AHPPI

Association for Human Pharmacology in the Pharmaceutical Industry

Clinical Trials Regulation

Transparency &
Commercially Confidential Information (CCI)
in early phase clinical research

Presented at:

Association for Human Pharmacology in the Pharmaceutical Industry Annual Meeting

Academy of Medical Sciences

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U Lorch MD FRCA FFPM - Richmond Pharmacology

Definition “Early Phase (Phase 1)” Research for the purpose of this presentation

Clinical trials

- in IMP & IMP/device combinations
- non-paediatric
- non-publicly funded
- performed in healthy volunteers and/or
- in patients with the target disease –
  who are not expected to gain any health benefit through study participation and
- in which therapeutic efficacy is not a primary objective of the clinical trial

Overview

- Aims of the EU Clinical Trials Regulation
- Its new transparency requirements affecting Phase 1 studies
- Regulatory requirements in relation to public accessibility of Phase 1 clinical trials' registration information and summary reports
  - US
  - Requirements of the International Committee of Medical Journal Editors (ICMJE)
- Potential benefits and risks arising for patients, health professionals and the public out of increased public accessibility of Phase 1 information
- Proposal of simple, transparent process and risk-benefit balanced approach to make Phase 1 trial registration information and summary reports publicly available in stages

Key aims of the Clinical Trials Regulation

"to boost clinical research in Europe by simplifying the rules for conducting clinical trials"

to give patients access to the most innovative clinical research and treatments, and to improve existing treatments

"clinical research" […] investment […] makes a significant contribution to the growth policy of the Europe 2020 agenda […]. Very significant costs "could be saved in regulatory costs and boost research and development in the EU, thus contributing to economic growth."

To reverse some unfavourable effects of the 'Clinical Trials Directive' of 2001 which has contributed "to a decrease of 25% of clinical trials conducted in the period between 2007 and 2011"

European Commission Press Release 17 July 2012: "Fostering EU's attractiveness in clinical research: Commission proposes to revamp rules on trials with medicines"

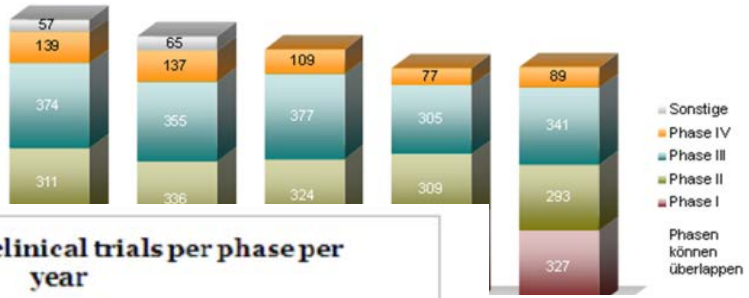
Research on Regulatory Web-Sites

Statistics – Numbers and types

	2010		2011		2012		2013	
	Number	%	Number	%	Number	%	Number	%
Phase 0	3	1	1	0	0	0	0	0
Phase I	75	29	70	31	51	23	48	23
Phase II	68	26	60	27	61	27	46	22
Phase III	98	38	71	32	86	38	81	40
Phase IV	15	6	23	10	26	12	30	15
Total	259		225		224		205	
Postponment	135	52	135	60	72	32	73	36
Refused	5		8		0		1	
Industry	190	73	148	66	139	62	131	64
IITs, Hospitals	48	19	65	29	60	27	65	32
Research groups	21	8	12	5	25	11	9	4
	259		225		224		205	
Amendments	4060		3908		3760		3568	

Klinische Prüfungen 2006 – 2010

Genehmigungsanträge beim BfArM



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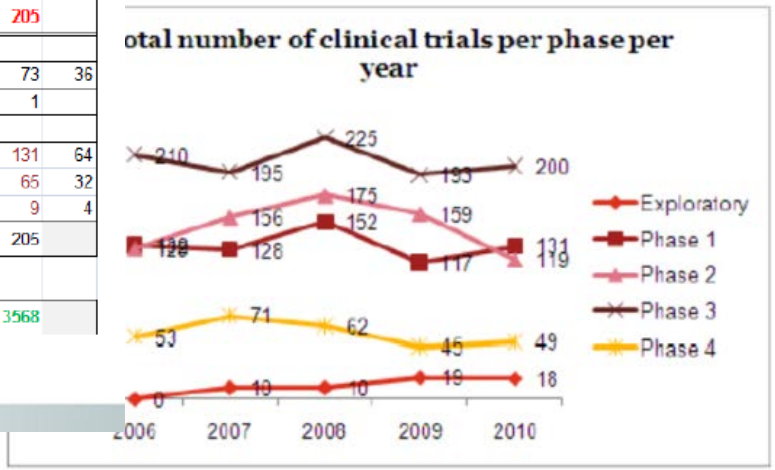
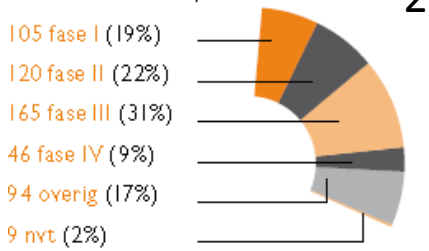


