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IMPLEMENTATION OF THE EU CLINICAL TRIAL DIRECTIVE

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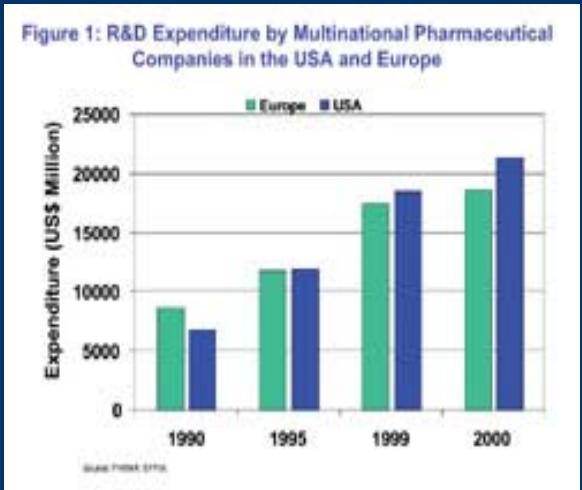
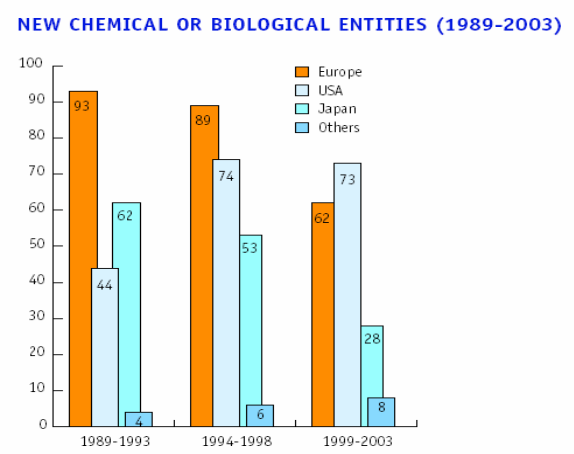
Trends in the global Pharmaceutical Industry



R&D Expenditure has moved from Europe to the US



More NCEs are coming out of the US than out of Europe

Intention of the Directive
Explanatory Memorandum of Commission 1997

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…Therefore this legislative proposition is designed to build on the existing experience of the Member States, ensuring the same lever of patient protection and scientific standards, but with a **rationalisation of the documentary and administrative procedures** involved in multi-centre clinical trials. Additionally, the proposal includes a **series of definitions which have been internationally agreed** and which codify the terms used in the Member States, on the basis of which clinical trial data generated in the European Union is internationally mobile….

…It is important to note that this proposal, based on article 100a, is in fact a **rationalisation of legislation** since overall **the administrative and bureaucratic requirements will be reduced** in fine with a 'risk-based' approach, thus allowing new medicines to be made available to patients in a timely manner.

