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The Clinical Trials Directive in the EU: Present and Future

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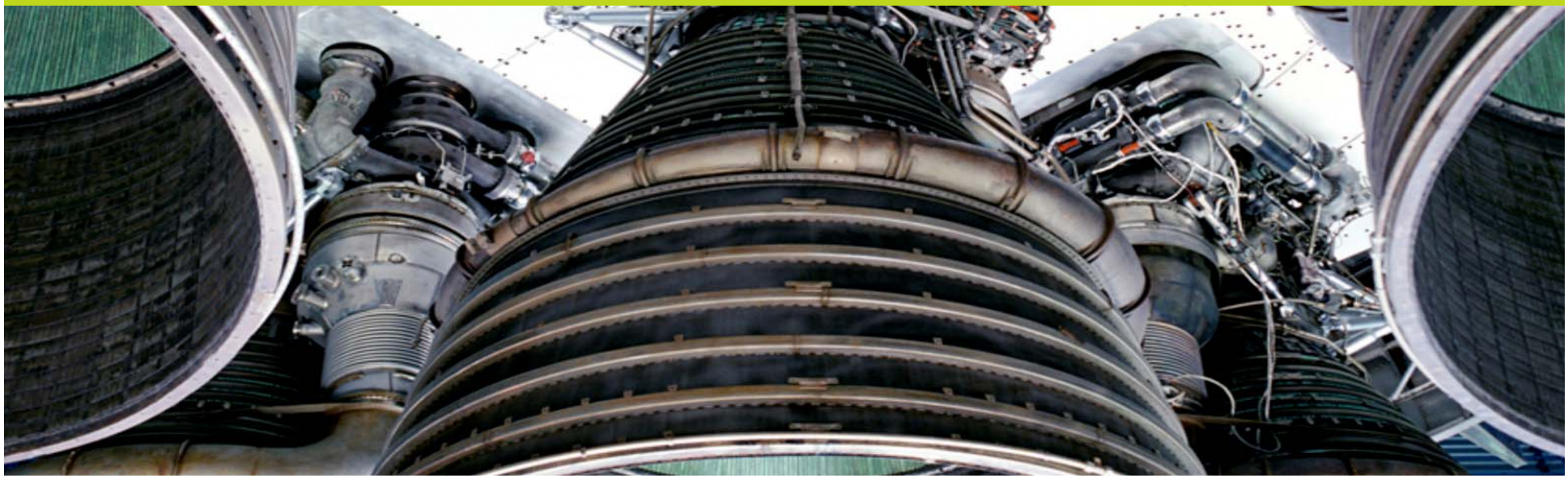


Background (1)

- **The Clinical Trials Directive 2001/20/EC**
- The intention of this Directive is to:
  - Ensure the protection of public health & safety of clinical trials participants;
  - Ensure the ethical soundness of the clinical trials;
  - Ensure the reliability and robustness of data generated in clinical trials; and
  - Simplify and harmonize administrative provisions governing clinical trials.
- In addition, a number of detailed guidelines have been adopted and published by the European Commission ("EudraLex Volume 10")

Background (2)

- Rules on clinical trials in the EU/EEA were traditionally based on differing regulatory approaches.

- 2001: Directive enters into force.
- 2004: May 2004 latest date for Member States to implement Directive.
- 2008: Review of Directive announced by EU Commission.
- 2009: Commission Public Consultation paper published.
- 2010: Most responses (approx 90) published on Commission website.

