The Clinical Trial Regulation:
Challenges for National Competent Authorities
Perspective of the Paul-Ehrlich Institut

Hartmut Krafft, PhD
VHP-Coordinator
Head, Clinical Trial Unit
Paul-Ehrlich-Institut
Paul-Ehrlich-Str. 55-59
63225 Langen
Germany

Fax: +49 (0)6103 771277
Phone: +49 (0)6103 771811
E-Mail: CT@pei.de
http://www.pei.de

Disclaimer

This presentation contains only my thoughts and not necessarily those of the Paul-Ehrlich Institut or other European Institutions!

per aspera ad astra

To the multi/national procedures of Regulation 536/2014

HMA
Heads of Medicines Agencies

Via the Voluntary Harmonisation Procedure

From National Approval

Major Points:

- All clinical trial applications/communications have to go via the EU-Portal:
  - For Sponsors; CROs; NCAs; Ethics Committees
  - Mono-center, mono-national vs multi-center, multi-national CTs ; IIT vs commercial Sponsors

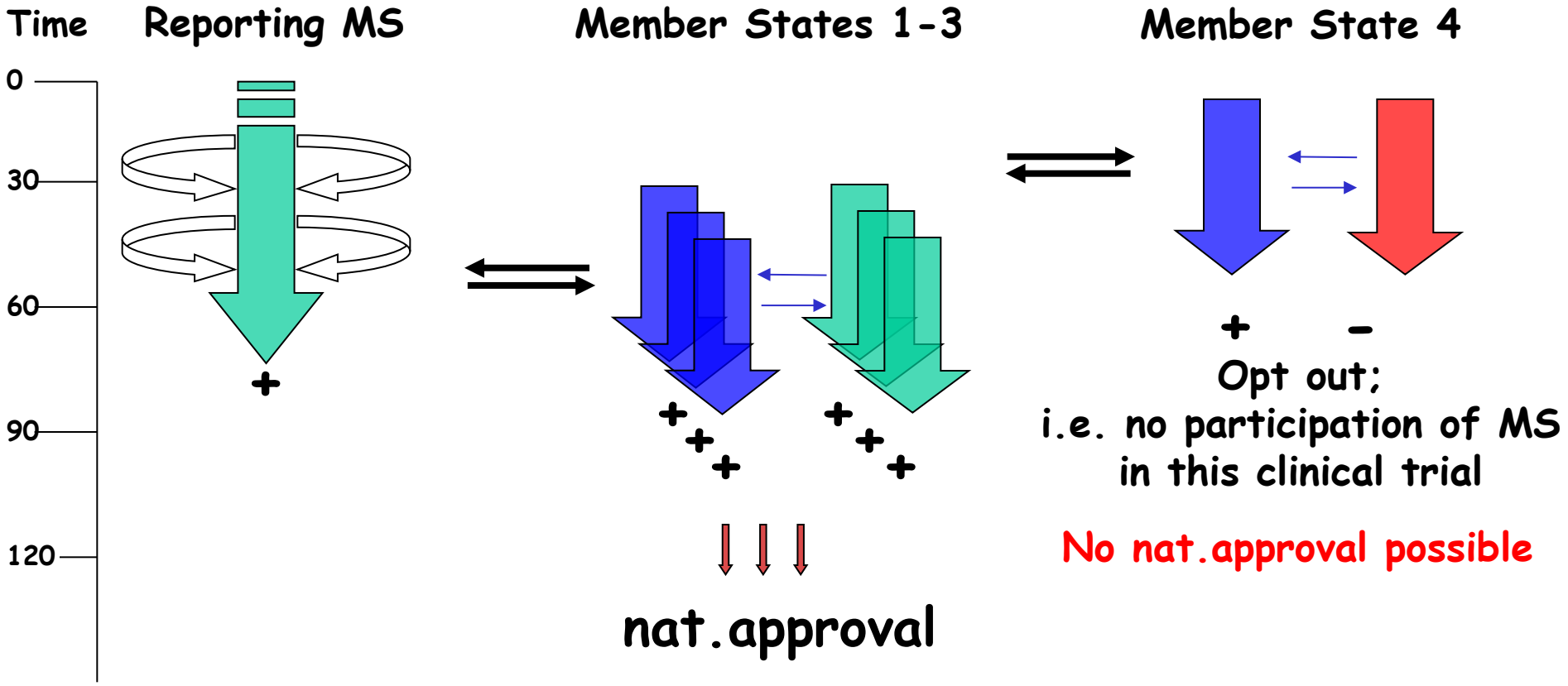
- EU database shall be publicly accessible unless confidentiality is justified
- No paper, only electronic submission
- Separation of part I and part II submission & assessment possible
- Proposal of Reporting MS in multinational CT by sponsor
- Tacit approvals possible
- One decision, one fee per Member State
- "Shortened" timelines
  - For Member States initial assessment (max 26/45 days)
  - For sponsors to address questions (max 12 days)
  - Additional time for some Biological IMPs
- Transition periods

Challenge 1

- **The Portal/Database:**
  - Many / most details still unclear
  - Functionality
    - Reports
    - Data warehouse
    - Timelines per CTA
    - Timelines per rMS duties; MSc duties;
    - Timelines for Substantial Modifications (SM)
  - Inter Member States work space
    - Means of communication / E-mails / structured Requests for information or assessment of responses
  - Intra Member State work space
  - Assessment report / templates / structured GNA/RFI
  - Which CTA parts will be confidential / how will access be restricted, if the restricted material is in within PDFs etc.

