New Frontiers in the Quality of Medicines

Workshop
New challenges for Pharmacopoeias

Moderators:
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Dr John Berridge

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New Challenges for Pharmacopoeias

Building Quality into Products: The Regulators Initiatives

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Pharmaceutical Quality – A New Vision

“Develop a harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science.”
Bruxelles July 2003

Q8: Pharmaceutical Development (step 5)
Q8 (R): under discussion
Q9: Quality Risk Management (step 5)
Q10: Pharmaceutical Quality System (step 2)
Discussion over the last few years

**General agreement:**
- Quality cannot be tested into the product, Quality has to be built into the product.
- Product specifications should be based on **mechanistic understanding** of how formulation and process factors impact quality.
- More systematic approach to pharmaceutical development.
- Use of risk management tools.
- The whole takes place within the frame of a Quality System (Q10 like).

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**Conventional Approach**
- Testing after each step
- Obtain Raw Materials → Blend Raw Materials → Tableting → Packaging

**Modern Approach**
- Material knowledge, process understanding, control strategy, .......... based on comprehensive pharmaceutical development working within a “Lifecycle Quality system” (“Knowledge Management, Continual Improvement, .................”)
Q8: Formalisation of some principles

- Process Analytical Technology.
- Real time release.
- Design Space.
- Formal experimental design.
- Lifecycle: update to support new knowledge.
- Continual improvement.
- Q8 drug product driven, but same principles/concepts can be applied for APIs (NCE’s and Biol.).
- Risk based regulatory decisions (reviews and inspections).
- Flexible (regulatory?) approach/opportunities.
- Closer collaboration between assessors and GMP inspectors.
Clarification

- It is up to the manufacturer to develop a product fit for use!
- It is up to the assessor to evaluate if the product is suitable for its intended purpose.
- The level of development will depend on the complexity of the process and product and on the opportunities (e.g. design space, real time release, choice of equipment, ........) proposed by the applicant and finally agreed by the authorities.
- Interaction between Competent Authorities and Applicants desirable:
  Scientific Advice e.g. with QWP and PAT team.

Purpose of a (the European) Pharmacopoeia

- To promote public health by the provision of recognised common standards.
- Such standards to be of appropriate quality as a basis for the safe use of medicines.
- Standards for APIs, excipients, methods for dosage forms (EP).
- General Notices:
  Quality standards represented by monographs are valid only where article in question are produced within the framework of a suitable Quality System.
Purpose of a (the European) Pharmacopoeia

- However:
  - A Pharmacopoeia does not manufacture APIs or medicinal products itself.

- Nevertheless:
  - It is expected that APIs, excipients are manufactured under GMP.
  - It is expected that pharmacopoeial standards will be matched when the drug product is manufactured, using Q8 principles.
  - Pharmacopoeial monographs need to cover multiple sources!

Challenges for Pharmacopoeias

- Monographs are very much end product testing for each component.
- Relationship between manufacturing process and end product specifications?
  - Correlation between measurements during the process (PAT) and release testing specifications (basis for release of the batch).
    - Different approach for specifications needed: predictability concept-additional specifications.
- End product testing still needed:
  - Industry
  - Competent Authority - OMCL
Compliance with the Pharmacopoeia:

« An article is not of pharmacopoeial quality unless it complies with all the requirements stated in the monograph. This does not imply that performance of all the tests in a monograph is necessarily a prerequisite for a manufacturer in assessing compliance with the Pharmacopoeia before release of a product. The manufacturer may obtain assurance that a product is of Pharmacopoeia quality from data derived, for example, from validation studies of the manufacturing process and from in-process controls. »

Current Contribution from European Pharmacopoeia

- General Monographs/General Chapters to support the new process e.g.
  - Analytical methods e.g. NIRS
  - Solid state properties
  - Functionality related characteristics (excipients)
  - Concepts of “Alternative Methods of Analysis”
  - Parametric release (chapter 5.1.1)
  - Production section
  - Certification of suitability
Certification of Suitability

- Problem of compliance of materials from multiple origins with EP monographs; discussed within CPMP/CVMP QWP
- Assessment of an application for a certificate: link between the manufacturing process and the pharmacopoeial specifications.
- Only those elements need to be controlled which are also relevant for the specific source material.
- GMP-Inspections regularly performed by NCAs on behalf of EDQM.