Content

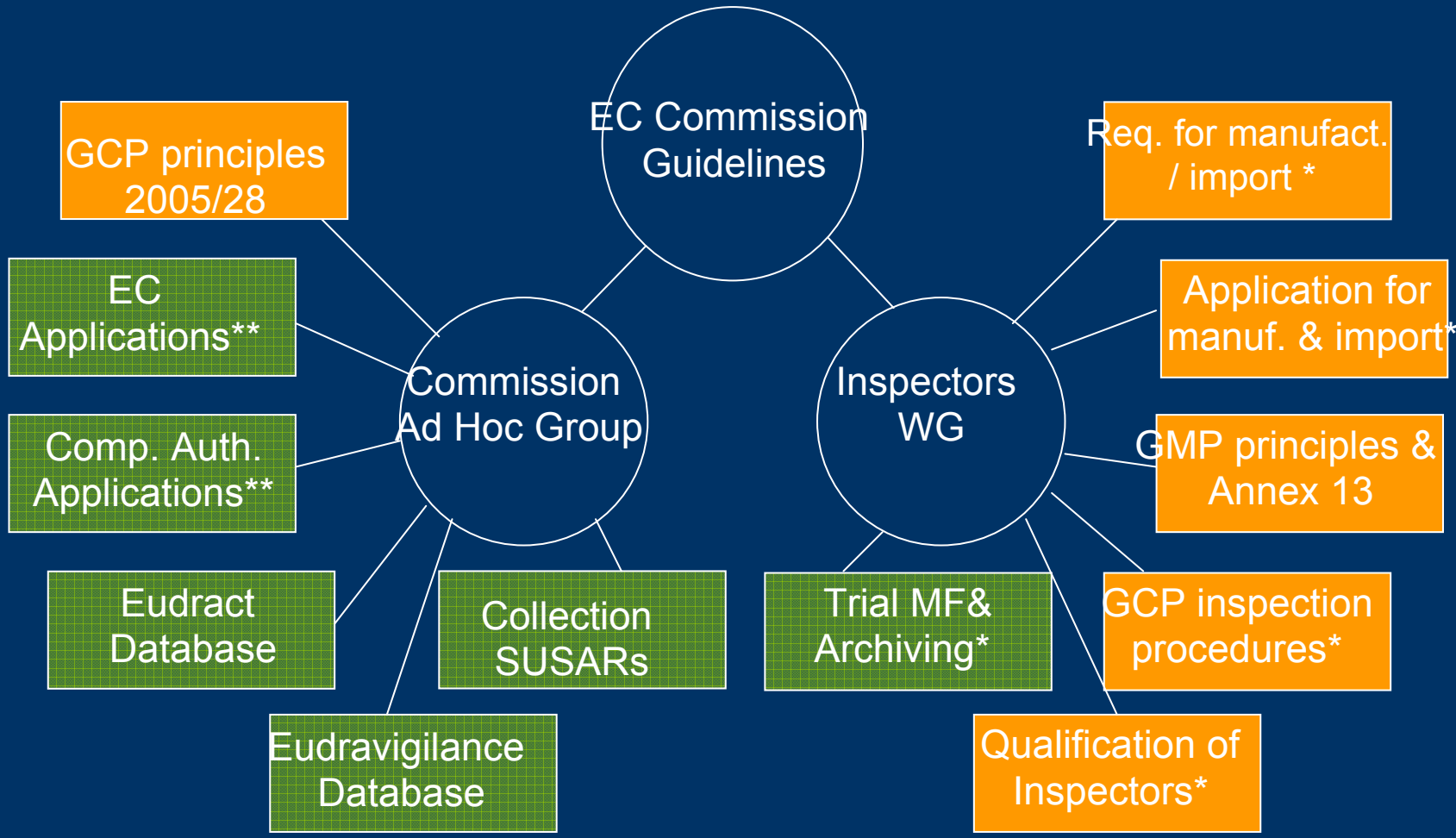
- Clinical Trial Directive –
  Status of Implementation in Europe
- Experience in Germany
- Future Perspective

Areas Impacted by Clinical Trial Directive

DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001

- Standardization of procedures with EC and Authorities
- Setting GCP standards
- Setting GMP standards for investigational medicinal products
- Requiring inspections against internationally accepted GMP and GCP standards
- Harmonization of collection of Safety Information

Explanatory Guidelines



**= revision under preparation

*=covered by 2005/28 published in May 2005

Working Groups / Insititutions

Clinical Trial Working Groups (EMEA)
Inspectors Working Group
EUDRACT Joint Operations Group
Eudravigilance Group

Clinical Trial Facilitation Group

- Established mid 2004
- Chair Dr. Martyn Ward, MHRA
- To coordinate the implementation of the EU Clinical Trial Directive across the Member States at an operational and national level.

History

1997 Initial Proposal by European Commission

1999 Opinion of the Economic and Social Committee

2001 Publication of Directive 2001/20/EEC

2004 Deadline for Implementation in Member States

2006 Review of Implementation by Commission?

Status of Implementation (June 2005)

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Deadline for Implementation: 1 May 2004

