Evolution of the European CT Regulatory Framework and its influence on competitiveness

Colombia
7-Nov-2014

Fabienne Zeegers, PhD
Global Clinical Trial Submission Unit & EU CT External Policies
Bristol Myers Squibb

Disclaimer: the views and opinions expressed in the following PowerPoint slides are my own and should not be attributed to Bristol Myers Squibb (BMS)or any organization with which the presenter is employed or affiliated

Objectives

- Share for clinical trials
  - Fundamentals
  - Metrics (worldwide, Europe, countries)
  - Current and future European framework
- Compare key aspects of EU and Colombia legislations

Set the stage…

Balanced approach when evaluating CT

- Risk/Benefit assessment
- Speed/Quality

Stakeholders

- Open and continuous Dialog
- Public Consultation periods

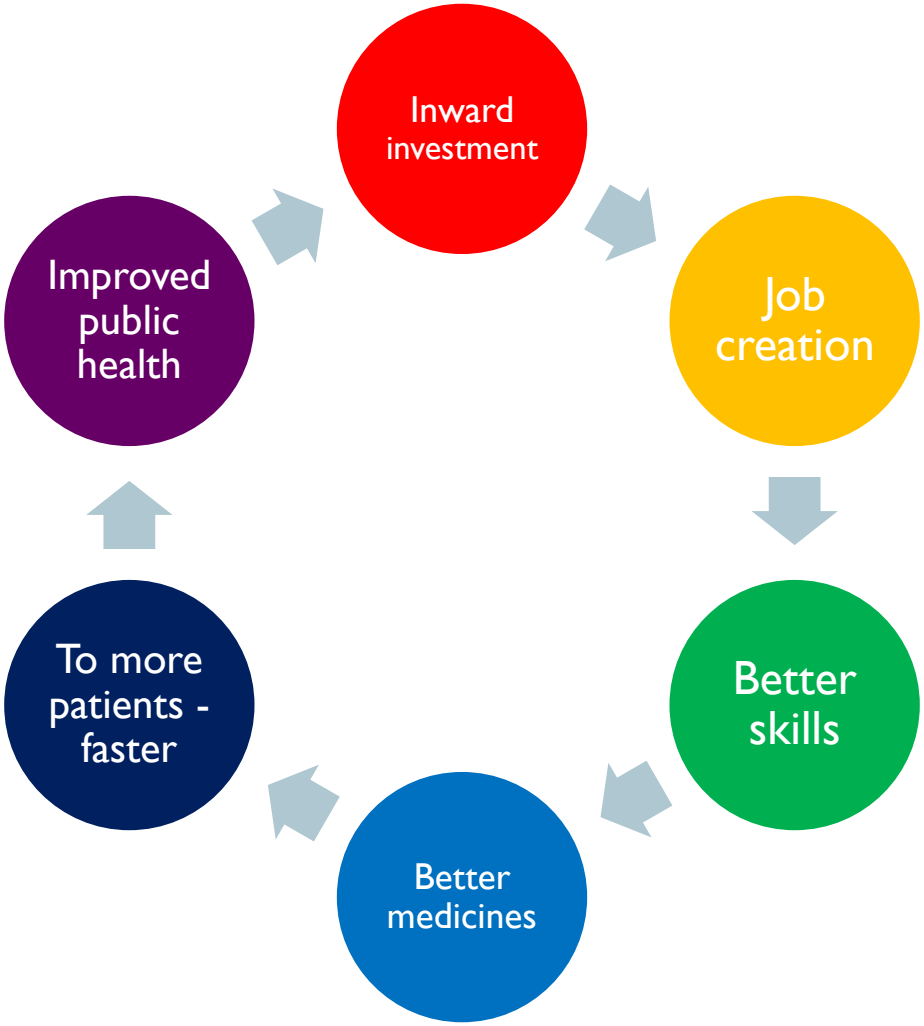
Patients at the center

TRUST

Environment

- Collaboration Nationally and Regionally
- Evolving Clinical Research

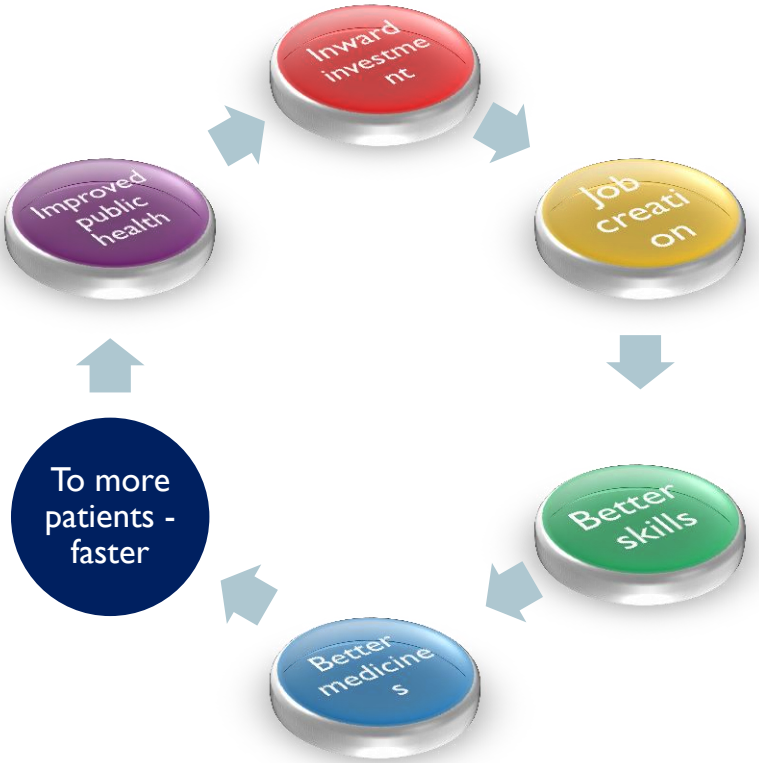
Europe 2020


Inward investment
Job creation
Better skills
Better medicines
To more patients - faster
Improved public health

Europe 2020

Patients' Needs ➔

- Quick access to innovative treatments
- Clinical trial close to Home
- Easy access to quality Information
- Have access to the latest medical knowledge and best standards



Europe 2020

INDUSTRY (EFPIA Total)	1990	2000	2011	2012
Production	63,010	125,301	205,622	210,000 (e)
Exports (1) (2)	23,180	90,935	288,573	305,000 (e)
Imports	16,113	68,841	212,135	225,000 (e)
Trade balance	7,067	22,094	76,438	80,000 (e)
R&D expenditure	7,766	17,849	29,192	30,000 (e)
Employment (units)	500,879	534,882	700,010	700,000 (e)
R&D employment (units)	76,126	88,397	115,695	116,000 (e)
Pharmaceutical market value at ex-factory prices	41,147	86,704	160,603	163,000 (e)
Pharmaceutical market value at retail prices	64,509	140,345	235,017	238,500 (e)
Payment for pharmaceuticals by statutory health insurance systems (3)	40,807	76,909	125,603	126,800 (e)

Impact on the Competitiveness of Europe and benefit of European Society ➔

- Reposition Europe at the centre of Global R&D
- Attract R&D Investment by creating a favourable environment of R&D
- Centre of new technology global development
- Centre of Excellence for Scientific Knowledge

EFP IA (The European Federation of Pharmaceutical Industries and Associations) – Key data - 2013

