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New Challenges for EMA and NCA: News from BfArM

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Agenda / Outline

- BfArM in the EU
- Experience with new variation regulation
- Experience with clinical trials in medical devices
- Benefit-risk, efficacy, effectiveness – challenges for regulatory bodies

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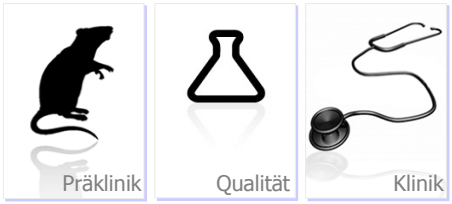
Clinical Trial Applications

about 1.100 Applications/Year

about 4.000 Applications/year

Validation



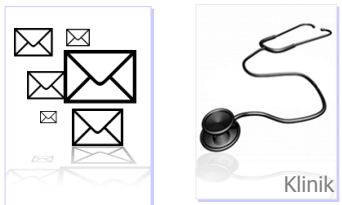
Approval

Variations

about 5.000 reports/year

about 10 inspektions/year

Pharmacovigilance



GCP-Inspektions

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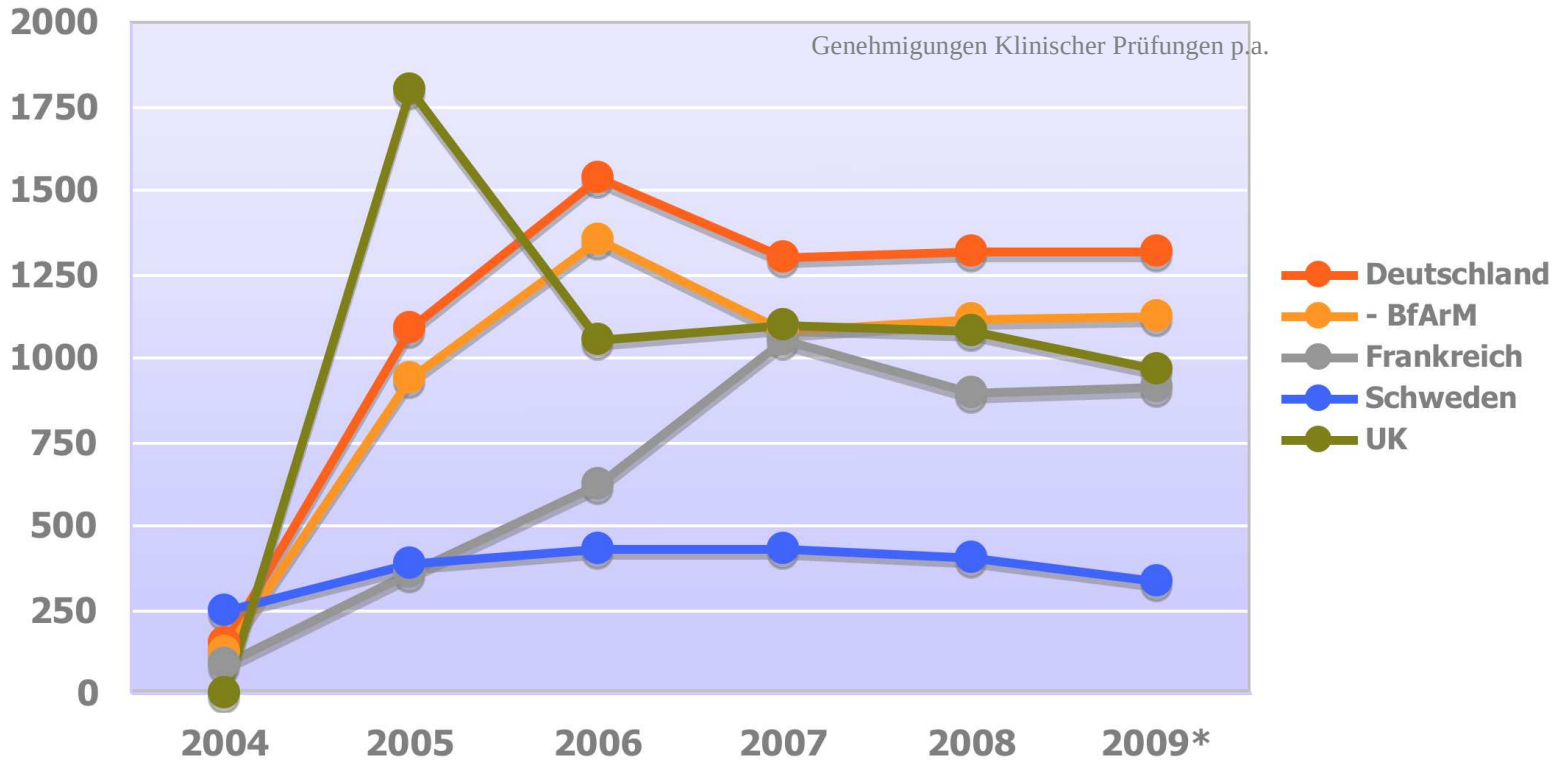
Germany in comparison to other NCA



