Quality by Design (QbD)

Helmut Hofbauer

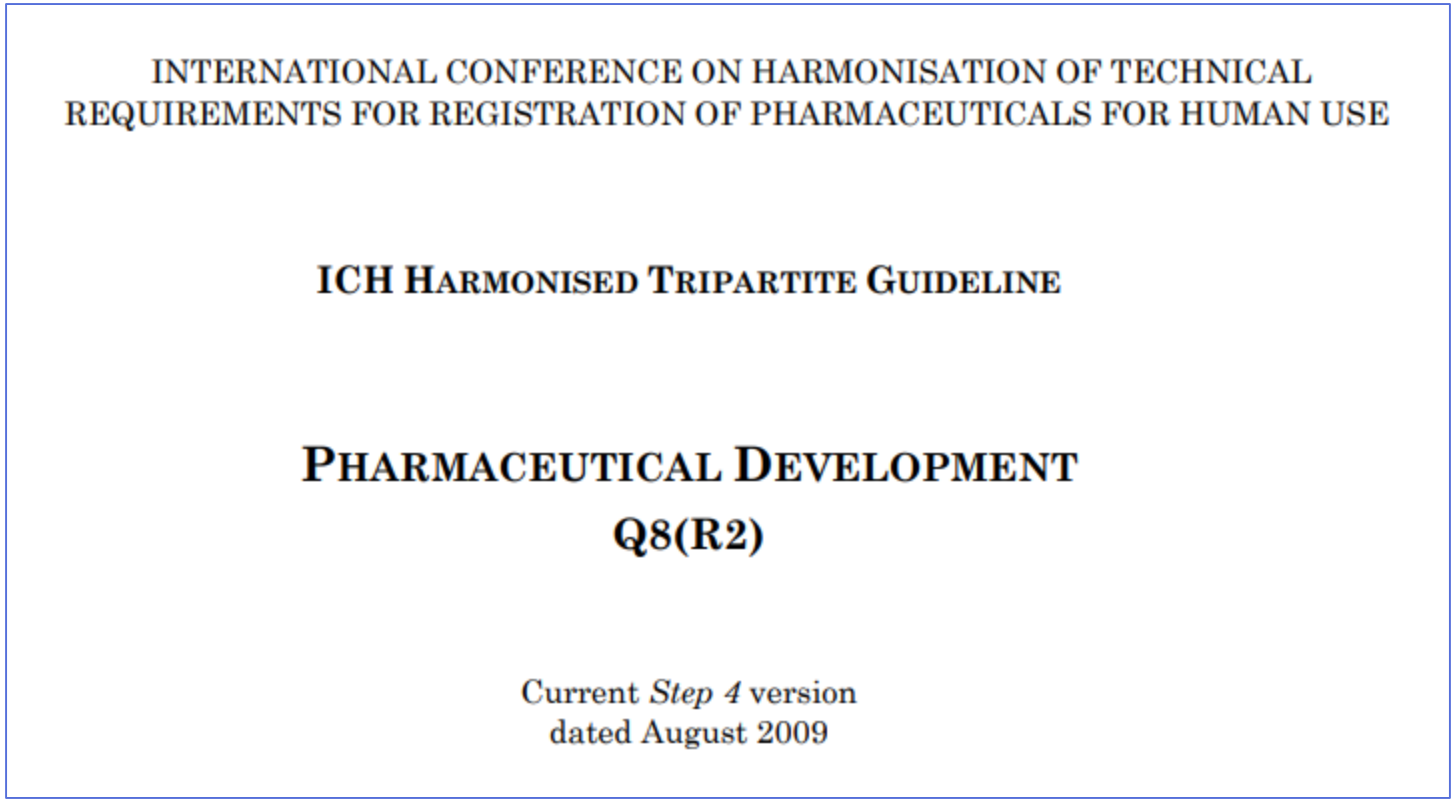
Journal Club, 6 December 2021

Issues

- What is part of Quality by Design (and what isn't)?
- Is only the enhanced approach QbD?
- Is the minimal approach also Qbd (as it involves risk assessment)?
- What was the development process before ICH Q8 (traditional approach)?
- To what extent is QbD mandatory?

ICH Q8 – from ICH website

https://database.ich.org/sites/default/files/Q8%28R2%29%20Guideline.pdf



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

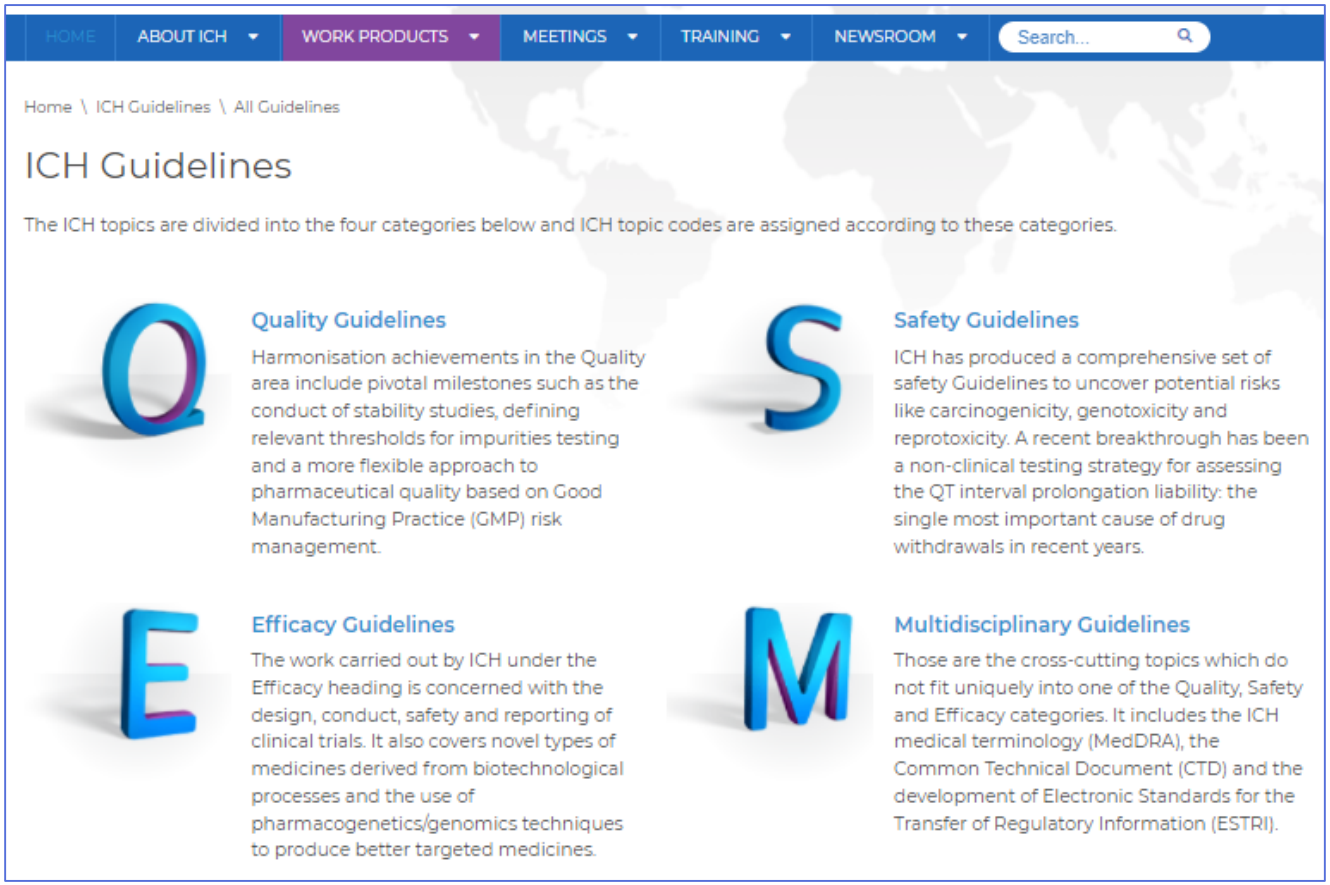
PHARMACEUTICAL DEVELOPMENT

Q8(R2)

Current *Step 4* version
dated August 2009

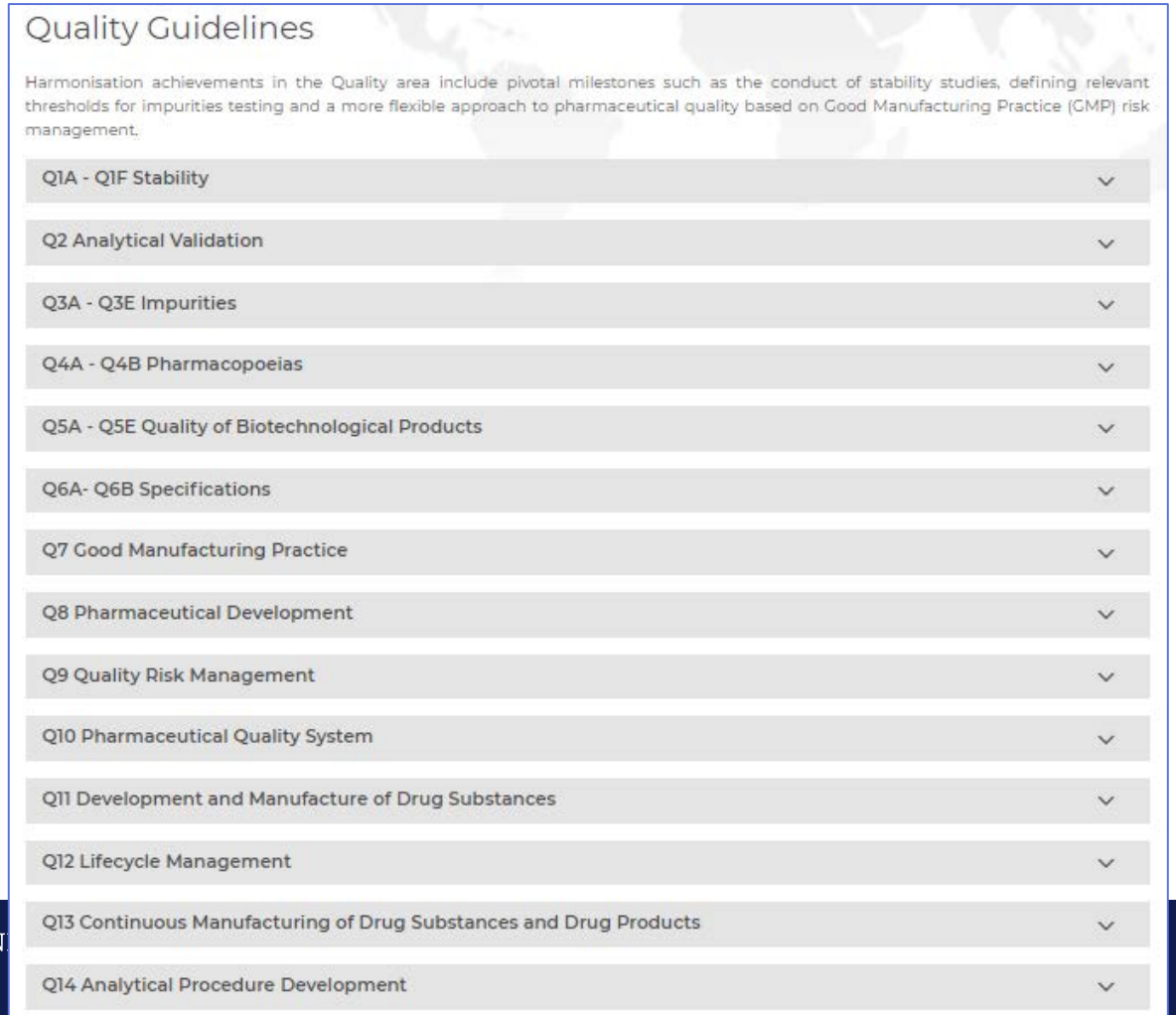
Where the documents can be found...

https://www.ich.org/page/ich-guidelines



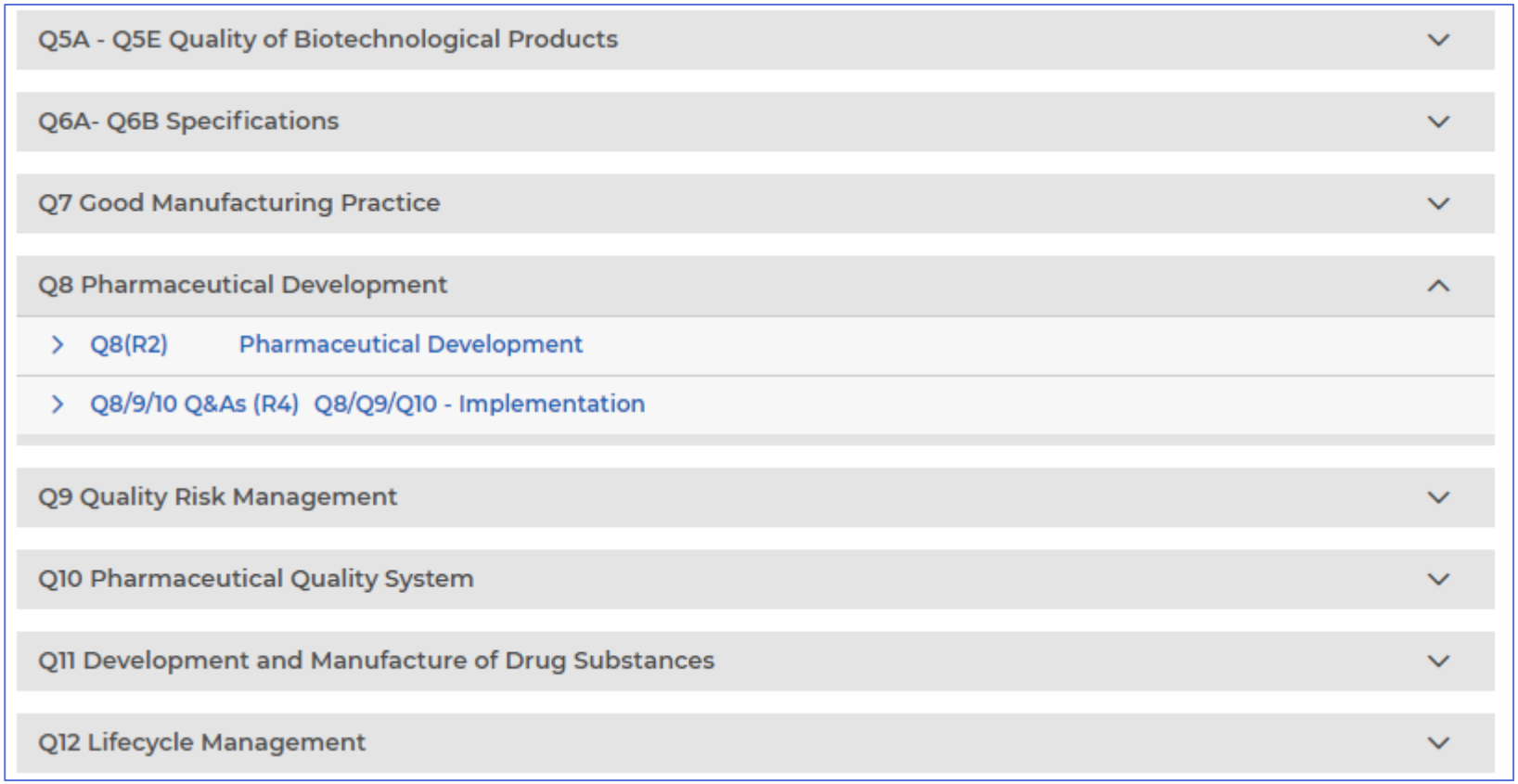
...on the ICH website

https://www.ich.org/page/quality-guidelines



...on the ICH website

https://www.ich.org/page/quality-guidelines



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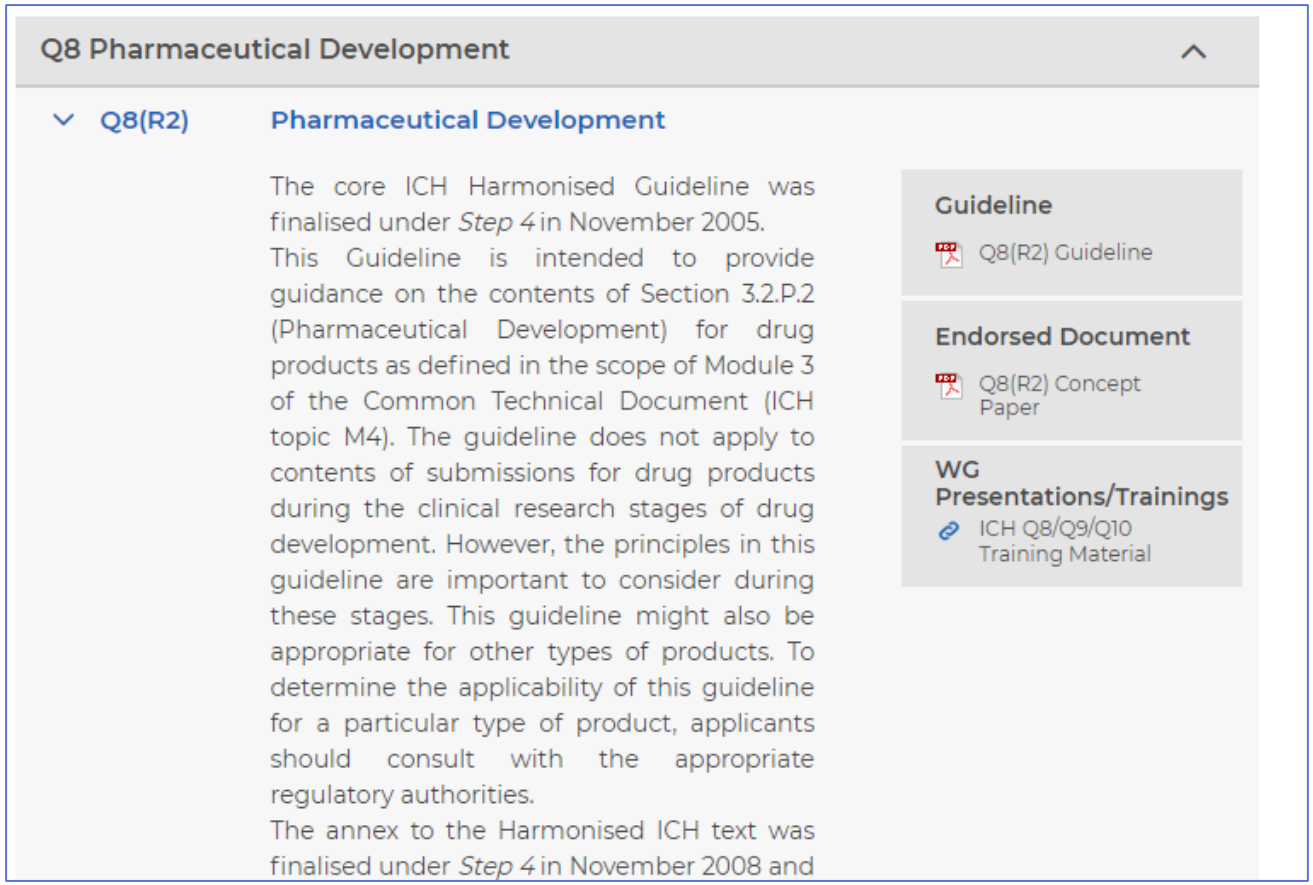


