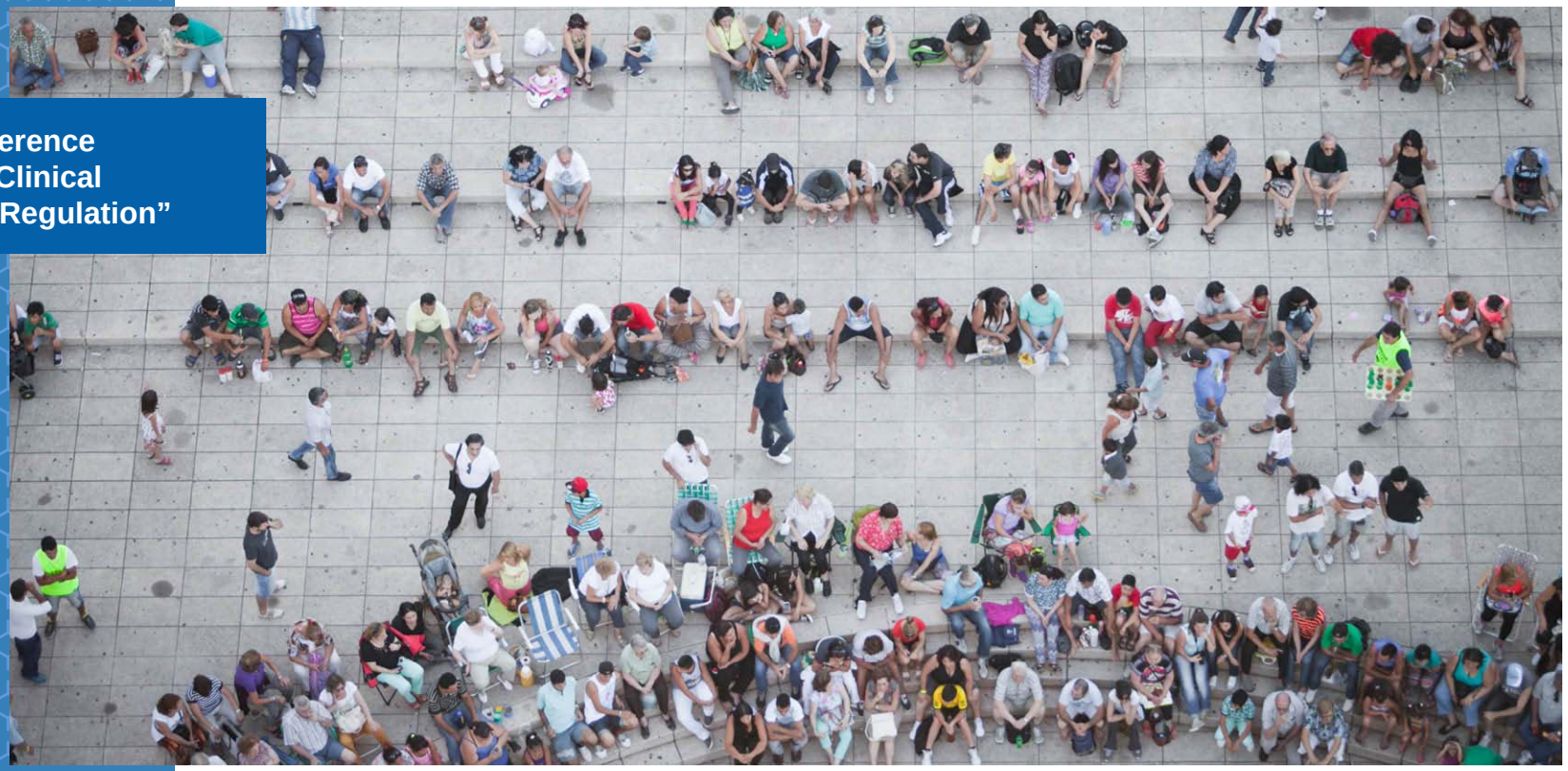
Conference
"EU Clinical
Trial Regulation"