swissmedic

2012



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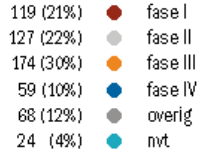
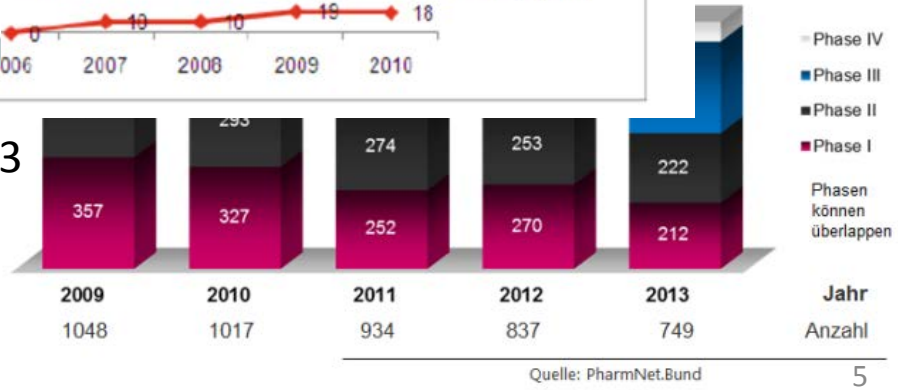