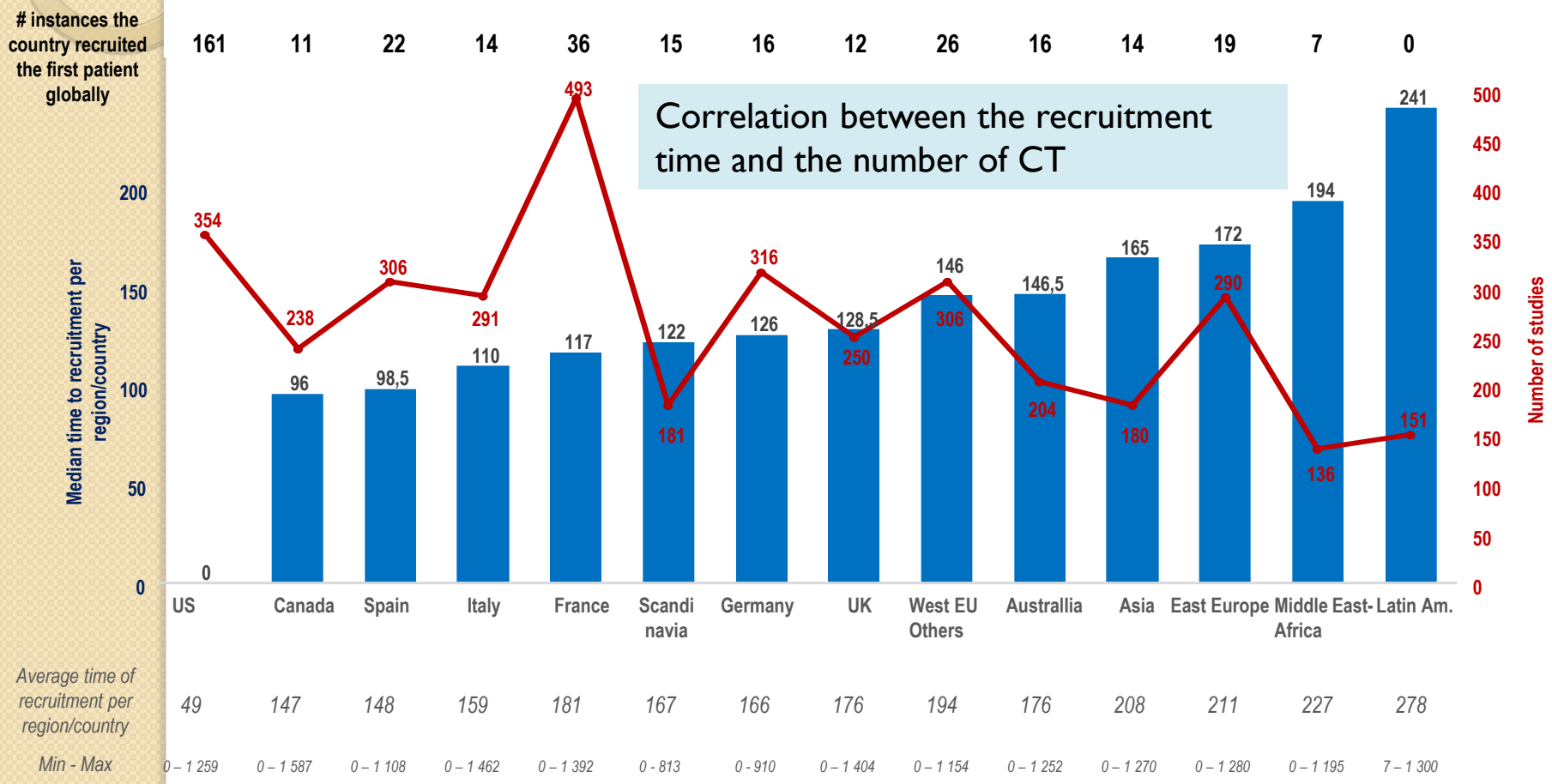
Europe 2020

The new clinical trials framework of tomorrow➔

- Innovative, smart and efficient clinical trials regulatory framework
- Eliminate or decrease the administrative bottlenecks
- Create fast, efficient, and satisfactory decision making process for multinational clinical trials that would live up to the fast-changing and ever-developing scientific state-of-the-art

Median Time to Recruitment of the first patient per country

(Recruitment date of the 1st patient of the country – recruitment date of the first patient globally)



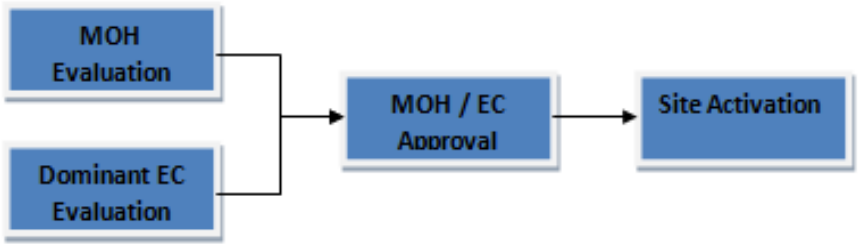
LEM – Survey Report 2014

International Timelines (from CT submission)

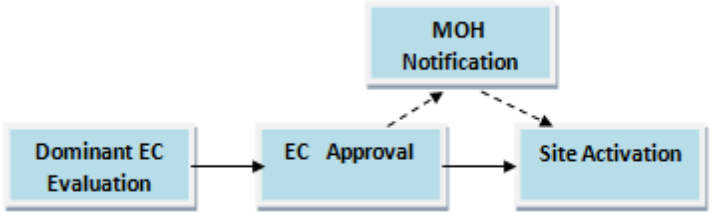
Country	Regulator approval time	Ethics committee approval time	Regulatory/ Ethics review	Total Approval Time
Singapore	30 days	30 days	In parallel	30 days
Australia	50 days	10-50 days	In parallel	50 days
South Korea	60 days	8 weeks	In parallel	60 days
EU Average	60 Days	60 Days	In Parallell	60 days
India	90 days	60 days	In parallel	90 days
Russia	55 days	60 days	EC approval first	115 days
Canada	30 days	120 days	In parallel	120 days
Columbia	90 days	30/50 days	EC approval first	140 days
Argentina	120 days	30 days	EC approval first	150 days
South Africa	120 days	45 days	HA approval first	165 days
Peru	195 days	42 days	EC approval first	237 days
China	330 days	60 days	HA approval	390 days
USA	30 Days	* Not defined in law	In parallel	

Compare own Regulatory framework with other countries or regions

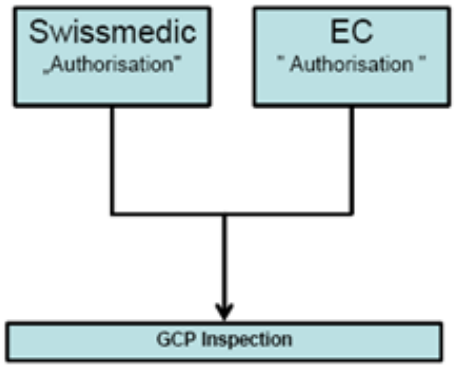
- Europe and Canada:
  - Evaluation MOH and EC in parallel
  - Dominant Committee (ICF revision)
  - The other ones will proof the local conditio
  - Import Permit is not required (Canada)



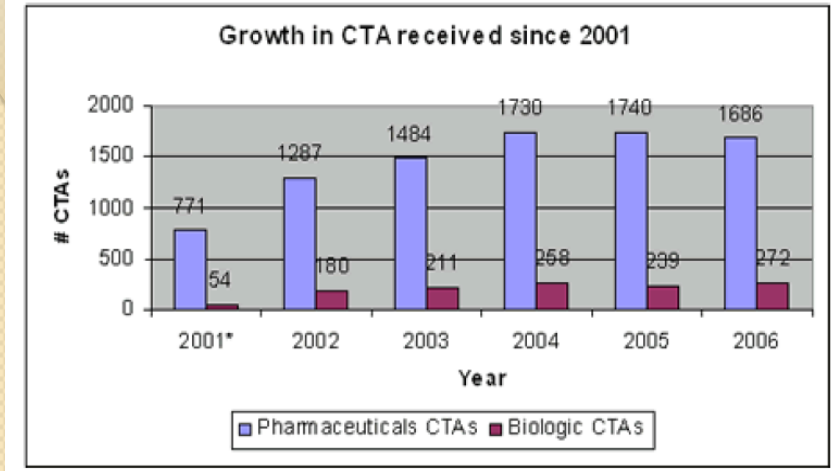
- Australia:
  - Dominant Committee (optional)
  - Local EC: Contract, and Site Staff Qualifications
  - MOH: Notification
  - Import Permit is not required



- Switzerland:
  - New Regulation:
    - One EC will evaluate the complete dossier,
    - The other ones will proof the local conditions
    - Parallel submission to Swissmedic (MOH) and EC (2 instances evaluate diffent topics)

