



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Learning from Quality by Design in the manufacturing section

CTTI – Bethesda – 23-24 August 2011
Workshop on Quality Risk Management: Making Clinical Trials Fit for Purpose

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An agency of the European Union





Disclaimer

The views presented in this presentation/these slides are those of the author and should not be understood or quoted as being made on behalf of the European Medicines Agency and/or its scientific committees



Introduction (1)

Regulation of the pharmaceutical sector

- The pharmaceutical sector is one of the most regulated industrial sector in industrialised countries
- This is not surprising taking into consideration the importance health issues have in the life of human beings and the many ethical problems that can arise from the use of medicines (e.g. clinical trials; adverse reactions; quality defects ...)
- Citizens need to be sure that pharmaceutical industry activities are effectively supervised by official bodies (assessment, inspections, pharmacovigilance ...)



Introduction (2)

- On the other hand, regulation (legislation, guidelines etc.) should not impair the development and manufacture of better medicines
- Need to find the balance: regulation of the pharmaceutical industry activities to protect public health without impairing research and innovation

*Develop a harmonised pharmaceutical quality system applicable across the **lifecycle** of the product emphasizing an integrated approach to **quality risk management and science**.....Brussels, 2003*



The 'New Quality Paradigm'

Nov 2005 & Nov 2008

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

Q8 (Q11)

November 2005

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

ICH HARMONISED TRIPARTITE GUIDELINE

QUALITY RISK MANAGEMENT
Q9

Current Step 4 version dated 9 November 2005

Q9

June 2008

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

ICH HARMONISED TRIPARTITE GUIDELINE

PHARMACEUTICAL QUALITY SYSTEM
Q10

Current Step 4 version dated 4 June 2008

Q10

Implementation support

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

Quality Implementation Working Group on Q8, Q9 and Q10 Questions & Answers (R4)

Current version dated November 11, 2010

ICH Secretariat c/o EMA, 11, Avenue Louise, 1205, Box 191, 1211 Geneva 19, Switzerland
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E-mail: ich@ich.org Website: www.ich.org

'Questions and Answers'

ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Quality IWG POINTS TO CONSIDER - DRAFT for sign off

Document date: June 18 2011

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'Points to consider'

Implementation of ICH Q8, Q9, Q10

ICH Q-IWG Integrated Training Programme

J.-L. Robert, Q-IWG Rapporteur

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use **ICH**

'Training & Workshop'



QbD: Regulatory tools

- ICH Q8 (R2) – Pharmaceutical Development - describes science and risk-based approaches to pharmaceutical development
- ICH Q9 – Quality Risk Management - describes systematic processes for assessment, control, communication and review of quality risks
- ICH Q10 – Pharmaceutical Quality System - describes Pharmaceutical Quality Systems applicable throughout the entire product lifecycle, including development
- Q8/9/10 together provide the foundation for an enhanced science based approach to development and manufacture of pharmaceutical products



Key concepts

- Quality by Design: A systematic approach to development that begins with predefined objectives and emphasises process and product understanding and process control, based on sound science and quality risk management (from ICH Q8)
- Process Analytical Technology (PAT): A system for designing, analysing, 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 (from ICH Q8)
- QbD approaches often need the use of Process Analytical Technology (PAT) tools; PAT is an enabling tool to a more systematic approach to pharmaceutical development (QbD)



- **Control Strategy:** A planned set of controls, derived from current product and process understanding that ensures process performance and product quality.
- **Quality Target Product Profile:** 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 product.
- **Critical Quality Attribute:** A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure desired product quality.
- **Proven Acceptable Range:** A characterised range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria.



