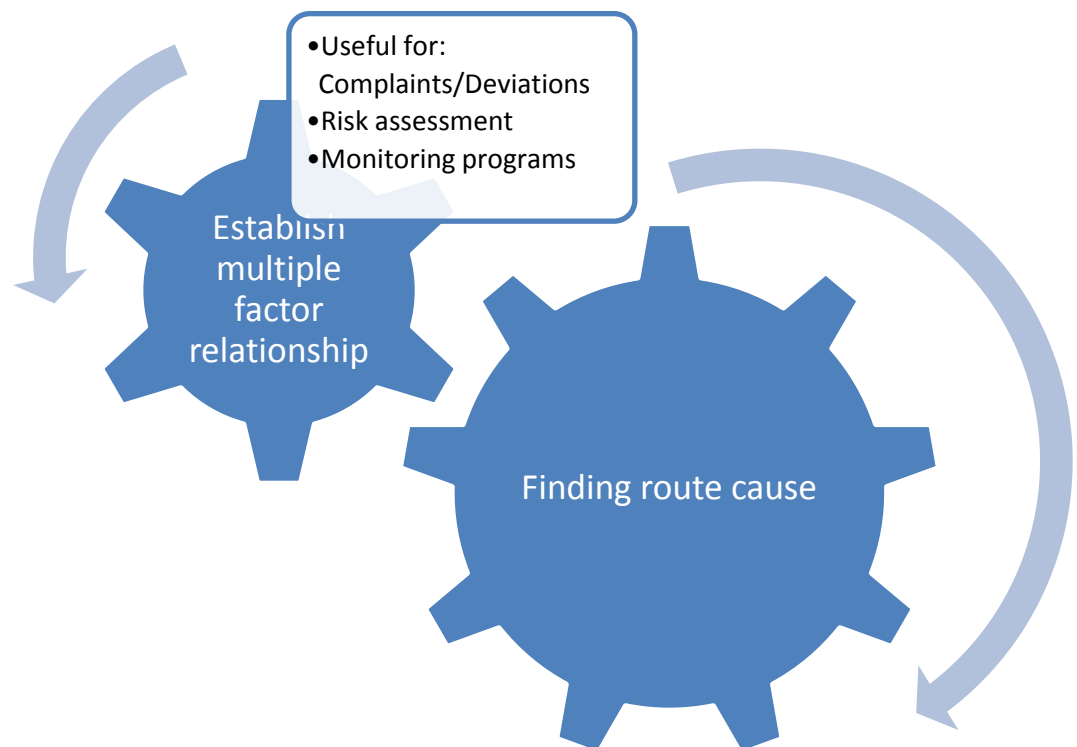


6.5.12.4. FTA – Fault Tree Analysis

This tool principle is based on the assumption of failure of the functionality of products or processes. It addresses one failure at a time but evaluates its multiple possible causes and therefore it is useful to establish causal chains. FTA requires a deep understanding of product and/or process.³³

Visually it is represented as a tree scheme of failure scenarios and uses logical operators to describe relations between them.³³

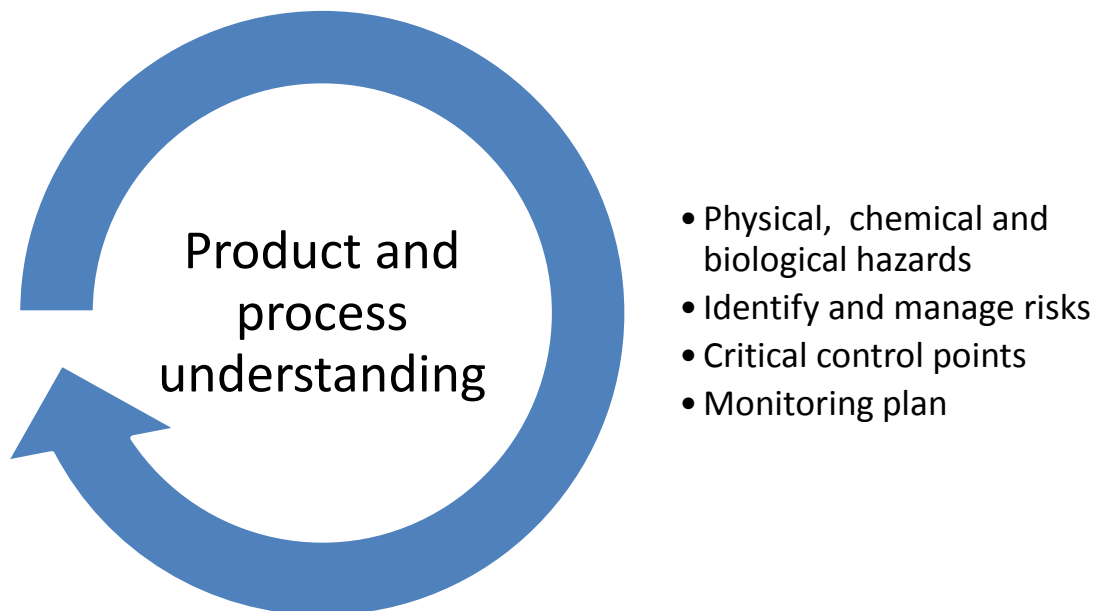
Figure 17 – Application of FTA



6.5.12.5. HACCP – Hazard Analysis and Critical Control Points

HACCP is a systematic approach for the prevention of hazards that may affect product quality and safety. This tool is based on seven principles and provides the basis to analyse and evaluate the risks; establish prevention measures and control points; set a monitoring plan and define corrective actions; and finally perform system verification, reviewing and data recording.³³

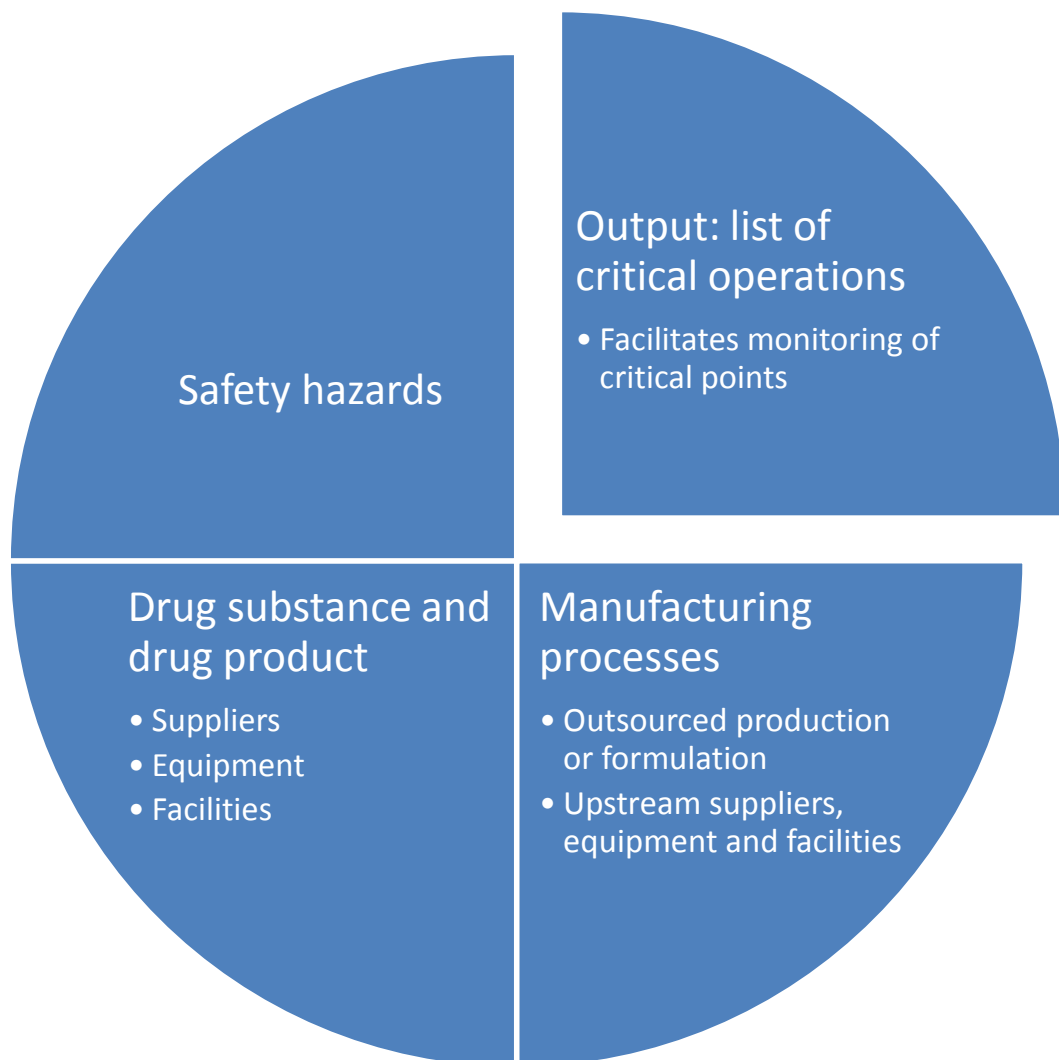
Figure 18 – Application of HACCP



6.5.12.6. HAZOP – Hazard Operability Analysis

HAZOP is a methodology to identify hazards caused by deviations to relevant design or operational parameters. It uses “guide-words” to approach different scenarios (e.g. Less than, More than, No) and evaluate its possible effects. The use of this tool requires adequate product or process related expertise.³³

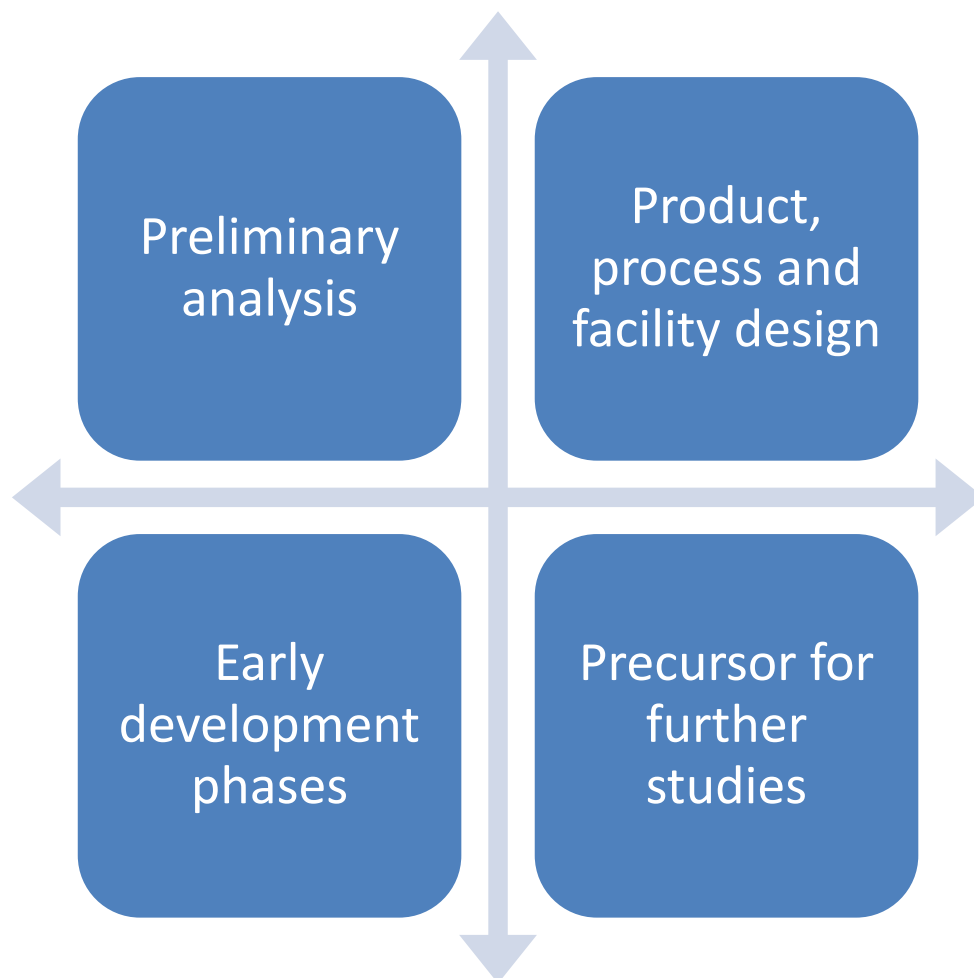
Figure 19 – Application of HAZOP



6.5.12.7. PHA – Preliminary Hazard Analysis

PHA is a tool to analyse potential hazards caused by a given hazards or failures. It is primarily used for events which may lead to an accident. It involves several activities such as identification of the potential hazards that may cause harm, ranking of the identified risks according to severity and probability and definition of controls and measures.³³

Figure 20 – Application of PHA



6.5.12.8. Risk Ranking and Filtering

Risk ranking and filtering is a useful tool for ranking and prioritise risks. Its methodology is based on the qualitative and quantitative scrutiny of each risk factor in order to find relevant components. A risk score is set to each individual risk which allows its ranking. Filtering involves reducing or increasing control of the risks according to the given score and management criteria.³³

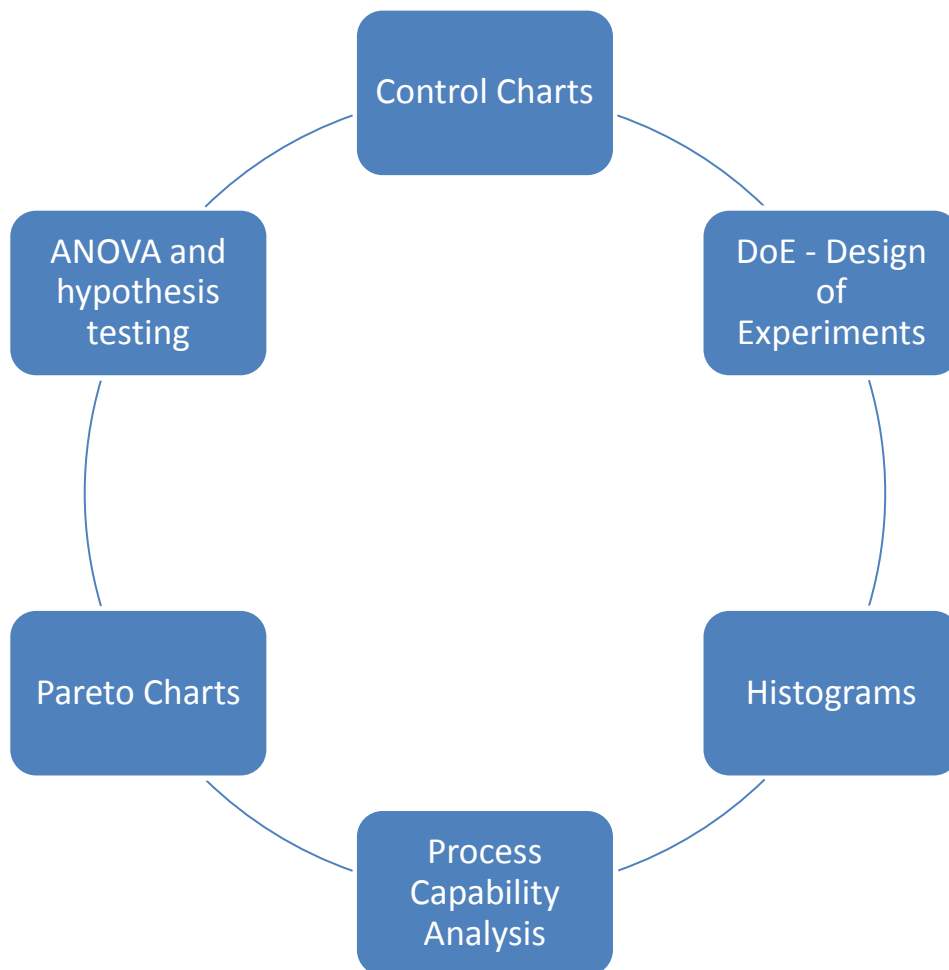
Figure 21 – Application of Risk Ranking and Filtering



6.5.12.9. Supporting Statistical Tools

A variety of statistical tools is available to assist risk management activities, namely by supporting assessment and confirming significance of data. The use of statistical tools also eases decision making.³³

Figure 22 – Supporting statistical tools



Adaptation of these tools to specific areas may be appropriate, on certain cases.

