EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The Clinical Trials Regulation EU No 536/2014: and Phase I trials

EUFEMED, Brussels, 20 May 2015

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Head, Inspections and Human Medicines Pharmacovigilance

A little bit of history

- 1965 - Directive 65/65/EC founds European pharmaceutical legislation but excludes medicines used for research purposes from its scope
- 1990 - EC GCP published
- 1991 - Directive 91/507/EC studies included in MAA to be run to GCP
- 1991 - Commission discussion paper on a future clinical trials legislation
- 2001 - Directive 2001/20/EC published includes clinical trial authorization and GCP and GMP requirements for IMPs in European Pharmaceutical legislation
- 2004 - Directive 2001/20/EC comes into force
- 2012 - Commission proposal for a Regulation on clinical trials
- 2014 - Regulation (EU) N0. 536/2014 is published

And now …….Europe's opportunity to enhance its global status as the base for innovation in clinical research and medicines development

- Phase I trials in EU – data from EudraCT
- Clinical Trial Regulation and EU portal and database
- EU portal and database and Phase I trials – other aspects

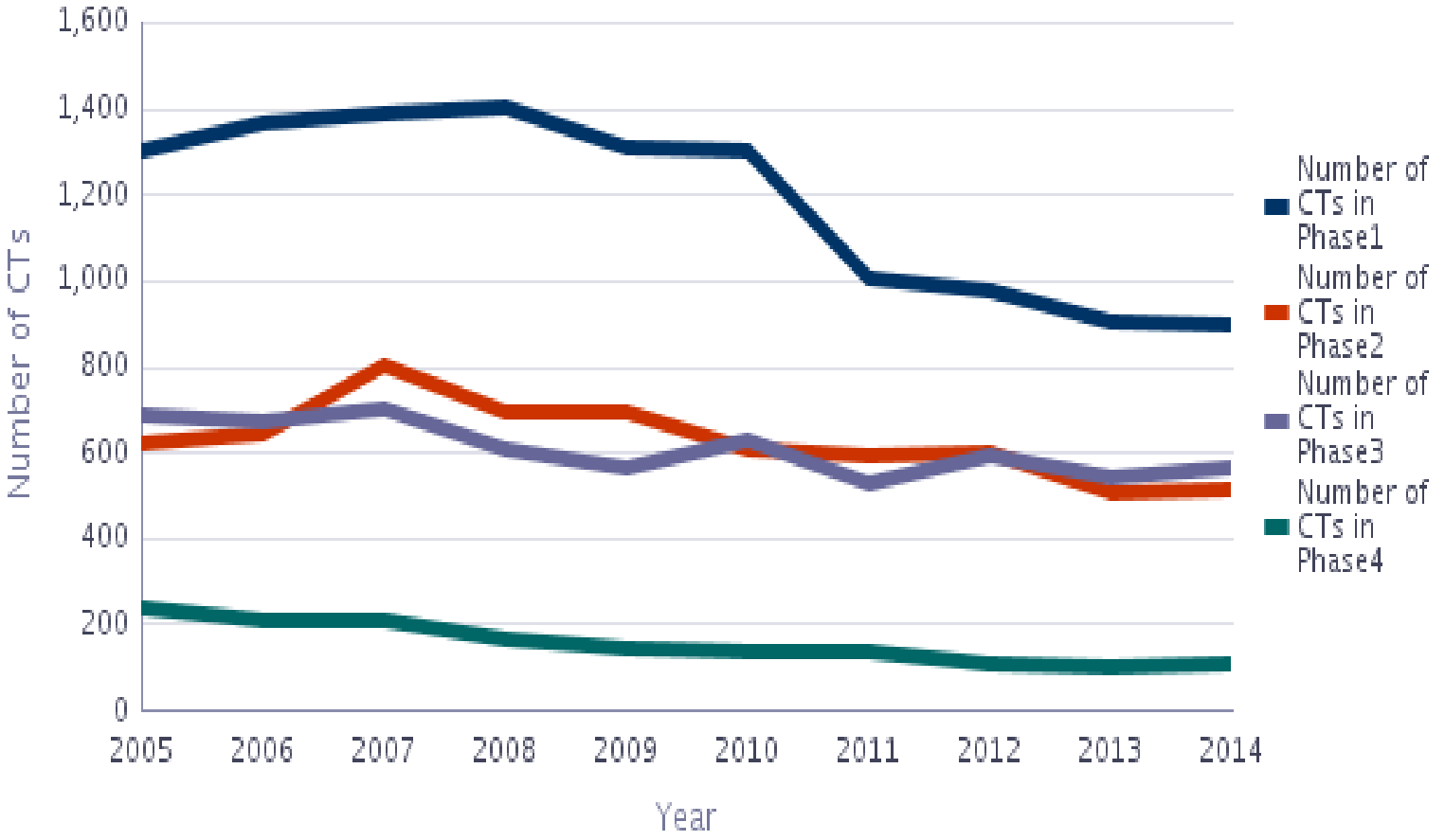
Phase I trials in EU – data from EudraCT

Clinical Trial Regulation and EU portal and database

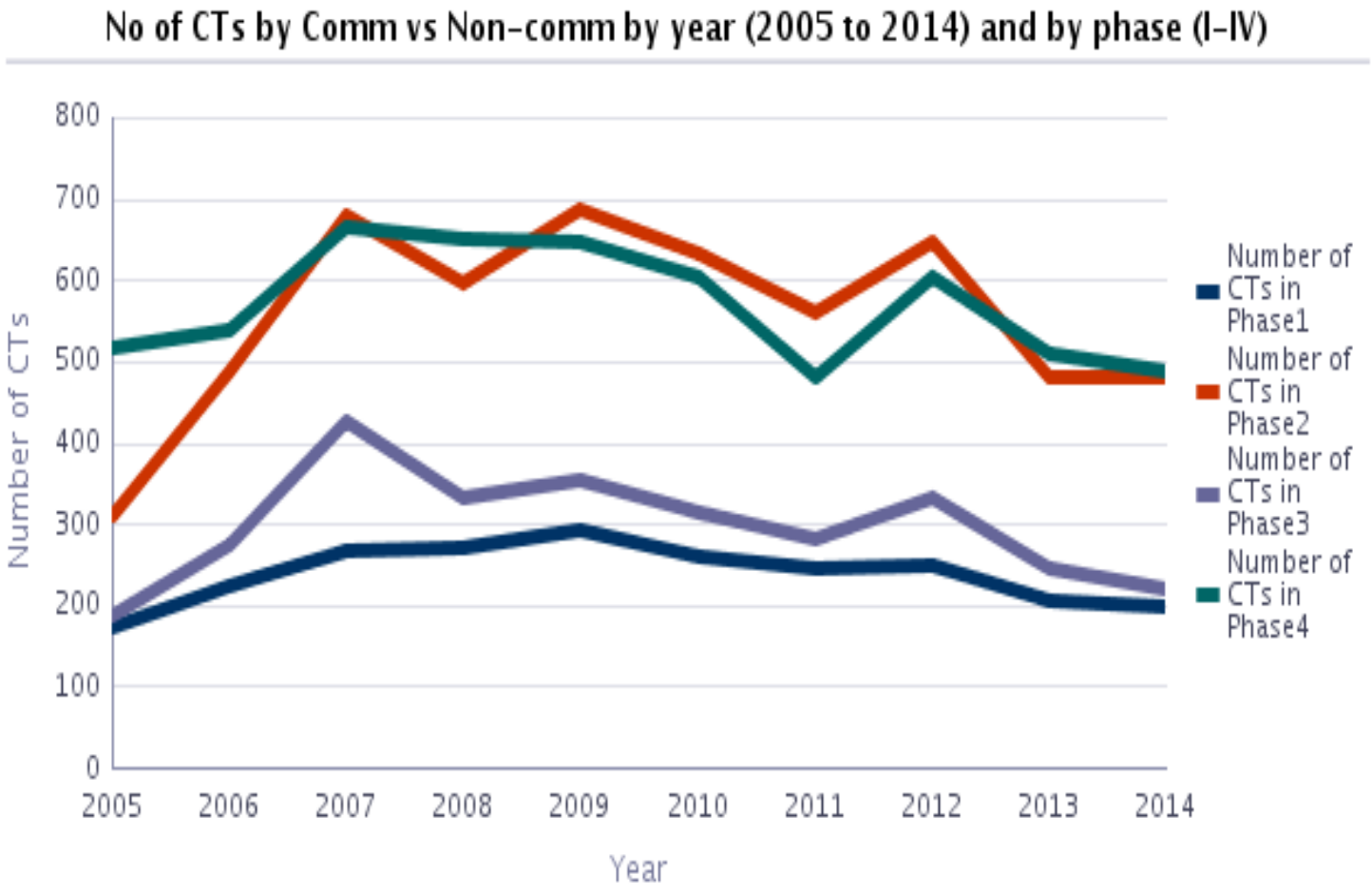
EU portal and database and Phase I trials

