Clinical Trials, Quality and Inspection

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EMEA

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- What does EMEA expect from Clinical Trials in Marketing Authorisations?
- How does EMEA assure their Quality?
- GCP and the role of GCP inspections
- Ensuring quality across the EU network – the role of the EMEA GCP Inspectors Working Group
- Clinical trials performed outside the EU – the challenges for EMEA
- Numbers and statistics
- EMEA’s Strategy and action plan
Legislative provisions

- "Clinical Trials Directive" (2001/20/EC)
  - Protection of public health and rights and integrity of research participants
  - Legal basis for GCP and GMP in clinical trials
  - Facilitation of research by harmonising requirements
  - Applies to Phases I-IV of clinical research
  - Applies to both industry sponsored and academic clinical research
  - Applies to all (investigational) medicinal products

- "GCP Directive" (2005/28/EC)
  - 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
  - INSPECTION PROCEDURES

- "Pharmaceutical Code" (2001/83/EC)
  - Dossier requirements to be submitted for marketing authorisation applications

GCP

- Protects patients/subjects
  - who will participate in clinical trials
  - who are participating in clinical trials
  - who will be treated with marketed medicinal products
• Ethical requirements apply
  » To all medicinal products authorised in the EU
  » For clinical trials conducted outside the EU, 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

• 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.
Marketing Authorisation Application
Common Technical Dossier

1.0 Regional Administrative Information
1.1 ToC of Module 1 or overall ToC, including Module 1

Module 1
1.0
2.1
2.2

Module 2

Module 3

Module 4
Nonclinical Study Reports

Module 5
Clinical Study Reports

2.1 ToC of the CTD (Mod 2,3,4,5)
2.2 Introduction
2.3 Quality Overall Summary
2.4 Nonclinical Overview
2.5 Clinical Overview
2.6 Nonclinical Written and Tabulated Summaries
2.7 Clinical Summary

Clinical Study Reports (CSRs)
CRF.CRFRF.CRFRF.CRFRF.CRFRF.CRFRF

Patients records, consent forms

Review of MAA by agencies

Review by national authority

Post-marketing Maintenance
Pharmacovigilance
Clinical Trials
Variations
Inspection
Inspection in study
Inspection post study

SmPC
Clinical Overview
Application Module 5 - Clinical section
Clinical Study Reports (CSRs)
CSR - CSR - CSR - CSR - CSR

CrF.CRF.CRF.CRF.CRF.CRF.CRF

Patients records, consent forms

source data

IEC review

Inspection

April 09
Review of clinical trial quality during the centralised procedure

- **At time of Application**
  - Verification for need for GCP inspection (e.g., vulnerable populations children, psychiatric indications)
  - List of trials conducted outside the EU
  - Routine inspection proposals

- **During Evaluation**
  - 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)

Acceptance of non EU clinical trials in MA applications to EU regulatory system

**Considerations:**
- Ethical issues
- Data quality issues
- Applicability to EU population
- Applicability to EU medical practice

- Pivotal data?
- Supporting data?
- Need for bridging studies?
- Acceptability?
ICH E5 “Ethnic factors” in a EU context

- Look at clinical data package
- Does it cover EU population?
- Can it be extrapolated to cover EU population?
- Is a bridging study necessary?
- Important factors to be considered:
  - Non linear Pharmacokinetics, narrow therapeutic range, low bioavailability…
- Consider intrinsic (genetic, gender, race, age… and extrinsic (medical practice, culture..) factors

EU requirements for Clinical trials performed in non-EU countries

- Requirements Apply
  - To all clinical trials that are included in a MAA submitted to EMEA or an EU authority
    - Regardless of the route (Centralised, Mutual Recognition, Decentralised
    - Regardless of the country
  - However there is no specific legal framework for review of a clinical trial dossier by a EU authority before the conduct of the trial in a non EU country
GCP Inspection and the centralised procedure

EMEA GCP Inspection approach laid down by “GCP Inspection Policy”

- Agreed by the CHMP, HMA and GCP IWG
- Objective: Best Use of resources
- Classifies types of GCP inspections
  - Routine
  - Triggered
Routine inspection

