



# **Workshop on PAT for Biologicals**

**5<sup>th</sup> EGA Symposium on biosimilars**

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# Background: Pharmaceutical Quality – A New Vision

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**“ Develop a harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science.”**

**Brussels July 2003**

**Q8: Pharmaceutical Development**

**Q9: Quality Risk Management**

**Q10: Pharmaceutical Quality System**



# Background: Pharmaceutical Development

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1. **Minimum: conventional approach**
2. **In addition: PAT or QUALITY by DESIGN concept.**

**Enhanced knowledge of product performance over wider range of material attributes, processing options, process parameters, can lead to the establishment of a design space, real time release and to more flexible opportunities.**

**Risk based approach to development**



# Background:

## ICH Q8: Incorporation of new concepts

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- **Process Analytical Technology**
- **Real time release**
- **Design Space**
- **Formal experimental design**
- **Flexible (regulatory) approach/opportunities**
- **Risk based regulatory decisions (reviews and inspections)**
- **Lifecycle: update to support new knowledge**
- **Continual improvement**
- **Knowledge versus data**



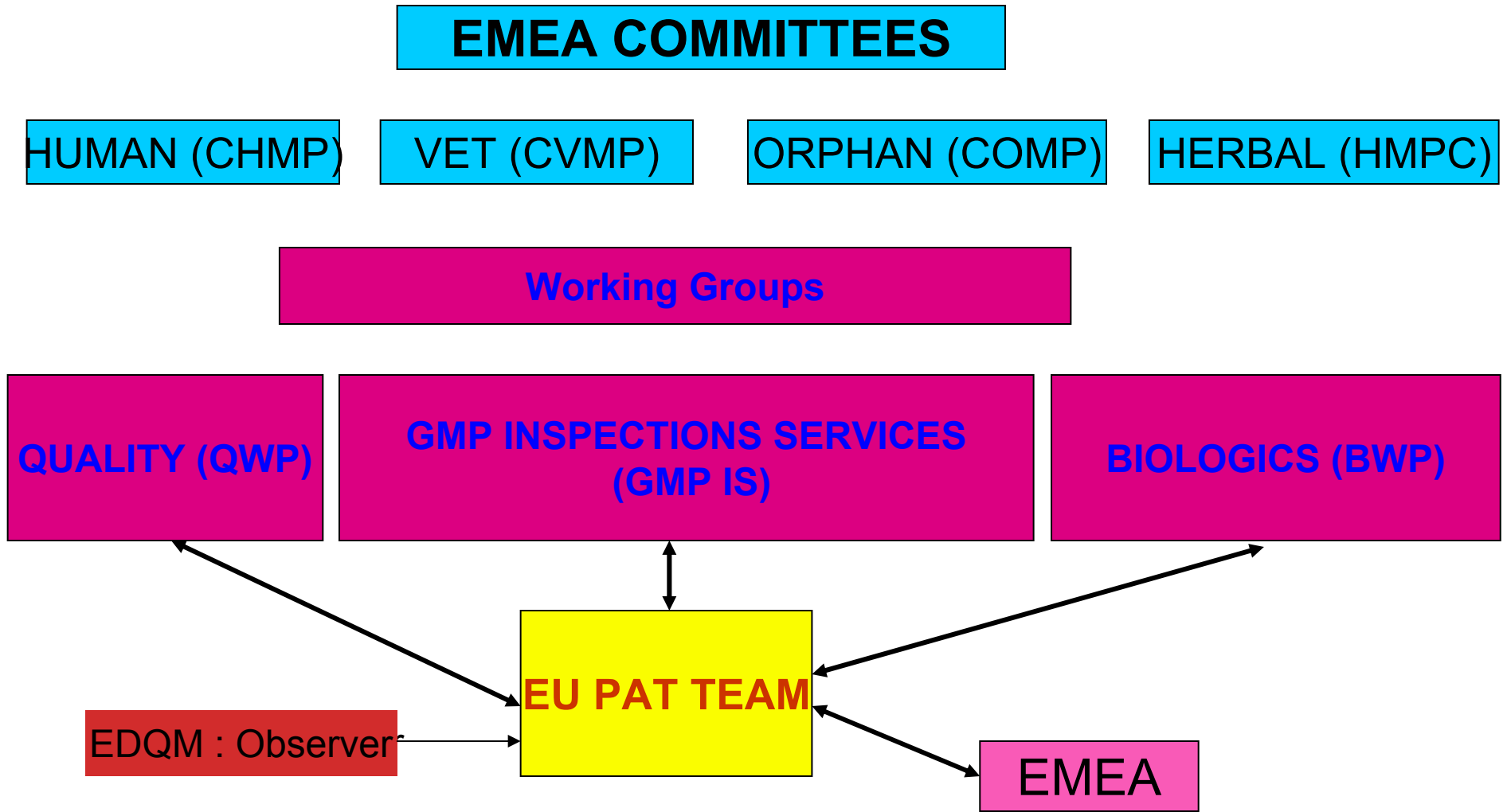
# Format of Workshop

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- **Introduction - Regulatory (BWP, PAT, QWP, Inspectors)**
- **General Industry presentations (EGA, EFPIA)**
- **Confidential Industry presentations**
- **General Conclusions (all)**



# European Regulatory Structure - PAT



# Role of BWP

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- **In general...**
  - » Assists CHMP in the assessment of new applications.
  - » Assists SAWP in the assessment of request for scientific advice.
  - » Produces guidelines ( EU/ ICH)
- **in particular...**
  - » Together with the EMA PAT team discuss PAT and QbD aspects with interested parties