New Trend and Conventional Specifications

- Still a place for “public standards” or can everything be solved by PAT? e.g. typical specifications:
  - Identification
  - Purity
  - Assay
  - Dissolution
- Development and studies on polymorphism
  - Appearance of a new polymorphic form on a marketed product: dramatic influence on in vitro dissolution rate.
  - Would the appearance of this new polymorphic form have been detected by a PAT approach e.g. Real Time Release?
Conclusion

- Public standards will still be needed in the future.
- How to get there is another story or better the company’s choice (e.g. end product testing versus real time release).
- Pharmacopoeias need to continue to develop –together with their stakeholders- activities to take account of and to facilitate the PAT process.
- What else can Pharmacopoeias do to support scientific improvement?
Quality by Design (QbD) – FDA Perspective

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Strasbourg, France
June 14, 2007

Outline

- FDA Quality Initiatives
- FDA View on QbD
  - Design Space
  - Role of Public Standards
- Conclusion
FDA Quality Initiatives

- Critical Path Initiative (Final Report)
- 21st Century Initiative
- ONDQA’s PQAS & CMC Pilot Program (QbD)
- FDA Workshops

- 2004: PAT Guidance Finalized, after two years of intensive efforts
- 2005: ICH Q8/QbD Finalized, ICH Q9 Finalized
- 2006: Quality Systems Guidance Finalized
- 2007: OGD QbR Announced

FDA View on QbD

- Quality by Design is:
  - Scientific, risk-based, holistic and proactive approach to pharmaceutical development
  - Deliberate design effort from product conception through commercialization
  - Full understanding of how product attributes and process relate to product performance

  **QbD information and conclusions should be shared with FDA**
QbD System

**Product & process design and development**
- Define desired product performance upfront; identify product CQAs
- Design formulation and process to meet product CQAs

**Risk assessment and risk control**
- Continuously monitor and update process to assure consistent quality
- Identify and control sources of variability in material and process
- Understand impact of material attributes and process parameters on product CQAs

**Quality by Design (QbD) – A Comprehensive Systematic Approach to Pharmaceutical Development and Manufacturing**

<table>
<thead>
<tr>
<th>Aspects</th>
<th>Traditional</th>
<th>QbD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmaceutical Development</strong></td>
<td>Empirical; typically univariate experiments</td>
<td>Systematic; multivariate experiments</td>
</tr>
<tr>
<td><strong>Manufacturing Process</strong></td>
<td>Fixed</td>
<td>Adjustable within design space; opportunities for innovation (PAT)</td>
</tr>
<tr>
<td><strong>Process Control</strong></td>
<td>In-process testing for go/no-go; offline analysis w/ slow response</td>
<td>PAT utilized for feedback and feed forward at real time</td>
</tr>
<tr>
<td><strong>Product Specification</strong></td>
<td>Primary means of quality control; based on batch data</td>
<td>Part of the overall quality control strategy; based on desired product performance (safety and efficacy)</td>
</tr>
<tr>
<td><strong>Control Strategy</strong></td>
<td>Mainly by intermediate and end product testing</td>
<td>Risk-based; controls shifted upstream; real-time release</td>
</tr>
<tr>
<td><strong>Lifecycle Management</strong></td>
<td>Reactive to problems &amp; OOS; post-approval changes needed</td>
<td><strong>Continual improvement</strong> enabled within design space</td>
</tr>
</tbody>
</table>
Why QbD?

- Higher level of assurance of product quality
- Cost saving and efficiency for industry and regulators
  - Facilitate innovation to address unmet medical needs
  - Increase efficiency of manufacturing process and reduce manufacturing cost and product rejects
  - Minimize potential compliance actions, costly penalties and recalls
  - Enhance opportunities for first cycle approval
  - Streamline post approval manufacturing changes and regulatory processes
  - More focused PAI and post approval cGMP inspections
  - Opportunities for continual improvement

Design Space

- Definition
  - The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality
    - Traditional one dimensional process range doesn’t meet Q8 definition and will not lead to “regulatory flexibility”
  - Regulatory Significance
    - Working within the design space is not considered as a change
- Important to Notice
  - Design space is proposed by the applicant and is subject to regulatory assessment and approval.
Elements of a Design Space

