Quality Systems

Indian Pharmaceutical Alliance

Advanced GMP Workshops 2017

Presented by Patrick Costello on November 2017
Principal Scientific Administrator Manufacturing & Quality Compliance
Summary

1. Quality by Design and Product Development
2. Quality Risk Management - How have regulators and the industry adopted Quality Risk Management since 2005?
3. Current concepts of quality systems
4. Quality System Indicators and Tools to evaluate GMP compliance
1. Quality by design and product development
Quality by Design (QbD) ≠ Designing a robust Quality System

• Important to understand that QbD and the Pharmaceutical Quality System (PQS) are different but complimentary

• Art 6 of Directives 2003/94/EC and 91/412/EEC require manufacturers to establish and implement an effective pharmaceutical quality assurance system. The term Pharmaceutical Quality System is used in the interests of consistency with ICH Q10 terminology

• Pharmaceutical Quality System (PQS): Management system to direct and control a pharmaceutical company with regard to quality. (ICH Q10 based upon ISO 9000:2005)
Quality

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 (ICH Q6A).

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)).

“Quality cannot be tested into products, quality should be built-in by design”.

https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm128080.htm
Old paradigm: *Quality by End-product testing*

A *relatively old paradigm* of producing medicinal products, which consists of the following four-step sequential process:

1. **Manufacturing** → **Quarantine** → **End product Testing**
2. *Meet spec?*
3. **Batch release**
4. **Batch rejection**

- Product quality is *checked at the end of the manufacturing process* “after the fact”
- Yes/No outcome
- No possibility for adjustments

10/30 out of 10,000,000
Quality by testing- limitations

This approach ignores real-world variability in materials and process controls resulting in slower time to market, cost over-runs and unproductive delays.

When a failure is observed, defective products have already been produced and the cost of poor quality in terms of scrap, rework or warranties is increased.

Studies\[i\] show that

- The industry average for both rework and discarded product is 50%,
- On hold product inventories are on average 40-60 days,
- Plants work at 40-50% of their capacity,
- Average cycle times are in the 30-90 day range,
- Laboratory tests can add as much as 75% to the cycle time


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How can we improve the current state?

W.E. Deming’s Quality, Productivity, and Competitive Position (1982) :

“...To accomplish this you must understand your processes so well that you can predict the quality of their output from upstream activities and measurements...”

Need for a shift in paradigm:

From compliance

to enhanced product and process understanding
## Approaches to pharmaceutical development

<table>
<thead>
<tr>
<th>Minimal or Traditional approach</th>
<th>Enhanced QbD Approach</th>
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<tbody>
<tr>
<td>- Empirical</td>
<td>- <strong>Systematic</strong> (understanding linkages between material attributes and process parameters that have an impact on product quality)</td>
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<td>- Conducted one variable at a time</td>
<td>- Multivariate experiments</td>
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<td>- Fixed manufacturing process</td>
<td>- <strong>Adjustable manufacturing process</strong> within the Design Space</td>
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<td>- Focus on optimisation and reproducibility</td>
<td>- Focus on control strategy and <strong>robustness</strong></td>
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<td>- Control strategy based on end-product testing and off-line analysis</td>
<td>- <strong>Risk-based control strategy</strong></td>
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<td>- Specifications: primary means of control</td>
<td>- Quality control <strong>shifted upstream</strong> into the process</td>
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<td>- Reactive lifecycle management (i.e. problem solving and corrective action)</td>
<td>- <strong>Real time release</strong>*</td>
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**QbD** is preferable as it implies:

- Knowledge of product/process
- Control of variability
- Prevention of batch failure and costs
- Flexible regulatory approaches

Both approaches are acceptable, the usual situation is **somewhere in between**

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Traditional approach

Variable inputs → Process → Variable outputs

Enhanced approach

Variable inputs → Process adjusted, taking into account input and process variables → Consistent output

Measurements fed to process → Process controls/PAT → Measurements fed to process

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Why QbD?