The use of statistical tools in conjunction with risk management methods can be advantageous as it may provide versatility and facilitate implementation of risk management concepts. Once again, the level of formality and effort dedicated to risk management should be commensurate with existing knowledge, complexity and criticality of the risk in question.³³

6.5.13. Quality risk management in industry and regulatory operations

Appropriate quality risk management, when incorporated in quality systems, will support science-based and informed decisions, however it does not dismisses industries from their duty to follow all regulatory obligations. Nevertheless, the implemented risk management systems that substantiate these informed decisions can provide assurance to regulators about a company's preparedness to deal with risks and may lead to a reduction of regulators supervision activities. Ultimately, efficient quality risk management provide the basis to an improved use of resources by all stakeholders.³³

Amongst other advantages, adequate implementation of risk management originates greater understanding of product and processes, facilitates decision-making steps and improves confidence in the results. To achieve this, quality risk management must be integrated into current operations, and be properly documented.³³

Quality risk management must be taken seriously by drug product manufacturers. Management commitment and involvement is essential to³⁶:

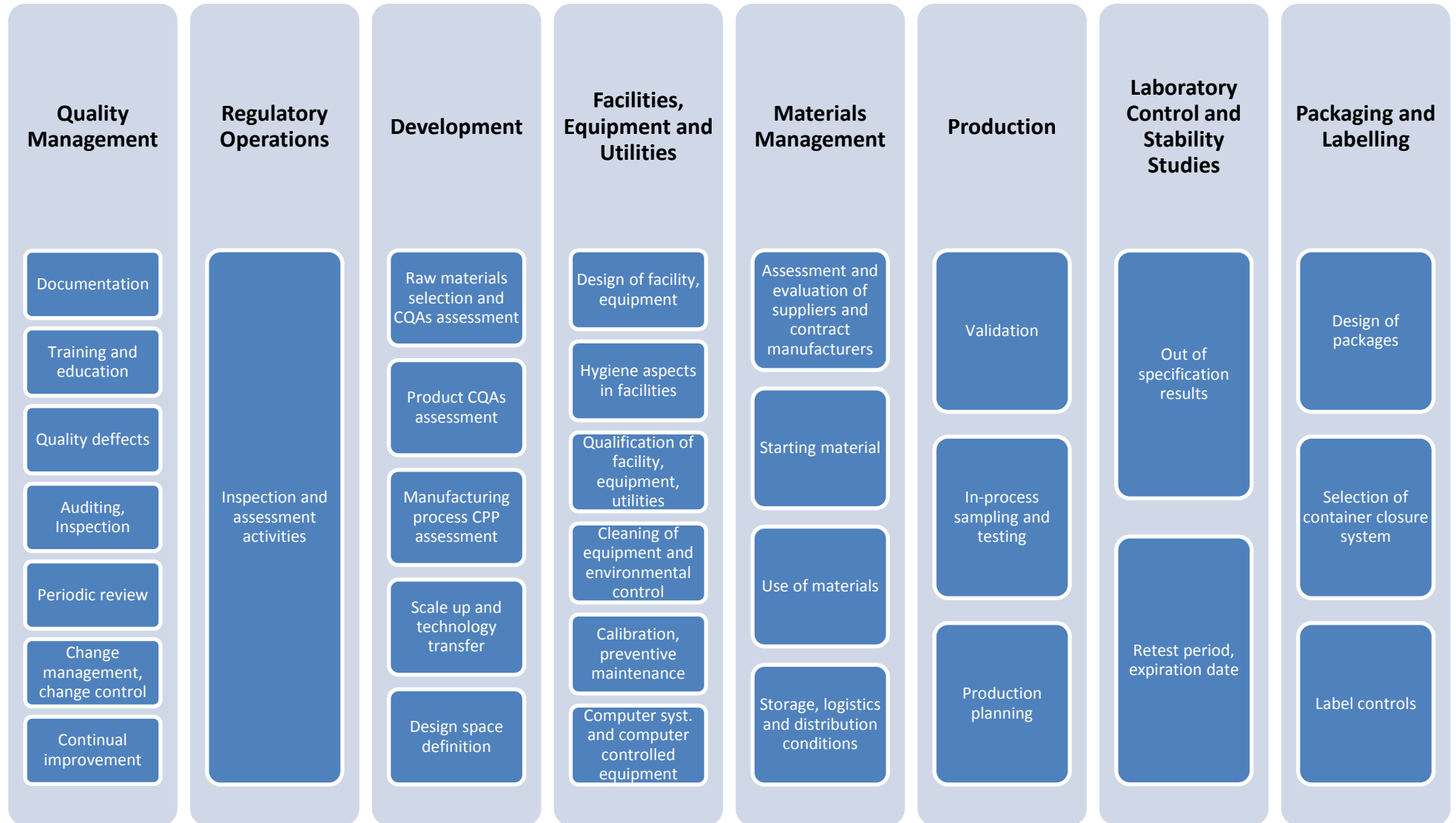
- set out QRM plans, teams, trainings, tools, procedures;
- clarify roles and responsibilities;
- formally monitor results and review progresses

Risk management is a systematic, scientific and data-driven approach which provides the opportunity to prioritize (risk ranking), improve decision making, build in quality and improve communication.³⁵

The mutual understanding and use of risk management concepts can promote confidence and coherent decisions among different regions and regulators.³³

Potential applications of Quality Risk Management include, but are not limited to:

Figure 23 - Potential applications of Quality Risk Management³³



7. Pharmaceutical Quality System Q10

7.1. History

Following the consensus vision reached in July 2003 that envisaged the development of a pharmaceutical quality system, the ICH Steering Committee endorsed the final concept paper of the Q10 Pharmaceutical Quality Systems guideline on 10 November 2005. This paper highlighted the importance of developing a guideline to provide a harmonized view of modern quality systems and thus guarantee quality and continuous improvement over the lifecycle of a drug product.³⁷

The Q10 guideline would use concepts from existing quality systems related documents such as ISO standards (ISO 9000; ISO 9001:2000; ISO 9004; ISO 13485:2003) and GMP guidances, help implementing ICH Q8 and Q9 guidelines and serve as a connection between different regions.³⁷

The ICH Pharmaceutical Quality Systems guideline (Q10) was approved under Step 2 by the SC and released for public consultation on May 2007. Approval (Step 4) and recommendation by the Steering Committee for adoption to the ICH regulatory bodies took place in June 2008³⁸:

- EMA: Adopted as CHMP/ICH/214732/07 on July 2008, and later superseded by EMA/INS/GMP/79818/2011 as part of EU GMP Guide Part III.
- MHLW: Adopted on February 2010 (PFSB/NCD Notification No. 0219-1).
- FDA: Adopted on April 2009. Published in the Federal Register, Vol. 74, No. 66, p. 15990-1.

7.2. Objective

The existence of different interpretation of quality systems, its principles, applications and expectations between industries and regulators, especially concerning new concepts as quality by design or risk management, created the need of a guideline to harmonize practices amongst the interested parties and provide the basis for more effective processes. In parallel, other benefits that would arise from such guideline would not only relate to the potential of quality by design and risk management implementation but also³⁷:

- strengthening the role of GMPs;
- improving quality by minimizing variability;
- promoting more robust processes;
- enabling continual improvement;
- linking development to commercial manufacturing;
- encouraging knowledge and science based decisions;
- promote preventive culture

The new guideline could be seen as an attempt to avoid future unwanted situations where divergent approaches to quality systems (inappropriate leverage of available resources, product unavailability for patients, lack of coordination between the three regions in terms of expectations during conduction of inspections, implementation of innovation and continual improvement or even obstacles to quality by design and continual improvement) could exist. Therefore, issues to be solved included definition of: concepts; quality management systems; product realisation; and measurement, analysis and improvement.³⁷

7.3. Scope

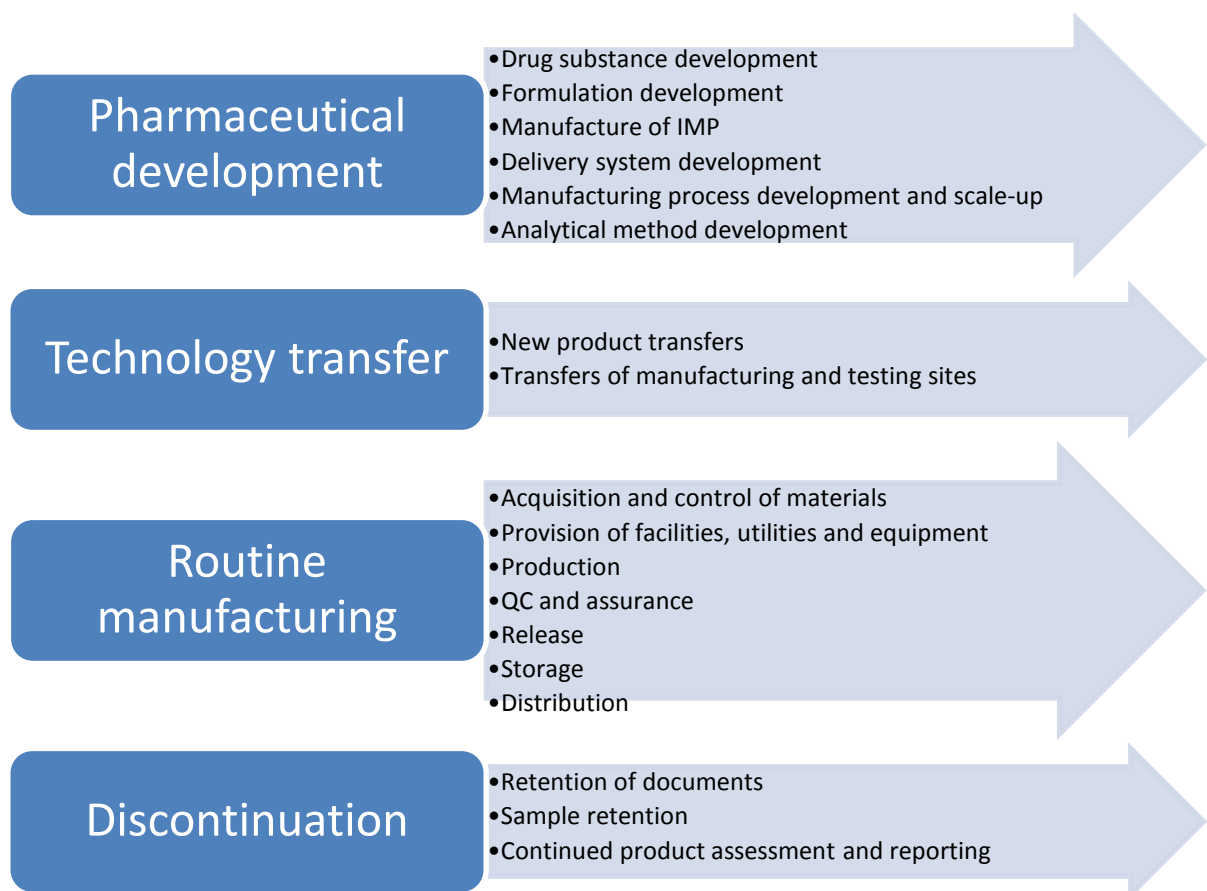
The ICH Q10 guideline describes a model for an effective quality management system. The model is based on ISO quality concepts, incorporates GMP regulations and articulates with ICH Q8 and Q9 guidelines. It does not intend to create new expectations other than current regulations, therefore, all additional content to current GMPs should be seen as optional.³⁸

This guideline can be applied to drug substances and drug products, including biotechnology and biological products, throughout the different stages of a product lifecycle, comprising development, technology transfer and commercial manufacturing. It is applicable either to products developed by the traditional or the enhanced approach.^{37,38,25}

The principles introduced by the ICH Q10 guideline should be implemented to each of the product lifecycle phases, according to the specificities of a company's activities.³⁸

Product lifecycle stages, in the context of ICH Q10, include the following aspects:

Figure 24 – Product lifecycle stages³⁸



7.4. Structure

The ICH Q10 guideline is structured in four main topics and two annexes.³⁸

Table 6 – Q10 structure

ICH Q10 Pharmaceutical Quality System		
Pharmaceutical Quality System	Introduction	
	Scope	
	Relationship of ICH Q10 to Regional GMP Requirements, ISO Standards and ICH Q7	
	Relationship of ICH Q10 to Regulatory Approaches	
	ICH Objectives <ul style="list-style-type: none"> Achieve product realisation Establish and maintain a state of control Facilitate continual improvement 	
	Enablers: Knowledge Management and Quality Risk Management	
	Design and Content Considerations	
	Quality Manual	
	Management Responsibility	Management Commitment
		Quality Policy
		Quality Planning
Resource Management		
Internal Communication		
Management Review		
Management of Outsourced Activities and Purchased Materials		
Management of Change in Product Ownership		
Continual Improvement of Process Performance and Product Quality	Lifecycle Stage Goals <ul style="list-style-type: none"> Pharmaceutical development Technology transfer Commercial manufacturing Product discontinuation 	

ICH Q10 Pharmaceutical Quality System

	<p>Pharmaceutical Quality System Elements</p> <ul style="list-style-type: none"> Process performance and product quality monitoring system Corrective action and preventive action system Change management system Management review of process performance and product quality
Continual Improvement of the Pharmaceutical Quality System	Management Review of the Pharmaceutical Quality System
	Monitoring of Internal and External Factors Impacting the Pharmaceutical Quality System
	Outcomes of Management Review and Monitoring
Glossary	
Annex 1: Potential opportunities to enhance science and risk based regulatory approaches	
Annex 2: Diagram of the ICH Q10 Pharmaceutical Quality System Model	

7.5. Principles and Concepts

7.5.1. Relationship to regional guidances, standards and regulatory approaches

The ICH Q10 has its grounds in regional GMP guides and ISO standards for Quality Management Systems. While perceiving that there was a gap in pharmaceutical industry concerning the harmonization of quality systems expectations, it was recognised that the existing standards used across different industries could be highly valuable. This guideline explores the different regional regulations and forms a solid backbone for an integrated approach together with ICH Q8 and Q9³⁸:

- “Quality Management Systems”: ISO 9000; ISO 9001: 2000; ISO 9004; ISO 13485: 2003
- Regional GMPs
- ICH Q7a: “GMP Guidance for APIs”

This guideline also intends to complement GMPs by introducing specific elements and responsibilities.³⁸

7.5.2. Product Realisation

Product must present the appropriate quality attributes to meet the needs of patients, and the expectations of regulators and health professionals. Hence a pharmaceutical quality system must be adequately established and maintained to assure the achievement of the desired product quality.³⁸

7.5.3. State of Control

In order that process performance and product quality are suitable and capable to provide assurance, a control and monitoring system must be developed and implemented. Quality risk management plays an important role in setting the control and monitoring strategy.³⁸

7.5.4. Knowledge Management

Product and process knowledge should be built from development throughout the entire product lifecycle. Scientific approaches during these phases provide product and process understanding, enabling a company to implement ICH Q10 successfully. Knowledge management comprehends the systematic gathering, analysing, documenting and communicating information about all aspects related to product and processes.³⁸ It encompasses people competence development, process and product understanding and how this knowledge is managed and available within the company's PQS.

Figure 25 – Knowledge management components³⁸



7.5.5. Quality Risk Management

Quality risk management (ICH Q9) is an important component of a pharmaceutical quality system. It provides the means to proactively manage quality risks and facilitate continual improvement. Together with knowledge management, empowers pharmaceutical quality system to perform effectively.³⁸

7.5.6. PQS Design

The pharmaceutical quality system must be well organized and transparent within the company organisation. It should be well designed and supported in terms of documentation and resources. Responsibilities, including management responsibilities, must be well defined within the quality system. Adequate processes should be established.³⁸

The elements laid down in the guideline, namely monitoring of product quality and process performance, change management, corrective and preventive actions and management review, should be put in practice, nevertheless, its use depends on the product lifecycle stage characteristics, available knowledge, company dimension and other specificities. Furthermore, the pharmaceutical quality system should cover the quality evaluation of outsourced activities and all acquired materials.³⁸

Company size is a factor impacting the overall design of the quality system. The system design can be applied crosswise multiple plants, yet, the implementation and maintenance of an effective quality system must be verified at plant level. Systematic monitoring should be in place to measure the performance of the quality system processes.³⁸

7.5.7. Quality Manual

The pharmaceutical quality system description should be documented. The Quality Manual should address the quality policy, the scope of the system, its processes and respective relationships, and management responsibilities.³⁸ It should be easily understandable to management, collaborators and inspectors.³⁹

7.5.8. Management responsibilities

Top management holds the responsibility of assuring that an adequate system is implemented and maintained. Responsibilities, roles and authority should be clear and communicated inside the organisation. Some particular responsibilities within the pharmaceutical quality system are required to be independent from top management, in some regions. Top management should participate actively in all phases starting with the design of the quality system and it is their duty to give support and make their commitment evident, across the company.³⁸

Important tasks under the responsibility of top management are: allocating the necessary human, financial and material resources; performing continuous monitoring and reviews; encouraging continual improvement; ensuring that all relevant aspects are understood at all levels inside the company; ensuring a strong linkage between all functions; and defining a quality policy for the organisation.^{38,25}

The quality policy should be coherent with the company's regulatory environment and its objectives. It should be communicated to and understood by all company members, and be reviewed to ensure it keeps actual and appropriate.³⁸

Objectives should be defined and communicate. Those should be consistent with the company's policy and all the necessary resources should be provided as appropriate. The quality objectives must be monitored and reviewed periodically.³⁸ Adequate communication processes should be established to ensure appropriate flow of information across the different structures.³⁸

Management responsibilities include assessment of outsourced operations and incoming materials. Activities that fall under the responsibility of the pharmaceutical quality system management are the evaluation of third parties competence to perform activities or to supply materials, the verification that approved sources and supply chains are used, definition of quality related responsibilities and communication channels, monitoring and revision of the performance of third parties and incoming materials.³⁸

Management should ensure that responsibilities are continuously defined, including when product ownership is changed.