EU Clinical Trial Regulation – A View from Legal and Regulatory

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NOVARTIS

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Agenda

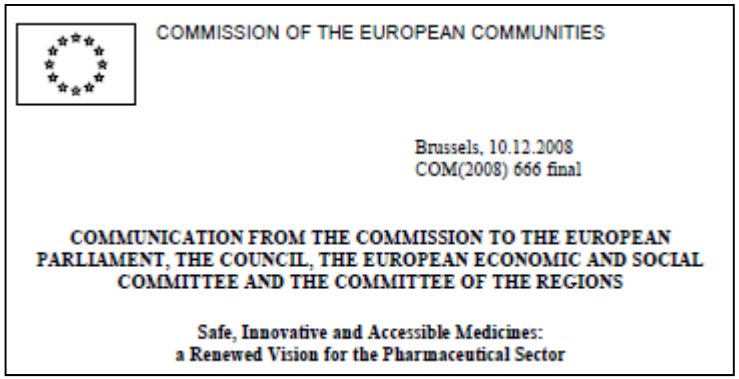
- **Regulation 536/2014 - Reasons & Background**
- **New Terminology**
- **EU Portal and database**
- **Key Provisions**
- **Conclusion**

Introduction

Clinical trials ("CTs")	o **investigations in humans** o **conducted with the intention to discover or verify the effects of one or more investigational medicinal products ("*IMPs*").**
4 April 2001	**Directive 2001/20/EC** on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use **("*Clinical Trials Directive*")**
16 April 2014	**Regulation 536/2014** on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC **("*Clinical Trials Regulation*")**

Background & Legislative Process

10/12/2008: EU Commission announces Assessment of CT Directive



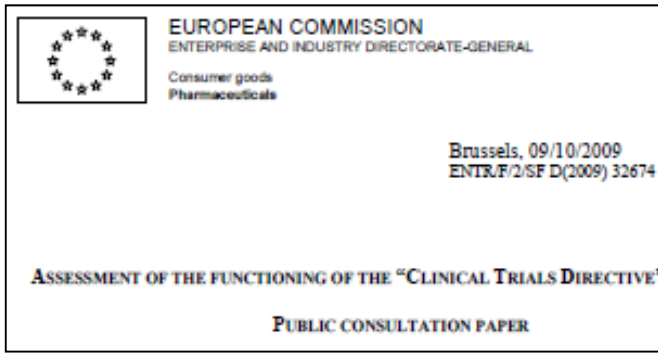
COMMISSION OF THE EUROPEAN COMMUNITIES

Brussels, 10.12.2008
COM(2008) 666 final

COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS

Safe, Innovative and Accessible Medicines:
a Renewed Vision for the Pharmaceutical Sector

09/10/2009: Public Consultation – key issues:



EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Brussels, 09/10/2009
ENTR/F/2/SF D(2009) 32674

ASSESSMENT OF THE FUNCTIONING OF THE "CLINICAL TRIALS DIRECTIVE"

PUBLIC CONSULTATION PAPER

- Multiple and divergent assessments of CTs
  - Increase of administrative costs w/o added value.
  - "Patchwork" of separate assessment procedures by the national competent authorities ("NCAs")
  - Delays for starting clinical trials (FPFV)
  - NCAs do not use resources efficiently.
- Inconsistent Implementation of CT Directive
- Regulatory Framework not always adapted to practical requirements
- Adaptation to Peculiarities in trial participants and trial design

Background & Legislative Process

9 February 2011: Public Consultation on a concept paper on the Revision of the "Clinical Trials Directive" 2001/20/EC - presenting:

- "*Preliminary appraisal*" of which option appeared to be the most suitable one to address some of the key concerns of the CT Directive, and
- Main figures used to evaluate the impacts of the different policy options.

