QbD: A Global Implementation Perspective
The EU Perspective

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Overview of the Presentation

- QbD: The EU Vision
  - Available regulatory tools
  - Different approaches to pharmaceutical development
  - Benefit for industry and additional opportunities
- Implementation of QbD in the EU
  - The Regulatory System in the EU
  - EU PAT Team
  - Work Sharing Project

ICH Q8/9/10/(11) – 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"

Brussels, 2003

Quality by Design

- Quality: *The suitability of either the drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity* (from ICH Q6A and ICH Q8)
- 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 annex, step 3)
- 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)

Current vs Desired State

Current State

- Pharmaceutical products marketed in the EU are of good quality (quality itself is not an issue) but pharmaceutical development and manufacturing can be improved

Desired State

- Enhanced product and process understanding through enhanced, Quality by Design approach to pharmaceutical development

Regulatory Tools

- ICH Q8 – Pharmacutical Development (Implemented)
- ICH Q8 annex (step 3 of the ICH process – public consultation)
- ICH Q9 – Quality Risk Management (step 5 – regional implementation)
- ICH Q10 – Pharmaceutical Quality System (step 5 – regional implementation)
- ICH Q11 – Development and Manufacture of Drug Substances (step 1 – concept paper)
- Q/As from the ICH Q8-9-10 Implementation working Group clarifying concepts in the guidelines e.g. Pharmaceutical Quality Systems, Knowledge Management, Design Space, Real Time Release, Control Strategy (early draft to be discussed at ICH meeting in Brussels beginning of November 2008)

ICH Q8 – Approaches to Pharmaceutical Development

Minimal approach

- Empirical development
- One variable at a time
- Fixed manufacturing process
- Focus on reproducibility
- Off-line analysis
- Quality assured by testing
- Reactive lifecycle management (corrective actions)

Enhanced, QbD approach

- Systematic approach to development
- Multivariate experiment
- Manufacturing process adjustable within the design space
- Focus on control strategy and robustness of the process
- PAT tools utilised for feed forward and feed back process control
- Risk based control strategy (Real Time Release)
- Preventive lifecycle management (and continual improvement)

✓ The enhanced approach leads to enhanced product and process understanding

✓ Both approaches (and everything in between) are acceptable, QbD is preferable and provides the basis for flexible regulatory approaches

QbD: Benefit for Industry

- Better understanding of the process
- Less batch failure
- More efficient and effective control of change
- Return on investment/cost savings

QbD: Additional 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)

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)
- DS defines a multidimensional space; once a DS has been authorised, movements within the DS 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

EMEA and the Regulatory System in the EU

- EMEA is not the European FDA
- EMEA co-exists with over 40 National Competent authorities in the EU/EEA, forming an integrated network
- The centralised procedure (EMEA) for Marketing Authorisation co-exists with MA procedures at national level (national procedures, de-centralised procedures, mutual recognition procedures)
- EMEA co-ordinates the existing scientific resources in Member States and provides an interface between all parties
- EMEA works towards harmonisation of regulatory and technical requirements within the EU

EU PAT Team

- Mandate (general objective)
  - A forum for dialogue and understanding between Quality and Biologics Working Parties and GMDP Inspectors Working Group to prepare a harmonised approach in Europe on assessment of applications and inspections of products/systems/facilities for Process Analytical Technology, including Quality by Design principles and manufacturing science in the context of PAT
- Composition
  - Chair; 5 quality assessors (chemicals and biologicals); 4 GMP inspectors; chairs of the QWP, BWP and GMDP IWG; observer from EDQM; EMEA staff (4).
  - 1 delegate only (either quality assessor or GMP inspector) per involved country
  - Representation to cover both human and veterinary products expertise

EU PAT Team Activities

- 4 meetings/year
- Liaison with a number of companies, equipment manufacturers and PAT topic groups, including biologicals
- Liaison with FDA (Teleconferences)
- Participation to workshops e.g. Design Space Workshop (May 2006), Workshop on PAT for Biologicals (March 2007), Seminar on Quality by Design/PAT (April 2008)
- Site visits to manufacturers using PAT techniques
- Training of assessors and inspectors

EU PAT Team: Progress to Date

- Published documents:
  - PAT Q/As: clarifying regulatory requirements for changes to the manufacturing process when PAT use is implemented
  - Reflection Paper on PAT related information in the MA dossier
- A mock (CTD P.2) submission (examplain) for a QbD/PAT finished product application has been discussed with industry and published by EFPIA
- Input to QbD/PAT applications in the Centralised Procedure and in the context of the Work Sharing Project
- Input to future PAT applications by discussion with applicants
- Training for assessors and inspectors (Sep 2004/Jan 2006)

EU PAT Team: Ongoing Activities

- Continue and build the existing dialogue with companies on both general and product-related issues
- Further develop existing expertise
- Work with industry on a mock (CTD S.2) submission for a QbD/PAT biotech active substance application
- Develop guidance for assessors, inspectors and applicants on:
  - Impact of PAT on batch release
  - Impact of PAT on assessment of quality
  - Impact of PAT on inspection practise

Other Ongoing Related Activities

- Revision of the NIR Guideline
- Revision of the Parametric Release Guideline (to take into account RTR concepts)

Work Sharing Project

- The Work Sharing Procedure for PAT Variations to Nationally Authorised Products was published in June 2006
- Describes an approach for work sharing between NCAs in the EU
- Has been developed for QbD/PAT related variations to nationally authorised products
- Before the procedure was published, companies were coming to EMEA identifying difficulties in dealing with purely national variations
- Dealing with QbD/PAT variations at national level was perceived by companies as a major barrier to introduction of QbD and/or PAT techniques
- The procedure is co-ordinated by EMEA and aims at pooling and using the best available expertise in the EU on QbD/PAT
- The procedure is not legally binding, however, it has been agreed by the Head of Medicines Agencies and EMEA

WS Project: Results

- 3 applications were assessed within the project, involving the EU PAT Team
- All the applications were successfully finalised
- RTR was authorised for one product within the project, based on combination of extended knowledge of the process, use of information obtained using PAT techniques and use of conventional information

Conclusion

- QbD approach is supported by the regulatory community in the EU
- Appropriate regulatory tools, developed in the ICH context, for the implementation of QbD are available; others are under development
- QbD implementation in the EU is ongoing; however, applications including QbD and PAT elements have been already authorised both in the centralised procedure and within the work-sharing project (variations to nationally authorised products)
- The Design Space concept is now included in the EU legislation
- The PAT Team is the key for implementation of QbD in the EU

WEB References

- PAT page (EMEA website): http://www.emea.europa.eu/Inspections/PAThome.html
- QWP page (EMEA website): http://www.emea.europa.eu/Inspections/QWPhome.html

Thank you for your attention!

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