7.5.9. Continual Improvement of Process Performance and Product Quality

This concept is transversal to ICH Q8, Q9 and Q10 guidelines and is a keystone of the quality systems. It consists in the identification, by proactively using trended data, and implementation of appropriate product, process or system improvements as well as innovation to increase the capability to meet quality goals. Quality risk management can enable continual improvement by helping identifying and prioritising areas eligible for enhancement.³⁸

Continual improvement generates expanded knowledge which is fed back to development.¹⁶

Process performance and product quality should be continuously monitored and subject to continual improvement when appropriate. Continual improvement should be present throughout all stages of the product lifecycle, namely pharmaceutical development, technology transfer, commercial manufacturing and product discontinuation. Continual improvement creates the opportunity to facilitate the realisation of the stage goals.³⁸

Continual improvement must be an ongoing objective and is more effectively reached if it is well ingrained in the industry's policy and philosophy.

Figure 26 – Continual improvement during the product lifecycle³⁸

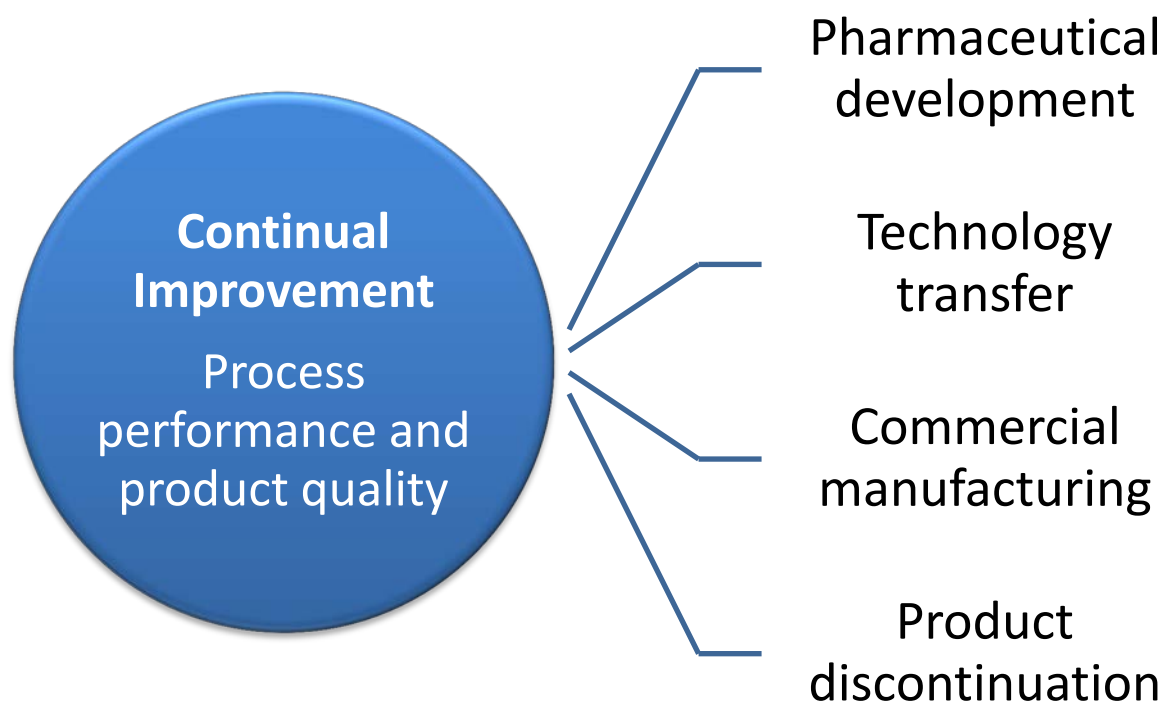


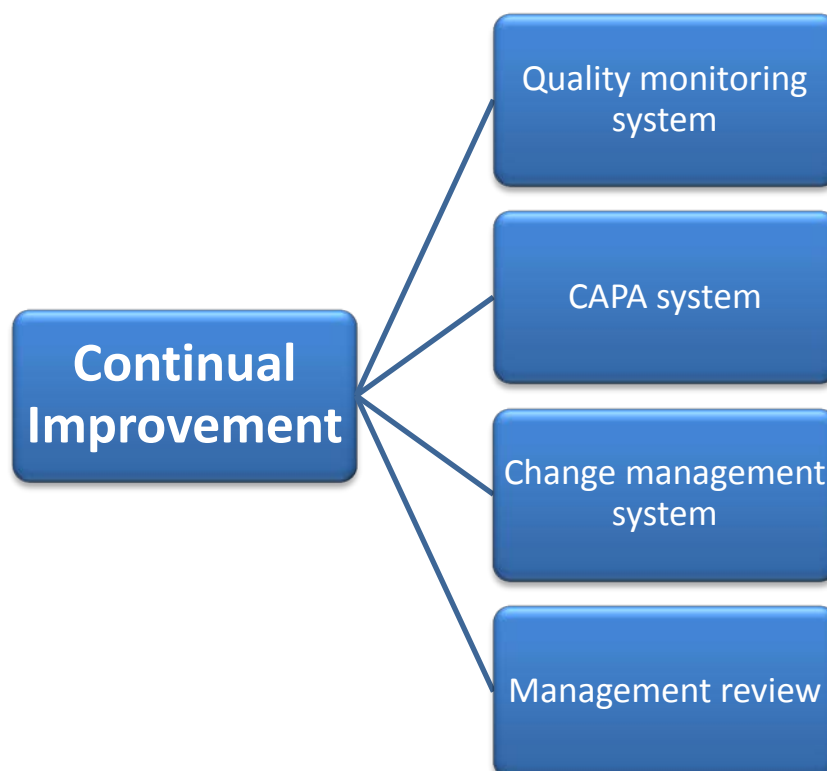
Table 7 – Opportunities for continual improvement³⁸

Pharmaceutical development	Technology transfer	Commercial manufacturing	Product discontinuation
<ul style="list-style-type: none"> • Design a product and manufacturing process • Intended performance • Meet the needs of all stakeholders 	<ul style="list-style-type: none"> • Transfer product and process knowledge ensuring product realisation • Development phase to manufacturing phase • Between manufacturing sites 	<ul style="list-style-type: none"> • Product realisation meeting desired quality • Process performance • State of control • Facilitate continual improvement • Expand knowledge 	<ul style="list-style-type: none"> • Manage effectively the discontinuation of the product • Ensure all regulatory obligations

The pharmaceutical quality system elements should be applied during the product lifecycle stages. Its application will depend on the specific characteristics of each phase.

The objective is that companies proactively identify opportunities to embrace innovation, improve product quality and process performance.³⁸

Figure 27 – Sources for continual improvement³⁸



The inputs from the different areas provide information that augments knowledge about the products and processes. This expanded knowledge is used, in a feedback mechanism, to foster continual improvement.²⁵

In the same way, the application of ICH Q9 and Q10 to legacy products can be beneficial, as there is certainly room for improvement and optimisation. Expanded knowledge is an enabler for finding and solving issues or problems, therefore companies are encouraged to improve legacy products and processes.²⁵

7.5.10. Quality monitoring system

A system for monitoring product quality and process performance should be designed and put in place to guarantee a state of control. Such system provides assurance that the process can produce a product meeting the intended quality and also provides the input for continual improvement activities.³⁸

The planning of the control strategy should use quality risk management and may concentrate on materials and product attributes, process or equipment parameters, facility operating conditions, the control methods and control frequency.³⁸

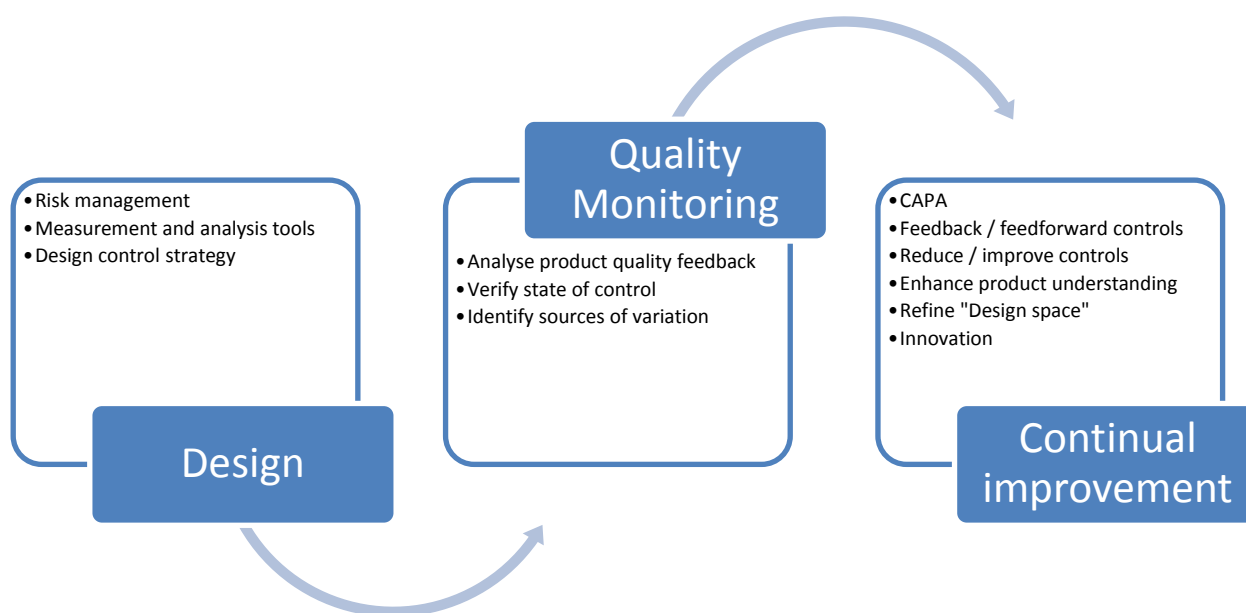
The quality monitoring system should use appropriate tools to warrant the implementation of the control strategy, such as data management or statistical tools.³⁸

The system implemented should permit to verify if the process is maintained in a state of control, promote the identification of sources of variation and evaluate all reported information regarding product quality, generated internally or externally to the company.³⁸

The identification of points eligible for improvement may lead to definition of CAPAs, introduction of feedback/feed-forward controls, eliminate, reduce or improve controls.³⁸

Ultimately, the monitoring system should result in the promotion for innovation, augmented product and process understanding and, if applicable, refinement of the “design space”.³⁸

Figure 28 – Quality monitoring system contribution for continual improvement³⁸



7.5.11. CAPAs System

There should be a system for the management and implementation of corrective and preventive actions. Investigations of deviations or any other unexpected or unwanted event must be conducted and the need to define CAPAs should be assessed.³⁸

The definition and implementation of CAPAs fosters product and process enhanced understanding and continual improvement.³⁸ CAPAs management system should provide the means to evaluate, approve, implement and document corrective and preventive actions.

7.5.12. Change Management System

The systematic identification of opportunities for continual improvement, create the need for change. In order to effectively manage changes, the organisations should implement an appropriate system.³⁸

During the product lifecycle, changes will take place. Changes can be proactive (business driven or due to technical reasons) or reactive as consequence of CAPAs.¹⁶

The change management system should provide the means to evaluate, approve, implement and document changes. The system should ensure that the degree of formality employed in the change management is proportionate to the level of risk and regulatory obligations, that the change is managed in a timely manner and that the impact in other products, processes and areas is adequately assessed.³⁸

The change management system should incorporate risk management, as appropriate, and knowledge management and should involve the participation of teams from relevant expertise areas.³⁸

The regulatory impact of the proposed change should be taken into account. The evaluation whether the change implies the need for regulatory submission, or not, should be conducted, including the consideration of the established “design space”.³⁸ Movement within the design space should be managed in the company’s change management system.³⁹

Criteria for the subsequent evaluation of the implemented change should be set beforehand and a final evaluation to verify if the objectives were met without negative impacts should take place.³⁸

7.5.13. Management Review

In favour of ensuring that process performance and product quality are accomplished throughout the product lifecycle, a management review should be performed. It should be conducted at different levels of management and appropriate communication channel should exist to bring pertinent issues to proper higher levels.³⁸

Management review should analyse outputs coming from³⁸:

- inspections and audits;
- regulatory commitments;
- results of customer satisfaction;
- outcomes of process performance and product quality monitoring;
- evaluation of effectiveness of changes implemented;
- follow-up activities from former reviews.

The outputs of the management review can include activities to improve processes and products, adjustment or qualification of resources and knowledge handling.³⁸

Table 8 - Application of management review in the different stages of the product lifecycle³⁸

Element	Pharmaceutical Development	Technology transfer	Commercial manufacture	Product discontinuation
Monitoring Quality System	Establish control strategy for manufacturing.	Confirm successful transition to manufacture. Develop control strategy.	Maintain the state of control. Identify improvement opportunities.	Continue monitoring till completion of studies.
CAPAs	Incorporation of CAPAs during design and development.	Used for feedback / feed-forward control. Continual improvement.	Use of CAPAs and evaluation of its effectiveness.	CAPA should continue after discontinuation. Impact on marketed product and other products should be evaluated
Change Management System	Change should be documented. Formality should be proportionate to the stage.	Manage and document adjustments.	Formal system in place. Appropriate science and risk based assessments.	Changes should continue to be managed through the system.
Management Review	Ensure adequacy of product and process design.	Ensure that manufacture at commercial scale is successful.	As a structured system, it will enhance continual improvement.	Continue to review ongoing studies and product quality feedback.

7.5.14. Continual Improvement of the PQS

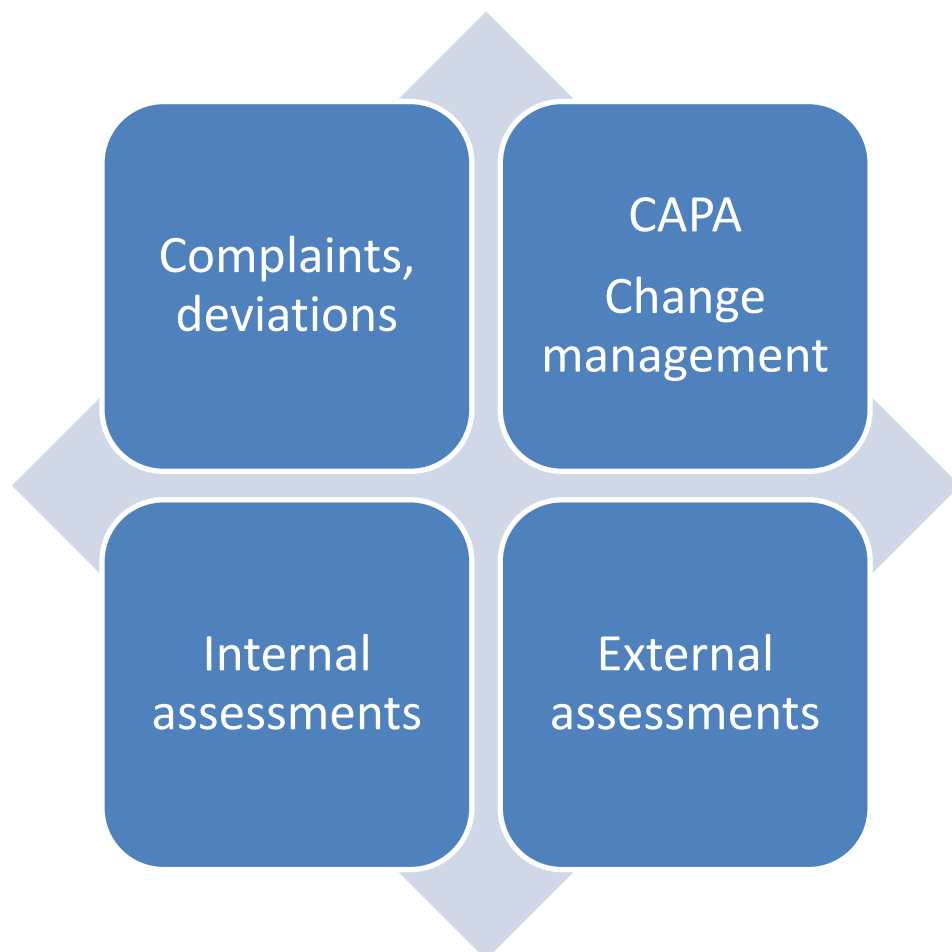
The pharmaceutical quality system should also be continually improved. Periodic reviews of the system performance should be carried out.³⁸ A formal process should be implemented to perform regular management reviews of the PQS.³⁸

The review should comprise accomplishment of objectives and performance of PQS processes, through the evaluation of indicators.³⁸

Additionally, the factors impacting the PQS should be monitored and evaluated such as new guidelines, regulations, innovative approaches and changes in business or ownership.³⁸

The inputs from the different areas provide information that augments knowledge about the PQS. This expanded knowledge is used, in a feedback mechanism, to foster continual improvement.²⁵

Figure 29 – Examples of inputs from management review, that can foster continual improvement³⁸



The management review should be performed in a timely manner and documented. It can result in changes to improve the system, readjustment of resources, modifications to policies and objectives. The results should be communicated to the interested parties accordingly to its relevance to quality.³⁸

Continuous improvement must be entrenched in the company's human structure, as part of the culture.¹⁶

A program to perform internal audits can be implemented to ensure that the system is functioning and to identify possible opportunities for improvement.³⁹

8. Q8, Q9 and Q10 connected

A new quality paradigm emerged following the ICH consensus vision. In this new vision, quality is based on three main pillars, such as: the pharmaceutical quality system; science-based knowledge; and quality risk management. Attaining the desired quality is a challenge that demands a continuous effort throughout the entire lifecycle of the product.⁴⁰

The new quality model stresses out the importance of quality by design, innovative science, quality risk management, pharmaceutical quality systems and integration of the quality with the different stages of product realisation.⁴⁰

Figure 30 – New Quality model⁴⁰



The tripartite guidelines have originated a change in the paradigm of pharmaceutical development and quality system management.