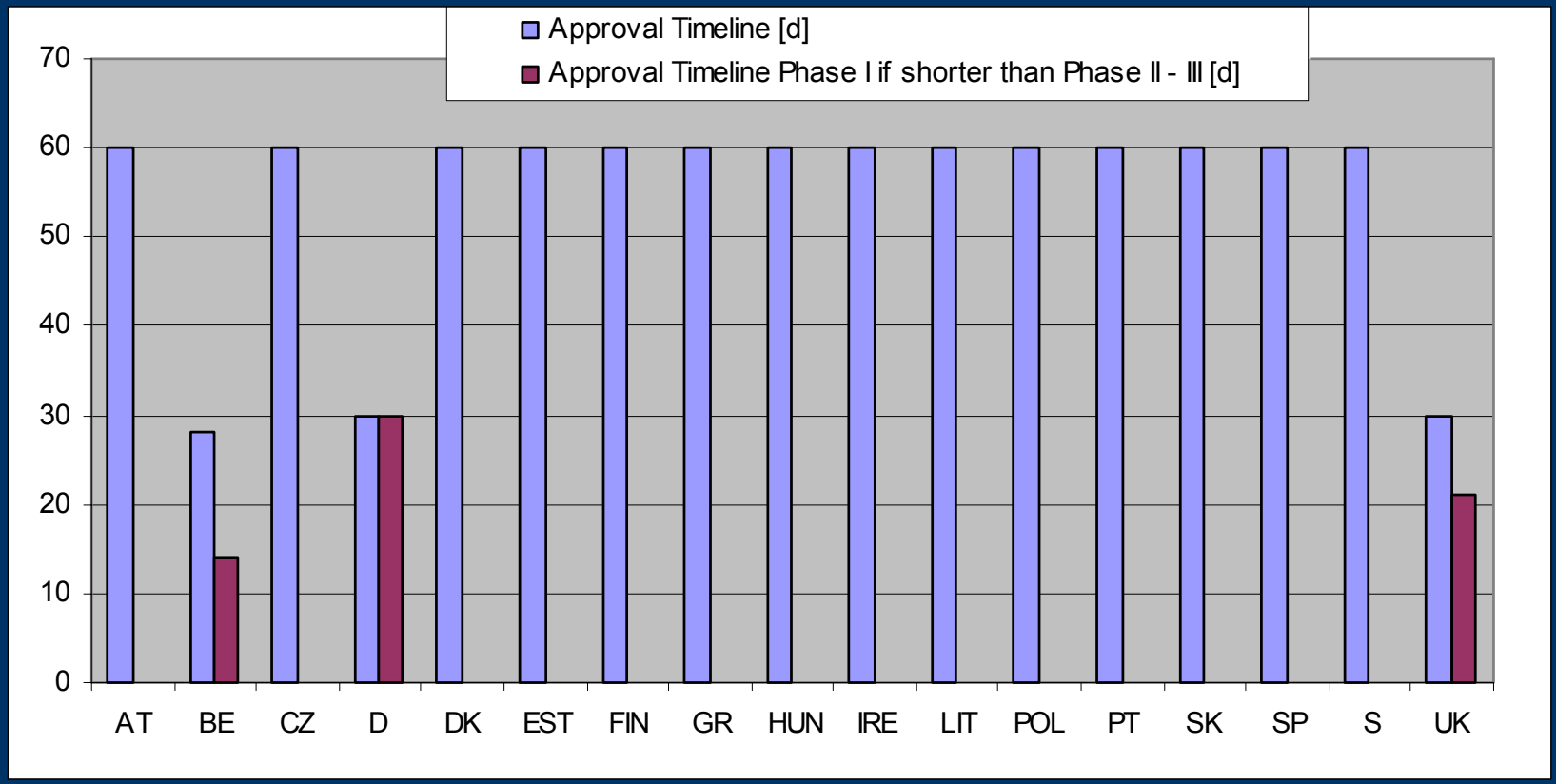
Implemented:

Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Lithuania, Poland, Portugal, Slovakia, Spain, Sweden, UK

Unimplemented or partially implemented:

France, Hungary, Italy, Latvia, Netherlands, Slovenia

Legislation Timelines for Approval of Competent Authorities (NCE)



Approval timelines including Phase I trials (if different).

Experience in Europe

Harmonization has not been fully achieved due to additional national requirements, e.g.