Sponsor Status Commercial

No of CTs by Comm vs Non-comm by year (2005 to 2014) and by phase (I-IV)



Sponsor Status Non-Commercial



Clinical Trials per Number of Member States Involved and Year, Commercial Sponsor

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	Number of Member States Involved																									Total
Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	
2005	1,873	251	174	102	94	65	71	44	32	19	26	16	5	8	8	1	5	1								2,795
2006	1,892	222	139	117	96	78	72	43	33	31	25	16	18	15	11	5	6	4	4	2	2	1		1		2,833
2007	1,937	237	159	137	94	88	69	69	50	35	33	28	19	21	15	6	2	7	1	2	2	1		1		3,013
2008	1,754	226	153	119	97	85	70	59	46	37	31	30	18	14	11	7	6	5	3	3		3	2	3		2,782
2009	1,665	201	174	111	96	91	65	53	47	25	27	18	26	9	18	3	7	3	3	4	1				1	2,648
2010	1,566	193	158	96	112	87	72	57	60	36	39	17	23	8	11	7	11	9	6	7	3	2	1		1	2,582
2011	1,228	194	143	103	121	70	65	66	64	38	23	23	15	14	12	5	4	3	3				1			2,195
2012	1,292	160	129	119	99	79	61	61	42	43	29	18	22	10	12	11	5	2	2	1		2	2	1		2,202
2013	1,105	170	116	116	78	81	90	53	40	25	21	12	19	16	10	9	4	1	2	3	2	1	1			1,975
Grand Total	**14,312**	**1,854**	**1,345**	**1,020**	**887**	**724**	**635**	**505**	**414**	**289**	**254**	**178**	**165**	**115**	**108**	**54**	**50**	**35**	**24**	**22**	**10**	**10**	**7**	**6**	**2**	**23,025**

al Trials per Number of Member States Involved and Year, Non-Commercial

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	Number of Member States Involved																Total
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
2005	1,094	35	17	8	7	6	4	2	1			2					1,176
2006	1,387	50	19	11	7	3	6	3	2				1	1			1,490
2007	1,903	56	34	15	2	1	4	1	1	1	2		1				2,021
2008	1,768	34	21	14	8	3	1	1									1,850
2009	1,873	44	19	10	4	5		2	2	1		1				1	1,962
2010	1,706	38	19	9	2	4	4	1	3		2	1		1	1		1,791
2011	1,460	31	17	9	7	3	8	3	1	1	1						1,541
2012	1,700	43	22	12	10	4	1	3	1	1	4						1,801
2013	1,309	37	20	9	6	3	5	3	1	1							1,394
l Total	**14,200**	**368**	**188**	**97**	**53**	**32**	**33**	**19**	**12**	**5**	**9**	**4**	**2**	**2**	**1**	**1**	**15,026**

Planned Patients by Year by Phase by Sponsor Status (F.4.2.1)