The combination of pharmaceutical development (Q8) and risk management (Q9) with a capable pharmaceutical quality system (Q10) enhances product and process understanding, augments knowledge and creates the opportunity for flexible regulatory approaches and continual improvement. ICH Q8 guideline reinforces the connection between development and manufacturing while ICH Q9 sets up risk management as an enabler for pharmaceutical development and pharmaceutical quality system activities. Successful implementation of PQS enhances continual improvement of products, processes and of the PQS itself. Furthermore, it will facilitate GMP compliance, increase confidence between industry and regulators, improving the efficiency and reducing the frequency of audits and inspections.²⁵ Successful implementation of the new quality paradigm should result in higher assurance of product quality, increased manufacturing efficiency, less deviations and waste and consequently avoid drug shortages.

The implementation of the integrated guidelines could be beneficial for any drug product, from new to legacy products, simple or complex molecules or dosage forms. Its implementation could also be advantageous for products in which the development approach is either the traditional or the enhanced one. Both industry and regulators can take advantage of the use of these guidelines.⁴⁰

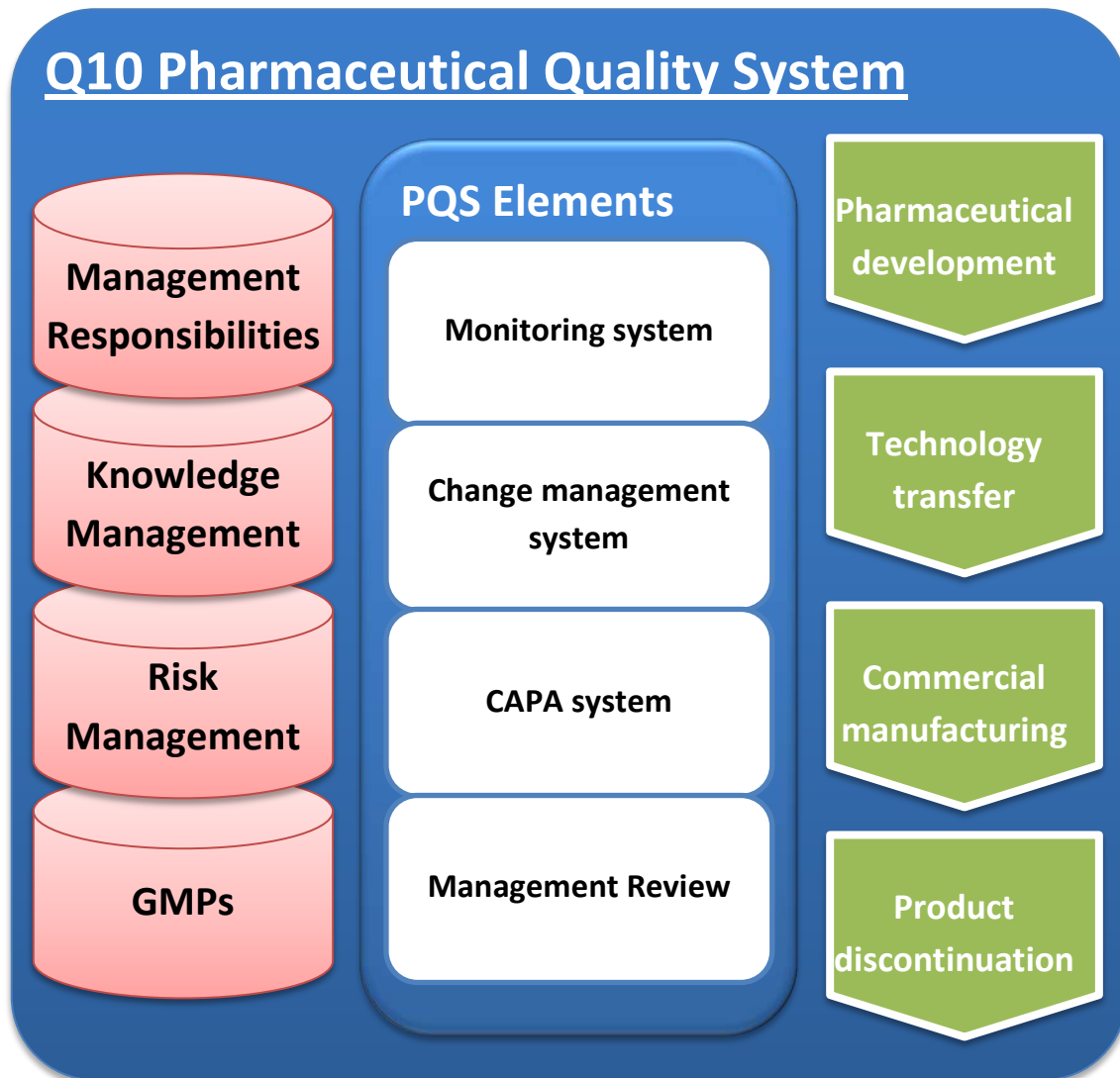
The integration of pharmaceutical development, risk management and quality systems new approaches aspire to encourage adoption of innovative science and technology and to ensure that resources are applied in the most relevant quality topics, by means of risk prioritisation. It also provides the opportunity to improve and align the CMC review with the cGMP inspections.

Ultimately, protection of the patient is the central focus of the ICH vision and, consequently, the integrated guidelines were designed bearing in mind patient's welfare.

8.1. Integration of ICH Q8, Q9 and Q10

The integration of ICH Q8, Q9 and Q10 and the relationship between the different elements are represented in the following scheme.³⁸

Figure 31 – Representation of the PQS and its relation to the product lifecycle stages³⁸



On the left hand side column, the scheme highlights the importance of management responsibilities, displays that both knowledge management and risk management are essential aspects that warrant the basis for a robust PQS. GMPs are an integrant part of the PQS as it is applicable to manufacturing of medicinal products (either commercial or investigational products). In the middle column the elements that support the PQS are depicted. On the

right hand side the lifecycle of the product is represented, showing that all stages are embraced by the PQS.

The PQS is essential for all activities: development, facilities and equipment, technology transfer and production. The PQS leads and administrates planning, protocol development, test requirements, data generation and assessment structures.²⁹

The key objectives of the PQS are to achieve product realization, establish and maintain a state of quality control, while facilitating continual improvement. In order to reach these goals, the main task is to use risk management and knowledge management (collect, document, retain, analyse and share product and process knowledge).⁴¹

The Implementation Working Group (IWG) at ICH level issued Q&As to provide clarity and further guidance on the integrated implementation of ICH Q8, 9 and 10. This document (firstly issued in April 2009) was revised to contain 4 four sets of questions (latest revision in November 2010). A document containing “Points to Consider” was also prepared by this group to supplement the Q&As (initially issued in June 2011 and revised in November 2011) providing additional clarification on the implementation of the new concepts.⁴²

8.2. Opportunities and consequences for Industry

8.2.1. Application of ICH Q8, Q9 and Q10 throughout the product lifecycle

The application of the concepts depicted by the ICH guideline Q8, Q9 and Q10 is dynamic and therefore may be differently applied throughout the several phases of product realisation.

The following schemes represent the typical applicability pattern of these guidelines throughout the different stages and activities.

Figure 32 - Applicability of ICH Q8, Q9 and Q10 guidelines throughout the different stages of product realisation⁴⁰



It can be seen that ICH Q8 activities are more intense at the beginning of the product lifecycle, while ICH Q10 gains importance as commercial manufacturing becomes a

reality. ICH Q9 is present throughout the entire product lifecycle and, together with Q8 and Q10 contributes to building knowledge and boost continual improvement.

The three guidelines contribute to elimination and mitigation of risks related to product and process design from development, commercial manufacturing through to product discontinuation. Increased knowledge and greater understanding of all the variables and their relations will lead to optimized processes and better quality pharmaceutical product, with less out of specification events.

The guidelines are intended to benefit industry and regulators by:

- Providing the basis for a better understanding of the process;
- Decreasing batch failure;
- Reducing post-approval regulatory submissions;
- Fostering innovation and processes improvement without regulatory resubmission (within the design space);
- Increasing the efficiency of transfer from development to manufacturing;
- Fastest time to market;
- Increasing confidence from regulators on product quality;
- Modernizing process validation approaches;
- Optimising resources usage;
- Reducing costs;
- Reducing deviations and investigations;
- Reducing end-product testing;
- Enabling continuous improvement.

The benefits that a company can get from implementing a QbD approach can be assessed by evaluating current products historical data, through research and development, scale-up, technology transfer, and commercial production and identifying cases where unexpected costs and delays occurred that could have been avoided if a QbD approach had been followed.⁴³

In general, the advantages of implementing a QbD approach are, but are not limited to⁴⁴:

- Mitigation of potential risks;

- Maximization of the understanding of the product and process;
- Establishment of relevant in-process controls.

Looking further into the different steps, it can be seen how each guideline may be applied during each activity.

8.2.1.1. Pharmaceutical Development

8.2.1.1.1. Formulation stage

During this stage, the ICH Q8 applicability is evident. Several activities are performed to gain as much information as possible about the drug substance, the excipients and its compatibility. The development of analytical methods is conducted and experiments are carried out to screen and select the components to optimize the formulation. Characterisation studies are executed, as well as stability and performance studies of the drug product.⁴⁰

ICH Q9 contributes by providing risk assessment methodologies to determine and evaluate risks related to the components, drug product and patients. Risk management is used to prioritize knowledge gaps needing further investigation.

ICH Q10 applicability is associated with knowledge management, risk assessment, collecting and registering information and all supporting activities.⁴⁰

8.2.1.1.2. Process development stage

The process development stage may involve the following ICH Q8 activities: screening of unit operations, experimentation to determine interactions and understand the criticality of parameters and material attributes, characterization of intermediates, definition of design spaces, scale up activities and establishment of online PAT.⁴⁰ The objective of the development stage is to reduce potential risks to safety and efficacy in order to achieve the desired clinical outcome.

Criticality of the quality attributes is assessed and is related to each process unit operation. The inputs and outputs of each operation are defined and then determine the process parameters and in-process controls. Control strategies consisting of RTRT are possible if supported adequately by development data.

As a support, the ICH Q9 related activities play a major role, allowing finding, assessing and controlling risks with potential to cause failures. It also provides the means to screen and rank risks, identify critical parameters and material attributes. Furthermore, it facilitates scale up activities and the definition and implementation of adequate control strategies.⁴⁰ As development activities are completed, risk gets reduced because understanding about the factors associated with the process and the way how they impact quality gets increased.

The PQS (ICH Q10) supports all activities, providing the ground for document and knowledge management, technology transfer activities, suppliers' qualification⁴⁰ and facilities/equipment qualification and maintenance.

8.2.1.1.3. Technology Transfer

This stage goal is to transfer product and process knowledge from development to manufacturing or between manufacturing sites, and constitutes an opportunity to use ICH Q8 principles and augment process and product understanding. Activities during this stage are supported by prior knowledge gained during development phases.

The development of the control strategy should take into account the impact of scale up on its validity¹⁹, different facilities and equipment. During the technology transfer and scale up phases it must be ensured that the process performs as expected and that the control strategy is suitable. The predictive models, if used, must be validated and verified continuously during the product lifecycle.¹⁹

QRM activities must take place during the introduction of new products to assess its impact on existing processes and products, to avoid cross-contamination or any other negative consequence.⁴⁵

Information from pharmaceutical development that is necessary to understand the rationale of the manufacturing process, CQAs, CPPs and the control strategy should be available at the manufacturing site.³⁹

ICH Q9 related activities underpin the manufacturing process, improve the control strategy, and enable process validation and continual improvement. ICH Q10 is present at this stage, permitting the management of knowledge gained and, subsequently, allowing using new data to further optimise processes and control strategies.⁴⁰

8.2.1.2. *Commercial manufacturing*

Commercial manufacturing involves ICH Q8 related activities as commercial scale design is defined and verified and PAT is implemented. Implementation of commercial manufacturing will be facilitated if a good development work has been performed. Data collected during commercial manufacturing as well as evaluation of implemented changes and its effects are fundamental to enhance product and process understanding, providing feedback knowledge to development. Change management is crucial to ensure that opportunities for improvement are carried out. Companies should be able to implement improvements without regulatory constraints when justifiable and supported by QRM.

ICH Q9 is useful as it supports: the settlement of a control strategy; procedure monitoring strategies; risk management in changes and in auditing. Documentation management, specific procedures, validation of analytical methods and process, change control management and knowledge management are examples of activities related to ICH Q10 that are carried out during commercial manufacturing.⁴⁰ QbD cannot exist without a robust PQS. The supervision by the PQS is essential for the release of consistent quality product, including RTRT.

8.2.1.2.1. *Process validation*

Process validation must ensure a continuous state of control and provides confidence in the product and process.

The former approach to process validation, focused on a three-batch approach, has motivated a passive attitude within the industry which, in turn, neglected opportunities for continuous improvements.⁴⁶

The adoption of the three ICH guidelines, also impacted the way process validation is realized, leading to a revision by both the FDA and EMA of their guidance documents, in 2011 and 2014, respectively.

A new approach has come into effect, in line with the ICH Q8, Q9 and Q10 guidelines, where process validation is no longer a one-time activity. It starts at an early stage and continues throughout the entire product lifecycle, linking knowledge from product and process development, process scale-up, technology transfer, commercial manufacture and quality risk management approaches. It is supported by continuous monitoring and evaluation (continuous process verification - CPV)⁴⁷ which provides the grounds for continuous improvement.¹⁶ The process must perform effectively and reproducibly to meet the required specifications and quality attributes. The manufacturer should ascertain whether a sufficient understanding has been gained providing high degree of assurance in its manufacturing process to allow for commercial distribution of the product.⁴⁸ When selecting the number of batches necessary, appropriate scientific data, risk management and statistical tools should be available. Process validation must confirm the control strategy developed.

Ongoing process verification to demonstrate that the process remains in a state of control is necessary and is the recognition that process validation extends throughout the product lifecycle.⁴⁷ It can be achieved through in-process controls, extended testing against in-process or end product specification limits, process monitoring, change controls, annual product reviews and ongoing risk management, supported by statistical analysis and trending.⁴⁵

The principles from ICH Q8, Q9 and Q10 can therefore be used to support a new enhanced approach to process validation. Although the traditional approach can still be acceptable, CPV or a combination of both can be used. CPV can be introduced at any time in the lifecycle of the product.⁴⁷

While the traditional validation approach tends to focus on meeting the final specification, CPV is directed to achieve a full understanding of the process and how the critical parameters affect the product quality.⁴⁹

The implementation of CPV is encouraged as it provides better means for acquiring knowledge and boost continual improvement. Moreover, CPV emphasises the lifecycle aspect of the product instead of focussing only on the first few commercial scale batches, resulting in an increased capability to detect problems and trends, and providing higher level of assurance of continual state of control as well as a higher level of knowledge about processes and product.¹⁹

Risk management is fundamental to define the amount of data and number of batches, based on the complexity of process and product, to achieve confidence in the process. The risk based approach during all product lifecycle stages, allows to continuously aim the resources and effort into those activities that are crucial. This enables continued knowledge gain and understanding leading to continuous improvement.

Validation of the process requires a comprehensive understanding and demonstration of adequate control throughout a manufacturing process lifecycle. The lifecycle begins with development and continues through validation activities to confirm that the manufacturing process works as expected and consistently produces the desired product. The process design is verified with ongoing assessments of process performance. The approach to validation should be based on risk assessment that considers the degree of confidence required with respect to potential impact on the end-user. It consists of process development, confirmation and continual verification. The number of studies and evaluations should be commensurate to the level of risk identified. Although the approach to process validation is different, the principles remain unchanged.²⁹

8.2.2. Manufacturing Quality Unit

8.2.2.1. Responsibilities

The manufacturing quality unit (or QA/QC) responsibility towards batch release is not changed by the implementation of new concepts such as RTRT or design space.

Its responsibility extends through product lifecycle and also comprises the mission of keeping the PQS aligned with the product specific features such as design space, predictive model or RTRT. Therefore it must provide the means for¹⁶:

- continual improvement during commercial production;
- maintenance of design space, predictive models and control strategies;
- application of risk management within the PQS;
- continual verification and monitoring;
- feedback/feed-forward mechanism between development and production.

In order that these duties can be fulfilled, product knowledge must be available at manufacturing site.¹⁶

The quality unit role must be cross functional with other areas, as marketing, research and development or regulatory departments.

