



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# Regulations: Help or Hurdle for Innovation

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Designing Quality, Efficacy and Sustainability into  
Pharmaceutical Processes – Bologna, 11 May 2010

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*The views presented here are those of the author and should not be understood or quoted as being made  
on behalf of the European Medicines Agency*

An agency of the European Union



# Content of the presentation

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- Introduction
- The EU regulatory system
- The new variation regulation
- Quality by design (a regulator point of view)
- Opportunities for dialogue with regulators
- Conclusions



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- Introduction

# Introduction (1)

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## Regulation of the pharmaceutical sector

- The pharmaceutical sector is one of the most regulated industrial sector in industrialised countries
- This is not surprising taking into consideration the importance health issues have in the life of human beings and the many ethical problems that can arise from the use of medicines (e.g. clinical trials; adverse reactions; quality defects ...)

## Introduction (2)

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- Citizens need to be sure that activities are effectively controlled by official bodies
- This role is undertaken by competent authorities (e.g. assessment of Marketing Authorisation applications; inspections; pharmacovigilance activities ...)

Need to find the balance: regulation of the pharmaceutical industry activities to protect public health without impairing research and innovation



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- The EU regulatory system

# EU Regulatory System (1)

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## Pre 1995

- 15 National Regulatory Authorities
  - 15 Parallel National Reviews
  - 15 Independent Marketing Authorisation
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- Poor resource utilisation
  - Divergent scientific opinions
  - Divergent information for patients and doctors

## EU Regulatory System (2)

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### Today

- A network of decentralised agencies (27 + 3 Member States/ 42 competent authorities)
- Member States have pooled some of their power for authorisation of medicines
- The European Medicines Agency (EMA) was created in 1995 to co-ordinate the existing scientific resources in the EU Member States

# MA Procedures in the EU

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National Procedure

Mutual Recognition Procedure (MRP)

Decentralised Procedure (DCP)

Centralised Procedure (CP)