This report contains the number of Planned Patients by Year, by Phase and by Sponsor Status in the EEA (section F.4.2.1)
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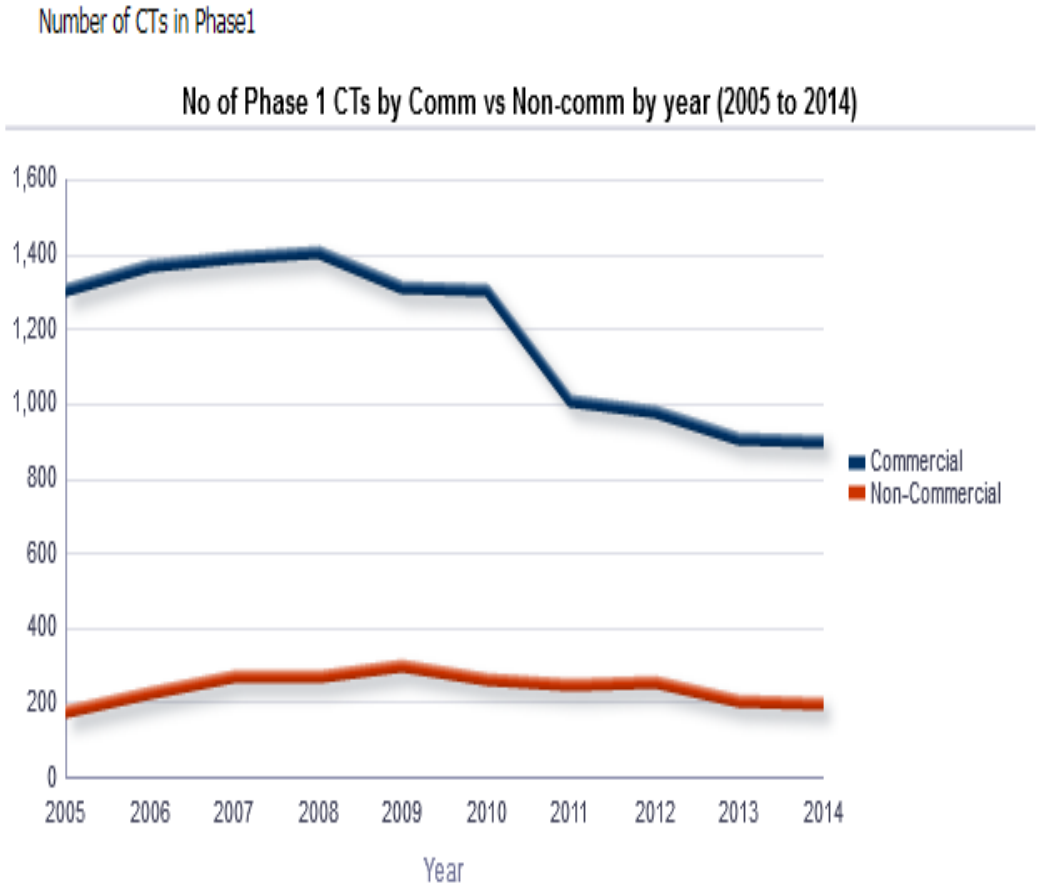
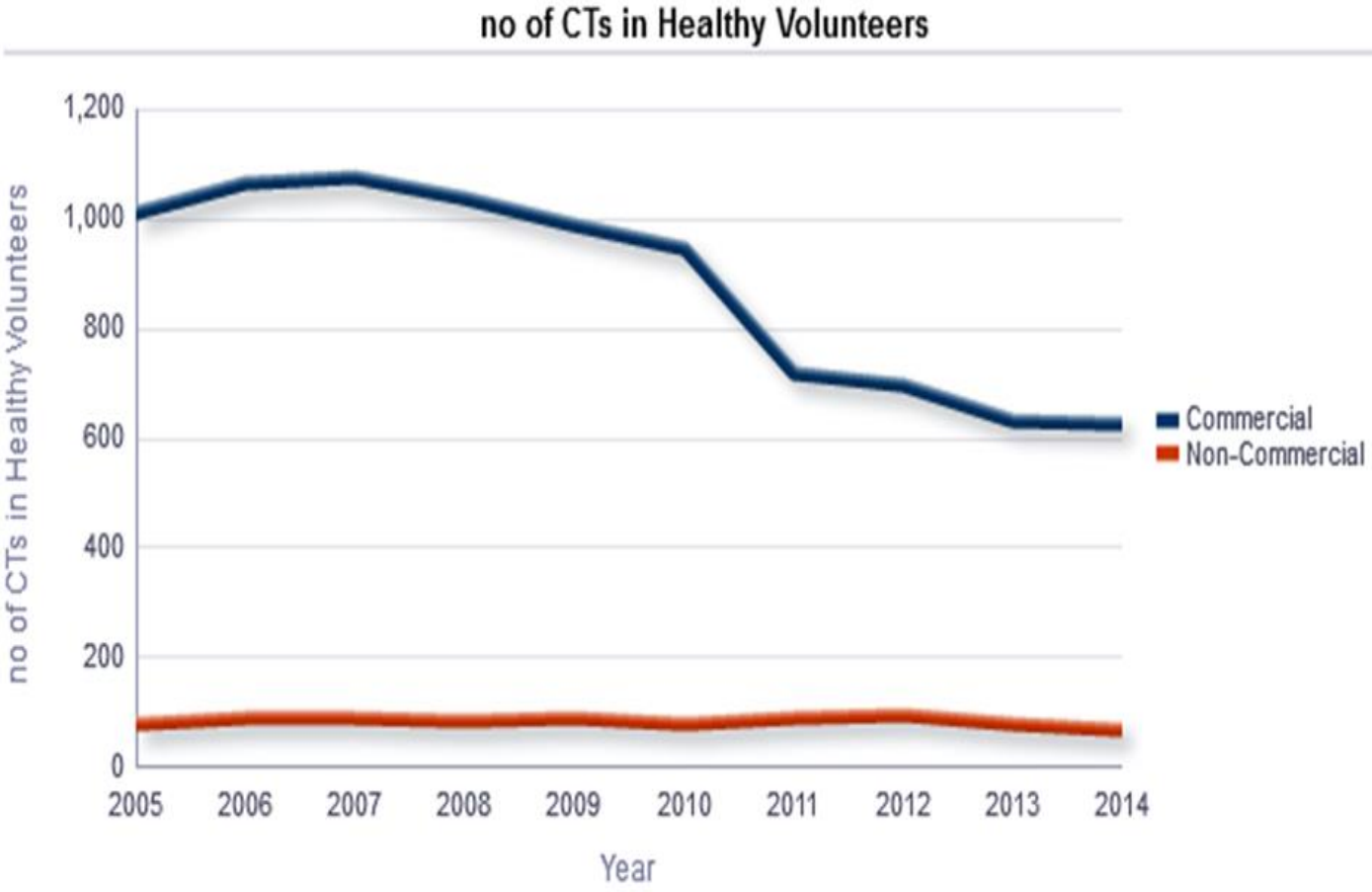
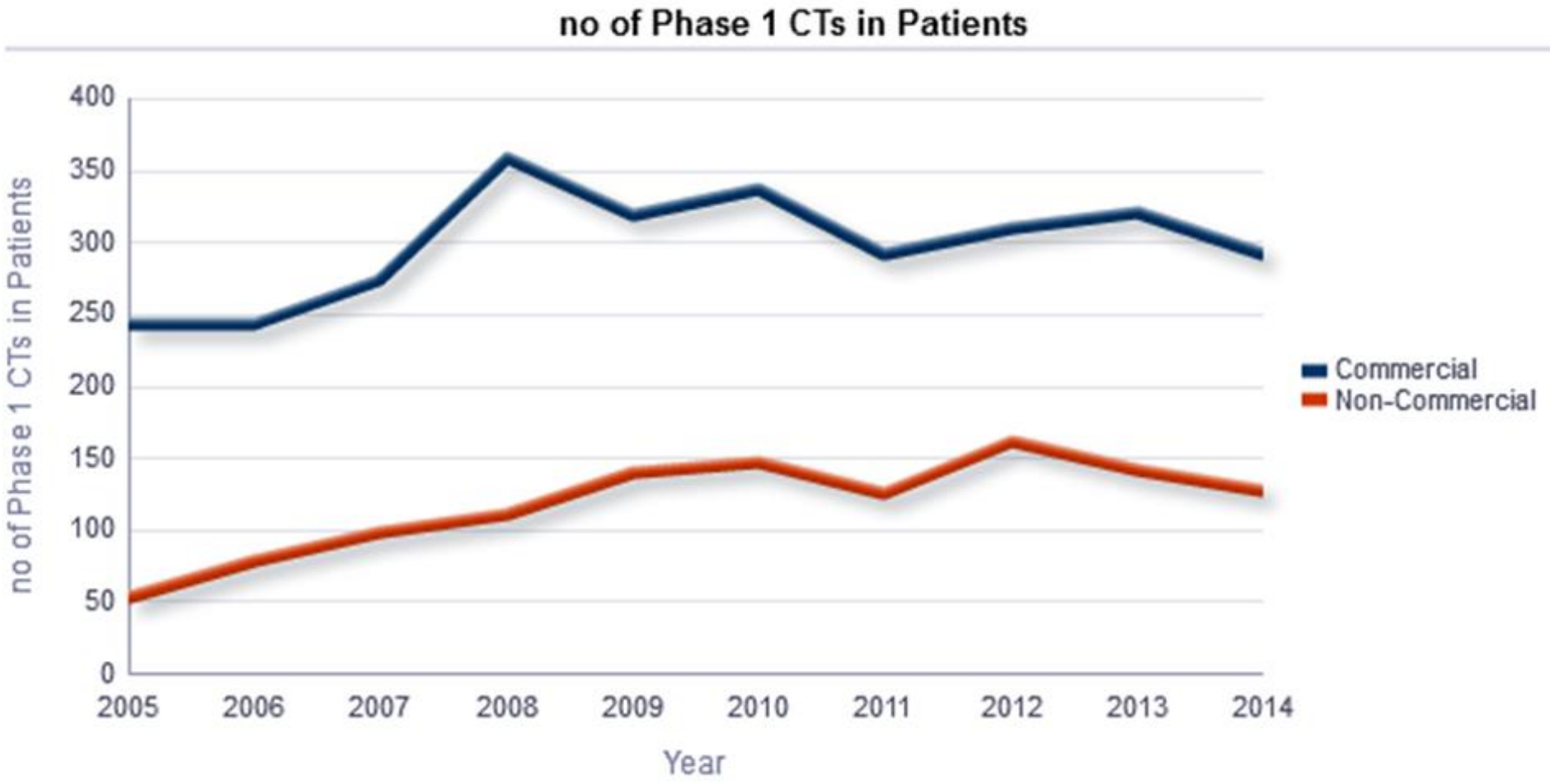
	B.3.1 and B.3.2 Sponsor Status	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Grand Total
Phase I_EEA	Commercial	14,346	27,451	28,346	17,716	23,032	21,764	23,948	14,936	12,054	12,018	12,101	4,021	211,733
	Non-Commercial	446	5,485	5,452	2,703	2,178	2,587	7,419	2,865	2,469	2,242	2,292	580	36,718
	Not Answered	0	273	301	68	70	150	188	60	90	0	24	20	1,244
Phase I_EEA Total		**14,792**	**33,148**	**34,086**	**20,479**	**25,280**	**24,501**	**31,525**	**17,861**	**14,613**	**14,260**	**14,417**	**4,601**	**249,563**
Phase II_EEA	Commercial	32,713	56,756	73,214	75,734	59,976	63,774	53,584	48,710	47,569	38,001	35,929	14,679	600,639
	Non-Commercial	1,694	17,637	15,246	13,888	8,336	12,292	10,985	15,066	12,761	19,132	14,604	6,187	147,828
	Not Answered	270	695	370	140	625	107	168	1,372	150	100	16		4,013