# EMEA Website

The screenshot shows a Microsoft Internet Explorer browser window displaying the EMEA website. The address bar shows the URL [www.emea.europa.eu](http://www.emea.europa.eu). The page title is "Inspections - Process Analytical Technology". The navigation menu includes "About Us", "What's New", "Human Medicines", "Veterinary Medicines", "Inspections", and "General Reporting". The main content area is titled "Inspections - Process Analytical Technology" and features a "fast track to Inspections activities..." dropdown menu. The page is divided into two columns. The left column contains a "What's New" section with links to "Certificates of Medicinal Products", "Counterfeit Medicines", "GCP", "Inspection Services Group", "GLP", "GMP", "Inspection Services Group", "EudraGMP", "Compilation of Procedures", "Joint Audit Programme", "Q&A", "Inspection Coordination", "GCP GLP GMP PhV PMF VAMF", "International Cooperation", "MRAs AU CA CH JP NZ US", "FDA", "ICH - VICH", "Process Analytical Technology", "Q&A", "Product Defects and Recalls", "Quality Working Party", "Guidelines", "Q&A", "Sampling and Testing", "Fees", and "Inspection Links". The right column is titled "Process Analytical Technology - Overview" and contains three paragraphs of text. The first paragraph defines PAT as a system for designing and controlling manufacturing through timely measurements. The second paragraph discusses Quality by Design (QbD) as an established concept in Europe. The third paragraph describes the EMEA PAT team, formed in November 2003, as a forum for dialogue between the Quality Working Party and the Ad Hoc Group of GMP Inspection Services. A "Documents of interest" section at the bottom lists a mandate and two presentations.

**Inspections - Process Analytical Technology** fast track to Inspections activities...

**What's New**

- Certificates of Medicinal Products
- Counterfeit Medicines
- GCP
- Inspection Services Group
- GLP
- GMP
- Inspection Services Group
- EudraGMP
- Compilation of Procedures
- Joint Audit Programme
- Q&A
- Inspection Coordination
- GCP GLP GMP PhV PMF VAMF
- International Cooperation
- MRAs AU CA CH JP NZ US
- FDA
- ICH - VICH
- Process Analytical Technology
- Q&A
- Product Defects and Recalls
- Quality Working Party
- Guidelines
- Q&A
- Sampling and Testing
- Fees
- Inspection Links

**Process Analytical Technology - Overview**

The term "Process Analytical Technologies (PAT)" has been used to describe "a system for designing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes for raw and in-process materials and also processes with the goal of ensuring final product quality". The PAT initiative focuses on building quality into the product and manufacturing processes, as well as continuous process improvement.