Design Space

Design Space: The multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality (ICH Q8)

- Once a Design Space has been authorised, movements within it are not considered a change from a regulatory point of view (no variation to be submitted)
- This is accepted in the EU and it has been recognised in the recently adopted revised Variations Regulations

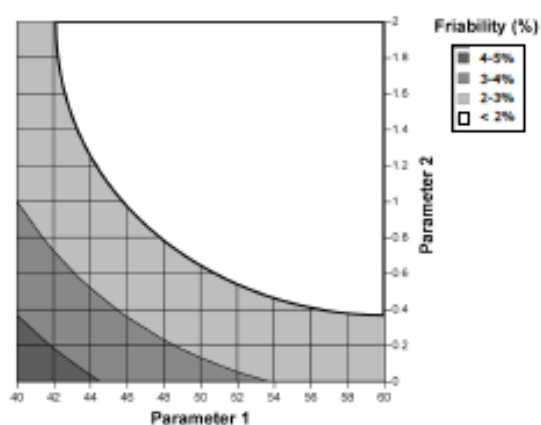
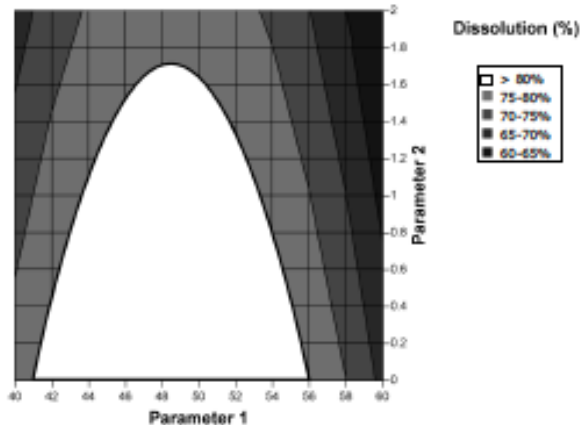


Figure 2a: Contour plot of dissolution as a function of Parameters 1 and 2.

Figure 2b: Contour plot of friability as a function of Parameters 1 and 2.

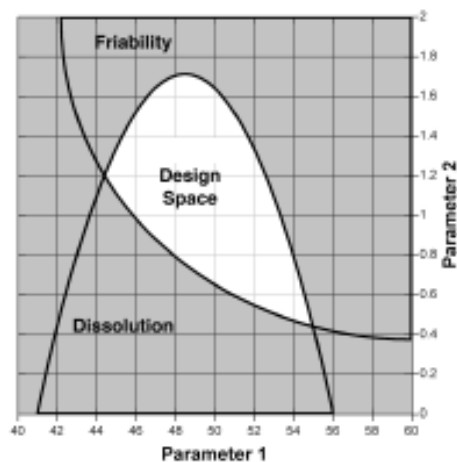


Figure 2c: Proposed design space, comprised of the overlap region of ranges for friability and or dissolution.



Q8: Opportunities for industry

An enhanced, QbD approach to pharmaceutical development provides opportunities for more flexible regulatory approaches, for example:

- Risk-based regulatory decisions (assessment and inspections)
- Manufacturing process changes within the approved Design Space without further regulatory review
- Reduction of post-approval submissions
- Real-time quality control, leading to a reduction of end-product release testing (Real Time Release Testing)



EMA PAT Team

- A forum for dialogue and understanding between quality assessors (chemical and biological products) and GMP inspectors, created in order to prepare a harmonised approach in EU on assessment of applications and inspections of products/systems/facilities when QbD principles and/or PAT technologies are applied
- Upon request, companies are regularly invited to PAT Team meetings in order to present and discuss their development strategies and the techniques they intend to use
- Meet four times per year



EMA PAT Team: Main achievements

The team has liaised with a number of companies and provided advice on their strategies for the implementation of QbD

It has developed guidance (Q&As/reflection paper) on QbD/PAT and contributed to any guidance document in this field at EU and ICH level

It has actively participated and organised various trainings related to QbD at EU and ICH level, for both industry and regulators

It has managed the work sharing project for QbD variations to nationally authorised products, in order to achieve harmonisation of assessment of QbD applications in the EU



Implementation Working Group on Q8, Q9, Q10

"....due primarily to departure from the traditional approaches to quality guidance, proper implementation of these concepts is provided by bringing clarity, further explanation and removing ambiguities and uncertainties" (ICH Q-IWG Concept paper Nov 01. 2007)