Quality culture within a company's structure is a major topic, as it dictates the credibility of their PQS metrics. To attain a quality culture, management and collaborators need to understand each person's role and establish a state where dedication, responsibility and liability are fundamental aspects to yield a high-quality product in a consistent manner. Management must provide the necessary education, training, tools and resources so that each person duties can be fulfilled, incorporated by a policy and mind-set that fosters perfectness and continual improvement.³

8.2.2.2. Outsourced services

Outsourcing services is an increasing trend for industry. Manufacturing, QC testing, packaging and distribution are examples of growing outsourcing services. This strategy is accepted, but responsibility and accountability remains within the company. For this reason, the PQS must ensure an appropriate state of control of its service providers, namely material suppliers and third party contractors. Adequate procedures must be in place to guarantee that the selection, assessment, definition of responsibilities, communication, monitoring and reviewing of the qualification status of such service providers are successfully performed.¹⁶

8.3. Opportunities and consequences for Regulators

8.3.1. Regulatory assessment

The implementation of ICH Q8, Q9 and Q10 creates the opportunity to facilitate regulatory assessment of applications. The use of systematic development approaches lead to wider knowledge which will potentially improve the efficiency of regulator's assessment. It creates room for science and risk based decisions and for better communication between assessors, inspectors and companies.¹⁶

QbD enables the adjustment of the regulatory scrutiny to level of process understanding. Continuous improvement is allowed within the design space without the need for submitting regulatory variations.

Regulatory assessment and the inspection programs must operate in a coordinated and synergistic manner.

8.3.2. Inspections

With the implementation of ICH Q8, Q9 and Q10, the inspections methodology and scope remain unchanged. However there are differences in the focus of the inspection.¹⁶

Under the new guidelines, the submitted dossier provides an important source of information regarding the product and its process design. For this reason, it constitutes an important reference to the inspection, where the process implementation at commercial scale can be evaluated. Consequently, inspectors discuss with reviewers and assessors previously to the inspection. Pre-approval inspection activities complement dossier assessment by verifying the validity on site of the information presented in the submitted dossier.¹⁶

The inspection will concentrate on evaluating the implementation of critical and non-critical process parameters, design spaces, control strategy, release strategy and predictive models, as well as the company's capability to maintain these through monitoring, change management and unexpected events management. The appropriateness of the PQS as regards to the characteristics of the product and to the company's dimension should also be considered.¹⁶

Post approval inspections will concentrate on the PQS and in verifying the state of control. Evaluation is focused on how the continual improvement of the PQS contributes to the continual improvement of the product and process.¹⁶

The implementation of the ICH guidelines enhance GMP compliance and can have a positive impact on the frequency and duration of inspections, as confidence between regulators and industry is strengthened. Regulators have the possibility to create models using risk management for planning inspections.¹⁶

8.3.2.1. Release strategy

The release strategy is closely connected to the control strategy, which is described in the approved marketing authorisation file.¹⁹ Inspections will also focus on the implementation of the batch release strategy. RTRT and models monitoring plans should be implemented once approved in the marketing authorisation.¹⁶

8.3.2.2. Outsourced activities

The inspection will address supplier management and outsourcing operations under the PQS as a critical aspect.¹⁶

8.3.2.3. Knowledge management

It is important to consider if there is a system in place to support knowledge management and see how the company converts gained knowledge into continual improvement.¹⁶

8.3.2.4. Technology transfer activities

The inspection will look at the technology transfer activities, verify predictions and assess new data not available at the time of submission.¹⁶

8.3.2.5. Risk management

During the inspection, special attention is given to potential variables and related risks not yet identified and that can impact product quality.¹⁶

9. Changing Paradigm in Pharmaceutical Development

Prior to the new quality mind-set imposed by the ICH Q8, Q9 and Q10 guidelines, quality decisions did not take fully into account science and systematic risk evaluation. There was a strong adherence to filing commitments and quality was tested by means of extensive sampling and testing.³⁹ Risk management was empirically used and poorly applied. Traditional pharmaceutical development did not require the establishment of functional relationships between CQAs and CPPs and studies to characterize the process were basically univariate, disregarding possible interactions. Although useful, these studies did not provide sufficient understanding of a variable criticality.²⁰

The traditional approach strategy to pharmaceutical development was aimed at defining quickly the target operational values that would result in an acceptable primary quality attribute target. The need to generate product for clinical trials was urgent, therefore the operational ranges selected were very limited because of no adequate studies and understanding of the product and process.¹⁸

The linkage established to early clinical batches prevented the improvement and optimization of many processes. The transition to manufacturing was focused on data transfer and, as a result, the empirically designed control strategy would not allow deviations to the narrow operational values, meaning a huge risk of non-compliance caused by the variable input and excursions outside the predefined ranges.¹⁸

Process defined the product, and consequently the process had to be performed under narrow operating controls to provide consistent product. Regulators expected it to be tightened after sufficient manufacturing data becomes available.²³

The tendency in industry was to avoid including much of the process knowledge and understanding in the CMC sections of their applications, and provide the minimum of data. The regulators can also be considered responsible for this mind-set, as they were encouraging such attitude. The regulators view has changed and in the new guidance the need to provide scientific evidence is of utmost importance and clearly replaces the need for big sets of documented evidence lacking knowledge or understanding.²⁹

Process validation was a one-time activity and improvement was inhibited by regulatory and business barriers. Overall, in the pharmaceutical industry, improvement and innovation was discouraged because changes would require the authority's scrutiny and

prior approval. The process was seen as fixed, not open to changes, and the attention was directed mainly to process reproducibility and compliance, ignoring that materials and process controls present variability.

On the other hand, production efficiency is not optimal, batch failures were frequent and scale-up difficult. Understanding of product and process was limited, despite the significant amount of data generated because there was no systematic methodology to convert data into knowledge.

With QbD, the product defines the process and, as a result, if the process is kept within the defined design space, product quality will consistently be achieved. Control strategy under QbD arises from a systematic science-based approach, where testing and controlling points are located upstream in the process, and performed extensively on-line or in-line. Specifications are based on knowledge and are kept wider, providing flexibility to the process.²³

Major differences between the traditional development approach and QbD are depicted in the following table.²³

Table 9 - Major differences between the traditional approach and QbD²³

Aspect	Traditional approach	QbD (enhanced approach)
Principle	Process defines the product. Design based on templates or existing practices. Empirical approach. Random and focussed on optimization. Retrospective.	Product defines the process. Design based on knowledge and product and process understanding. Systematic approach. Science and risk-based. Multivariate experimentation. Prospective.
Operating ranges	Narrow operating ranges. Some in-process testing.	Wider operating ranges (design space). PAT used. Continuous monitoring and trending evaluation.

Aspect	Traditional approach	QbD (enhanced approach)
Specifications	Narrowed, based on process performance. Primary means of quality control. Acceptance criteria based on limited data. Test to document quality.	Wider, based on product and process understanding. Part of quality control strategy. Acceptance criteria based on patient needs.
MA Dossier	Includes process description and product characterisation data. Presents the existing state.	Includes process and product knowledge and how the process is linked to the CQAs and the CQAs to safety and efficacy of the product.
Post-approval maintenance	High maintenance, increased regulatory activity.	Lower maintenance, reduced regulatory activity.
Continual improvement	Restricted. Keeping status quo. Changes are a burden.	Promoted. Proactive activities across the lifecycle. Changes are an opportunity.
Operational flexibility	Low. Fixed manufacturing process. Changes require prior approval. Control strategy based on testing and inspection. Variability avoided (not understood).	High. No submission required if inside the design space. Managed by the PQS. Control strategy based on risk. RTRT possible. Variability explored (understood) – Design space.
Non conformances	Investigation is difficult. Time consuming. Seen as a setback.	Investigation is facilitated by existing knowledge. Faster resolution. Seen as an opportunity to increase knowledge.

Overall, the pharmaceutical industry has already recognised many advantages on the use of QbD approaches^{50,60}:

- better product quality and process robustness;
- improved development methodology, speed and formulation design;
- cost/waste reduction and yield increase;
- reduced failures and deviations;
- reduced impact of raw materials variability;
- reduced time-to-market;
- improved stability;
- easier scale-up;
- enhanced use of science and risk-based approaches ;
- flexibility for lifecycle management;
- promotion of scientific discussion and collaboration between industry and regulators.

Pharmaceutical industry is slowly embracing the QbD elements and those companies that have implemented it have realized that the benefits fulfilled the initial expectations.⁵⁰

In 2009, the FDA issued a report⁵¹ about the state of QbD adoption and focussed the challenges preventing complete implementation. The report recognised that many companies are still sceptical about QbD and fail to perceive the advantage of adopting the enhanced approach. A classification of companies per level of maturity in QbD implantation was presented, consisting of 4 different classes: Novice (sceptical, no planning to implement QbD), Pilot (trying QbD, evaluating potential), Rollout (convinced about QbD, using regularly), Fully implemented (using in almost every development and production step). Companies were divided in three groups: New drug manufacturers, generic manufacturers and biologics manufacturers.⁵¹

Figure 33 – Level of maturity – implementation of QbD⁵¹

Group	Novice	Pilot	Rollout	Fully implemented	Total
New Drug	22%	33%	22%	22%	100%
Generic	40%	20%	40%	-	100%
Biologics	17%	67%	17%	-	100%

It could be clearly seen that new drug manufacturers were at a higher level of adoption, followed by biologics manufacturers. Generic drug manufacturers were at the lowest level of maturity.

In an IFPAC meeting in January 2013, an FDA CMC Reviewer/QbD Liaison in the Office of Generic Drugs presented the results of a study conducted on the status of the implementation of QbD in the generic industry.⁵²

Table 10 – FDA ANDAs submissions including QbD⁵²

Submission date	% of ANDAs including QbD elements
June 2012	24.6 %
July 2012	25.5 %
August 2012	53.3 %
October 2012	62.5 %
January 2013 (till 13/1/2013)	82.9 %

The numbers showed an increase in the adoption of QbD elements.

FDA has been strongly encouraged inclusion of QbD in ANDAs submissions to that agency. The FDA internal policy MAPP 5016.1 (effective since Feb. 2011) requires reviewers to review QbD elements in the application. Since January 2013, FDA expects to see at least 5 QbD components in these submissions:⁵³

- Quality target product profile (QTPP);
- List of critical quality attributes (CQAs) of the finished product;
- List of critical quality attributes (CQAs) of the drug substance and excipients;
- List of critical process parameters (CPPs);
- Control strategy.

In case of missing QbD elements, deficiency letter issued will clearly mention them.⁵³

In the biopharmaceutical area, a recent survey conducted by BioPharm International⁵⁴ revealed that 32% of the companies surveyed have not implemented QbD in their biopharmaceutical manufacturing operations because of⁵⁴:

- insufficient guidance and direction from regulatory agencies (46.2%);
- no process or quality gain is expected (30.8%);

- misunderstanding of the QbD initiative (23.2%);
- cost reasons.

Those who did implement QbD, identified the following main advantages⁵⁴:

- improved process understanding (68.4%);
- improved product quality (66.7%);
- reduced variability in product quality (57.9%);
- improved manufacturing efficiency (near 50%).

Another survey (2010 – 2012) by Pharma IQ⁵⁵ showed that 72% of the studied companies do not have a fully established QbD process in place and when asked about the key reasons for not implementing QbD, the responses revealed that over the years the opinion has diverged.⁵⁵

Table II - Key reasons for not implementing QbD⁵⁵

Year	Key reason for not implementing QbD
2010	42% ability to demonstrate return of investment
2011	40% integration with current practices
2012	59% lack of internal expertise

It is recognised that FDA has been more proactive in driving the adoption of QbD when compared to EMA.⁴⁹ As for what concerns EMA, after a decade of their initial efforts to set the new paradigm, it has been observed that the industry has been actively adopting the QbD principles, quality risk management and pharmaceutical quality systems guidelines, however, only a small number of applications incorporating the new concepts have been submitted to that agency. Among the companies that have successfully implemented the new concepts and that have benefited from it, are the international leading companies, whilst the majority of the companies have been unwilling to take on the enhanced quality approach.⁵⁶

During a workshop on QbD promoted by EMA and Parenteral Drug Association (PDA) in January 2014, where regulators and companies were present, it was noted that it is

still necessary to optimize and harmonize the regulatory review process of QbD, at a global level.⁵⁶ It was recognized that several obstacles are still blocking a more significant use of QbD, namely the assignment of criticality, the amount and type of information necessary to provide clarity about the company's approach, the verification of the design-space, changes to non-critical process parameters and the different use of QbD terminology.⁵⁶

In some cases, advanced and complex statistical calculations were incorporated in QbD applications which raised problems to the assessors, which generally do not hold the necessary knowledge to provide an adequate evaluation.⁵⁶ Innovation is still restricted by lack of expertise (in both industry and regulatory agencies), fear of regulatory challenges and deficiency of clear procedures on how to manage lifecycle changes.⁵⁶

The EFPIA, the European Biopharmaceutical Enterprises (EBE) and the European Vaccine Manufacturers (EVM) have pushed the EC to make clear in the regulation that changes within a design space do not constitute the need to submit variations. The EGA (European Generic Medicines Association) position is that despite the regulation provides clarification on the elements necessary to support the pharmaceutical development, several practical issues remain unclear about QbD implementation.⁵⁹

On August 2013 the first conclusions of the three-year pilot program launched by EMA and FDA three-year pilot programme for the parallel assessment of sections of applications that are relevant to quality by design were released. It was concluded that the program fostered agency collaboration and agreement on several QbD subjects. The conclusions included a Q&As document where clarification about quality target product profiles, CQAs, criticality and application of QbD in analytical method development was given. Later, on October 2013, a second set of Q&As on design space verification was published.⁵⁷

As regards to PQS as a key aspect to GMP compliance and quality, a significant number of major observations arising from inspections, import alerts and market recalls have been continuously observed.⁵⁸ The EU authorities are focussing their attention on the increasing number of quality defects in pharmaceutical manufacturing that have originated drug unavailability.⁵⁹ PQS are still reliant on large collections of SOPs and working instructions instead of product and process understanding. Most times these SOPs are not revised proactively and their structure does not facilitate its effective use.⁵⁸ Pharmaceutical

industry also requires further clarification from the regulatory agencies concerning how to implement a ICH Q10 compliant knowledge management system.

9.1. Future Trends

9.1.1. QbD

Although QbD has been encouraged by regulators since 2003, the adoption of the concepts laid down by ICH Q8 has not been fully achieved.

The industry itself, especially the biopharmaceutical branch, has recently posed EMA to promote QbD to a greater extent.⁵⁹ Multiple concerns by the industry have been addressed to EU authorities to issue more clear regulations and guidelines, making it more aligned with current industry practices.⁵⁹ QbD is still seen in EU as an option and not as a requirement. Nevertheless, EMA is considering adding some QbD elements to the regulation to force companies to include risk analysis of their processes into their submission files.⁵⁹

Pharmaceutical industry opinion is that clearer regulation and a stronger commitment is necessary by both EMA and FDA to raise the tripartite new vision implementation to a higher level. It defends that further clarification on the regulatory expectations for quality systems is still necessary, especially for change management and knowledge management.⁶⁰ Also, variation processes should be modernized and simplified to facilitate the use of new technologies supported by an enhanced approach.⁵⁶ Both the regulatory agencies and the pharmaceutical industry recognise that new qualification and expertise should be available to regulators⁵⁶ as well as to industry.

Both EMA and FDA have agreed on April 2014 to extend the pilot program of the QbD parallel-assessment for 2 more years, because further topics still need to be addressed. Further guidance is expected in 2014.⁵⁷ Regulators will continue to work together with industry to make the implementation of the new quality vision a reality. There must be a common objective to provide safe and effective new products to patients as quickly as possible, ensure improved quality and efficient manufacturing processes. The future should encompass an efficient and facilitated regulatory framework that could foster innovation and communication between industry and regulators.⁵⁶

Industry must change the way they design and document QMS so that they become more process-oriented.⁵⁸ PQS should be based on interpretation, judgement, dedication and continuous improvement by people with expertise and qualification to transform these

systems into concrete quality and compliant results, and not only establish a structure of complex and difficult documents and processes. People with the necessary expertise are fundamental for a company's ability to build up knowledge and understanding of their products and processes.⁵⁸ ICH Q10 introduced quality systems across the product lifecycle, focussed on continual improvement of product, process and the PQS itself. PQS are no longer simply based on GMP checklists. Companies need to manage complexity and modernize decision-making processes, build trust and confidence and improve communication. Ultimately, industry must have the capacity to convert data into knowledge. The desired state is a PQS supported by science-based decision making, in a legal and regulatory compliant environment.⁵⁸

Many challenges lie ahead to both pharmaceutical industry and regulators:

- Regulatory environment is changing rapidly, legislation raises new challenges;
- Pharmaceutical industry is highly regulated and external requirements are constantly increasing;
- Companies need to specialise, be fast and flexible to be competitive;
- Research and development activities are by nature very risky
- Projects are extremely long, increasingly complex, costly and prone to failure.

Markets are becoming more price-sensitive. In order to remain competitive, companies need become more efficient and quality oriented. Adoption of the new quality vision may therefore result in a competitive advantage. The pharmaceutical manufacturing needs new technologies and innovation, which can only be achieved by means of sound scientific methodologies.

Placing the patient as the main focus of the new quality paradigm and the introduction of new concepts like Quality Risk Management, Continual Improvement, Knowledge Management and scientific knowledge based decisions will change the way the industry develops and achieves product realisation. The new quality paradigm is slowly gaining terrain, especially amongst the leading pharma companies, where full implementation on new developed products is already a reality. It is expected that QbD expands to more legacy products, generic drugs and biotech products.⁶⁰

It is Pharmaceutical industry's general belief that QbD will eventually become the norm⁵⁰.

