Clinical trial authorisation framework in Europe - overview

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EMA – SME meeting 28 May 2010

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- **Legal provisions for CTs in EU**
- **NCAs perspectives**

European legislation (1)

Clinical trials directive 2001/20/ CE May 2001

GMP directive Oct. 2003

Annex 13 (2010)

GCP directive April 2005

Q and As

Detailed guidances Volume 10 Eudralex

The CTA dossier for the competent authority (Oct. 2005 ; March 2010)

The CT dossier for Ethics committee (Feb. 2006)

CT Safety reporting (Apr. 2006)

Content of the 2 data bases
- **EudraCT (2003)**
- **Eudravigilance CT module (2004)**

Guidance on IMP and other MP used in CTs

European legislation (2)

ICH guidelines (all)

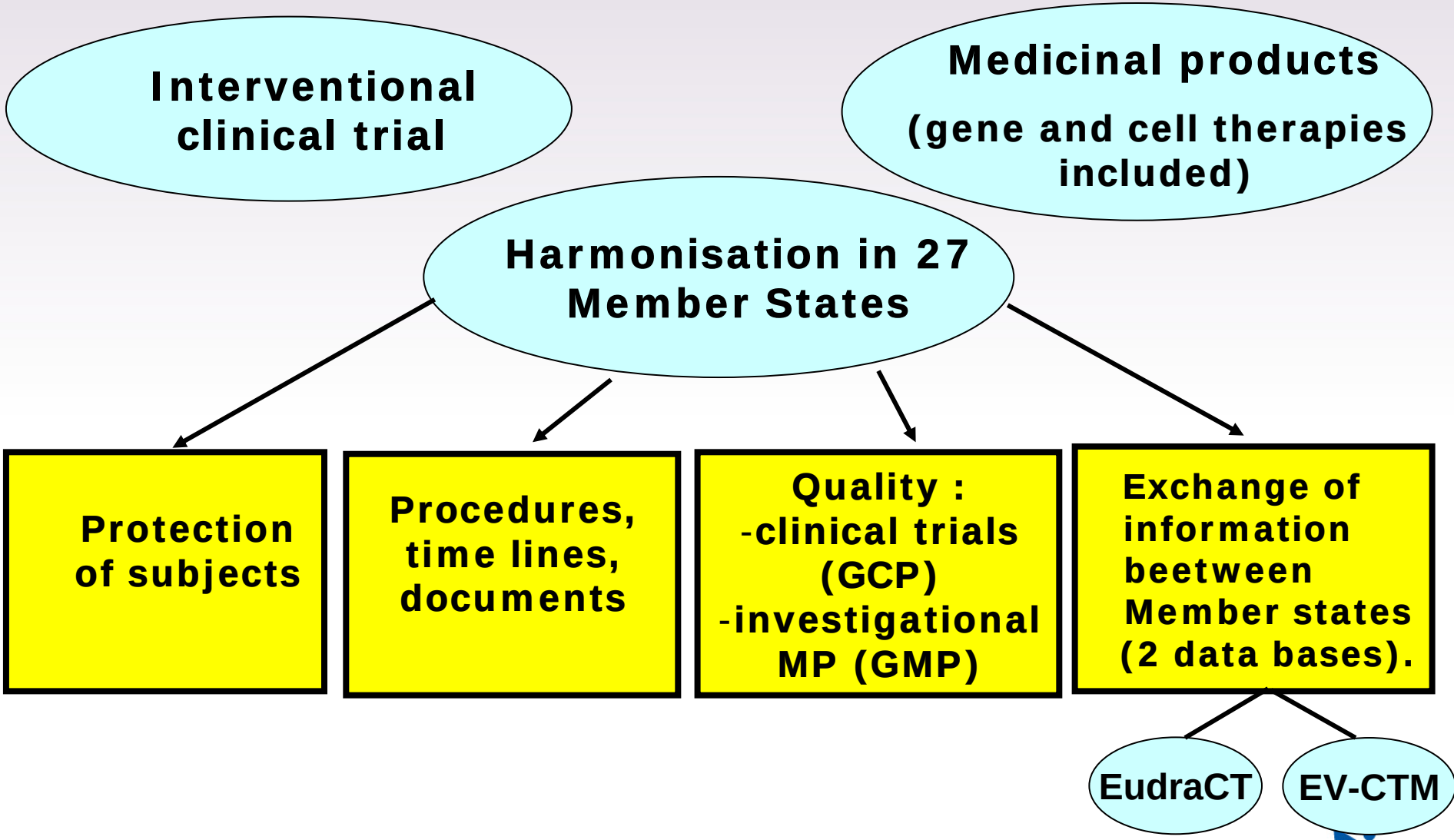
Quality of IMPs :
- Requirements to chemical and pharmaceutical quality documentation (EMA - 2006)
- For biologicals (public consultation)