17 July 2012: EU Commission adopted the proposal for a "Clinical Trials Regulation"

16 April 2014: Adoption of the new Regulation No 536/2014

- Entry into force: 16 June 2014
- **Applies** "*no earlier than 28 May 2016*"
- current timeframe: **October 2018** (6m after Commission publishes notice of confirmation of full functionality of EU portal & database through independent audit)

27.5.2014 EN Official Journal of the European Union L 158/1

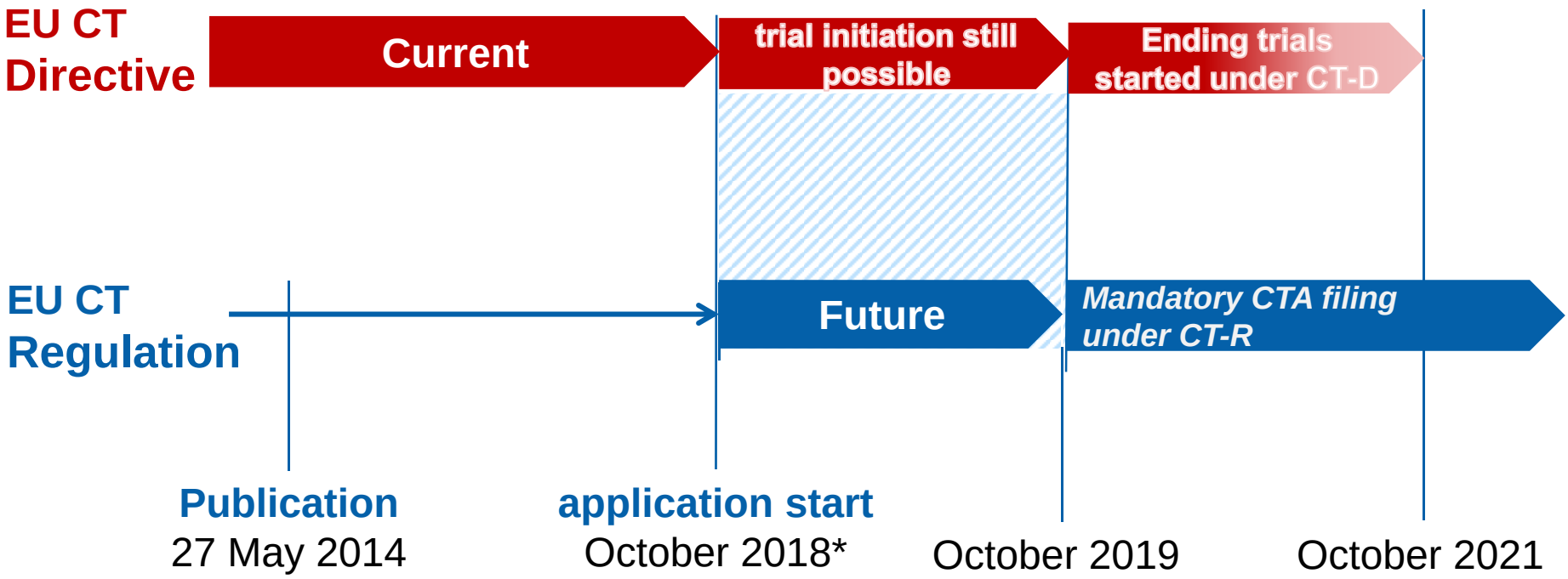
I

(Legislative acts)

REGULATIONS

REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 16 April 2014
on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC
(Text with EEA relevance)

Transitional Phase – Phase-in of the CT Regulation



*6 months after publication of EU Commission notice of confirmation of full functionality of EU portal & EU database through independent audit

CTA: Clinical Trial Application
CT-D: Clinical Trial Directive 2001/20/EC
CT-R: Clinical Trial Regulation 536/2014

Goals of new Clinical Trial Regulation

Environment favourable to conducting clinical trials for all EU Member States ("MSs") with the highest standards of patient **safety**