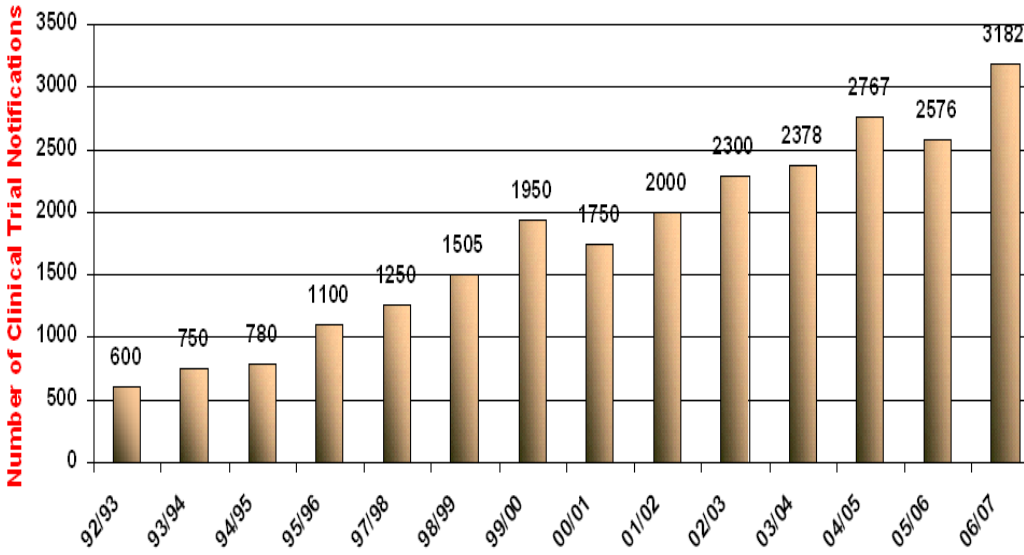


Canada and Australia

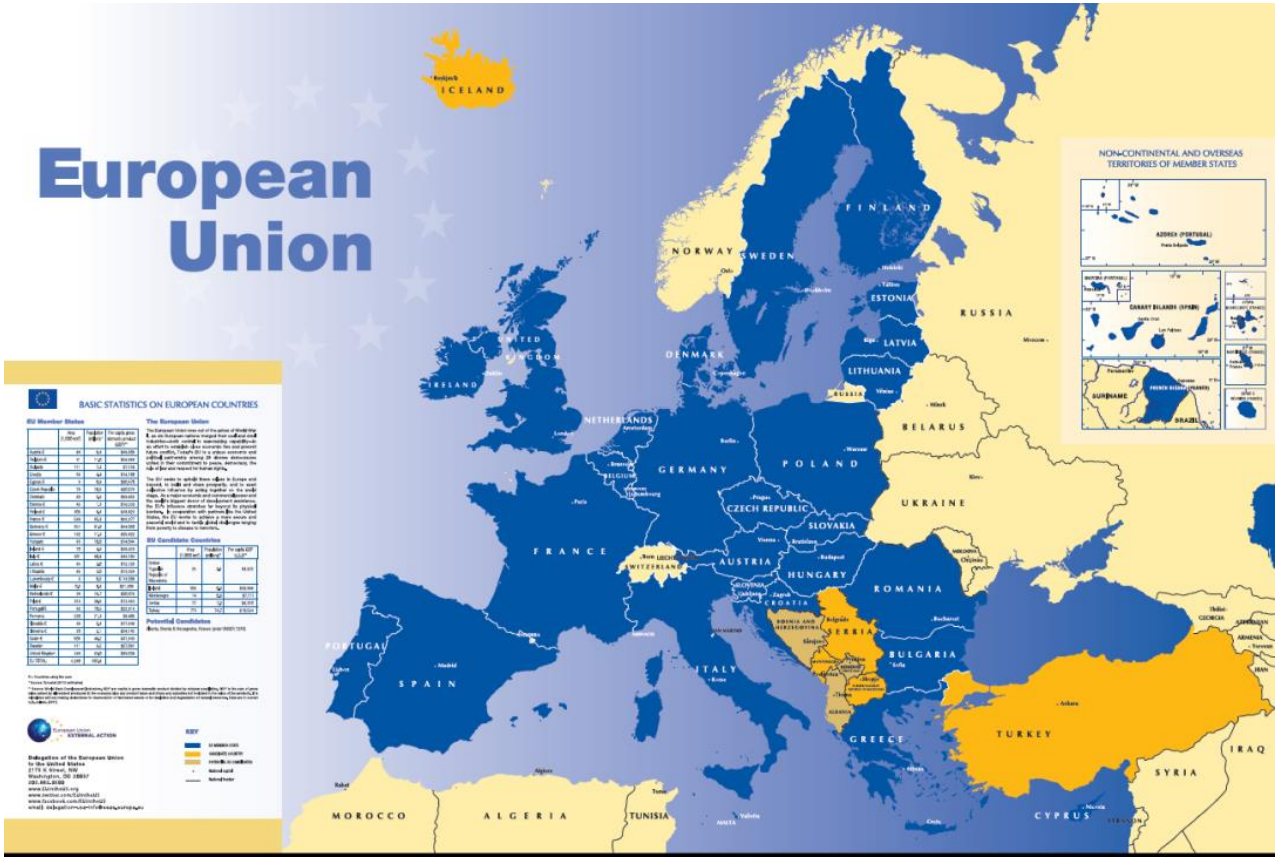


- 2001: Ministry of de Canada
  - ✓ Change regulation to increase competitively
  - ✓ Promotion and education activities
  - ✓ Annual grown of 6.2% between 2002 and 2006

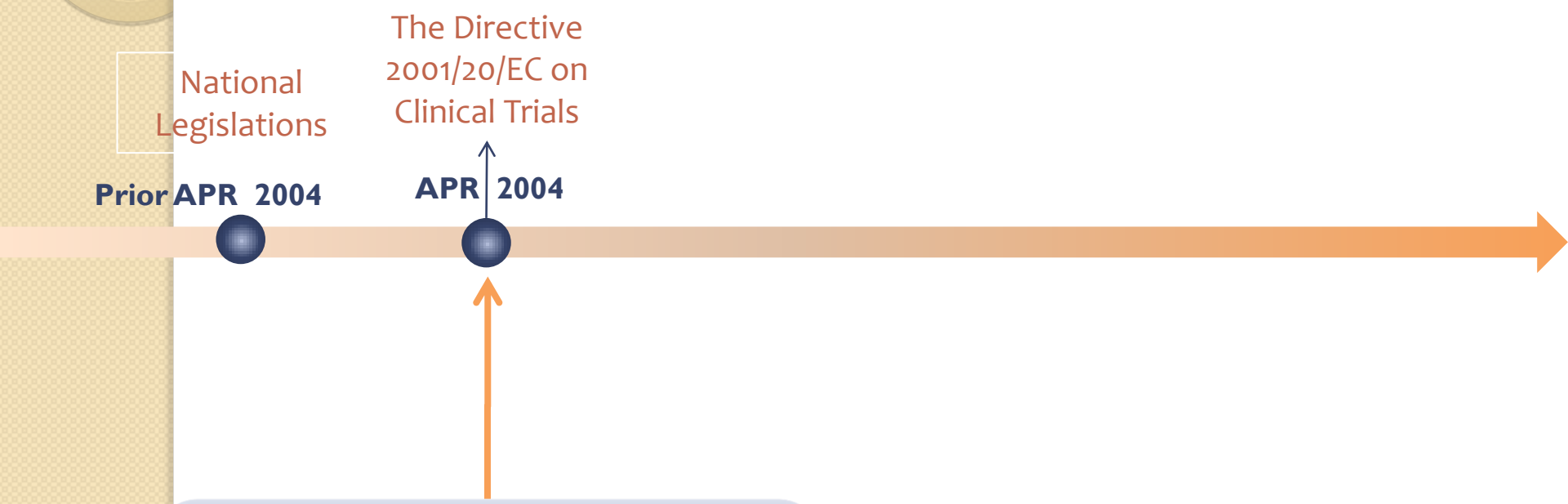
Australia – Change the legilsation in early '90



Europe


European Union
ICELAND
NORWAY
SWEDEN
FINLAND
RUSSIA
ESTONIA
LATVIA
LITHUANIA
DENMARK
IRELAND
NETHERLANDS
BELGIUM
GERMANY
POLAND
BELARUS
UKRAINE
CZECH REPUBLIC
SLOVAKIA
FRANCE
AUSTRIA
HUNGARY
ROMANIA
SWITZERLAND
CROATIA
SERBIA
BULGARIA
PORTUGAL
SPAIN
ITALY
GREECE
TURKEY
SYRIA
IRAQ
MOROCCO
ALGERIA
TUNISIA
CYPRUS
NON-CONTINENTAL AND OVERSEAS TERRITORIES OF MEMBER STATES
BASIC STATISTICS ON EUROPEAN COUNTRIES