Quality by design is an established concept in Europe. Even before the introduction of the Common Technical Document (CTD), the regulatory systems required information on the pharmaceutical development of the medicinal product. This part of the dossier focussed on a comprehensive analysis of the active substance, the choice of the composition, the manufacturing method, as well as the identification of the critical process parameters and the development of suitable analytical methods.

While the requirements for gaining a level of process understanding are not new, it is recognised that the use of multivariate analysis, in combination with modern process analytical chemistry methods and knowledge management tools can enhance the identification of critical parameters that affect the process and thus result in a more in-depth process understanding. One of the goals is to ensure that all sources of variability affecting a process are identified, explained and managed by appropriate process measurements, so that the finished product consistently meets its predefined characteristics from the start ("right first time"). This is in accordance with the fundamental principle that quality cannot be tested, but is instead built into the medicinal product by design.

In order to support the PAT activities in EU, an EMEA PAT team was created in November 2003. It is a forum for dialogue and understanding between the Quality Working Party and the Ad Hoc Group of GMP Inspection Services with the aim to review the implications of PAT and 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 team's [mandate](#) provides further information on the make-up and aims of the team.

The EMEA PAT team believes that the current regulatory framework in Europe is open to the implementation of PAT in marketing authorisation applications. Reference is made to the existing guidance on Development of Pharmaceuticals ([CPMP/QWP/054/98](#)), the Note for Guidance on Parametric Release ([CPMP/QWP/3015/99](#)) and Annex 17 to the EU GMP Guide. In addition, the ICH Guideline on Pharmaceutical Development (ICH Q8), now adopted by EU, also includes provisions on the use of PAT applications. In order to clarify the EMEA PAT team's position on a number of issues raised by the Industry, a "Questions and Answers" document and a [reflection paper](#) have been published. The PAT team will regularly update these documents to reflect new developments and to include accumulated experience.

**Documents of interest:**

- Mandate of EMEA PAT Team
- Presentation given by the Chair of the Quality Working Party at a seminar organised by EDQM in Cannes, 3 May 2004.
- Presentation given by a member of the team at a training course for EU inspectors and quality assessors organised by the Swedish Medical Products Agency in collaboration with EMEA in