- National application forms
- Specific statements and confirmations
- Translations
- Submission of samples

Experience in Europe

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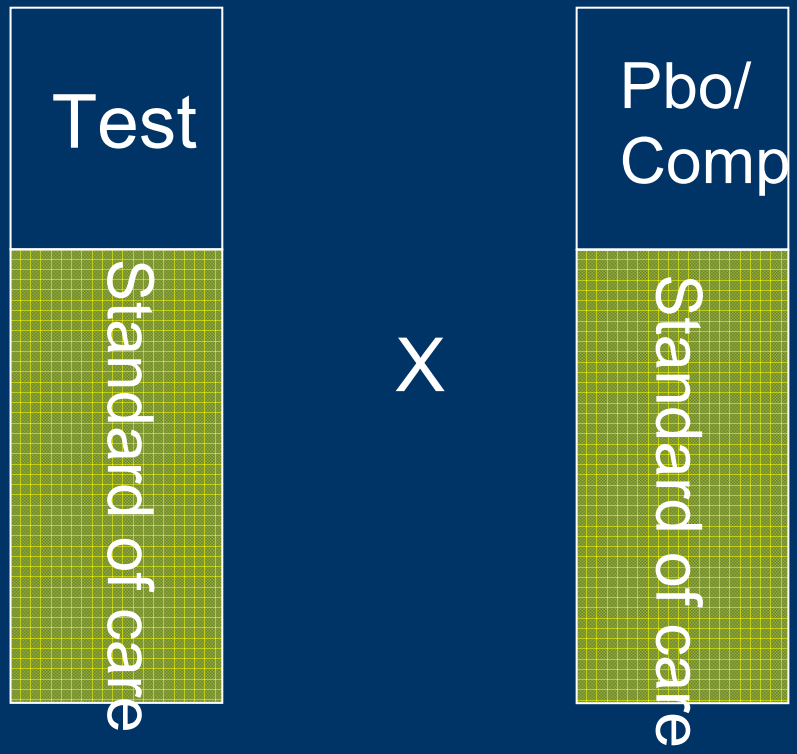
Differences in Implementation and Interpretation between Member States

- Safety Reporting (SUSARs)
- Definition of the Investigational Medicinal Product (non-modified comparator, standard of care, challenge agents)
- GMP requirements
- CMC requirements

Differences in Expedited Reporting of SUSARs

To Competent Authority	• All SUSARs regardless of country (most) • All SUSARs related to the trial in the country (FIN, LT) • Local SUSARs only (GR, FL, N)
To Ethics Committee	• All SUSARs regardless of country (most) • All SUSARs from protocol approved by EC (CZ) • Local SUSARs only, QLL for foreign cases (CZ, EST, FIN, GR, IS, IRL, LT, N, E, UK) • Not defined (I, FL, M, NL, P)
To Investigators	• All SUSARs regardless of country (AT, F, D, H) • Local SUSARs only, QLL for foreign cases (CZ) • Periodic line listings (DK, I) • Not specified (all others)

Definition of the IMP



Test, PBO = IMP

Comparator / SOC if approved medication used unchanged and within the approved indication/= IMP (?)

Will have impact on packaging / labeling, documentation for IMP and approval, safety reporting and cost of the trial.

GMP Requirements in addition to 2001/20/EE`C and 2003/94/EEC

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Country specific requirements

- GMP certificate from 3rd country (non MRA)
- Re-analysis requirements despite 2003/94/EEC

Incomplete implementation of 2001/20/EEC

- Request for national import license instead of import authorization

National administrative requirements

- IMP Labeling mock-ups
- TSE certificate in addition to IMPD
- QP declaration in country specific format

CMC requirements

Member States have requested level of data more in line with MAA than with CTA:

- Increased detail on stability
- Validation data according to ICH
- CoAs for all batches
- Data on comparator

⇨EU Guideline under development – national guidelines should be withdrawn or adapted

⇨Guideline necessary for biologics as well

Experience in Europe

Amendments (35 days)

- Timelines for amendments are too long, especially for Phase I where they often exceed the actual duration of the trial.
- Decision on whether an amendment is substantial should be made by the sponsor.
- In principle, an amendment should only be required when patient safety could be negatively impacted.