Phase II_EEA Total		**34,677**	**75,088**	**88,730**	**89,732**	**68,937**	**76,113**	**64,617**	**64,778**	**60,480**	**57,133**	**50,549**	**20,866**	**751,700**
Phase III_EEA	Commercial	160,129	239,014	255,223	320,569	244,424	182,365	222,201	149,918	179,709	192,235	158,976	31,434	2,336,197
	Non-Commercial	14,080	50,278	61,547	61,357	29,962	35,644	51,493	33,356	34,570	47,067	29,043	12,328	460,725
	Not Answered	1,136	965	703	220	298	334	403	5,051	202	0	0		9,312
Phase III_EEA Total		**175,091**	**283,968**	**317,103**	**382,076**	**274,624**	**218,343**	**274,097**	**187,065**	**214,481**	**239,302**	**188,019**	**43,762**	**2,797,931**
Phase IV_EEA	Commercial	14,390	51,468	70,447	69,481	36,585	32,265	27,556	32,994	15,473	33,347	20,469	12,985	417,460
	Non-Commercial	5,057	51,057	34,863	49,254	17,105	37,276	31,507	63,567	33,800	35,392	32,376	8,208	399,462
	Not Answered	0	180	697	306	275	4,452	1,176	7,212	2,160	0	264	0	16,722
Phase IV_EEA Total		**19,447**	**102,645**	**105,957**	**119,041**	**53,940**	**69,663**	**59,905**	**103,383**	**51,433**	**68,739**	**53,109**	**21,193**	**828,455**

