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The EU regulatory perspective on PAT

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Overview of the presentation

- **EMEA and key aspects of the European regulatory environment**
- EMEA's current thinking on PAT/QbD
- EU toolkit on PAT
  - Guidelines at EU and ICH level
  - EMEA-PAT team
- Status up to now
- Concepts for discussion
- Conclusions

Key Principles

- The EU is a Single Market for pharmaceuticals - Over 400 million people. 25 Member States, 20 languages !
- In order to sell a medicinal product in the EU, a company needs a Marketing Authorisation

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Marketing Authorisation

- Need objective evidence of Quality , Safety and Efficacy
- Prepare a Dossier in CTD format
- May need Scientific Advice before commencing studies
- Submission of dossier possible through one of a number of routes (procedures):
  - National / Mutual Recognition
  - De – Centralised
  - Centralised

⬇

Different legal provisions for each route + a mass of common technical advice and data requirements

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COMPLEX

but Flexible ! : depending on product type and applicant's marketing strategy

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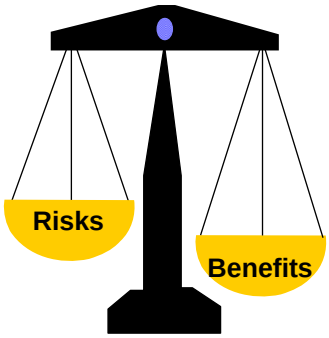
Key elements in medicines evaluation: Benefit/risk balance



- Quality and manufacturing
- Safety (including ERA)
- Efficacy
- Risk Management Program

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Centralised procedure

- Offers the possibility of a single pan-EU authorisation and marketing in ALL MS
- 'Spirit' – Simultaneous availability in ALL MS
- One tradename and identical patient information in ALL EU languages

NB – Centralised route is Mandatory for therapeutic oncology products and others. Optional in the case of "significant scientific, technical or therapeutic innovation " or new active substance)

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EMEA coordinates the centralised procedure

- Established by virtue of EU Regulations (1993 and 2004) as a 'coordinating body' to coordinate the existing resources of Member States and manage the centralised procedure
- A 'virtual' agency, scientific and technical interface among partners

- EMEA is coordinating the scientific evaluation → Scientific Opinion
- The European Commission grants the Commission Decision (Pan European Marketing Authorisation) on the basis of this Opinion
- Legally binding to all MS

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EMEA's Role in Human Medicines Field

- Foster innovation and competitiveness – support research and give advice on product development *(Scientific Advice)*
- Evaluation of applications for *orphan designation* in EU
- Coordination of *evaluation of applications* for Marketing Authorisation for human medicinal products using the Centralised Procedure or referred by Member States
- *Coordination of Inspections* (GMP, GCP, GLP, PhV) in connection with the assessment of applications and/or the assessment of matters referred by Member States
- Control of Safety of centrally authorised products through a *Pharmacovigilance Network*
- Provision of good and independent *information to patients and health professionals*

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EMEA's current thinking on PAT/QbD

- In Europe there had always been a focus on the Pharmaceutical Development as a requirement in MAAs
- PAT is an enabling tool to a more systematic approach to pharmaceutical development *(often called as "QbD")*
  - Analytical measures for dynamic process control
  - Statistical and risk management tools to identify and control critical process and product attributes
- Most tools used in a PAT application (analytical, statistical, risk management) are not novel.

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EMEA's current thinking on PAT/QbD

•Important is the focus on process understanding and the combination of existing technologies and tools to understand in depth the process, with a goal for

- •Continuous improvement
- •Real-Time release based on IPCs
- •Reduced waste

•Although the current EU regulatory framework does not specifically describe PAT, it is open to the implementation of PAT in Marketing Authorisation Applications.