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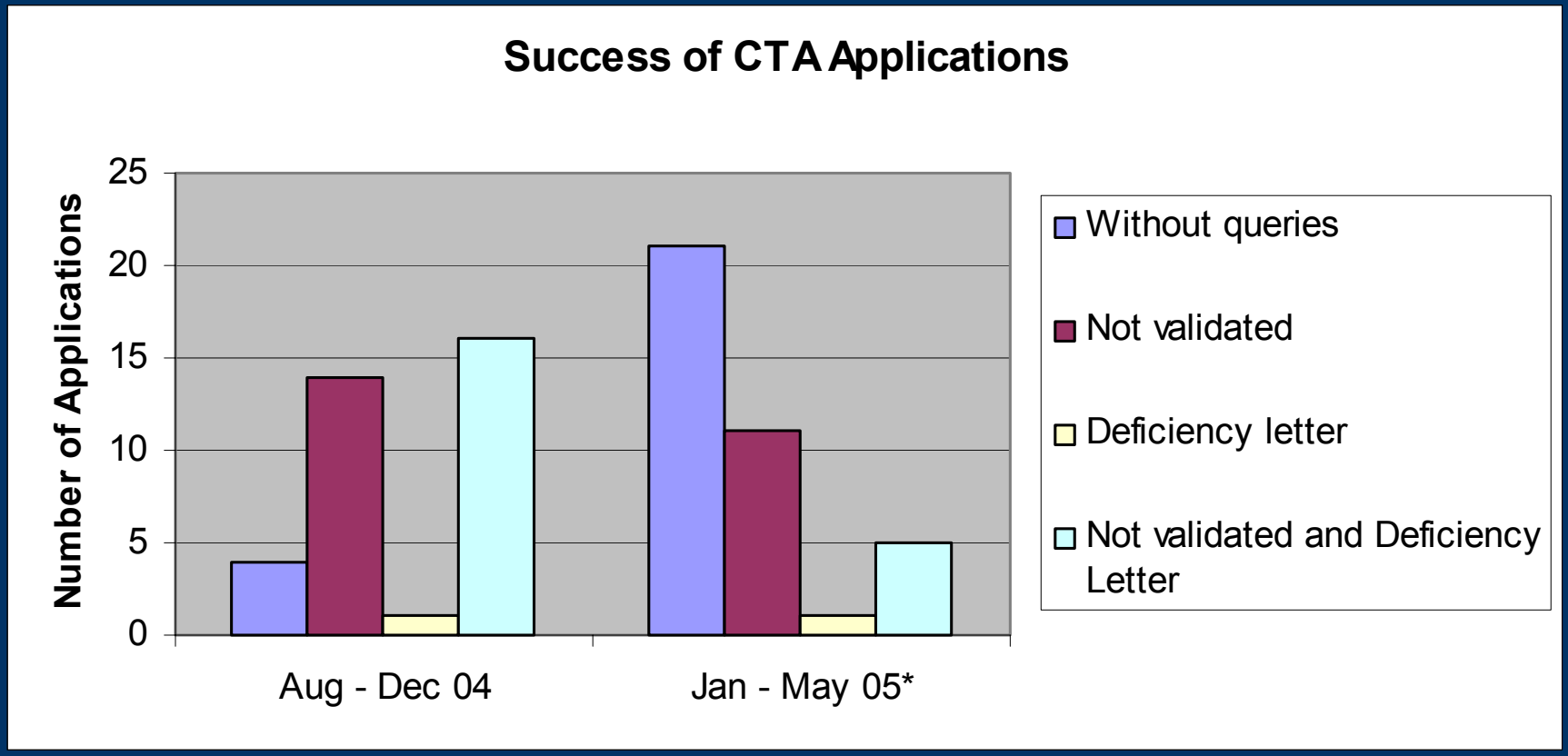
Approval timelines Phase I (AGAH survey)

	Aug - Dec 04	Jan – May 05*
Approval timelines BfArM (from submission until approval)	∅ **55 days** (range 28 - 151 d) n = 36	∅ **38 days** (range 17 - 99 d) n = 38
Approval timelines Ethics Committee (from submission until positive assessment)	∅ **36 days** (range 13 - 77 days) n = 29	∅ **31 days** (range 12 – 73 days) n = 30