*bis einschließlich 26.11.2009

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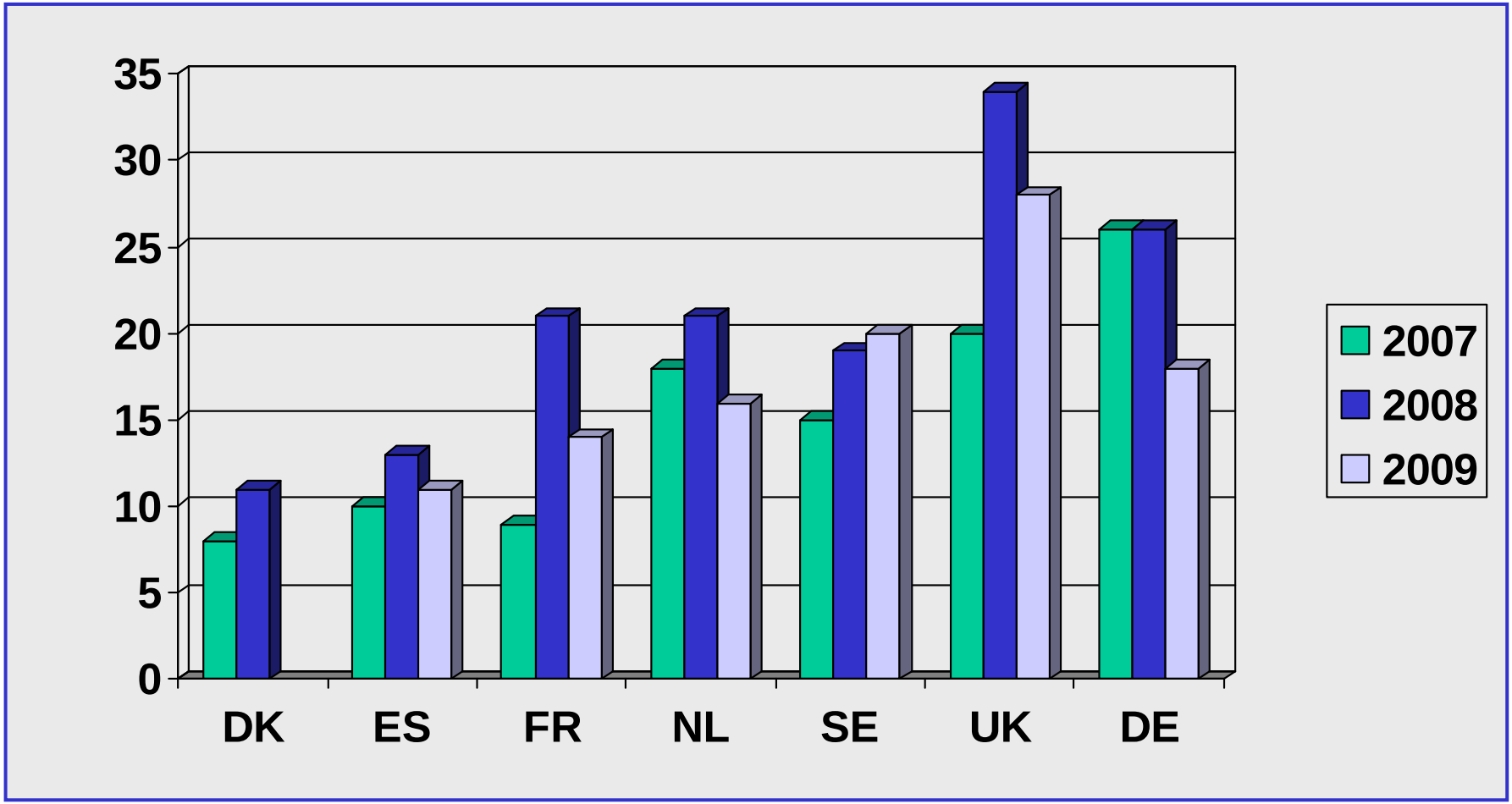
BfArM in Europe: Centralized Procedures