9.1.2. Modelling

Predictive models are a useful tool to characterise, predict and control a process. It is widely used in many industries and, with the new paradigm introduced by ICH Q8, Q9 and Q10, it is starting to get instilled to the pharmaceutical industry. PAT plays a major role in modelling as it increases the capability of measuring and collecting data from the process.⁶¹

Different approaches for predictive modelling are possible. Models can be statistically (univariate or multivariate) or mechanistically (first-principles) based. The latter can provide a greater understanding and extrapolation outside the area defined by the former statistical models.⁶¹

Modern software solutions leverage the potential of predictive modelling, and permits modelling unit operations and even the whole process, in specific cases.⁶¹

Some achievements have been made in the pharmaceutical industry, sustained by new PAT solutions. The use of modelling has been reported in solid dosage drug manufacturing unit operations, namely in fluid-bed and tablet coating processing. Exceptional cases where full continuous process modelling has been implemented are also known.⁶¹ The application of model predictive designs is, however, still taking its first steps in drug product manufacturing.⁶¹

The full potential of modelling resides in complete modelling of a manufacturing process, with implemented advanced automatic process control and online-monitoring tools, where variability is controlled and shaped in every step of the process to result in a consistent quality product.⁶¹ The growing interest of the industry in continuous processing can be strengthened by the emerging predictive modelling and PAT initiatives.⁶²

The process of gathering the necessary knowledge to draw a model, contributes for an enhanced development and to a reduction of risks. Furthermore, correct use of predictive modelling can optimize development efficiency by decreasing time and costs. Development of models is strictly connected with the experimental development phase. Both activities synergistically contribute to knowledge gain.⁶¹ The ultimate aim of QbD is to reach a mechanistic understanding of the process and consequently more control, flexibility and quality assurance.⁶²

Companies need to balance the expenses with the level of accuracy needed when developing a model, bearing in mind that time and costs will raise as the process complexity increases.⁶¹

9.1.3. Biopharmaceuticals

Biopharmaceutical molecules continue to grow, comparing to classical small molecules. Companies continue to increase focus on specific clinical areas, as well as on the development of biosimilars and biobetters.^{63,64} Companies are investing more time and money in biopharmaceuticals development than in smaller molecule drugs.⁶⁴ The market is very competitive and difficult to reach. Moreover, the extremely high cost of developing a new molecule represents a huge obstacle. Companies will have to make improvements, namely by reducing costs and creating easier to use medicines (smaller volume dosages, less frequent and easier administration).⁶³ Smaller, local, multiproduct, modular single-use manufacturing facilities will become more common, as the need meet the needs of local markets, improve quality and lower costs will drive the business strategy.^{63,64} More cost-effective manufacturing will create room for increasing automation and continuous manufacturing as well.⁶⁴ Production will continue to shift to low-cost manufacturers located in emerging markets. Assuring global regulatory and GMP compliance will be a continuous challenge for regulators as low quality medicines and counterfeit medicines need to be kept out of the global distribution chain.⁶³

Apart the need to reduce costs, improve manufacturing processes and product itself, it is recognized that one of the key limiting aspects of biopharmaceutical drug manufacturing is the improvement of the analytical methods and the characterisation of the molecules.

The effort conducted by regulators, for over a decade, to improve and modernize biopharmaceutical production and regulatory guidances has not met yet the expectations of all involved stakeholders. The initiatives launched by the FDA in the early 2000's – "Pharmaceutical Quality for the 21st Century" – to stimulate manufacturers to modernize and embrace innovation has achieved some results, however the desired state is far from being reached. QbD is still not ingrained in the biopharmaceutical industry. Problems such as product defects and high rejection rates, unnecessary product destruction, waste of resources, market shortages, restriction of improvements to products and processes, continue to be prevalent.⁶⁵

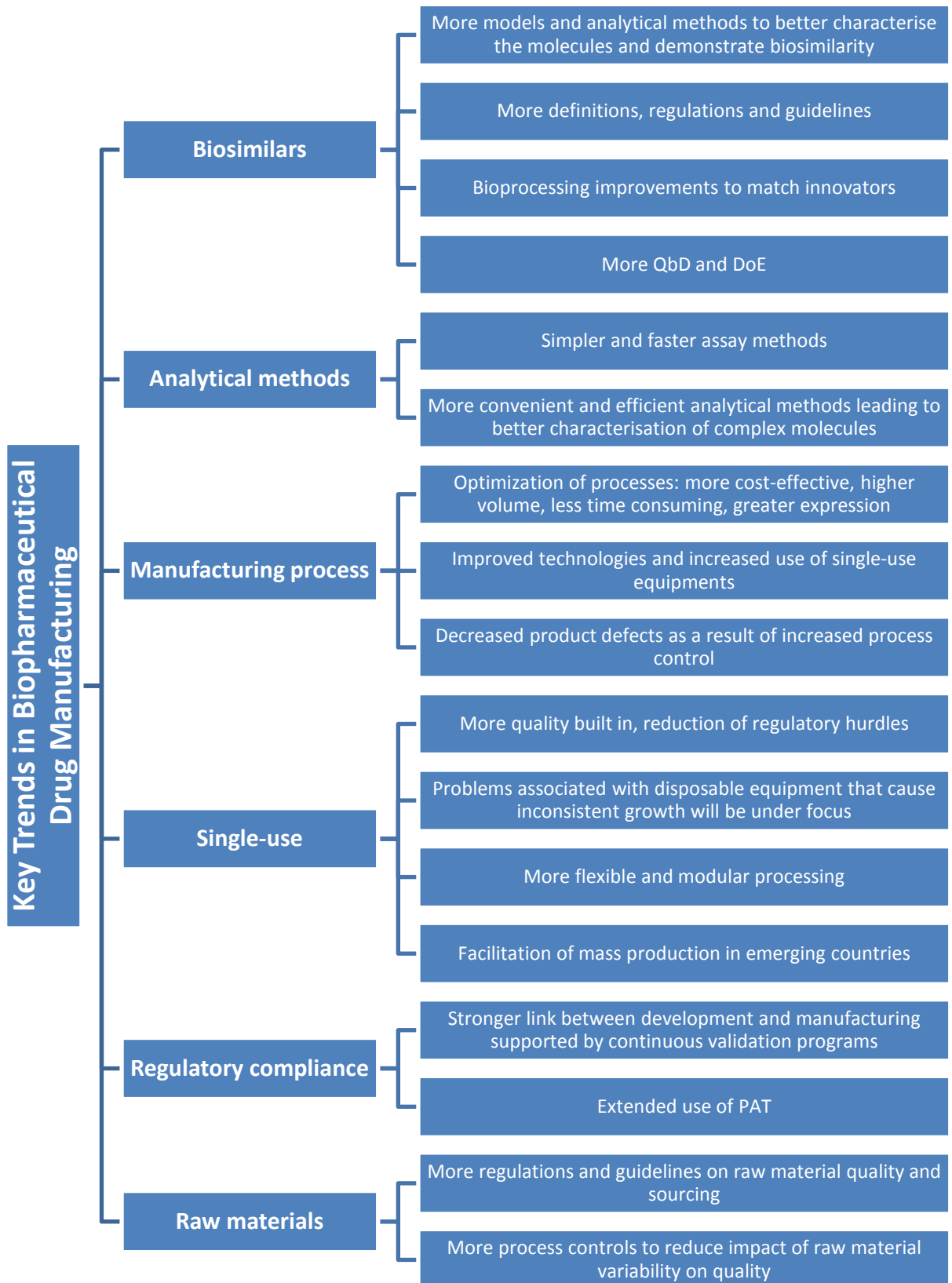
Pharmaceutical companies are not willing to invest in QbD and in modern technologies unless they can see a clear potential for cost reduction, fast approvals, facilitated reimbursement schemes, as well as no negative impact on patent coverage time and time-to-market. The demand for higher quality products may challenge facilitated patient access to new and better drugs, creating an additional hurdle to companies and regulators.⁶⁵ Even if the regulators are prepared to approve a drug that have already proven good results during clinical scale, manufacturers show insufficient skills to quickly develop drugs for commercial scale.⁶⁵ The scale up activities are constricting the development phase, delaying the time to reach the market. Adoption of QbD to ease the transition from development to commercial production would be advantageous as it would reduce unexpected events, improve efficiency and have a positive outcome on future inspections.⁶⁵

Much advancement has been achieved following the implementation of the new ICH vision. Many companies have successfully implemented QbD and risk management principles. There is a growing use of extended continuous online manufacturing process monitoring solutions and data evaluation software.⁶⁵

A small number of QbD applications have been submitted in Europe, and so far none has been granted yet. The complex and unpredictable nature of biologics pose a serious barrier to the implementation of QbD elements. On the other hand, companies have many times failed to interpret QbD terminology and apply risk management, but still expect flexibility without a strong supportive rationale.⁶⁶

Regulators face a demanding test as the new paradigm implicates their availability, competence and expertise to conduct inspections and to provide advice on modern quality systems.⁶⁵

Figure 34 - Key trends in biologics manufacturing⁶⁴

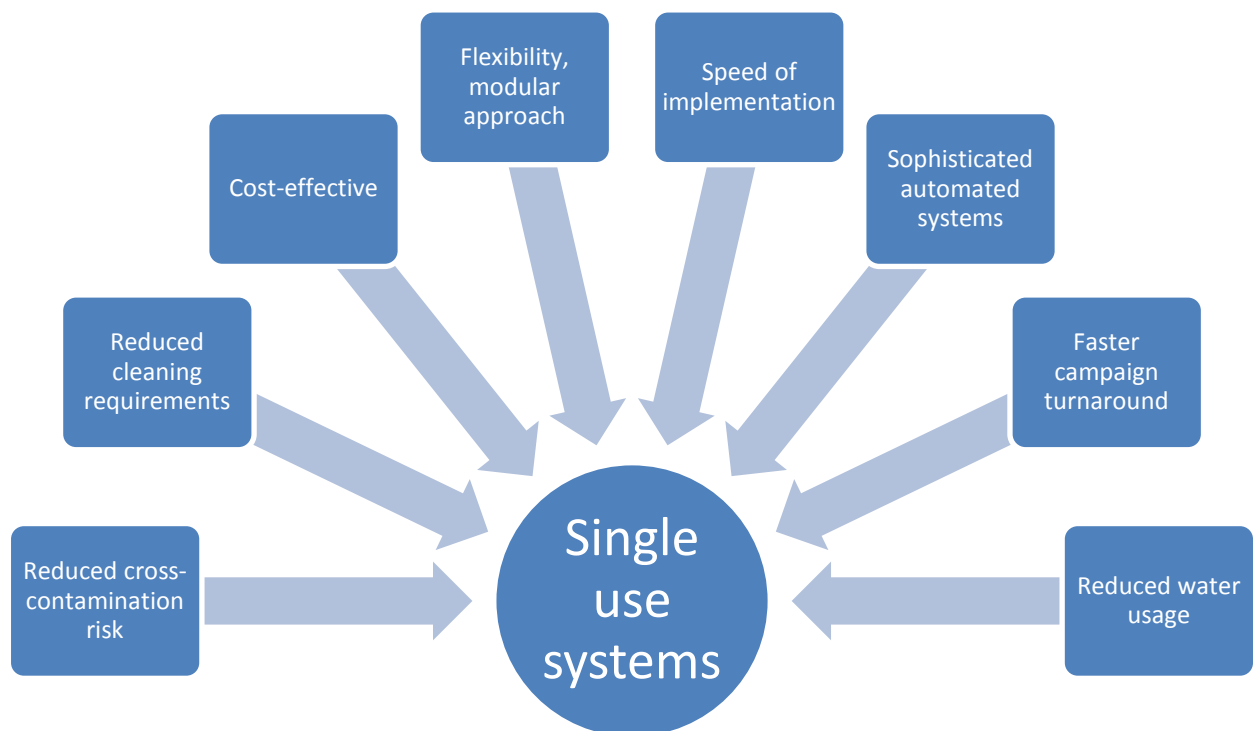


9.1.3.1. Flexible Facilities- Single Use Systems

Single use systems employ disposable technology and have become an important alternative for biopharmaceutical manufacturing, since it emerged a decade ago. In fact, the implementation of this technology continues to increase (BioPlan's 10th Annual Report).^{67, 68}

Disposable systems offer significant advantages over standard reusable systems.

Figure 35 – Advantages of single-use systems



The major unfavourable aspect of this technology is the concern about particles, leachables and extractables, as new disposable materials become available.⁶⁷

On one hand, the use of plastic materials may raise fear about particles, leachables and extractables, but on the other hand, it will motivate higher dedication to the investigation of all risks related to the materials. This results in better characterisation and knowledge about product and processes.⁶⁸

Single use systems are also seen as an opportunity to improve protection of the patients, as it can positively impact product quality and safety. By reducing contamination risk, single-use technologies can play an important role in the biopharmaceutical sector. Cleaning is no longer a major risk and cross-contamination is avoided because the equipment is not reused.⁶⁸

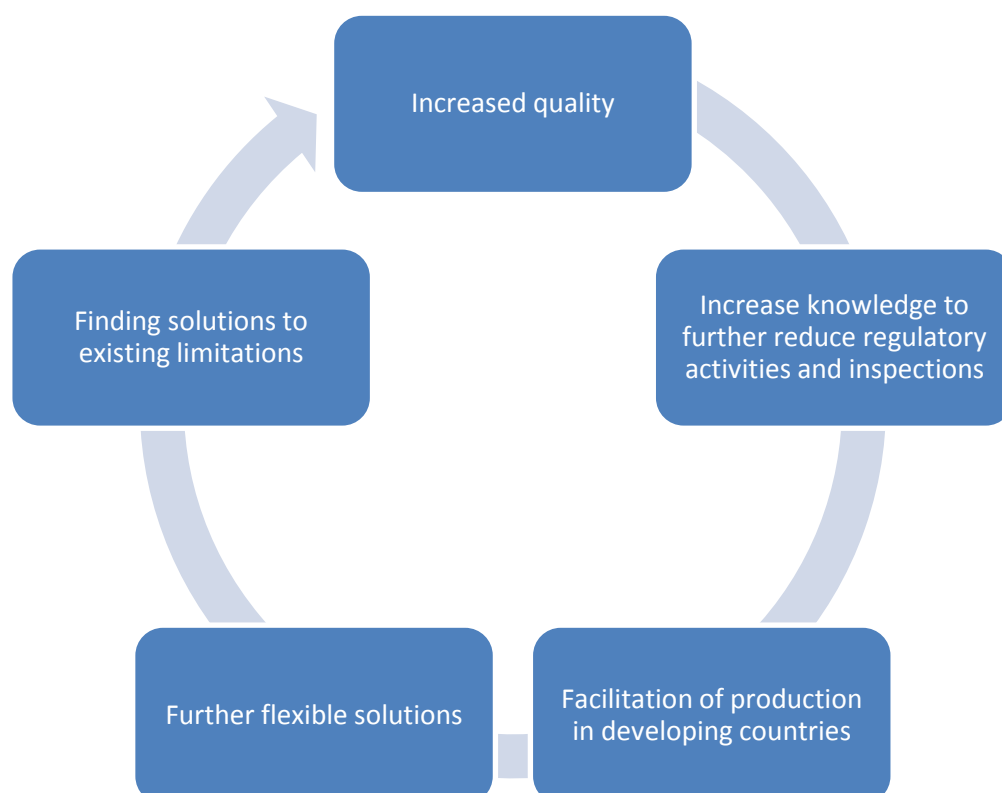
The industry recognition of disposable systems advantages and the start of its application at commercial scale have fostered innovation and development of this kind of equipment and solutions. As a consequence, vendors have been strongly investing in R&D to offer better and wider range of solutions.⁶⁷

The use of disposable systems, together with the ongoing effort of vendors to present new solutions, provides flexibility and facilitates integration of PAT and software metrics, resulting in more efficient processes.

Single use technologies have evolved to a point that it can afford to design processes closed from the upstream process to the purified drug substance. No further open steps carrying risks to the operators or contamination are necessary. This new approach is a major achievement and only possible by using innovative technologies, QRM and QbD.⁶⁹

Over time, it is expected that companies continue to see huge potential benefits and adopt single-use technologies from R&D through commercial production, in upstream and downstream processes. As standard equipment become depreciated or worn out, it will get replaced by disposable equipment solutions. Modular and flexible manufacturing processes will be preferred as more cost-effective alternatives.⁶⁷

Figure 36 - Trends that will shape disposable equipment's market⁶⁷



The capability of the manufacturers to offer flexibility, as regards scaling, multiple product manufacturing and quick campaign switches, will be a key factor for success.⁷⁰

9.1.4. Analytical methods

Similarly to manufacturing process development and validation, a lifecycle approach should be applied to analytical methods. Validation of analytical methods must not be seen as a one-time effort. An analytical method can be seen as a process which delivers data of desired quality, and therefore, QbD concepts may be applied similarly as to manufacturing processes. Focus on how the analytical method performs after validation, should continue throughout routine operation and method transfers activities.⁴⁶

Major differences observed between the traditional approach and the lifecycle approach are depicted in the following table.⁴⁶

Table 12 – Analytical methods: traditional approach vs. QbD approach⁴⁶

Aspect	Traditional approach	QbD (enhanced approach)
Validation principle	Check-list approach against ICH Q2 characteristics.	Analytical target profiles designed for each method/application.
Variability	Limited understanding of variation impact on method parameters and performance.	Structured approach to identify and understand method variables.
Transfer activities	Method transfer seen as a separate exercise from validation.	Transfer exercises are part of the lifecycle approach to validation.
Interpretation of concepts	Confusion over the difference between method verification, transfer and validation.	Improved clarification about the contribution of each activity for the lifecycle approach to validation.
Post-approval maintenance	High maintenance, increased regulatory activity.	Lower maintenance, reduced regulatory activity.