* with new organization at BfArM

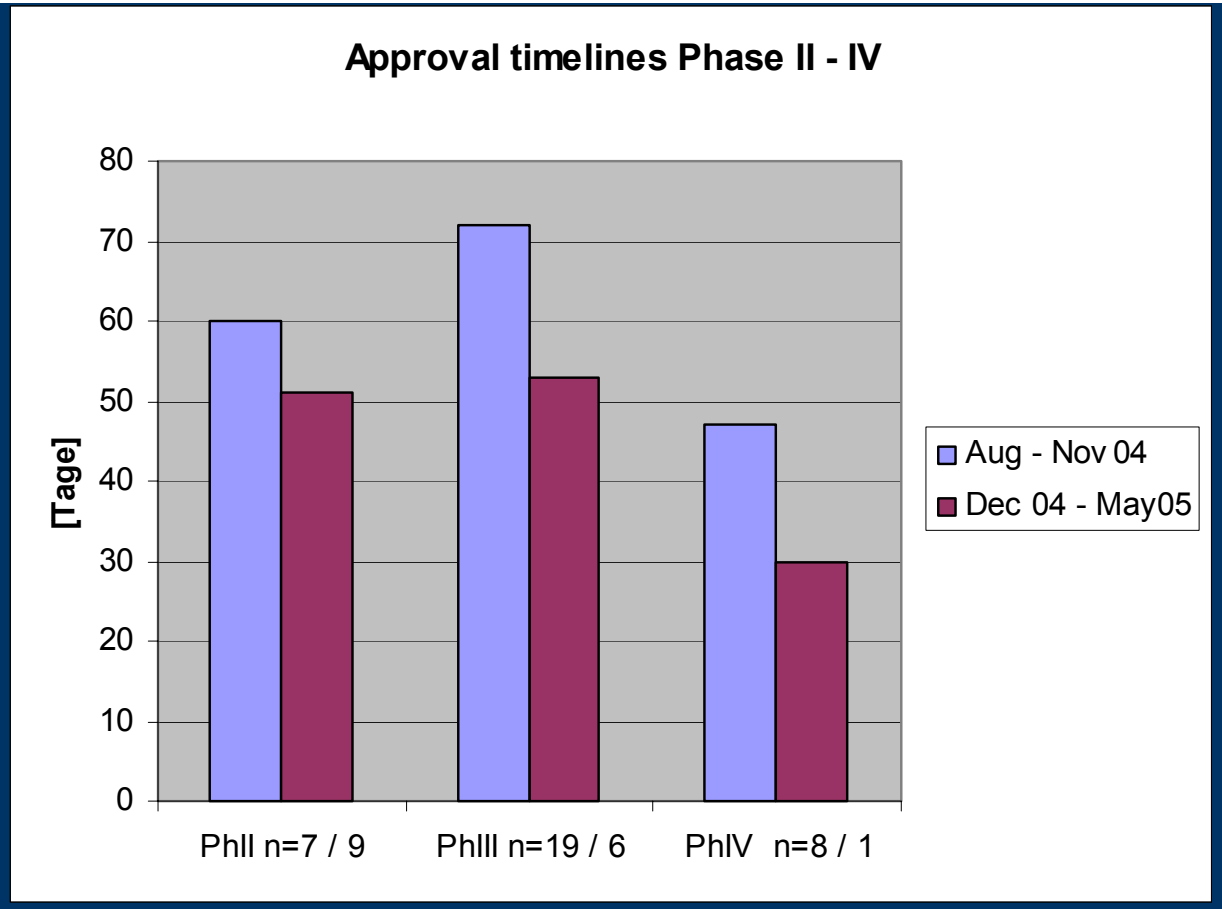
Approval timelines Phase I
Steps in approval process (AGAH survey)