- Higher level of assurance of product quality
- Cost saving and efficiency for industry & regulators
  - Reduce cost/product rejects
  - Increase manufacturing efficiency
  - Facilitate innovation
  - Minimize/eliminate potential compliance actions
  - Regulatory flexibility: Streamline post-approval changes & regulatory process
  - Opportunities for continual improvement

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Key elements of QbD approach

- **Product Profile**
  - QTPP – Quality Target Product Profile

- **CQAs**
  - Determine potential **Critical Quality Attributes**

- **Process Characterisation**
  - Link material attributes and process parameters to CQAs - **Critical Process Parameters (CPPs)**

- **Design Space**
  - Develop a **Design Space** (optional not required)

- **Control Strategy**
  - Design and implement a **control strategy**

- **Lifecycle Management**
  - Manage product lifecycle, including **continual improvement**
Benefits from QbD approach

QbD → better process and product understanding → more robust process

- Less batch failures and batch recalls
- Minimise out of stock situations
- Opportunities for more flexible regulatory approach (Design space, RTRt)

Benefit to the Patient-Industry Regulators

WIN-WIN-WIN
2. How have regulators and the industry adopted **Quality Risk Management** since 2005?
Evolution of guidance to reflect risk

- At the time of ICH Q9 drafting, Risk Assessment was not a new requirement and there were many references to Risk in the GMP Guideline.

- 10 years later, we have an 8 fold increase in references to risk in the GMP Guideline.

QRM 2005-2015

2015

250 references to “risk” in the EU GMP Guide

2005

30 references to “risk” in the EU GMP Guide
ICH Q9 - <10 Years on

• Following adoption of ICH Q9 in Nov. 2005, the EU GMP has gone through significant changes to harmonise and incorporate the principles of QRM
• ICH Q8, Q9, Q10 and Q11 resulted in major efforts to modernise the EU GMP and reflect risk-based concepts in almost all areas
• ICH Q9 is a regulatory framework that empowers organisations to make science-based decision making in a wide range of areas
• ICH Q9 applies to both Industry and Regulatory Authorities
QRM in EU GMP Guidelines (I)

Part I (Finished Products)

- **Chapter 1 Pharmaceutical Quality System** (July 2008): QRM required to be an element of the PQS and a link is made to ICH Q9
- **Chapter 3 Premise and Equipment** (March 2015): The measures to prevent cross-contamination should be commensurate with the risks. QRM principles should be used to assess and control the risks.
- **Chapter 5 Production** (March 2015): The level of supervision (of suppliers of starting materials) should be proportionate to the risks posed by the individual materials.
  - *Guidelines on the formalised risk assessment for ascertaining the appropriate GMP for Excipients of medicinal products for human use (March 2015)*
  - **Chapter 8 Complaints & Product Recalls** (March 2015): The concepts of QRM and risk assessment, risk-based decision making and risk-reducing actions were introduced.
QRM in EU GMP Guidelines (II)

Part II (APIs) (July 2010) was revised to introduce the QRM principles.

Part III (for Finished Products)

- **Annex 11 Computerised Systems** (June 2011): As part of a risk management system, decisions on the extent of validation and data integrity controls to be based on a justified and documented risk assessment of the computerised system.

- **Annex 15 Qualification & Validation** (Oct 2015): The basis by which process parameters and quality attributes were identified as being critical or non-critical should be clearly any risk assessment activities.

Questions and answers on GMP

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp&m id=WC0b01ac05800296ca%20-%20section16
QRM for Regulatory Authorities

• The EU Quality Manual for EU GMP Inspectorates updated to incorporate QRM principles in their quality systems
• QRM has a direct applicability for inspections and assessment activities
  • Inspection Planning (frequency, intensity, resource allocation)
  • Assessment of findings and CAPAs following inspections
  • Assessment of Quality Defects, CAPAs and any market action
  • Risk Based Market Surveillance Testing
Issues noted during Inspections

• Increasing use of risk assessment and QRM activities by industry
• Four key problems noted during inspections about risk assessment and QRM
  • **Lack use of good science** (historical data, modelling data, preventive controls, assumptions regarding severity and detection not supported by data)
  • **Lack of rigour in applying the methodology** (using risk question that are too high level, or not specific for the objective, focusing on too many failure modes and only treating them superficially or subjectively)
  • **Poor management of knowledge** (overlooking or ignoring existing and sometimes key knowledge during risk assessments)
  • **Overuse of formal risk assessments** (many issues managed through the formal risk assessments, sometimes formal but flawed risk assessments provide a sense of security in decision making)

Global GMP Issues – EMA Perspective

• **Non-compliant sites due to basic GMP failings**
  • Data Integrity, Sterility issues and Risk of Contamination accounted for **85%** of the findings that led to GMP Non-Compliance in 2016.

• **Product recalls, potential or actual shortages due to manufacturing and quality problems;**
  • Lack of supply chain resilience;
  • Lack of proactivity in risk-assessment and risk mitigation measures;
  • Reduction in manufacturing capacity with no alternatives registered in Marketing authorisation.