...on the ICH website

https://ich.org/page/presentations

Presentations

Basic Training	
Introduction to ICH and the new Quality Paradigm	ppt
ICH Q9: Quality Risk Management	Q9 Briefing pack
How ICH Q8, Q9, Q10 Guidelines are working together throughout the product life cycle	ppt swf
Enhanced Training Elements: Key Messages	
Design Space	ppt
Control Strategy	ppt
Pharmaceutical Quality System	ppt
Quality Risk Management	ppt

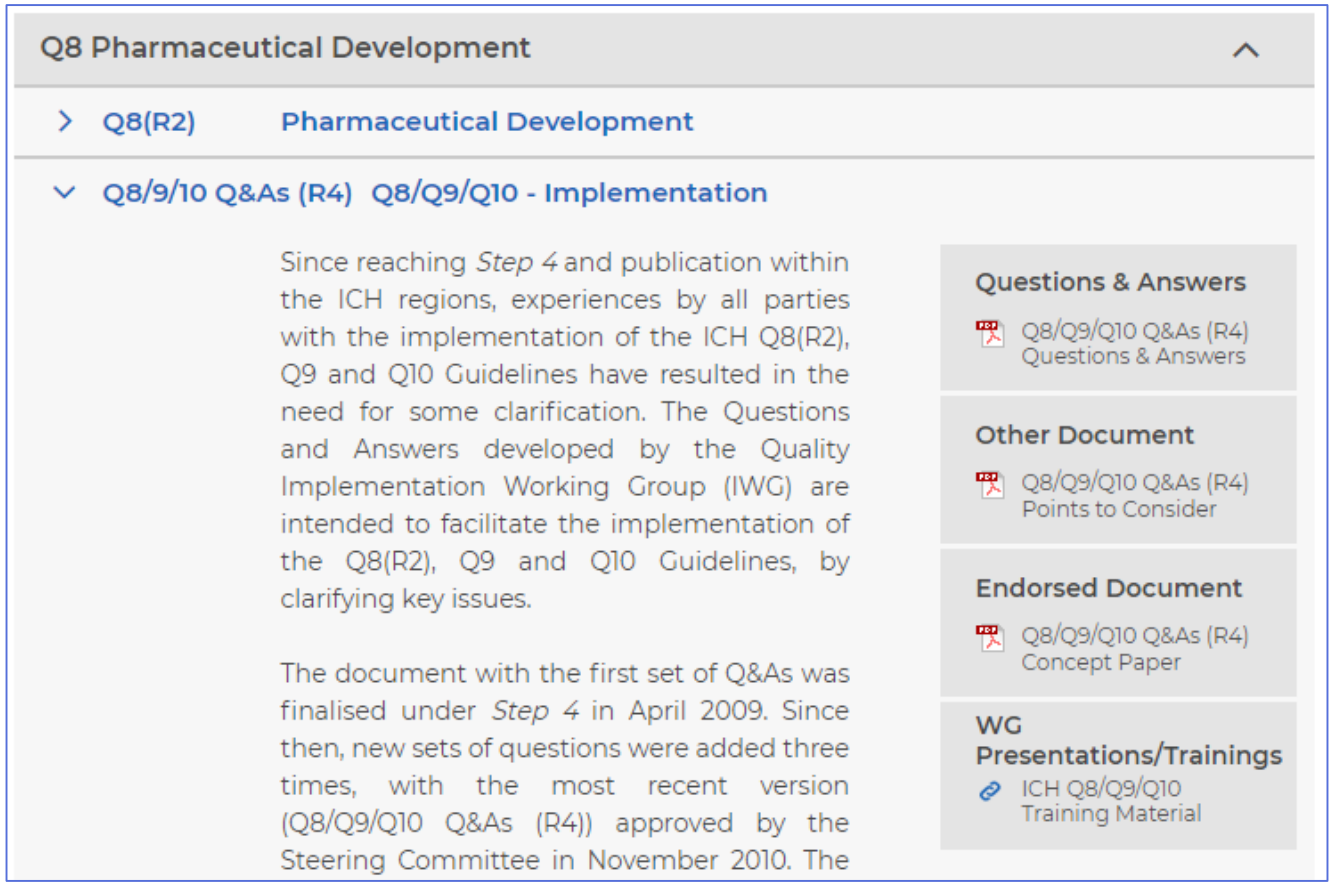
...on the ICH website

https://ich.org/page/presentations

Quality Risk Management	ppt
Enhanced Training Element: Case Study	ppt
Product Development	ppt swf
Regulatory Assessment	ppt swf
Manufacturing Implementation and PQS Considerations	ppt swf
Inspection	ppt swf
Questions & Answers Document	pdf
Report on ICH Q-IWG Activities	ppt swf

...on the ICH website

https://www.ich.org/page/quality-guidelines



...in Eudralex Vol. 3 – EMA scientific guidelines

https://ec.europa.eu/health/documents/eudralex/vol-3_en

EMA scientific guidelines for QdB

https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/quality/quality-quality-design-qbd

- Adaptive pathways
- Advanced therapies
- Clinical trials
- Compassionate use
- Compliance
- Data on medicines (ISO IDMP standards)
- Ethical use of animals
- Innovation in medicines
- Medicines for older people
- Orphan designation
- Paediatric medicines
- Pharmacovigilance

Quality: Quality by Design (QbD)

Share

Table of contents

The European Medicines Agency's scientific guidelines on Quality by Design help medicine developers prepare marketing authorisation applications for human medicines.

For a complete list of scientific guidelines currently open for consultation, see Public consultations.

Guidelines

- ICH Q8 (R2) Pharmaceutical development
- ICH Q9 Quality risk management
- ICH Q10 Pharmaceutical quality system
- ICH guideline Q13 on continuous manufacturing of drug substances and drug products
- ICH Q8, Q9 and Q10 - questions and answers
- ICH guideline Q13 on continuous manufacturing of drug substances and drug products
- Real time release testing
- Use of near infrared spectroscopy (NIRS) by the pharmaceutical industry and the data requirements for new submissions and variations

...in Eudralex Vol. 3 – EMA scientific guidelines

https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-11.pdf

22 June 2017
EMA/CHMP/ICH/167068/2004
Committee for Human Medicinal Products

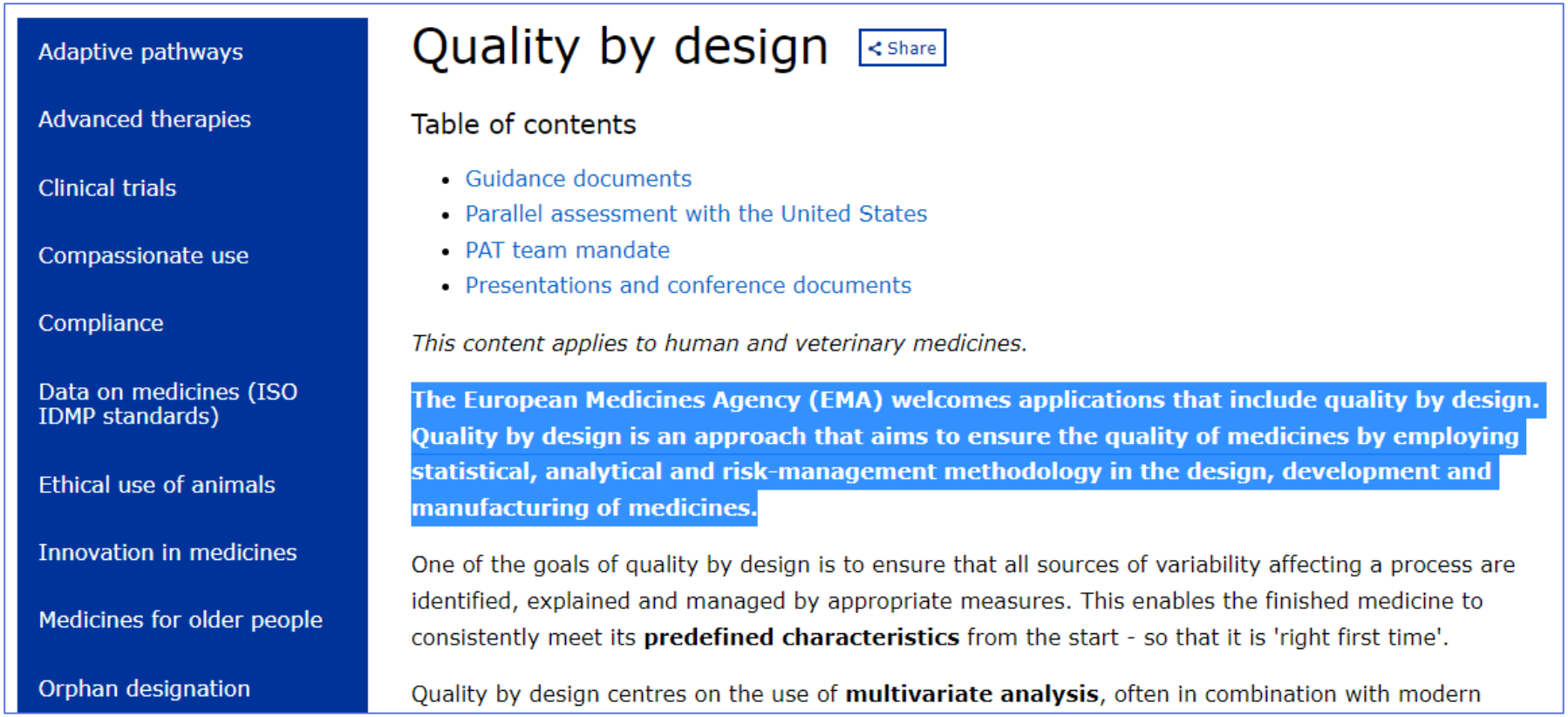
ICH guideline Q8 (R2) on pharmaceutical development

Step 5

Transmission to CHMP	December 2004
Transmission to interested parties	December 2004
Deadline for comments	June 2005
Final adoption by CHMP	November 2005
Date for coming into effect	May 2006
Editorial corrections	August 2009

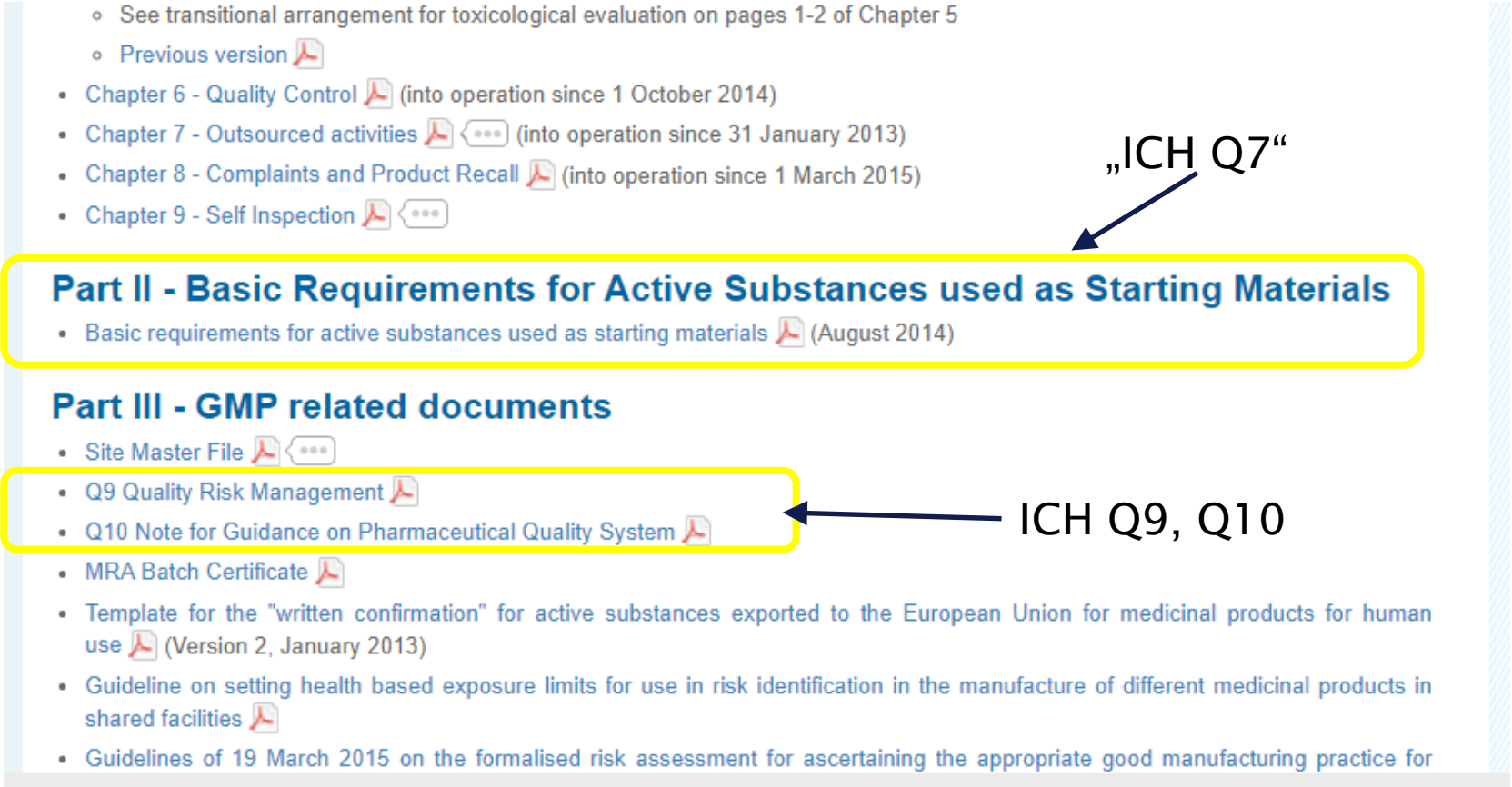
EMA website for Qdb

https://www.ema.europa.eu/en/human-regulatory/research-development/quality-design



...in Eudralex Vol 4 (Good Manufacturing Practice)

https://ec.europa.eu/health/documents/eudralex/vol-4_en



Objective of ICH Q8

Title of ICH Q8 is “PHARMACEUTICAL DEVELOPMENT” – not “QUALITY BY DESIGN”!

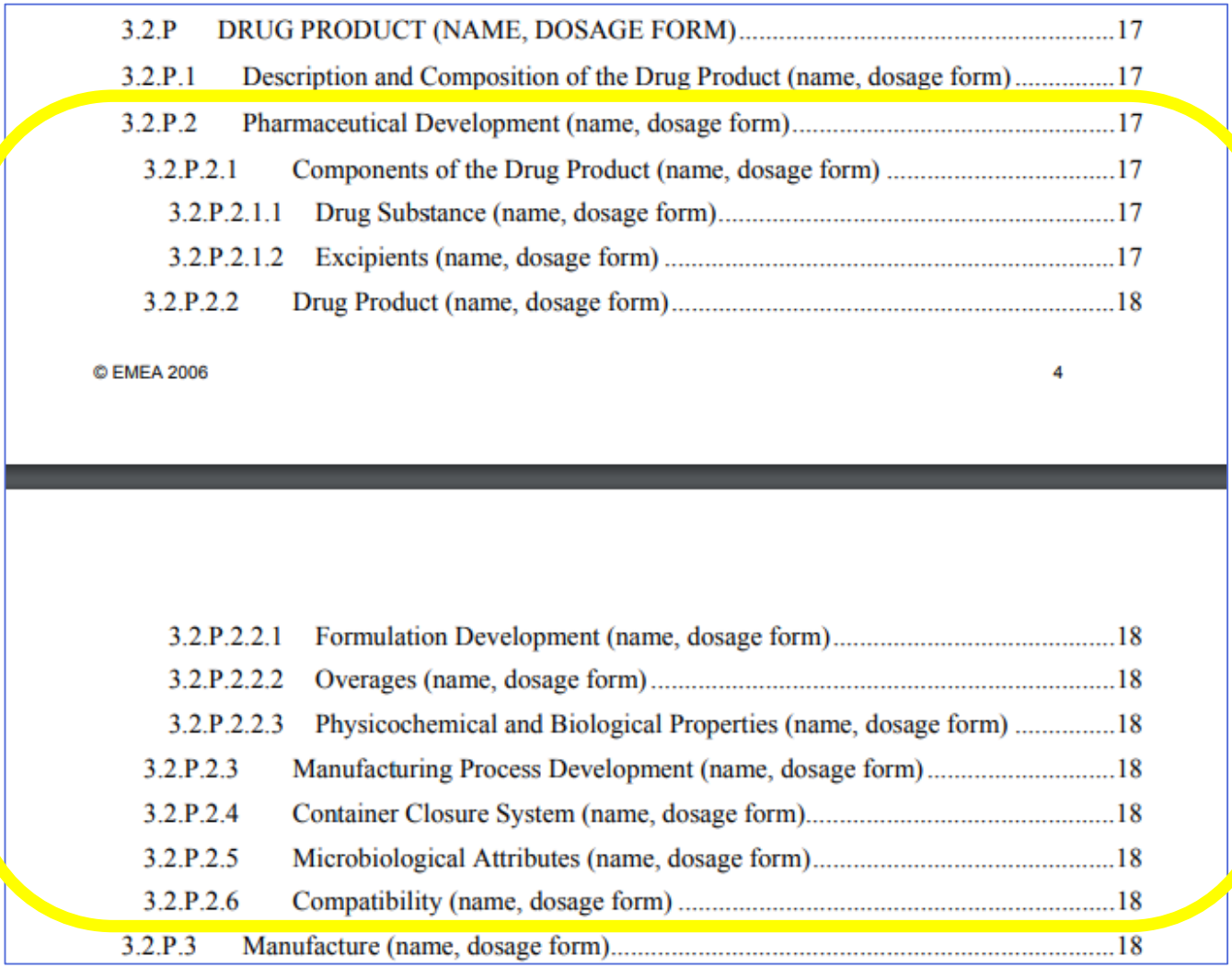
„1. INTRODUCTION

1.1 Objective of the Guideline

This guideline describes the **suggested contents for the 3.2.P.2 (Pharmaceutical Development) section** of a regulatory submission in the ICH M4 Common Technical Document (CTD) format”

ICH Q8(R2), part I.