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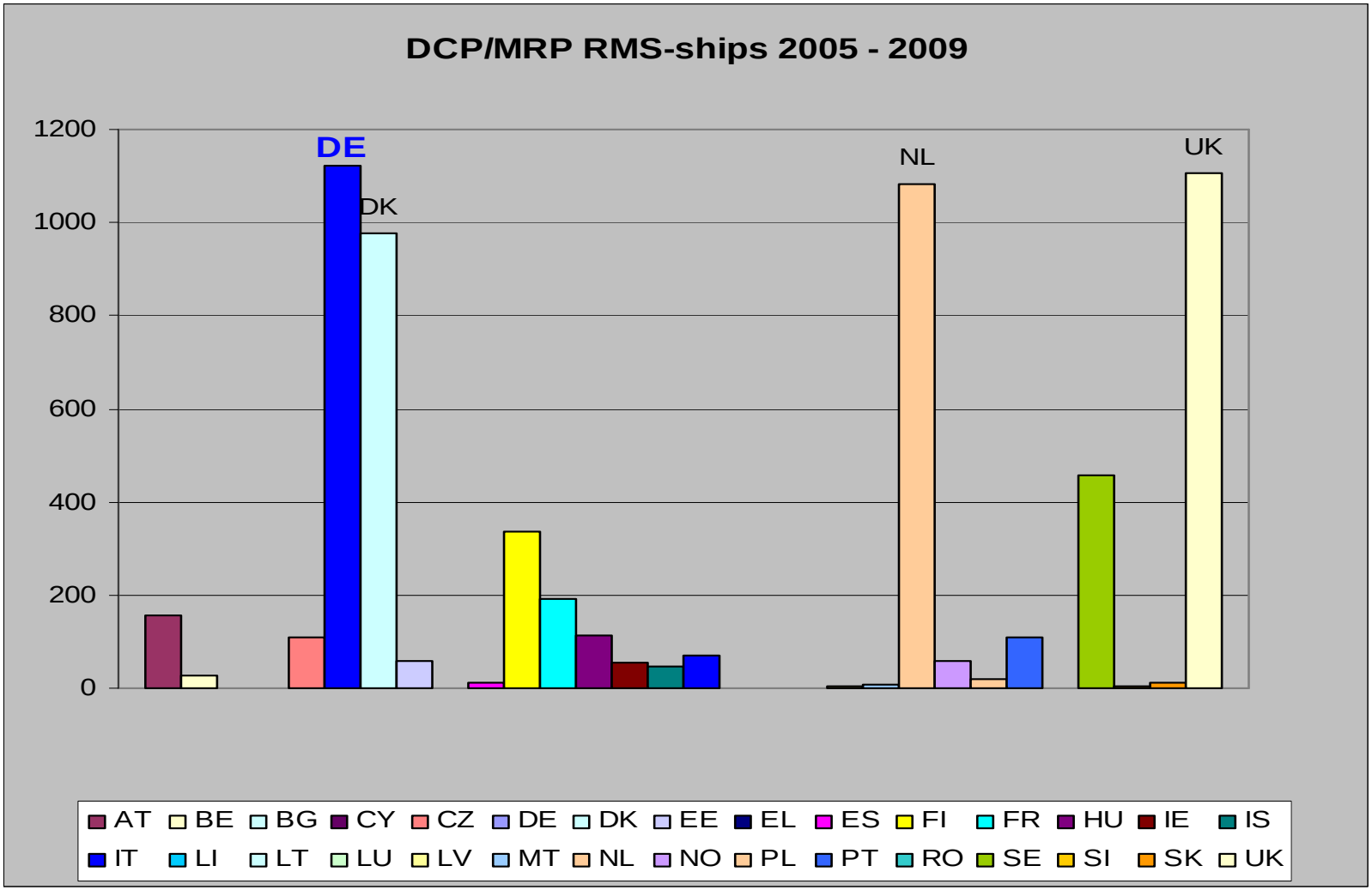
BfArM in Europe: decentralized Procedures



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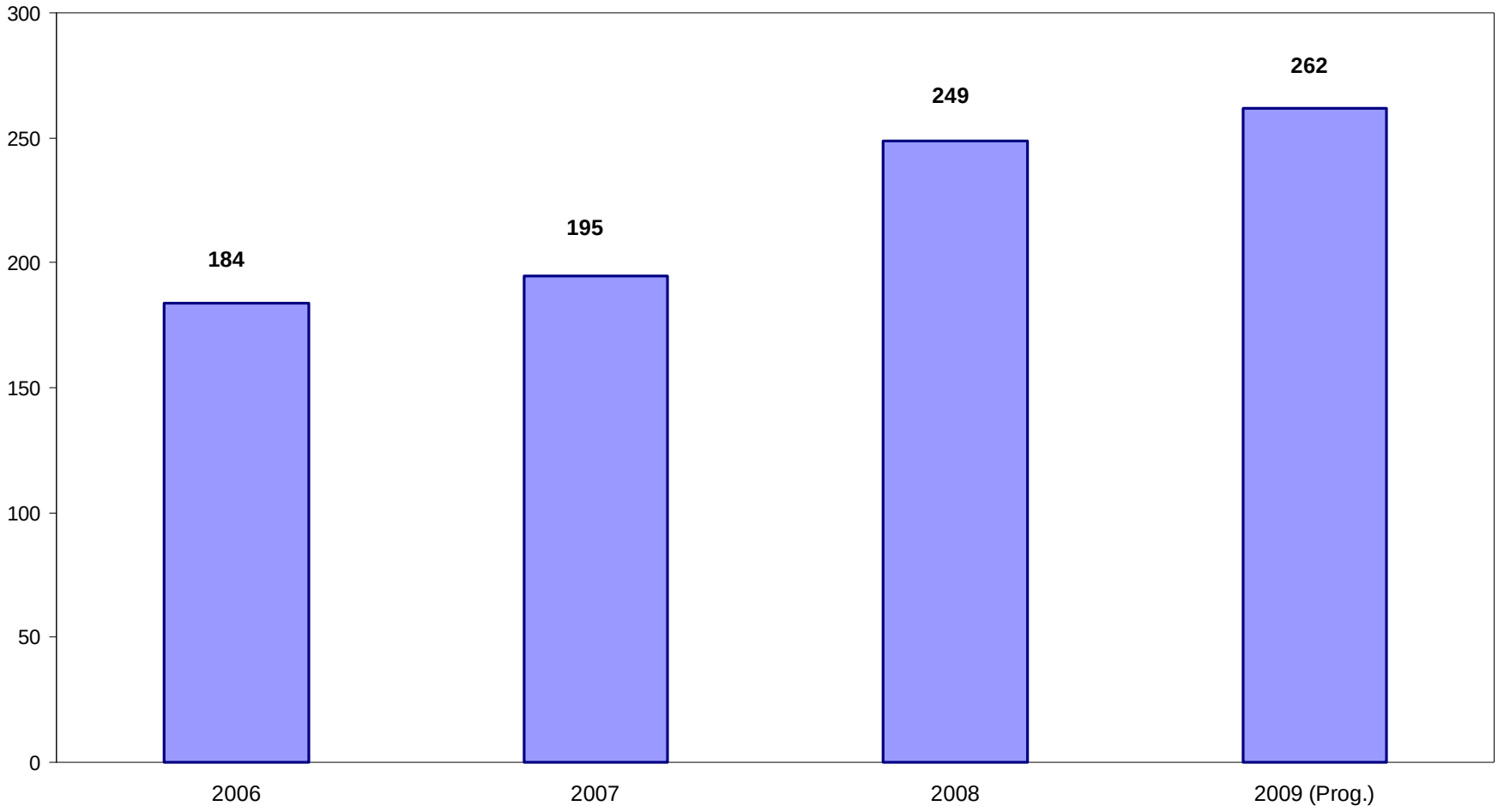
Working Volume of finalized Procedures
(Total in Thousand Working Hours)