Increased Transparency of trial information

Simplification of current rules, e.g.:

- **Streamlined application procedure via a single entry point - EU portal and database – for all CTs conducted in Europe.**
- **Single authorisation procedure for all clinical trials**
  - ensuring one single assessment outcome and authorisation per MS
  - allowing a faster and thorough assessment of a CTA by all MSs concerned
- The **extension of the tacit agreement principle** to the whole authorisation process (more legal certainty to sponsors and researchers)

Key Differences of Directive 2001/20/EC and Regulation 536/2014

	Directive 2001/20/EC	Regulation 536/2014
Legal Effect	▪ Binding for the MSs ▪ Transformation into local law needed (11 pages)	▪ Binding & directly applicable in all MSs (74 pages, 35 definitions)
Sources	**Supporting EC guidance on:** ▪ Application dossier ▪ Safety reporting ▪ Labelling	**Annexes to the Regulation:** ▪ Application dossier ▪ Safety reporting ▪ Labelling ▪ Summary/lay summary of results
Scope	Interventional clinical trials	Clinical trials & low-intervention clinical trials (*new terminology!*)
Risk approach	No risk differentiation	Different study concepts (e.g. low-intervention clinical trial)
Sponsorship	Single sponsor	Also possibility of co-sponsor
Review clause	No	Yes – every 5 years

Further activities for Implementation

EU Commission

- Implementing Acts
- Delegated Acts

EMA

- Set up of the EU portal & database
- Guidelines

Member States

- Role of Ethics Committees ("*ECs*") and other bodies
- National implementation measures (e.g. implementing law)

- Regulation 536/2014 - Reasons & Background
- **New Terminology**
- EU Portal and database
- Key Provisions
- Conclusion

New Terminology - Clinical study vs. clinical trial

Clinical Study

***any* investigation in relation to humans *intended* to:**

(a) discover / verify the clinical / pharmacological / other pharmacodynamic **effects** of one of more Medicinal Products ("*MPs*")

(b) identify **any adverse reactions** to one or more MPs, or

(c) study the **absorption, distribution, metabolism and excretion** of MPs;

with the objective of ascertaining the safety and/or efficacy of those medicinal products

Art 2(2.)(1) CT Regulation

New Terminology - Clinical study vs. clinical trial

Clinical Trial

Clinical Study which fulfills the following criteria:

(a) Assignment to the therapeutic strategy is decided in advance & not within normal clinical practice of the Member States concerned ("*cMS*")

(b) decision to prescribe the investigational medicinal product ("*IMP*") & to include subject in the study are taken together

(c) diagnostic or monitoring procedures in addition to normal clinical practice

Low-intervention Clinical Trial

(a) IMPs - excluding placebos - are authorised;
(b) according to the protocol
  (i) IMPS are used in accordance with the terms of the MA; or
  (ii) use of IMPs is evidence-based and supported by published scientific evidence
(c) minimal additional risk by additional diagnostic or monitoring procedures

Non-Interventional study

Consequences of new Terminology

- **Regulation 536/2014 ("CT Regulation") applies to all clinical trials conducted in the EU**
  - **It does NOT apply to non-interventional studies**

    Art 1 CT Regulation
- **A clinical trial may be conducted *only if***
  - the rights, safety, dignity and well-being of subjects are protected and prevail over all other interests, and
  - it is designed to generate reliable and robust data

  Art 3 CT Regulation
- **Authorisation Procedure for a Clinical Trial**
  - Subject to scientific and ethical review by an Ethics Committee
  - Authorisation required in accordance with the CT Regulation

  Art 4 CT Regulation

Consequences of new Terminology

- **Ethical Review for a Clinical Trial**
  - By an EC in accordance with the law of the cMS
  - MSs has to ensure that timelines and procedures for the review by the EC are compatible with the CTA assessment timelines and procedures
    Art 4 CT Regulation
- **Some special rules for low-intervention Clinical Trials**, e.g.
  - Sponsor has to propose a cMS where the use is evidence-based as reporting Member State ("*rMS*")
    Art 5(2) CT Regulation
  - Justification required as to why the clinical trial is a low-intervention clinical trial, in cases where this is claimed by the sponsor
    Art 25(1)(e) CT Regulation
  - Informed consent may be obtained by simplified means
    Art 30(3)(c) CT Regulation