Ratio of Applications without queries raised substantially

* with new organization at BfArM

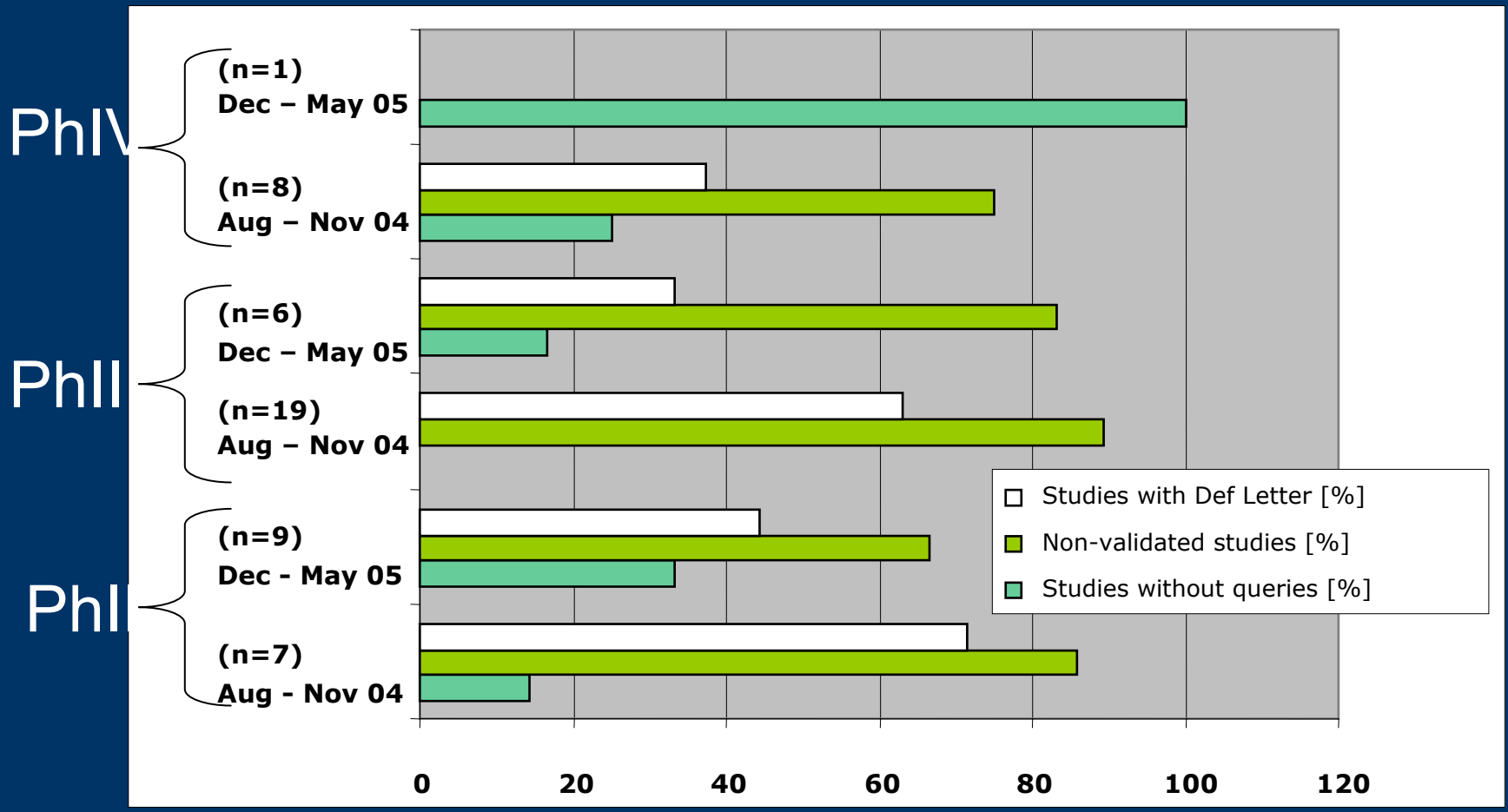
Approval timelines Phase II – IV (AGAH survey)



Approval timelines BfArM including response time of the sponsor.

* Dec 04 – May 05 = with new organization at BfArM

Percentage of studies with / without queries (VFA survey)



Percentage of studies without queries is increasing.

Experiences Germany

- In the beginning, “teething problems” especially with regard to some special requirements (statement on gender distribution, data protection, phototoxicity, male fertility).
- Overall approval timelines have been reduced since beginning of 2005.
- Lower ratio of non-validated studies / studies with deficiency letters.
- Recommendations for next studies with approval letter are considered helpful.
- However, shorter review for subsequent Phase I studies with 14 days approval timeline has practically not been implemented yet.

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Impact on the Efficiency of Clinical Development
Timelines

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Average number of trails per development Phase:

- Phase I: 5- 10 trials
- Phase II: 2 – 3 trials
- Phase III: 2 trials

Phase I trials: short duration and„build“ on results of previous trials

⇨ thus impossible to start compilation of CTA earlier

⇨ prolongation of Phase I approval timelines directly affects overall development timelines.