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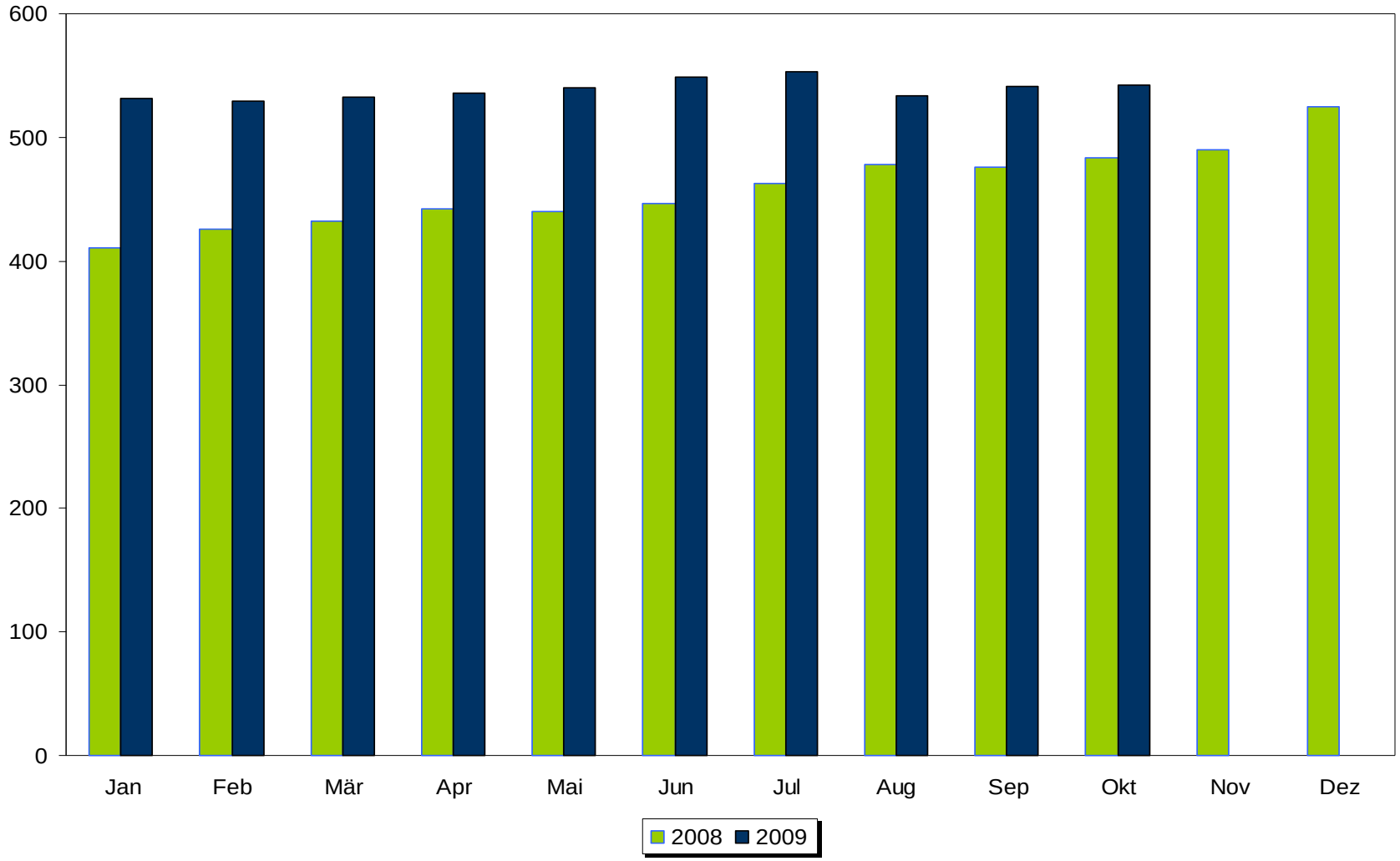
Working Volume of Open Procedures
(Total in Thousand Working Hours)



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The revised Variation Regulation Commission Regulation(EC) 1234/2008

First experience after 4 months…

Many questions in the first 8 weeks, e.g.