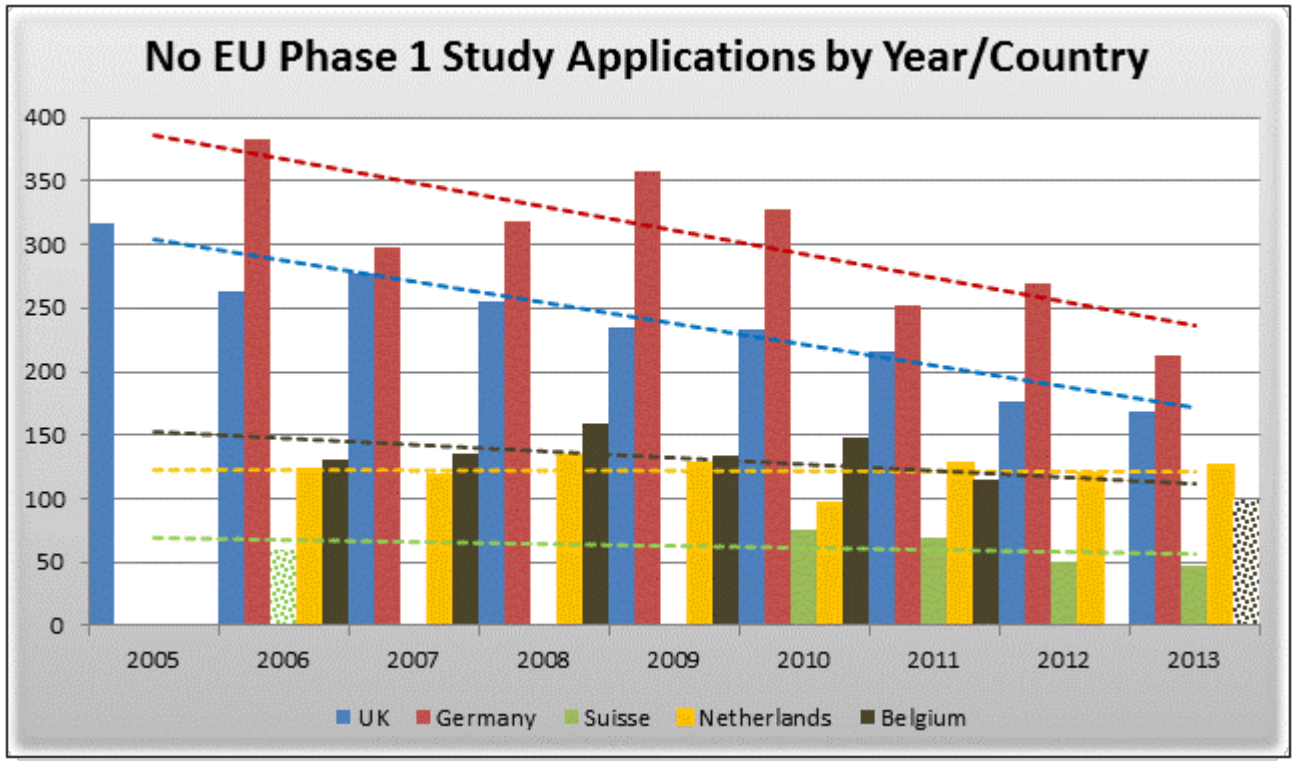
2013



Quelle: PharmNet.Bund

EU

CTA data from regulatory agencies show a decline in Phase I trials. Most notably for the UK and Germany. Particularly the Netherlands have shown a consistent number of trials over the entire period of this survey.



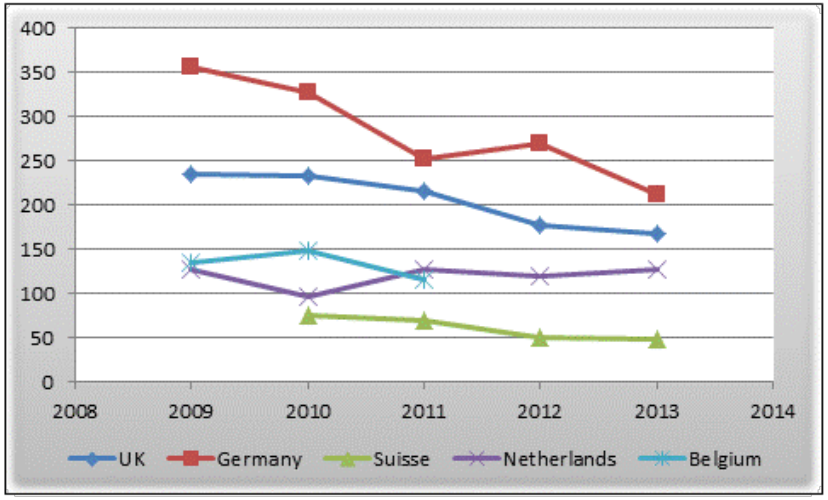
Note: The data has been extracted form the regulatory agencies' official publications: Belgian and Swiss data were incomplete: therefore the 2013 (Belgium) and 2006 (Switzerland) numbers were extrapolated (shaded bars) to allow for an assessment of trends.

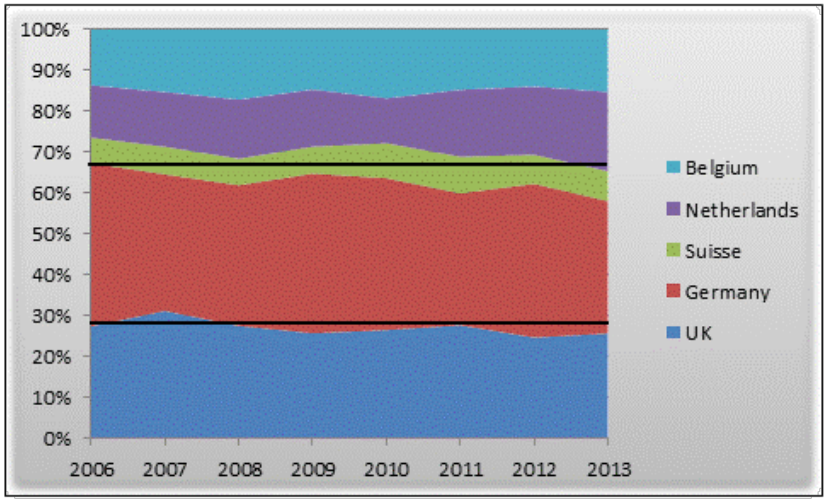
Phase I Trials
EU: main players only

- There is an overall decline in the number of Phase I studies conducted in Europe.

  Only the Netherlands have achieved a constant number of trials and have therefore extended their relative market share.

	% change peak to last
UK	**-47%**
Germany	**-45%**
Suisse	**-36%**
Netherlands	**-5%**
Belgium	**-28%**





CTR: new transparency requirements for Phase 1 studies in Europe

Once the CTR is implemented, Phase 1 studies

- must be registered on a publicly accessible international trials registry platform of the World Health Organization (WHO ICTRP)
- and published as summary reports and lay summaries within one year from the end of a clinical trial
- for marketing authorisation applicants to publish clinical study reports within 30 days of a regulatory decision on the application being taken
- The information will be published by the EU database's publication module.
- The CTR permits commercially confidential information to remain confidential, i.e. this type of information does not need to be publicly accessible.