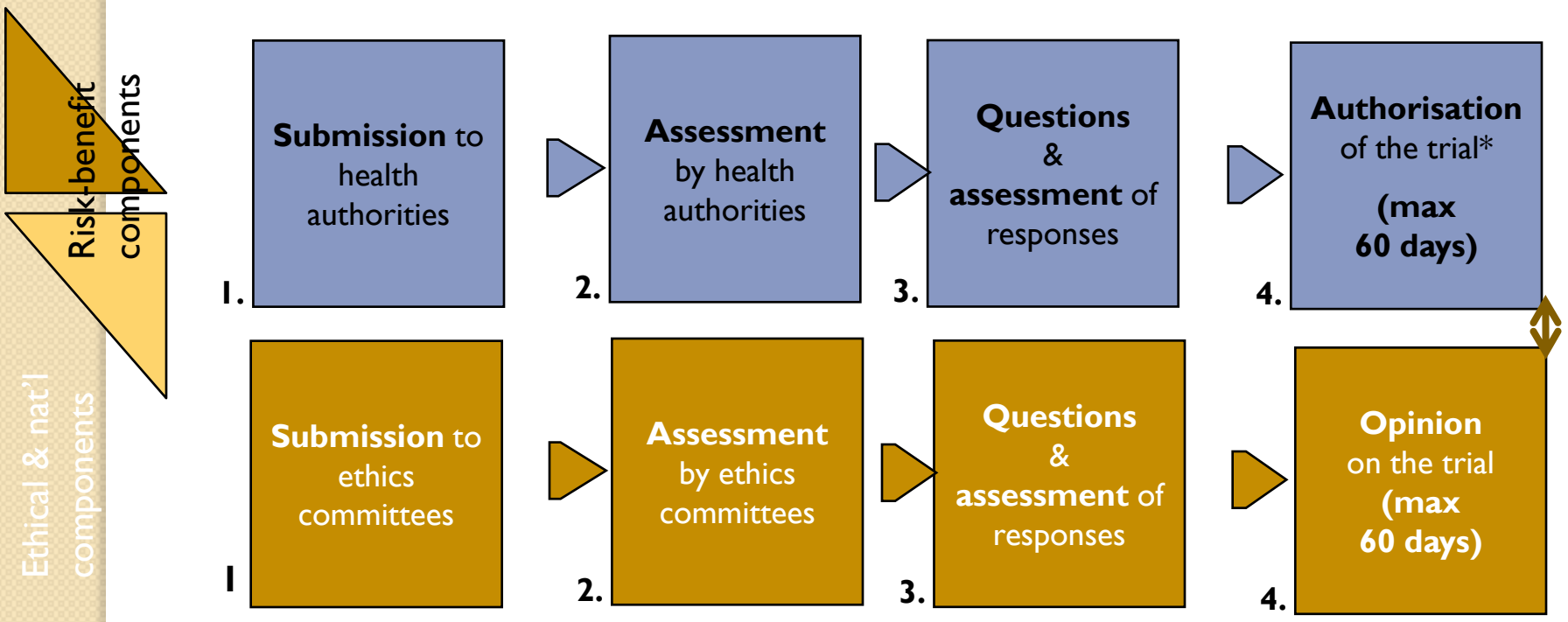
EUROPEAN CT REGULATORY FRAMEWORK



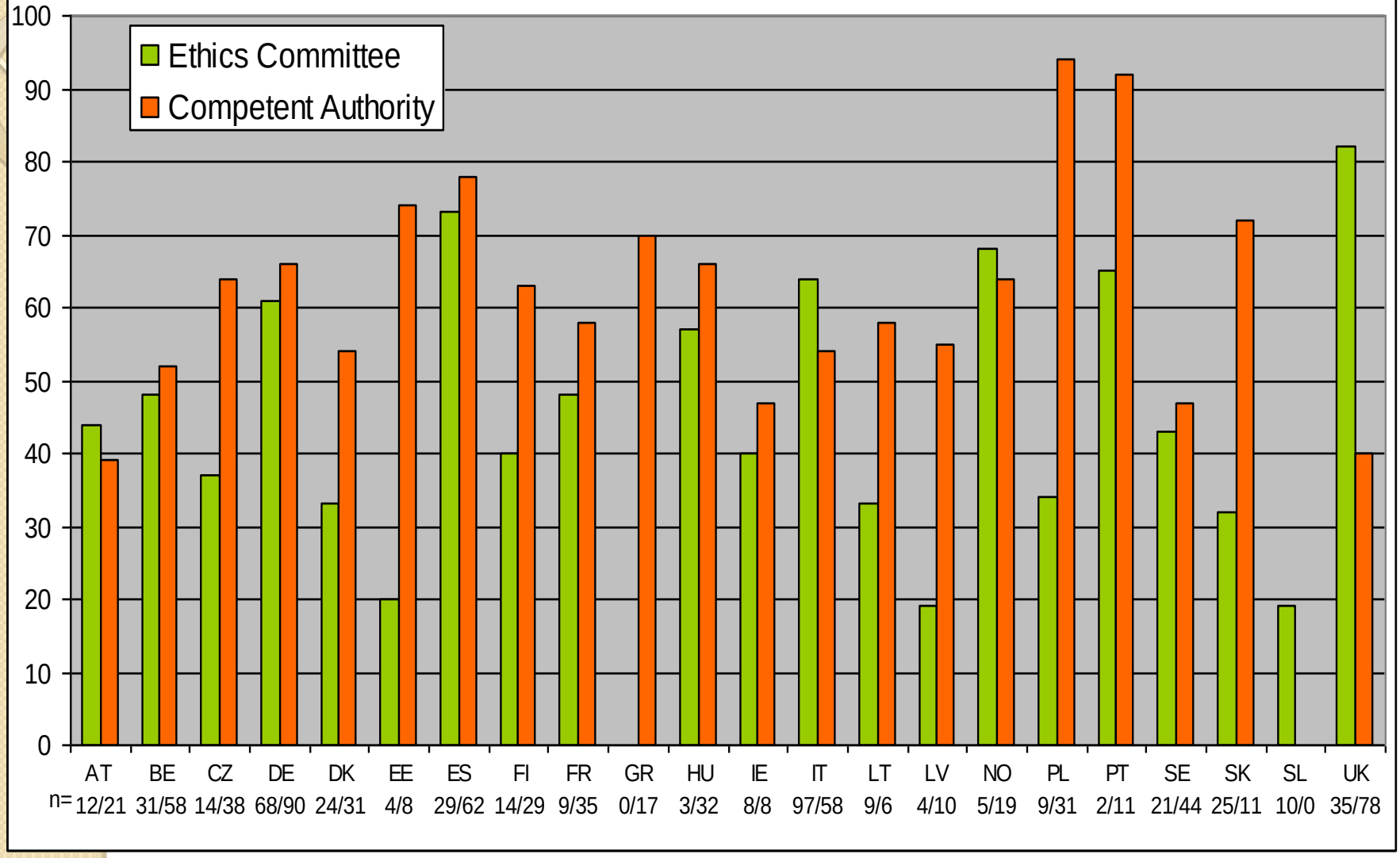
Aims to harmonize the Start Up, Conduct and closure of Clinical Trials across the Union
Introduce Substantial Amendments (Affect Patient Safety or Scientific value of the CT) : 35 days approval
Non-substantial amendments do not require approval

Assessment and Authorisation System

- The clinical trial application process consists of four steps, carried out in **each of the member states** for both health authority and ethics committee submissions
  - Common core Clinical Trial Application dossier



Time by CA and EC from Submission to Approval for a CTA for Phase II - IV Trials [days]



2005 EFPIA – PHRMA SURVEY ON THE IMPLEMENTATION OF THE CLINICAL TRIAL DIRECTIVE IN EUROPE

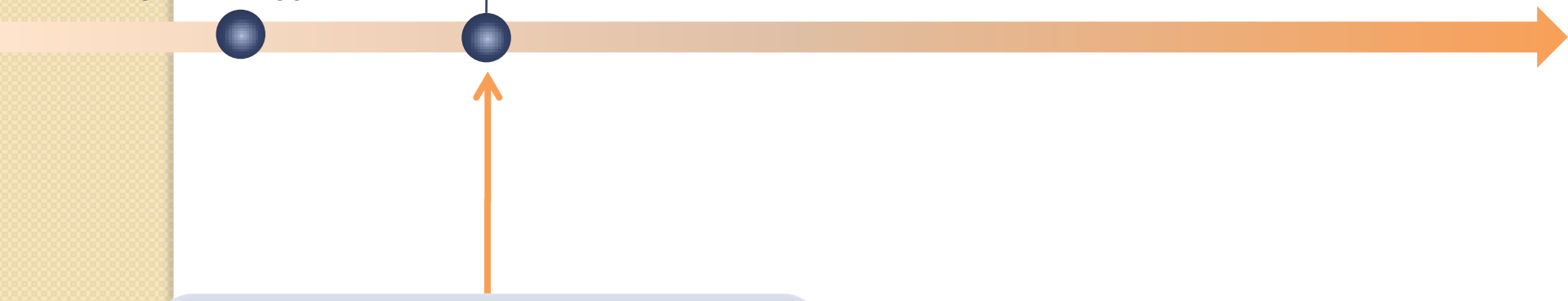
EUROPEAN CT REGULATORY FRAMEWORK

National Legislations

Prior APR 2004

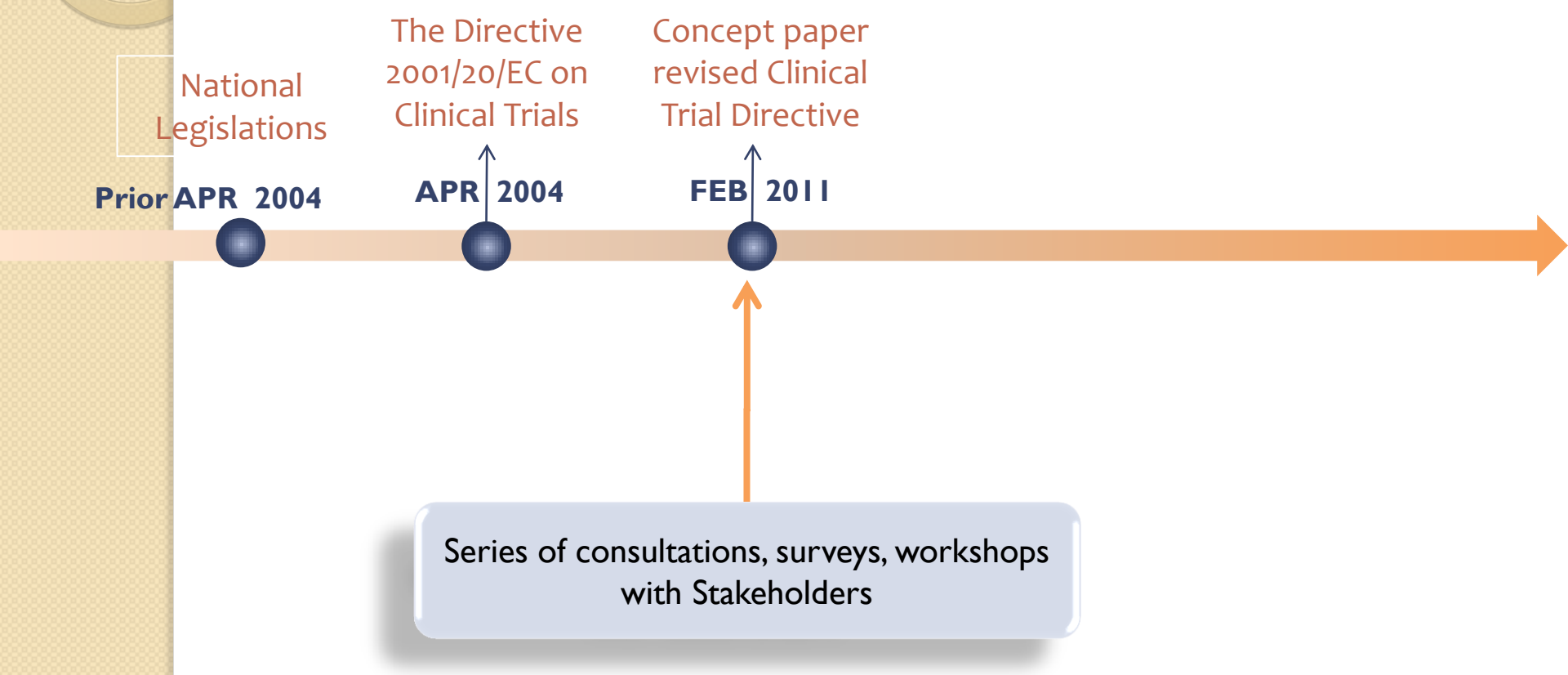
The Directive 2001/20/EC on Clinical Trials