Assessment Procedure for multinational Clinical Trials according EU-CTR

Competent Authorities and Ethics Committees

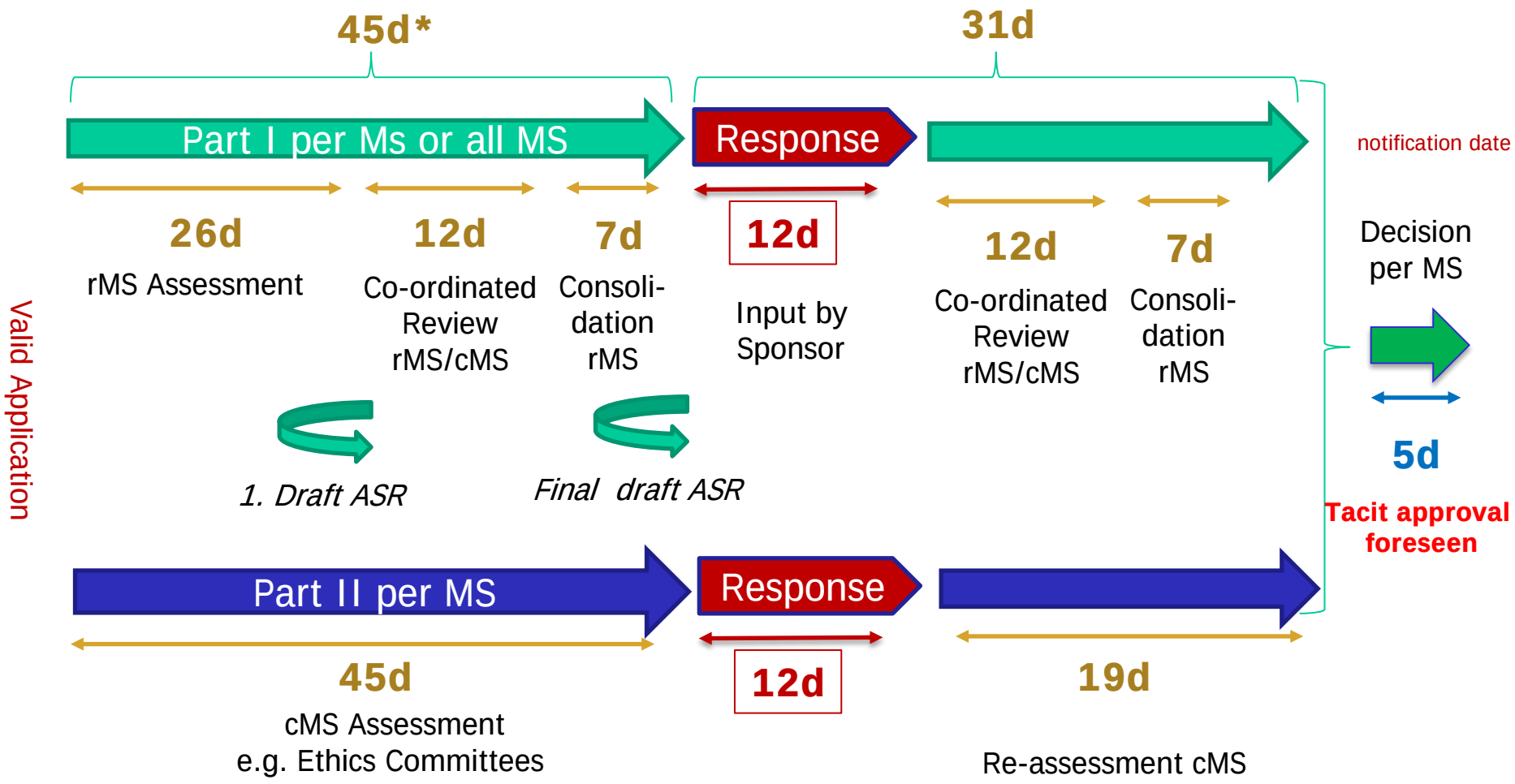


Challenge 2

- **The timelines:**
  - Validation (NCA+EC)
  - Assessment either as a rMS or MSc (NCA+EC)
  - Request for Information (RFI) (NCA+EC)
  - Coordinated review (NCA+EC)
  - Consolidation of Request for Information by other MSc
  - Assessment of response by Sponsor (NCA+EC)
  - Consolidation of assessment of response by Sponsor (NCA+EC)
  - Decision as a rMS or MSc (NCA+EC)

WHY ARE TIMELINES A CHALLENGE?

Timelines "standard procedure Part I and Part II"