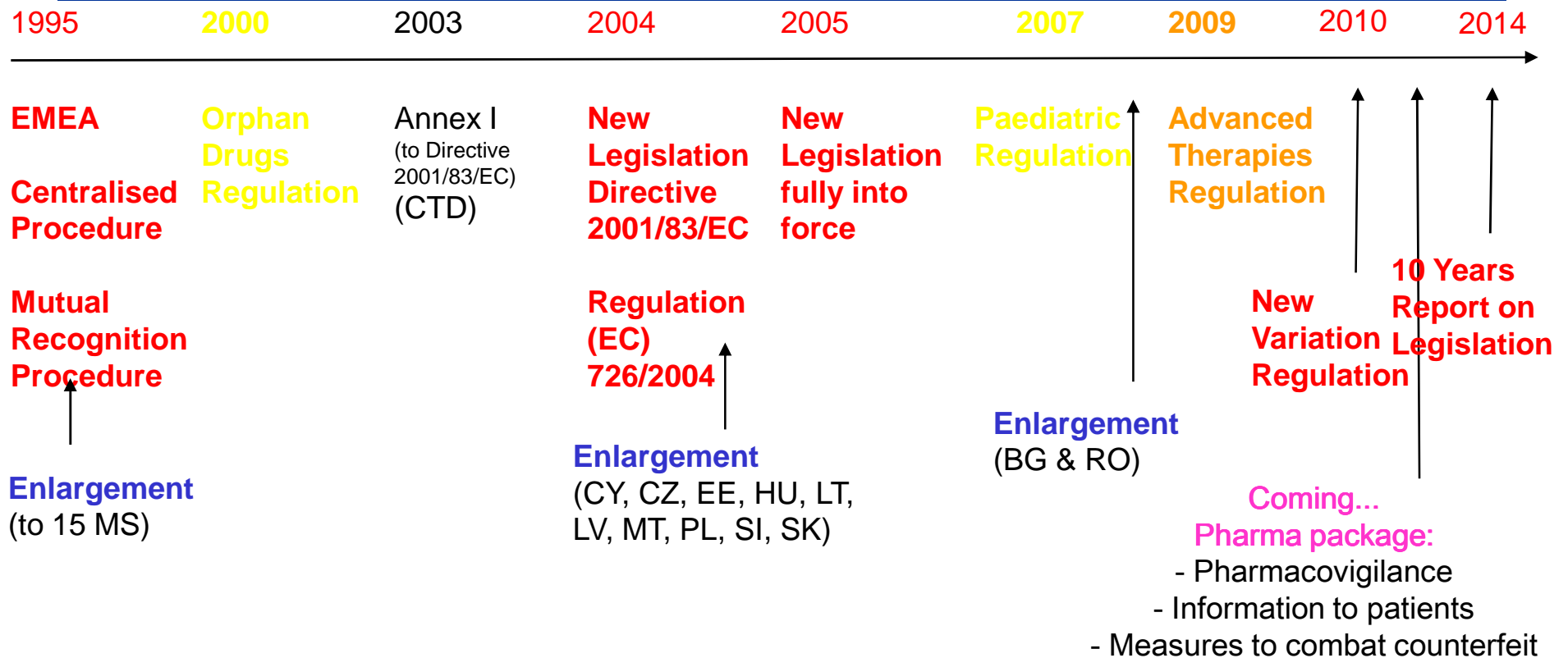
## The philosophy of the EU system

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- Protect and promote public and animal health
- Facilitate access by patient to new and better medicines
- Provide a platform for discussion of public health issues at European level
  
- Single EU market for pharmaceuticals
- Allow further development of European based pharmaceutical industry



# The evolution of the EU system





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- The new variation regulation

# New Variation Regulation: Background

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Review process started by the European Commission in 2006, in the context of the “better regulation” initiative

Current regulations considered considerable burden for both authorities and industry (hurdle to innovation)

Objectives:

- Clearer, simpler, more flexible, reduce administrative burden, adapt to ICH concepts, further harmonisation, without compromising human and animal health



## The revision project

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Harmonisation (common set of rules regardless of authorisation route)

Content of the regulation

## Main changes (1)

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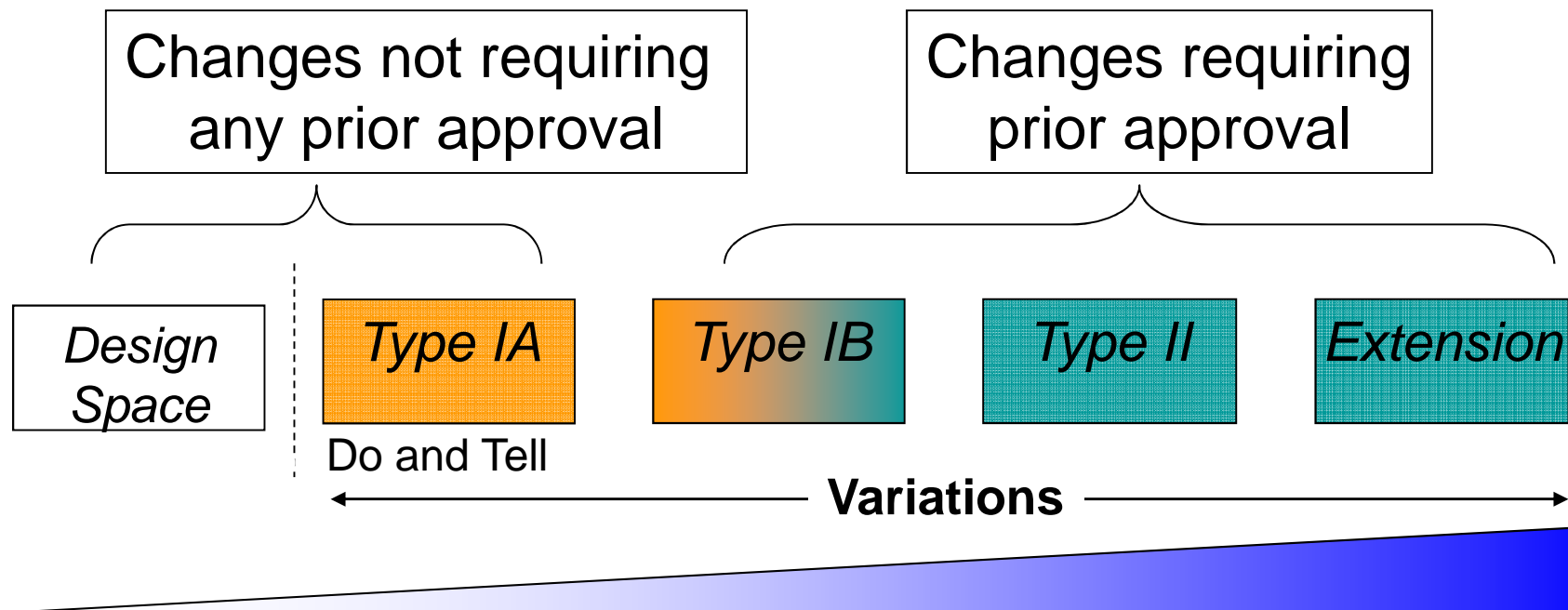
- Changes inside the Design Space are not considered a variation
- Type IA variations to be notified by 12 months after implementation (“do and tell”) e.g. through annual reports
- Unlisted variations type IB by default