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

Draft functional specifications for the EU portal and EU 3 database to be audited 4, 10 October 2014 1 EMA/42176/2014 2

Commercially Confidential Information

- Article 67 […] “Publicly available information contained in the EU database should contribute to protecting public health and fostering the innovation capacity of European medical research, while recognising the legitimate economic interests of sponsors.”
- Article 81: 4. “The EU database shall be publicly accessible unless, for all or part of the data and information contained therein, confidentiality is justified on any of the following grounds:
  - protecting personal data in accordance with Regulation (EC) No 45/2001;
  - protecting commercially confidential information, in particular through taking into account the status of the marketing authorisation for the medicinal product, unless there is an overriding public interest in disclosure;”

US: what are the FDA requirements in relation to registration and submission of results?

Name	Type	Intervention Type	Registration Policy Scope	Results Submission Policy Scope
Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801) (PDF)	U.S. Federal law enacted in 2007	Drugs, biologics, and devices	Controlled clinical investigations of a Food and Drug Administration (FDA)-regulated drug, biologic, or device, **other than Phase 1 (drugs/biologics)** or **small feasibility studies**	**Same scope as registration,** but **interventional studies of FDA-approved drugs, biologics, or devices**

http://clinicaltrials.gov/ct2/manage-recs/background

What are the registration requirements for publication in accordance with the ICMJE?

- Registration of all interventional studies, including Phase 1 studies as a condition of the publication of research results generated by a clinical trial
- Completion of at least the 20-item standardized WHO trial data registration set

  - British Journal of Clinical Pharmacology
  - European Journal of Clinical Pharmacology
  - American Journal of Clinical Pharmacology
  - PLOS One (Open access)

are not listed as journals following the International Committee of Medical Journal Editors' recommendations

http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

http://www.icmje.org/journals-following-the-icmje-recommendations/#C

Examples of potential benefits of publication of Phase 1 trial registration for patients, health professionals and the public

There is a need to ensure that decisions about health care are informed by all of the available evidence

Provide information to potential participants and referring clinicians

Improving awareness of similar or identical trials will make it possible for researchers and funding agencies to avoid unnecessary duplication

Making researchers and potential participants aware of recruiting trials may facilitate recruitment

Help institutional review boards (IRBs) determine the appropriateness of a research study

Most potential benefits of registration
[stated on ClinicalTrials.gov and WHO/International Clinical Trials Registry Platform (ICTRP)]
are **not applicable** to
Phase 1
non-therapeutic
non-paediatric
non-publicly funded clinical trials

Sources:
ClinicalTrials.gov: https://clinicaltrials.gov/ct2/manage-recs/background;
WHO/International Clinical Trials Registry Platform (ICTRP): http://www.who.int/ictrp/trial_reg/en/; http://www.who.int/ictrp/results/en/; CTR

Potential benefits of publication of Phase 1 (lay) summary results for patients, health professionals and the public

Provide a public record of basic study results in a standardized format

Promote the fulfilment of ethical obligations to participants and the overall contribution of research results to medical knowledge

Facilitate systematic reviews and other analyses of the research literature

Reduce publication and outcome reporting biases;

There is a particular concern that trial results which may be viewed as "negative", are less likely to be submitted, or accepted, for publication in the scientific literature or made public in other ways

Relevance for the various purposes and benefits **may occur at different times** during a drug or drug/device development process. **This may be earlier or later than one year from the end of a Phase 1 trial.**

The underreporting of unfavourable data can lead to **duplication** of work and **safety issues**. Due to the nature of Phase 1 studies, this is **unlikely to affect ongoing clinical research at the time**, as all parties involved are fully informed about study design and safety information and any changes thereof.