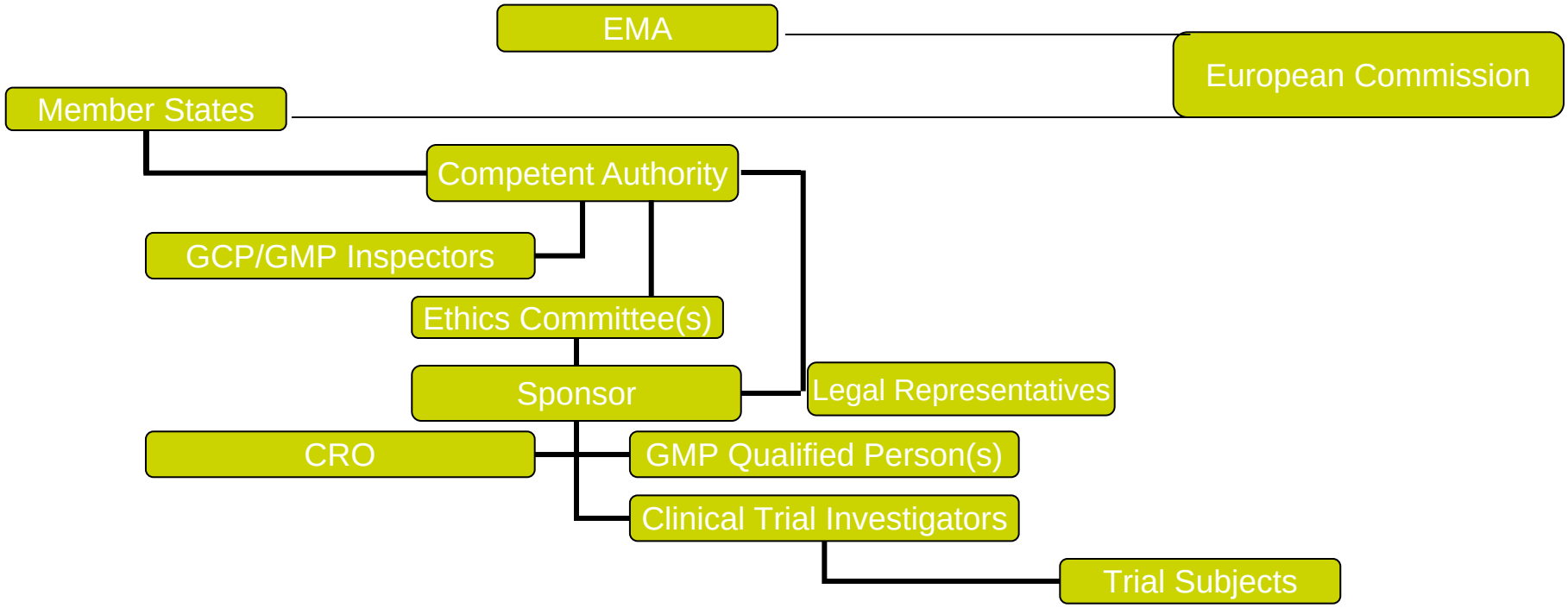
With thanks to Ray Creswell (GlaxoSmithKline)

Background (3)

- 4000-6000 clinical trials (per Eudract number) performed each year in EU/EEA.
- 45,000 clinical trials applications in the Member States since 2004.
- Each year – approx 500,000 clin trial participants planned for inclusion in EU trials.
- 64 % of trials sponsored by pharma industry.
- Risk profiles of trials vary considerably.
- Commission claim Directive has improved protection for trial participants.
- But Directive also thought to have led to decline in attractiveness of research on patients in EU.

With thanks to Ray Creswell (GlaxoSmithKline)

Key Players


EMA
European Commission
Member States
Competent Authority
GCP/GMP Inspectors
Ethics Committee(s)
Sponsor
Legal Representatives
CRO
GMP Qualified Person(s)
Clinical Trial Investigators
Trial Subjects

Legal Representative

- Where sponsor is not established in Europe, it must appoint a Legal Representative in the EEA
  - *EEA consists of 27 EU Member States plus Iceland, Liechtenstein and Norway (not Switzerland)*
- Only one Legal Representative per clinical trial
- Same Sponsor for several different trials = several Legal Representatives possible
- Possible to either use a corporate entity as a legal representative, or an individual, an institution or an organization
- Possible to have one central Legal Representative in EEA for all clinical trials

Legal Representative and Insurance

- **Is the legal representative liable under civil and criminal law?**
- A recent Q&A guidance document states:
  - "responsibility in terms of civil law (i.e. liability, for example compensation for damages occurred to a patient), or criminal law (i.e. punishment, for example criminal sanction of a bodily injury caused by negligence), is not governed by Directive 2001/20/EC. In this respect, the applicable laws of the Member States apply. […] While the existence of a legal representative within the EU/EEA might be supportive to ensure effective sanctioning under national civil or criminal law, the rules for civil and criminal liability remain governed by the national laws of the Member States."
- In practice, this means that Sponsor must have insurance to cover its civil & criminal liability; Legal Representative may also be required to have its own 'supportive' insurance, increasing again the costs of EU/EEA clinical trials

No Centralised Authorisation

- **To commence a clinical trial:**
  - Need positive opinion from Ethics Committee, and
  - No disapproval from the Competent Authority (CA)

- **Submission to CA**
  - Sponsor can amend request once to address deficiencies
  - CA review may not exceed 60 days
    - 30 day extension for gene, somatic cell, GMO
    - Member States can shorten review timeframe
  - Can be simultaneous with Ethics Committee submission

- European Medicines Agency (EMA) is **not involved** in the approval of clinical trials in the EU/EEA

No Centralised Authorisation

- However, EMA may give scientific advice to companies:
  - on the design of trials to assess safety and efficacy in a new indication expected to bring significant clinical benefit compared to existing therapies
  - on the design of trials to assess safety and efficacy in a new indication for a well established substance
- Ask!