Structure of CTD section 3.2.P.2



ICH Topic M 4 Q Common Technical Document for the Registration of Pharmaceuticals for Human Use - Quality. Step 5.

Structure of ICH Q8

PART I: PHARMACEUTICAL DEVELOPMENT

Drug substance | excipients | drug product | formulation development | overages | physicochemical and biological properties | manufacturing process development | Microbiological attributes | compatibility

PART II: ANNEX TO PHARMACEUTICAL DEVELOPMENT

- Quality Target Product Profile (QTPP)
- Critical Quality Attributes (CQAs)
- Risk Assessment
- Design Space
- Control Strategy
- Product Life Cycle Management

QdB!

SUBMISSION OF PHARMACEUTICAL DEVELOPMENT (in CTD)

- Quality Risk Management and Product and Process Development
- Design Space
- Control Strategy
- Drug Substance Related Information

Appendix 1 (Differing Approaches…)

Appendix 2 (Illustrative Examples)

Mention of QdB in part I of ICH Q8

2. PHARMACEUTICAL DEVELOPMENT

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

Information from pharmaceutical development studies can be a basis for quality risk management. It is important to recognize that quality* cannot be tested into products;

* See Glossary for definition

1

Pharmaceutical Development

i.e., quality should be built in by design. Changes in formulation and manufacturing

Background: QdB – initiative of the FDA

"At an **October 2005** workshop […] FDA deputy commissioner Janet Woodcock discussed the state of drug development. She described it as **"costly, wasteful, and encouraging industry to conduct more tests and file more data than needed [leading] to drug shortages, slower drug development, and intensive regulatory oversight"** (**3**).

In an effort to address those issues, the FDA established a **pharmaceutical quality assessment system (PQAS)** and outlined the agency's thinking in the article *Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach* (**1**).

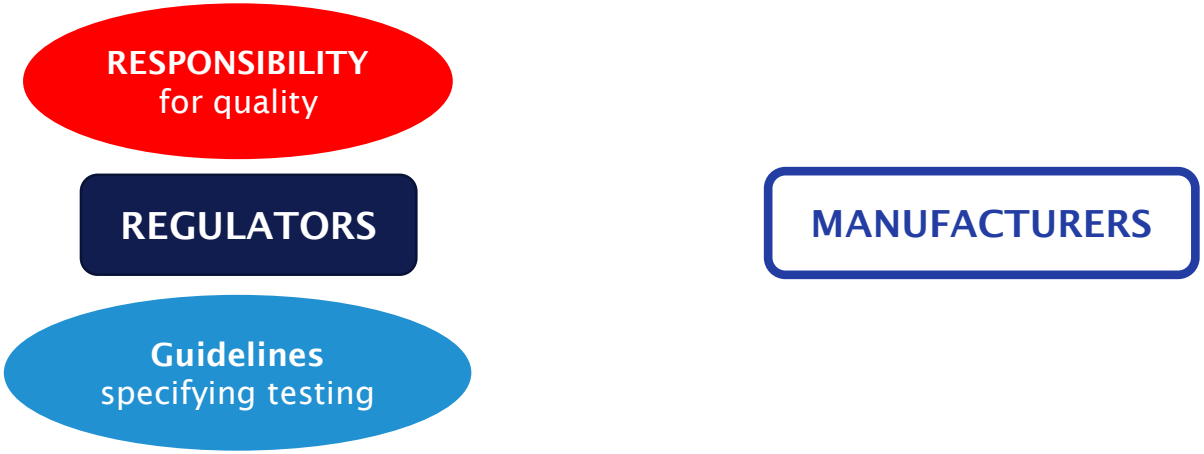
The PQAS was designed to stimulate manufacturers to adopt modern pharmaceutical product-development approaches leading to a desired state of drug regulation, which would result in, according to Woodcock, "a maximally efficient, agile, flexible pharmaceutical-manufacturing sector **that reliably produces high-quality drugs without extensive regulatory oversight**" (**3**).

To that end, the concept of QbD was introduced as a means for manufacturers to achieve the desired state."

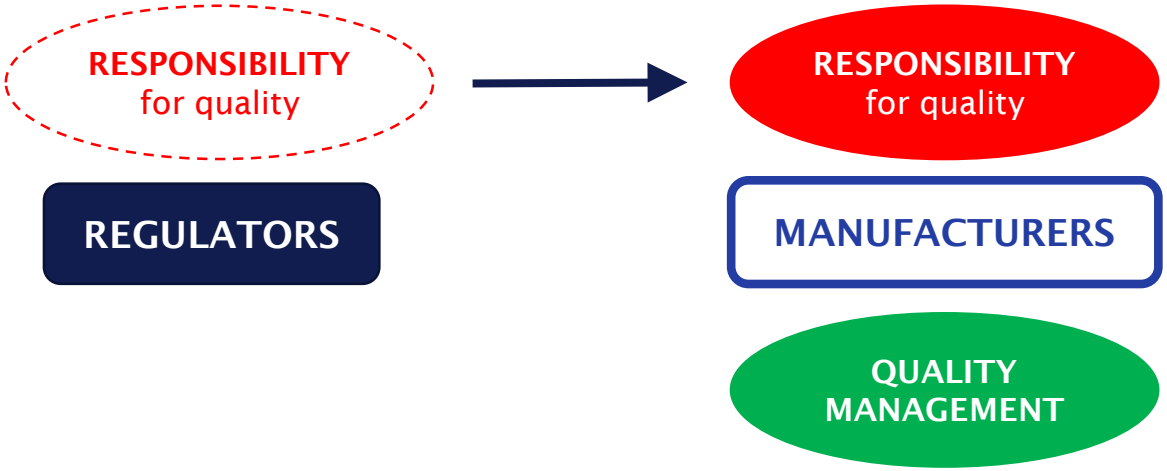
Michael Torres: „ Challenges in Implementing Quality By Design: An Industry Perspective" (16 June 2015)
https://bioprocessintl.com/analytical/downstream-development/challenges-in-implementing-quality-by-design-an-industry-perspective/

From „Testing quality into products“ to QbD

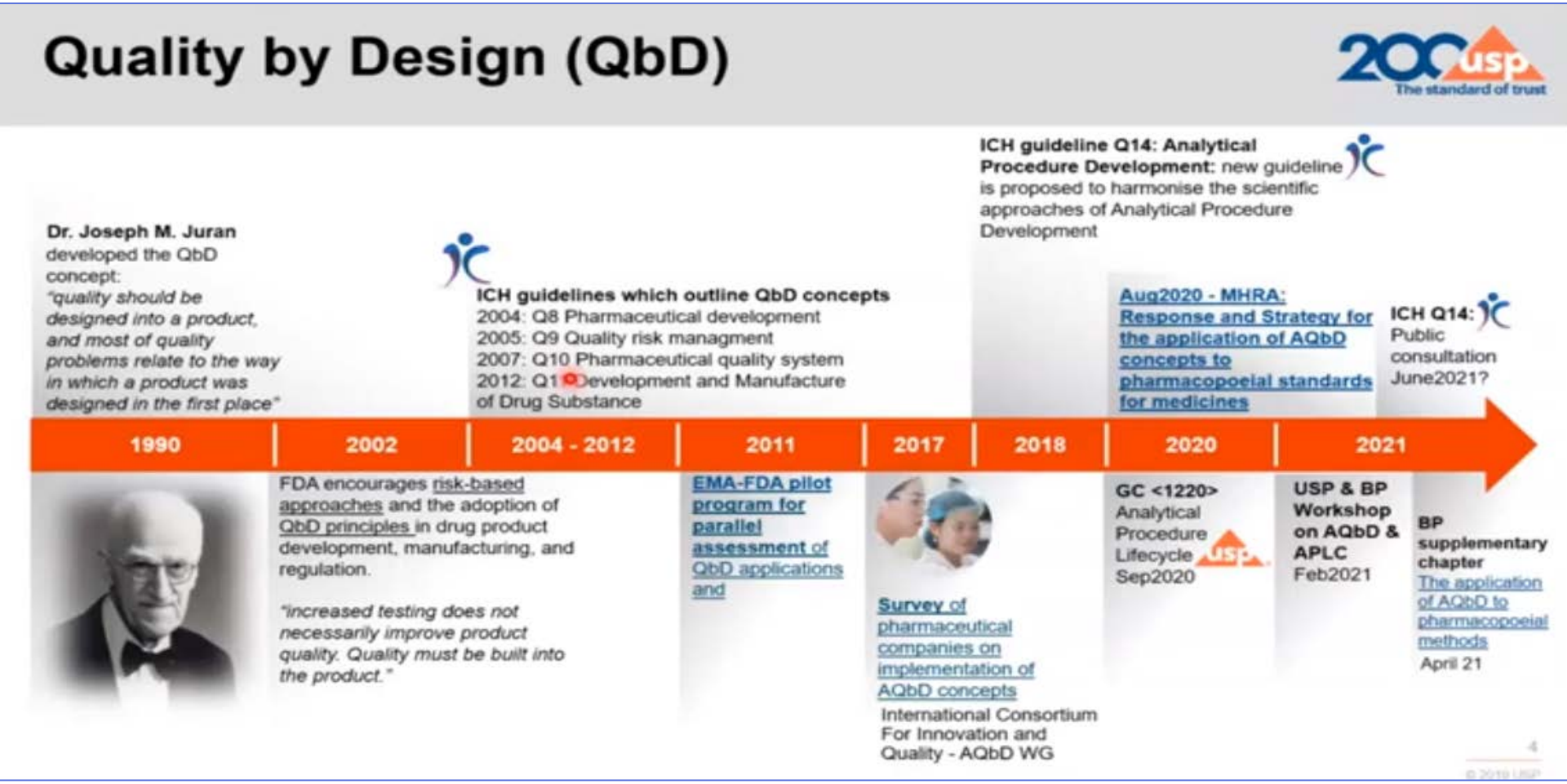
„Testing quality into products“



Quality by Design:



History of QdB in pharmaceutical development



Amanda Guiraldelli (US Pharmacopoeia): "Introduction to Analytical Quality by Design (AQbD)principles", 15 April 2021. https://www.youtube.com/watch?v=ZoYBTeTJmm4&t=1021s

Quality by Design (QbD)

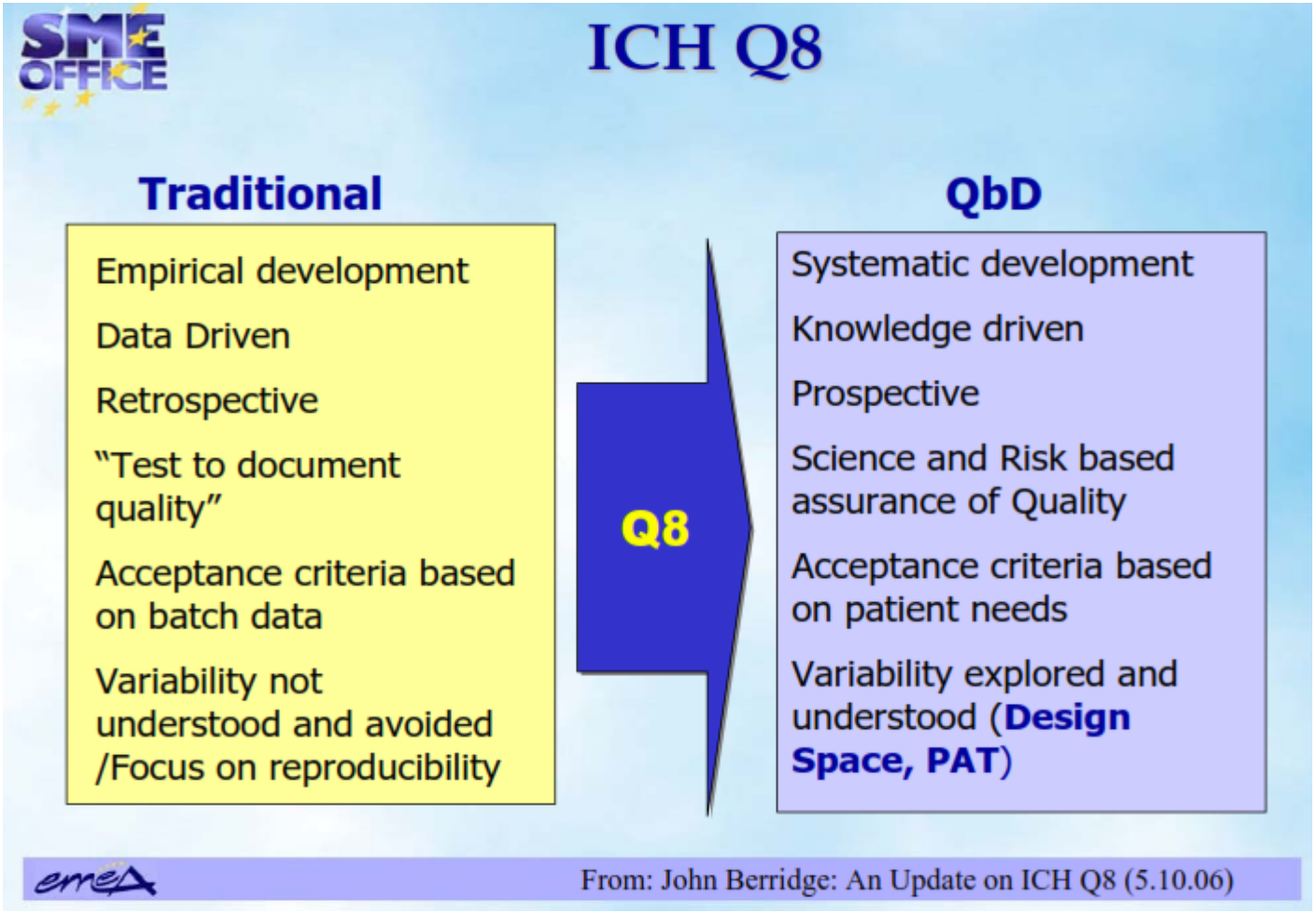
Definition

Quality by Design (QbD):

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

ICH Q8(R2), part II, Glossary

Traditional approach vs. QbD



Dr Evdokia Korakianiti "Quality by Design". Process Analytical Technology and Risk-based CMC development", 2nd EMEA Workshop for SMEs: "Focus on Quality" https://www.ema.europa.eu/en/documents/presentation/quality-design-process-analytical-technology-risk-based-cmc-development-kowid-ho_en.pdf

Design space and real time release testing are not part of QdB

Question	Answer
„Is it always necessary to have a Design Space (DS) or Real Time Release (RTR) testing to implement QdB?“	„Under Quality by Design, establishing a **design space or using real time release testing** is **not** necessarily expected [ICH Q8(R2), Step 4].“

ICH guideline Q8, Q9 and Q10 – questions and answers volume 4, step 5.

Process Analytical Technology (PAT)

Definition

Process Analytical Technology (PAT):

A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

ICH Q8(R2), part I, Glossary

= Testing, without drawing samples (in-line), of CQAs and CPPs & controlling the process on the basis of the test results

Real Time Release Testing

Definition

Real Time Release Testing:

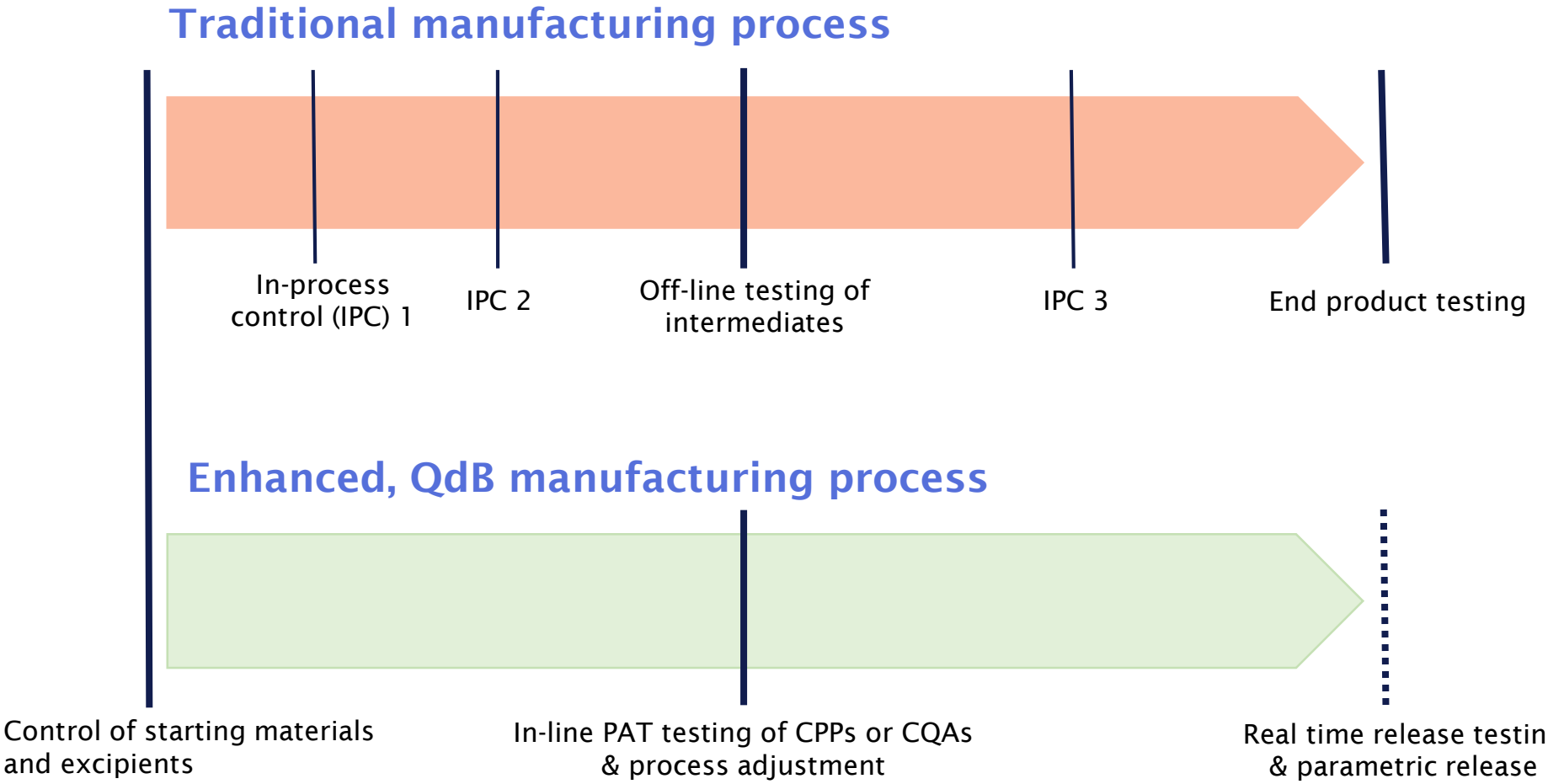
The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls.