Impacts on the Efficiency of Clinical Development Documentation Requirements

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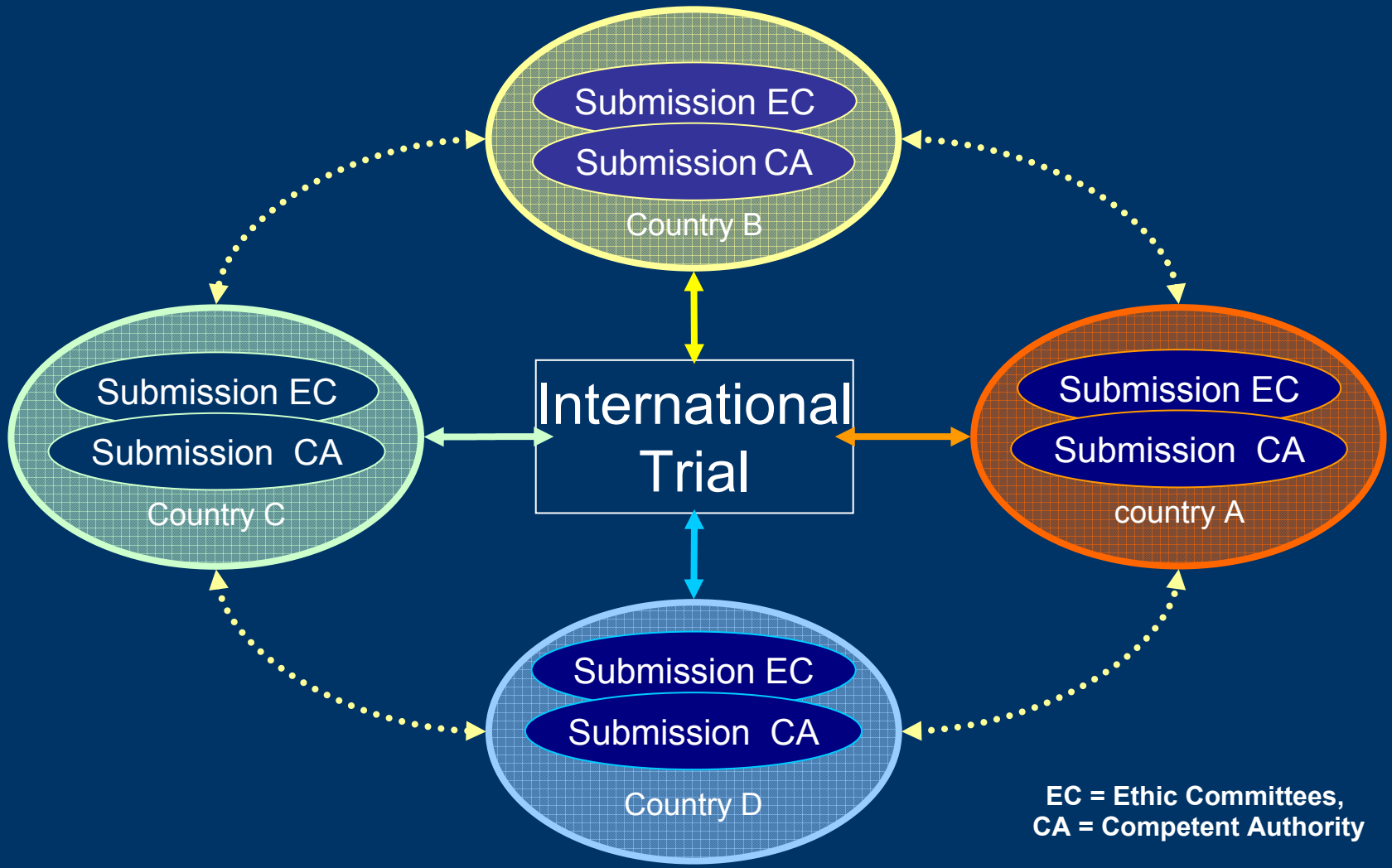
	IND requirements versus IMPD requirements	Comment
Exploratory Phase I	IMPD >>> IND	Specific new US Guidance with lower requirements
Phase I	IMPD > IND	Higher requirements on validation of methods, stability data, generally higher level of detail
Phase II	IMPD ~ IND	
Phase III	IMPD < IND	IND is reviewed by FDA with regard to NDA

Impacts on the Efficiency of Clinical Development Harmonized Decisions



Wishlist….

- Full harmonization of documentation requirements within the EU
- Focus on essential requirements
- „Pan-European“ CTA without complicated recognition procedures
- Special requirements for early Phase I trials with regard to documentation requirements and timelines
- Bridging of EU and US requirements