



**Clinical trials  
in developing countries  
submitted to EMEA for  
regulatory purposes**

**Rome, UNICRI/AIFA**

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# Agenda

- Challenges
- EU regulatory requirements for clinical trials
- Facts and Figures
- Next steps



## What are the challenges?

- Globalisation of clinical research
- Reaching a common understanding and framework for ethical and scientific standards
- Achieving a strong regulatory and ethical framework in all countries where clinical trials are conducted
- Assistance through sharing of expertise and capacity building



## **Directive 2005/28/EC “GCP Directive” Directive 2001/20/EC “Clinical Trials Directive”**

- Protection of public health and rights and integrity of research participants
- Legal basis of GCP and GMP in clinical trials
- Applies to all (investigational) medicinal products, all phases, both industry sponsored and academic clinical research



## **Directive 2001/83/EC as amended and Directive 2003/63/EC (I)**

MAH statement that clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC.

“it should be verified, at the time of the evaluation of the application for authorisation, that these trials were conducted in accordance with ... GCP...”

“...ethical principles that are reflected, for example, in the Declaration of Helsinki.”



## **Clinical trials conducted in third countries**

### **Requirements apply:**

- To all clinical trials conducted in third countries that are included in a MAA submitted in the EU/EEA regardless of the third country involved
- no specific legal framework for review of a clinical trial dossier by an EU regulator before the conduct of the trial in a third country



## Acceptance of third country trials in MA applications to EU

- Ethical issues
- Data quality issues
- Applicability to EU population
- Applicability to EU medical practice



## Numbers of clinical trials registered in EudraCT (1 May 2004 to 1 Nov 2008)

- Clinical trial applications: **35,571**
  - Involving **18,154** different clinical trials
- Type of sponsor
  - Commercial sponsor: **79.4%**
  - Non-commercial sponsor: **20.6%**
- Countries
  - Including third country sites: **18,410**

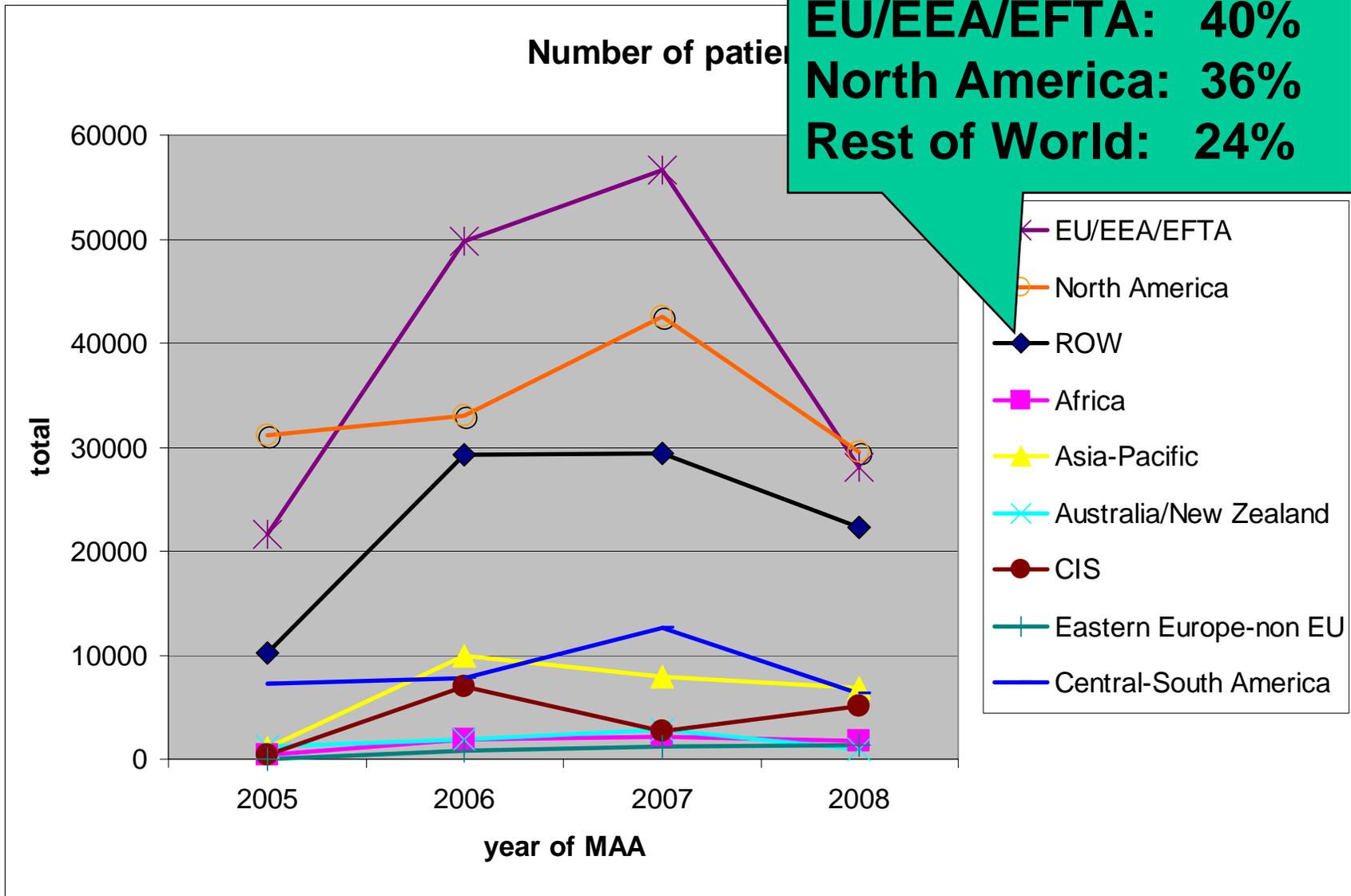
**52% of EU based trial applications also indicate involvement of sites in third countries**