ICH Q8(R2), part II, Glossary

= Ensures CQA of intermediates or final product by measuring CMAs and CPPs (in-line).

= May substitute end product testing

Traditional vs enhanced manufacturing process



Real time release (RTR) testing does not affect batch release and product specifications

Question	Answer
„How is batch release affected by employing real time release testing?“	„Batch release is the final decision to release the product to the market regardless whether RTR testing or end testing is employed. […] Batch release involves independent review of batch conformance to predefined criteria through review of testing results and manufacturing records together with appropriate GMP compliance. […]“
„Does real time release testing mean the elimination of end product testing?“	Not necessarily: „For example, an applicant may propose RTR testing for some attributes only or not all. […]“
„Is a product specification still necessary in the case of RTR testing?“	„Yes product specifications [see ICH Q6A and Q6B] still need to be established and met, when tested.“

ICH guideline Q8, Q9 and Q10 – questions and answers volume 4, step 5.

Critical Quality Attribute (CQA)

Definition

Critical Quality Attribute (CQA):

A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

ICH Q8(R2), part II, Glossary

Critical Process Parameter (CPP)

Definition

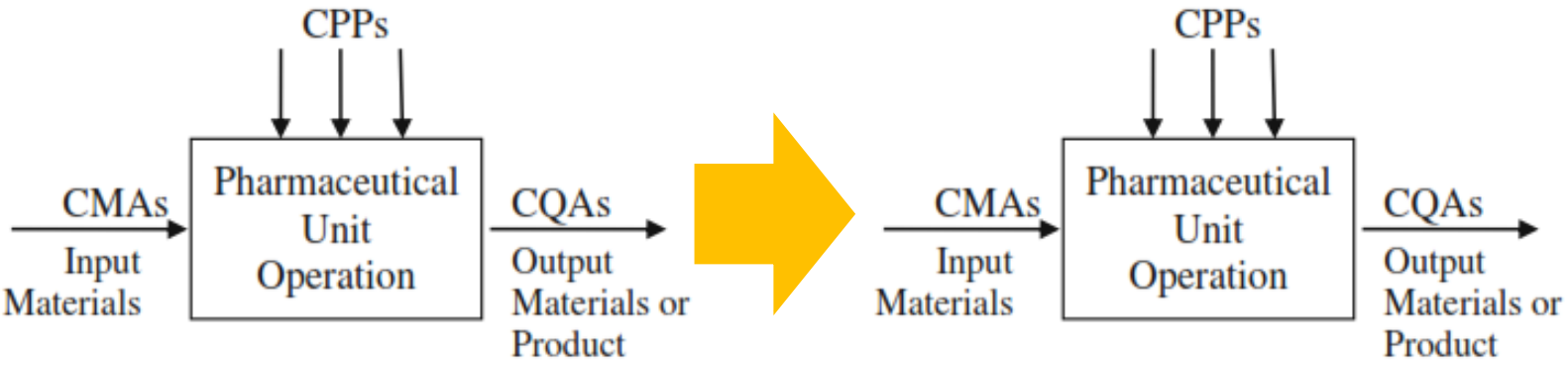
Critical Process Parameter (CPP):

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

ICH Q8(R2), part II, Glossary

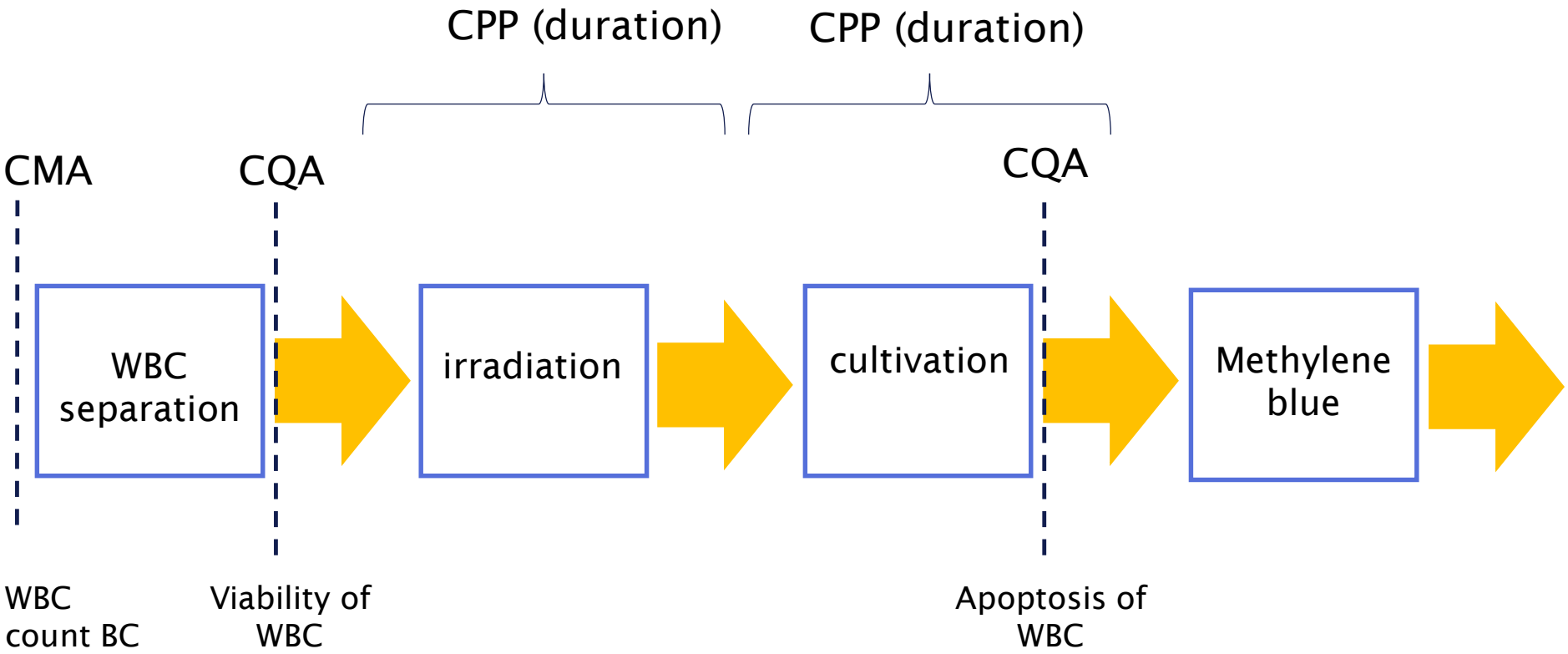
CMAs, CPPs, CQAs and Unit Operations

Understanding pharmaceutical quality by design.
Yu LX, et al. AAPS J. 2014. PMID: 24854893 Free PMC article. Review.



CMAs, CPPs, CQAs and unit operations

Unit operations:



Traditional approach vs. QbD

Appendix 1. Differing approaches to pharmaceutical development

The following table has been developed to illustrate some potential contrasts between what might be considered a minimal approach and an enhanced, quality by design approach regarding different aspects of pharmaceutical development and lifecycle management. The comparisons are shown merely to aid in the understanding of a range of potential approaches to pharmaceutical development and should not be considered to be all-encompassing. The table is not intended to specifically define the only approach a company could choose to follow. In the enhanced approach, establishing a design space or using real time release testing is not necesserily expected. Current practices in the pharmaceutical industry vary and typically lie between the two approaches presented in the table.

Aspect	Minimal Approaches	Enhanced, Quality by Design Approaches
Overall	Mainly empirical	Systematic, relating mechanistic

ICH Q8(R2), Appendix 1

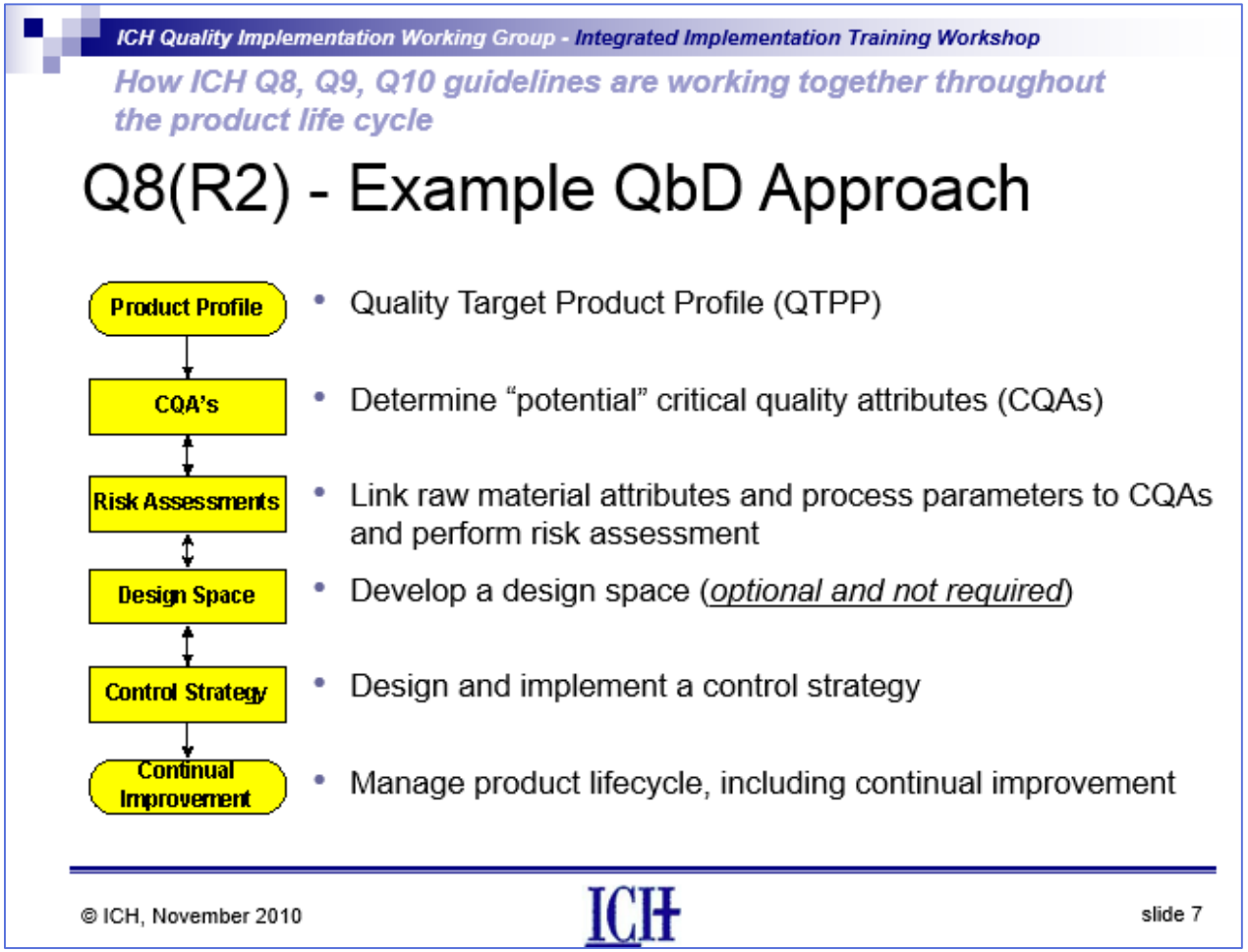
„Minimal approach“ vs. QbD - table

Aspect	Minimal approaches	Enhanced, QdB Approaches
Pharmaceut. Development	• Mainly empirical • Research on variable at a time	• Systematic (relating CMAs & CPPs to CQAs) • Multivariate experiments • *Design space* • *PAT*
Manufacturing Process	• Fixed • Validation based on initial full-scale batches • Focus on optimisation & reproducibility	• Adjustable within design space • Lifecycle approach to validation (ideally continuous process verification) • Focus on control strategy & robustness • Use of statistical process control methods
Process Controls	• In-process controls for go/ no-go decisions • Off-line analysis	• PAT tools with feed forward & feedback controls • Process operations tracked & trended
Product Specifications	• Primary means of control • Based on (available) batch data	• Part of control strategy • Based on desired product performance
Control Strategy	• Drug product quality controlled by in-process and end product testing	• Drug product quality ensured by risk-based control strategy • Quality controls shifted upstreams (→real-time release testing or reduced end product testing
Lifecycle Management	• Reactive (=problem solving)	• Preventive action • Continual improvement facilitated

ICH Q8(R2), Appendix 1, table, p. 18

Quality by Testing (QbT) vs QbD

ICH presentation: How ICH Q8, Q9, Q10 guidelines are working together throughout the product life cycle



„Pharmaceutical development should include at a minimum, the following elements:“

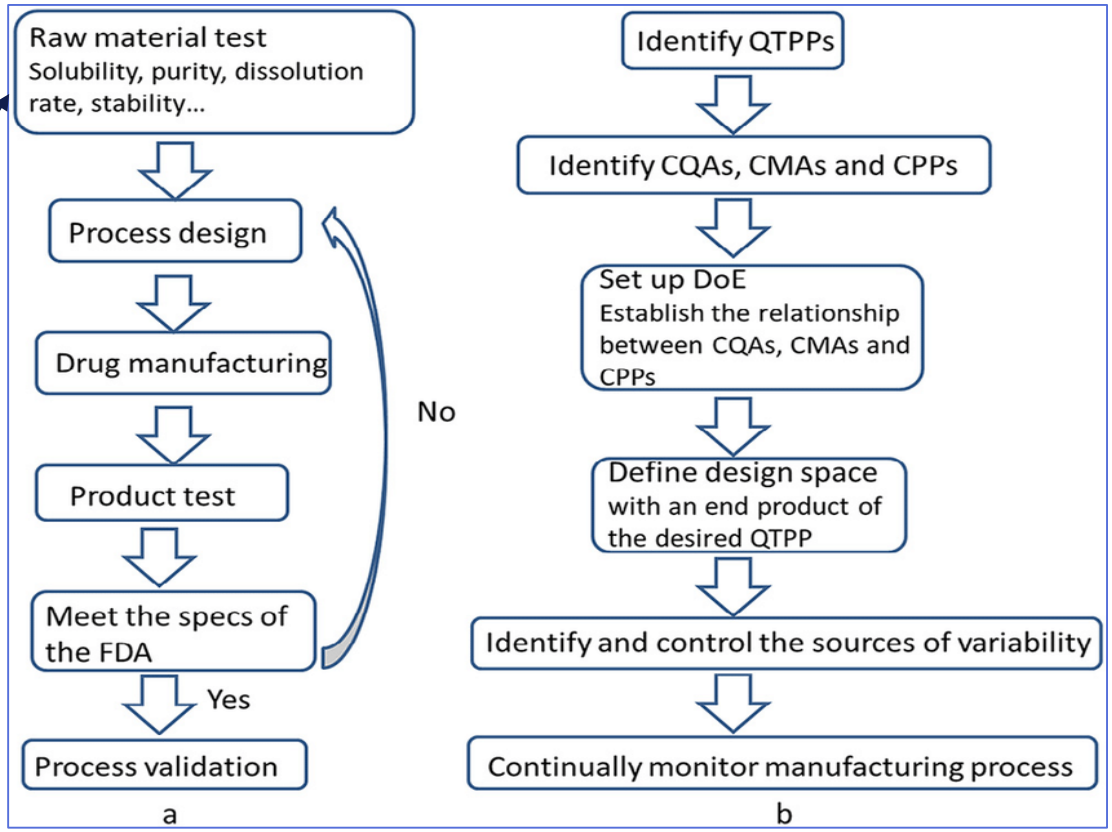
Minimal	Enhanced, QdB strategy
• Defining QTPP	• Defining QTPP
• Identifying drug product CQAs	• Identifying drug product CQAs
• Determining CQAs of drug substance, excipients, etc.	• Determining CQAs of drug substance, excipients, etc.
• Selecting appropiate manufacturing process	• Selecting appropiate manufacturing process
	• Identifying (through prior knowledge, experimentation & risk assessment) CMAs and CPPs that can have an affect on drug product CQAs
	• Determining functional relationships between CMAs, CPPs & CQAs
• Defining a control strategy	• Defining a control strategy which can incluce design space(s) and real-time release testing

ICH Q8(R2), part II, p. 10

Quality by Testing (QbT) vs QbD

Lan Zhang, Shirui Mao, Application of quality by design in the current drug development, Asian Journal of Pharmaceutical Sciences (2016), doi: 10.1016/j.ajps.2016.07.006

