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PAT from a European Perspective

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Overview of presentation

- Introduction
- Pharmaceutical development and Design space
- Understanding and its possible implications on post-approval variation
- Real-time quality assurance
- Reflections

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Introduction

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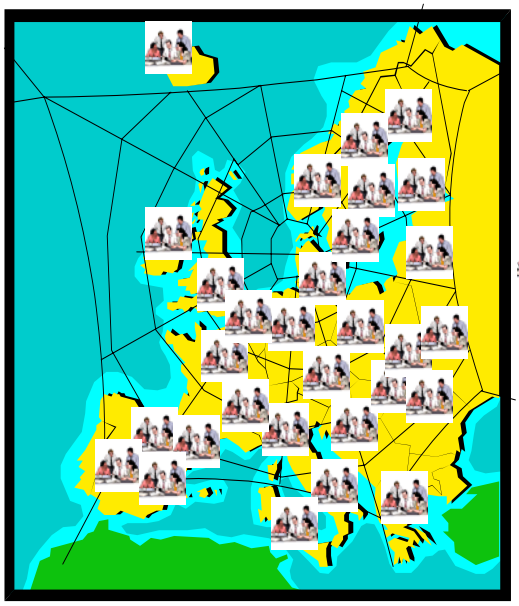

EMEA: a virtual agency based on a network of the competent authorities of EU

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Guiding principles in respect to new approaches to manufacturing and control

- science-based policies and standards
- risk-based orientation
- integrated quality systems orientation
- international cooperation
- strong public health protection

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From “Work programme for the European Medicines Agency (EMEA) 2005”

Cooperation on the ICH/FDA initiative on quality systems/GMP is expected to build on the need for interaction between GMP inspectors and quality assessors.

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Present tripartite discussions*

- ICH Q8 Pharmaceutical Development, in operation from May 2006
- ICH Q8, Annex: Specific Dosage forms, draft
- ICH Q9 Quality Risk Management
- ICH Q10 – Quality system, draft
- PAT and biological products

*No veterinary equivalents at the moment. However, VICH is considering Q9-10.

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ICH Q8 (annex), draft: Specific dosage forms

Purpose

To show by examples how new tools (i.e. design space, PAT), and the QbD-concept could be put into practice and result in regulatory flexibility.

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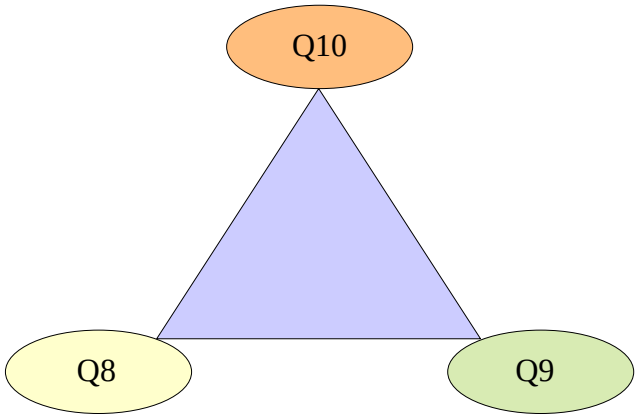
ICH-guidelines system to simplify regulatory implementation of FDA´s initiative



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Quality system (ICH Q10)

Develop a harmonized pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to quality risk management and science.

(ICH meeting 2003, Brüssel)

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ICH Q10 Quality System
(Drafting group)

- Key elements from ISO 9001:2000 and ISO 9004 to complement existing GMPs (active substance, products)
- To promote continual improvements over the life-cycle of the product without regulatory submission when it is clear that the changes are low risk.

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From “Work programme for the quality working party (QWP) and the Ad Hoc Inspectors Group, 2006”

- Impact of PAT on quality aspects of assessment and inspection
- Training on new technologies

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EMEA´s PAT Team

- 4 GMP inspectors *(Denmark, Germany, Italy, UK)*
- 7 assessors of QWP and BWP *(Germany, Luxembourg, Sweden, The Netherlands, UK)*
- EDQM-observer
- EMEA secretariat

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Mandate of EMEA´s PAT-Team

- Forum for dialogue and understanding between QWP and Ad Hoc Group of GMP Inspection Services
- Prepare harmonised approach in Europe on assessment of applications and inspections including new approaches (PAT, QbD- principles, Manufacturing science)

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EMEA PAT Team activities

- 12 formal meetings since start January 2004
- Training events: Uppsala, Bradford, visits to API and products manufacturing sites
- Several interactions with drug companies, EFPIA, FDA
- Invited lecturers at workshops/conferences
- EMEA´s webside:
  - 4 Q&A´s
  - reflection paper
  - invitation to worksharing exercise–quality variations (pilot phase)

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Pharmaceutical Development and Design Space

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Pharmaceutical Development: *To give reviewers and inspectors a comprehensive understanding*

- increased reliance owing to focus on
  - critical quality attributes and their relevance to Safety and Efficacy
  - to which extent the variation of critical formulation attributes/ processing options/ process parameters have an impact on product quality
- to justify control strategies