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EU toolkit for PAT

- Guidelines at EU and ICH level
- EMEA-PAT team

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EU guidelines

Pharmaceutical development studies to…

...identify formulations and processing aspects crucial for quality reproducibility of batch and dosage units

Note for guidance on Development Pharmaceutics (CPMP/QWP/155/96)

Christina Graffner, Regulatory milestones in EU with respect to PAT
http://www.emea.eu.int/Inspections/docs/PAT%20Uppsala%20040923.pdf

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EU guidelines

..results of in process tests and controls may constitute sufficient grounds for batch release and provide greater assurance of the finished tablet meeting certain criteria in the specification without the tests being repeated on a sample of the finished product...

Note for Guidance on Parametric Release
(CPMP/QWP/3015/99)

Christina Graffner, Regulatory milestones in EU with respect to PAT
http://www.emea.eu.int/Inspections/docs/PAT%20Uppsala%20040923.pdf

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EU guidelines

…use of PAC, such as NIR and Raman spectroscopy, usually used in combination with multivariate analysis. Spectral data monitored on-line controlling content of active substance, polymorphism, water content, blending homogeneity, particle/powder properties or film thickness could thereby replace end-product testing like e.g. uniformity of content, tablet strength and drug dissolution...

Note for Guidance on Parametric Release
(CPMP/QWP/3015/99)

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ICH guidelines

The implementation of PAT and /or “QbD” is facilitated by the following ICH guidelines:

- Q8 : Pharmaceutical Development (step 5)
  - plus ICH Q8 R (still ongoing before step 2)
- Q9 : Quality Risk Management (step 5)
- Q10 : Pharmaceutical Quality System (step 2)

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ICH Q8: Pharmaceutical Development

- ICH Q8 introduces the concept of Design Space
- A more creative approach but essentially formalising existing concepts on a systematic and in-depth pharmaceutical development
- Provides the opportunity of flexible regulatory approaches when the applicants demonstrate an enhanced knowledge of product performance over a range of material attributes, processing options and process parameters
- *Issue: to develop a common understanding on the meaning of “regulatory flexibility” in practice*

**Flexibility might refer to:*

- *Risk based decisions (reviews and inspections)*
- *Manufacturing process improvements without prior regulatory approval (within the approved design space)*
- *Real time quality control, leading to a reduction of end product release testing*

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ICH Q9: Quality Risk Management

- Provides guidance on the principles and examples of risk management tools that can be used throughout the lifecycle of a medicinal product
- Opportunity for better decision making by contributing to a greater insight of risks and their impacts

- At EU level: Working on the harmonised implementation *(Q9 implementation group at the EMEA level for GMP related matters and a working group of assessors at QWP level)*

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ICH Q10: Quality Systems

- Q10 could be tool for the implementation of Q8 and Q9 principles:
  - Derived from ISO norms which will facilitate implementation

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EMEA PAT team*

•Created in Nov 2003

General objective:

•Forum for dialogue and understanding between assessors and inspectors

•Prepare a harmonised approach within EU on assessment of applications and performing GMP inspections of systems/facilities for Process Analytical Technology, including quality by design principles and manufacturing science in the context of PAT.

www. emea.eu.int/Inspections/PAT

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EMEA PAT team

Composition:

- 9 members: Assessors and GMP inspectors and BWP members
- EDQM-observer
- Support from EMEA secretariat

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EMEA PAT team Objectives

- Review legal and procedural implications on EU regulatory systems and European Pharmacopoeia
  - Revision of existing guidelines
  - New guidelines
  - Revision of assessment / inspection practices and quality system approaches
  - Sampling and testing arrangements by OMCLs
  - Ph. Eur. activities
- Review documents/ publications produced by other organisations

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EMEA PAT team Objectives

- Avoid inconsistencies with other regional approaches
- Review “mock” submissions of PAT related applications
- Develop a procedure for assessment / inspection of PAT related applications
- When requested, to provide specialist input into dossier assessment and scientific advice
- Communicate the outcomes to the relevant WPs (e.g. QWP, BWP, IWP and Ad Hoc GMP inspection Services).
- Identify training needs of assessors and inspectors

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EMEA PAT Team's Activities

- Interaction with interested parties
  - Applicants : Several meetings with companies and visits to manufacturing sites / Review of mock submissions
  - Industry associations e.g. EFPIA
  - Open and ongoing dialogue with FDA
  - Other e.g. ASTM
- To generate guidance documents that formalise the accumulated experience
  - Q&A
  - Reflection paper on the information that needs to be presented in a PAT submission