.....Ensuring harmonised implementation

Training has been a major achievement of Q-IWG

- ICH regions: EU June, US October, Japan: October 2010
- ASEAN, Kuala Lumpur: July 2010
- IFPMA/DIA, Seoul: April 2011
- HC, Ottawa: September 2011
- APEC/AHC, Seoul: October 2011

Material available



Experiences with QbD submissions in the Centralised Procedure

The number of applications including QbD/PAT elements received at EMA is slowly but steadily increasing

So far, applications came from big pharmaceutical companies and were related to chemical products, but pharmaceutical industry have shown big interest in applying QbD to biological products

A pilot project for joint assessment of QbD applications between EMA and FDA has recently been launched



Summary

Q8 - Pharmaceutical Development

Q9 – Quality Risk Management

Q10 – Pharmaceutical Quality System

Quality by Design:

- Quality Target Product Profile
- Critical Quality Attributes
- Risk Assessment
- Design Space
- Control Strategy
- Product Lifecycle Management and Continual Improvement

Extensive Multiregional Training – regulators and industry

EMA PAT Team – Assessors and Inspectors,

EMA – FDA pilot joint assessment of QbD applications



Defining quality and risk based quality management in clinical trials.



Defining Quality

Quality sufficient to support the decision making process on medicines throughout the clinical development and use post-marketing authorisation

Collecting data, generating information, enabling decision making by:

- Sponsors
- Ethics Committees
- Regulators
- Investigators
- Healthcare professionals
- Study subjects
- Patients



Risk based approaches to clinical trial
supervision and conduct -
Overview of international activities.



Workstream 3: Qualitative Assessment of Monitoring Techniques

Methods:

In seeking to determine how best to ensure the reliability of study results and protect trial participants, the project team has recognized that monitoring should be one component of an overall quality framework that identifies and addresses potential issues. An expert meeting was held to propose an integrated model of quality management that will promote more efficient approaches to monitoring clinical trials.

Results:

On October 13 and 14, 2010, CTTI convened a group of experts to discuss approaches to quality management of clinical trials that would support more efficient approaches to monitoring.

[Click here](#) to view the agenda, presentations, and list of meeting participants.

[Click here](#) to view the WS3 Summary Report

Key Objectives:

- Describe, discuss, and evaluate novel approaches to clinical trial oversight
- Identify the critical aspects of clinical trials that should be the focus of risk-based approaches to creating quality systems
- Propose an integrated model of quality management that will promote more efficient approaches to design, conduct and oversight of clinical trials

Participants:

- Representatives from a broad cross-section of the clinical trial enterprise including regulators, government sponsors of clinical research, academia, industry, patient advocates, clinical investigators, and other interested parties



European Science Foundation



The top five recommendations to strengthen IDCT in Europe as ranked by the consensus conference were as follows:

1. To improve the education, training and career structure and opportunities for scientists involved in patient-oriented clinical research.
2. To increase levels of funding for IDCT.
3. To adopt a 'risk-based' approach to the regulation of IDCT.
4. To streamline procedures for obtaining authorisation for IDCT.
5. To ensure that IDCT are carried out with an appropriate number of patients to produce statistically reliable results so that the trials are 'correctly powered'.

http://www.esf.org/fileadmin/links/EMRC/FL_IDCT.pdf



OECD

ORGANISATION
FOR ECONOMIC
CO-OPERATION
AND DEVELOPMENT



OECD Global Science Forum

“Towards international recommendations to facilitate cooperation in international non-commercial clinical trials”

- **Working Groups** (in progress, finalisation May 2011)
 - Risk-based approach to CTs
 - Regulatory frameworks & harmonisation
 - Infrastructure, education & training practices
- **Report** including recommendations (October 2011)



ADAMON

German initiative – BfArM and academia

CLINICAL
TRIALS *ARTICLE*

Clinical Trials 2009; **6**: 585–596

Risk analysis and risk adapted on-site monitoring in noncommercial clinical trials