APR 2004



Divergent practices between countries
Content, format or language requirements
Timelines for the review of a CTA
Different set of questions
Varying final decisions
Country-specific modifications

EUROPEAN CT REGULATORY FRAMEWORK



National initiatives

Initiatives taken by EU countries to attract CTs

PUBLIC-PRIVATE DRIVEN

LEAD: MINISTRY OF HEALTH
- "Healthy Growth" Plan
- Improving conditions for private-public partnerships in health research & innovation

LEAD: ABPI & MHRA
- Improving legal framework (IPO, clarity, ...)
- Access to information for industry (toolkits, web, routemaps, ...)

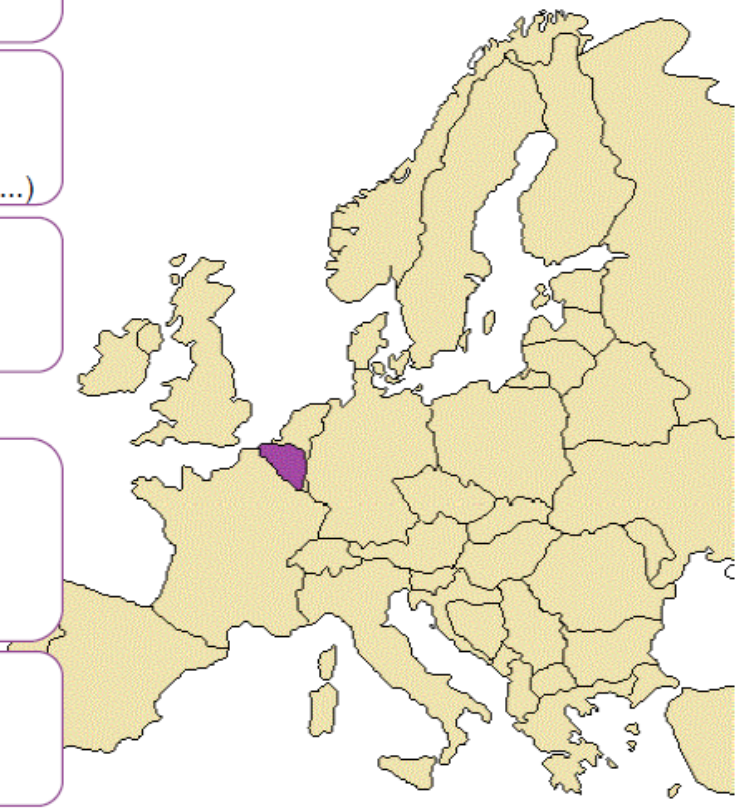
LEAD: LEEM & CeNGEPS (public-private)
- Development of national network of CT centres
- Patient recruitment (CT registry, website, awareness, ...)

SECTOR DRIVEN

LEAD: NEFARMA
- Standardization/one-stop shop concept (forms, contracts,...)
- Professionalization (performance monitoring, training, ...)
- Patient participation (volunteer registry, ...)

LEAD: INFARMA
- Advocacy activities (gov't, industry, ...) & public education
- Transparency (self-regulation doc, CT registry websites)

LEAD: Pharma.be
- Standardization of documents (IC, contracts...)
- Professionalization (website, working groups with agencies)

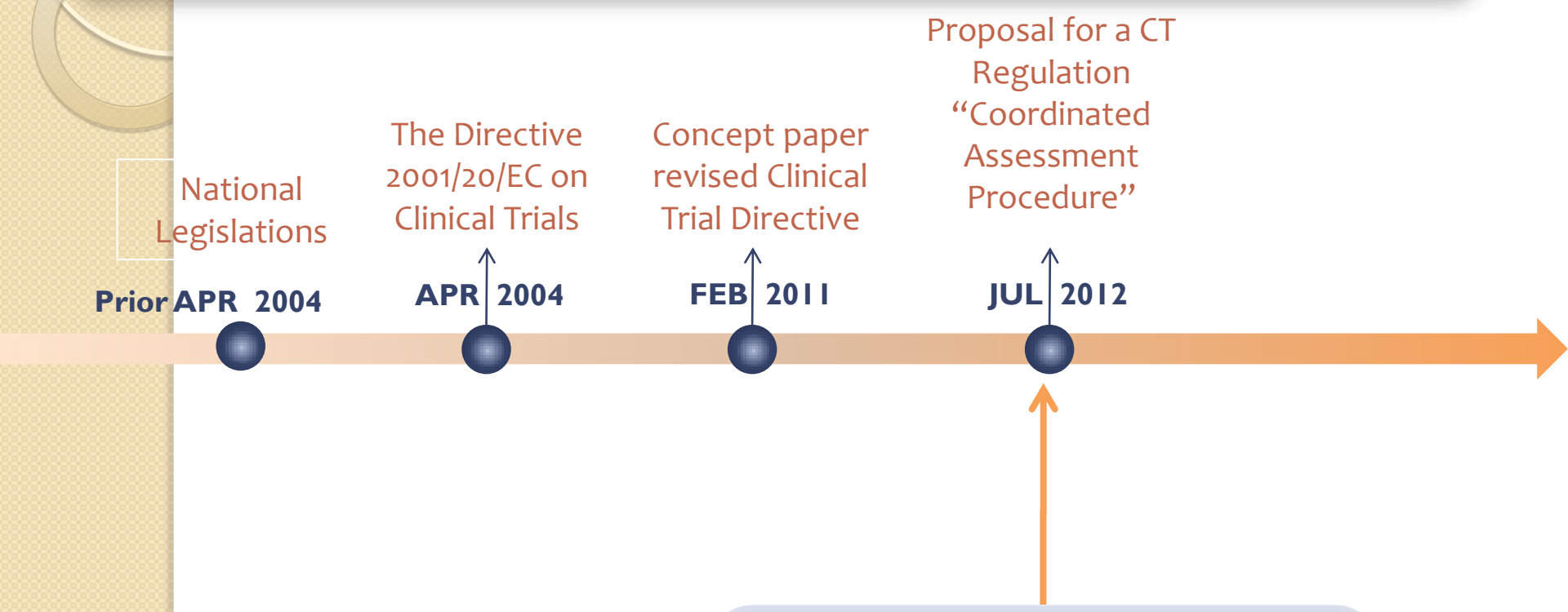


France – Timelines per study phases (2014)

Phase	Number of studies	Median # days between submission and approval by HA (ANSM)	Median # days between submission and approval by central EC (CPP)	Median # days between the sumission and the signature of the 1st hospital contract
	2014	2014	2014	2014
Phase I	118	54	58	118,5
Phase II	177	55	63	126
Phase III	284	54	63	124
Phase IV	14	44	56	133
Total	**593**	**54,5**	**62**	**122,5**