(2) Design Space

- Material Attributes
- Process Parameters

(1) Design Criteria

- Process (or Process Step)
- Product (or Intermediate) Quality Attributes

(3) Linkage
(Qualitative or Quantitative)

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Elements of a Design Space – with Process Analytical Technologies (PAT)

(2) Design Space

- Material Attributes
- Process Parameters

(1) Design Criteria

- Process (or Process Step)
- Product (or Intermediate) Quality Attributes

(3) Linkage

- Monitored Parameters or Attributes
- Additional Linkage

PAT
Quality Control Strategy

Quality Control Strategy encompasses design space, process controls and specifications.

Quality Control Strategy

Design Space/Process Understanding

Specifications (Raw Materials, Intermediates, Product)

Process Controls

Role of Public Standards

- Traditional vs. QbD
- Product release testing vs. PAT
- Sampling
- Batch release vs. Shelf-life testing
- Validation vs. Continuous quality verification
Conclusions

- **The current system is adequate for regulatory submission**
  - Quality is assured by testing and inspection
  - Considerable regulatory oversight

- **However, QbD is the desired approach**
  - QbD principles should result in a higher level of assurance of product quality
  - Additional product and process understanding may result in regulatory flexibility

- **Focus remains on availability of safe, effective and high quality pharmaceuticals**

THANK YOU

MERCI
The Opportunities and challenges of Quality by Design - an Industry Perspective

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Senior Regulatory Consultant
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Presentation Outline

• Our Quality Vision
• What is QbD?
• The challenges and opportunities
• What are the implications?
• Future needs and opportunities
Industry’s “Quality” Vision:

- Pharmaceutical and Manufacturing Sciences leading continuous product and process improvement
  - A transparent, science- and risk-assessment based approach to product development, dossier submission, review, approval and post-approval changes
  - Manufacturers empowered to effect continual improvement throughout the product life-cycle and supply chain
  - Efficient, effective and consistent Regulatory oversight
    - Consistent too with the level of process and product understanding and quality systems

ICH Q8, 9 and 10 support this vision

And ICH Q8, 9 and 10 define Quality by Design

**Pharmaceutical Development:** + **Quality Risk Management:** + **Modern Effective Pharmaceutical Quality Systems**

“**Systematic** approach to pharmaceutical development and product **lifecycle** management.”

J-L Robert: Jan 2007
Challenge: Completion of Q8 left many questions unanswered

- General/technical terms described only at a high level
  - They are not well understood
- What is Quality by Design? (not mentioned in Q8)
  - What's the difference from the way pharmaceutical development has been approached and described until now
- How exactly does the applicant describe and use the concept of Design Space
- Do all regions see it the same way?

Industry uncertainty
- Is it going to be worth the effort?

As part of the development of Q8(R), the ICH Steering Committee charged us to describe the principles of QbD

Challenge: QbD – is it a means to an end or an end in itself?

Basic QbD → Elements of QbD → Comprehensive QbD

- Using a spectrum approach has implication that we could create 'cQbD'
- Should we agree that QbD is an aspirational goal?
QbD brings opportunities

- **Good for business**
  - Greater supply chain reliability and predictability
  - Innovation and improvement facilitated
  - Should provide opportunities for more flexible regulatory approaches

- **Good for the patient**
  - Improved product reliability and reproducibility

- **Good for the Regulator**
  - Knowledge rich submissions make review decisions more facile
  - Greater confidence in product and process performance

Some key QbD concepts

<table>
<thead>
<tr>
<th>Critical Quality Attribute</th>
<th>Critical Process Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>A quality attribute (a physical, chemical, biological or microbiological property or characteristic) that must be controlled (directly or indirectly) to ensure that the product meets its intended safety, efficacy, stability and performance</td>
<td>A process parameter whose variability impacts a critical quality attribute and presents a significant risk to the process failing to produce the desired quality.</td>
</tr>
</tbody>
</table>

Quality Risk Management – ICH Q9
Design Space – new word or old concept?

Baseline Method:
Carry out the reaction at pH 2-5 and between 30 and 60°C = ‘Proven Acceptable Ranges’

Why/how does Design Space provide flexible regulatory approaches?