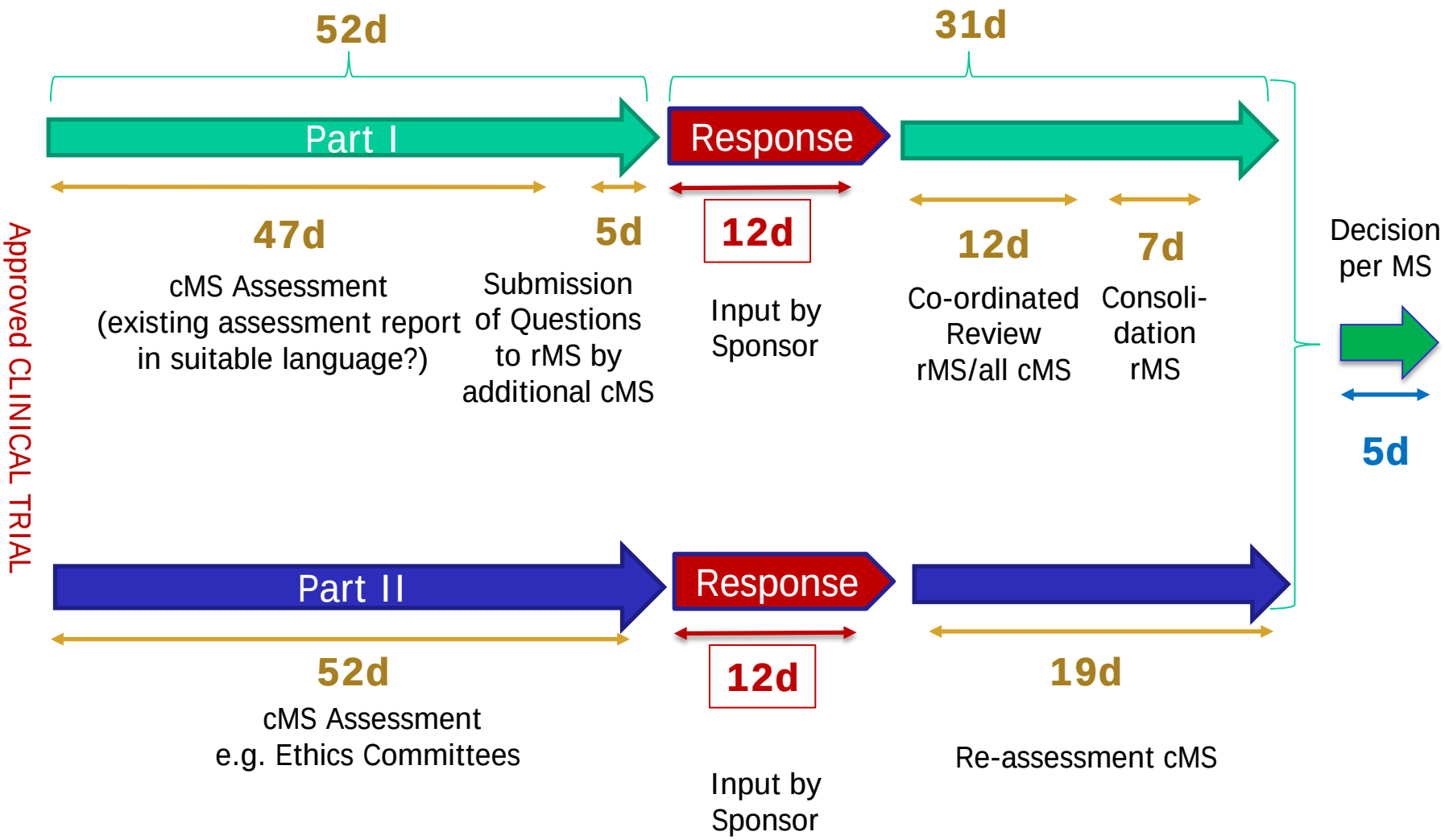


* +50d ATMP & Annex I 726/2004

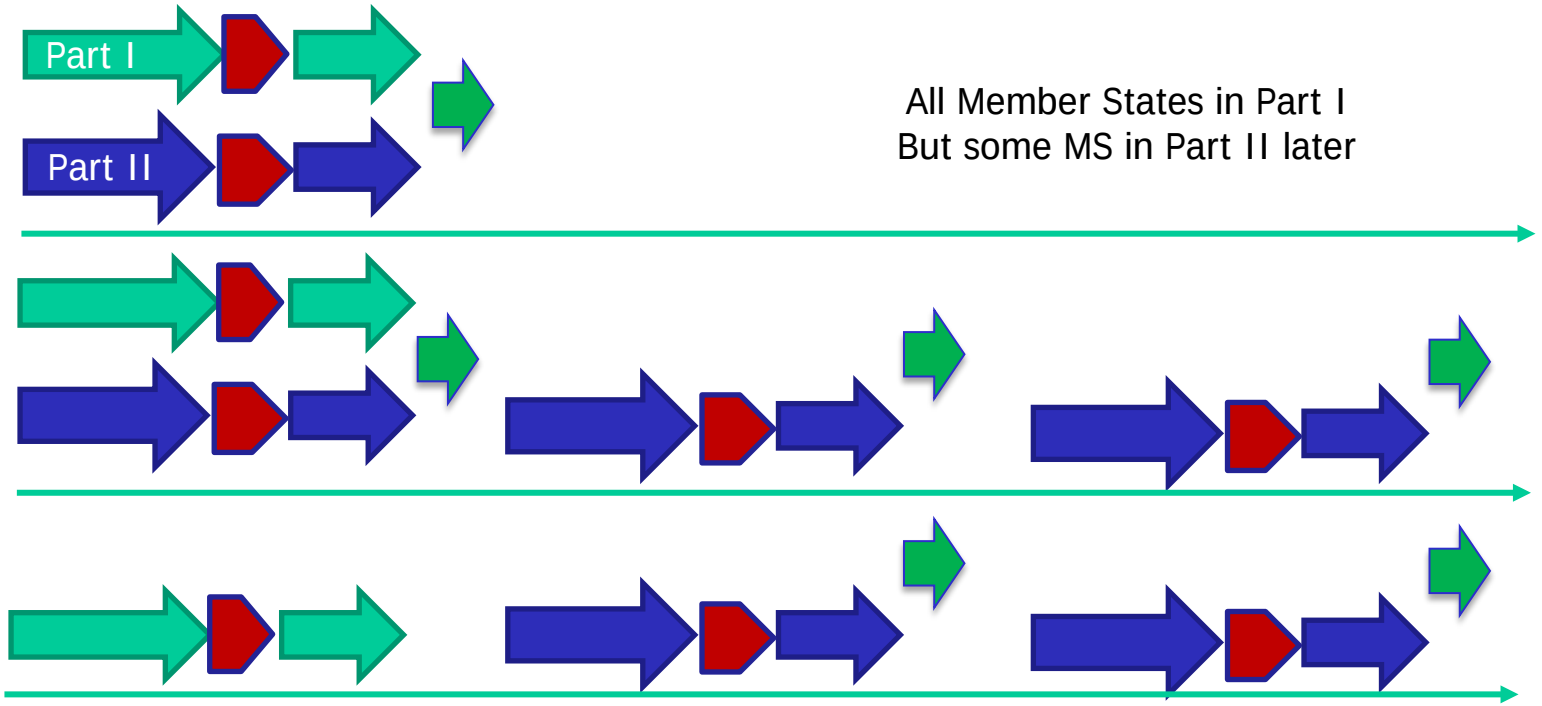
Timelines of a CTA are not made of stone