<http://www.emea.europa.eu/Inspections/PAThome.html>



# Specificities of biologicals



**IgG**  
~660AA, MW: ~150 000 Da



**Interferon alfa,**  
165AA, MW: 19 625 Da



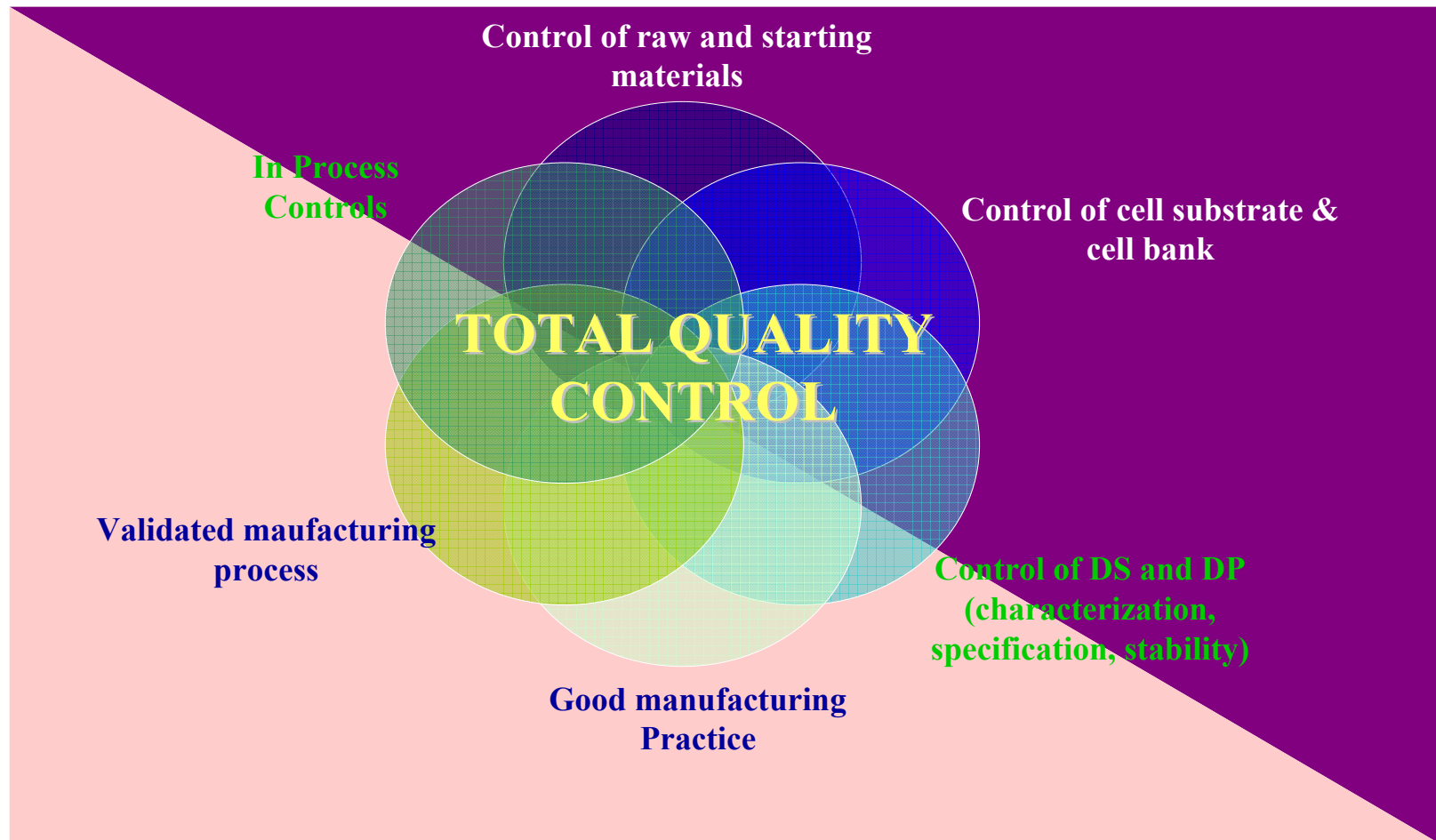
**Aspirin,**  
MW: 180 Da

## Specificities of biologicals

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- **Process Complexity**
  - » Culture of living organism: genetic stability / mutation, viral safety
  - » Harvest: complex matrix dependant on starting/raw materials and process conditions
  - » Purification adapted to protein of interest, impurities and contaminants
- **Process specificity**
  - » Post-translational profiles
  - » Host Cell Proteins

# Specificities of biologicals



# Regulatory Aspects

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- **Application of PAT on biologics**
  - » *Part or complete process:*
    - Single module (e.g. bioreactor)
    - Set of modules (e.g. purification steps)
    - Globally (e.g. complete process ?)
  - » *Before / after MA*
    - before MA: validation and demonstration of robustness
    - after MA: "knowledge" confirmed by marketing and clinical experience

# Regulatory Aspects

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- Biotech specificities:
  - » Paradigm for the last 25 years: **Process ↔ Product**
  - » Biotech guidances: mostly address manufacturing issues
- **"Not revolution but evolution" of tools and concepts**
  - » Additional analytical tools, additional tools to treat data, but "spirit" already there for biologics
  - » New words on concepts not clearly defined / applied
  - » Regulatory implications – risk / flexibility



# Interaction: Industry - Regulators

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- **Informal meetings**
  - » Contact through PAT group
  - » BWP scientific involvement
- **Requests for scientific advice**
- **Applications (variations possible now)**
  - » Stepwise process

# Outlook

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- **Gaining experience with Q8, Q9 and Q10**
  - » Implementation
  - » Survey of already assessed files
- **Development and manufacturing for APIs**  
**Taking into account the principles and concepts outlined in Q8 together with risk management tools.**
- **Revision of existing guidelines:**  
e.g. specifications (Q6A/B)
- **Revision of QOS:**  
use as an assessment tool
- **Need for change of the legislation ?**



# Thank you for your attention !

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- For your information:

- » EMEA Website: <http://www.emea.europa.eu>

- » Biosimilars:

- <http://www.emea.europa.eu/htms/human/humanguidelines/multidiscipline.htm>

- » [Peter.Richardson@emea.europa.eu](mailto:Peter.Richardson@emea.europa.eu)