- **Regulation 536/2014 - Reasons & Background**
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EU Portal

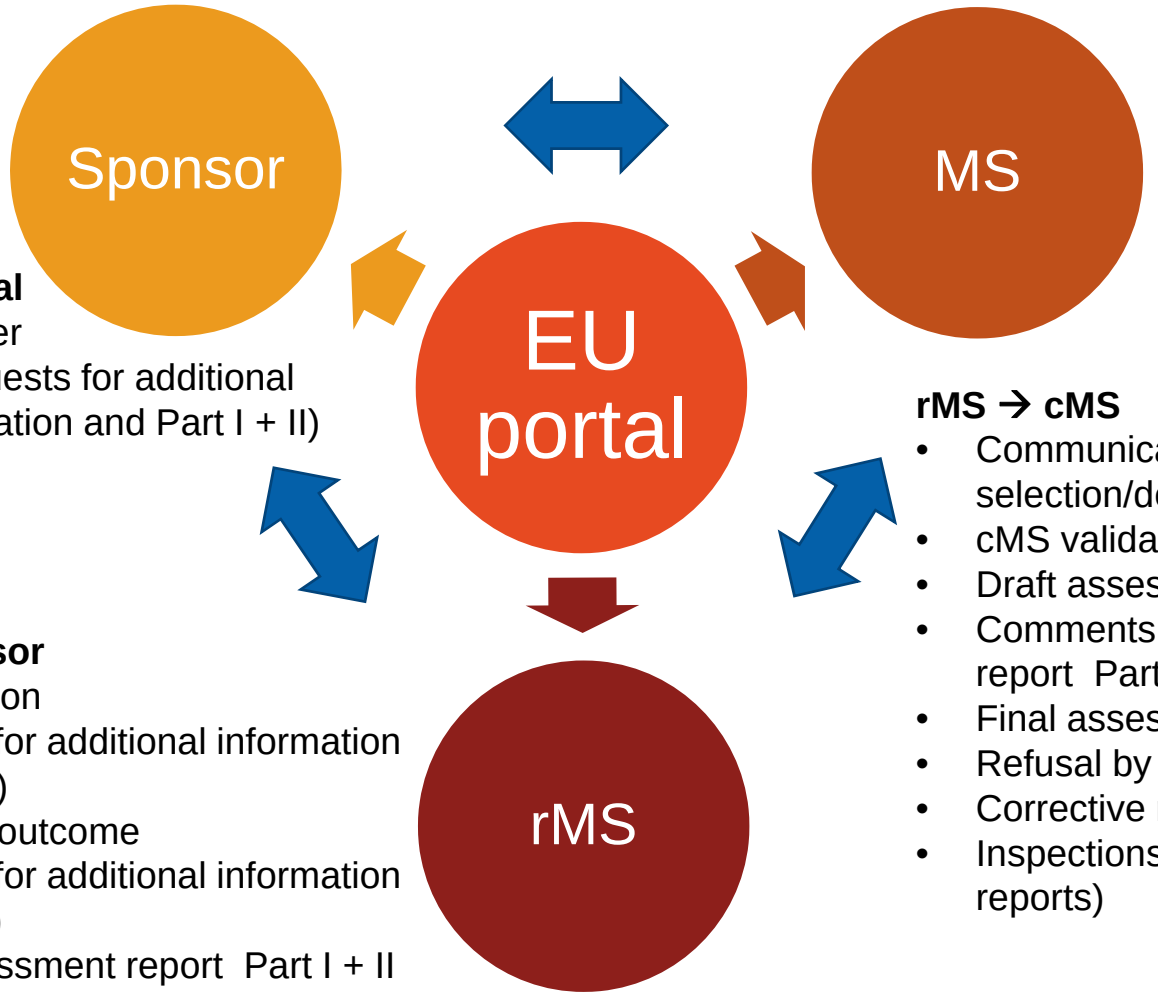
- **EMA to set up & maintain an EU portal & to store the data submitted in a respective EU database**