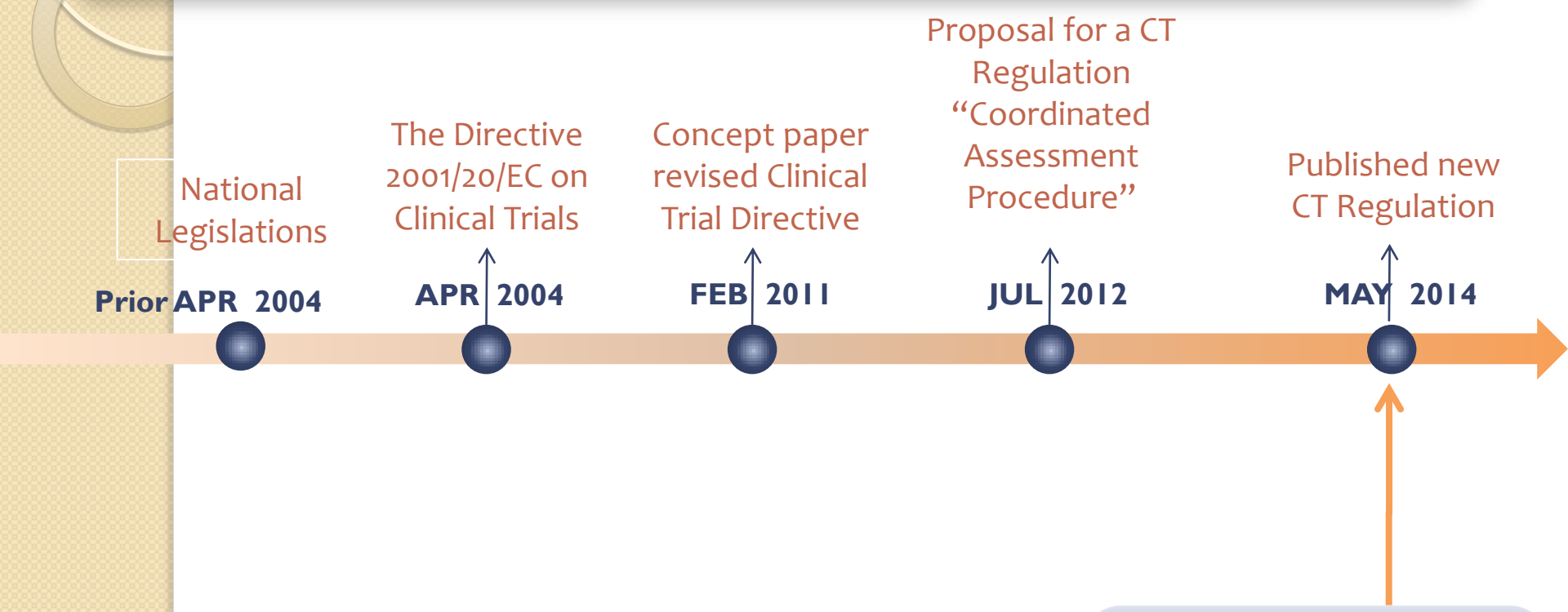
LEM (France National Trade Association) Survey - 2014

EUROPEAN CT REGULATORY FRAMEWORK



- High interactions with Stakeholders throughout the legislative process
- High involvement of National and Regional Trade Associations

EUROPEAN CT REGULATORY FRAMEWORK

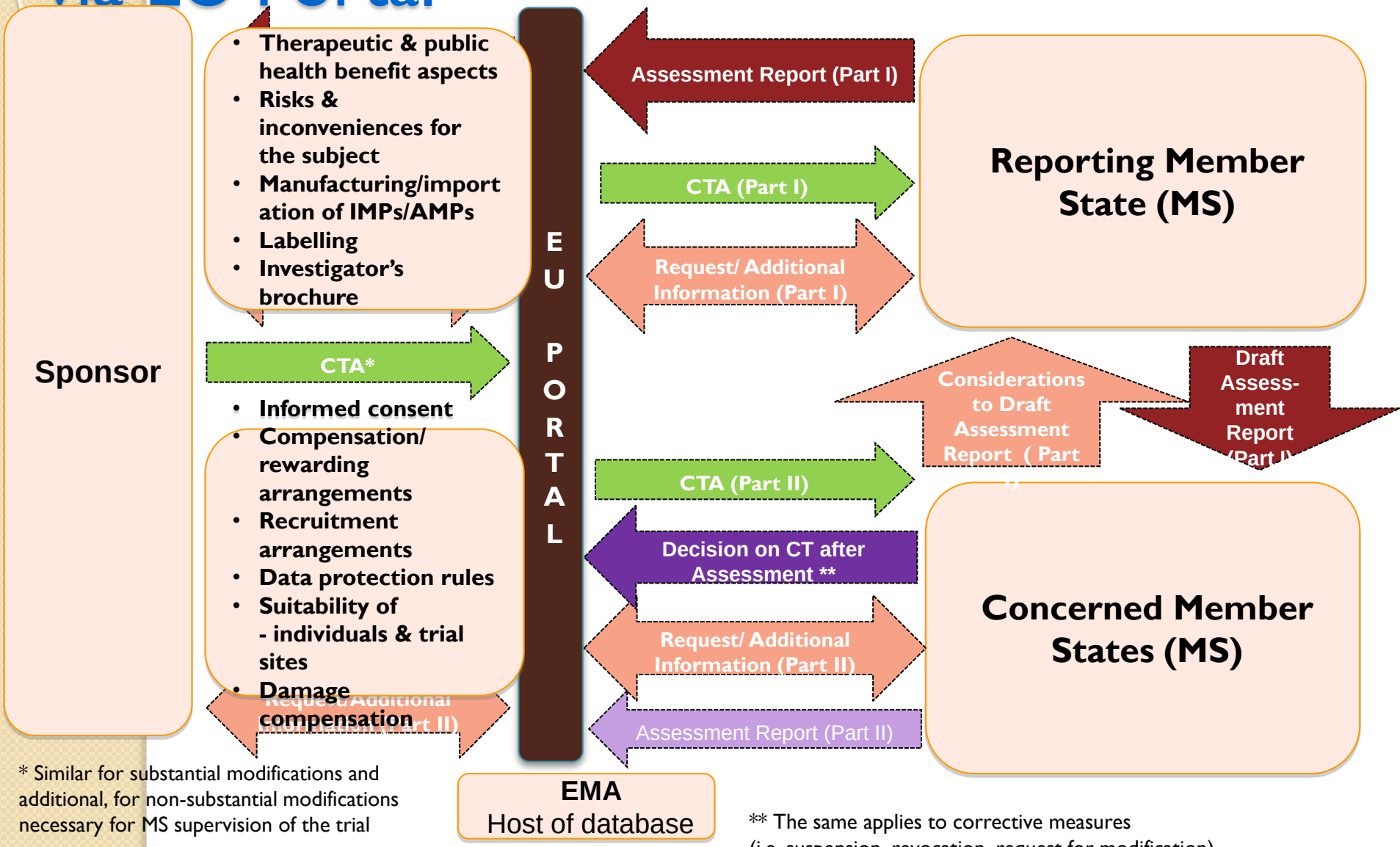


Will apply as from six months after the publication announcing the functionality of the EU Portal, but in any event no earlier than 27 May 2016.

Current and Future

Directive 2001/20/EC	Clinical Trial Regulation
Directive to be transposed into National Legislation	Regulation binding in its entirety and directly applicable in all MSs
Scope Interventional Clinical Trials	Scope Interventional Clinical Trials
No Risk differentiation	Risk-based assessment: Low-intervention CT • Authorized IMP, used in accordance with MA • Do not pose more than minimal additional risk or burden to safety of subject

CT Authorisation Process Communication via EU Portal



* Similar for substantial modifications and additional, for non-substantial modifications necessary for MS supervision of the trial

** The same applies to corrective measures (i.e. suspension, revocation, request for modification)

For Part II

Current and Future

Directive 2001/20/EC	Clinical Trial Regulation
Tacit approval for the MS	Tacit approval for RMS and Tacit withdrawal for sponsors
60-days for EC and CA assessment in parallel	60- days (Max. 106 days) • Predictable • Harmonized
No review clause	Provisions to re-evaluate the CT Regulation each 5 years • Evolving environment • Monitoring of its functioning

Colombia

Analysis of some requirements

Colombia	Europe (Current)	Europe (Future)
Submittion and approval is requested for Each relabeling process	• Information about stability for relabeling only provided with the initial submission (with re-assay plan) • IVRS automate Use Date Extension	Idem
Paper Submission	Paper and Elecronic	Electronic – EU Portal/EU Database
Local Ethics Committees	Central EC But local EC still operate in some countries	Central EC Role of local ECs questionned
Any changes must be authorized (all amendments)	Fast track for amendment not affecting patient safety or scientific value of the trial	Fast track for amendment not affecting patient safety or scientific value of the trial

Analysis of some requirements

Colombia	Europe (Current)	Europe (Future)
Both EC and MOH review overlaping aspects of clinical trial	Delineation of EC and MoH reviews varies per country	• National and Regional collaboration for HA • EC Network being discussed
Safety Reporting 1)All SAE in 7 days (local format) 2) SUSAR every 2 months (local format) 3) Annual Safety Report in a local format	SUSAR 7 or 15 days Line listing allowed in some countries	SUSAR 7 or 15 days Through a Portal
Critical deviations requested by MOH	No deviations to be sent to MOH	Serious Breaches through the EU Portal