First in human CTs (EMA – July 2007)
Other guidelines on MP development (EMA)

Guideline on virus safety evaluation of biotechnological IMPs (EMA 2008)

Ethical considerations for CTs in children (2008)

The clinical trials directive and guidances



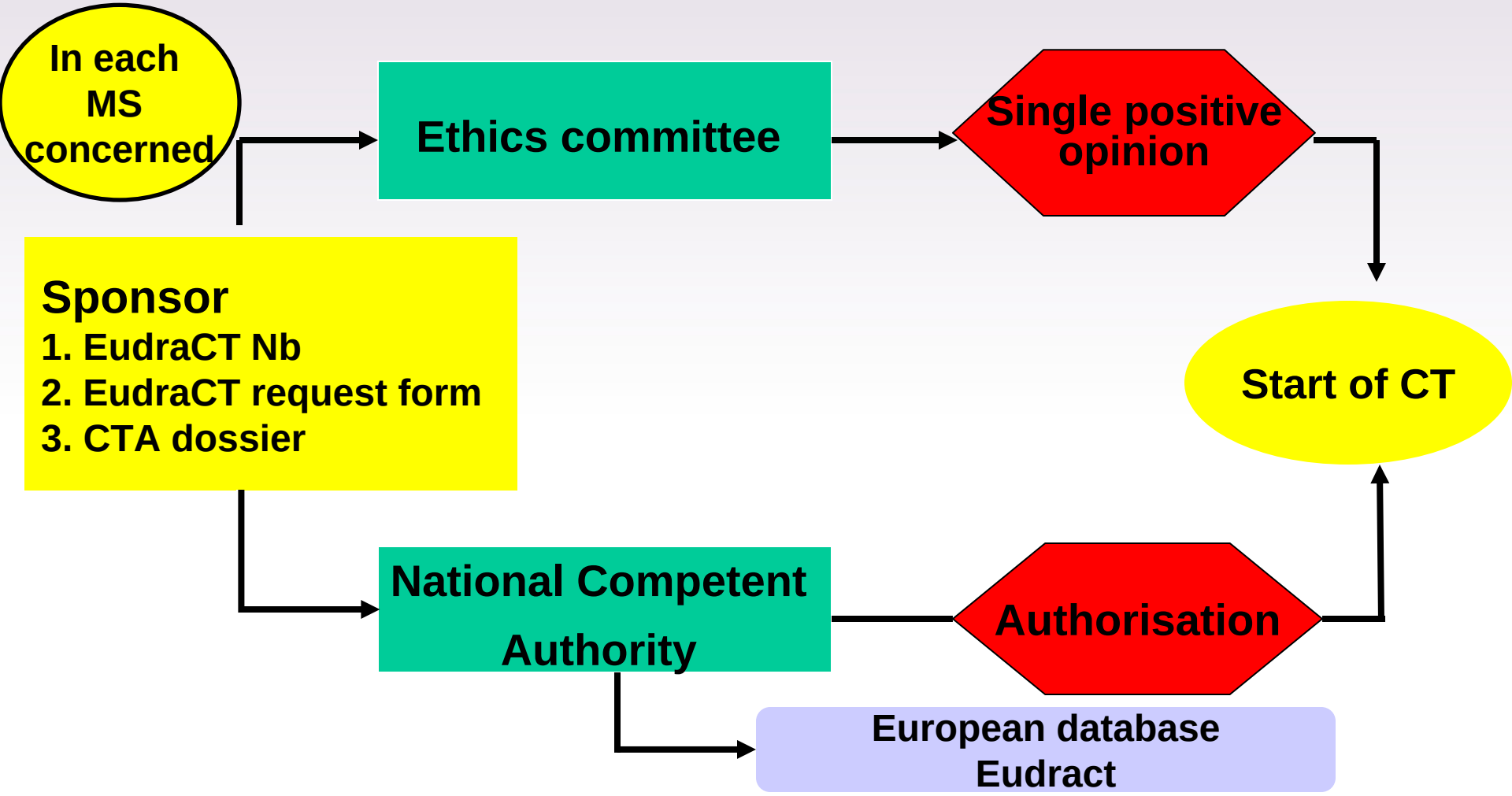
Protection of the CT subjects

- Anticipated benefit and public health benefit justify the risks ➡ risk permanently monitored