*Oana Brosteanu^a, Peggy Houber^a, Kristina Ihrig^b, Christian Ohman^f, Ursula Paulus^d,
Beate Pfistner^{d,e}, Gabriele Schwarz^f, Anke Strenge-Hesse^{g,h} and Ulrike Zettelmeyer^d*

Version 28th March 2011

MRC/DH/MHRA Joint Project

Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products

Pilot launched spring 2011

Appendix 1: Guidance on risk-adapted approaches within the scope of the Clinical Trials Directive

Appendix 2: Guidance on risk-proportionate approaches to the management and monitoring of clinical trials (To be added following completion of the pilot phase)

<http://www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf>



EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Public Health and Risk Assessment
Pharmaceuticals

Brussels, 09/02/2011
SANCO/C/8/PB/SF D(2011) 143488

REVISION OF THE ‘CLINICAL TRIALS DIRECTIVE’ 2001/20/EC

CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION

2. BETTER ADAPTATION TO PRACTICAL REQUIREMENTS AND A MORE HARMONISED, RISK-ADAPTED APPROACH TO THE PROCEDURAL ASPECTS OF CLINICAL TRIALS

Various procedural aspects of EU regulation on clinical trials are not addressed in much detail in the legislation or fail to take into account practical limitations and requirements. This has led to a situation where Member States have slightly divergent national provisions based on identical concepts.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 4 August 2011
2 EMA/INS/GCP/394194/2011
3 Compliance and Inspection

4 Reflection paper on risk based quality management in
5 clinical trials
6 Draft

7

Draft Agreed by the CTFG ¹ for release for consultation	31 May 2011
Draft Adopted by the GCP Inspectors Working Group for consultation	14 June 2011
End of Consultation (Deadline for Comments)	15 February 2012

Reflection paper on risk based quality management in clinical trials

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Introduction and problem statement

Purpose of the paper - facilitate the development of a more:

- systematic,
- prioritised,
- risk-based approach to quality management of clinical trials,
- to support the principles of GCP and to complement existing quality practices, requirements and standards.

Problem can be summarised:

- current practices are not proportionate
- nor well adapted to achieving the desired goals
- generally very costly,
- resulting either in success at an unnecessarily high cost or failure which is also very costly.