» Surveillance of the quality of studies submitted
» Not all applications give rise to a GCP inspection
» Sampling of applications and clinical trials:
  – Size of sponsor company: Large/Medium/Small company
  – Type of product: gene therapy, cell therapy, orphan product etc.
  – Geographic origin of data/clinical trial
  – Therapeutic area
  – Patient population (paediatric, adult, geriatric)
  – Scope of clinical package – single/small trial, standard package, retrospective data collection/bibliography

Triggered inspection

» Problems identified by Rapporteur/Co-Rapporteur assessors
» Targeted, (potential) cause for concern
  – issues identified by assessors
  – major impact factor - e.g. a vaccine to which an entire infant population might be exposed
  – critical dependence on a single, or small group of studies
  – implausible results
    • biologically unlikely
    • conflicting results between studies
  – analytical or data management problems
  – other information about the sites or study e.g. previous negative inspection outcome
Overview of Centralised Evaluation Procedure

Routine Inspection  Triggered Inspection  LoOl clock stop D 180

Pre-submission  Primary Evaluation  Stop Clock  Secondary Evaluation  Opinion  Post Authorisation

D.0  D.120  D.121  D.210  D.330

Inspections by Inspection Type (1997-2008)

Inspection by Inspection type

 Routine  Triggered


2008  37  23  12  3  14  5  10  3  1  1  1
2007  13  8  4  1  1  1  1  1  1  1  1
2006  12  8  4  1  1  1  1  1  1  1  1
2005  3  1  1  1  1  1  1  1  1  1  1
2004  14  8  4  1  1  1  1  1  1  1  1
2003  5  1  1  1  1  1  1  1  1  1  1
2002  10  8  4  1  1  1  1  1  1  1  1
2001  3  1  1  1  1  1  1  1  1  1  1
2000  1  1  1  1  1  1  1  1  1  1  1
1999  1  1  1  1  1  1  1  1  1  1  1
1998  1  1  1  1  1  1  1  1  1  1  1
1997  1  1  1  1  1  1  1  1  1  1  1
Inspections by Type of site (1997-2008)

- **Inspection by type of site**
  - Other
  - Laboratory
  - CRO
  - Clinical investigator
  - Sponsor

**Inspection by type of site (1997-2008)**

- **EMEA inspection programme**
  - MAA driven (centralised procedure) wherever site is located
  - Routine inspection
  - Triggered inspection

- **National inspection programmes**
  - Within each Member State
    - Ongoing clinical trials
      - Sponsor and CRO systems
      - Investigator sites, Academic institutions
  - Routine inspection and Triggered inspection
  - MAA driven (DCP, MRP, National), wherever site is located

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**EU GCP Inspections**

- **c. 1200 in EudraCT 2004-2009**

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Potential Consequences of inspection

- Positive outcome / pointers for future improvement

- Negative outcome –
  » Consequences for ongoing clinical trials or for the application or marketing authorisation
    – Refusal or suspension of all or part of an application
  » Consequences for individual sponsors, investigators, CROs or other involved parties/facilities
    – Curtailment of participation in clinical trials, civil or criminal prosecution – competent authorities enforcement responsibilities

Assuring consistency across EU GCP Inspectors Working Group

GCP inspectors:
  » EU Member States
  » EEA
  » Turkey, Croatia and FYRoM - observers
  » Switzerland - observer

- Mandate
  Coordination and harmonisation of GCP advice
  Links with scientific committees and working parties
  Pharmacovigilance, clinical assessors, GMP inspectors
  Training of inspectors and assessors
GCP IWG

- Harmonisation through practice
- Shared experience, discussion, conclusion
- Policy development
- Network of contacts between inspectors
- Joint multistate inspections on most
  Centralised inspections and a number of
  national/MR/DCP inspections

April 09

Number of Patients included in clinical trials submitted in MAA to EMEA (2005-2008)