No of phase 1 CTs by Comm vs Non-comm by year (2005 to 2014)

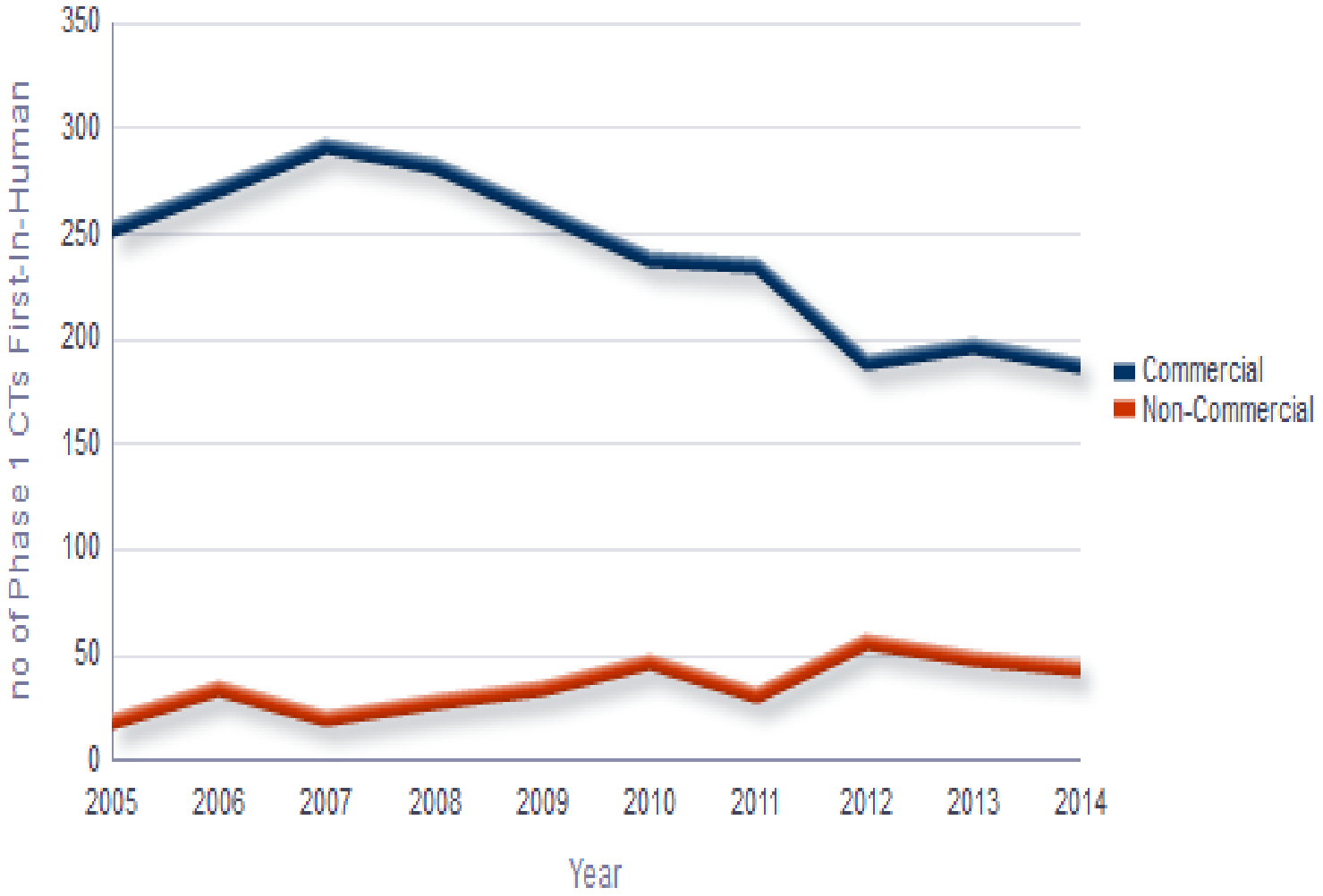


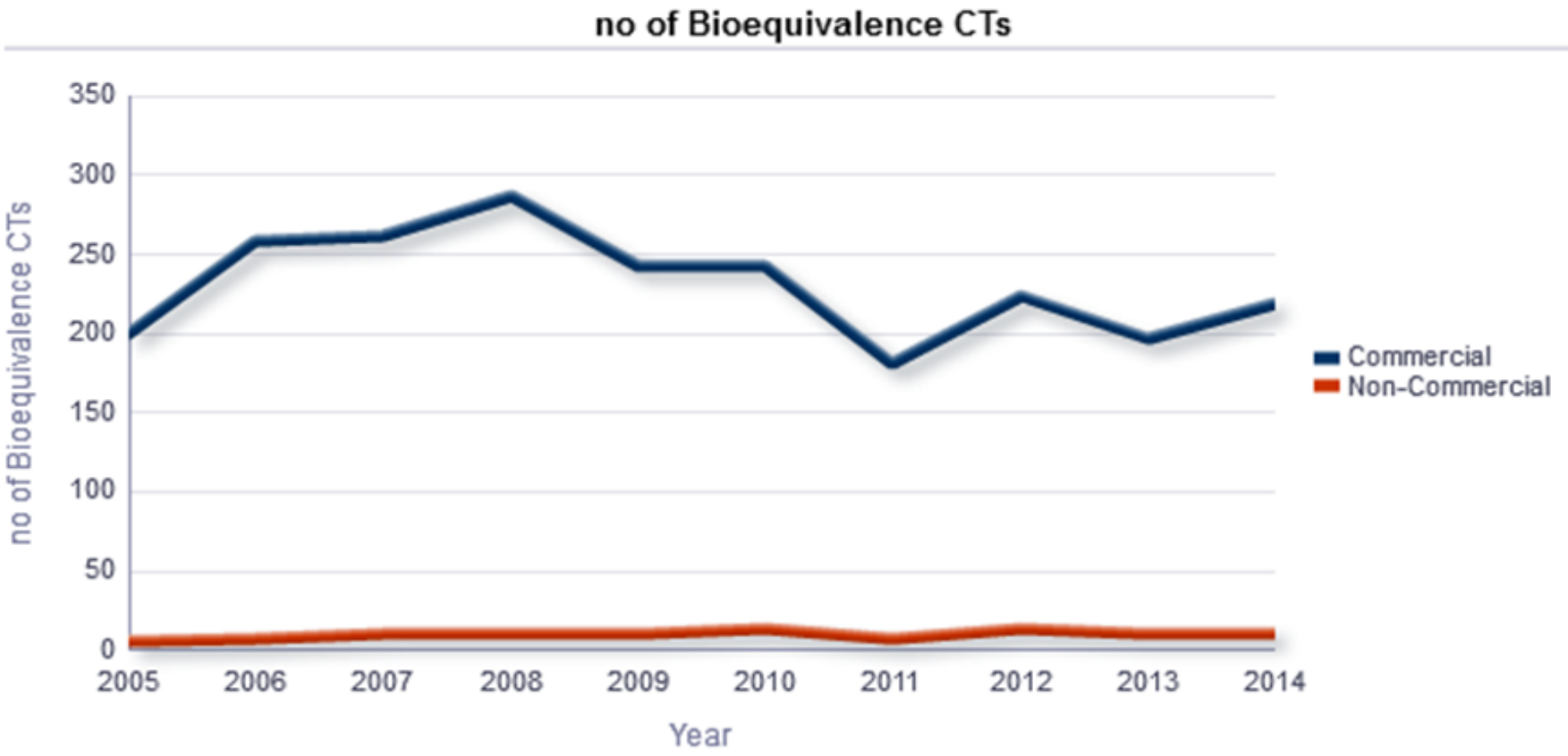
Year	Sponsor Status	Number of CTs in Phase1
2005	Commercial	1,300
	Non-Commercial	175
2006	Commercial	1,369
	Non-Commercial	223
2007	Commercial	1,392
	Non-Commercial	268
2008	Commercial	1,405
	Non-Commercial	271
2009	Commercial	1,310
	Non-Commercial	295
2010	Commercial	1,306
	Non-Commercial	262
2011	Commercial	1,004
	Non-Commercial	247
2012	Commercial	979
	Non-Commercial	251
2013	Commercial	905
	Non-Commercial	206
2014	Commercial	901
	Non-Commercial	199
Grand Total		**14,268**


no of CTs in Healthy Volunteers
1,200
1,000
800
600
400
200
0
no of CTs in Healthy Volunteers
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Year
Commercial
Non-Commercial

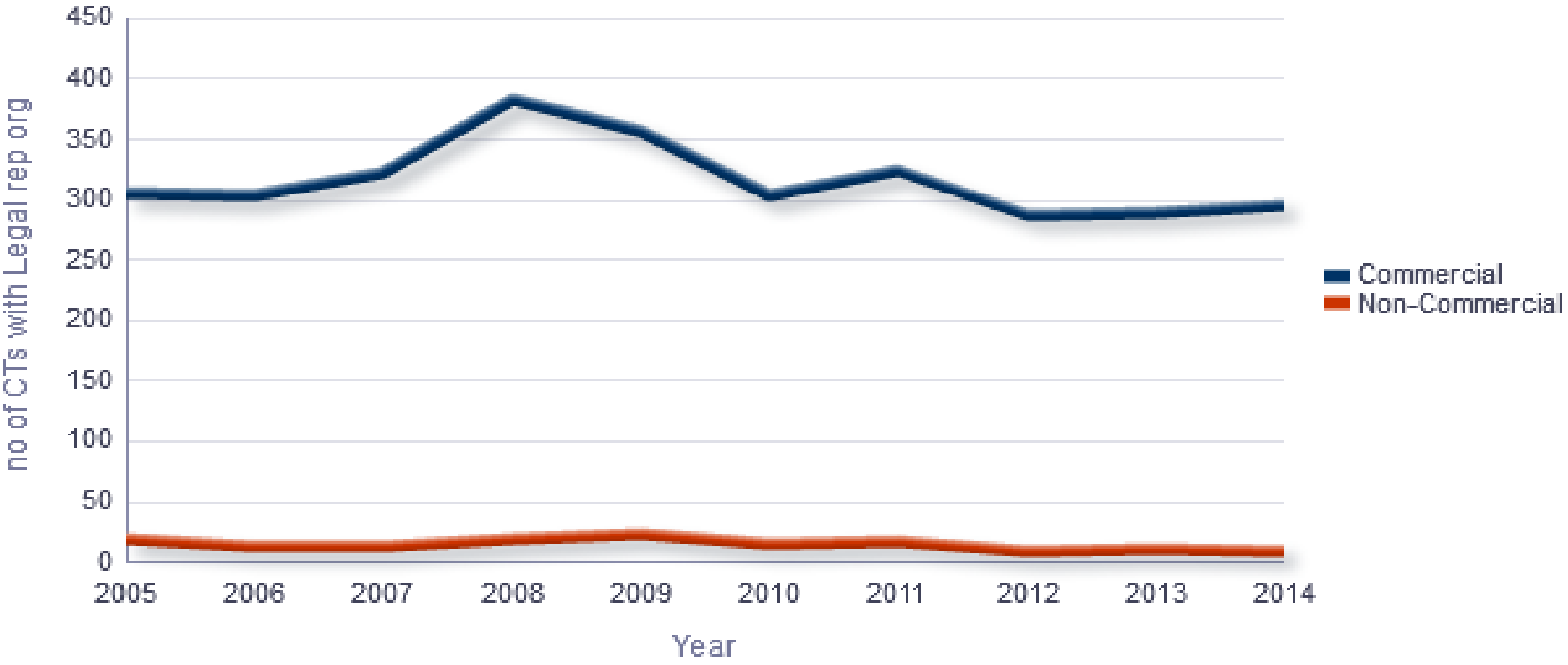

no of Phase 1 CTs in Patients
no of Phase 1 CTs in Patients
400
350
300
250
200
150
100
50
0
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Year
Commercial
Non-Commercial

no of Phase 1 CTs First-In-Human




no of Bioequivalence CTs
no of Bioequivalence CTs
350
300
250
200
150
100
50
0
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Year
Commercial
Non-Commercial

no of CTs with Legal rep org



Phase I trials in EU – data from EudraCT

Clinical Trial Regulation and EU portal and database

EU portal and database and Phase I trials

Regulation Key components and objectives

- Scope (unchanged) – interventional clinical trials of medicinal products
- Single EU portal and database to support:
  - One application dossier for each clinical trial or modification to it
  - Coordinated approach to clinical trial authorization and supervision
  - Transparency of clinical trial authorization, conduct and results
- Protection of trial subjects, including special provisions to enable trials in emergency situations and cluster trials
- Streamlined safety reporting for SUSARs and Annual Safety Reports
- Proportionate approach to trial supervision and conduct

Single EU portal and database

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One clinical trial application form and supporting dossier to cover:

- One or more Member States, and all regulatory and ethics assessment
- Public registration of the trial and its subsequent updates, including the necessary elements of international registration at WHO ICTRP portal
- Providing the trial design elements to support subsequent entry and publication of the summary of results

EU substance and product numbers to identify products and substances to underpin linking and aggregation of information on IMPs (with MA via art 57, without MA EU number provided via CT system before or during CT assessment)