EudraCT Registration

- Database of EU clinical trials (EudraCT).
- EudraCT provides a common guidance for CTs conducted in EU.
- Sponsor must register trial and obtain registration number.
- Some elements confidential and accessible only to CAs, EMA, European Commission e.g., extracts of clinical trial information, amendments, inspections.
- Information on paediatric trials made public, including results.

EMA-FDA GCP initiative

- Joint initiative to collaborate on international GCP inspection activities.
- Initiative considered to be an important contribution to ensuring the protection of clinical-trial subjects in the context of the increasing globalization of clinical research.
- 18-month pilot phase commenced 1 September 2009.

EMA-FDA GCP initiative

- Key objectives:
  - To conduct periodic information exchanges on GCP-related information in order to streamline sharing of GCP inspection planning information, and to communicate effectively and in a timely manner on inspection outcomes.
  - To conduct collaborative GCP inspections by sharing information, experience and inspection procedures, cooperating in the conduct of inspections and sharing best-practice knowledge.
  - To share information on interpretation of GCP, by keeping each regulatory agency informed of GCP-related legislation, regulatory guidance and related documents, and to identify and act together to benefit clinical research.

Towards Modernization of Clinical Trials Directive

Towards Modernization of the Clinical Trials Directive

- Five years have elapsed since the implementation into national law of EU Member States of the CT Directive
- Now considered to be an appropriate time to consider ways to improve on current EU legislation
- 9 October 2009, the European Commission launched a public consultation on the assessment of the functioning of the CT Directive
- Consultation document identifies a number of shortcomings that have become apparent since the implementation of the CT Directive, and puts forward various options to address these

Key Issue One: Multiple and Divergent Assessments of Clinical Trials

- Issue
  - EU requirements are applied very differently by the CAs of individual EU Member States. This leads occasionally to divergent decisions.
- Consequences:
  - Longer delays and higher costs for clinical trials and thus for clinical research (without added value).
  - May reveal that specific expertise is not always readily available in all EU Member States – this goes to the detriment of safety of the clinical trials participants.

Key Issue One: Multiple and Divergent Assessments of Clinical Trials

- Proposed options to address the issue as regards the assessment by the CA:
  - reliance on voluntary cooperation of the CA.
  - EU-wide streamlining of CA authorization process for clinical trials
    - A “mutual recognition procedure”
    - A “centrally authorized procedure”

Key Issue One: Multiple and Divergent Assessments of Clinical Trials

- Proposed options to address the issue as regards the assessment by the Ethics Committees
  - One-stop shop for submission of assessment dossier.
  - Strengthening networks of national Ethics Committees involved in multinational clinical trials.
  - Clarifying the respective scope of assessment of national CAs and Ethics Committees.

Key Issue Two: Inconsistent Implementation of the Clinical Trials Directive

- Issue
  - The aim of the CT Directive was to lead to harmonization between Member States as regards approval of clinical trials.
  - Only limited success due to inconsistent application of provisions.
- Consequences:
  - Insufficient patient protection.
  - Divergences of application have created an important increase of administrative costs for sponsor.

Key Issue Two: Inconsistent Implementation of the Clinical Trials Directive

- Proposed options to address the issue
  - Reviewing the CT Directive with a view to clarifying provisions, where necessary.
  - Adopting the text of the CT Directive in the form of a Regulation.

Key Issue Three: Regulatory Framework not Always Adapted to the Practical Requirements

- **Issue**
  - The CT Directive and its implementing guidelines have introduced regulatory obligations and restrictions which, in some cases, are widely considered not to match practical considerations and requirements:
    - Risk for a CT participant varies considerably depending on the actual circumstances of the CT. The CT Directive does not address this sufficiently.
    - The need for a "Single Sponsor" creates major difficulties: in particular where CAs seek to enforce the CT Directive vis-à-vis sponsor located in another EU Member State. Also difficult for academic/non commercial sponsor to take responsibilities for CTs performed in another EU Member State.