  Art 80 CT Regulation

- **Goals of EU portal & database**
  - Support of cooperation between cMSs
  - Support of communication between MSs and Sponsors
  - Enable access of EU citizens to CT information
  - Information publicly accessible in easily searchable format

- **Sponsors interact via EU database/portal during CTA authorisation procedure & trial conduct**

The communication channels within the EU Portal



Sponsor → EU portal

- Application dossier
- Response to requests for additional information (validation and Part I + II)
- Withdrawal

rMS → cMS

- Communication during rMS selection/decision process
- cMS validation comments?
- Draft assessment report Part I?
- Comments on draft assessment report Part I?
- Final assessment report Part I
- Refusal by cMS
- Corrective measures
- Inspections (intention, findings, reports)

rMS → Sponsor

- rMS decision
- Requests for additional information (validation)
- Validation outcome
- Requests for additional information (Part I + II)
- Final assessment report Part I + II
- Application outcome

Trial Notifications and Transparency

- **Notification of start, FPFV, end, temporary halt & early termination of a clinical trial through the EU portal**

  Art 36-38 CT Regulation

- **Summary of results and lay friendly summary within 12m of CT end**
  - Content determined by Annexes IV & V
  - Extension of deadline can be justified in the protocol
- **Clinical study reports (CSRs)**
  - Only for trials intended to be used for obtaining an MA
  - Submit within 30 days *after* MA grant / completion of MA procedure / withdrawal of MA application
- **Patient level data**
  - Commission to produce guidelines for formatting and sharing of data on a voluntary basis