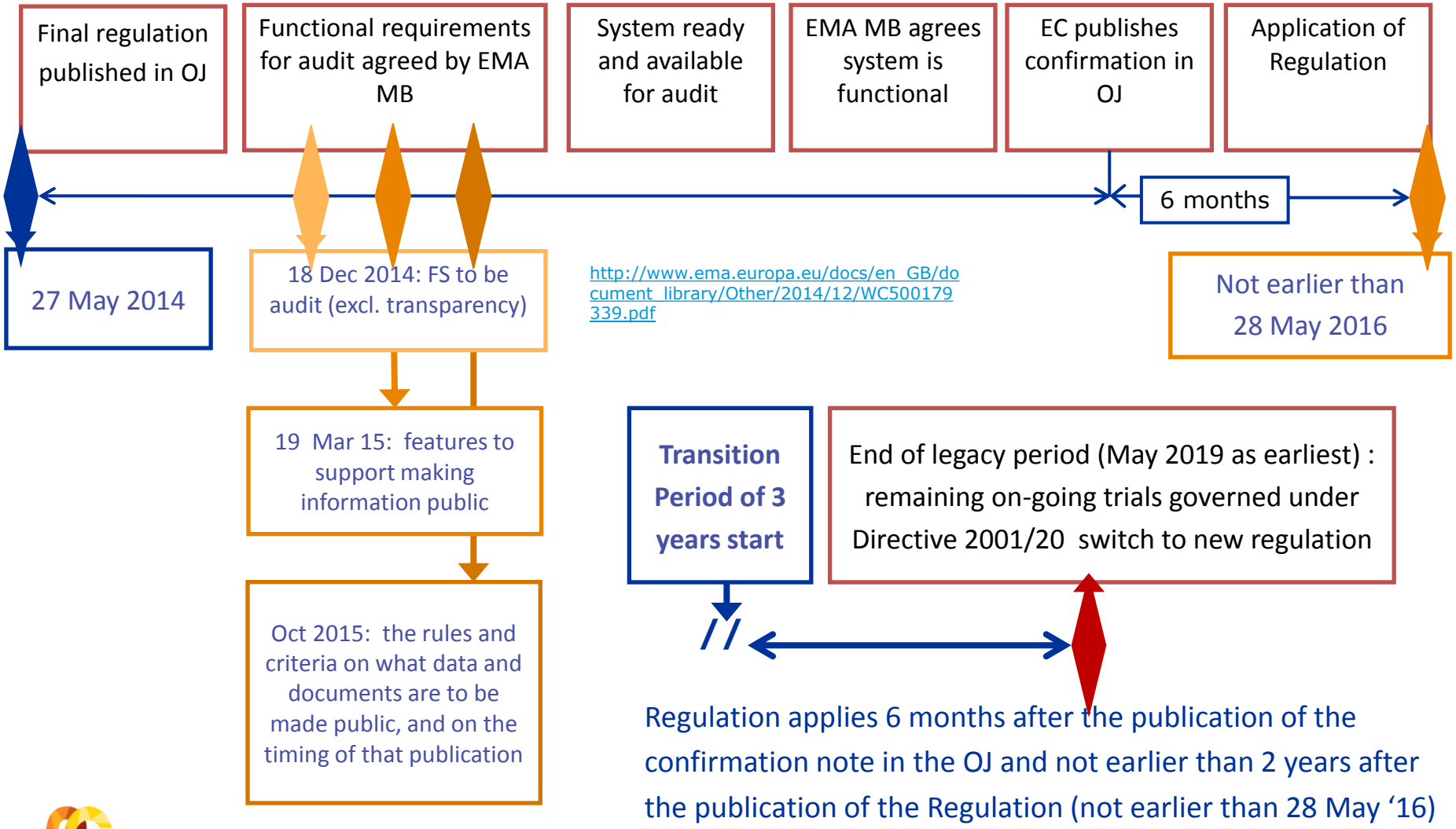
EU trial number – one per trial

Authorisation procedure

- Part I – including joint assessment for trial in more than one MS (role of the RMS) + Part II national part
- Single assessment of Part I with single set of questions and responses and single outcome, regardless of the number of MS involved (1-28),
- Combines and consolidates best expertise of the MS involved
- Strictly defined timelines
- Ethics committees involved in the assessment in parts I and II as applicable according to the law of the MS concerned (no derogation from timelines)
- Single decision per MS (including regulatory and ethics review) in line with coordinated assessment of Part I
- Tacit approval if the MS fails to comply with deadline

Clinical Trial Programme

CT regulation timelines/key milestones

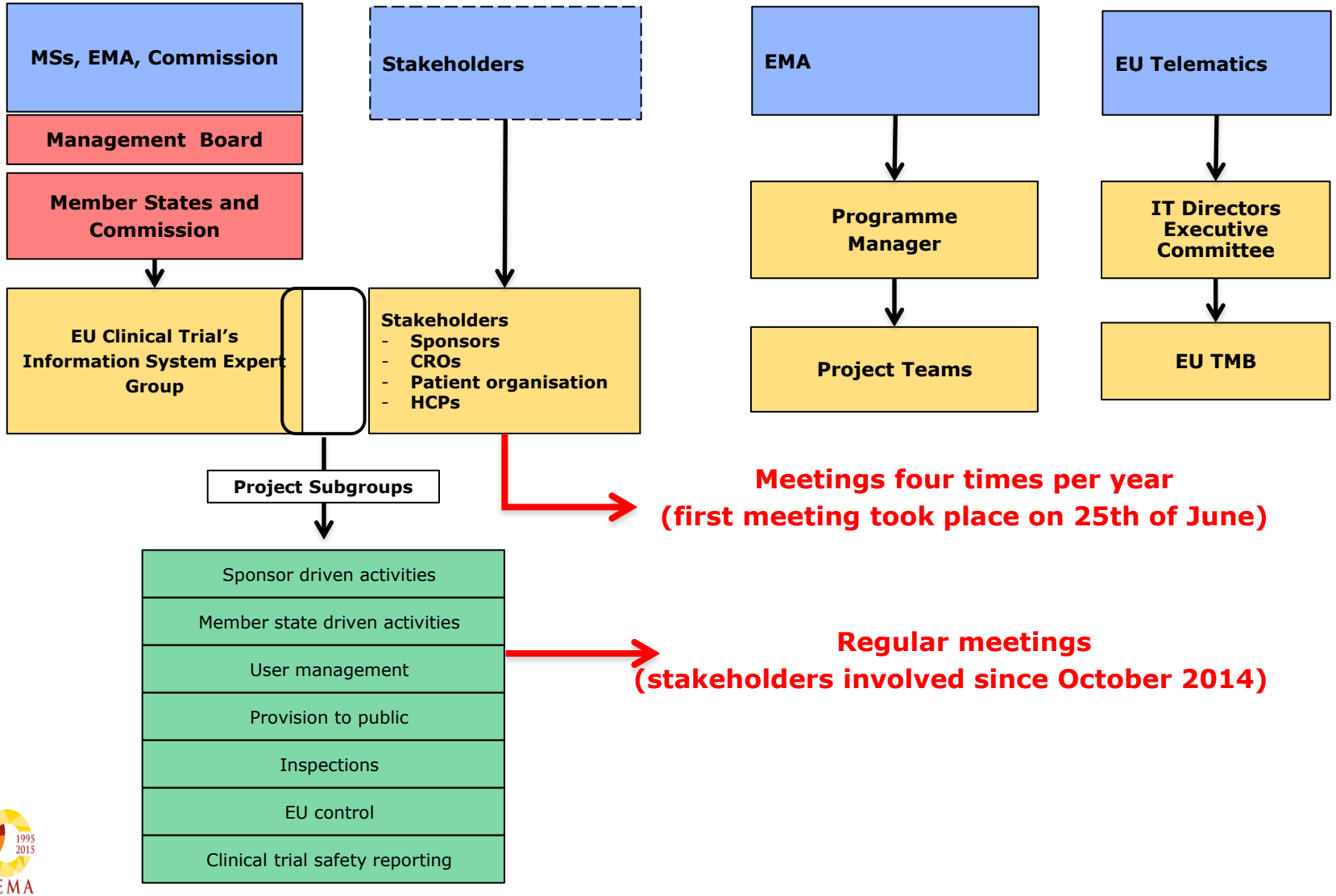


Clinical Trial Programme

The Agency has to deliver, maintain and update the IT platforms needed for the implementation as required by regulation:

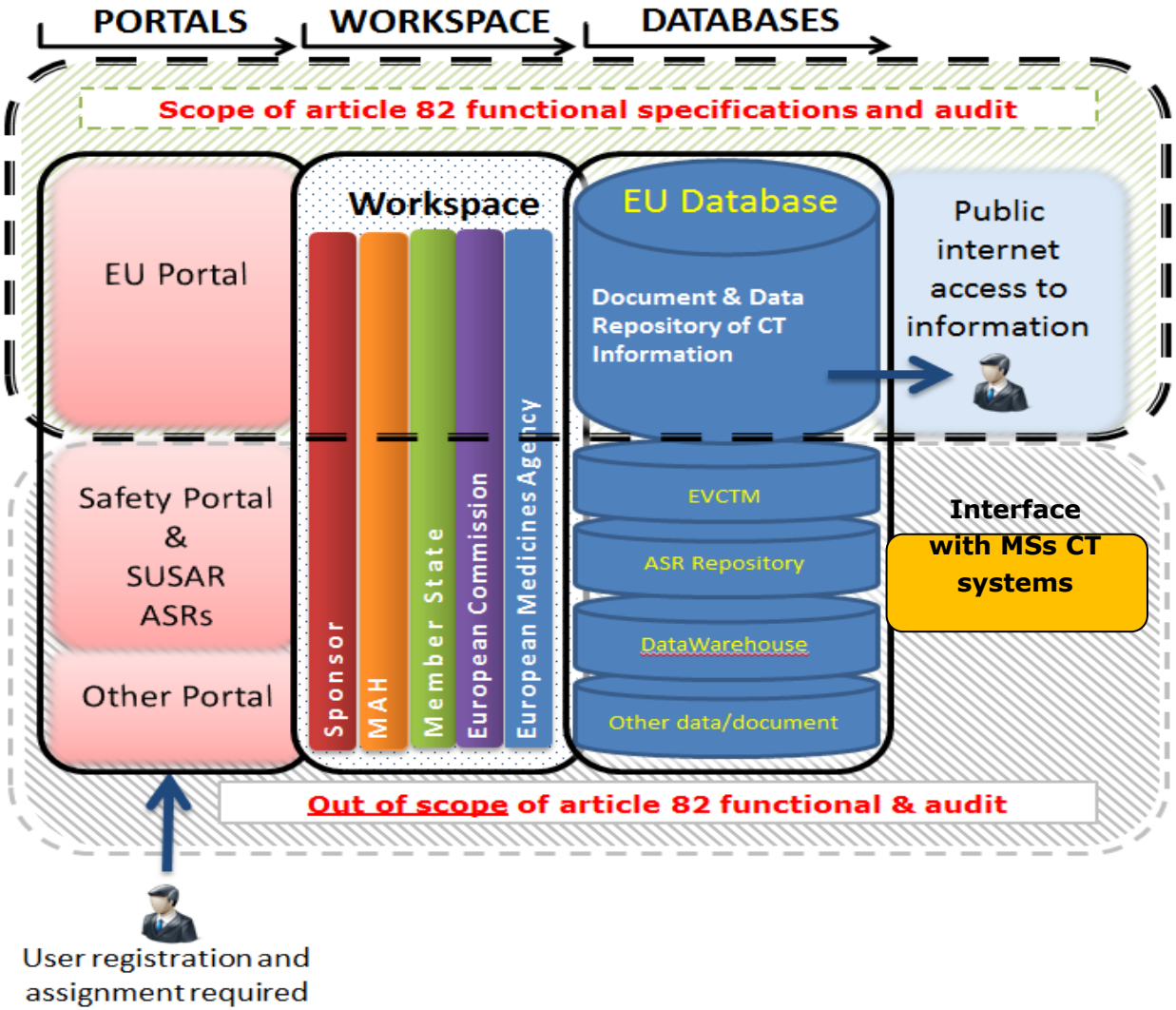
- EU portal and database and medicinal product dictionary (Art. 80, 81, 82 and 84)
- Safety reporting (Art. 40 and 44)
- EudraCT and EU CTR legacy (Art. 98)
- A data warehouse is considered part of these projects to facilitate the reporting and link of CT related information within each system or among them.