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EMEA PAT Team's Activities

- Training for assessors and inspectors
- Participation in PAT related conferences
- Organisation of related workshops
  - Design Space Workshop (co-organised with IPS, EFPIA, EUFEPS, APV)
  - Workshop of PAT and BIO

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MAAs status up to now

- Received and already authorised products with PAT and/ or DS elements
  - 8 either authorised or under evaluation
  - Several at pre-submission level

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Concepts for further discussion

- Implications of design space (DS)
  - Presenting the DS in submissions
  - Maintaining and extending DS / Regulatory flexibility
- Process validation
- Specifications and design space

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Design space in submissions

- The design space is proposed by the applicant and is subject to regulatory assessment and approval
- Changes within the design space ⇒ no need for regulatory approval
- Challenges:
  - The level of information to be submitted
  - The interpretation of regulatory flexibility

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Extensions to the approved Design space

- Annex I to Directive 2001/83 EC :

  "…After a Marketing Authorisation has been granted, any change to the data in the dossier shall be submitted to the competent authorities in accordance with the requirements of the Commission Regulations (EC) No 1084/2003 and EC 1085/2003…"
- Movement outside the approved design space is considered to be a change and would normally initiate a regulatory post approval review process
- Very much depends on how the information is presented in the dossier
- The revision of the Variation Regulation can be seen as an opportunity to introduce new concepts, however Q8/9 cannot be seen as tools to circumvent the existing Variations Regulation
- However we have already authorised products where a certain degree of flexibility has been incorporated in the dossier, e.g. alternative equipment, manufacturers, manufacturing processes

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Process validation

- Where a product is subject to enhanced process understanding and monitoring, a state of continuous validation could be achieved based on approved process signatures.
- The need for product equivalence validation (e.g. PQ with 3 batches) could be eliminated provided that the validation strategy is adequately justified.
- The *GMP Annex on process validation* already allows validation without 3 batches

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Real Time Release (RTR) Specifications

- Real time release is based the predictive modelling of finished product quality attributes.
- Current EU legislation requires two specifications: release and end of shelf-life
- A key issue is translating finished product specification acceptance criteria into acceptance criteria for a PAT/Real-Time Release System
- When tested after release using conventional methods the product should comply with the end of shelf life specifications.

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Challenges for the Regulators

- Enhanced collaboration between Assessors and Inspectors (at submission and during the lifecycle of the product)
- Change in review process
  - Need for appropriate expertise
  - Need to ensure a harmonised approach in the review. It may be difficult in the complex EU regulatory environment, but is feasible
- Training

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Conclusions

- There is a lot of activity in this area.
- The technology to realize a PAT environment is now effectively mainstream.
- There are no real technical barriers to deploying a PAT based production process.
- PAT will help manufacturers develop efficient process and right first time products.
- It is not first time that we are faced with new approaches. The EU regulatory system has absorbed successfully in the past other new technologies.

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Conclusions

- The EMEA PAT team is working to ensure that the European regulatory framework and the authorities are prepared for and adequately equipped to conduct thorough and effective evaluations of PAT-based submissions.
- The EMEA PAT team welcomes any discussion on PAT related applications with Industry….

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Thank you for your attention!

Acknowledgements

G. Wade

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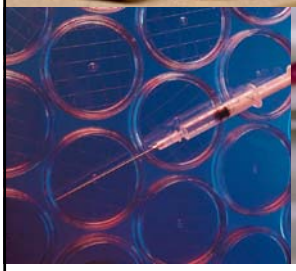
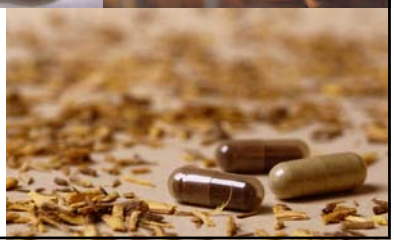
Any Questions?

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