- No QTPP
- No risk assessment



Traditional approach

QdB approach

Process Robustness

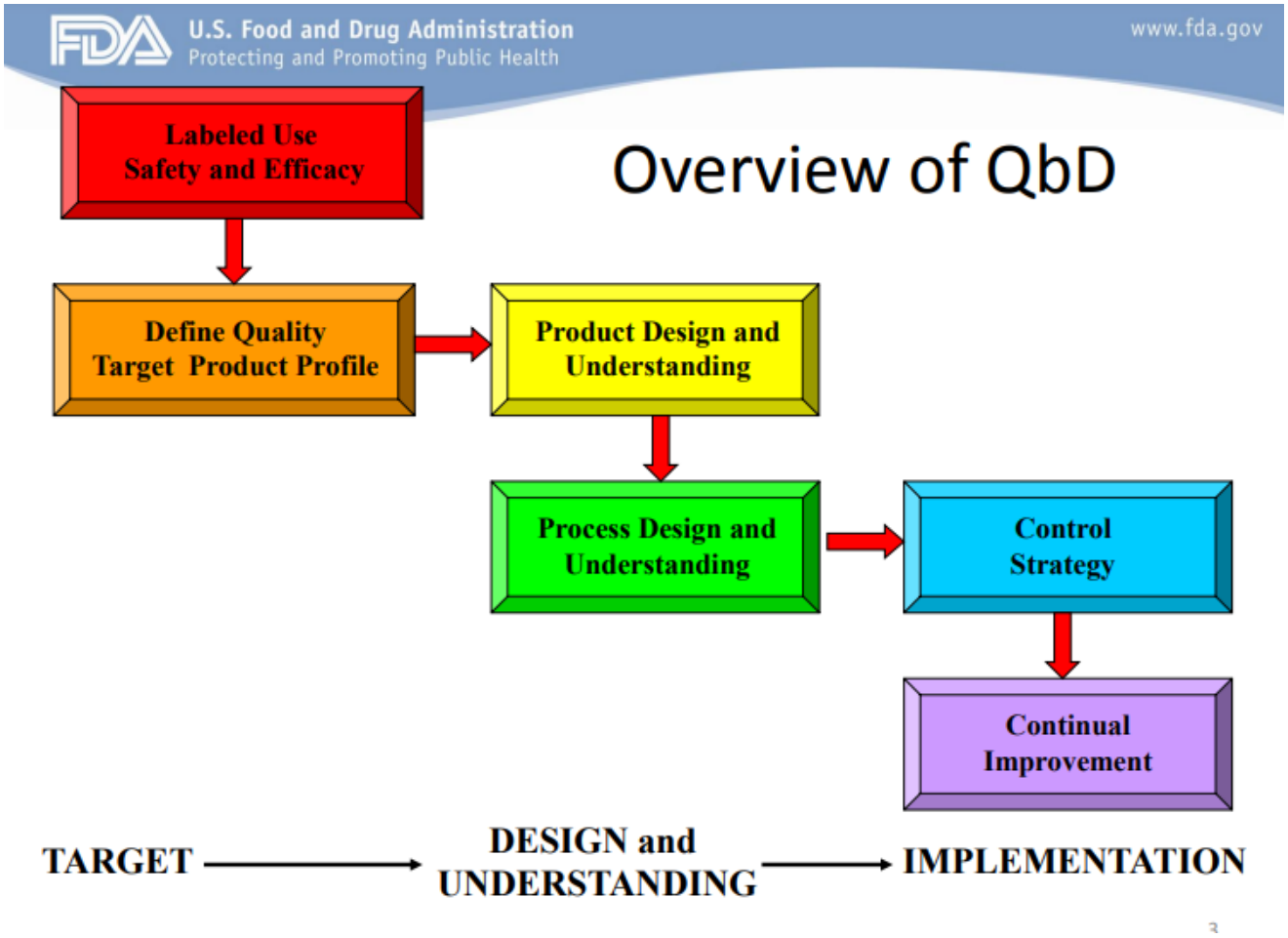
Definition

Process Robustness:

Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality.

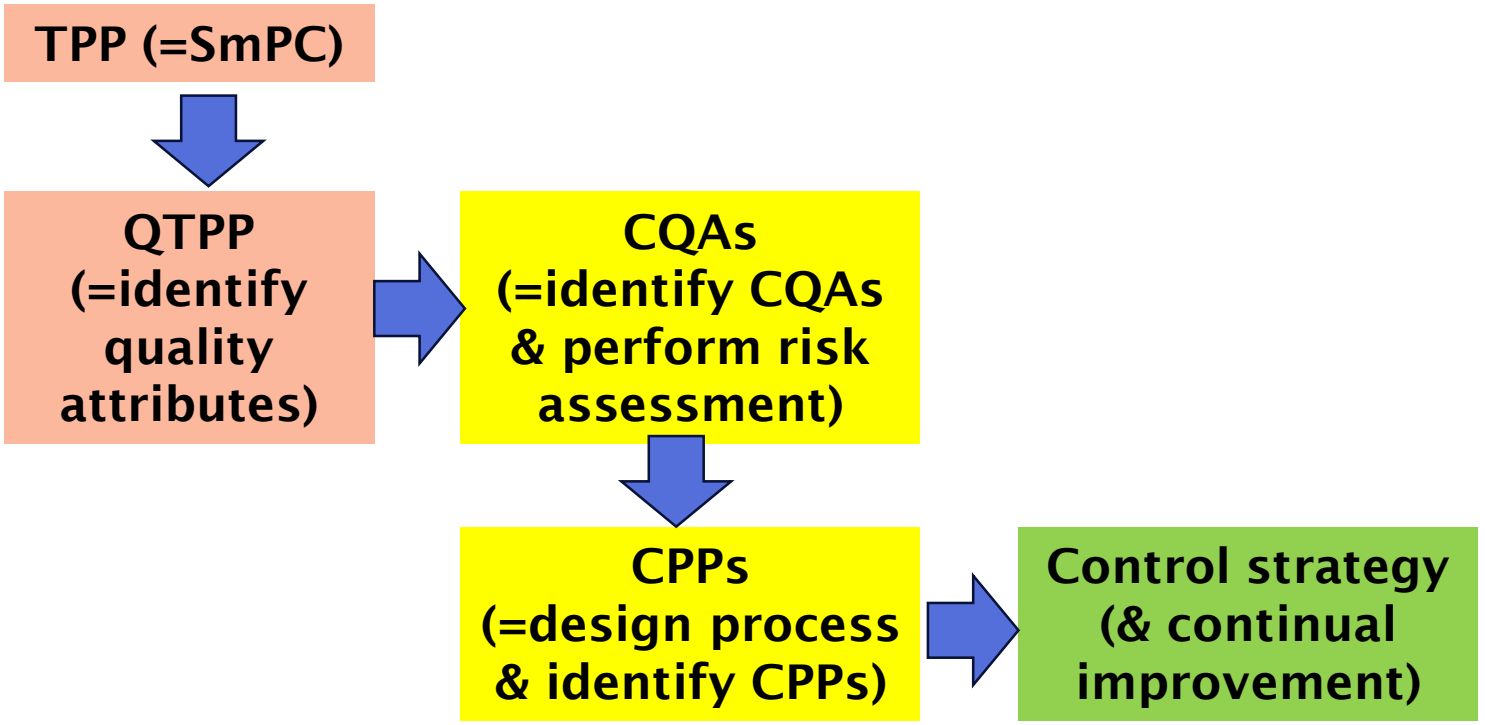
ICH Q8(R2), part I, Glossary

QbD process steps



Andre S. Raw (FDA): "Quality by Design (Qbd) for Topical Dermatologic Products", https://pqri.org/wp-content/uploads/2015/08/pdf/Raw.pdf

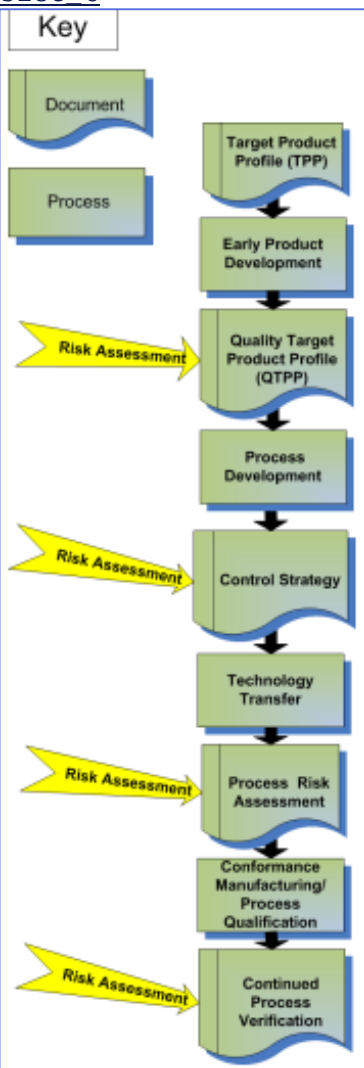
QbD process steps



Processes and documents in QdB

Gary Warren: "Quality by Design (QbD) Overview", Oct. 2015, CSL Behring Pty Ltd, Broadmeadows, Victoria, Australia.
https://www.pda.org/docs/default-source/website-document-library/chapters/presentations/australia/quality-by-design-(qbd)-overview.pdf?sfvrsn=f022b28e_6

TPP,
QTPP and
control
strategy
understood as
documents!



Understanding QbD

- Initial Confusion
- Research and discussion
- Reaching understanding:

  QbD is a process defined by documentation requirements

- QbD
  - Is similar to PDCA (iterative)
  - Focuses on risk based approaches
  - Encourages continuous improvement
  - Intends to design capable processes

Quality Target Product Profile (QTPP)

Definition

Quality Target Product Profile (QTPP):

A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.

ICH Q8(R2), part II, Glossary

Quality Target Product Profile (QTPP)

07_The_Case_Study.ppt, Slide 9

Case Study

Quality Target Product Profile

defines the objectives for development

Dosage form and strength	Immediate release tablet taken orally containing 30 mg of active ingredient
Specifications to assure safety and efficacy during shelf-life	Assay, Uniformity of Dosage Unit (content uniformity) and dissolution
Description and hardness	Robust tablet able to withstand transport and handling
Appearance	Film-coated tablet with a suitable size to aid patient acceptability and compliance Total tablet weight containing 30 mg of active ingredient is 100 mg with a diameter of 6 mm

Information as in Summary of Product Characteristics (SmPC) (=Beipackzettel, Fachinformation)

Quality Target Product Profile (QTPP)

07_The_Case_Study.ppt, Slide 10

Case Study

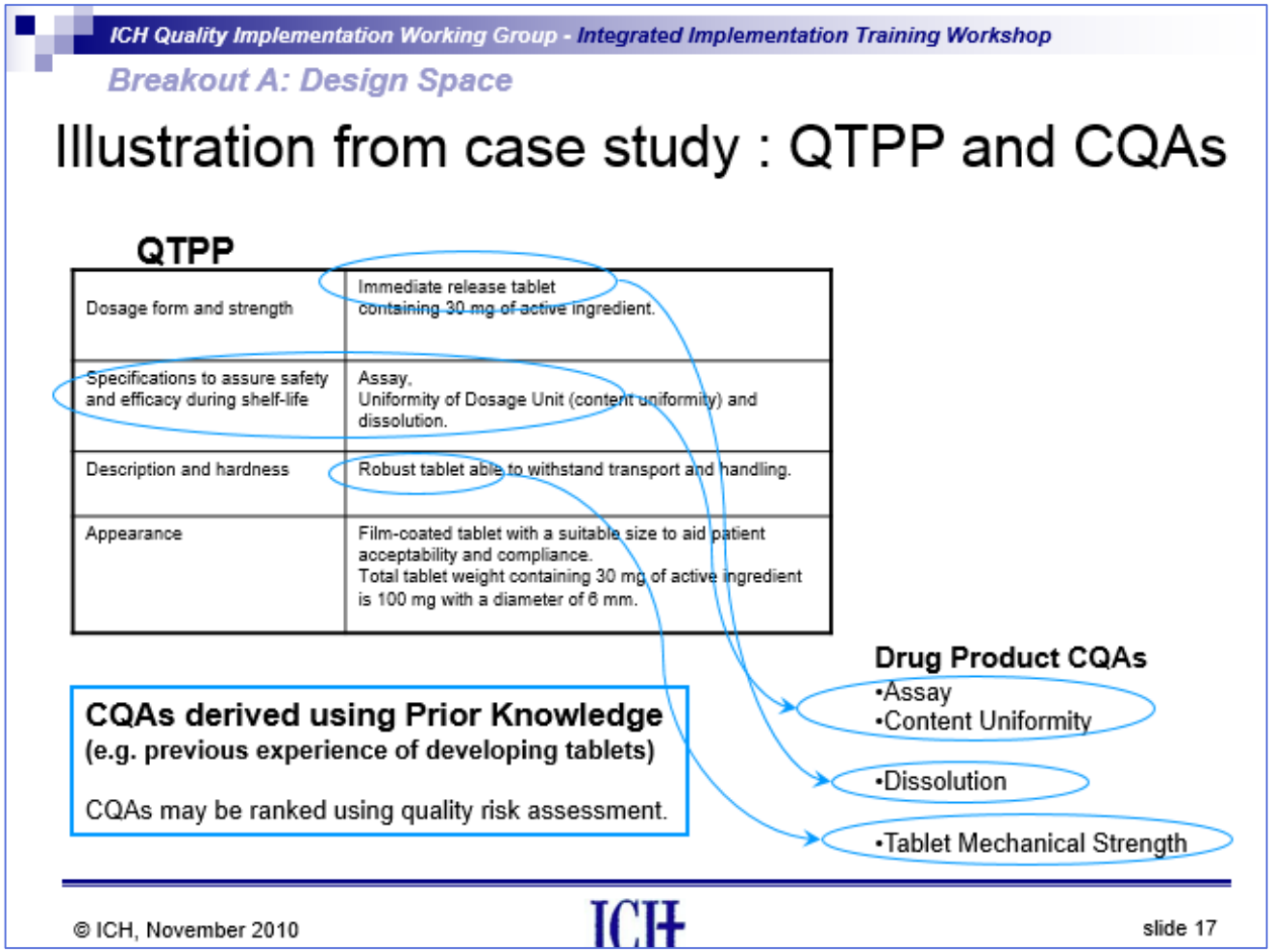
Quality Target Product Profile (QTPP)

Safety and Efficacy Requirements

Tablet	Characteristics / Requirements	Translation into Quality Target Product Profile (QTPP)
Dose	30 mg	Identity, Assay and Uniformity
Subjective Properties	No off-taste, uniform color, and suitable for global market	Appearance, elegance, size, unit integrity and other characteristics
Patient Safety – chemical purity	Impurities and/or degradates below ICH or to be qualified	Acceptable hydrolysis degradate levels at release, appropriate manufacturing environment controls
Patient efficacy – Particle Size Distribution (PSD)	PSD that does not impact bioperformance or pharm processing	Acceptable API PSD Dissolution
Chemical and Drug Product Stability: 2 year shelf life (worldwide = 30°C)	Degradates below ICH or to be qualified and no changes in bioperformance over expiry period	Hydrolysis degradation & dissolution changes controlled by packaging

Quality Target Product Profile (QTPP)

ICH presentation: Breakout A Design Space



Risk Assessment

Function

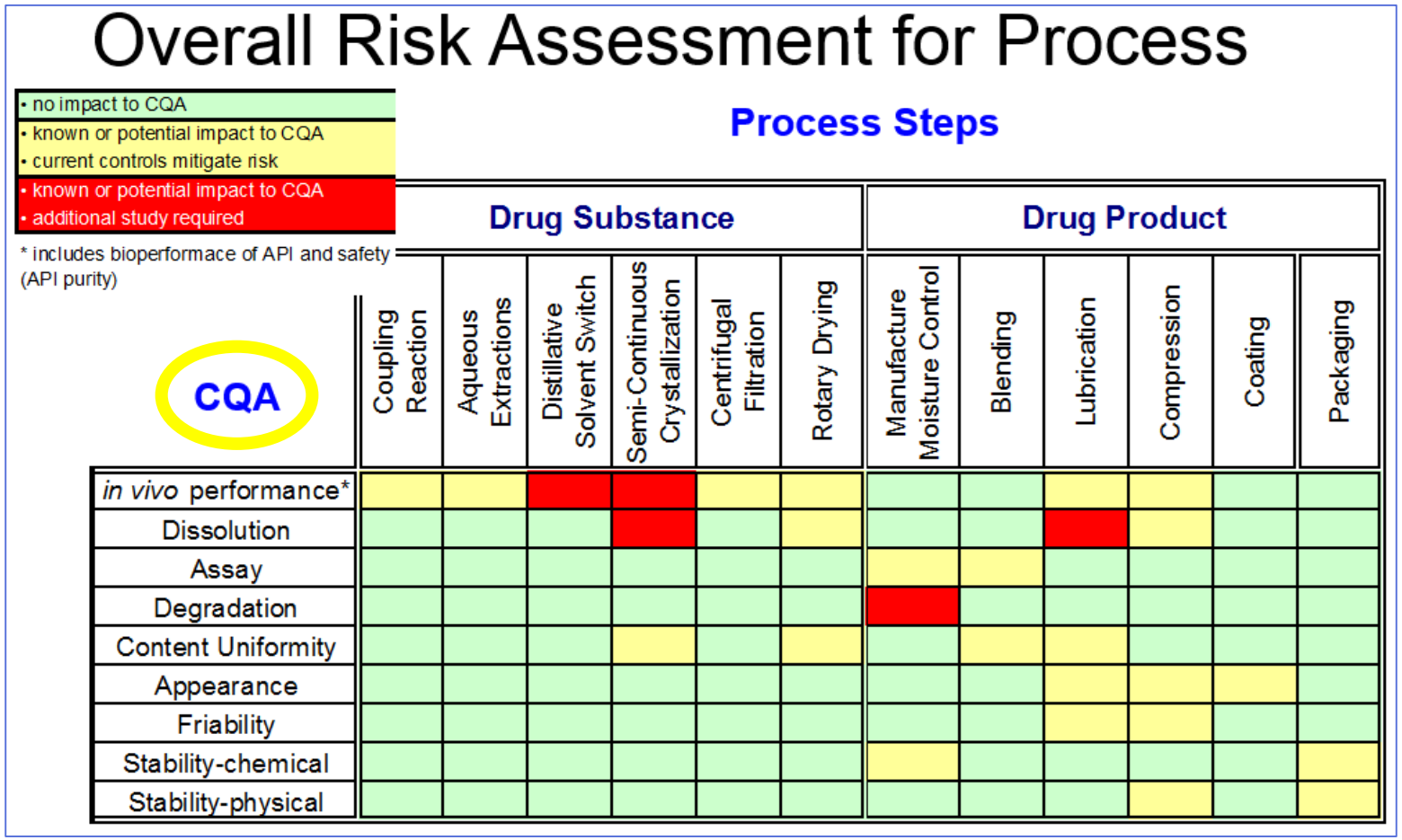
2.3 Risk Assessment: Linking Material Attributes and Process Parameters to Drug Product CQAs

Risk assessment is a valuable science-based process used in quality risk management (see ICH Q9) that can aid in **identifying which material attributes and process parameters potentially have an effect on product CQAs**.