Aspect	Traditional approach	QbD (enhanced approach)
Submission application	Method validation is a key component of the CMC document.	Method qualification documentation is a review topic during inspections.
Guidance	Generally separate guidance on each activity: validation, verification, transfer.	Single guidance to a lifecycle approach to method validation.

More recently, industry has been making efforts to apply QbD concepts in the area of analytical methods. Risk assessments and statistically designed experiments can be useful to define target profiles and operational ranges for analytical methods, however there is no common agreement on the definition and applicability of the QbD concepts in this area. This approach is being assessed by regulators in parallel to the manufacturing process QbD elements, on a case-by-case basis.²⁶

QbD has been used to optimize analytical methods, including liquid chromatography, using DoE and to define a design space for the operating factors which ensure optimal separation.^{71,72} QbD and DoE helps to improve analytical methods precision, reduce errors and prevent costly and time consuming validation activities.⁷³

Method development using QbD in conjunction with intelligent modelling software helps reducing the number of experiments, time and costs, as well as defining a design space to allow greater flexibility in routine quality control.⁷⁴

In July 2013, the members of the United States Pharmacopoeia Validation and Verification Expert Panel, working under the direction of the General Chapters—Physical Analysis Expert Committee, posted a Stimuli article to the revision process proposing how the QbD approach modern concept of a lifecycle model, based on process validation and ICH guidelines Q8, Q9, and Q10, could be applied to analytical procedures.⁷⁵

9.1.5. Continuous Pharmaceutical Processing

Continuous manufacturing is a common technology already strongly implemented in other industries (chemical and food industries). Pharmaceutical Industry has recognized the advantages of this concept⁶³ and the adoption of continuous operations is in a growing pace.²¹

Continuous manufacturing consists in individual batch processing units that are connected in one process sequence and is enabled by the use of PAT and QbD. It represents a possible solution for the problems presented by the traditional batch production such as inefficiency and batch variability.⁷⁶

The main challenge is to install the necessary PAT into the continuous process and integrate the information collected into process control systems. In this conception, feedback-feedforward or closed-loop controls constantly adapt CPPs to maintain the process within desirable attribute ranges. Ultimately, the objective is to have a complex modular process behaving as one, under the control of all-encompassing automated system.³⁰

The process must have the necessary mechanisms and technology in place to ensure adequate tracking of the materials throughout the continuous process, for traceability reasons. A first-in/first-out principle, at material and intermediates level, is therefore extremely important.³⁰

The advantages of continuous processing are:^{30,77}

- Reduced scale-up problems
- Reduced material used in development studies and more efficient development process
- More flexible manufacturing processes
- Reduced equipment footprint
- Improved quality and process stability by using PAT
- Easier and faster development process

In many cases, the same equipment can be used for development and commercial manufacturing, reducing scale up effort.³⁰ This approach will become more common, especially in the biopharmaceuticals processes, as the demand for highly specialised processed and lower product volumes become a reality.⁷⁷

Continuous manufacturing, supported by PAT, incorporating closed-loop process controls and RTRT are seen as the possible future of pharmaceutical manufacturing, to a higher degree on solid dosage forms manufacturing processes.³⁰

9.1.6. Data and systems management

It is recognized that the level of knowledge gained, and not the volume of data, provides the basis for successfully meet quality goals. The complex amount of data generated throughout the different stages of the product lifecycle needs to be managed and evaluated in an effective manner to facilitate science-based approaches. For that end, development and manufacturing will rely more deeply on technology.

PQS plays a major role in providing the supportive structure for managing data throughout the product's lifecycle. Its performance is therefore dependent on data and systems management solutions. More elements of the PQS are managed through computerised systems. Those systems must be conveniently integrated to provide assurance of a consistent process and product quality.

Enterprise-wide systems are very important to establish connection between local, regional and central systems within a global company. Managing data in multiple and sometimes redundant systems may threaten traceability and communication, resulting in reduced system's efficiency.⁷⁸

It has been reported that companies have already implemented cloud-based electronic quality document systems, allowing a company to have a scalable and accessible system worldwide. Such system helps to identify areas that need process improvements, by tracking and monitoring product deviations. Easy reporting and access to key performance indicators permits early detection of potential issues, before it actually becomes a real problem. Automatic generation of reports and alerts by the system provide a useful metrics of the different areas, and help improve manufacturing efficiency and quality.⁷⁹

10. Conclusion

The ICH is the most significant organisation driving the global harmonisation of requirements with regard to the medicinal products. Following the generalised concern that pharmaceutical manufacturing has not kept up with modern technology and scientific progress and lags behind other industries, the ICH SC members recognised that a significant paradigm shift would be necessary. The need for global regulatory harmonisation and increasing problems of market shortages, manufacturing inefficiency, waste of materials and resources, product defects, market recalls, delays in marketing introduction, delays in the implementation of changes and inadequate information to support quality decisions have also motivated ICH to contribute to improving the status quo.

Areas for improvement were identified, an agreement was reached and a new ICH quality vision emerged (Brussels, July 2003). ICH effort resulted in the materialisation of 3 guidelines – ICH Q8 Pharmaceutical Development, ICH Q9 Quality Risk Management and ICH Q10 Pharmaceutical Quality System. **The new vision** changed the focus from product to ‘patient benefit’, and proposes to establish a new regulatory framework supported by science and an integrated approach of pharmaceutical quality system, development and quality risk management applied across the lifecycle of the product. The new elements of the ICH guidelines collide with industry established practices. Revolutionising the way how the industry develops and manufactures their products is a big challenge and requires a new mentality. A clear commitment from regulatory authorities to support industry with clear messages, instructions and further guidelines would be necessary, as well as platforms for discussion and collaboration between all interested parties. A transition period was of course necessary, in which the implementation of ICH Q8, Q9 and Q10 would be optional.

The established regulatory framework was seen as one of the reasons why modernisation and technological evolution are far behind scientific progress. **The traditional approach** to development based in trial-and-error did not generate the necessary understanding about the impact of materials, product and process variables. The development was seen more as an art and less as a science. Not knowing the criticality of the variables and their relationships, resulted in a process with fixed or narrow operational and control parameters. Risk management was not efficiently applied and resources were not assigned to the most critical aspects. Manufacturing processes were therefore usually “frozen” after regulatory approval. Regulatory hurdles such as the need to submit variations

which would be subjected to regulator's evaluation and approval, lack of mechanistic understanding and the risk of moving out of the comfort zone discouraged companies from performing changes and consequently opportunities to improve were generally lost.

Quality by Design supported by risk management and modern PQS constitutes the core of the modern holistic approach to pharmaceutical quality. QbD approach to pharmaceutical development aims to replace the empirical traditional development. It focuses on critical attributes affecting quality and patient, reducing the product variability.

The new approach can **benefit** pharmaceutical industry by opening minds to step new territories, providing the basis to acquire knowledge and creating confidence between companies and regulators. Many advantages are expected after adoption of the new paradigm, based not only on messages from the regulatory agencies and key opinion leaders but also on reports from companies and consultants that have successfully implemented and experienced QbD. The implementation of the tripartite guidelines new concepts will facilitate the identification and justification of quality target product profiles; enhance materials, product, equipment and process understanding; ensure capable control strategies; enable quality risk-based decision-making; provide more robust processes and consistent product; enable continuous improvement and innovation (PAT, RTRT, Software applications...); facilitate the adoption of the new process-validation approach; lower end-product testing; provide more flexibility and reduced regulatory burden (Design Space); reduce the impact of variability of raw materials; decrease costs and eliminate waste; reduce failures, deviations and investigations; cut down market recalls; enable a lifecycle approach to quality; provide more efficient control of changes; reduce inspections; and reinforce top management responsibility towards quality.

As regards to regulatory agencies, by accomplishing enhanced understanding about the risks to product quality and patients at drug approval and across product lifecycle, reviewers can improve review efficiency; reduce approval timelines; apply a more scientific and risk-based regulatory oversight; reduce inspections; provide regulatory flexibility; and optimise resources allocation without jeopardising quality. The necessary conditions, concepts and tools are hence available to capacitate the pharmaceutical industry to reliably produce high quality pharmaceutical products without burdensome regulatory supervision.

A decade has passed by and the initiative does not appear to have improved quality and innovation to the extent originally expected. Several **hurdles** seem to be blocking wider adoption of the new concepts by the pharmaceutical industry such as: misinterpretation or

misuse by both regulators and industry; misunderstanding of the objectives and advantages of QbD; difficulty in understanding criticality of quality attributes; reluctance to get out of the comfort zone; disbelief that QbD does not increase time-to-market, but reduces it; organisational resistances to change; no commitment from top management or policy not aligned with the new vision; lack of qualification and expertise; unwillingness to invest or fear of no return of investment; concern that using prior knowledge from older processes will expose themselves to additional regulatory examination; insufficient impulse and guidance from regulatory authorities.

As for the regulatory agencies, difficulties are also being experienced such as: QbD submissions giving rise to increased work load to reviewers; companies not using correct terminology; submissions containing unclear or insufficient information and scientific rationale; misinterpretation of QbD concepts; deficient assignment of criticality to quality attributes; unpreparedness of reviewers on risk assessment and QbD-related topics.

Global harmonization to the new paradigm regulatory requirements is a major concern to the pharmaceutical industry. It is uncertain if non-ICH countries will accept QbD-based submissions, and if they do, it is not known how they will assess it. If harmonisation is not achieved, then companies will face a significant obstacle to entering new markets. They will have to design their projects to generate the level of data consistent with the type of product and regional regulatory specificities. Non-ICH countries agencies will have to adapt to the new approach, otherwise there will be a risk that new medicinal products will not penetrate their markets. Those countries should analyse their own needs and expectations and adapt their organisational resources accordingly, because the new paradigm seems inevitable and at the end is the logical path to progress. On the other hand, there is also criticism about the new approach. India, a country with a powerful pharmaceutical manufacturing sector, and some patient groups are quite apprehensive about the ICH harmonisation effort.⁸⁰ The reason is due to the fact that, besides regulatory agencies, there are also industry organisations represented in the ICH SC.⁸⁰ There is fear that the new paradigm will introduce too high standards and costs that will only favour the world's top companies and protect their products from underdeveloped countries competition.⁸⁰

On the 8th of July 2014 it has been announced that Swiss Authority (Swissmedic) and the Canadian Authority (Health Canada) became members of the Steering Committee. It was also revealed that ICH is currently discussing its future governance model.⁸¹ This could

be an important step towards increased global harmonisation. Despite these latest events, adoption of the tripartite guideline by non-ICH countries is still a distant reality.

One of the main objectives of the new ICH quality approach is to promote **innovation and continual improvement**. It is clear how the guidelines will enable continual improvement opportunities, however the guidelines will not introduce new technologies by themselves. It is up to the industry to take the opportunities raised by the enhanced approach to development. The need to meet the expectations of acquiring enhanced knowledge and understanding should foster the use of modern and advanced equipment, systems and techniques. In fact, a QbD approach may require application of DoE, multivariate analysis, complex statistical analysis and implementation of automated systems for monitoring and control. Managing all complex data generated along the product lifecycle will call for efficient computing capacity and integrated software systems.

Implementation of QbD is a decision that each company has to take by itself. The decision requires a balancing act between the risks and consequences, bearing in mind that there are costs involved but also many potential benefits. At the end, the decision depends on the company and on the specificities of their products. If a high quality product is being produced, then changing may not be necessary. Executing QbD requires a significant change in mind-set. A dedicated, strong and continuous commitment, particularly from top management is fundamental. Many challenges lie ahead in applying a QbD approach. Companies need to build a strong business case and be aware that it is necessary to assess and plan structural and organisational changes, including the following activities: adapt the PQS; implement Quality Risk Management; re-qualify and train personnel; heighten in-house competence, such as statistics expertise; enhance data solutions; establish Knowledge Management; invest in modern technology, such as PAT. To be successful, companies need to understand the effort necessary to implement QbD. Internal resistance to change and the unwillingness to share knowledge with the regulatory agencies need cultural transformation. QbD means intensive, time and resource consuming activities during development, whose benefits will probably be realized further downstream in the product lifecycle. A step-by-step approach is therefore advised to allow the company to gain confidence and momentum to fully embrace the new quality vision. A slow progression is acceptable, as long as it is persistent and in the right track.

At the end, QbD is a promise yet to be fulfilled. Many companies hardly understand the concept, value, and how to implement it effectively because the guidelines are about

elements and concepts and not descriptive about the way to do it. Adoption of QbD has progressed slowly and there is still a learning process to go through for both industry and regulatory agencies. Top pharmaceutical companies have been in closer collaboration with regulatory agencies and have implemented QbD to a greater extent. Some companies opted for partial implementation while others opted to wait and see. Some resistance is seen in generic companies, whose efficiency could be improved by adopting QbD principles. However their priority is to reach the market as fast as possible, and any change that could impact their developing schedule represents a serious risk.

The current paradigm in pharmaceutical manufacturing is worrisome and requires a change. The ICH initiative is therefore welcomed as it presents a smarter approach to deal with existing problems. Overall, the advantages from implementing QbD are clear, as described in the available guidance and those who did implement QbD have seen its benefits.

The way forward is not to follow a fit-to-all plan to implement QbD. Companies need to weight all aspects, including its business needs and expected benefits, when deciding to go for full, partial or no QbD approach. Those who do not perform this assessment and opt to go for QbD simply because of pressure from regulators, might fail.

Eventually, successful adoption of QbD will payback companies not only on the operational, economic and competitive side, but also by creating a quality culture that improves the product and benefits the patient. The pharmaceutical industry lives in a highly competitive market. In addition, differentiation of manufacturers based on quality could be on the horizon of the regulatory agencies, using pharmaceutical manufacturing metrics and market rewards for quality⁸². For these reasons, those who engage earlier the new quality paradigm will be in a stronger position to succeed.

The future will reveal which companies have taken the right decision.

11. Bibliography

¹ JURAN, J.M. - How to think about quality planning. Juran on Quality by Design. United States of America: Juran Institute, Inc., 1992. ISBN: 0-02-916683-7, p. 4-14

² ICH - Press Release: "Step 4 for the ICH6 Program". Brussels, 2003. [Accessed on 8 June 2013]. Available on Internet:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnsweronCurrentGoodManufacturingPracticescGMPforDrugs/ucm071843.htm>

³ SCHNIEPP, Susan J. - Linking Drug Shortages and Quality Metrics. Biopharm International. Volume 27, number 5 (May 2014). p. 12-13

⁴ ABBOUD, Leila; HENSLEY, Scott - New Prescription For Drug Makers: Update the Plants. The Wall Street Journal. (Sept. 3, 2003). [Accessed on 8 June 2013]. Available on Internet:
<http://online.wsj.com/news/articles/SB10625358403931000>

⁵ EMA – Quality by design. Human regulatory. [Accessed on 22 June 2013]. Available on Internet:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000162.jsp

⁶ FDA - Guidance for Industry, PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance. (Sept. 2004) [Accessed on 8 June 2013]. Available on Internet: <http://www.fda.gov/downloads/Drugs/Guidances/ucm070305.pdf>

⁷ FDA - Challenges and Opportunities Report, Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products (Mar. 2004) [Accessed on 8 June 2013]. Available on Internet:
<http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm077262.htm>

⁸ FDA - Pharmaceutical cGMPs for the 21st Century - A Risk-Based Approach, Final Report - Fall 2004 (Sept. 2004) [Accessed on 8 June 2013]. Available on Internet:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnsweronCurrentGoodManufacturingPracticescGMPforDrugs/ucm137175.htm>

⁹ FDA - Critical Path Opportunities for Generic Drugs (May 1, 2004) [Accessed on 8 June 2013]. Available on Internet:

<http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm077250.htm>

¹⁰ ICH – Introduction, Training Programme for Q8/Q9/Q10 [Accessed on 8 June 2013].

Available on Internet: <http://www.ich.org/products/guidelines/quality/training-programme-for-q8q9q10.html>

¹¹ WECHSLER, Jill - FDA's CMC Pilot Program Moves Forward. EPT- The Electronic Newsletter of Pharmaceutical Technology. (Sept. 12, 2006). [Accessed on 8 June 2014]. Available on Internet:

<http://www.pharmtech.com/pharmtech/article/articleDetail.jsp?id=371948>

¹² EMA - EMA-FDA pilot program for parallel assessment of Quality by Design applications.