Enhanced Understanding - Design Space:
Carry out the crystallisation to create particles at size/shape <criterion> varying the temperature, stirring rate and super saturation according to the relationship:
Size = f(temperature) + f(stirring) + f(super saturation) + f(time)

QbD process can capitalise on different control strategy

<table>
<thead>
<tr>
<th>Inputs</th>
<th>Process</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical</td>
<td>Fixed (variability unknown) – test &amp; reject</td>
<td>Fixed within univariate ranges</td>
</tr>
<tr>
<td>QbD</td>
<td>Variability understood</td>
<td>Learning – adaptive to variability</td>
</tr>
</tbody>
</table>

QbD with PAT can remove need for end product testing
**Classical Control Strategy**

- **Sample & Test**
  - API
  - Excipient
  - Excipient

- **Blend** → **Screen** → **Blend** → **Tablet**
  - Sample & Test
  - Sample & Test
  - Sample & Test
  - Pass or Fail

**Fixed processes**

**Quality Criteria met if:**
- Meets specification(s) (off-line QC tests)
- GMP Procedures followed

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**QbD Control Strategy**

- **API** → **Blend** → **Screen** → **Blend** → **Tablet**
  - Characterise
  - PAT
  - PAT
  - Real time release

**Adaptive processes**

**Standards and acceptance criteria for a PAT/QbD approach are not the same as a ‘Test to Document Quality’ approach**
Implications of QbD Control Strategy

Input material variability drives adaptive process
Process controlled within Design Space(s)
=> CQAs will be met
No need for end product sampling and testing for release

“Would comply if tested”

Is this an example of a ‘Flexible Regulatory Approach’?

Implications for Specifications

Traditional Approach
- Relies heavily on end-product testing
- Pharmacopoeial standards are appropriate
- Acceptance criteria based on precedent + process capability ensure necessary quality and reproducibility
- Q6A

QbD approach
- Links product and process performance to ‘customer’ needs
- Relevant Pharmacopoeial standards still helpful
- Acceptance criteria based on controlling Critical Quality Attributes
  - Process capability no longer the primary driver
  - Q6A decision trees may not be appropriate
Still many gaps and opportunities - Q8(R)

Core guideline (Section P2)
• Design Space

Q8(R) - QbD principles
• Critical attribute/parameter
• Control strategy

Implementation
• How to define critical
• How to establish control strategy
• What is a design space
• How to describe design space
• Flexible Regulatory Approaches

Conclusions

Industry does
• View QbD as opening the door to new opportunities for
  ■ Science & risk-based product and process development
  ■ (Quality) control strategies
• Want to ensure that the (potentially) increased investment brings appropriate regulatory recognition
  ■ Greater emphasis on science and risk-based reviews
  ■ Reduction in post-approval change burden
• Implementation and understanding to be consistent globally
  ■ Much to do to address gaps in understanding both within and outside ICH processes
New concepts into quality viewpoint of the inspection

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Contents

- Reminder
- Key elements
- ICH Q8
- ICH Q9
- ICH Q10 : current status
- Conclusion
Reminder

Who is an inspector?

Somebody who likes concrete things.

Key element

One challenge for the new ICH quality documents:

To be understandable by inspectors
ICH Q8

Linked with the notion of quality by design (QbD) with the endless question:

Quality by Design : a new Paradigm ?

QdB is not understandable by inspectors who are not interested to hear about it.

ICH Q8

But inspectors are very interested to look at and invest time into principles like:
- Real time release,
- Control strategy and especially with the definition mentioned in Q10 document (step 2),
- Parametric release as defined in annex 17 of the EU GMP guide,
- Process analytical technology (PAT). Inspectors are involved in the PAT team created at the EMEA level.
ICH Q9

Status of Q9

- Adopted in November 2005
- Publication by Commission as Annex 20 foreseen
- This document is for both industry and competent authorities
- QRM implementation group established in GMP and quality guideline area

ICH Q9

For industry: implication of QRM in the GMP field

- ICH Q9 is not mandatory but QRM should be via a modification of the chapter 1 of the EU GMP guide. ICH Q9 will be presented as a possible model.
ICH Q9

How can QRM activity be inspected?

If the company explains that ICH Q9 has been used as reference for establishing the QRM, it will be used by inspectors.