# Pivotal Clinical Trials

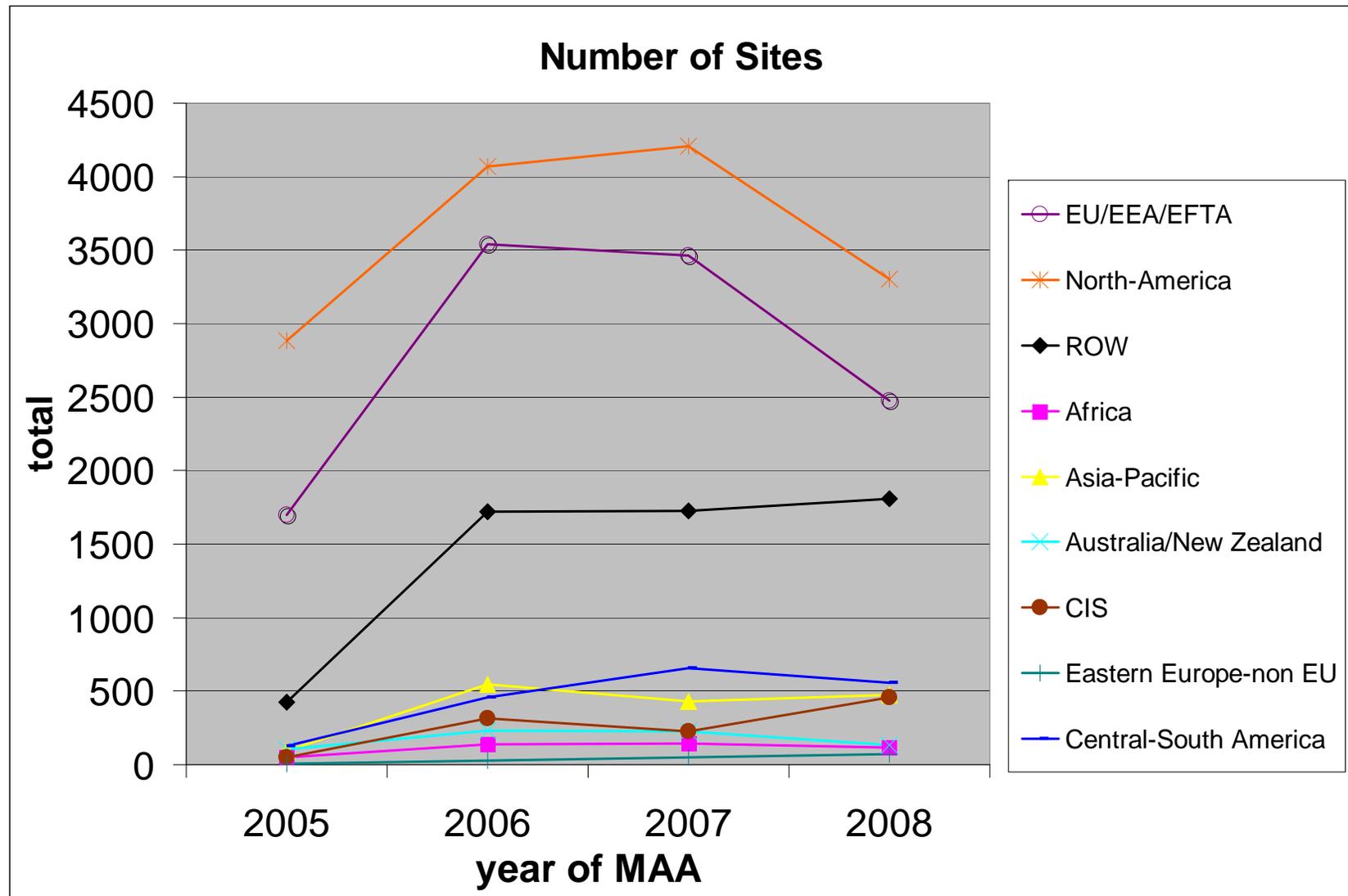
Entire observation period:

**EU/EEA/EFTA: 40%**  
**North America: 36%**  
**Rest of World: 24%**



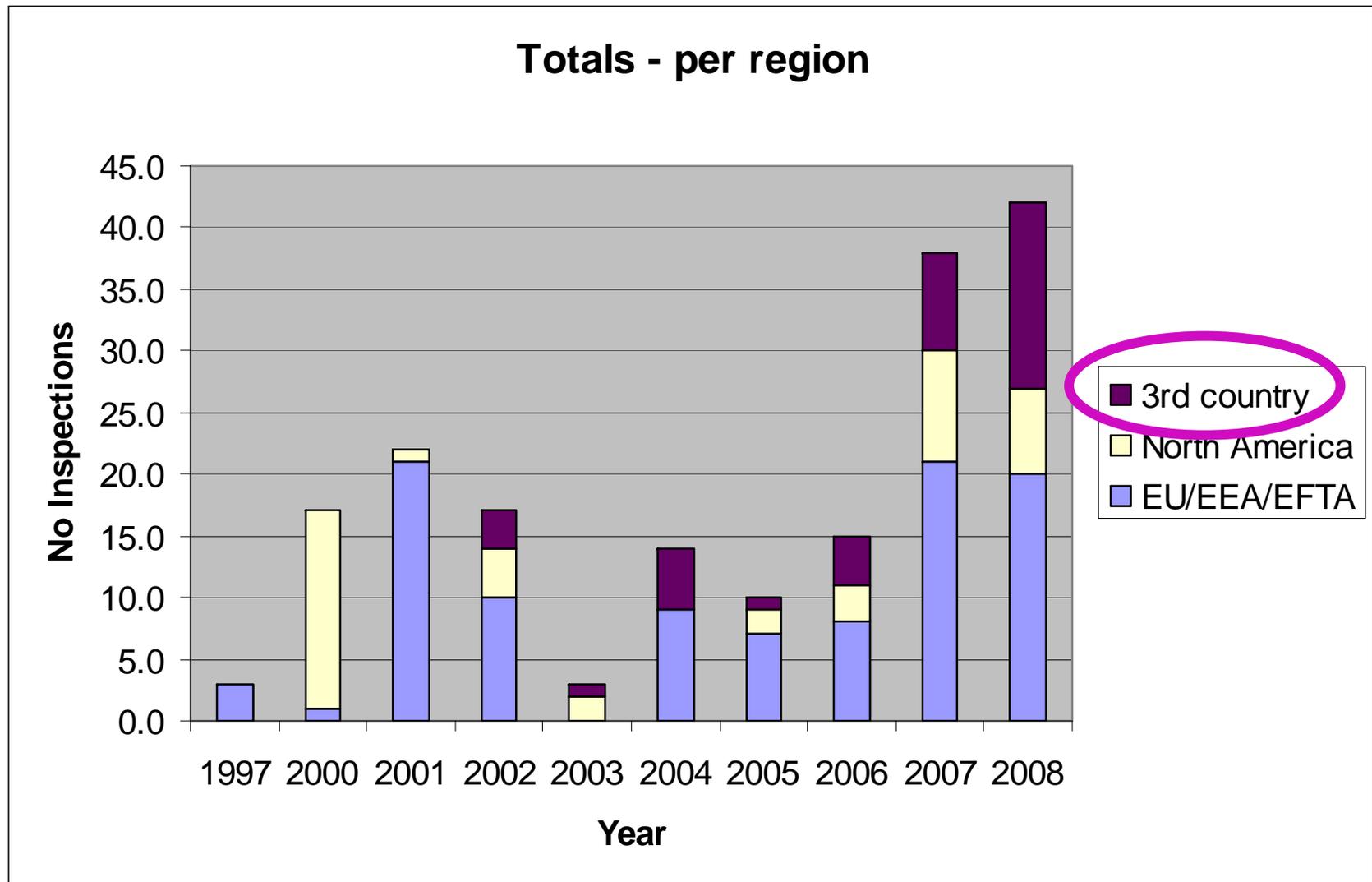


# Pivotal Clinical Trials in MA applications





# CHMP requested GCP inspections:





## CHMP requested GCP inspections

<b>Eastern-Europe-non EU:</b>	2	<b>Asia-Pacific:</b>	16
Croatia	1	China	4
Serbia	1	India	7
<b>CIS:</b>	9	Malaysia	1
Russia	6	Philippines	2
Ukraine	3	Thailand	1
		Turkey	1
<b>North America:</b>	44	<b>Africa</b>	4
Canada	7	Ghana	1
USA	37	Morocco	1
		S. Africa	2
<b>Central-South America</b>	6		
Argentina	1	Colombia	1
Brazil	1	Mexico	1
Chile	1	Peru	1



## Next steps

- consider the issues driving the recruitment of subjects in third countries
- review the actions available in response to non-compliance, and establish a policy
- include their presentation in EPARs (transparency)
- increase GCP inspections
- contribute to capacity building with developing countries in cooperation with Member States and European Commission





## **Backup slides**



## EU Regulatory Network

- EMEA
  - Centralised procedure
  - CHMP and WPs, COMP, PDCCO, SAWP..
  - Clinical trial database, EudraVigilance database (clinical trial and post-marketing)
- NCAs
  - DCP/MRP
  - Authorisation of Clinical Trials



## Clinical Trial database/registry and public information

- EudraCT – database of clinical trials
  - All trials with at least one site in the EEA
    - and
  - All trials included in a Paediatric Implementation Plan, including those conducted exclusively in third countries
- Paediatric trials publication information/results
  - Guideline in process of finalisation by Commission
  - Publication of paediatric trial information from EudraCT to start mid 2009, results in 2009
- Trials in other non-paediatric populations
  - Guideline published by Commission July 2008
  - Publication of information planned for mid 2009