EMA/172347/2011 (March. 12, 2011). [Accessed on 15 June 2014]. Available on Internet:

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/03/WC500103621.pdf

¹³ ICH - Final Concept Paper, Q8: Pharmaceutical Development. (Sept. 19, 2003). [Accessed on 15 June 2013]. Available on Internet:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Concept_papers/Q8_Concept_Paper.pdf

¹⁴ ICH - ICH Harmonised Tripartite Guideline, Pharmaceutical Development Q8(R2). (Aug. 2009). [Accessed on 15 June 2013]. Available on Internet:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf

¹⁵ ICH - ICH Harmonised Tripartite Guideline, The Common Technical Document For The Registration Of Pharmaceuticals For Human Use: Quality – M4q(R1), Quality Overall Summary Of Module 2, Module 3 : Quality. (Sept. 12 2002). [Accessed on 15 June 2013]. Available on Internet:

Available on Internet:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R1_Quality/M4Q_R1_.pdf

¹⁶ ICH Q-IWG – Enhanced Training Element: Case study, Implementation of ICH Q8, Q9, Q10. (Nov. 2010). [Accessed on 8 June 2013]. Available on Internet:

<http://www.ich.org/products/guidelines/quality/training-programme-for-q8q9q10/presentations.html>

¹⁷ LITTLE, Thomas A. – Essentials in Establishing and Using Design Space. *Biopharm International*. Volume 26, number 9 (Sept. 2013), p. 50-54

¹⁸ WEBER, Clinton et al. – Quality by Design: A CMO's Perspective on Gaining Knowledge Faster and Better. *Biopharm International*. Volume 26, number 7 (July 2013), p. 40-46

¹⁹ ICH Q-IWG - Points to Consider (R2), ICH-Endorsed Guide for ICH Q8/Q9/Q10 Implementation. (Dec. 6, 2011). [Accessed on 8 June 2013]. Available on Internet: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_9_10_QAs/PtC/Quality_IWG_PtCR2_6dec2011.pdf

²⁰ MITCHELL, Mark – Determining Criticality—Process Parameters and Quality Attributes, Part II: Design of Experiments and Data-Driven Criticality. *Biopharm International*. Volume 27, number 1 (Jan. 2014), p. 34-40

²¹ MARKARIAN, Jennifer –Optimising Solid Dosage Manufacturing. *Pharmaceutical Technology Europe*. Volume 26, number 3 (Mar. 2014), p. 12-17

²² ICH - ICH Harmonised Tripartite Guideline, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances Q6A. (Oct. 6, 1999). [Accessed on 15 June 2013]. Available on Internet: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q6A/Step4/Q6Astep4.pdf

²³ LOLAS, Anastasia G.; RATHORE, Anurag S. – Regulatory Challenges in the QbD Paradigm. *Biopharm International*. Volume 25, number 9 (Sept. 2012), p. 44-53

²⁴ PATIL, Umesh - Pharmaceutical “Quality by Design” (QbD): An Introduction, Process Development and Applications. *Process Validation*. (Aug. 21, 2012). [Accessed on 15 June 2013]. Available on Internet: <http://www.askaboutvalidation.com/51895-pharmaceutical-quality-by-design-qbd-an-introduction-process-development-and-applications>

²⁵ ICH Q-IWG - Enhanced Training Elements: Key Messages, Implementation of ICH Q8, Q9, Q10. (Nov. 2010). [Accessed on 15 June 2013]. Available on Internet: <http://www.ich.org/products/guidelines/quality/training-programme-for-q8q9q10/presentations.html>

- ²⁶ EMA - EMA-FDA pilot program for parallel assessment of Quality-by-Design applications: lessons learnt and Q&A resulting from the first parallel. EMA/430501/2013 (Aug. 20, 2013). [Accessed on 8 Feb 2014]. Available on Internet: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/08/WC500148215.pdf
- ²⁷ EMA – News: European Medicines Agency and US Food and Drug Administration release first conclusions of parallel assessment of quality-by-design applications. (Aug. 20, 2013). [Accessed on 8 Feb 2014]. Available on Internet: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/08/news_detail_001876.jsp&mid=WC0b01ac058004d5c1
- ²⁸ MITCHELL, Mark – Determining Criticality—Process Parameters and Quality Attributes, Part III: Process Control Strategies – Criticality throughout the Lifecycle. Biopharm International. Volume 27, number 3 (Mar. 2014), p. 26-35
- ²⁹ Representatives Of The US Food And Drug Administration And Industry – FDA's Pharmaceutical Quality Initiatives: Implementation of a Modern Risk-based Approach. Pharmaceutical Technology. (May 2, 2008). [Accessed on 15 June 2013]. Available on Internet: <http://www.pharmtech.com/pharmtech/Peer-Reviewed+Research/FDAs-Pharmaceutical-Quality-Initiatives-Implementa/ArticleStandard/Article/detail/515163>
- ³⁰ MARKARIAN, Jennifer – Process Analytical Technology and Process Control in Solid-Dosage Manufacturing. Pharmaceutical Technology Europe. Volume 25, number 4 (Apr. 2013), p. 30-36
- ³¹ ICH - Final Concept Paper, Q9: Quality Risk Management. (Nov. 11, 2003). [Accessed on 17 Aug. 2013]. Available on Internet: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Concept_papers/Q9_Concept_Paper.pdf
- ³² ICH - Final Business Plan, Q9: Quality Risk Management. (Nov. 11, 2003). [Accessed on 17 Aug. 2013]. Available on Internet: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Business_plan/Q9_Business_Plan.pdf
- ³³ ICH - ICH Harmonised Tripartite Guideline, Quality Risk Management Q9. (Nov. 2005). [Accessed on 17 Aug. 2013]. Available on Internet:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf

³⁴ ICH Q9-EWG – Q9 Briefing Pack. (July 2006). [Accessed on 17 Aug 2013]. Available on Internet: <http://www.ich.org/products/guidelines/quality/q9-briefing-pack/briefing-pack.html>

³⁵ GOUGH, Peter H. – ICH Q9 ‘Quality Risk Management’ - an industry view. Eli Lilly and Company. [Accessed on 17 Aug 2013]. Available on Internet: <http://www.nihs.go.jp/drug/PhForum/documents041122/Gough041122.pdf>

³⁶ LITTLE, Thomas A. – Essentials in Quality Risk Management. Biopharm International. Volume 26, number 5 (May 2013), p. 52-57

³⁷ ICH - Final Concept Paper, Q10: Pharmaceutical Quality Systems. (Sept. 9, 2005). [Accessed on 21 Sept. 2013]. Available on Internet: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Concept_papers/Q10_Concept_Paper.pdf

³⁸ ICH - ICH Harmonised Tripartite Guideline, Pharmaceutical Quality System Q10. (June 2008). [Accessed on 21 Sept. 2013]. Available on Internet: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf

³⁹ ICH - Quality Implementation Working Group on Q8, Q9 and Q10, Questions & Answers (R4). (Nov. 116, 2010). [Accessed on 21 Sept. 2013]. Available on Internet: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_9_10_QAs/Q-IWG_Q_A_R4_Step4_Nov.2010.pdf

⁴⁰ ICH Q-IWG - Basic Training, Implementation of ICH Q8, Q9, Q10. (Nov. 2010). [Accessed on 15 June 2013]. Available on Internet: <http://www.ich.org/products/guidelines/quality/training-programme-for-q8q9q10/presentations.html>

⁴¹ LUCAS, Ian - ICH Q10 Pharmaceutical Quality System. SeerPharma. Melbourne (Apr. 2012). [Accessed on 28 Sept 2013]. Available on Internet: http://www.seerpharma.com.au/sites/default/files/cck_articles_pdf/ICH_Q10_Pharmaceutical_Quality_System_Apr12.pdf

- ⁴² ICH - Q8, Q9, Q10 - Implementation. [Accessed on 28 Sept. 2013]. Available on Internet: <http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html>
- ⁴³ CATANIA, James P. - Quality by Design: The Case for Change (Part II). Biopharm International. Volume 24, issue 5 (May 1, 2011), p. 20-24. [Accessed on 28 Sept. 2013]. Available on Internet: <http://www.biopharminternational.com/biopharm/article/articleDetail.jsp?id=718073&sk=&date=&pageID=2>
- ⁴⁴ PRLOG - Quality by Design; Better Than the Traditional Approach of Process Validation. PRLOG Press Release Distribution. (Nov. 5, 2012). [Accessed on 28 Sept. 2013]. Available on Internet: <http://www.prlog.org/12015787-quality-by-design-better-than-the-traditional-approach-of-process-validation.html>
- ⁴⁵ MOLLAH, A. Hamid; BOZZONE, Scott; RATHORE, Anurag S. – Process Lifecycle Validation: Applying Risk Management. Biopharm International. Volume 26, number 8 (Aug. 2013), p. 28-33
- ⁴⁶ NETHERCOTE, Phil et al. – QbD for Better Method Validation and Transfer. PharmaManufacturing.com. (Aug. 13, 2010). [Accessed on 12 Oct. 2013]. Available on Internet: <http://www.pharmamanufacturing.com/articles/2010/060/>
- ⁴⁷ EMA (CHMP/CVMP) - Guideline on process validation for finished products -information and data to be provided in regulatory submissions. EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1. (Feb. 2014). [Accessed on 24 May 2014]. Available on Internet: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162136.pdf
- ⁴⁸ LITTLE, Thomas – Understanding and Modelling Product and Process Variation. Biopharm International. Volume 26, number 12 (Dec. 2013), p. 50-56
- ⁴⁹ MILMO, Sean – A Lifecycle Approach to Process Validation. Biopharm International. Volume 26, number 6 (June 2013), p. 14-16
- ⁵⁰ KOURTI, T.; DAVIS, B. - The Business Benefits of Quality by Design (QbD). Pharmaceutical Engineering. Volume 32, number 4 (July/Aug. 2012). p. 1-10. [Accessed on 12 Oct. 2013]. Available on Internet: <https://www.ispe.org/pe-ja12/kourti.pdf>

- ⁵¹ FDA - Understanding Challenges to Quality by Design, Final deliverable for FDA Understanding Challenges to QbD Project. (Dec. 2009). [Accessed on 23 Nov. 2013]. Available on Internet: <http://www.pharmaqbd.com/wp-content/uploads/2011/05/Understanding-Challenges-to-Quality-by-Design.pdf>
- ⁵² DAVIDSON, James - FDA Study on the Status of QbD Implementation in the Generic Industry. (Jan. 29, 2013). [Accessed on 23 Nov. 2013]. Available on Internet: <http://www.lachmanconsultants.com/fda-study-on-the-status-of-qbd-implementation-in-the-generic-industry.asp>
- ⁵³ DPT - What Is Quality By Design (Qbd) – And Why Should You Care? DPT Thought Leadership, Issue 11: 1st in a Series (2013). [Accessed on 23 Nov. 2013]. Available on Internet: <http://www.dptlabs.com/wp-content/uploads/2013/05/What-is-Quality-by-Design-QbD-and-Why-Should-You-Care.pdf>
- ⁵⁴ PETERS, Rita – 2014 Manufacturing Trends and Outlook. Biopharm International. Volume 27, number 1 (Jan. 2014), p. 24-26
- ⁵⁵ PHARMA-IQ - Process Analytical Technology (PAT) and Quality by Design (QbD), Overview, 2014. Changes in Investment and Implementation: 2010-2012. (2014). [Accessed on 8 June 2014]. Available on Internet: <http://www.patandqbd.com/redForms.aspx?eventid=8440&id=389080&FormID=%2011&frmType=1&m=16336&FrmBypass=False&mLoc=F&SponsorOpt=False>
- ⁵⁶ MILMO, Sean – Quality by Design – Bridging the Gap between Concept and Implementation. Pharmaceutical Technology Europe. Volume 38, number 4 (Apr. 2014), p. 18-20
- ⁵⁷ EMA – News: EMA and FDA extend pilot programme for parallel assessment of quality-by-design applications. (Mar. 06, 2014). [Accessed on 15 Mar. 2014]. Available on Internet: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/03/news_detail_002035.jsp&mid=WC0b01ac058004d5c1
- ⁵⁸ SCHMITT, Siegfried – Compliance in Quality Systems. Pharmaceutical Technology Europe. Volume 25, number 11 (Nov. 2013), p. 42
- ⁵⁹ MILMO, Sean – Advancing QbD in the EU. Pharmaceutical Technology Europe. Volume 25, number 4 (Apr. 2013), p. 14-16

⁶⁰ A Regulatory Perspective on the Current and Future State of Pharmaceutical Quality, International Conference on Drug Development, Austin, TX, Feb 26, 2013, Christine M. V. Moore, Ph.D., Acting Director, Office of New Drug Quality Assessment, CDER/FDA

⁶¹ MARKARIAN, Jennifer – Using Model-Predictive Design in Solid-Dosage Manufacturing Processes. *Pharmaceutical Technology Europe*. Volume 25, number 6 (June 2013), p. 27-30

⁶² MUZZIO, Fernando et al. – Model-Predictive Design, Control and Optimisation. *Pharmaceutical Technology Europe*. Volume 25, number 6 (June 2013), p. 31-33

⁶³ DRAKULICH, Angie – A Look Ahead in Biomanufacturing. *Biopharm International*. Volume 26, number 1 (Jan. 2013), p. 6

⁶⁴ LANGER, Eric – The Future of Biopharma. *Biopharm International*. Volume 26, number 1 (Jan. 2013), p. 22-24

⁶⁵ WECHSLER, Jill – Drug Quality at Center Stage for FDA and Manufacturers. *Biopharm International*. Volume 26, number 1 (Jan. 2013), p. 10-12

⁶⁶ STANTON, Dan – To QbD or not to QbD? That is the Question.... *In-Pharma Technologist.com*. (Jul. 24, 2013). [Accessed on 29 Mar. 2014]. Available on Internet: <http://www.in-pharmatechnologist.com/Processing/To-QbD-or-not-to-QbD-That-is-the-Question>

⁶⁷ LANGER, Eric – Ten Years Later: Innovation Driving Single-Use Technology Advances. Supplement to *Biopharm International*. (Apr. 2013), p. s4-s8

⁶⁸ ISBERG, Eric – The Overlooked Benefits of Single-Use Technology: Improved Quality and Increased Patient Safety. Supplement to *Biopharm International*. (Apr. 2013), p. s9-s10

⁶⁹ GALLIHER, Parrish; PRALONG, Alain – When the Process Becomes the Product: Single-Use Technology and the Next Biomanufacturing Paradigm. Supplement to *Biopharm International*. (Apr. 2013), p. s27-s30

⁷⁰ GOTTSCHALK, Uwe – The Future of Downstream Processing. Supplement to *Biopharm International*. (Aug. 2013), p. s39-s45

⁷¹ DEBRUS, B. et al. – A New Method for Quality by Design Robust Optimization in Liquid Chromatography. *LCGC Europe*. Volume 26, number 7. (July 2013), p. 370-377

- ⁷² KORMÁNY, R.; RIEGER, Hans-Jürgen; MOLNÁR, I. – Application of Quality by Design to a Pharmaceutical Sample Using UHPLC Method Development with Modelling Technologies. Supplement to LCGC Europe. (Oct. 2013), p. 14-19
- ⁷³ LITTLE, Thomas A. – Design of Experiments for Analytical Method Development and Validation. Biopharm International. Volume 27, number 3. (Mar. 2014), p. 56-60
- ⁷⁴ MOLNÁR, I.; KORMÁNY, R.; FEKETE, Jenő – Quality by Design in Pharmaceutical Analysis Using Computer Simulation with UHPLC. LCGC Europe. (May 1, 2014), p. 240-254
- ⁷⁵ MARTIN, G. P. et al. - Stimuli to the Revision Process: Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification. (July 2013). [Accessed on 29 Mar. 2014]. Available on Internet: http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/revisions/lifecycle_pdf.pdf
- ⁷⁶ CLAYTON, Jamie; YIN, John – The Role of Powder Characterisation in Continuous Manufacturing. Pharmaceutical Technology Europe. Volume 26, number 6 (June 2014), p. 30-35
- ⁷⁷ DRAKULICH, Angie – A Look Ahead at Biopharma, Manufacturing and Regulation. Biopharm International. Volume 26, number 1 (Jan. 2013), p. 26-31
- ⁷⁸ KARU, KR – Data and Systems Management. Biopharm International. Volume 26, number 5 (May 2013), p. 48-50
- ⁷⁹ GOLDSMITH, Jennifer – One Step Back, Two Steps Forward to Improved Quality Processes. PharmTech.com (May 8, 2014). [Accessed on 29 Mar. 2014]. Available on Internet: <http://www.pharmtech.com/pharmtech/QC%2FQA/One-Step-Back-Two-Steps-Forward-to-Improved-Qualit/ArticleStandard/Article/detail/842874?contextCategoryId=49222>
- ⁸⁰ ECA – GMP News: India blocks further Expansion of the ICH Harmonisation. (July 09, 2014). [Accessed on 2 Aug. 2014]. Available on Internet: http://www.gmp-compliance.org/enews_04382_India-blocks-further-Expansion-of-the-ICH-Harmonisation.html
- ⁸¹ ICH – Press Release: Minneapolis, MN, USA, June 2014 (July 2014). [Accessed on 2 Aug. 2014]. Available on Internet: http://www.ich.org/fileadmin/Public_Web_Site/News_room/B-Press_Releases/ICH_GCG_Press_Releases/Press_Release_Minneapolis_2014.pdf

⁸² MOORE, Christine M. V., Acting Director, Office of New Drug Quality Assessment CDER/FDA – A Regulatory Perspective on the Current and Future State of Pharmaceutical Quality. In: International Conference on Drug Development, Austin, TX (Feb. 26, 2013). [Accessed on 17 Aug. 2013]. Available on Internet: <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM359267.pdf>