BACK – UP SLIDES

Europe 2020

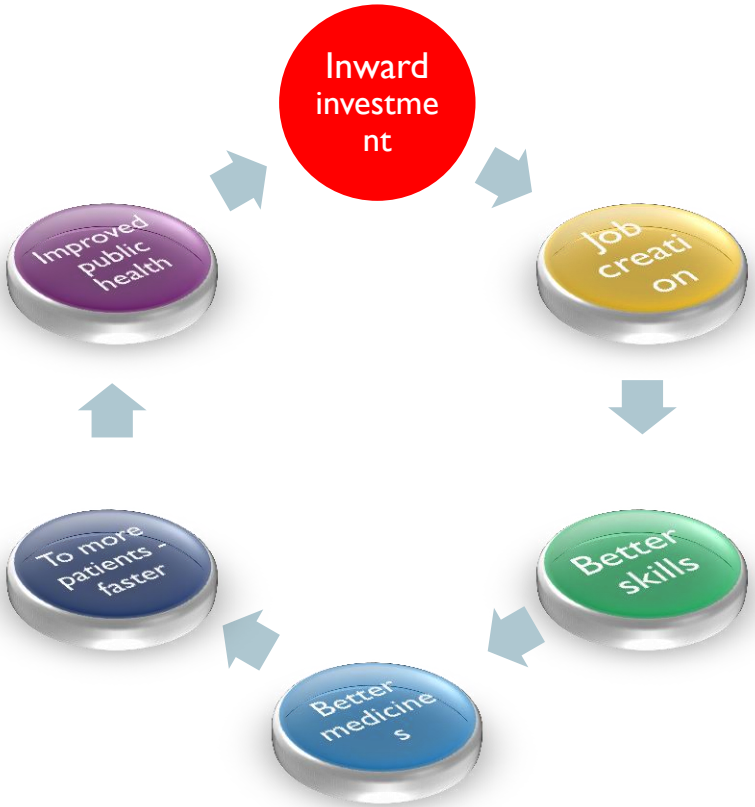
Europe effectively facing societal challenges ➔
Need for new adapted and medical solutions / technology for growing patients unmet needs

- Active and healthy aging
- Antimicrobial resistance
- Pediatric Drugs
- Availability of clinical trials for all diseases including Rare Diseases

Europe 2020

Innovative Europe ➔
Deliver medical innovations and new technologies focusing on European patients needs
Medicines of Tomorrow

- Personalised Medicines
- Biotechnology & Nanobiotechonology
- Changing Development Paradigm

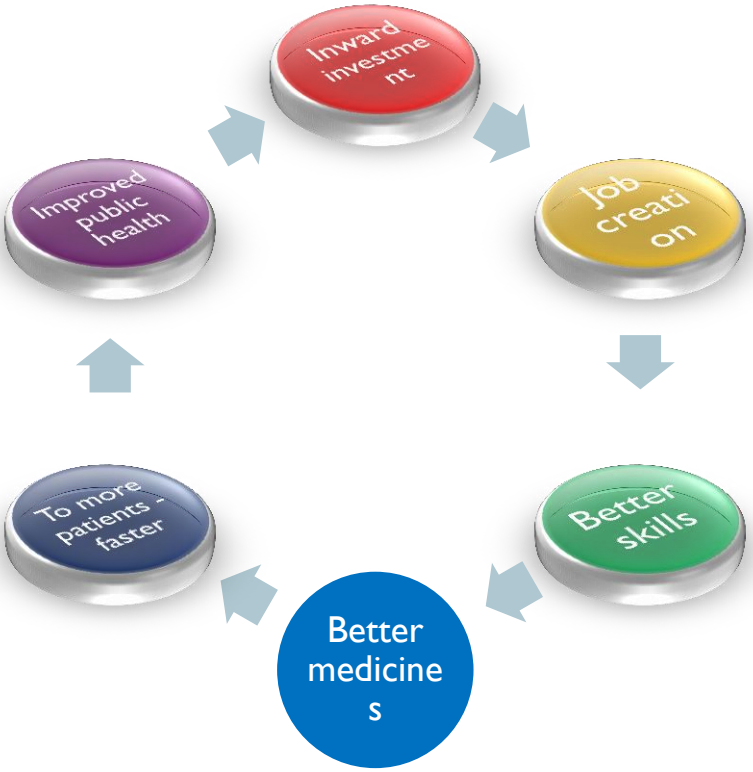


Europe 2020

Medical Research Community's Expectations

➔

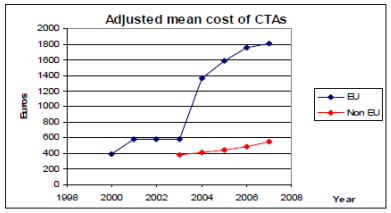
- Ability to participate in development of the EU medical and clinical knowledge
- Reduce excessive administrative requirements
- Participate in cutting-edge research and exchange with global scientific communities
- Stop brain drain
- Commercial and Academic sponsors depend on each other



After the EU Directive…

Conference on the
Impact on Clinical Research of European Legislation
Results & Discussion
Diamant Centre, Brussels, Belgium

COST OF CTAs

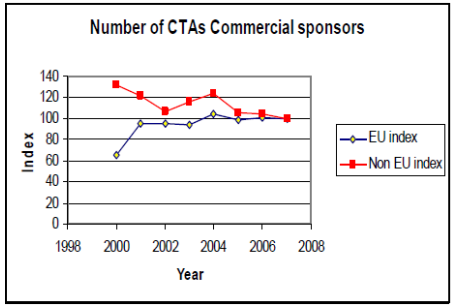


Mean cost in 2003	491,13 €
Mean cost in 2007	1633,23 €
Increase (2007 / 2003)	**+ 232.5%**

Dr. Gonzalo Calvo, 2 December 2008
Impact on competent authorities

Conference on the
Impact on Clinical Research of European Legislation
Results & Discussion
Diamant Centre, Brussels, Belgium

NUMBER OF CTA SUBMITTED BY COMMERCIAL SPONSOR (II)



OVERALL

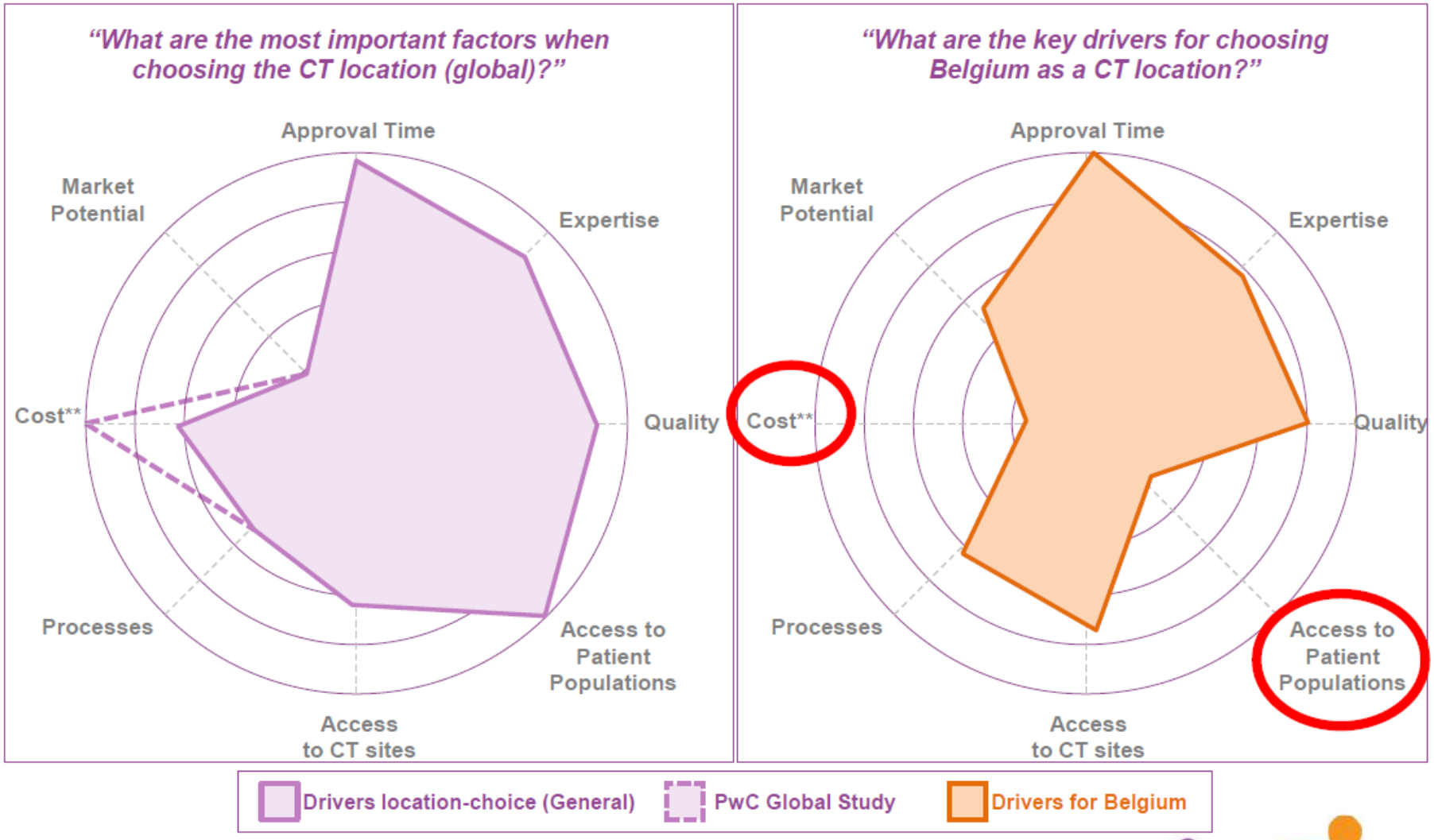
EU
- Total CTA 2003 = 7240
- Total CTA 2007 = 7735