- Which grouping is allowed
- Documentation to be submitted
- Unclassified variations
- Definition of one MA (incl. strength and pharmaceutical form)
- Numbering
- FEES!!!
- Electronic submission (eCTD)

Meanwhile…

- New procedures are well adapted
- Grouping in all types IA, IB and type II submitted in large numbers (but so far no extension application concerned)
- Number of IA-grouped applications for more than one MA is growing continuously
- First worksharing procedures (with NCA and EMA as reference authority) are positively finalized but only few procedures
- Many Article 5-recommendations

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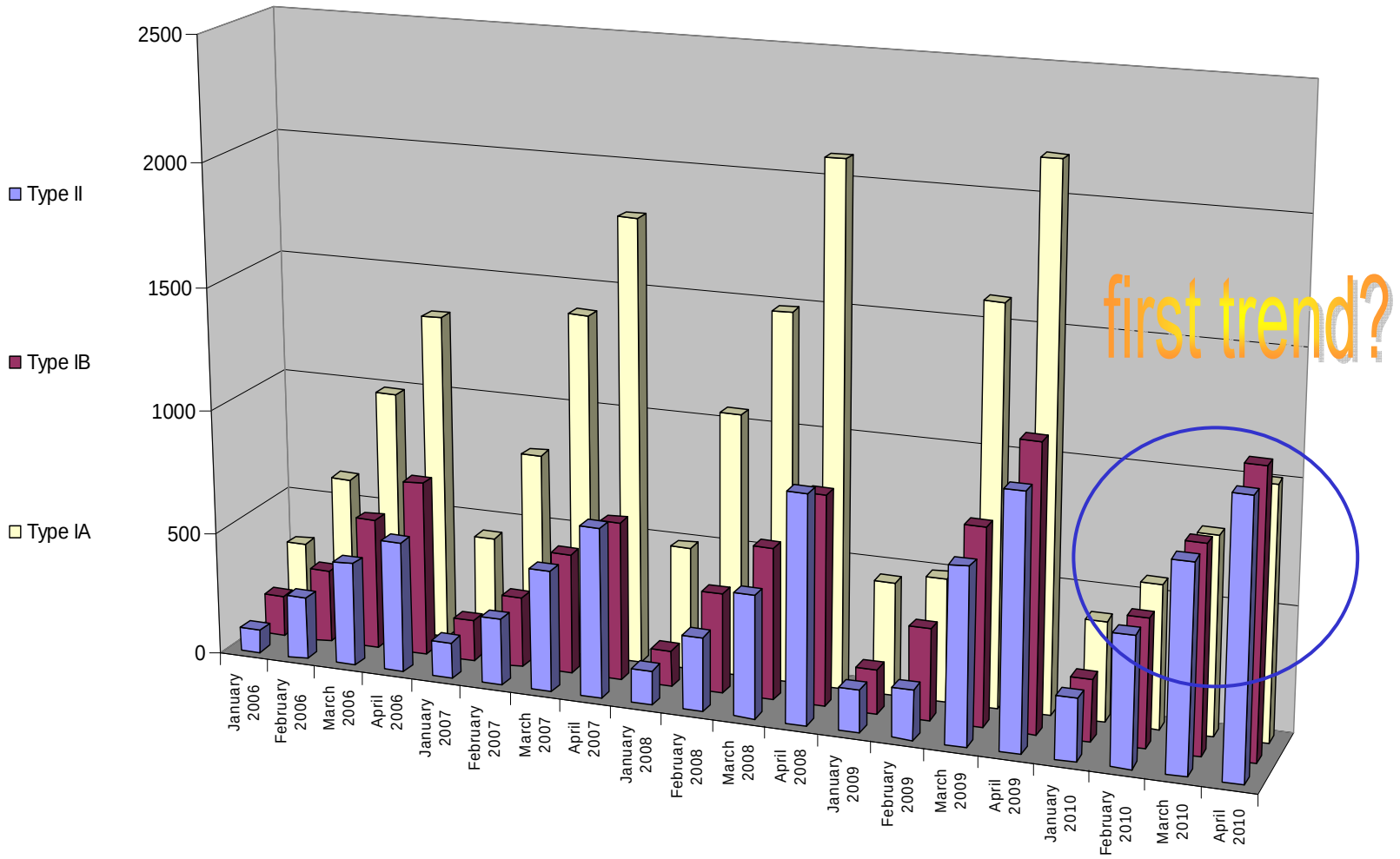
Submissions Jan.-April 2006-2010