• **Known problems in development getting through to commercial manufacturing: failures in technology transfer**
  • Lack of continuous improvement;
  • Lack of investment;
  • Poor quality interactions / communication between the industry and the regulator.
Quality Risk Management: ICH Q9 – The Process
QRM is implemented properly if these are all present:

1. Risk **Assessment/Control/Communication/Review**
2. Integrated into the **QMS/PQS**
3. Systemic process for **QRM**
4. Ultimately linking to **patient safety**
5. Based on **scientific knowledge** and **experience** with the process
6. Level of **effort**, formality and documentation is **commensurate** with level of risk
7. QRM is a **lifecycle effort** and requires **vigilant management** of risks

Source: Ian Thrussell, “QRM – An enabler in the QMS and product life cycle.”
Using QRM to Improve Quality

- More QRM competencies development through training and knowledge management
- Effective risk assessments based on good science and robust data (data integrity is key)
- Shift focus from reactive to proactive risk management and more explicitly assess supply chains and transport risks as part of procurement and contract management and corporate governance processes
- Improve pre- and post-incident communication on disruptions
- Develop supply chain resilience
3&4. Current concepts of quality systems & Quality System Indicators and Tools to evaluate GMP compliance
Quality Culture is intrinsic to a Quality System
Indicators of mature Quality Culture:

• Led from the top, empowered from below

• Communication of priorities
  • To personnel
  • To shareholders
  • To clients
  • To regulators

• Relevant monitoring
  • Critical review of what metrics are monitored, and the environment in which they are being monitored.
Metrics: careful selection

• Careful selection of metrics is required
  • What behaviours do the metrics demonstrate?
  • What behaviours do the metrics influence?
  • What is the relevance of each metric to product quality or patient safety?

“The only true measures of quality are the outcomes that matter to patients”

Michael E. Porter and Thomas H. Lee, MD
Metrics: careful selection

- Is the company monitoring the right things?
- NOW
- IN FUTURE

The Iceberg Of Ignorance

Adapted from "Quality Improvement and ISO 9001 Management of Healthcare, Medical and Life Sciences" by Victor McDevitt

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Metrics: careful assessment

• The need for context is paramount when interpreting metrics

Deviations per batch

Is this a problem?

• Metrics which give context are as important as the metrics themselves
The importance of context

"Investigations closed within 30 days"

On time
- Poor investigations?
  - Poor quality?
- Poor decision making?
  - Supply disruption?

Late
- Good investigations?
  - Improved quality?
- Good decision making?
  - Consistent supply?
  - Patient benefits?
Applicable to all key Quality System Components

- Change controls
- Document changes
- Deviations / Non conformance
- Complaints
- Recalls / Returns
- Adverse event and reaction reporting
What “Quality Metric like data” is available to inspectors/regulators?

Post-authorisation information:
• Recalls
• Quality defects
• PV signals
• Withdrawals/Shortage
• Testing results

Review of onsite data (e.g. PQR):
• Includes many if not all data outlined
• Process validation reports

Product Quality Review (inter alia):
• Supply chain traceability of active substances
• OOS and trending
• Deviations / non-conformances
• Changes to processes and/or analytical methods
• MA variations
• Stability monitoring results
• Quality-related returns and complaints
• Corrective actions
Conclusion

- Understand difference between Quality by design and a Robust Pharmaceutical Quality System
- Quality Risk Management and its importance to regulators and industry
- Brief Overview of Quality System Indicators and Tools to evaluate GMP compliance
Thanks

• EMA Quality Colleagues – Delores Hernan / Brian Dooley
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• MHRA friends – David Churchward
Any questions?

Further information

Patrick Costello
Patrick.costello@ema.europa.eu

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 Facsimile +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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Back Up Slides
**Additional Guidance QbD**

- ICH Q-IWG Q&A and Points to consider
  


- QbD EMA webpage
  

- Joint European Medicines Agency/Parenteral Drug Association QbD workshop
  
**Additional Guidance QbD**

  

- Guideline on the use of **near infrared spectroscopy** by the pharmaceutical industry and the data requirements for new submissions and variations EMEA/CHMP/CVMP/QWP/17760/2009 Rev 2
  
Additional Guidance QbD

- Guideline on **process validation for finished products** – information and data to be provided in regulatory submissions EMEA/CHMP/QWP/BWP/70278/2012-Rev1

- **Draft** Guideline on **process validation for the manufacture of biotechnology-derived active substances** and data to be provided in the regulatory submission

- Post Approval - EU variation system / **Variations guideline**
Future perspectives for QbD

- ICH Q12 Guideline: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management
  In progress - step 1 Concept paper published

- Implementation of QbD:
  To discuss your QbD submission in EU:
  - Contact the PAT Team (qwp@ema.europa.eu)
  - Seek formal scientific advice (scientificadvice@ema.europa.eu)