Non EU
- Total CTA 2003 = 214
- Total CTA 2007 = 184

Dr. Gonzalo Calvo, 2 December 2008
Impact on competent authorities

-Increase of administrative burden
- Decline in the number of CT

General drivers for location choice vs. drivers for choosing Belgium*

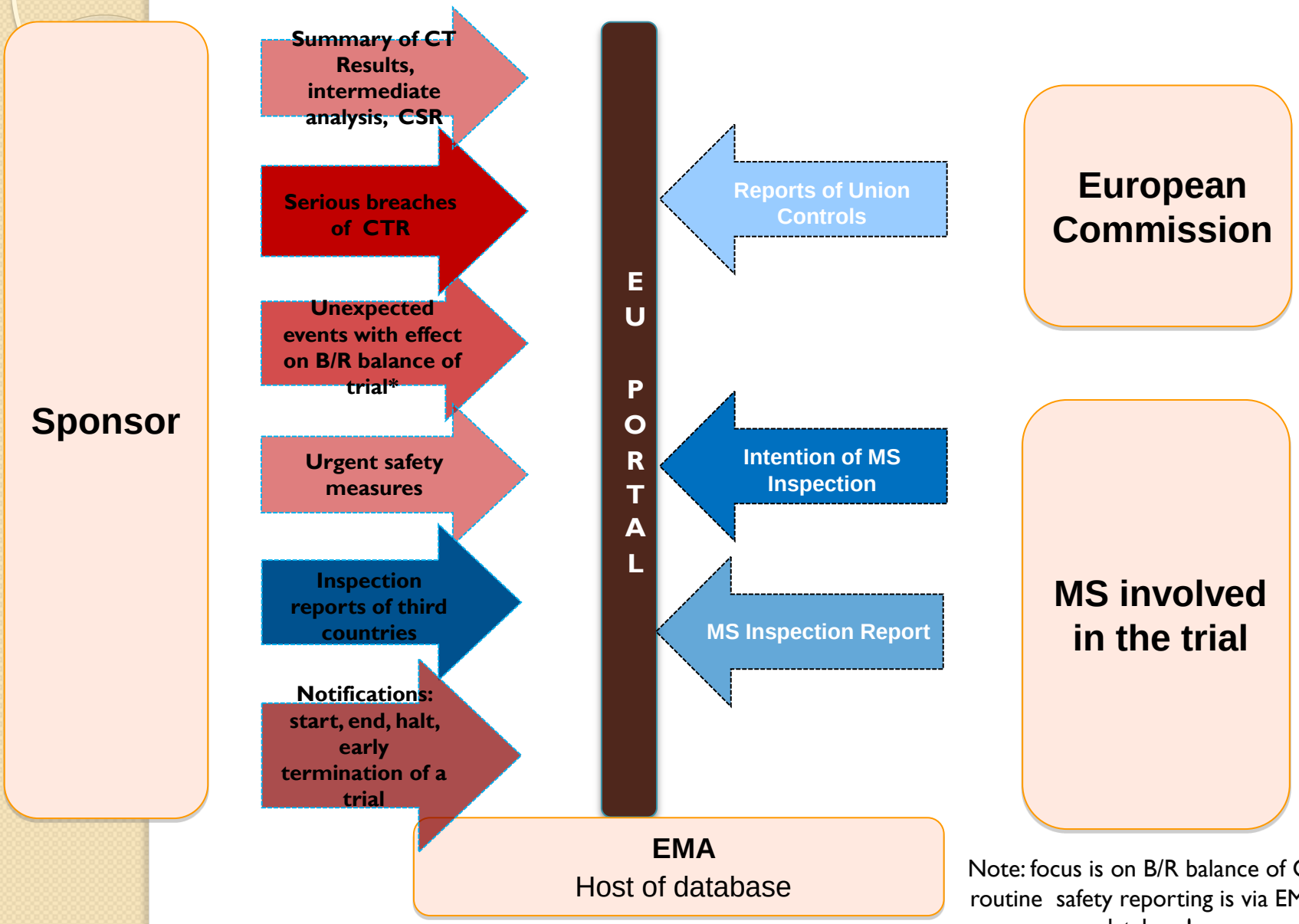


* *Chart depicts relative values, not absolutes*

** *PwC global study shows cost to be a highly critical factor*

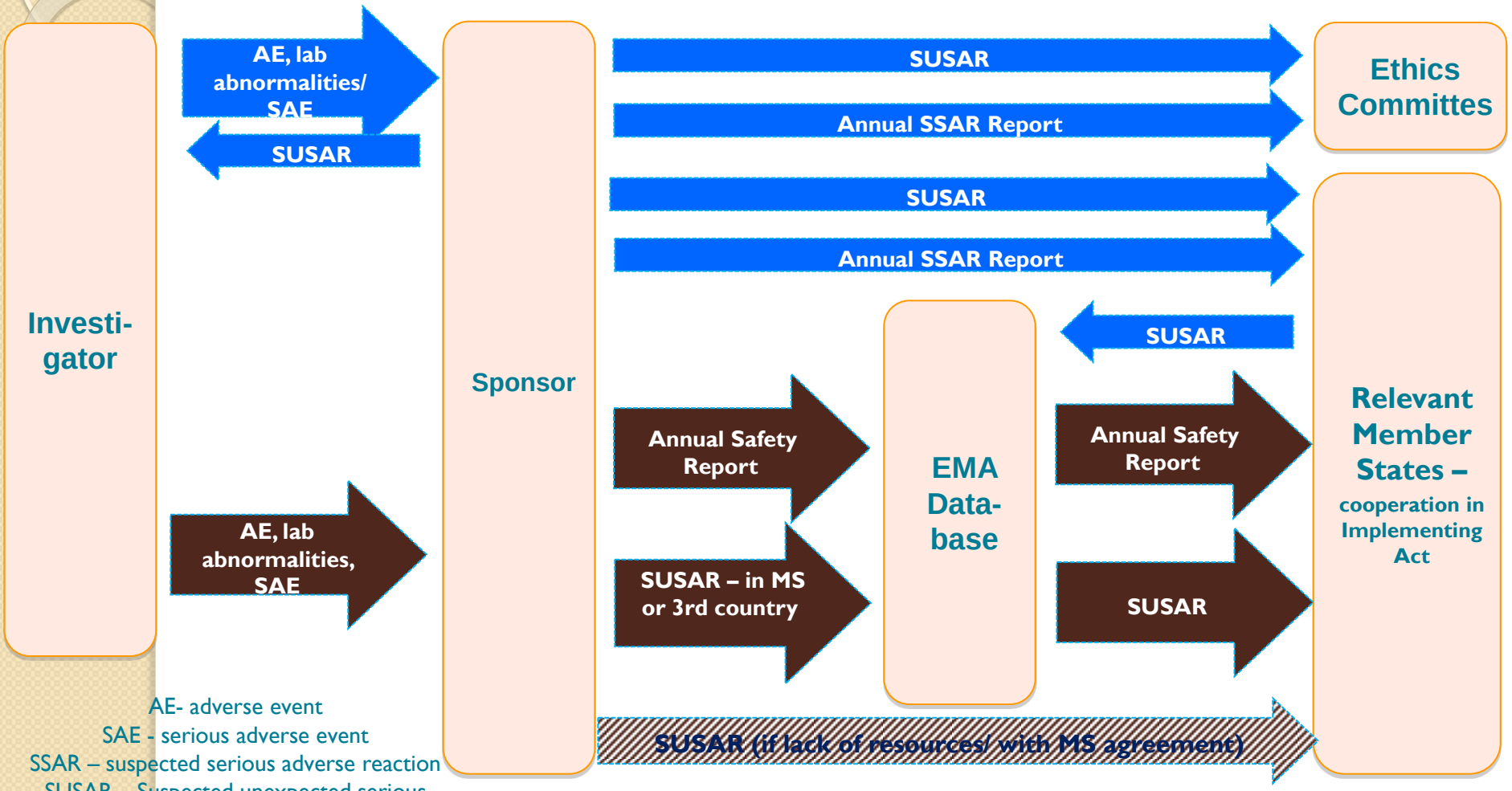
the Belgian pharmaceutical conference

EU Portal Exchange of Additional Info



Note: focus is on B/R balance of CT, routine safety reporting is via EMA database!

Safety Reporting Comparison CTD - CTR



AE- adverse event
SAE - serious adverse event
SSAR – suspected serious adverse reaction
SUSAR – Suspected unexpected serious adverse reaction (classification by sponsor!)

Clinical Trials Directive – CTD/ Regulation - CTR