- Informed consent and Prior information
- Rights of subjects
- Modalities for consent

- Insurance
- Qualified doctor/dentist
- CT in minors/incapacited adults : additional requirements
- Ethics Committees established by member states (MS)

Procedure for starting a clinical trial in EU



Ethics committee's opinion

- **EC's opinion prior commencement of a CT:**

  - Subjects protection:
  - Written information/informed consent: content and modalities
  - Justification for CT on incapable persons/minors
  - Indeminity/compensation
  - Insurance
  - Arrangement for recruitment

  - The trial
  - Relevance of the CT, CT design
  - Evaluation B/R is satisfactory

  - Facilities
  - Suitability of investigators/staff
  - Quality of facilities

The CTA assessment by NCA

1. **Benefit/risks of the CT is satisfactory**
2. **Quality of IMP and of CT is ensured**
3. **Safety of subjects is monitored and acceptable**
4. **Taking into account all data in IMPD**

Commencement of the CT : Time frames

- **NCA decision within 60 days (no clock stop)**
  - ± 30 days (gene, cell therapy ; GMO)
  - ± 90 days (if experts group)

- **EC's opinion within 60 days (clock stop)**
  - **±** 30 days (gene, cell therapies, GMO)
  - **±** 90 days (if experts group)

The CTA dossier

Today	Tomorrow (new guidance)
1 General information - Cover letter - Eudract number - CTA request form - List of NCAs concerned - GMP certificate, labelling…. **2** Protocol related folder : - Current protocol +synopsis - EC's opinion 3 IMP related folder : - Investigator's brochure (IB) - Investigational Medicinal Product Dossiers (IMPD) (all) - Scientific advices 4 Some National requirements	1. Cover letter 2. CTA request form 3. Protocol (incl. synopsis) 4. IB or doc. replacing IB 5. IMPD (all IMPs) 6. NIMP dossier if applicable 7. EC's opinion 8. Scientific advice, Pedco opinion if applicable 9. Labelling 10. Fees if applicable

The IMP dossier (IMPD)

- Quality data
- Non clinical data (module 4 CTD)
- Clinical data (module 5 CTD)
- B/R analysis

- Content adapted to the level of knowledge (phase of development)
- Summaries of studies and not the study reports

- A simplified dossier is possible
- Cross reference is possible (previous CTA)

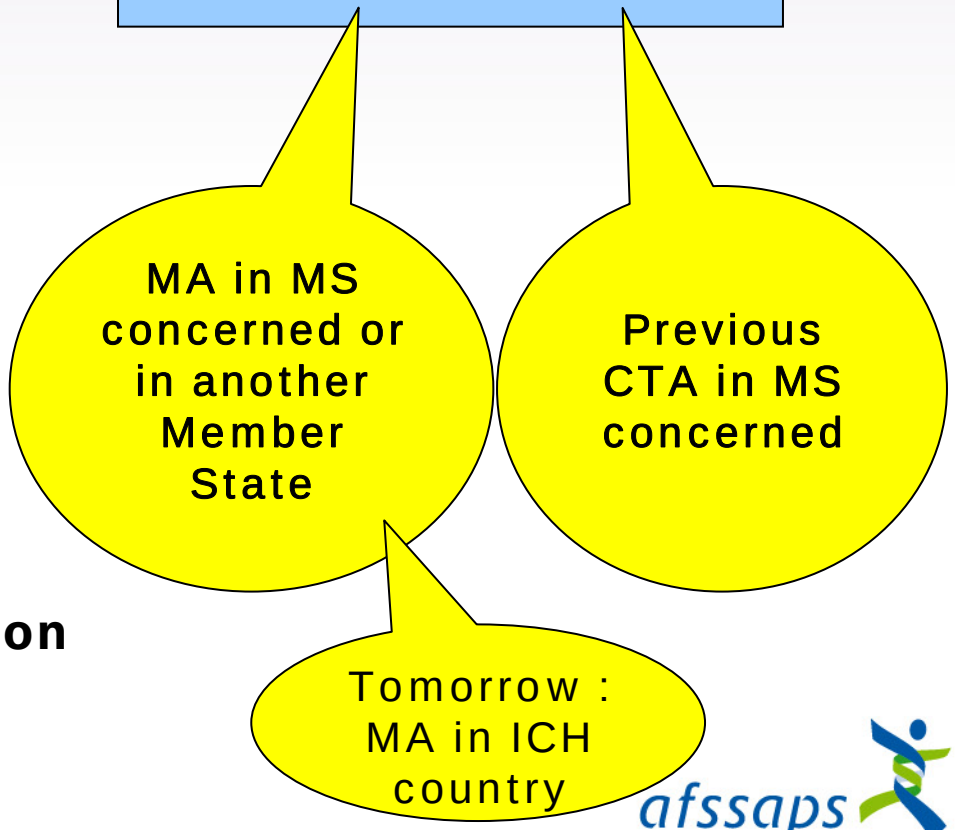
- IMP: tested IMP and comparator (placebo included)

