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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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’

**Implementation support**

- **Nov 2005 & Nov 2008**
  - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
  - ICH Harmonised Tripartite Guideline
  - Pharmaceutical Development

- **November 2005**
  - Quality Risk Management
    - Q9
  - Current Step 4 version
dated 3 November 2005

- **June 2008**
  - International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
  - ICH Harmonised Tripartite Guideline
  - Pharmaceutical Quality System

- **Q8 (Q11)**
- **Q9**
- **Q10**

- ‘Questions and Answers’
  - Quality Implementation Working Group on Q8, Q9 and Q10
  - Questions & Answers (R4)
  - Current version
dated November 11, 2010

- ‘Points to consider’
  - Quality TPG
    - Points to consider
    - DRAFT for sign off

- ‘Training & Workshop’
  - ICH Q-IWG Integrated Training Programme
    - J.-L. Robert, Q-IWG Rapporteur
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

http://www.ich.org/products/guidelines/quality/training-programme-for-q8q9q10.html
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
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 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)*
Risk analysis and risk adapted on-site monitoring in noncommercial clinical trials

Oana Brosteanu, Peggy Houbert, Kristina Ihrig, Christian Ohman, Ursula Paulus, Beate Pfistner, Gabriele Schwarz, Anke Strenge-Hesse and Ulrike Zettelmeyer
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
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.
Reflection paper on risk based quality management in clinical trials

Draft

<table>
<thead>
<tr>
<th>Draft Agreed by the CTFG¹ for release for consultation</th>
<th>31 May 2011</th>
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<td>Draft Adopted by the GCP Inspectors Working Group for consultation</td>
<td>14 June 2011</td>
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<td>End of Consultation (Deadline for Comments)</td>
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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.

The origins of the problem are multifactorial.
Information gathering
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.
Initiate
Information on Systems and Project
Set the priorities

Risk Identification & Assessment
What may go wrong?
What would be in particular the impact on trial subjects’ rights/well being/safety and the reliability of the trial results?

Review
Results and new Information (e.g. new pre-clinical data, updated Investigator Brochure, Protocol Amendment) and ongoing review (e.g. Data Monitoring Committee Meeting Output, Audit Report concerns)

Risk Control
Decision made to reduce and/or accept risks. Where risks are to be mitigated, the methodology adapted to conventional GCP should be defined (e.g. intensive, regular or reduced on-site monitoring and/or central monitoring, targeted SDV on primary endpoint variable etc)

Communication
Documentation of Process (e.g., Risk management measures) with reviews of the measures as necessary Communication to all stake holders/decision makers

Implementation
Putting in place the actions identified, particularly for high risks, but conversely there may be implication on low risks.
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!