Sources:
ClinicalTrials.gov: https://clinicaltrials.gov/ct2/manage-recs/background;
WHO/International Clinical Trials Registry Platform (ICTRP): http://www.who.int/ictrp/trial_reg/en/; http://www.who.int/ictrp/results/en/; CTR

Potential risks of early publication of Phase 1 registration and (lay) summary results for patients, health professionals and the public

Information that may be considered commercially confidential:

- Pharmaceutical details
- Novel molecular target(s)
- Non-clinical data
- Formulation/formulation switches and new delivery route(s)
- Projected timelines & key milestones e.g. First-in-Human, Proof of Concept and NDA/MAA
- Disease indication(s) being pursued
- Biomarkers employed
- Clinical trial designs
- Development strategy
- Lifecycle management strategy

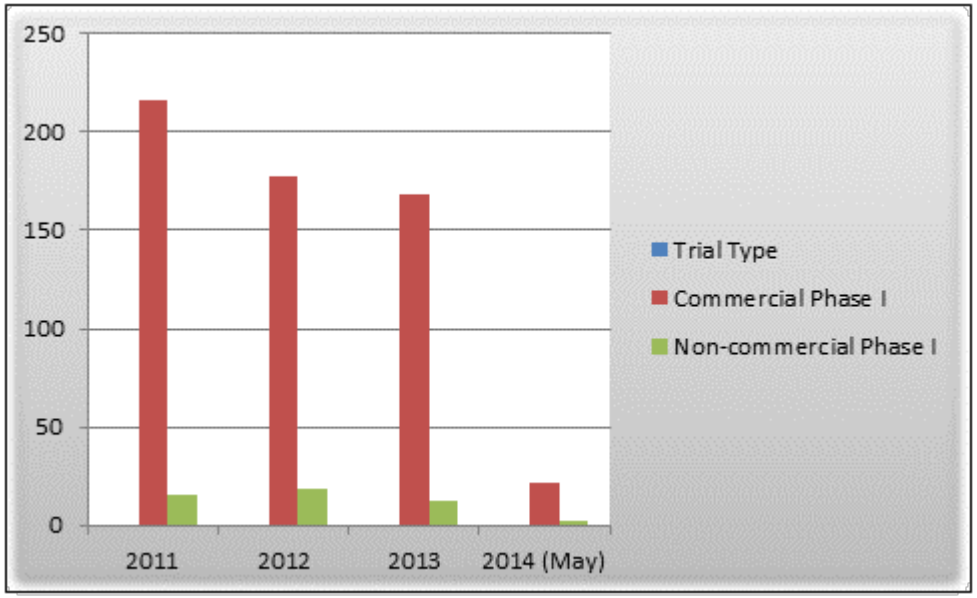
No requirement to publish Phase 1 registration and summary results in the US

In locations outside Europe the risks in relation to early disclosure of commercially confidentially information will be less.

Sponsors may choose to conduct early phase and follow-on later phase studies outside Europe

Phase I Trials non-commercial vs commercial

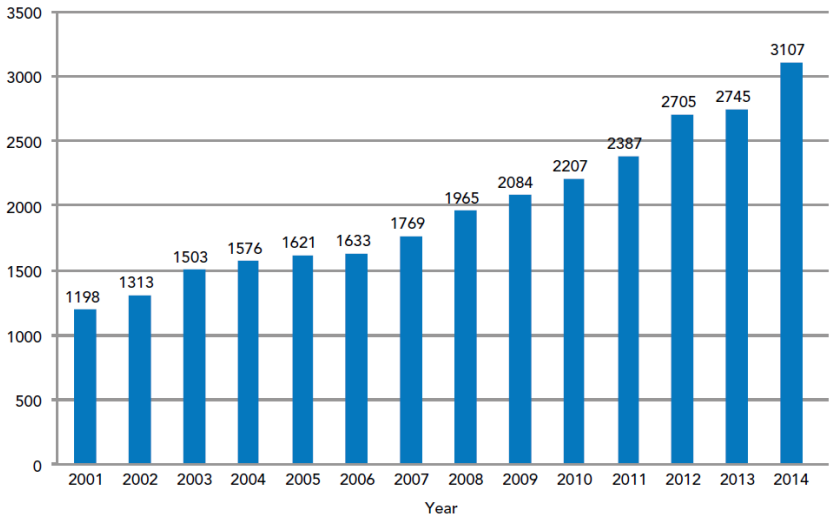
There is only a very small number of ***non-commercial*** trials in the UK.