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of Patients</th>
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<tbody>
<tr>
<td>EU/EEA/EFTA</td>
<td>179,741</td>
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<tr>
<td>Initial EU/EEA countries</td>
<td>128,991</td>
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<tr>
<td>accession countries (2004)</td>
<td>42,735</td>
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<tr>
<td>accession countries (2007)</td>
<td>6,500</td>
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<tr>
<td>Switzerland</td>
<td>15,150</td>
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<td>North-America</td>
<td>1,674,81</td>
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<tr>
<td>USA</td>
<td>1,494,00</td>
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<tr>
<td>Canada</td>
<td>180,81</td>
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<tr>
<td>ROW</td>
<td>125,798</td>
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<tr>
<td>Central-South America</td>
<td>46,588</td>
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<tr>
<td>Middle East-Asia-Pacific</td>
<td>36,878</td>
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<tr>
<td>CIS</td>
<td>17,011</td>
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<tr>
<td>Africa</td>
<td>14,484</td>
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<tr>
<td>Australia/New Zealand</td>
<td>7,334</td>
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<tr>
<td>Eastern Europe-non EU</td>
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### Number of clinical trial sites in pivotal trials in MAA to EMEA (2005-2008)

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of clinical trial sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU/EEA/EFTA</td>
<td>12355</td>
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<tr>
<td>Initial EU/EEA countries</td>
<td>5514</td>
</tr>
<tr>
<td>Accession countries (2004)</td>
<td>2235</td>
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<tr>
<td>Accession countries (2007)</td>
<td>1465</td>
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<tr>
<td>Switzerland</td>
<td>141</td>
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<tr>
<td>North-America</td>
<td>15542</td>
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<tr>
<td>USA</td>
<td>14109</td>
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<tr>
<td>Canada</td>
<td>6345</td>
</tr>
<tr>
<td>ROW</td>
<td>2001</td>
</tr>
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<td>Central-South America</td>
<td>2001</td>
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<td>Middle East-Asia-Pacific</td>
<td>1769</td>
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<td>CIS</td>
<td>1116</td>
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<tr>
<td>Australia/New Zealand</td>
<td>742</td>
</tr>
<tr>
<td>Africa</td>
<td>556</td>
</tr>
<tr>
<td>Eastern Europe-non EU</td>
<td>161</td>
</tr>
</tbody>
</table>

### Third countries with at least 0.5% of patients in the pivotal trials included in the MAA submitted to EMEA (2005-2008)

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>13255</td>
</tr>
<tr>
<td>Argentina</td>
<td>10725</td>
</tr>
<tr>
<td>China</td>
<td>858</td>
</tr>
<tr>
<td>India</td>
<td>6139</td>
</tr>
<tr>
<td>Israel</td>
<td>6227</td>
</tr>
<tr>
<td>South Africa</td>
<td>13828</td>
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<tr>
<td>Thailand</td>
<td>3356</td>
</tr>
<tr>
<td>Ukraine</td>
<td>13255</td>
</tr>
<tr>
<td>Croatia</td>
<td>2542</td>
</tr>
<tr>
<td>Taiwan</td>
<td>2619</td>
</tr>
<tr>
<td>Korea</td>
<td>2297</td>
</tr>
<tr>
<td>Peru</td>
<td>3333</td>
</tr>
</tbody>
</table>
Challenges facing EU regulators

- 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
- Facilitation of cooperation of Regulatory Authorities through global regulatory network
EU/EMEA international activities- GCP area

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

Specific challenges relating to non EU trials

- Increasing recruitment outside EU
  - Greater patient populations, prevalence of disease, lower cost
- Ensuring these trials can be used in EU
- Dealing with GCP non-compliance
- Addressing ethical concerns
- Ensuring Transparency of processes
Clinical studies outside of EU – EMEA
Strategy and Action plan

- 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

Conclusion

- Quality and ethical oversight of clinical trials performed in EU are assured through provisions of Clinical Trial Directive
- Assessment and inspection procedures verify this as part of the authorisation
- Greater attention to trials performed outside the EU will improve quality of trials and protect patients both inside and outside the EU
Thank you

Abbreviations

- GCP Good Clinical Practice
- SmPC Summary of Product Characteristics
- ToC Table of Contents
- CTD Common Technical Document
- CSR Clinical Study Report
- CRF Case Report Form
- LoOI List of Outstanding Issues
- IEC Independent Ethics Committee
- CHMP Committee for Human Medicinal Products
- HMA Heads of Medicines Agency
- IWG Inspectors Working Group
- MAA Marketing Authorisation Application
- EU European Union
- EEA European Economic Area
- EPAR European Public Assessment Report