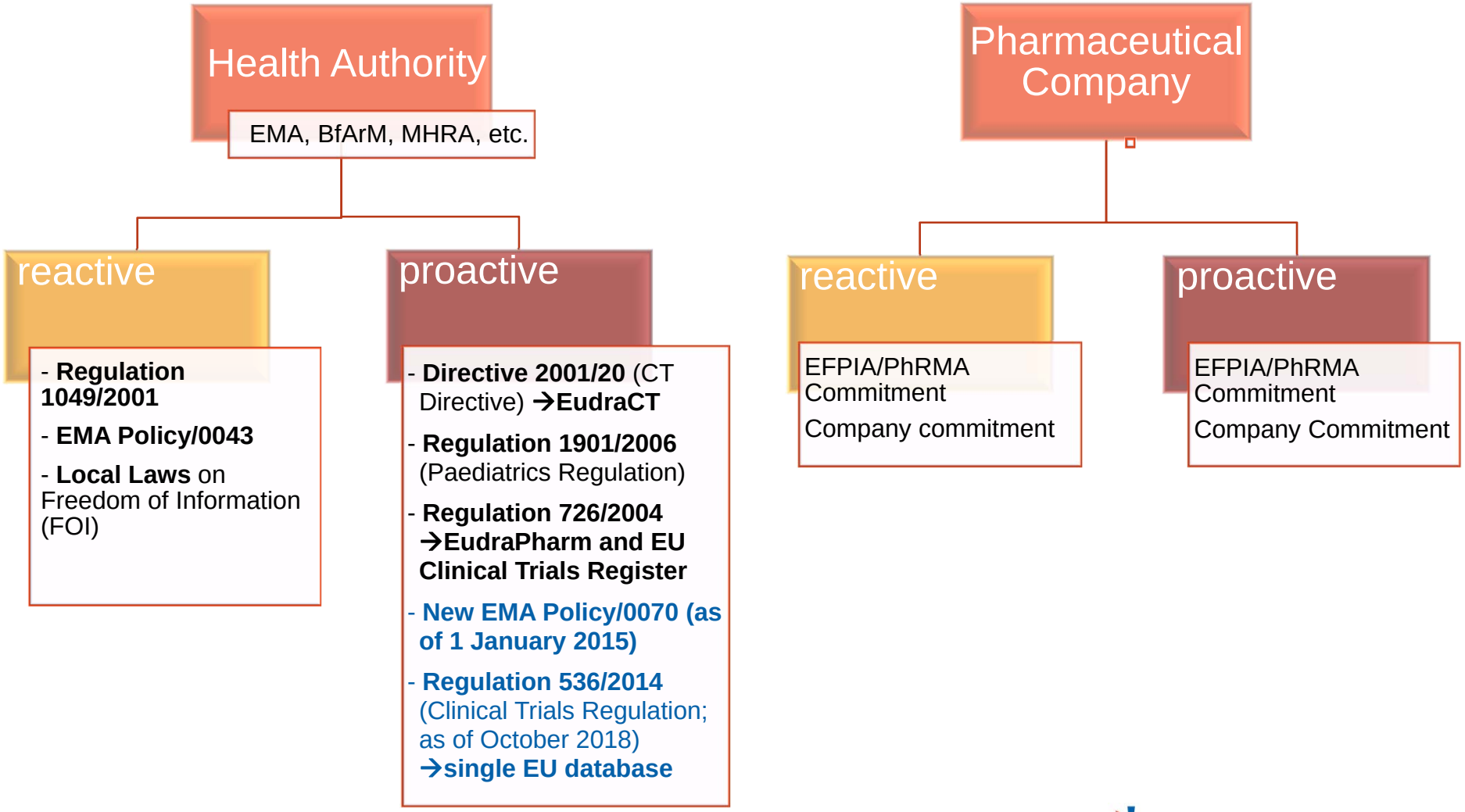
Trial Notifications and Transparency

- **EU database to be publicly accessible unless confidentiality is justified**
  - to protect personal data
  - to protect commercially confidential information (CCI) – taking into account the status of the MA
  - to protect confidential communication between MSs
  - to ensure effective supervision of the conduct of a CT

  Art 81(4) CT Regulation
- **In general, data contained in application dossier shall not be publicly accessible before the decision on the CT has been made**, i.e.
  - when the MA has been granted
  - the decision-making process has been completed
  - the MAA has been withdrawn

  Art 81(5) CT Regulation

CT Data Disclosure – (legal) basis



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CTA assessment in order to obtain the CT authorisation

- **Sponsor shall submit a CTA dossier to the intended cMSs through the EU portal**
- **Sponsor shall propose one of the cMS as rMS**
  - If one or more MS is willing, then MSs decide who will be rMS
  - If no MS is willing or if no agreement, then *proposed* rMS must be rMS

- **rMS notified to sponsor and MSs via EU portal within 6 days (!) after submission**

Art 5(1) CT Regulation

Summary of submission, assessment report and decision on the CT

One format¨/ content (Annex I/ II)

For all communication: Sponsor – MS & between MS

By each concerned MS on Part I & II

Defined opt-out mechanisms for MS from joint Part I assessment

- **Assessment**
  - Part I and II assessed within the same overall timelines
  - Part I (general dossier): jointly by reporting MS and concerned MS
  - Part II (national dossier): national by all participating MS
  - MS to organise the process by authorities and ECs
- **Request for additional information by the rMS only between validation and reporting date** *Art 5(8) CT Regulation*

Subsequent addition of a cMS and Substantial modifications of a CT

- **Extension of an authorised CT to another MS possible**
  - Submission of an application dossier to hat MS through the EU portal
  - Additional MS to take a decision
- **Substantial modifications can be made after initial authorisation, e.g.**
  - Addition of a CT site
  - Change of a principal investigator in the CT site
- **Authorisation of those substantial modifications follows same review process with the same rMS**
  - Can be for Part I or Part II only, or both Part I&II
- **Timelines slightly shorter than initial process**
  - Validation – 6-21 days
  - Assessment and decision – 43 -74 days