If not, inspectors might review:
- Whether the quality risk management performed is integrated in the Quality System of the organization
- Traceability, transparency
- How was the decision made?
- Was a (risk) problem / question defined?
- Did the process performed answer this question?
- Were the appropriate functions allocated to all teams?
- Were the right documents recognized?
- Was the decision based on scientific knowledge?

ICH Q9

How should QRM outcomes be reviewed and inspected?

Competent authorities should check if the science used for the quality risk management process is acceptable

Competent authorities check if the risk questions has been appropriately defined

Competent authorities may not accept the outcome of the risk management process if it is not satisfactory in terms of science (i.e. in assessing a quality defect => withdrawal of a product)

Debate and seek agreement on science
ICH Q9

For competent authorities, the compilation of EU will be modified and especially:

- Quality Systems Framework
- Inspection Planning
- Handling of Reports of Suspected Quality Defects
- Training and Qualifications of Inspectors
- Conduct of Inspections

ICH Q9

Conclusion

Q9 should:

- allow an international harmonization of QRM
- facilitate a better comprehension between stakeholders as QP, regulatory affairs, producers belonging to companies and assessors, GMP inspectors, the EMEA, the EU Commission, Heads of Agencies
- be used both by industry and Competent Authorities (CA)
- allow a better use of resources
- increase confidence between industry and CA
Q10 : status report

Where we are ....

- Step 2 of the document reached during ICH meeting in Brussels (5-10 May 2007)
- Document will be published by the European Commission for public consultation (should be 6 months)
- Comments will be discussed in an ICH meeting in Spring 2008 with the goal to reach step 4.

Q10 : status report

The document is divided in 5 parts and one annex

1. The Pharmaceutical Quality System
2. Management responsibility
3. Continual improvement of process performance and product quality
4. Continual improvement of the pharmaceutical quality system
5. Glossary
6. Annex 1 concerning potential opportunities to enhance science and risk based regulatory approaches
Q10 : status report

Annex 1 concerning potential opportunities to enhance science and risk based regulatory approaches

- This section describes 4 different scenarios considering implementation or not of ICH Q8, Q9 and Q10 documents and envisages potential opportunities which could occur.

- The actual regulatory process will be determined by region.

Q10 : status report

- This document is one model for implementing a PQS throughout the different stages of a product lifecycle.

- Implementation of Q10 as described in annex 1 should conduct to potential opportunities.

- This document is product related and not system related.

- Which is different from current GMP.

- And complicates the understanding of the document.
ICH Q10

Pharmaceutical Development → Technology Transfer → Manufacturing → Discontinuation

Management Responsibilities
- Process Performance & Product Quality monitoring
- CAPA
- Change Management
- Management review

PQS éléments

Enablers
- Knowledge Management
- Quality risk Management

GMP

Design Georges France

QS over the lifecycle
- product 1
  - Development
  - Technology Transfer
  - Manufacturing
- Product 3
- QS over the lifecycle
  - product 2
  - Development
  - Technology Transfer
  - Manufacturing
  - Product Discontinuation

Quality system for GMP

Should be considered as part of GMP
**Q10 : status report**

- This document facilitates the implementation of ICH Q8 and Q9 but can be used independently from them.
- It could be used only for one (or more) step(s) of the product lifecycle.
- When implemented, the effectiveness of the pharmaceutical quality system can normally be confirmed during a regulatory inspection.

**Conclusion**

Inspectors are also convinced by the necessity to modify inspection activities and methodologies. There is a need for:

- having better contacts with assessors and develop closed collaboration with them,
- defining new training courses to gain knowledge and better practices in the field of pharmaceutical development, quality risk management and quality systems,
- opening discussions with industry to have common understanding in these areas.
Conclusion

We cannot have two worlds:
- One between experts working at ICH levels developing too theoretical concepts,
- One living in the real life of industry (notably at the manufacturing sites) and competent authorities (notably assessors and inspectors).

Conclusion

The EU regulatory point of view on integration of different ICH quality concepts.

- Quality Risk Management (Q9)
- Pharmaceutical Development (Q8)
- Quality System (Q10)
- Existing GMP
- Quality system
- Pharmaceutical development
- The Regulatory system
Thank you for your attention