IMPD

Full IMPD

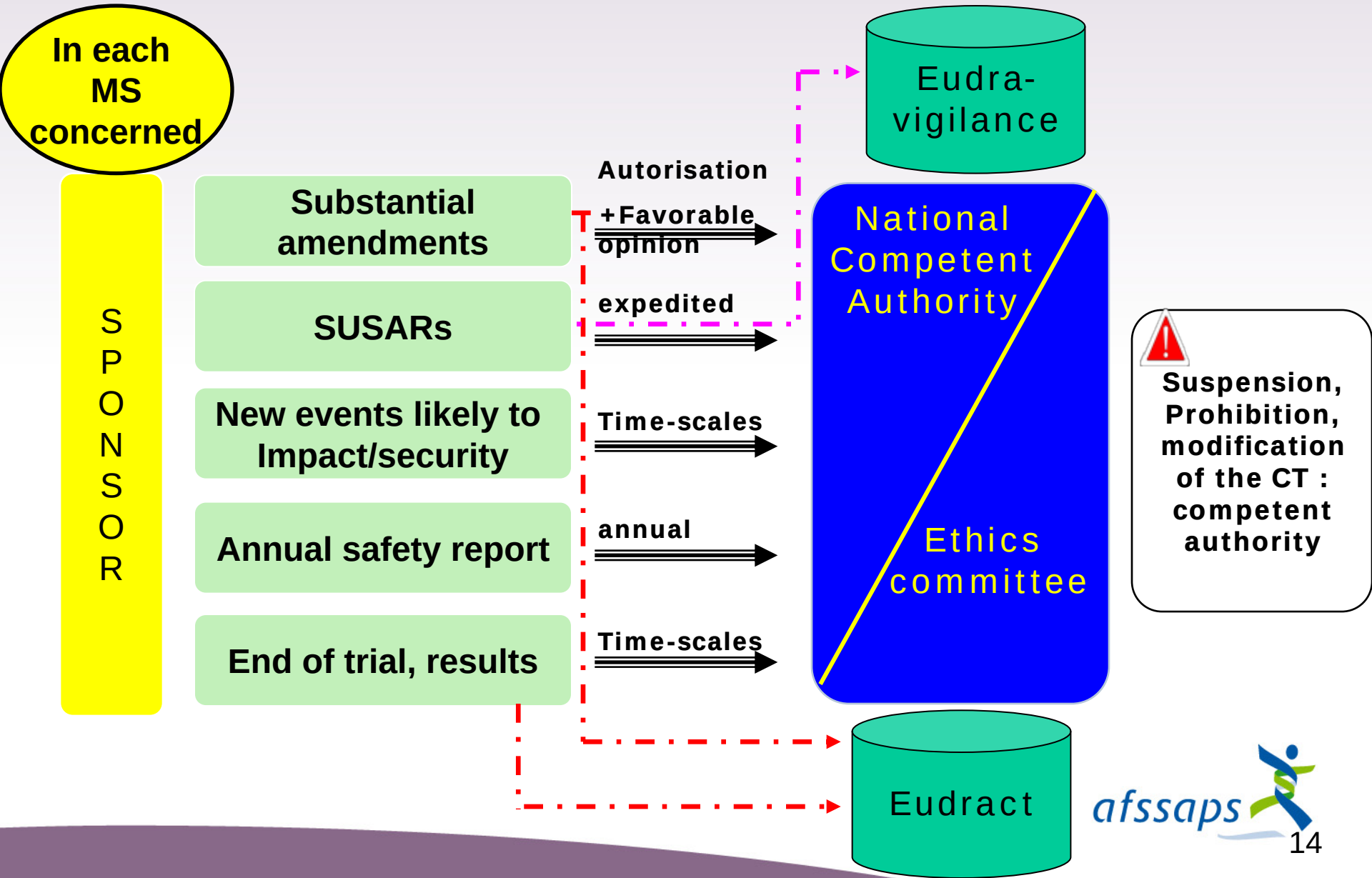
or

Simplified IMPD



MA : Marketing Authorisation

Procedure for the conduct of the CT



Standard documents

- **The same forms and formats :**
  - In each MS, for Ethics Committee and the NCA
  - In Europe, for all Member States
- **Forms and formats recommended by European guidances :**
  - CTA request form + ECs form
  - Substantial amendment form
  - End of CT form
  - Investigational medicinal product dossier (IMPD)
- **But also by ICH :**
  - Content of the protocol
  - Content of the investigator's brochure
  - Summary of the CT results

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During the CT : NCAs' assessment of safety data

- Serious and unexpected adverse reactions (SUSARs)
  - Access to Eudravigilance CT module
  - All MS
- Annual safety reports (ASRs)
- New events likely to have impact on subjects' safety
- All IMPs

- Safety measures by NCA : modification of protocol ; suspension or prohibition of CT…

Quality

- **Quality of IMPs :**

  1. **Manufacture or importation of IMPs is subject to the holding of authorisation**
  2. **A qualified person is permanently available**
  3. **GMP or standards at least equivalent to GMP**
  4. **Traceability of IMPs – labelling (annex 13)**

- **Quality of Clinical trials**

  - **GCP rules are mandatory (see ICH E6)**

Inspections

- GMP and GCP
- appointed by NCAs
- information in EudraCT
- Site of the trial, sponsor's or CRO's facilities, other establishements.

Exchange of information

Two EUROPEAN DATABASES AVAILABLE TO NCAS, EUROP. COMMISSION AND EMA

EudraCT

- **European database of CTs**
- **Electronic handling**
- **EudraCT number**
- **Content :**
  - **Extracts of CTA application form**
  - **Substantial amendments (request/protocol)**
  - **EC opinion**
  - **End of CT**
  - **Inspections**
- **Electronic alerts to NCAS; NCAs reports; queries**

Data entered by sponsors and NCAs

Eudravigilance CT module

- **European database on Susars**
- **Electronic submission**
- **Queries, reports available to NCAs**

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Proposals of improvement by the EU National Competent Authorities (CTFG progresses and actions).