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ICH Q8: Pharmaceutical Development (in operation from May 2006)

- **opportunity** to present knowledge gained through application of scientific approaches to product and process development (= scientific understanding)
- create basis of flexible regulatory approaches by reducing uncertainty
  - facilitate risk based regulatory decisions
  - continuous improvements without the need for regulatory review
  - ”real time” quality assurance

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ICH Q8: Formulation/Dosage form design

Summarized description of

- pharmaceutical development from initial concept to final design
- identification of attributes and interacting variables critical for product quality
  - i.e. drug substance, excipients (ranges), container closure system, dosing device (if relevant), manufacturing process,…
- formulations from pivotal clinical safety/efficacy studies

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DESIGN SPACE
- exploring its scientific, developmental and regulatory dimensions (8-9 May 2006, London)*

"Creating a shared vision between industry and regulators"

*This highly interactive workshop was attended by reviewers and inspectors from Regulatory Authorities of all 25 European Member States
Organised by FIP in co-operation with EMEA and EFPIA. Supported by EUFEPS, ISPE and APV.

(www.qualityworkshop.nl)

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Design Space – Workshop: discussed questions

1. When and how to start with developing DS
2. Defining the attributes and boundaries of DS
3. Presenting DS in submissions
4. Maintaining and extending DS
5. DS and existing products
6. Regulatory flexibility and DS
7. Specifications and DS
8. API DS
9. DS, quality risk management and control strategy
10. Process signature and process validation

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1. When and how to start with developing DS: Questions to be clarified

- Quality by design (QbD) versus Design space (DS)
- Interaction and dialogue between Regulatory Agencies and Industry. When and how?
- Mechanism for post-approval change to DS
- Mechanism for DS submissions to be reviewed "centrally"
- Prior knowledge?

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Quality by design is about doing things consciously.

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Quality by design and well understood product and processes

- All critical sources of variability are identified and explained
- Variability is controlled by the process
- Product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, environmental and other conditions.

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Design space (ICH Q8)

Multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters demonstrated to provide assurance of quality.

DS is proposed by applicant and is subject to regulatory assessment and approval.

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Boundaries of Design Space

- prior knowledge*
- formal experimental designs (DoE, MVA)
- experienced lifecycle knowledge
- adequate risk management approach

* *literature, previous products, present marketed products,…)*

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2. Defining attributes and boundaries: Definitions needed to be clarified

- An attribute is a characteristic of a material or the end product relating to final performance (safety & efficacy)
  - should be objective, measurable
  - could be qualitative or quantitative
- Critical attributes should be well controlled and non critical attributes should be monitored
  - critical to business or to safety and efficacy?

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3. Presenting Design Space in submissions

- Regulatory interactions as DS submissions are built. Scientific advice process?
- Need for guidance/reflection on regulatory agreement

(www.emea.europa.eu : Reflection paper)

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From "Work programme for the European Medicines Agency (EMEA) 2005"

Scientific advice …

- key area of activity in particular with respect to fostering new innovative technologies and therapies
- facilitate and improve earlier availability of medicinal products
- to promote innovation and research

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Reflection paper*: Chemical, pharmaceutical and biological information to be included in dossiers when PAT is employed

Working document remaining under development due to continuous interactions with industry and experience from submissions.

*(www.emea.europa.eu)

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4. Maintaining and extending Design Space

- Expanded DS due to continuously increased knowledge
- Nature and extent of regulatory interaction when extending/contracting depends on how the DS or control strategy are affected.

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Expanded Design Space to facilitate more flexible regulatory approaches*

Inclusion of continuous increased under-standing during product lifecycle of

- material attributes
- manufacturing processes
- " controls

* reduction of post-approval submissions

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Shared understanding

Maximum benefit to Industry of Quality by Design/Design Space concepts cannot be realised until Q10 and revision of Variations regulations deliver.

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5. Design Space and existing products

Majority of existing products are approved nationally. Harmonized approach for national variations needed across Europe.

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6. Regulatory flexibility and Design Space

- Industry already has regulatory flexibility to make changes within DS under the current system.
- Working within design space (multidimensional region) not considered as a change.
- Movement out of design space is a change → normally initiating a regulatory post approval change process.

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7. Specifications and Design Space

- Finished product release and shelf-life specifications as defined in ICHQ6a
- Product to comply if tested
- At present too much focus on end product testing
- Acceptance criteria: Desirable to better link process capability **and** criteria to safety and efficacy. How?

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8. API Design Space

- Overlying Quality by design principles similar for active substance and drug product process development
- API is key input variable for product manufacturing
- API design space separated into areas related to physical and chemical purity, including their interrelationship (“more understanding needed”).

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9. Design Space, Quality Risk management and control strategy

- Control strategy and specification not necessarily the same.
- Specification versus process limits?
- Process control feed-back/feed forward understanding (as alternative to testing).
- Criticality – does not go away but risk can be mitigated.

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10. Process signature/Process validation

- ASTM definition of Process signature: “A single or multi-dimensional signal indicative of the attributes of the process.”
- EMEA´s proposal: “A collection of batch specific information that shows a batch has been produced within the design space for the product.”