- Which calendar for the time of rMS selection?
- Timelines (days) in the CTR are maximum timelines i.e. can be shortened by each rMS (e.g. 10 days instead of 26 for rMS assessment, or 5 days instead of 12 days for sponsor response)
- No clock stops foreseen (maybe exception for Christmas)
- Many CTAs in parallel (part I; part I and II; Article 14
- Many Substantial Modification (SM) in parallel

Timelines according article 14 (second Wave with an approved CT)

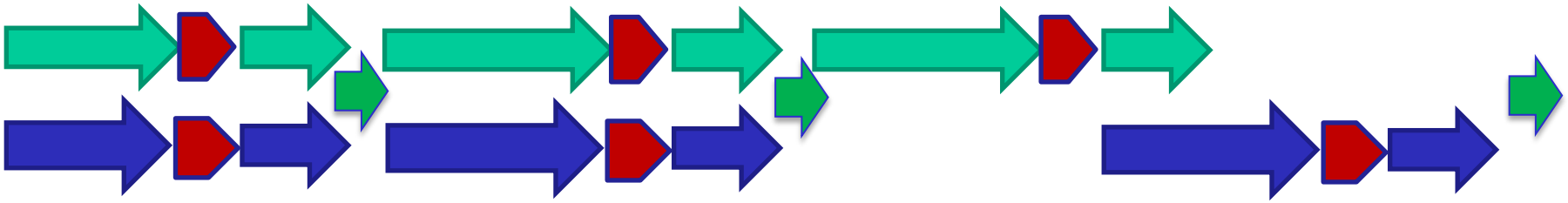


Submission options



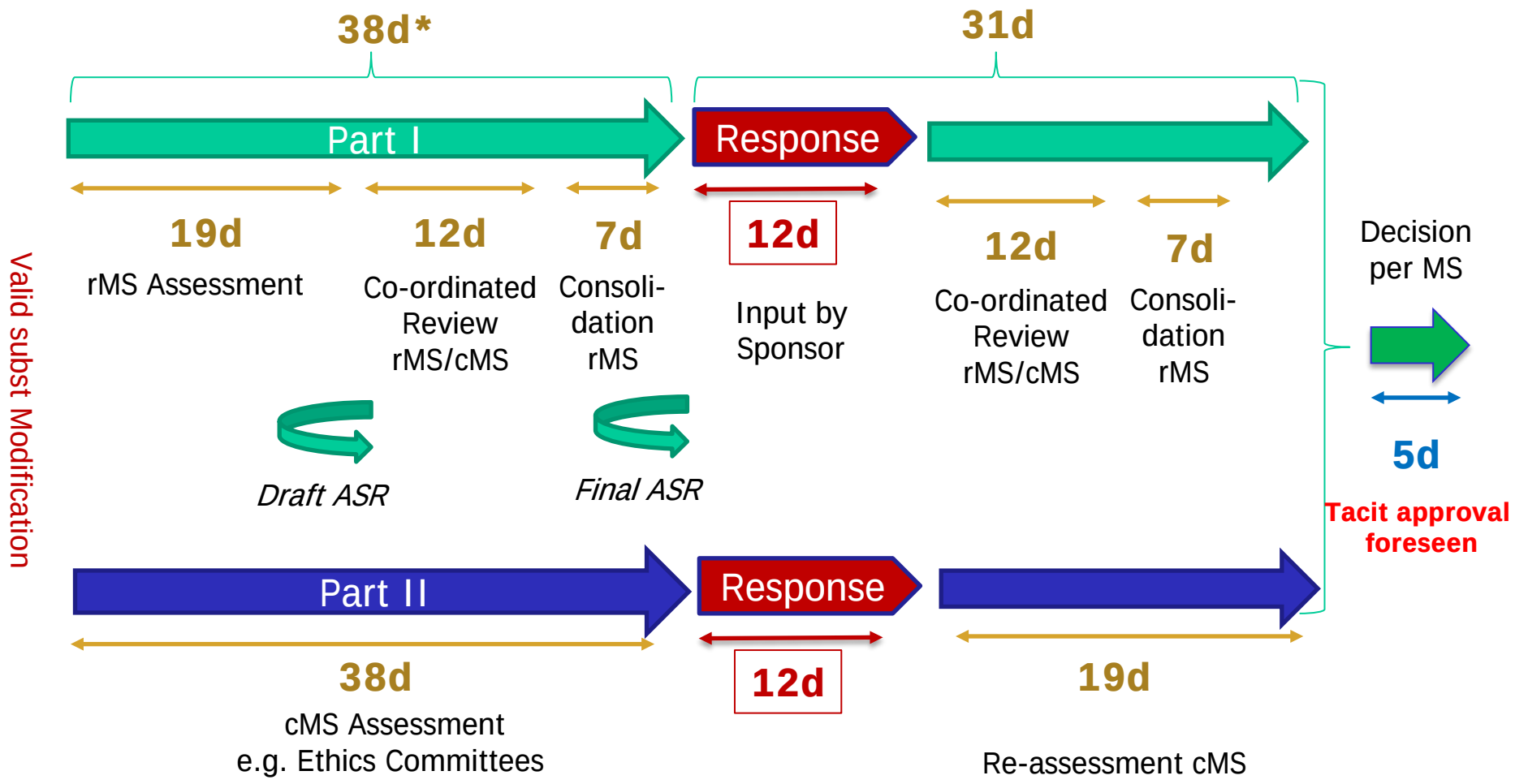
All Member States in Part I
But some MS in Part II later