## Main changes (2)

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- Grouping of variations
  - Group of variations for the same MA to be submitted and assessed at the same time
- Work sharing
  - Same variation or group of variations which applies to different MAs of the same MAH to be submitted to Reference Member State or EMEA (if at least one of the MAs is centralised)
- Post approval management protocols

# Types of variations



Evaluation Procedure adapted to the level of risk



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- Quality by Design (a regulator point of view)

## ICH Q8/9/10/(11) – 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, 2003

# Pharmaceutical Development

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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

## QbD: Regulatory Tools

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ICH Q8 – Pharmaceutical Development

ICH Q8 annex

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, Control Strategy

ICH Q11 – Development and Manufacture of Drug Substances (step 1 – concept paper)

# ICH Q8 – Approaches to Pharmaceutical Development

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## Minimal approach

Empirical development

One variable at a time

Fixed manufacturing process

Focus on reproducibility

Off-line analysis

Quality assured by testing

Reactive lifecycle management (corrective actions)

## Enhanced, QbD approach

Systematic approach to development

Multivariate experiment

Manufacturing process adjustable within the design space

Focus on control strategy and robustness of the process

PAT tools utilised for feed forward and feed back process control

Risk based control strategy (Real Time Release)

Preventive lifecycle management (and continual improvement)

- ✓ 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: Regulatory Opportunities for Industry

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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)



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- Opportunities for dialogue with regulators

## EMA Scientific Advice (1)

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- The EMA Scientific Advice (SA) procedure can be requested for all medicinal products irrespective of eligibility for the centralised procedure or not
- The Scientific Advice procedure is used for scientific issues concerning quality, non-clinical and clinical aspects relating to the proposed future development of the medicinal product
- Scientific Advice focuses on development strategies rather than pre-evaluation of data to support a MA application

## EMA Scientific Advice (2)

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- Scientific Advice received from the EMA is applicable throughout the EU
- A SA consultation does not preclude the possibility of consultations with national competent authorities
- Even if SA is not legally binding with regard to any future marketing authorisation application of the product(s) concerned, it is a formal official advice given by EMA through its scientific committees

## EU PAT Team

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- A forum for dialogue and understanding between quality assessors (chemical and biological products) and GMP inspectors, created in order to prepare a harmonised approach in EU on assessment of applications and inspections of products/systems/facilities when QbD principles and/or PAT technologies are applied
- Upon request, companies are regularly invited to PAT Team meetings in order to present and discuss their development strategies and the techniques they intend to use
- The advisory role of the PAT Team will be strengthened in the near future



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- Conclusions

## Conclusions

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- Regulation of pharmaceuticals is needed to protect public health, but should not obstacle innovation
- Efforts have been made by regulators in the EU to make the applicable regulatory requirements more in line with the need of the pharmaceutical industry without compromising public health
- The new Variation Regulation and the activities undertaken to implement the QbD concepts are examples of such an effort



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# Thank you for your attention!

Any question?

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