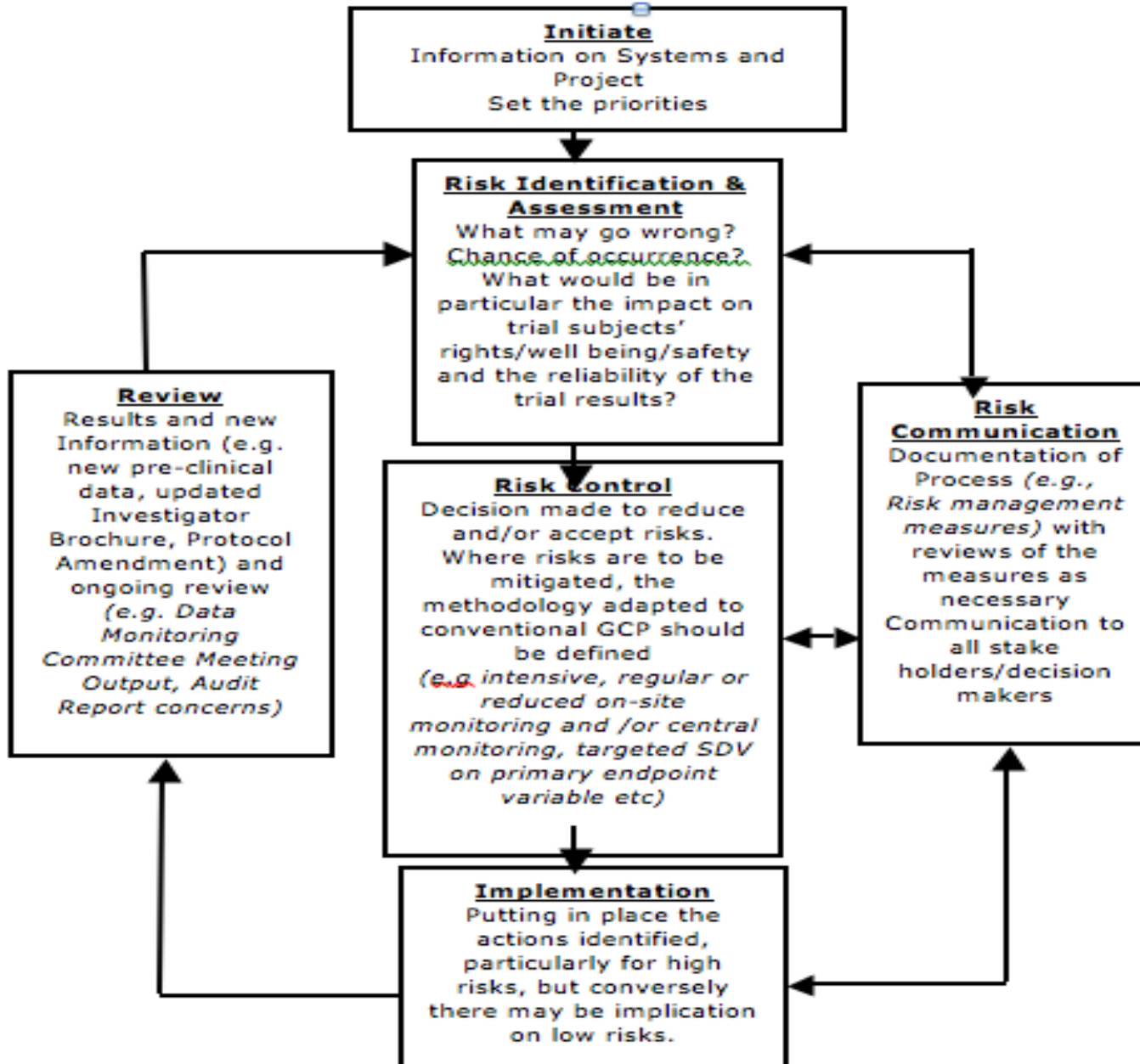
The²⁸ origins of the problem are multifactorial.

System level

- Organisation structures and responsibilities
- Quality systems of organisations
- Computerized systems
- Human resources including qualifications of personnel
- Compliance metrics: quality audit and/or inspection outcomes.

Project level

- Physico-chemical properties of the active ingredient(s),
- Manufacturing process of the investigational product
- Pharmacokinetic, pharmacological and toxicological and clinical trials
- Study budget, clinical trial sites selection and management, CRO involvement, laboratory setup, setup of trial databases, monitoring and management of safety data etc.
- Complexity of trial design, subject population etc.





QUALITY TOLERANCE LIMITS

- Establish the acceptable variation or tolerance limits for the clinical trial procedures involved.
- Bearing in mind the statistical design of the trial and the potential impact of the different levels of variability on the power of the trial.
 - a) Trial data
 - b) Trial protocol procedures and GCP
 - c) Trial management procedures

REPORTING QUALITY

- Clear qualitative and quantitative report,
- Extent the trial has operated within the tolerance limits,
- Conducted to an acceptable level of quality.



Prioritization and risk mitigation approaches across several dimensions:

- Protection of trials subjects - Rights and Integrity, Safety
- Credibility of data and results

Stratified according to knowledge of product (MA status).

Customised approach depending on:

- Protocol complexity
- Therapeutic indication and nature of endpoints, including population and co-medications
- Administration of the product, dose, formulation
- Complexity of study procedures and measurement, including the nature of the intervention
- Vulnerability of the study population



...and don't forget, you don't need to wait

Most, if not all, that is described is already within the scope of existing legislation and guidance.....

....change preconceived ideas, ingrained practices....

.....technology and ideas are there....

.....practice is lagging behind.



European Medicines Agency

**Thank you for your
attention!**