ICH Q8(R2), part II

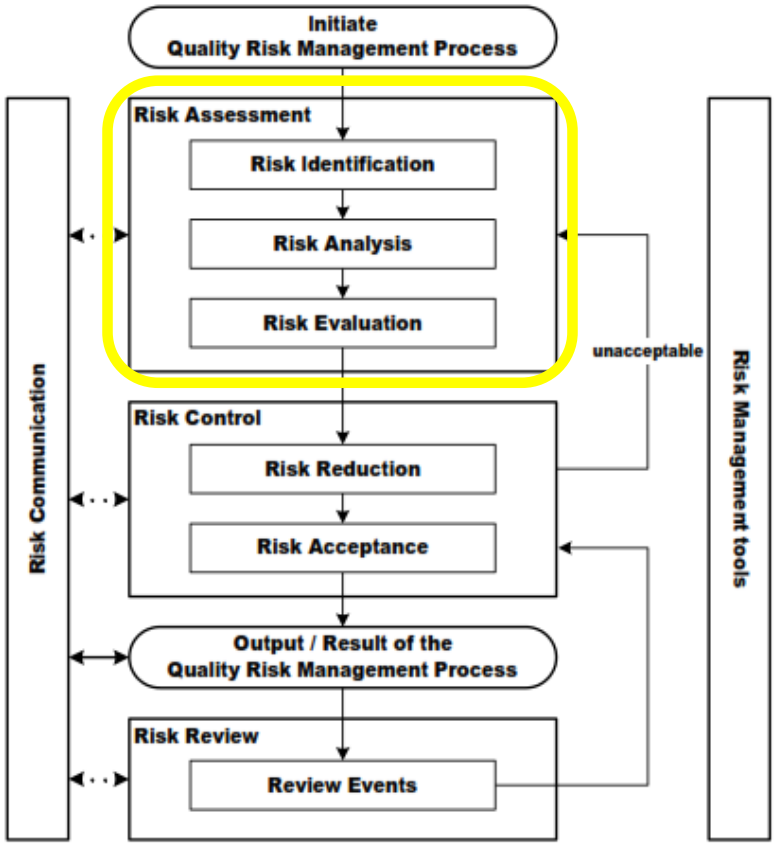
Risk Assessment

07_The_Case_Study.ppt, Slide 15



Risk Assessment is part of the Quality Risk Management process

Figure 1. Overview of a typical quality risk management process



ICH Q9, Step 5, Fig. 1.

Risk management activities usually undertaken by **interdisciplinary teams**:

- e.g., quality unit,
- business development,
- engineering,
- regulatory affairs,
- production operations,
- sales and marketing,
- legal, statistics and clinical

Risk assessment is only the 1st step. Further steps are:

- Risk reduction
- Risk acceptance
- Risk communication
- Risk review(s)

Risk assessment – focus on dissolution

07_The_Case_Study.ppt, Slide 45

Initial Quality Risk Assessment

- Impact of formulation and process unit operations on Tablet CQAs assessed using prior knowledge
  - Also consider the impact of excipient characteristics on the CQAs

	Drug substance particle size	Moisture content in manufacture	Blending	Lubrication	Compression	Coating	Packaging
in vivo performance							
Dissolution							
Assay							
Degradation							
Content uniformity							
Appearance							
Friability							
Stability-chemical							
Stability-physical							

- Low risk
- Medium risk
- High risk

Risk Assessment

07_The_Case_Study.ppt, Slide 21

Risk Assessment (FMEA): Purity Control

What is the **Impact** that ---------- will have on purity? 1) minimal 5) moderate 9) significant
What is the **Probability** that variations in ---------- will occur? 1) unlikely 5) moderately likely 9) highly likely
What is our **Ability to Detect** a meaningful variation in ---------- at a meaningful control point? 1) certain 5) moderate 9) unlikely

Unit Operation	Parameter	IMPACT	PROB.	Detect	RPN	Comments
Distillative Solvent Switch	Temperature / Time, etc.	1	5	1	5	Distillation performed under vacuum, at low temperature, minimizing risk of hydrolysis
Distillative Solvent Switch / Crystallization	Water content at end of Distillation (Crystallization Feed)	9	5	1	45	Higher water = higher degradation In process control assay should ensure detection and
Crystallization -- API Feed Solution	Feed Temperature	9	5	1	45	Higher temperature = higher degradation Temperature alarms should enable quick detection and control
Crystallization -- API Feed Solution	Addition Time	9	1	5	45	Longer time = higher degradation Detection of prolonged addition time may occur too late to prevent some degradation
Crystallization	Seed wt percentage	1	1	1	1	This parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs.
Crystallization	Antisolvent percentage (charge ratio)	1	1	1	1	This parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs.
Crystallization	Crystallization temperature	1	5	1	5	Temperature is low enough that no degradation will occur.
Crystallization	Other crystallization parameters	1	1	1	1	These parameters cannot impact impurity rejection, since no rejection of hydrolysis degradate occurs.

Risk Assessment

07_The_Case_Study.ppt, Slide 27

Risk Assessment:

Particle Size Distribution (PSD) Control

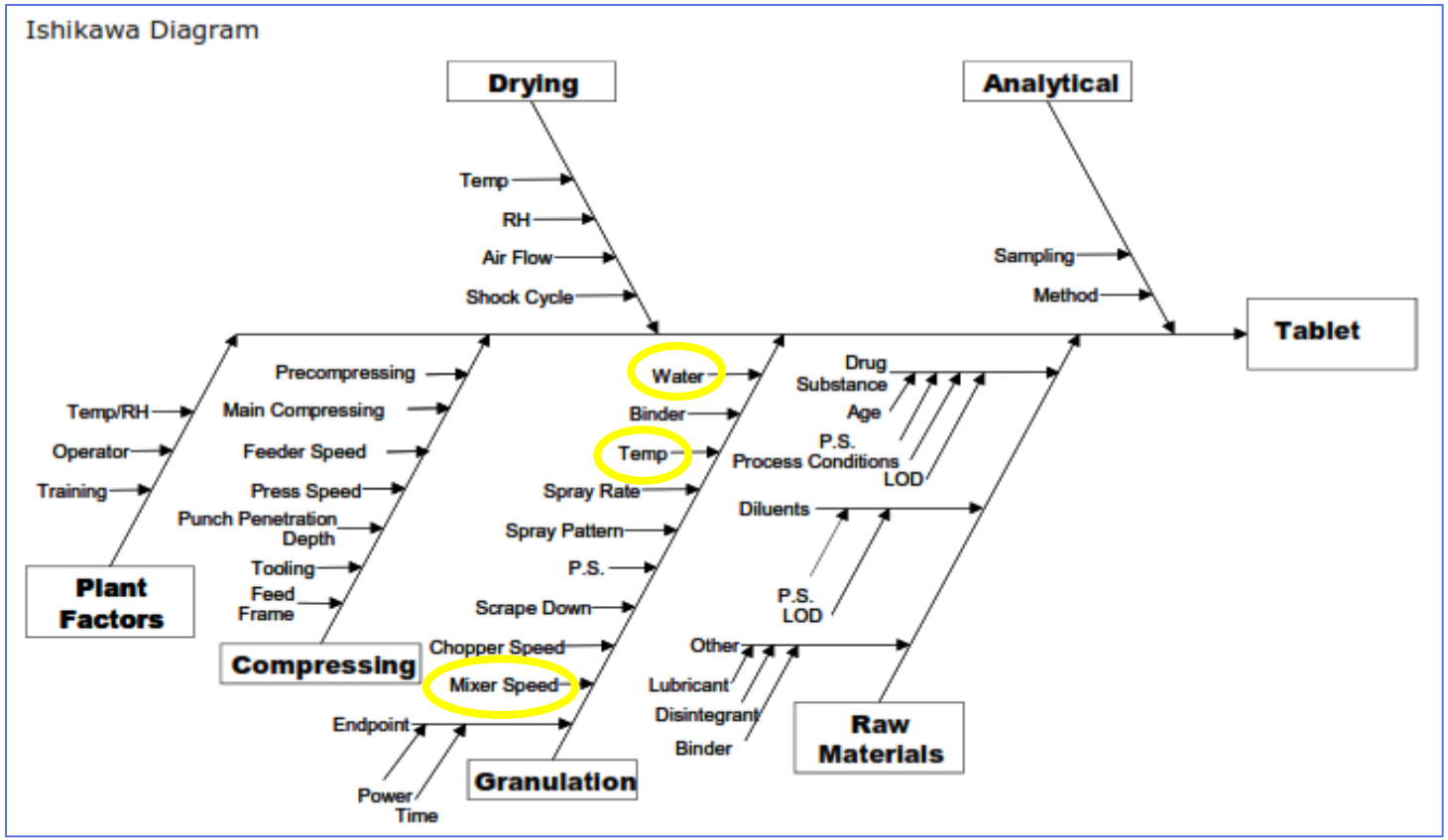
What is the **Impact** that ---------- will have on PSD? 1) minimal 5) moderate 9) significant

What is the **Probability** that variations in ---------- will occur? 1) unlikely 5) moderately likely 9) highly likely

What is our **Ability to Detect** a meaningful variation in ---------- at a meaningful control point? 1) certain 5) moderate 9) unlikely

Unit Operation	Parameter	IMPACT	PROB.	Detect	RPN	Comments
Crystallization	Feed Temperature	1	5	1	5	Prior knowledge (slowness of crystallization kinetics) ensures that the hot crystallizer feed will be well dispersed and thermally equilibrated before crystallizing. Hence no impact of feed temp variation on crystal size.
Crystallization	Water content of Feed	1	5	5	25	Prior knowledge (solubility data) shows that small variations in water do not affect crystalliation kinetics.
Crystallization	Addition Time (Feed Rate)	9	5	9	405	Fast addition could result in uncontrolled crystallization. Detection of short addition time could occur too late to prevent this uncontrolled crystallization, and thus impact final PSD.
Crystallization	Seed wt percentage	9	5	5	225	Prior knowledge (Chemical Engineering theory) highlights seed wt percentage variations as a potential source of final PSD variation
Crystallization	Antisolvent percentage	1	1	1	1	Yield loss to crystallization already low (< 5%), so reasonable variations in antisolvent percentage (+/- 10%) will not affect the percent of batch crystallized, and will not affect PSD
Crystallization	Temperature	9	5	9	405	Change in crystallization temperature is easily detected, but rated high since no possible corrective action (such as, if seed has been dissolved)
Crystallization	Agitation (tip speed)	9	5	5	225	Prior knowledge indicates that final PSD highly sensitive to agitation during crystallization, thus requiring further study.
Crystallization	Seed particle size distribution	9	1	1	9	Seed PSD controlled by release assay performed after air attrition milling.
Crystallization	Feed Concentration	1	1	1	1	Same logic as for antisolvent percentage

Risk Assessment – Fishbone diagram



(1.) **Identify** variables with potential impact on desired CQAs
(2.) **rank** them based on probability, severity & detectability using failure mode effects analysis (FMEA)
(3.) **study** higher ranked variables using DoE or other experimental methods

ICH Q8(R2), Appendix 2, A. Use of a risk assessment tool

Interactions between different CPPs

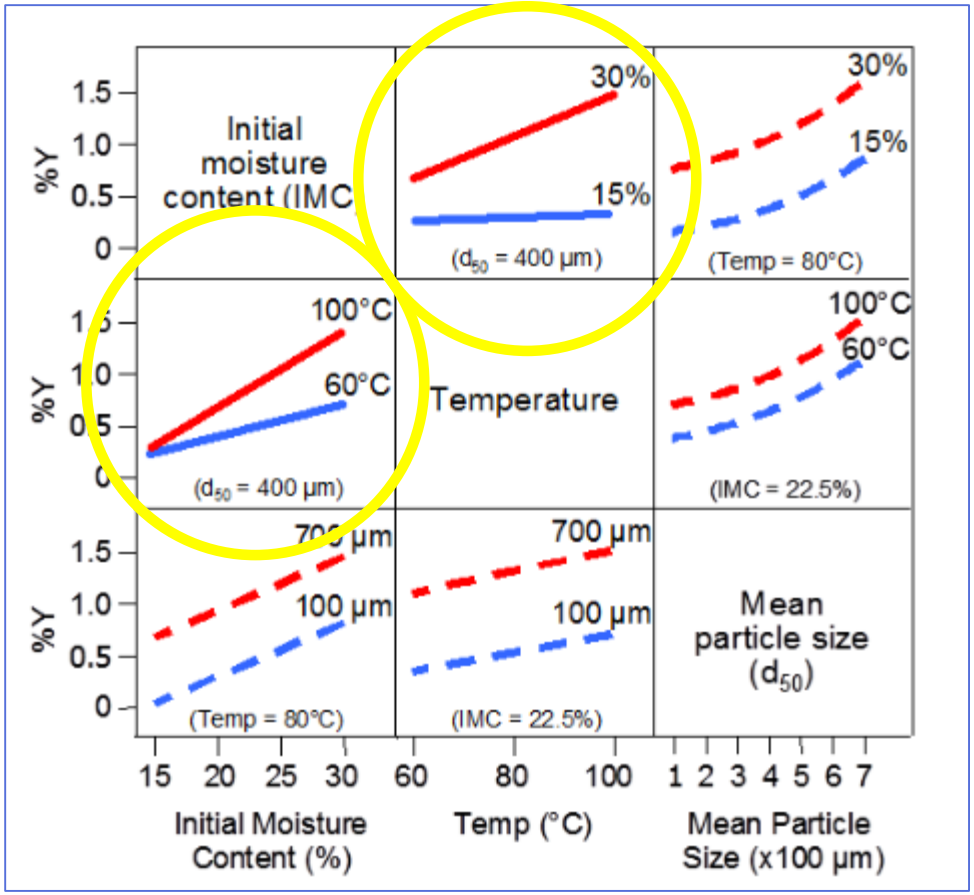


Fig.: Interactions between 3 CPPs of a drying operation of a granulate on degradation product Y.

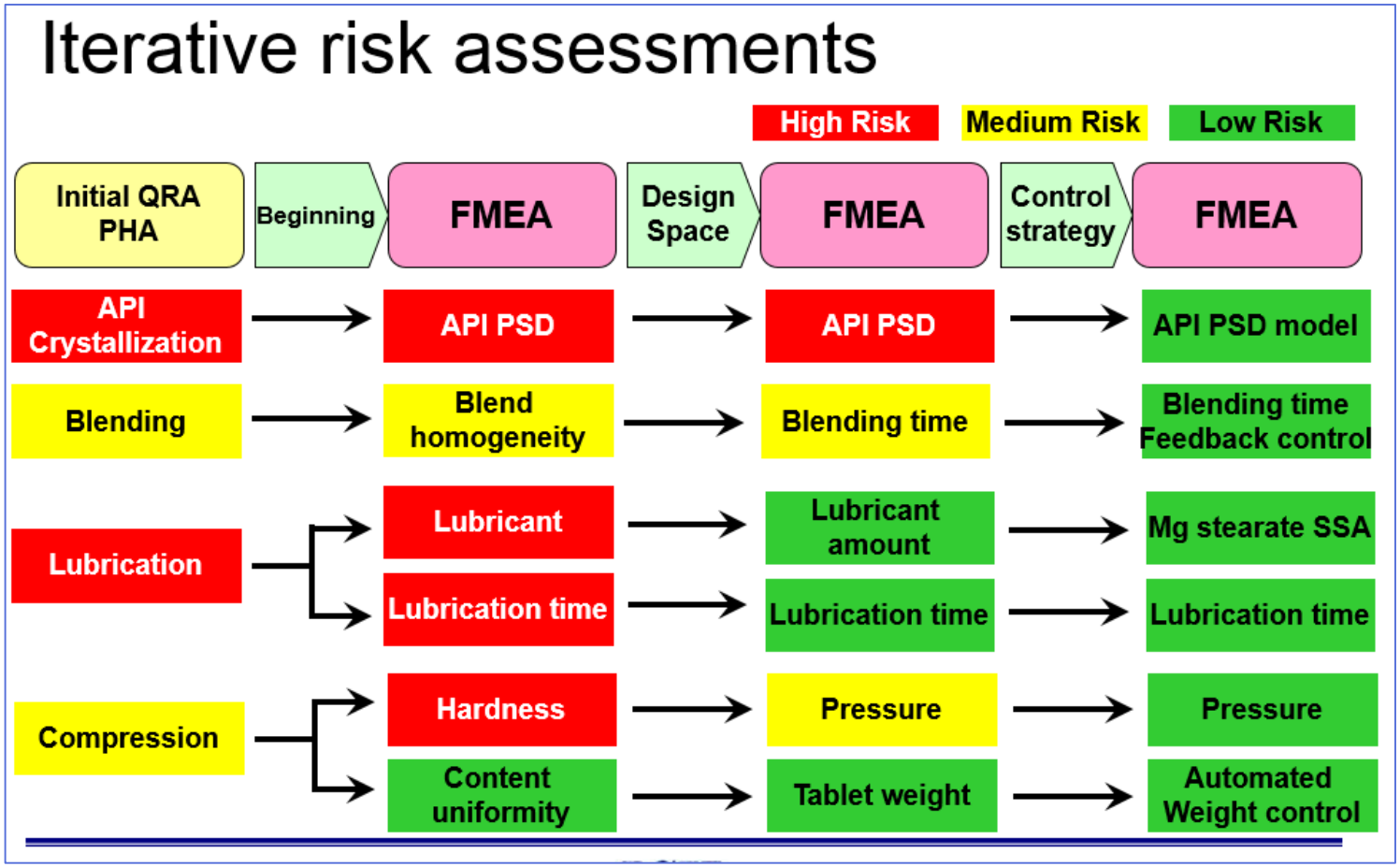
Interactions between:
- IMC & temperature

NO interaction between:
- IMC & mean particle sice
- Temperature & mean particle size

ICH Q8(R2), Appendix 2, B. Depiction of interactions

Risk Assessment

07_The_Case_Study.ppt, Slide 64



„…the level of risk can change as a result of risk management.“ (Q8/Q9/Q10 Q&As (R4) Points to Consider)

Design of Experiments (DoE)

Definition

Formal Experimental Design:

A structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as “Design of Experiments”.