Note: The data has been extracted form the regulatory agencies' official publications

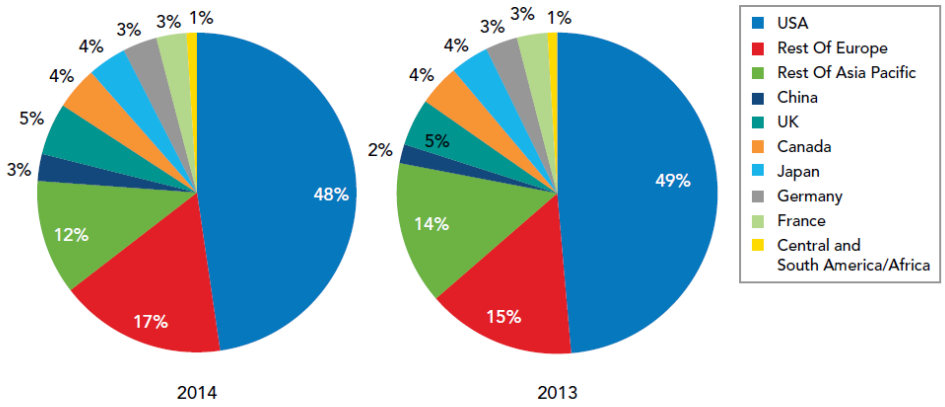
Transformation of the Pharma R&D Ecosystem

Figure 4. Total Number of Companies with Active Pipelines 2001-2013



Source: Pharmaprojects® Pipeline®, January 2014

Figure 5. Distribution of R&D Companies by HQ Country/Region 2013 and 2014

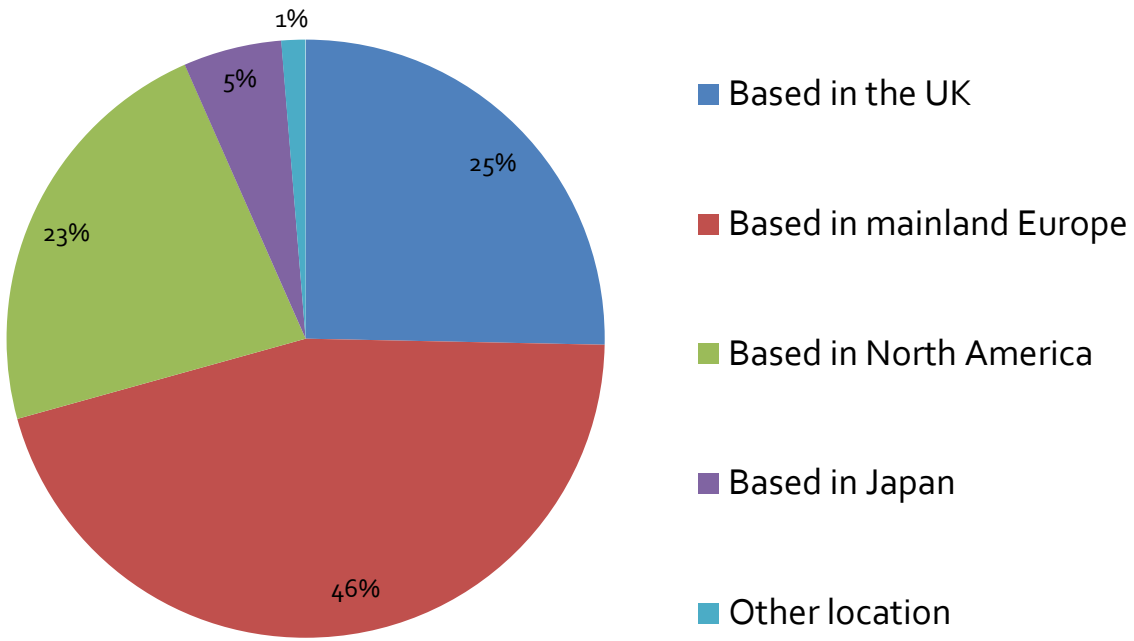


Source: Pharmaprojects® Pipeline®, January 2014

- The number of companies with active drug development projects has increased from 1,576 to 3,107 (+97%) between 2004 - 2014
- Only c. 10% of drugs in the pipeline originate from Top 10 Pharma
- The majority of companies are SMEs that rely on external investment (venture capital or public markets)
- 95% of these companies are headquartered outside of the UK, with the majority in the USA

UK CROs' dependence on international sponsors

- A 2014 survey of UK-based CROs showed their sponsor base to be heavily dependent on non-UK based clients (75%)
- Nearly a quarter of sponsors come from North America although for some CROs, US sponsored trials can make up nearly 60% of their work