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10. Process signature/Process validation, (cont.)

- Process signature (e.g. pattern recognition) do not need to be in the dossier, but some means to demonstrate working in the DS.
- No common understanding of process signature so far. Do we need the concept?
- Validation is not used to prove the DS.
- Change viewpoint from validation to continuous verification.

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Process signature

Examples given are e.g.

- amount of water added in relation to time *(wet massing)*
- air flow rate and bed temperature during fall rate drying *(fluidized bed drying)*

(Compare in-process control points: end-point limits for e.g. granule moisture content)

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Understanding and its possible implications on post-approval variations

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Procedure for worksharing- quality variations - *Outline of procedure and call for nominations*

Pilot programme:

MAH´s developing PAT related variations to products authorised by national procedures are invited to request inclusion in a pilot phase (*www.emea.europa.eu).*

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Pilot programme

- Request for assessment to all affected NCAs
- Assessment by two rapporteurs
- All NCA´s included in the procedure for information and later opportunity to comment
- After initial discussion of AR and comments by EMEA´s PAT Team normally an inspection will be triggered.

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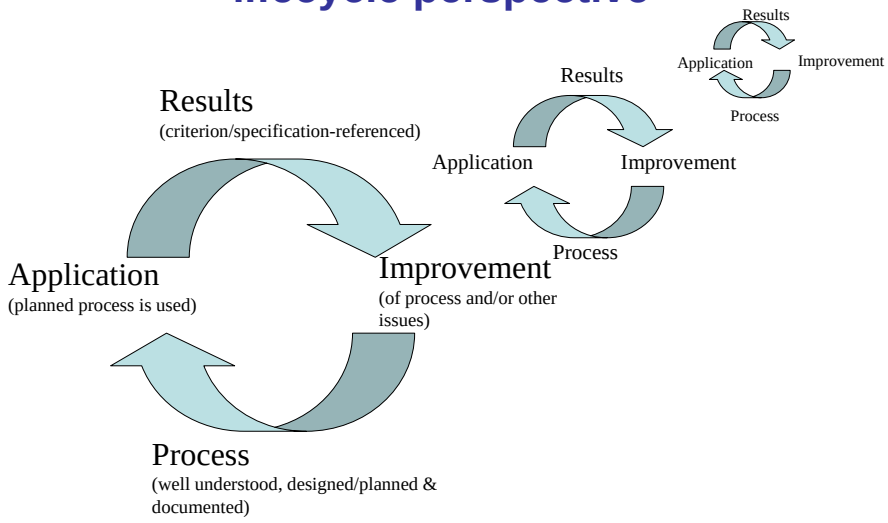
Aim: Continuous improvements process – lifecycle perspective



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Continuous improvements following approval – lifecycle perspective

- Within design space → Regulatory relief
- Outside design space → Regulatory process
- Continuous change of design space →
  → Regulatory process

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Real-time quality assurance

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Real-time release (RTR) instead of finished product testing?

- RTR control based on prediction modelling of finished product quality attributes.
- Current EU legislation requires two specifications: release and end of shelf-life.
- Does RTR mean a third specification?

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Commission directive 2003/94/EC

(Principles and guidelines of GMP in respect of medicinal products for human use…)

Transposition to

Swedish regulation LVFS 2004:

§21 Quality control

……

When a manufacturer has applied and has got approval from MPA to apply another means (than results from tests on final product etc.) like parametric release or real-time release, the approval from MPA will describe how the requirements in this paragraph should be applied.

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Compliance with European Pharmacopoeia (Ph.Eur.)

…does not imply that performance of all tests in a monograph is necessarily a prerequisite for a manufacturer in assessing compliance with the Ph.Eur. before release of a product. The manufacturer may obtain assurance that a product is of Ph.Eur. quality from data derived, e.g. from validation studies of the manufacturing process and from in-process controls.

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Examples on finished product tests which are shown possible to be replaced by RTR

- Functionality properties of active substance/excipients
- Water content
- Uniformity of mass
- Uniformity of content
- Dissolution

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Reflections

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Benefit for pharmaceutical industry: *Improved efficiency and flexibility whilst maintaining high quality standards.*

- Rapid introduction of state-of-the art science and technology
- Encouraged continuous manufacturing process improvements
- Real-time quality control → reduced end-product release testing

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Challenges for Industry

- Amount/level of information to present to regulators (e.g. chemometrics/statistics)
- Validation of association between measurements during manufacture versus release testing according to specification → basis for release of batch

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Challenges for Regulators

- Change in review process
- Enhanced collaboration between assessors and inspectors:
  - at submission and during lifecycle
  - clarification of respective responsibility
- New definitions and specifications (?)

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EMEA PAT Team - Reflections

- Lot of activity in the area
- Companies using different approaches and philosophies and are at different stage of progress
- Internal discussions within companies are key factor

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EU PAT Team is actively working to ensure that regulators and inspectors across EU are ready to assess any PAT related submission.

So, please, take the initiative and submit PAT-applications.

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EMEA Contact details

e-mail: GMP@emea.europa.eu or QWP@emea.europa.eu

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