ICH Q8(R2), part I, Glossary

DoE – experimental setup

07_The_Case_Study.ppt, Slide 48

Developing Product and Process Understanding: DOE Investigation of factors affecting Dissolution

Multifactorial DOE study of variables affecting dissolution

- **Factors:**
  - API particle size [API] unit: log D90, microns
  - Mg-Stearate Specific Surface Area [MgSt] unit: cm^2/g
  - Lubrication time [LubT] unit: min
  - Tablet hardness [Hard] unit: N
- **Response:**
  - % API dissolved at 20 min [Diss]
- **DOE design:**
  - RSM design
  - Reduced CCF (quadratic model)
  - 20+3 center point runs

Exp No	Run Order	API	MgSt	LubT	Hard	Diss
1	1	0.5	3000	1	60	101.24
2	14	1.5	3000	1	60	87.99
3	22	0.5	12000	1	60	99.13
4	8	1.5	3000	10	60	86.03
5	18	0.5	12000	10	60	94.73
6	9	1.5	12000	10	60	83.04
7	15	0.5	3000	1	110	98.07
8	2	0.5	12000	1	110	97.68
9	6	1.5	12000	1	110	85.47
10	16	0.5	3000	10	110	95.81
11	20	1.5	3000	10	110	84.38
12	3	1.5	12000	10	110	81
13	10	0.5	7500	5.5	85	96.85
14	17	1.5	7500	5.5	85	85.13
15	19	1	3000	5.5	85	91.87
16	21	1	12000	5.5	85	90.72
17	7	1	7500	1	85	91.95
18	4	1	7500	10	85	88.9
19	5	1	7500	5.5	60	92.37
20	11	1	7500	5.5	110	90.95
21	12	1	7500	5.5	85	91.95
22	13	1	7500	5.5	85	90.86
23	23	1	7500	5.5	85	89

Note: A screening DoE may be used first to identify which of the many variables have the greatest effect

Design Space

Definition

Design Space:

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.

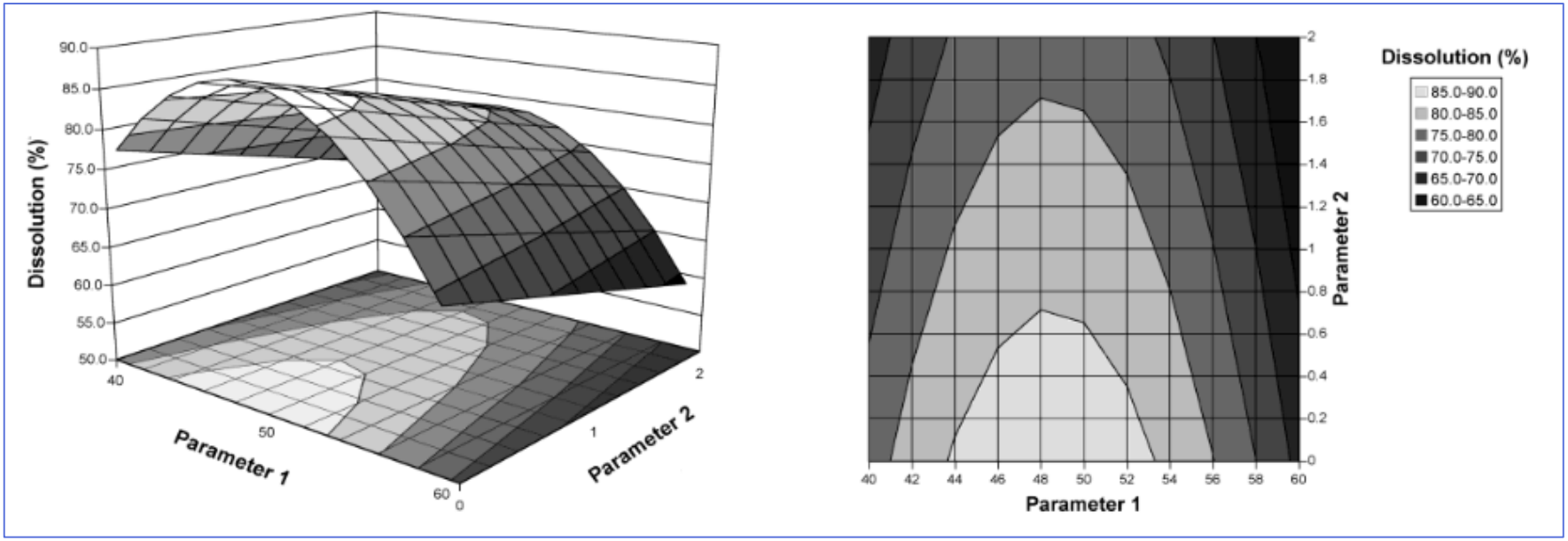
Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval (ICH Q8).

ICH Q8(R2), part II, Glossary

Design Space – Example 1

Parameters 1&2: factors of a granulation operation that affect the dissolution rate of a tablet – e.g.: excipient attribute, water amount, granule size

Dissolution > 80% is desired.



Surface plot **Contour plot**

ICH Q8(R2), Appendix 2, Example 1, Figures 1a & 1b

Design Space – Example 1

Fig 1c & 1d: Two design spaces for two granulation parameters delivering satisfactory dissolution (>80%)

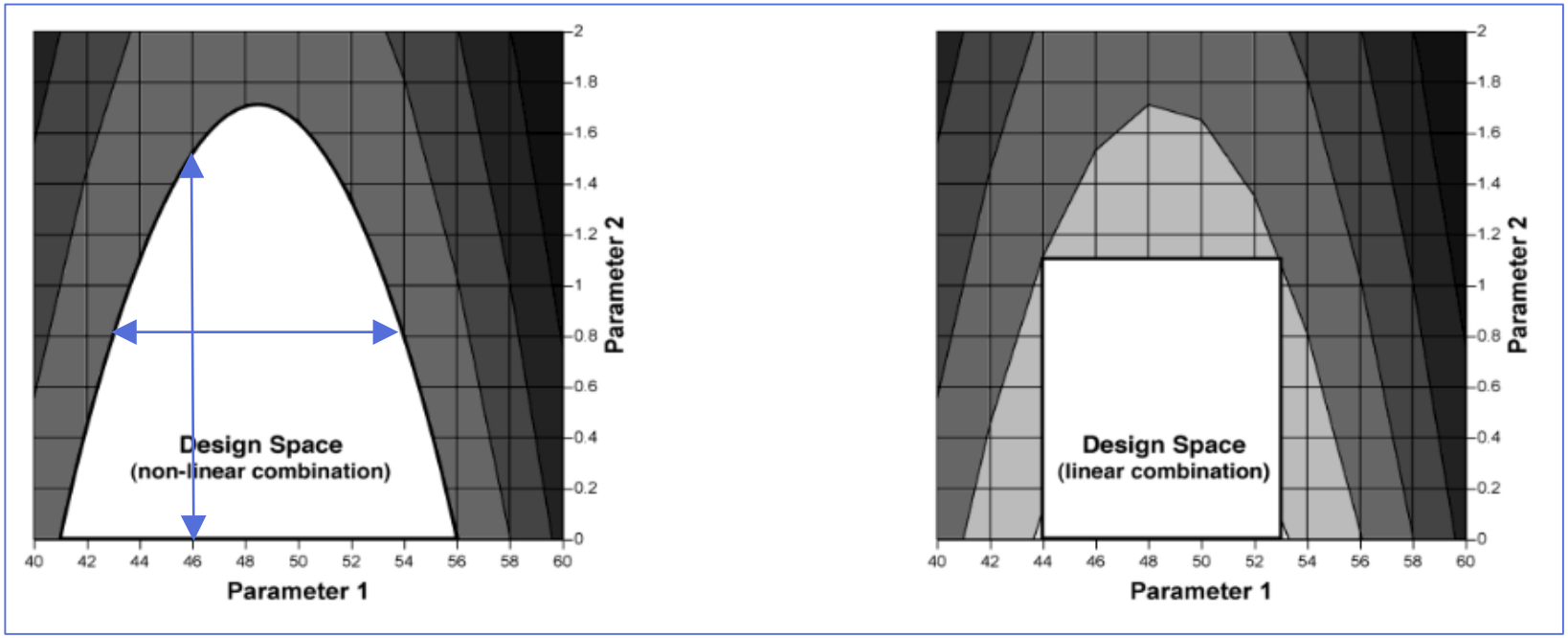


Fig 1c: If Parameter 1= 46, then Parameter 2 = 0 to 1.5. If Parameter 2 = 0.8, then Parameter 1 = 43 to 54.	**Fig 1d:** Applicant may prefer a smaller design space for operational simplicity.

ICH Q8(R2), Appendix 2, Example 1, Figures 1c & 1d

Design Space – Example 2

Fig 2a & 2b: Design space determined from the combination of two CQAs: dissolution + friability;

Parameter 1 and 2 in Fig. 2a & 2b are the same parameters, e.g. water amount & granule size

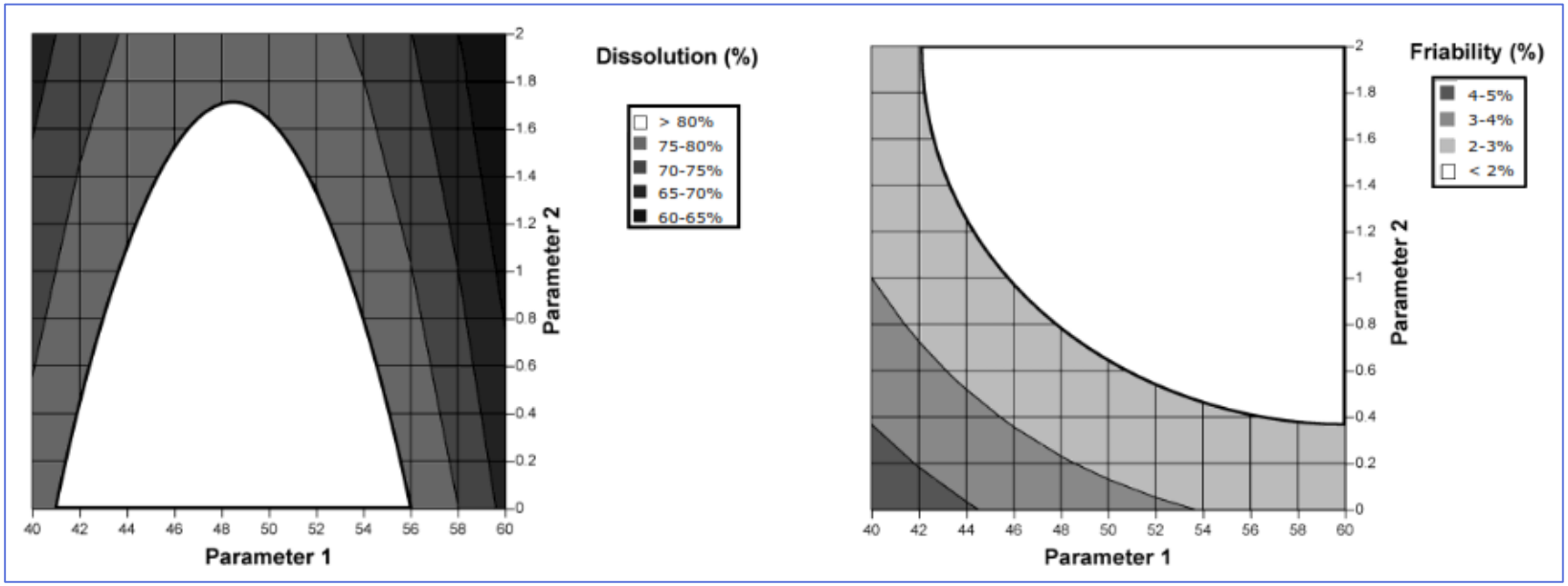


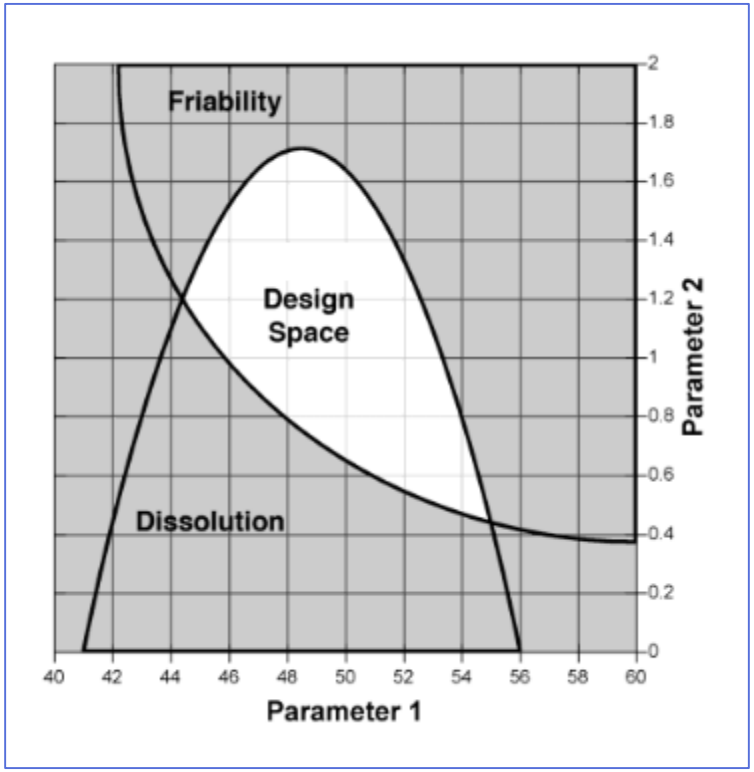
Fig 2a: Contour plot: dissolution
as a function of parameters 1 & 2

Fig. 2b: Contour plot: friability
as a function of parameters 1 & 2

ICH Q8(R2), Appendix 2, Example 1, Figures 2a & 2b

Design Space – Example 2

Fig. 2c: Design space comprised of the overlap region of ranges for friability & dissolution.



ICH Q8(R2), Appendix 2, Example 1, Figure 2c

Control Strategy

Definition

Control Strategy:

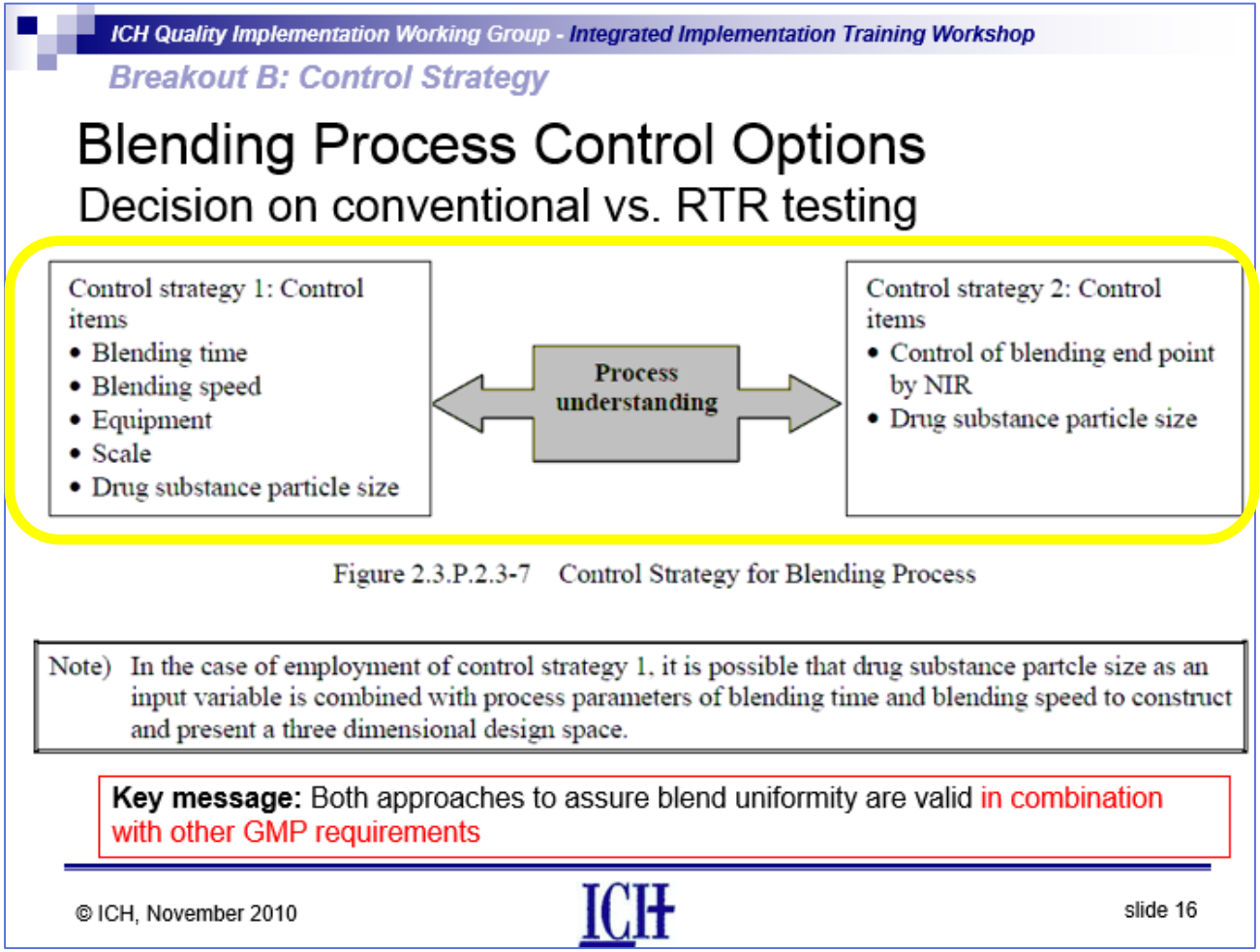
A planned set of controls, derived from current product and process understanding that ensures process performance and product quality.