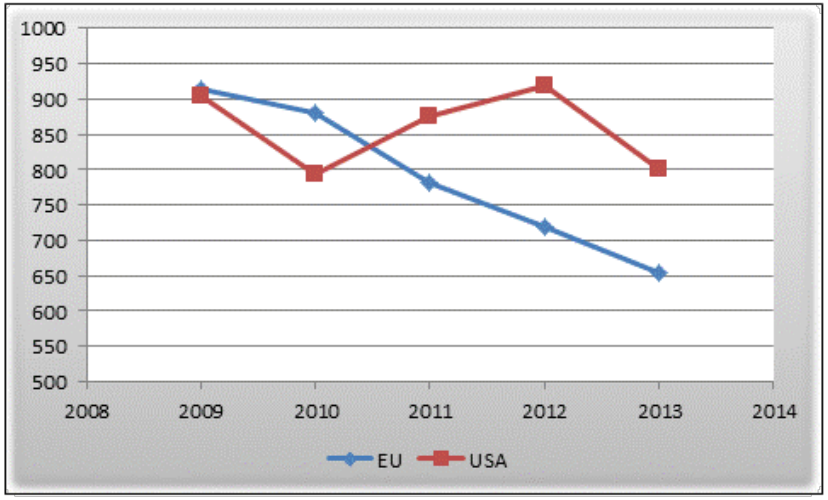


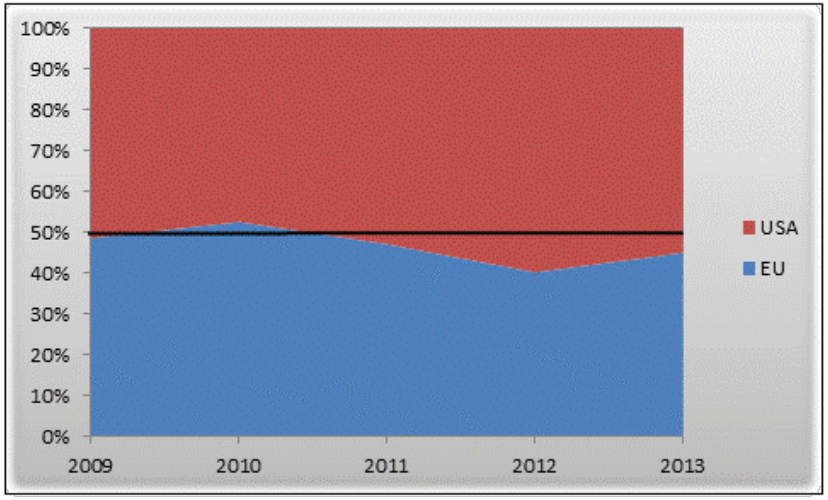
Phase I Trials
EU vs USA

- There is an overall decline in the number of Phase I studies conducted in the western hemisphere.

  In the USA this decline is 12% from the peak in 2009 in EU it is twice that at 23% comparing 2013 to 2009.

  Consequently the market share between the continents has shifted in favour of the USA.





One proposed process for publication of Phase 1 registration information and results balancing benefits and risks within the remit of the CTR

(1) First stage public access to registration information

To make a limited amount of non-commercially confidential registration information publicly accessible via the EU database following clinical trial authorisation and prior to study commencement

(2) Further public access to registration information and (lay) summary reports

The clinical study protocol defines all further publication milestones in relation to development phases rather than actual dates

These milestones are approved as part of the protocol by way of the regulatory authorisation to conduct the clinical trial

(3) Substantial Modifications

Any changes to the authorised publication process and timelines are submitted as a Substantial Modification and need to have regulatory authorisation prior to implementation.

(1) First stage public access to registration information
(based on current EudraCT database, subheadings only)

A	Trial Identification
A1	**Member State (Country in which the submission is made)**
A2	**EudraCT number**
A3	**IMP name only, no study title**
A4	**Sponsor's protocol number**
A5	**Additional international study identifiers, if available**
A6	**Re-submission Y/N**
A7	**Part of Paediatric Investigation Plan Y/N**
A8	**EMA decision number of PIP**
B	Identification of the sponsor
B1	**Sponsor details**
B3	**Commercial/non-commercial**
B5	**Contact point designated by the sponsor for further information on the trial**
C	Applicant Identification
C1	**Request for the Competent Authority**
C2	**Request for the Ethics Committee**
E	General information on the trial
E7.1	**Trial Phase (to confirm "applicability", i.e. Phase 1)**
F	Population of trial subjects
F1	**Age range (to confirm "applicability", i.e. non-paediatric study).**

(2) Further public access to registration information

Voluntary full publication prior to study start

Publication when information becomes relevant in relation to the development plan

- Sponsor determines and justifies the publication timelines in the CSP when applying for Clinical Trial Authorisation.
- Timelines will depend on the nature of the study and the relevance of the information for the public

Publication due to termination of a study on safety grounds

- The CSP should state what will happen in case of study termination due to safety issues (e.g. remaining registration information and the reason for termination will be automatically published following notification of termination through the Safety/EU portal)

