PAT

The European Regulatory View

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Overview of the Presentation

- History
- European developments
- ICH initiatives
- Potential contribution from the European Pharmacopoeia
- Reflections/challenges ahead
- Conclusions

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History

- Companies using PAT for many years in manufacturing, in parallel to normal registered testing requirements.
- New Technologies Forum (RPSGB)(1998-)
- FDA - Pharmaceutical cGMPs for the 21st Century: A risk based approach (8/02)

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History (continued)

- QWP/INSWP - company presentations (2002-)
- FDA - Guidance for Industry PAT - “A framework for Innovative Pharmaceutical Manufacturing and Quality Assurance” (8/03)
- EU PAT team set up (1/04)
- FDA - Guidance for Industry “PAT - A framework for Innovative Pharmaceutical Manufacturing and Quality Assurance” (9/04)

European Union

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EMEA (European Medicines Evaluation Agency)

- EMEA – co-ordinates the existing scientific resources of Member States
- A “virtual” agency providing an interface between all partners
- EMEA is not an FDA for Europe
- Network of 3000 European experts

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European regulatory procedures:

- Centralised (co-ordinated by EMEA)
- Mutual recognition (National Marketing Authorisations linked by a European procedure)
- National

EUROPEAN REGULATORY STRUCTURE

EMEA COMMITTEES

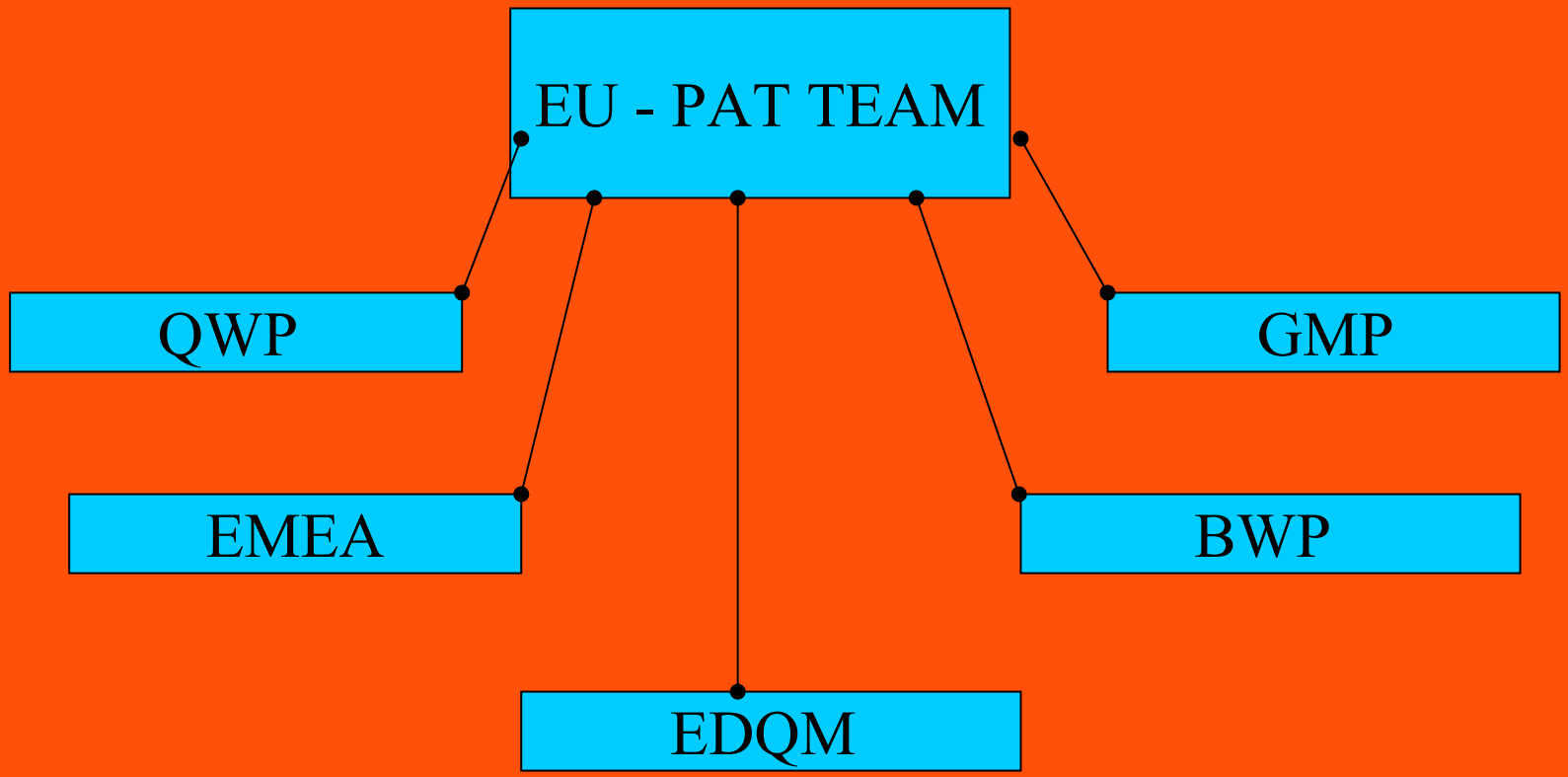
HUMAN | VETERINARY | ORPHAN | HERBAL

Working Groups

QUALITY | GMP INSPECTIONS SERVICES | BIOTECHNOLOGY

EU PAT TEAM

EU PAT TEAM



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EU-PAT Team

Composition:

- 4 Assessors (QWP) + 4 Inspectors (INSWP- GMP)
- Representative from BWP
- EMEA
- EDQM : Observer

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GMP-QWP PAT-Team

Mandate:

– Definition of PAT

– Review legal/procedural implications

- Need for revision of existing guidelines and for new guidelines
- Batch release
- Sampling and testing arrangements by OMCLs
- Need for revision of assessment/inspection practices and quality system approaches
- Impact on European Pharmacopoeia activities

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GMP-QWP PAT-Team

Mandate (continued):

– Forum for presentations from companies
– Review and assessment of mock submissions
– Review of documents produced by other organisations
– Avoid disharmony with other regional approaches
– Develop procedure for assessment of PAT related applications (Assessor / Inspector)
– Training

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Definition

"PAT is considered to be a system for designing , analyzing, 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." - FDA document

EU-PAT Team very much in agreement with the framework of this document

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Claimed Benefit for Industry

– Better understanding of the process
– Introduction of real time release
– Reduction of cycle times
– Less batch failure
– More efficient and effective control of change
– Regulatory relief
– Cost savings ?

Regulatory Guidelines

Quality (ICH)/GMP

Notice to Applicants

- Development Pharmaceutics
- Near Infra Red
- Q6A - Specifications: Test procedures and acceptance criteria
- Parametric Release
- GMP
- Variations - Type I Dossier requirement

EU PAT Team - Progress to date

- 5 meetings
- Liaison with FDA (Teleconference)
- Presentations from a number of companies
- Participation at various conferences
- Training for assessors and inspectors (Sep 04)
- No mock submissions to date

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PAT is one element of a broader process which has received some impetus with FDA's GMP initiative for the 21st Century and continues within the ICH process:

– Q8: Pharmaceutical Development

– Q9: Risk Management

– Q10: Quality Systems

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Q8 – Pharmaceutical Development

" The aim of the pharmaceutical development is to design a quality product and the manufacturing process to deliver the product in a reproducible manner."

"Information from pharmaceutical development is a basis for risk management and recognizes that quality cannot be tested into products. Quality has to be built in by design."

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Q8: two approaches, but no differences in quality

- minimum: as currently requested in EU

- additional (optional): PAT concept

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Q8 – Pharmaceutical Development

PAT option :-

"Enhanced knowledge of product performance over a wider range of material attributes, processing options and process parameters"

[Improved process understanding]

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Q9: Risk Management

" The focus should be to identify hazards that have the potential for patient impact i.e. hazards that have the potential to affect product quality, safety and efficacy ."

Q10: Quality Systems - change control (?)

Contribution from the European Pharmacopoeia

Compliance with the Pharmacopoeia:

" 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. "

Elements of the PAT concept

Contribution from European Pharmacopoeia

- Concept of “Alternative Method of analysis”
- Parametric release - “Method of preparation of sterile products”. (Chapter 5.1.1)

Elements of the PAT concept

EU PAT Team - Reflections to date

- Lot of activity in the area
- Different companies using different approaches and philosophies and at are at different stages of progress
- Internal discussions within companies key, need full sign up.
- Some uncertainty and reluctance to take the initiative

Challenge for Regulators

- Change in review process
- Enhanced collaboration between assessors and inspectors, at time of submission and during life cycle of the product
- Clarification of respective responsibility
- New definition of specifications
- How will it fit into CTD ?
- Batch release, including from third countries
- Training

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Challenge for Industry

– Amount/level of information to be presented to the regulators (chemometrics/statistics)

– Correlation between measurements during the process and release testing specifications (basis for release of the batch)

Conclusion (1)

- Are regulators a barrier to implementation?

  NO

- PAT is already possible today

- Probable barriers
  - uncertainty of regulatory consequences (relief, flexibility)
  - Lack of sponsorship at the relevant level within companies
  - potential for delays in granting authorisations

Conclusion (2)

- System is in place to deal with the introduction of PAT
- Industry must take the initiative and submit applications

Conclusion (3)

- EU-PAT Team is actively working to ensure that regulators across Europe are ready to assess any PAT related submission.
- Please contact us to discuss any PAT initiatives

"Technology, sufficiently advanced is indistinguishable from magic."

Arthur C Clarke 1996