One or some Member States involved in Part I / Part II
but some MS in Part I and/or part II later



1st wave 2nd wave 3rd wave

Timelines Substantial Modification

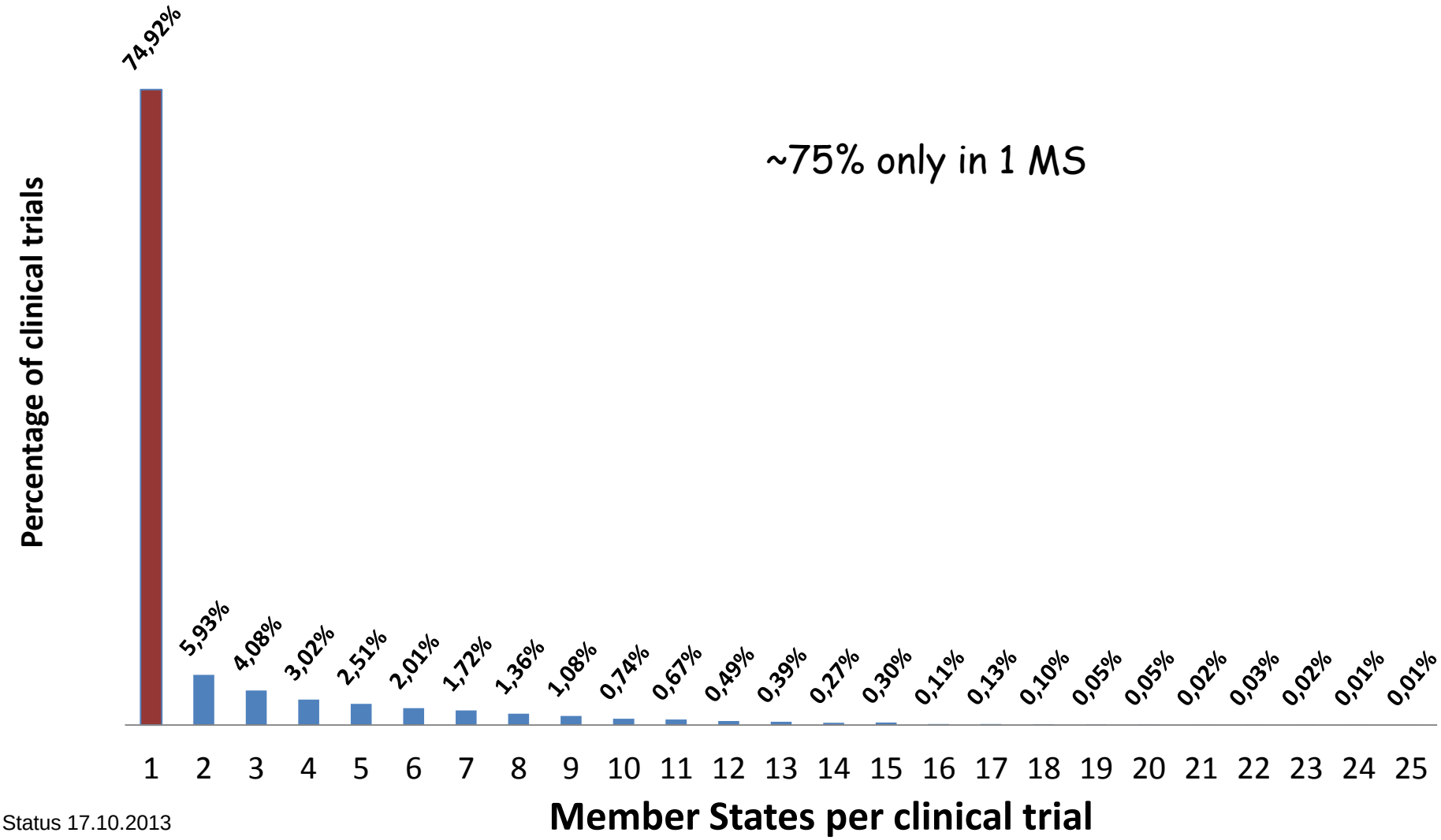


* Additional time (50d) for ATMP and products under point 1 of annex 1 of Reg. 726/2004 possible

Medicinal products developed by means of one of the following biotechnological processes:
— recombinant DNA technology,
— controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells,
— hybridoma and monoclonal antibody methods.