Issues mentioned …

- Former so-called „umbrella“ variations are much more complex now – every single minor change has to be specified for a grouped application instead of a major single variation (e.g. update of ASMF)
- Facilitation only in paper version – electronic submission still per marketing authorisation (no harmonised definition in the EC) and therefore resource intensive
- FEES!!! – No adjustment of the fees to the reduced workload with grouped applications in many competent authorities
- …

Improvements – present and planned

- Lots of guidances have been prepared and are still regularly updated:
  - Best Practice Guide for Variations (last update May 2010)
  - Q/A document for Variations (last update April 2010)
  - List of examples for acceptable and not acceptable Groupings (first published May 2010)
  - Explanatory notes for application form (last update April 2010)

- Update of Annex II of the Variation Regulation could be helpful for industry and agencies
  ⇨ proposal to introduce as alternative to Grouping a Type II variation for „high level" changes, e.g. update of ASMFs, update of product information etc.

- Electronic variation application form will soon be available

- Feedback from applicants is needed and welcome…

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Medical Devices Directive 2007/47/EG

- The amendment of the Act on Medical Devices (4. MPG-Novelle) is based on the directive 2007/47/EG
- Amendments of the directives 93/42/EWG und 90/385/EWG (21. September 2007)
- 17 of 23 articles of directive 93/42/EWG have been changed
- 9 of 12 appendices of directive 93/42/EWG have been changed

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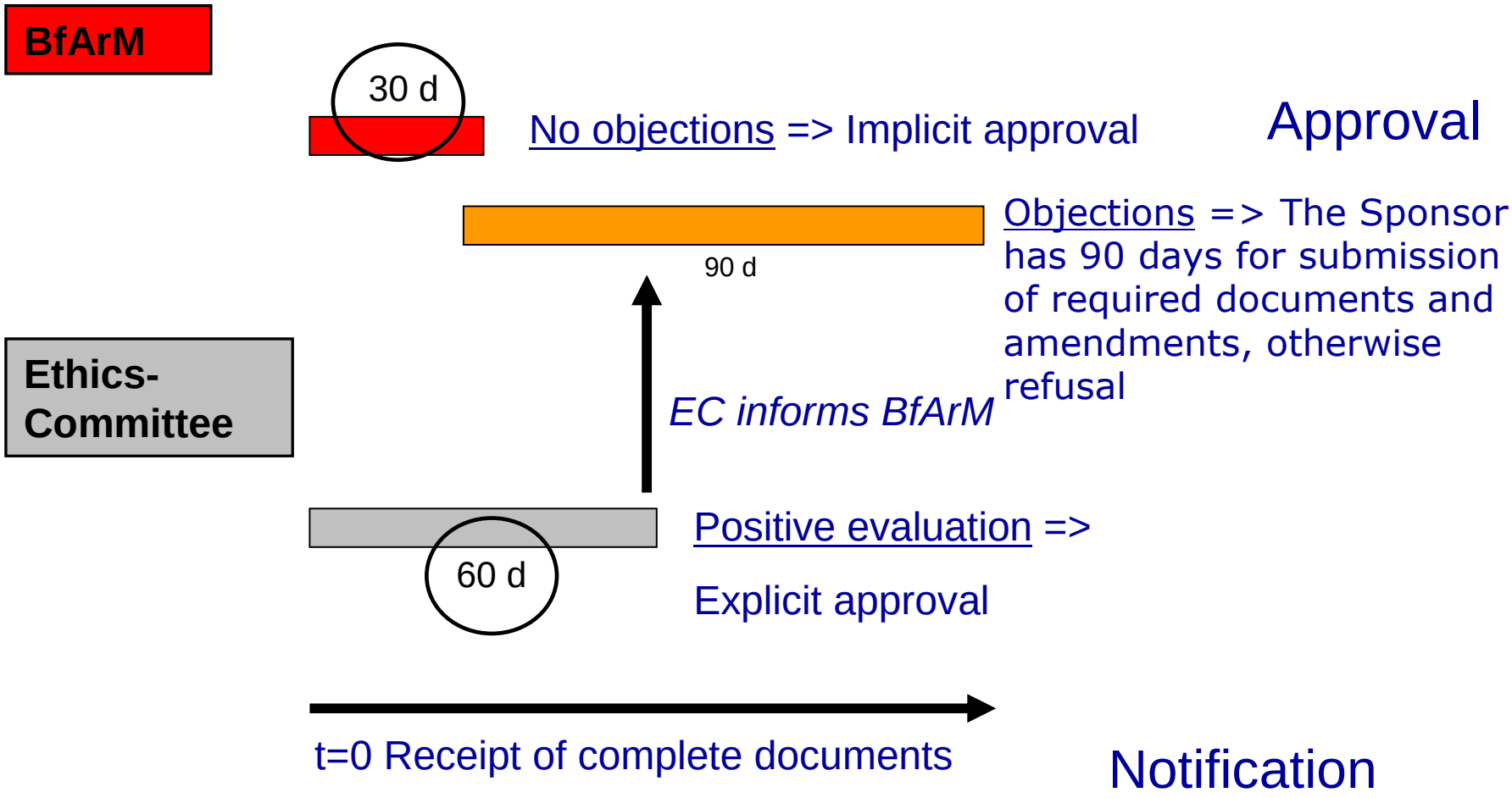
Important Amendments by Directive 2007/47/EG

