# Track III: International Clinical Trials: Global Compliance Norms and EU Focus

EU Focus

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# Rationale

- Clinical trials in EU important part of health care industry and government concern
- Harmonised legislative and regulatory frameworks paramount for patient safety and economic aspects
- Industry impact on EU Commission and Council legislation

# Agenda

- Directive 2001/20/EC: achievements and needs for improvement
- First-in-man clinical trials
- Risk Management Plan
- New developments at EMEA
- Transatlantic administrative Simplification

# Directive 2001/20/EC

Direction to Member States on implementation of GCP

## Difficulties

- Different interpretation by Member States leading to “inefficiencies” for applicants and competent authorities

## Solutions

- Harmonisation of national implementation texts
- Revision of Directive 2001/20/EC
- Inclusion of clearer framework for CPMP/ICH/135/95 GCP guideline in the directives and their implementation texts
- Identical CT legislation for products eligible for Centralised MAA (ideally as regulation rather than directive)
- Highly harmonised CT legislation for national products
- Stronger role of CT Facilitation Group in harmonisation

# Directive 2001/20/EC

**Contents**

- EU legal framework for GCP compliance
- Increased protection of patients through ethical approval procedures
- Promotion and facilitation of high-quality research

**Achievements**

- Implementation in Member States
- Awareness of GCP compliance

# Directive 2001/20/EC Harmonisation

**Needs for improvement**

- Definitions and interpretations of terms
- Tools and practices
- Defined responsibilities
- Streamlined safety reporting

**External Input**

- Dialogue between policy makers, stakeholders and interest groups, eg EuropaBio, industry

# Needs for Improvement

**Harmonisation of Definitions And Interpretations**

- Investigational Medicinal Product, non-IMP
- Substantial and non-substantial amendment
- Legal representative
- Commercial and non-commercial trial
- Content of QP declaration and batch release certificates
- Safety terminology (eg, expectedness, relatedness, significant event)

# Needs for Improvement

**Tools and Practices**

- Legal enforcement of review timelines
- Templates for legal contracts between sponsor/CRO and investigator/site
- Insurance requirements and coverage by public health system
- Single legislative framework for all clinical research as regulation rather than directive
- Differentiated application of legislation depending on product class or research category
- Identical application form and dossier content (incl label requirements)

# Needs for Improvement

**Roles and Responsibilities**

- Ethics committee, Regulatory authority
  - Proposed accreditation and QA system for ECs to ensure compliance with GCP
- Sponsor, Legal representative
- Quality QP and Inspecting authorities to ensure compliance with GMP
- Provide legal status for Clinical Trial Facilitation Group
- Patient groups

# Safety Reporting (1/2)

- Reporting timelines, e-reporting, EV database
- Differing implementation at national level
- Complex safety-data collection, reporting and review, esp for non-commercial sponsors
- Multiple report submission resulting in varied and uncoordinated measures
- Different reporting safety reporting and pharmaco-vigilance
- Complex EudraVigilance training

# Safety Reporting (2/2)

**Solutions**

- direct registration by CROs
- IMP-related (not trial related) Annual Safety Reports
- Mandatory e-reporting of SUSARs
- EudraVigilance not only for SUSARs but also SSARs
- Standard reporting forms
- Safety definitions harmonised across Member States

# Risk Management Plan

- To improve EU pharmacovigilance system
- Risk management = detection, assessment, minimisation, communication of product risks
- Risk Management Plan = outline of RM strategies
- 2008-2009 work programme
  - Agreed by Heads of Medicines Agencies (HMA) & EMEA
  - ERMS Facilitation Group

# Risk Management Plan

- Requested by EMEA for products in clinical development
- Obligatory for some marketed products: new active substance, generics with potential safety concerns
- Pharmacovigilance throughout product life-cycle:
  - Clinical development: Annual safety reports, SUSAR reporting
  - Marketing: PSUR, expedited reporting

# Guideline on First-in-Man trials (1/2)

*Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products*

**Trigger**

- Tegenero incidence in March 2006
- Insufficient regulatory guidance at the time
- Lack of defined non-clinical models to predict clinical effects

**Scope**

- guidance on transition from non-clinical to early clinical testing
- To identify risk factors and apply risk mitigation strategies accordingly
- Applicable to all new chemical and biological products, except gene and cell therapy

**Content**

- Demonstration of relevance of animal toxicology models for humans
- Full characterisation of primary and secondary PD in vitro and in vivo

# Guideline on First-in-Man trials (2/2)

- Safety Pharmacology
  - Standard battery (ICH S7A, S7B, S6, M3)
  - before first administration in humans
- Standard PK and toxicokinetics
  - Standard battery (ICH S3, S6, M3)
  - in all species used for safety studies
- Calculation of first dose in man
  - NOAEL (No Observable Adverse Effect Level)
  - MABEL (Minimal Anticipated Biologic Effect Level)

# Innovative Task Force

- Multidisciplinary group including scientific, regulatory and legal competences
- Forum for early dialogue with applicants (esp SME) through informal exchange of information
- Focus on emerging therapies and technologies, and borderline products for which there is no established EMEA scientific, legal and regulatory experience.
- Complements and reinforces existing formal regulatory procedures (eg, orphan drug designation, CHMP scientific advice)
- Guidance in early development process
- Liaison with EMEA scientific committees, working parties and expert groups

# Innovative Task Force

Product scope:

**Emerging therapies**:

- gene therapy
- cell therapy
- nano-medicines

**Emerging technologies**:

- genomics or proteomics surrogates
- new manufacturing approaches

**Borderline therapeutics**:

- combination of pharmaceuticals and devices
- medicinal nutrition supplements

# Transatlantic Administrative Simplification

- Focus on administrative rather than scientific simplification, no change of legislation
- Workshop in Nov 2007
  - EU Commission and FDA ,with EMEA and national agencies
- Part of ‘Framework for Advancing Transatlantic Economic Integration between EU and the USA’
- Benefits: to free up industry resources for R&D, sharing of regulatory expertise and practices
- Topics:
  - Harmonisation of Marketing Authorisation Dossiers
  - e-CTD
  - CTD Clinical Summaries
  - Common Understanding of Terminology and Regulatory Concepts
  - Facilitation of pedatric treatment development

# Transparency

- Legal reinforcement of registration and publication of information on ongoing trials and of data of completed trials
  - Comprehensive EU clinical trial register (eg, EudraCT)
- Legal basis for inspections of clinical trials
  - Incl publication of findings and reports
- Legal basis for publication of data in EudraVigilance
- Continued information of trial subjects
- Guidelines on Informed Consent and data protection

# Conclusions

- Directive 2001/20/EC milestone in EU clinical trials management
- Numerous improvements outstanding to foster harmonisation across Member States
- Close collaboration between EU Commission, Council, EMEA to release new or improve current guidelines
- Currently, implementation at assessment stays at Member State level – Do we need new EU Regulations?
- Continued focus on patient safety and advancement of drug development and Medicine, eg.ATmP
- Administrative and economic aspects to be considered, EU competitiveness