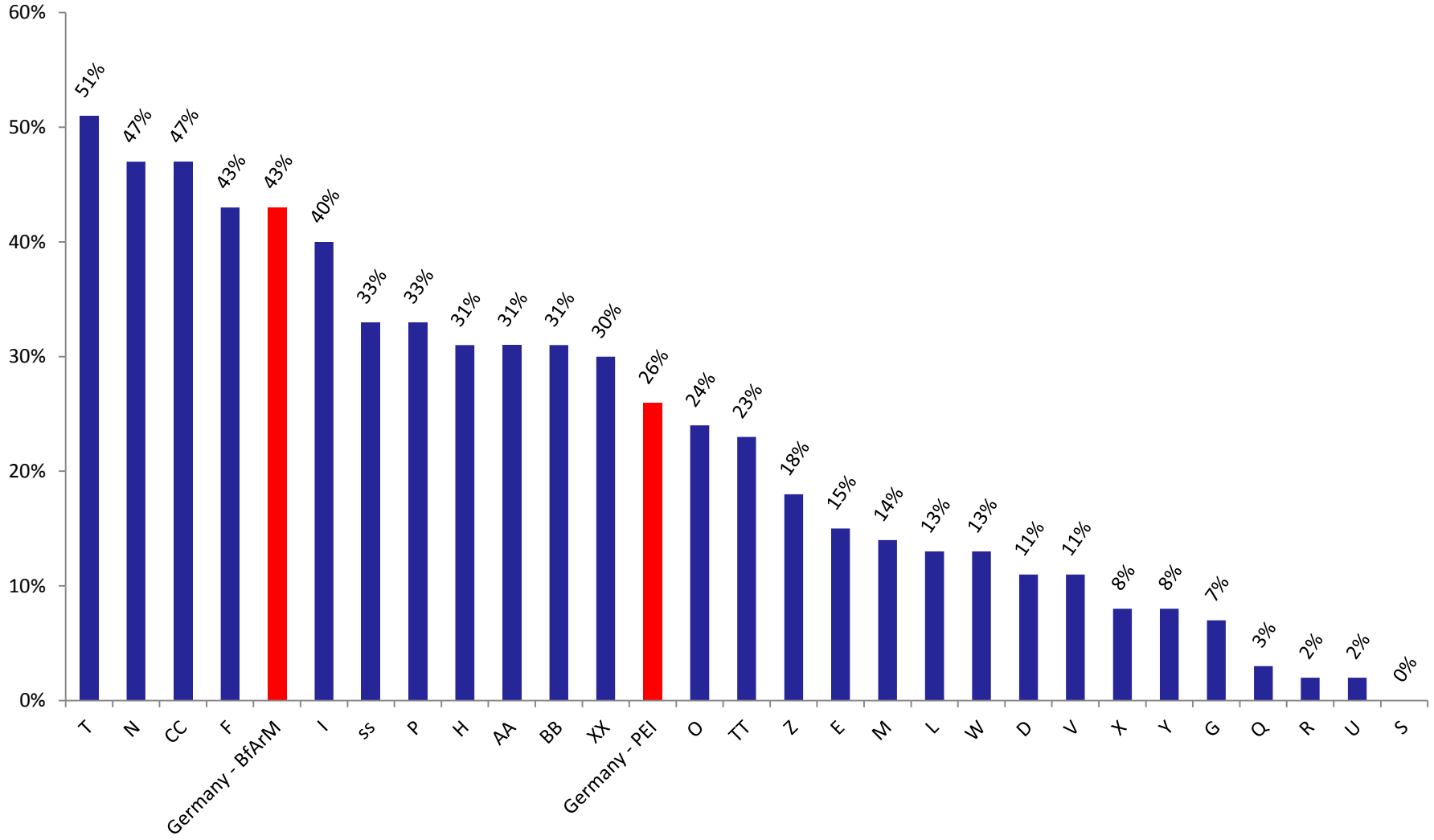
Distribution of Clinical Trials in Europe

in one Member State vs multinational in percent



Status 17.10.2013

How many CTA are mono-national in the Member States? (2013 – Feb. 2015)



Parallel Work at PEI

- Approx 70 CTAs ongoing at any time
  - ~ 50 CTAs Multi-national / 20 CTAs Germany only
- Approx 100 Substantial Modifications of CTAs ongoing at any time
  - ~ 74 CTAs Multi-national / 26 CTAs Germany only
- DSURs approx 400 per year
- Adverse Events .....
- Measures .....

BfArM approx 3x & Ethics Committees x 2

Parallel Work at Sponsors concerning PEI-Applications

- Approx. 3-7 CTAs ongoing at a time point for bigger companies

- Approx. 5-34 Substantial Modifications ongoing at a time point for bigger companies