- Clinical Trials and Clinical Evaluation
- Design dossier evaluation by Notified Bodies for products with medium to high risks (IIa / IIb devices)
- Establishment of an legal basis for uniform decisions on classifications within the EU
- Legal basis for an uniform notification and surveillance of Notified Bodies

Approval of the clinical trials

Time-Line



Evaluation according to § 20 (1) S. 4 Number 1, 5, 6 und 8 MPG

evaluated by BfArM

Risks/Benefits

Biological Safety

Technical Safety

Clinical Trial Protocol

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Approval Procedures at BfArM Statistics

- Total Number of Applications (March 21. to May 27. 2010) **47**
  - Clinical Trial Applications 31
  - Rejection/Objections of Approval 16
  - Approved Clinical Trials 1
  - Pending Approvals 46
- Clinical Trials sponsored by commercial entity 36
- Clinical Trials sponsored by University/ Science 11

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How can this be done ?

- **Further streamlining of registration and approval procedures**
  - Strategy group
  - Best practice guiding
- **Further improvement of IT-structure**
  - Data and workflow management system
- **Further development and professionalisation of the staff**
- **Dialogue and transparency**
  - BfArM in dialogue
  - Workshops

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Regulatory Dilemma ...

Benefit-risk-assessment

Effectiveness

Clinical Relevance

Early Access

Relative Efficacy

Efficacy

Comparative Effectiveness

Risk Management

Cost Effectiveness

Rel. Efficacy Data already available...

from: Eichler HG et al., NRDD 2010

Type of RE described	FDA medical review *n* out of 42 (%)	EPAR *n* out of 47 (%)
Active comparator trial of clinical efficacy in the medical review or EPAR	17 (40.5%)	24 (51.1%)
Active comparator trial of clinical efficacy in the label or SPC	13 (31.0%)	16 (34.0%)
Active comparator information on efficacy derived from an RCT with an active comparator and placebo group	2 (4.8%)	3 (6.4%)
Active comparator information on efficacy derived from an RCT with an active comparator group, but without placebo group	15 (35.7%)	21 (44.7%)
Superiority over active comparator was shown in a head-to-head RCT	1* (2.4%)	10* (21.3%)
Active comparator licensed in the relevant indication in the respective agency's jurisdiction?	15‡ (35.7%)	24‡ (51.1%)
Summary data of the active comparator trial(s) presented numerically (for example, mean, median, confidence intervals) in the medical review or EPAR	12 (28.6%)	24 (51.1%)

