European Perspective: Regulatory Aspects of Pharmaceutical Development and Manufacturing in the 21st Century

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EMA PAT Team

Mandate (general objective)

- A forum for dialogue and understanding between quality assessors (chemical and biological products) and GMP inspectors 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 Composition

Composition

- Quality assessors (chemicals and biologicals) and GMP inspectors, including the chairs of the main EMA groups/working parties dealing with quality (QWP; BWP; GMDP IWG)
- Representation to cover both human and veterinary products expertise
EMA PAT Team: Main Activities

Liaison with a number of companies, equipment manufacturers and PAT topic groups

Liaison with FDA (Teleconferences)

Organisation of/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
EMA PAT Team: the Future

EMA is working on strengthening the advisory role of the group for companies willing to discuss PAT QbD issues with regulators.

The current role of the team in developing the existing expertise among regulators in the EU on QbD/PAT will be maintained and possibly increased.

The production of guidance document will be achieved mainly by input to the work of the ICH Q8-9-10 Implementation Working Group instead of developing documents for Europe only.
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Pharmaceutical Development (1)

Pharmaceutical Development is not a novel concept in the EU, the QWP Guideline on Development Pharmaceutics (CPMP/QWP/155/96) was published in January 1998.

PD studies are required for any product to be put on the market.
Pharmaceutical Development (2)

In 1998, the scope of Pharmaceutical Development studies was stated as:

- to establish that dosage form and formulation are satisfactory for the purpose of the application
- to identify formulation and processing aspects crucial for batch reproducibility and which therefore need to be monitored routinely

✓ ICH Q8 shifts the aim of Pharmaceutical Development on design of the product, science based approach and enhanced understanding of product and process
Pharmaceutical Development (3)

Regulation 1901/2006/EC (the Paediatric Regulation) requires that applicants for products to be used in the paediatric population submit plans for development in the form of a Paediatric Investigation Plan (PIP)

Before clinical studies can be performed in the paediatric population, pharmaceutical companies may need to develop a specific paediatric formulation

Pharmaceutical development aspects for the paediatric population may be fundamentally different to those of the existing adult product

A Concept Paper on the development of a quality guideline on Pharmaceutical development of medicines for paediatric use has been published on the EMA website, a guideline will be published for external consultation
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Regulatory Tools

ICH Q8 – Pharmaceutical Development
ICH Q9 – Quality Risk Management
ICH Q10 – Pharmaceutical Quality System

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 Testing, Control Strategy

ICH Q11 – Development and Manufacture of Drug Substances (step 1)
Other Ongoing Regulatory Activities in the EU Related to QbD Implementation

Revision of the NIR Guideline (next step: 2\textsuperscript{nd} public consultation)

Revision of the Parametric Release Guideline to take into account RTRT concepts (next step: finalisation after external consultation)

Revision of the Process Validation Guideline to include continuous process monitoring/verification (next step: publication for external consultation)

Revision of the assessment report template and the related guidance document to be used in the centralised procedure to take into account QbD and change management protocols
## ICH Q8 – Approaches to Pharmaceutical Development

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<th>Minimal approach</th>
<th>Enhanced, QbD approach</th>
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<td>Empirical development</td>
<td>Systematic approach to development</td>
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<td>One variable at a time</td>
<td>Multivariate experiment</td>
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<td>Fixed manufacturing process</td>
<td>Manufacturing process adjustable within the design space</td>
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<td>Focus on reproducibility</td>
<td>Focus on control strategy and robustness of the process</td>
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<td>Off-line analysis</td>
<td>PAT tools utilised for feed forward and feed back process control</td>
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<td>Quality assured by testing</td>
<td>Risk based control strategy (real time release testing)</td>
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<td>Reactive lifecycle management (corrective actions)</td>
<td>Preventive lifecycle management (and continual improvement)</td>
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- 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 testing Testing)
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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 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
New Variation Regulation: Regulatory Oversight Level

- Changes not requiring any prior approval
  - Design Space
    - Type IA
      - Do and Tell
  - Type IB
  - Type II
  - Extension

- Changes requiring prior approval

Evaluation Procedure adapted to the level of risk associated to the variation
New Variation Regulation: Post Approval Change Management Protocols

Currently

Evaluation of a proposed variation as a ‘whole’ (Strategy + Results)

Strategy
• Planned studies
• Acceptance criteria
• Methods

+ Results

Early Step 1:
Submission of a Change Management Protocol

Type II Variation

Fast Step 2:
Reporting of implementation of a change in accordance with an approved protocol

Type IA or IB Variation

Type II Variation

Type IA or IB Variation
Post Approval Change Management Protocols

Post approval CMPs could be very important for the application of QbD in the EU

Currently there is no experience on their application

The CHMP Quality Working Party is working on Q/As clarifying practical aspects related to their application

The variation classification guideline could be revised once more experience on post approval CMPs application is gained
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QbD Submissions in the Centralised Procedure

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

All these applications came from big pharmaceutical companies and are related to chemical products, but pharmaceutical industry have shown big interest in applying QbD to biological products.
Inspections

So far less than 5 pre-approval inspections have been carried out in the context of QbD applications, one of them jointly with FDA.

All these inspections have been requested in cases when Real Time Release Testing had been applied for.

The need for inspection to authorise RTRT is not surprising taking into account that it is common practice to carry out an inspection in order to authorise parametric release (for sterility testing).
Post-Approval Flexibility

Proposal for post-approval flexibility had to be rejected till 2009, because the legislation did not allow for it.

The new variation regulation, in force from 1\textsuperscript{st} January 2010, includes provisions for it (Post Approval Change Management Protocols)
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Conclusions (1)

The new concepts introduced with Q8 and the other related ICH guidelines are now fully accepted by regulators (this includes RTRT)

The EU PAT Team has been created in order to achieve an harmonised implementation of QbD/PAT concepts in Europe, it includes the key regulators in the context of QbD/PAT (assessors and GMP inspectors)

The team is open to discuss with companies QbD/PAT strategies, issues and foreseen applications, such discussion can be very useful to achieve a common understanding with regulators; the advisory role of the team for companies will be likely reinforced and more formalised in the future
Conclusions (2)

The Design Space concept is now included in the EU legislation, changes inside an approved DS do not trigger any regulatory procedure.

Post-Approval Management Protocols are also foreseen in the new variation regulation and could further help with the implementation of QbD in the EU.

Applications including QbD/PAT elements have been already approved in the EU; the number of applications received in the centralised system is slowly but steadily growing.
Further Information

EU legislation (EUDRALEX) webpage

EMA website

Questions?
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Thank you for your attention!