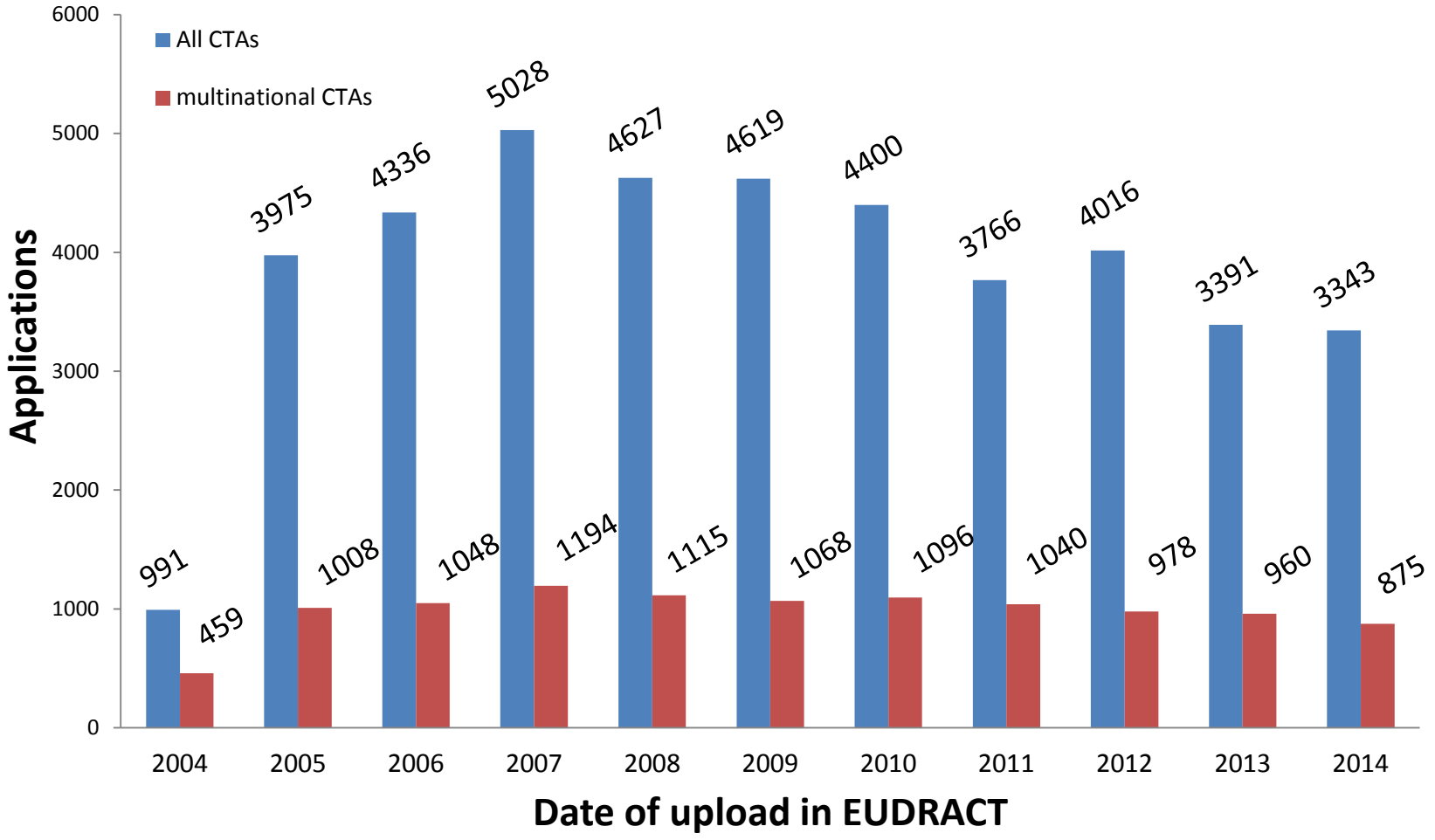
BfArM approx 3x

Challenge 3

- **The Coordination:**
  - The Coordination at the different steps between NCA and Ethics Committees per Member State will require additional work
  - Being a rMS will require extra work directly dependent on the number of participating Member States
  - Multi-procedures (e.g. IB or IMPD - updates between different CTAs with several different rMS) will require extra work directly dependent on the number of CTs

  - Explicit coordination is not foreseen in the Regulation
  - Explicit discussion between Member States on questions e.g. from the sponsor before or within a CTA is not foreseen in the Regulation
  - rMS selection and a fair distribution of work between Member States will become an issue

Number of clinical trials in Europe
All CT per year including multinational CT



A fair distribution of the work would require

- Work sharing between the Member States
- Reasonable numbers of personnel in all NCA
- Clear distribution of responsibilities and best practises in Member States and between Member States
- Sponsors that are willing to support the fair distribution of the work of multinational CTA

Who will become rMS

- The Regulation defines the Sponsors proposal as binding as long as not all MSc agree to define a different Member State as the rMS

- The VHP, that comprises about 20% of all multi-national clinical trials, shows today, what can happen, when the CT Regulation will go live
  - As already today the sponsor has to propose a REF-NCA (rMS) in the VHP
  - Already today the MS try to work-share

Who will become rMS (by VHP experience)

- **Sponsor proposal for REF-NCA today in VHP consists of only 2 countries in most cases**
  - - Germany and the UK are more than 80% of the sponsors proposal (January 2015 to April 2015)
- **Only 8 different Member States of 23 Member States, participating in VHP, are proposed by sponsors at all as REF-NCA**

- **REF-NCA ships are shared by 12 Member States**

  (January 2015 to April 2015)

  - 3 Member States do about 20 - 25% each of the work

Conclusion:

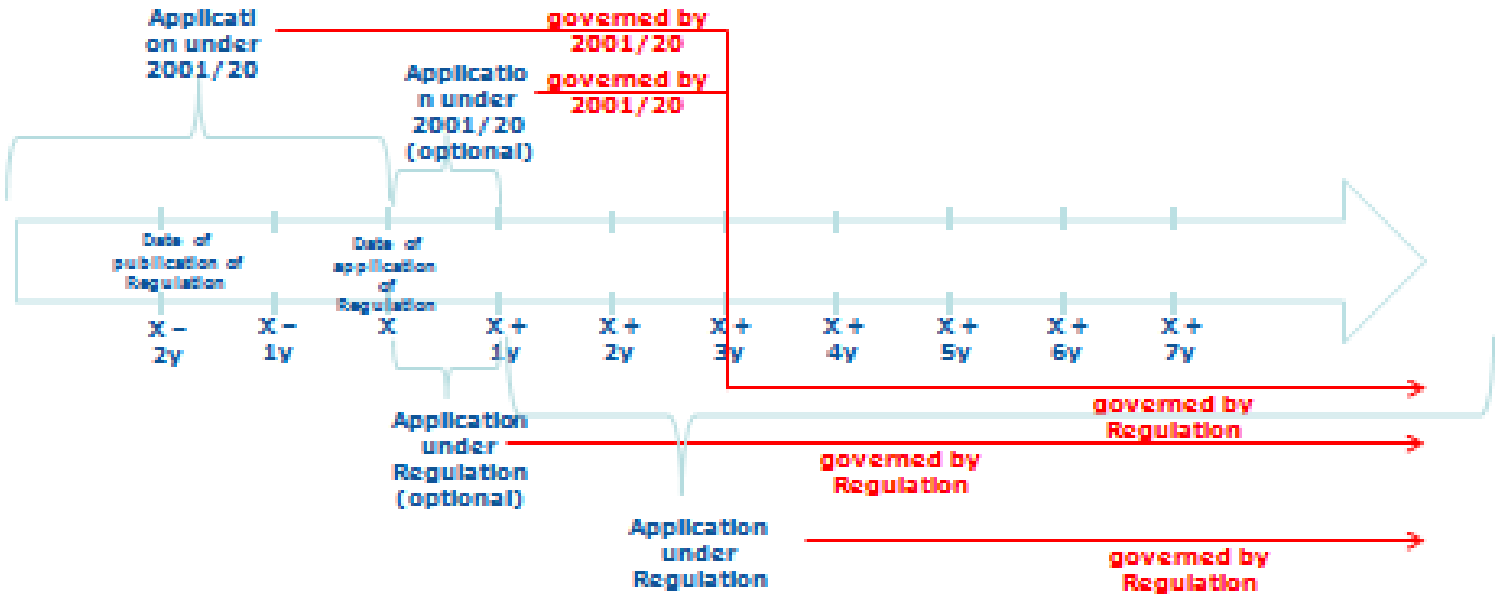
A fair distribution will not come by itself