The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

ICH Q8(R2), part II, Glossary

Control Strategy

Ich presentation: Breakout B Control Strategy



Slide shows:
Different control strategies (control strategy 1 or control strategy 2) are possible.

Process understanding is decisive.

Continual improvement – the FDA takes it seriously

https://www.qualitydigest.com/inside/twitter-ed/taking-holistic-approach-quality-design.html
(Die Grafik stammt ursprünglich von der FDA, kommt zB. Vor in der Präsentation von Christine M. V. Moore, Texas 2012.)

QbD – not mandatory, just opportunities

Part II: Pharmaceutical development - Annex

1. Introduction

This guideline is an annex to ICH Q8 Pharmaceutical Development and provides further clarification of key concepts outlined in the core guideline. In addition, this annex describes the principles of quality by design**1** (QbD). The annex is not intended to establish new standards or to introduce new regulatory requirements; however, it shows how concepts and tools (e.g., design space**1**) outlined in the parent Q8 document could be put into practice by the applicant for all dosage forms. Where a company chooses to apply quality by design and quality risk management (ICH Q9, Quality Risk Management), linked to an appropriate pharmaceutical quality system, opportunities arise to enhance science- and risk-based regulatory approaches (see ICH Q10, Pharmaceutical Quality System).

ICH Q8(R2)

Is QdB mandatory in the US?

"The current regulatory trend for required QbD elements in submissions will soon make a mandate a reality. In the broader pharmaceutical realm, as of **2013, the QbD framework for generic drug development is mandatory**. For instance, according to FDA internal policy, MAPP 5016.1 (which became effective February 2011) (**16**), FDA CMC reviewers are instructed to review submissions for the following ICH Q8, Q9, and Q10 elements:

- quality target product profile (QTPP)
- critical quality attributes (CQAs) of a product
- product design and product understanding
- process design and understanding
- product and process control strategies."

Michael Torres: „ Challenges in Implementing Quality By Design: An Industry Perspective" (16 June 2015)
https://bioprocessintl.com/analytical/downstream-development/challenges-in-implementing-quality-by-design-an-industry-perspective/

Implementation of Quality by Design (QbD) Principles in Regulatory Dossiers of Medicinal Products in the European Union (EU) Between 2014 and 2019

Judith P. ter Horst[1] · Sada L. Turimella[1] · Frans Metsers[1] · Alex Zwiers[1]

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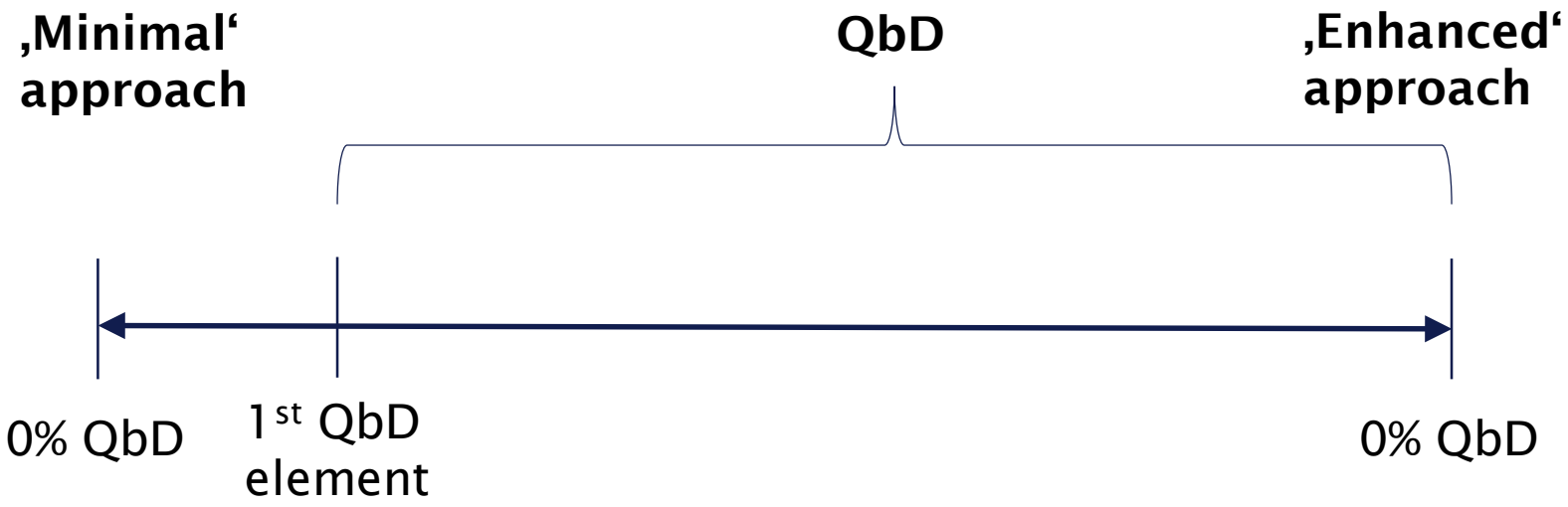
Abstract

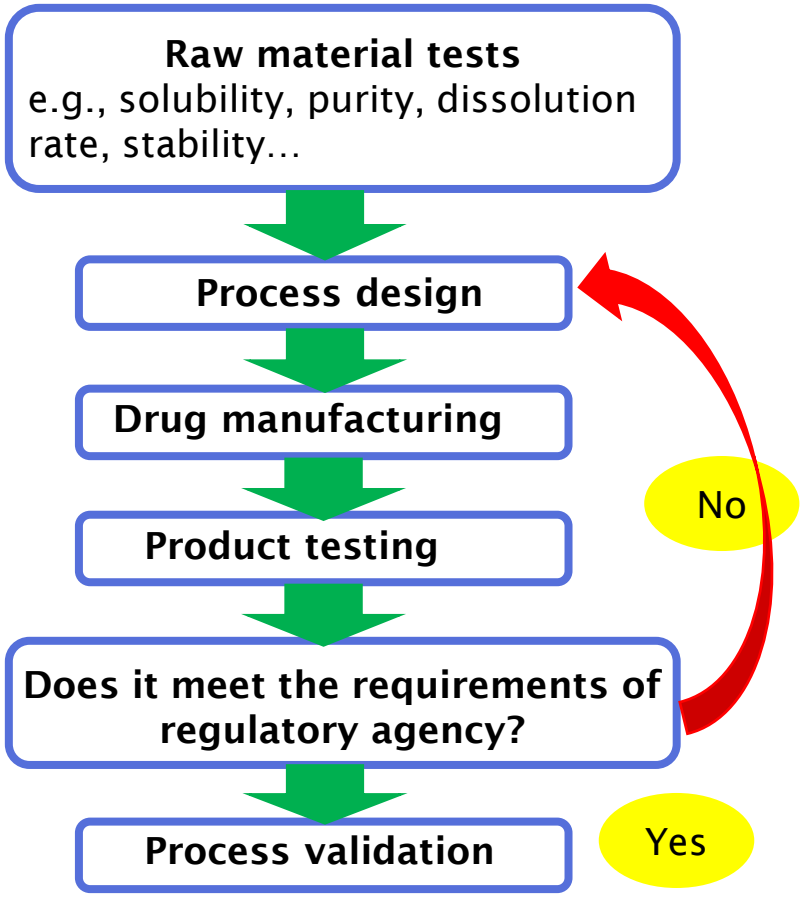
Background Quality by Design (QbD) is a systematic risk-based approach to development, with predefined characteristics and quality risk management throughout the life cycle of a product. International Conference on Harmonization (ICH) guidelines Q8–Q11 give guidance on QbD applications with ICH Q8 (R2)—approved in 2009—describing the principles of QbD in detail. Since its adoption over 10 years ago, more information about QbD usage for the development of medicinal products is expected to be written in regulatory dossiers by companies.

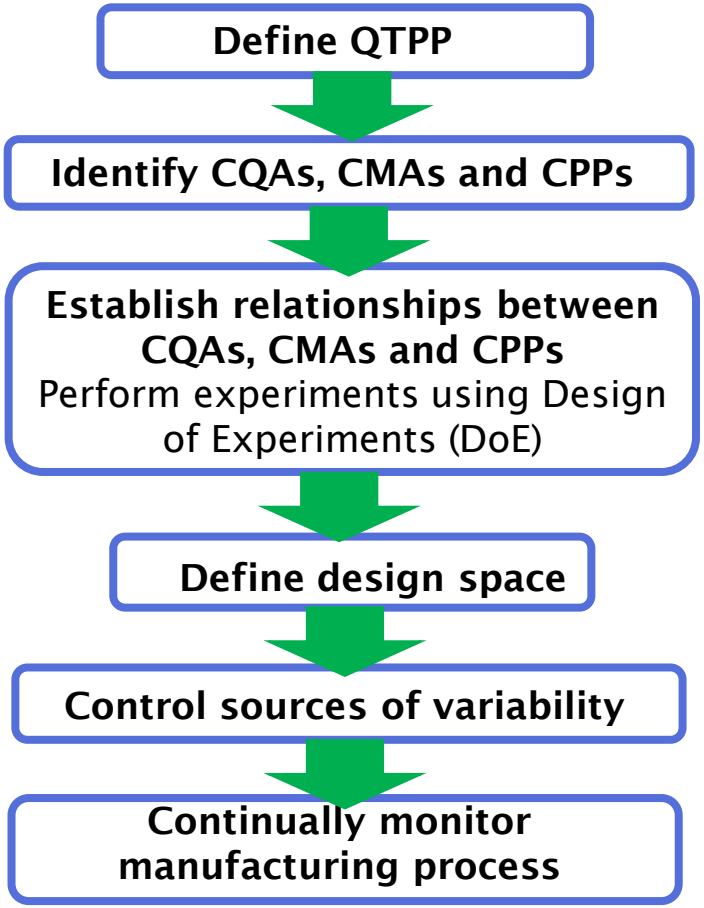
Methods The present study set out to evaluate the implementation of QbD principles and elements in all EU approved marketing applications (MA) ($n = 494$), based on information available in the European Public Assessment Reports (EPARs), for a period of six years (2014–2019), starting 5 years after QbD adoption.

Results Of the 494 MAs, 271 were submitted with a full dossier (article 8(3)). According to EMA (38%), out of the 271 full dossier submissions, only 104 were developed using full QbD. This figure did not increase during this period. Interestingly, between 2014 and 2019, several MAs were not developed via full QbD implementation but used one or more QbD elements during development, including design space. In addition, a higher percentage of small molecule products were developed with QbD as opposed to biotechnology-derived products (78% vs. 22%, respectively).

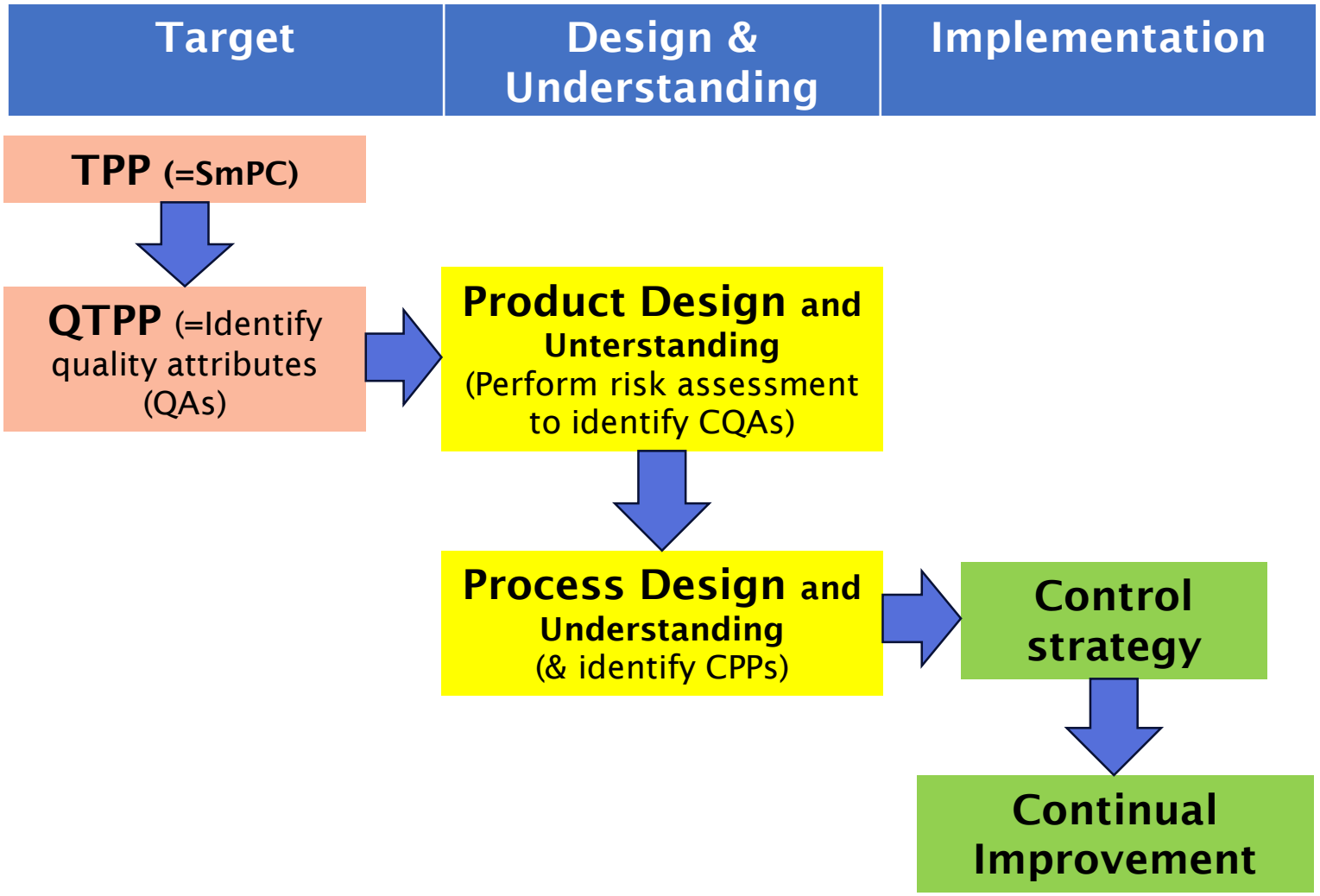
Conclusion Overall, QbD during development of medicinal products is still not commonly described in dossiers. However, more companies started mentioning QbD elements, thus making it a promising step toward QbD as the standard for development in the future.


‚Minimal‘ approach
QbD
‚Enhanced‘ approach
0% QbD
1st QbD element
0% QbD


Raw material tests
e.g., solubility, purity, dissolution rate, stability…
Process design
Drug manufacturing
Product testing
Does it meet the requirements of regulatory agency?
No
Yes
Process validation


Define QTPP
Identify CQAs, CMAs and CPPs
Establish relationships between CQAs, CMAs and CPPs
Perform experiments using Design of Experiments (DoE)
Define design space
Control sources of variability
Continually monitor manufacturing process

QbD process steps

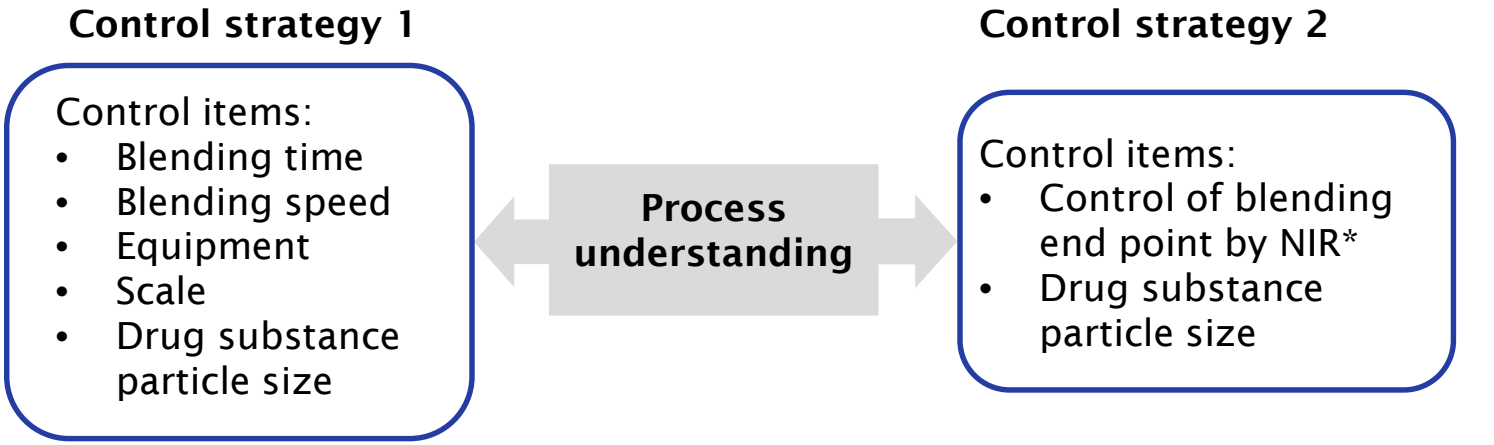


QTPP characteristics	QTPP requirements
Dosage form & strength	Immediate release tablet, 30 mg of active ingredient
Specifications for safety & efficacy	Assay, content uniformity and dissolution
Description & hardness	Robust tablet able to withstand transport & handling

CQAs:

- Assay
- Content Uniformity
- Dissolution
- Tablet Mechanical Strength

Control strategy



**NIR = Near-infrared spectroscopy*