Art 15 ff CT Regulation

Safety reporting (SUSARs & Periodic reports)

- **Rules have been streamlined, simplified and modernized**
- **EMA will develop a web-based form for reporting SUSARs (*Suspected Unexpected Serious Adverse Reactions*)**
- **Simplified submission of annual safety report by sponsor**
- **Investigator must:**
  - record and document AEs & lab abnormalities identified in the protocol or all AEs unless the protocol says differently
  - report SAEs<24 hours to the sponsor
  - report to the sponsor a serious adverse incident with a suspected causal relationship to the IMP that occurs after trial end

Art 40 ff CT Regulation

Safety reporting (SUSARs & Periodic reports)

- **Sponsor must report SUSARs to Eudravigilance**
  - < 7 days in case of fatal and life-threatening SUSARs
  - < 15 days in case of non-fatal and non-life-threatening SUSARs
- **It includes those occurring**
  - in a third country site
  - in another trial with the same active substance (IMP)
  - after the end of the trial
- **Sponsor to submit an electronic annual report on the safety of each IMP to the EMA**
  - Possibility to submit a single safety report on all IMPs in one trial
  - The report shall contain aggregate and anonymised data
  - No annual reporting by the sponsor to the MAH

Protection of Subjects & Informed Consent overall unchanged

- **Legal Basis: Charter of Fundamental Rights of EU**
- **Substance of rules established in Directive 2001/20/EC unchanged, i.e.**
  - General rules and Informed consent
  - CT in incapacitated subjects
  - CT on minors
  - Application of provisions of Data Protection Rules

  Provisions for obtaining informed consent in cluster trials, where groups of subjects rather than individual subjects are allocated to IMP
  Art 30 CT Regulation
- **Specific conditions for clinical trials:**
  - In emergency situations: Informed consent may be given after start of CT subject to specific conditions
  - On pregnant and breastfeeding women

Manufacturing of IMPs

- **Definition of manufacture is aligned with Directive 2001/83/EC**
  - Reconstitution is not considered "*manufacturing*"
- **Manufacture and import of IMPs in the EU requires the holding of an authorisation** *Art 61 CT Regulation*
  - Hospitals, health centres or clinics are exempted from holding an authorisation for the following activities:
    - Re-labelling or re-packaging
    - Preparation of radiopharmaceuticals used as diagnostic IMPs
- **A qualified person (QP) shall ensure that each batch of IMP manufactured in, or imported into, the EU shall comply with GMP**
- **Commission to issue delegated acts to specify the principles and guidelines of GMP and inspections for IMPs**
- **Archival function of the CT Database - Cross-reference to previous CTAs facilitated!**

Sponsorship & Co-Sponsorship

- **Sponsorship** *Art 71 CT Regulation*
  - A CT may have one or several sponsors (tasks & responsibility delegation)
  - Any sponsor may delegate, in a written contract, any or all of its tasks to an individual, a company, an institution or an organization - BUT: responsibility stays!)
  - The investigator and the sponsor may be the same person
- **In case of Co-Sponsorship: All sponsors shall be subject to the responsibilities of a sponsor, *unless* otherwise contractually clarified** *Art 72 CT Regulation*
- **One of the group needs to be responsible for each of the following:**
  - Obligations of authorization procedures (Chapters II and III)
  - Responses to all questions from subjects, investigators or MS
  - Implementing measures Article 74 (termination, suspension, modification)

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Conclusion

- **High Expectations from all stakeholders**
- **Does the new CT Regulation really improve the environment to conducting clinical trials?**
  - “One stop shop” for multinational clinical trials within EU
  - Will new process work? (Pilots!)
  - Role of Ethics Committee
- **CT Data Transparency Debate**

Any Questions???

Thank you

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