Key Issue Three: Regulatory Framework not Always Adapted to the Practical Requirements

- Consequences
  - Increased costs for conducting clinical research in the EU. These costs not necessary due to achievement of objective of the CT Directive.
  - Disincentives to conduct clinical research in the EU.
  - Long-term consequence in that patients are deprived of innovative treatments and the competitiveness of EU clinical research is reduced.

Key Issue Three: Regulatory Framework not Always Adapted to the Practical Requirements

- Proposed options to address the issue
  - Review of existing implementing guidelines (in particular for safety reporting, labeling of IMP, content of CT application).
  - Review of the existing CT Directive and adaptation of requirements to practical necessities.
  - Review of the existing CT Directive and exclusion from its scope of clinical trials by “academic” sponsors.

Key Issue Four: Adaptation to Peculiarities in Trial Participants and Trial Design

- Issue:
  - CT are performed in many different settings, and with different groups of trial participants. Raises question: are various computations adequately addressed?
  - Particularly relevant for:
    - Paediatric CT, there is a risk that clinical research to develop treatments and medicinal products for children is hindered or unnecessarily burdensome
    - Emergency CT (how to obtain informed consent?)
- Proposed option to address the issue
  - Adaptation of CT Directive while continuing to ensure protection of participants

Key Issue Five: Ensuring Compliance with GCP in CT performed in Third Countries

- Issue:
  - 65% of all data/patients submitted in pivotal clinical studies in the framework of an application for an EU-wide marketing authorization are generated in third countries.
  - Some CTs performed in third countries may exploit the particular vulnerability of their population. However, fundamental ethical rules for CTs should be applied everywhere.
- Consequence:
  - Continuing risk that medical research and authorization of medicinal products in the EU are based on clinical research in third countries that does not comply with international standards of safety and ethics (GCP compliance).

Key Issue Five: Ensuring Compliance with GCP in CT performed in Third Countries

- Proposed options to address the issue
  - Supporting regulatory framework and capacity-building where necessary.
  - Self-regulation by EU-based sponsors.
  - Strengthening international cooperation in GCP inspection and mutual recognition of GCP rules.
  - Optional assessment of Third Country clinical trials by the EMA.
  - Strengthening a culture of transparency.
  - Strengthening scrutiny of clinical trials results of which are submitted to the EU, or which are financed in the EU.

Towards Modernization of the Clinical Trials Directive

- Consultation procedure ran until 8 January 2010.
- 106 responses received.
- Approx 90 responses published on 11 February 2010.
- Modified roadmap published on 23 March 2010
- Summary of responses published on 30 March 2010.
- As anticipated by the European Commission, the comments received were largely negative.

Towards Modernization of the Clinical Trials Directive

- Example: Association of the British Pharmaceutical Industry (ABPI) considers that differing requirements remain for submission components and there is a need for EU harmonization of content:
  - "*we also need harmonization of definitions and interpretation*"
  - "*Variations in definitions and interpretations of some issues, such as substantial amendments, non-investigational medicinal products or reporting requirements for suspected and unsuspected serious adverse reactions (SUSARs), cause difficulties for applicants trying to implement a global study protocol*"

Towards Modernization of the Clinical Trials Directive

- CAs from EU Member States (e.g., MHRA, Afssaps) remain opposed to a “decentralised/centralised procedure” for the authorization of clinical trials conducted in different EU Member States"
- Other respondents generally welcome such options and, in particular, the proposition for a central authorization which would lead to a “continuum” in terms of marketing authorizations for centrally authorized products.

Towards Modernization of the Clinical Trials Directive

- Respondents underlined a number of difficulties linked to the inconsistent implementation and application of the Directive in the EU Member States.

- Despite the number of issues that have been highlighted, respondents remain divided as to whether a Regulation is appropriate.

Towards Modernization of the Clinical Trials Directive

- Commission considers four main instruments that could be used to achieve these aims:
  - amending the Directive;
  - replacing it (partly) by a Regulation;
  - revising the EU guidelines and infringement procedures; and
  - relying on voluntary EU Member State co-operation in order to address the problems
- During 2010, European Commission will continue to gather additional data regarding the impact of clinical research on human health, through both in-house expertise and dedicated meetings with experts and other stakeholders.

Towards Modernization of the Clinical Trials Directive

- European Commission considers that the consultation exercise on the review of the CT Directive has yielded some useful information on the shortcomings of the legislation.
- It is now looking at the various policy options for tackling these
- However, it does not envisage adopting any new legislative proposals until October 2011.

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