(2) Further public access to (lay) summary reports

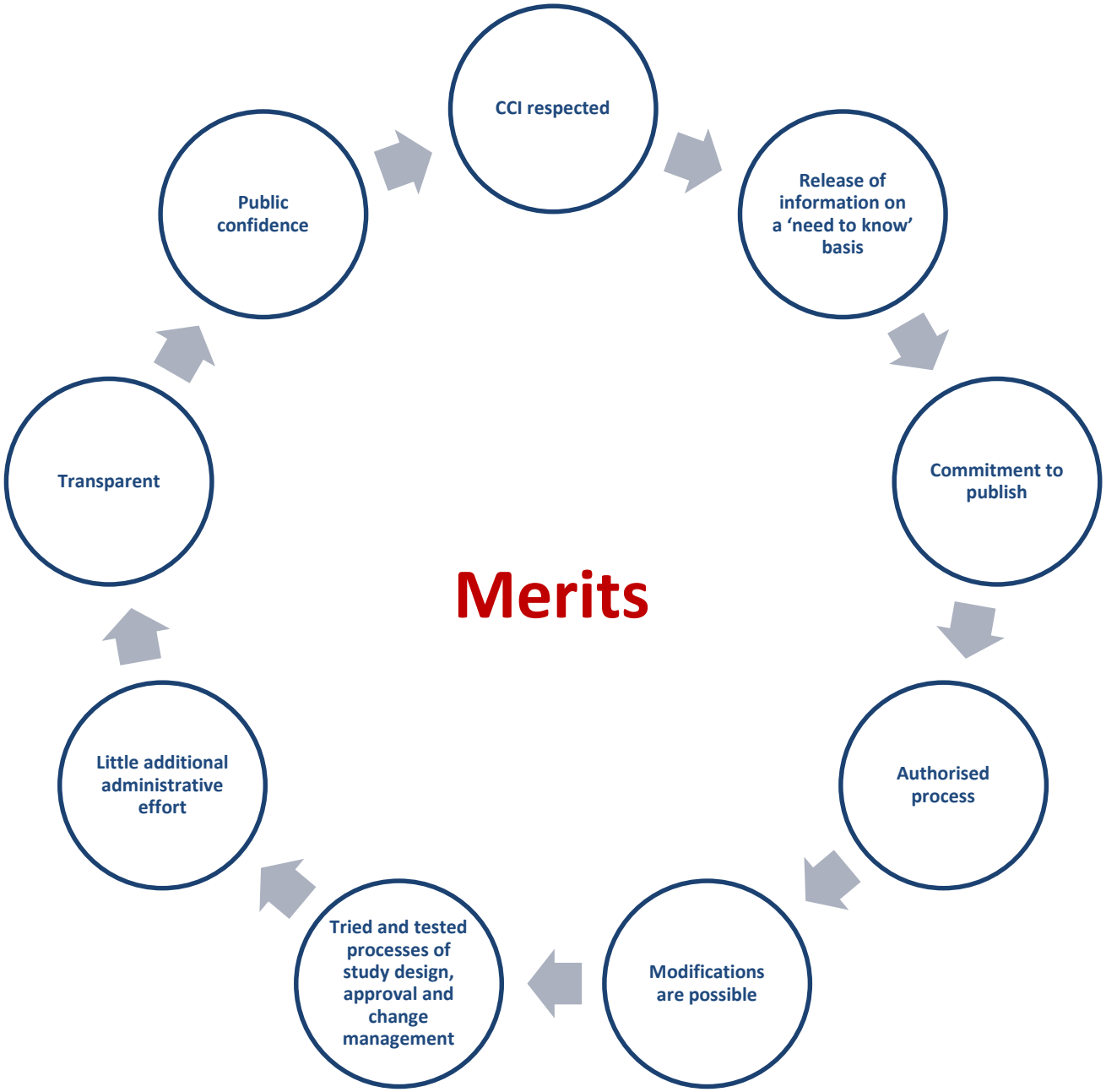
Voluntary publication within one year from the end of a study

Publication in case of termination of a study on safety grounds

- The CSP should state that this will occur within one year from the end of a study

Publication when information becomes relevant in relation to the development plan

- The CSP submitted to the EU portal specifies and justifies when the summary report and lay summary will become publicly available via the EU database publication module


Merits
CCI respected
Release of information on a 'need to know' basis
Commitment to publish
Authorised process
Modifications are possible
Tried and tested processes of study design, approval and change management
Little additional administrative effort
Transparent
Public confidence

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