CT Programme: governance

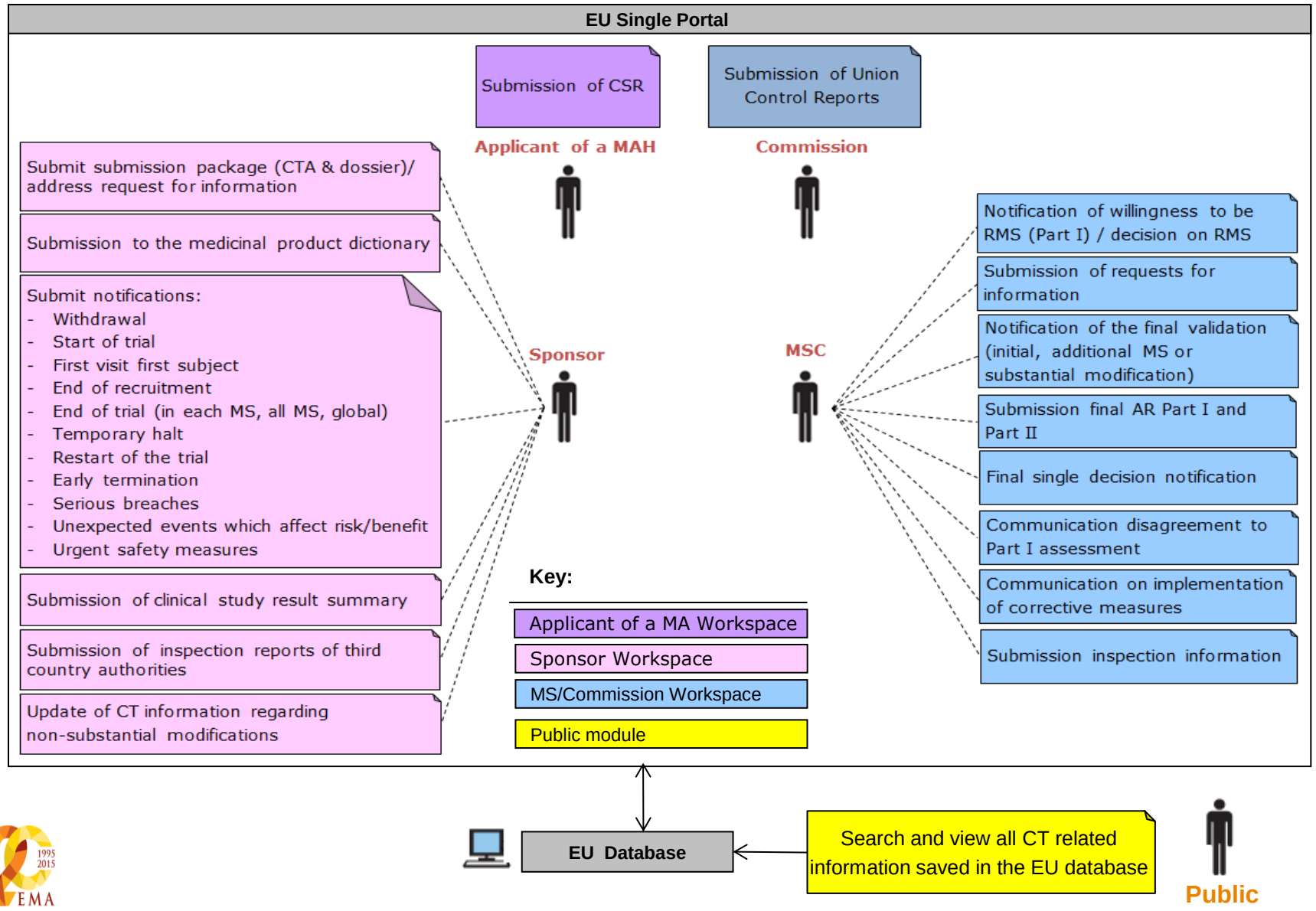


EU portal and database

CT Programme: medium level view



EU portal and EU database: "To be" process



Transparency legal requirements: Clinical Trials Regulation

Article 81(4) of Regulation (EU) No. 536/2014

- EU database publically accessible by default, with exceptions justified on any of the following grounds:
  - Protection of personal data;
  - Protection of commercially confidential information in particular taking into account the MA status of the medicinal product, unless there is an overriding public interest in disclosure;
  - Protecting confidential communication between MS in relation to the preparation of the assessment report;
  - Ensuring effective supervision of the conduct of a clinical trial MSs.

Clinical Trials Regulation: public disclosure of information

- Have all clinical trials been publicly registered?
- Is there a trial in which I could participate?
- What was the outcome of the trial I did participate in?
- What trials were the basis of the marketing authorisation, what were their results?
- What is known about the medicine I am taking/prescribing?
- Can we review the data used to support the marketing authorisation?
- Has the trial we are designing already been conducted? Were there problems with similar trials?

Functional specifications of EU portal and database

- Strike the right balance between:
  - respecting patients' and doctors' needs and the publics' entitlement to extensive and timely information about clinical trials;
  - and developers' and researchers' need to protect their investments;
  - a balanced approach is needed to protect public health and also foster the innovation capacity of European medical research.

Functional specifications of EU portal and database

- "Functional specifications for the EU portal and EU database to be audited" final published 19 December 2014
- "Draft proposal for an addendum, on transparency, to the 'functional specifications for the EU portal and EU database to be audited"
  - Public consultation from 21 January 2015 – 18 February 2015
- Seek stakeholders' views on the application of these exceptions set out in article 81 of the Regulation

What is being made public:

- At the time of decision on the trial:
  - the main characteristics of the trial (as set out in the clinical trial application form - being in effect a structured synopsis of the clinical trial protocol) – similar to what appears in EU CTR or clinicaltrials.gov
  - Information on investigator sites
  - the protocol summary
  - the conclusion on the assessment of Part I of the trial
  - the decision on the trial including reasons for refusal if the trial is not authorised (or where applicable the reason for its withdrawal)
  - the start of the trial

What is being made public:

- During the trial:
  - the first visit of the first subject in the trial in each MS concerned
  - substantial modification of the trial
  - temporary halt or early termination of the trial
  - notification on the end of recruitment in each MS concerned
  - end of the trial
  - other documents and notifications set out in Regulation (inspections, safety measures, serious breaches …)
- 12 months After the end of the trial:
  - summary clinical trial results and lay summary
- 30 days After Completion of the Marketing Authorisation process (whatever the outcome):
  - the clinical study report for trials authorised under the new Regulation and included thereafter in a MA dossier

What is being made public:

- All information in the database will be public with the exception of the IMPD quality/manufacturing section and its related assessments, and the financial contracts between investigators and sponsors
- Timing of release of details of phase I trials may be deferred until 12 months after the trial (and published with the summary results)
- Protocols, subject information sheets, IMPDs and investigator brochures, may be deferred differentially dependent on the nature of the IMP and of the trial
- Results of trials are proposed to be made public as foreseen:
  - 12 Months after the end of the trial – summary results and layperson summary
  - 30 days after the decision on marketing authorization or its withdrawal by the applicant – the clinical study report of trials authorized under this Regulation and included in a EU marketing authorization application (central or national)

Disclosure of information from the EU database
Three groups of clinical trials can be identified – based on the nature of the IMPs being studied and what is being studied

- Phase I trials in healthy volunteers and patients - include so called phase 0, BE and BA studies for novel product or generics/biosimilars, new formulations or indications
- Therapeutic (or prophylactic or diagnostic trials) in target population on indications or formulations outside of the authorised uses
- Post authorisation trials that are either phase IV within the terms of the Marketing Authorisation or are established medical practice in one of the Member States concerned (includes Phase IV and low-intervention trials)

Proposal regarding Information to be made public at the time of decision on the trial – possible deferral for Phase I trials in healthy volunteers (see 4.2.).

Proposed option for sponsor to choose to defer publication of major characteristics of the trial for Phase I, from the default "at time of decision on trial" (and updates during the trial), to the time of publication of the summary of results, 12 months post end of the trial

End of trial defined as: *Article 2(26) 'End of a clinical trial' means the last visit of the last subject, or at a later point in time as defined in the protocol;*

- Allow time for filing of patent applications. In addition timing of disclosure of protocol, subject information sheet, IMPD and IB till later point either at time of MA using that clinical trial or a fixed number of years after the end of the trial.
- Allow sponsors to undertake first steps with a new product or formulation with limited disclosure. But maintain public disclosure of clinical trial information and summary results.

Next steps

1. Revised section 6 of the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014" setting out technical features to support making information public was endorsed by Management Board on 19 March 2015.
2. EMA in close collaboration with the MSs and the European Commission will revise and agree the rules on transparency, i.e. the choices to be made on publication of information following the consultation.
3. The agreed rules will be submitted for endorsement in the October 2015 Management Board.
4. Perform a "Privacy Impact Assessment" in parallel

Phase I trials in EU – data from EudraCT

Clinical Trial Regulation and EU portal and database

EU portal and database and Phase I trials – other aspects

Non-EU sponsor - Article 74
Legal representative of the sponsor in the Union

1. *Where the sponsor of a clinical trial is not established in the Union, that sponsor shall ensure that a natural or legal person is established in the Union as its legal representative. Such legal representative shall be responsible for ensuring compliance with the sponsor's obligations pursuant to this Regulation, and shall be the addressee for all communications with the sponsor provided for in this Regulation. Any communication to that legal representative shall be deemed to be a communication to the sponsor.*

2. *Member States may choose not to apply paragraph 1 as regards clinical trials to be conducted solely on their territory…..provided that they ensure that the sponsor establishes at least a contact person on their territory in respect of that clinical trial who shall be the addressee for all communications with the sponsor provided for in this Regulation.*

Medicinal product dictionary

Phase I trials and in particular first in human trials will often be the first contact between a particular active substance/IMP and the EU medicinal product dictionary

Process for sponsor to register product and substance in dictionary – before the trial or as part of the clinical trial application

Substance and product numbers used as key for data quality linking trials, adverse reaction data and other information on medicines

User Access and management

- Sponsor applies for a clinical trial via the portal, or
- Sponsor designates a CRO to make application, CRO accesses portal,
- Sponsor (if registered) or CRO can delegate users and access to data and portal
- Sponsor can authorize cross reference to core documents initially filed with another clinical trial application

Conclusion

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A real opportunity for EU to innovate and to lead

- in clinical trial regulation and
- in innovation of new medicines and better use of existing medicines,

Streamlined, coordinated, proportionate and transparent

- Single electronic submission of data and documents to cover trial application, modification, registration and results reporting
- Streamlined and coordinated clinical trial between and within MS, using best expertise in the MS concerned
- Streamlined safety reporting,
- Proportionate supervision of clinical trials,
- Transparency supporting public confidence, participation and critique and enabling innovation.

Thank you for your attention

Further information

Contact me at Fergus.Sweeney@ema.europa.eu

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