CTA Assessment : What is required to NCAs by sponsors?

1 . Need to improve harmonisation of the administrative process

- Avoid :
  - **National CTA requirements**
  - **National divergent decisions**
  - **Bureaucratic burden**

2. Need to facilitate the administrative process

- **Same CTA dossier**
- **A single repository**
- **An electronic submission**
- **Application in English**

3. Need to improve the scientific review outcomes

- **A coordinated scientific decision on the same CT**

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What CTFG offers to sponsors

- *In order to accelerate CTA and improve CT safety*
- *Voluntary NCAs cooperation*
- *Simplification of processes*
- *Coordination of CT assessment by NCAs*

Coordination of assessment of Multinational CTA by NCAs

The CTFG Guidance document

for a

Voluntary Harmonisation Procedure

(VHP) of CTA assessement

http://www.hma.eu/77.html

CT safety data work sharing

- **Annual safety reports**
  - **The development safety update report (DSUR) :**
    - **ICH step 4**
    - **2010**
  - ***Preparation of ASR-DSUR Work sharing by NCAs* within CTFG**

Perspectives in EU

- **CTFG action plan 2010-11**

  - Coordination or sharing of multinational CTs assessment
  - Development of new tools and procedures
  - Harmonisation of processes and practices
  - with the aim to set up best practices between MS

  and to propose changes or clarification of guidelines and legislation

  - Public meetings: Bonn April 2010, Paris 11 June 2010, Brussels 18 Nov 2010.

- **EU Commission's updated guidances**
  - CTA guidance (CT1) : 30 March 2010
  - CT Safety reporting : 2010-11
  - CTD Impact analysis → Change the directive? (end 2011)

- **EU CT registry by EMA (2010)**

Where to get information on CTs in EU

- **European Commission website**

http://ec.europa.eu/enterprise/sectors/pharmaceuticals/human-use/clinical-trials/

- **CTFG website :**

http://www.hma-eu/77.html

Contact points, mandate, activity report, action plan, VHP, public presentations…

Thank you!

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