## **Directive 2005/28/EC “GCP Directive”**

- **GOOD CLINICAL PRACTICE FOR THE DESIGN, CONDUCT, RECORDING AND REPORTING OF CLINICAL TRIALS**
  - *GOOD CLINICAL PRACTICE*
  - *THE ETHICS COMMITTEE*
  - *THE SPONSORS*
  - *INVESTIGATOR’S BROCHURE*
- **MANUFACTURING OR IMPORT AUTHORISATION**
- **THE TRIAL MASTER FILE AND ARCHIVING**  
(+guidance to be published by Commission)
- **INSPECTORS and INSPECTION PROCEDURES**  
(+guidance to be published by Commission)



- Annex I to Directive 2003/63/EC
  - applicants shall take into account the scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use
  - **clinical trials**, conducted outside the European Community, which relate to medicinal products intended to be used in the European Community, shall be **designed, implemented and reported** on what **good clinical practice and ethical principles** are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki.



- Ethical requirements apply
  - To all medicinal products authorised in the EU
  - For clinical trials conducted outside the Community verification at the time of the evaluation for authorisation, that these trials were conducted
    - In accordance with good clinical practice and
    - Ethical requirements equivalent to the EU legislation
    - Statement in the dossier



## Role of EMEA/CHMP

- Application time
  - Verification for need for GCP inspection (e.g. vulnerable populations children, psychiatric indications)
  - List of trials conducted in third countries
  - Routine inspection proposals
- Evaluation time
  - Possible GCP inspection upon CHMP request
  - Special attention to data quality and ethics issues
  - Specific report in the assessment report and in the public assessment report (EPAR)



## Strategy paper

- EMEA strategy paper:
  - “Acceptance of clinical trials conducted in third countries, for evaluation in Marketing Authorisation Applications.”
- Developed by EMEA to implement Work Programme
- Strategy paper to be translated into a detailed work plan for 2008-2010



## Detailed Work Plan

- Three year plan of activities:
  - to improve the process of clinical development not only at the time of Marketing Authorisation Application (by which time the pre-authorisation clinical trials have mostly been completed) but at earlier stages before and during the conduct of the clinical trials.
  - starting with the early activities such as Scientific Advice, Orphan Designation and Paediatric Investigation Plan and continuing through the finalisation of opinions on initial MAAs and clinical trials conducted post-authorisation.



## Next steps

- Preparation of work plan for 2009-2011
- Development of the individual specific activities
- Communication/consultation within network and in public domain
- Implementation



## EU/EMA establishing exchanges

- Confidentiality arrangements
  - EU/USA, EU/Canada, EU/Japan
  - Bilateral discussions between European Commission and China, India, Russia
  - Clinical trial information contact – e.g. India...
- Agreeing standards and requirements
- Helping each other, building expertise and systems
- EU/WHO
- Reducing duplication of effort
- Filling the gaps in the global network



## Action areas

- Action areas to be addressed within the scope of EMEA's responsibilities, and in the context of other initiatives being undertaken by the European Regulatory Network and the European Commission, include:
- Planning and development:
  - Clarify the practical application of ethical standards for clinical trials
  - Consider the issues driving the recruitment of subjects in third countries
  - Review the actions available in response to non-compliance, and establish a policy
  - Ensure links, with other initiatives taken by the EU/Member States in this area, in consultation with the European Commission DG Enterprise and the Heads of Medicines Agencies.
- Practical application
  - Training and awareness of EMEA, experts and Marketing Authorisation Holders/sponsors
  - Submission, validation, assessment and inspection
  - Transparency, including improvement of EPAR content and consistency.
  - Contribution to capacity building with developing countries in cooperation with Member States and European Commission initiatives



## **Directive 2001/83/EC as amended and Directive 2003/63/EC (II)**

“shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki.”