WHAT WILL WE SEE IN THE FUTURE?

Future 1

- **Rare use of the CTR in the transition period**

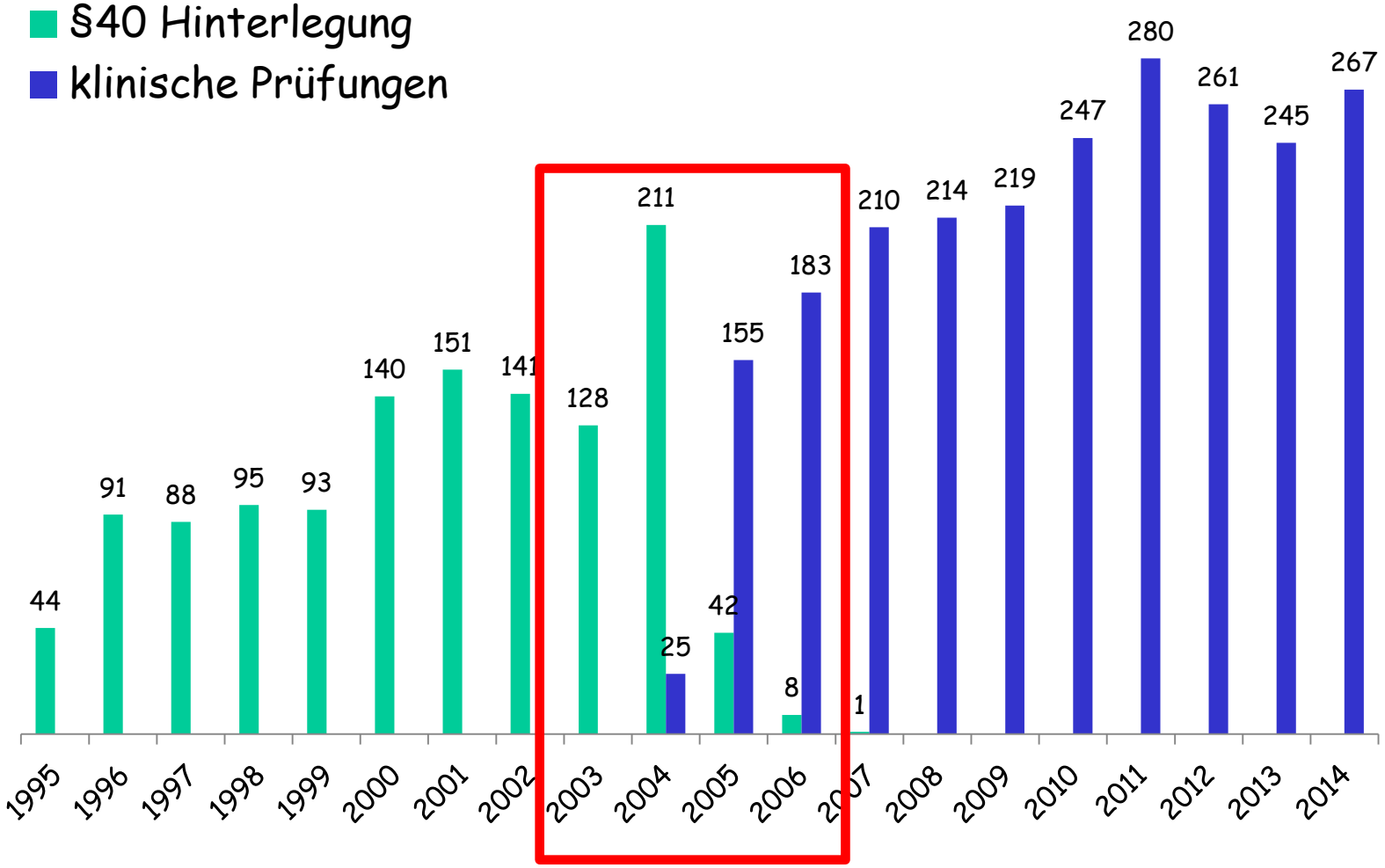
DATE OFAPPLICATION



DGRA 2015: CT Regulation: Challenges for NCA / PEI;
From S. Führing; DIA; EuroMeeting Amsterdam 6.3.2013; Session 0305

Future 1

- **Rare use of the CTR in the transition period**



What will see in the Future? 2

- New concepts of scientific advise
- Pre-assessment of CTAs by PEI
  - To prepare a CTA for the short response times (12 days max.)
  - To achieve a complete CTA by several rounds of assessments and responses before submission
- New concepts of the rMS role, when coordinating the CTA assessment with Ethics Committees/NCAs in other Member States
- Use of the 7 years VHP-Experience by the Paul-Ehrlich-Institut in the coordination of CTA as a Ref-NCA

Will the CT regulation reduce the work-load?

Paul Ehrlich in his study

Thank you for your attention!