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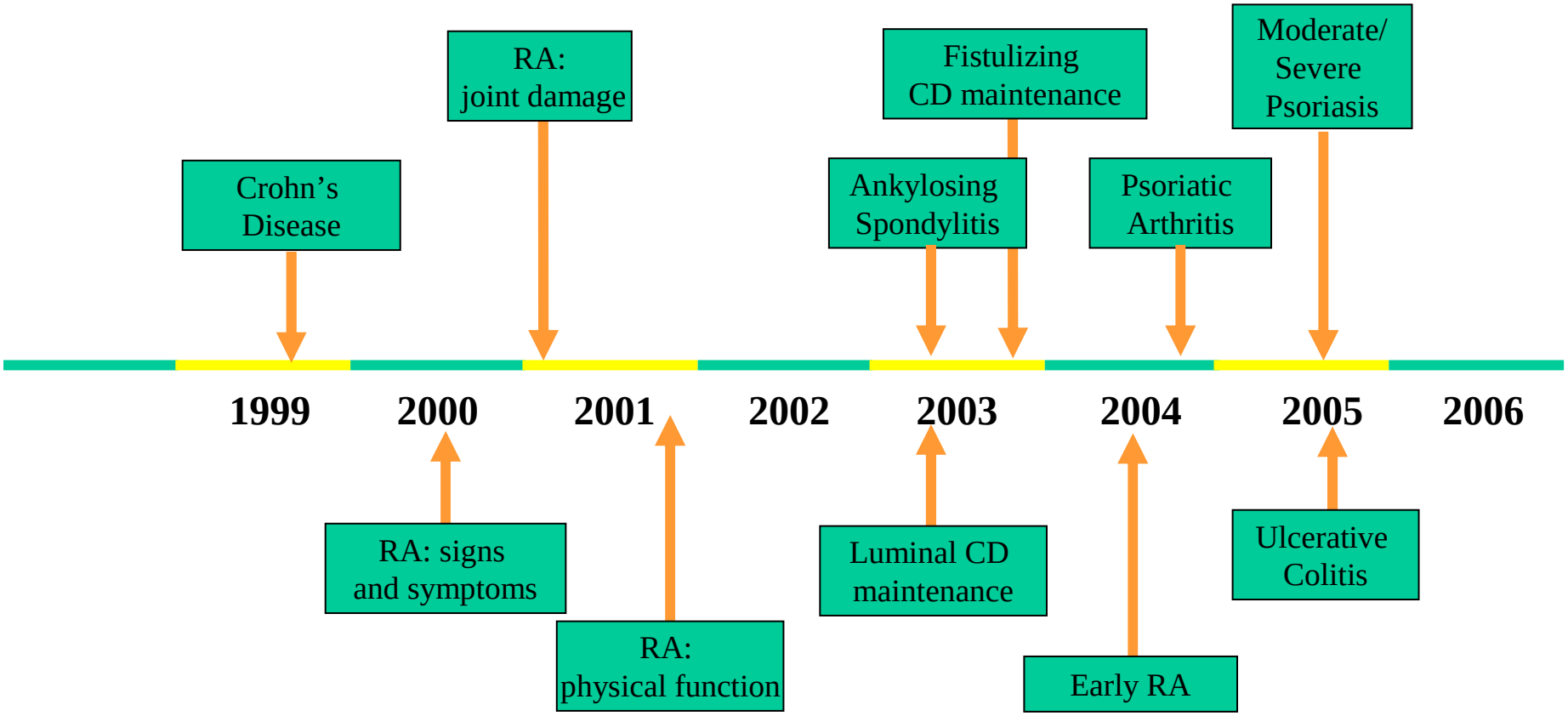
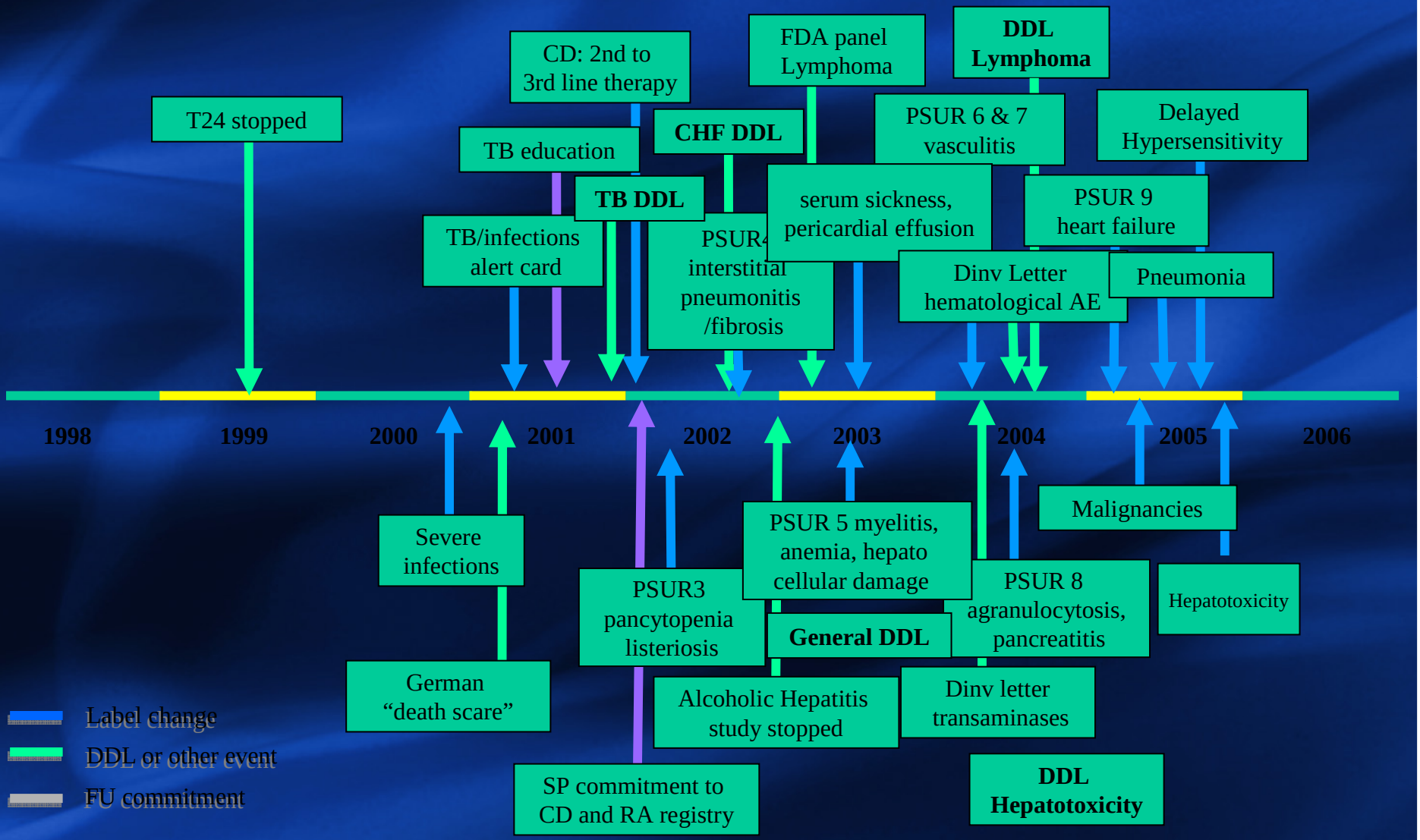
Evolution of Remicade (EU): Efficacy

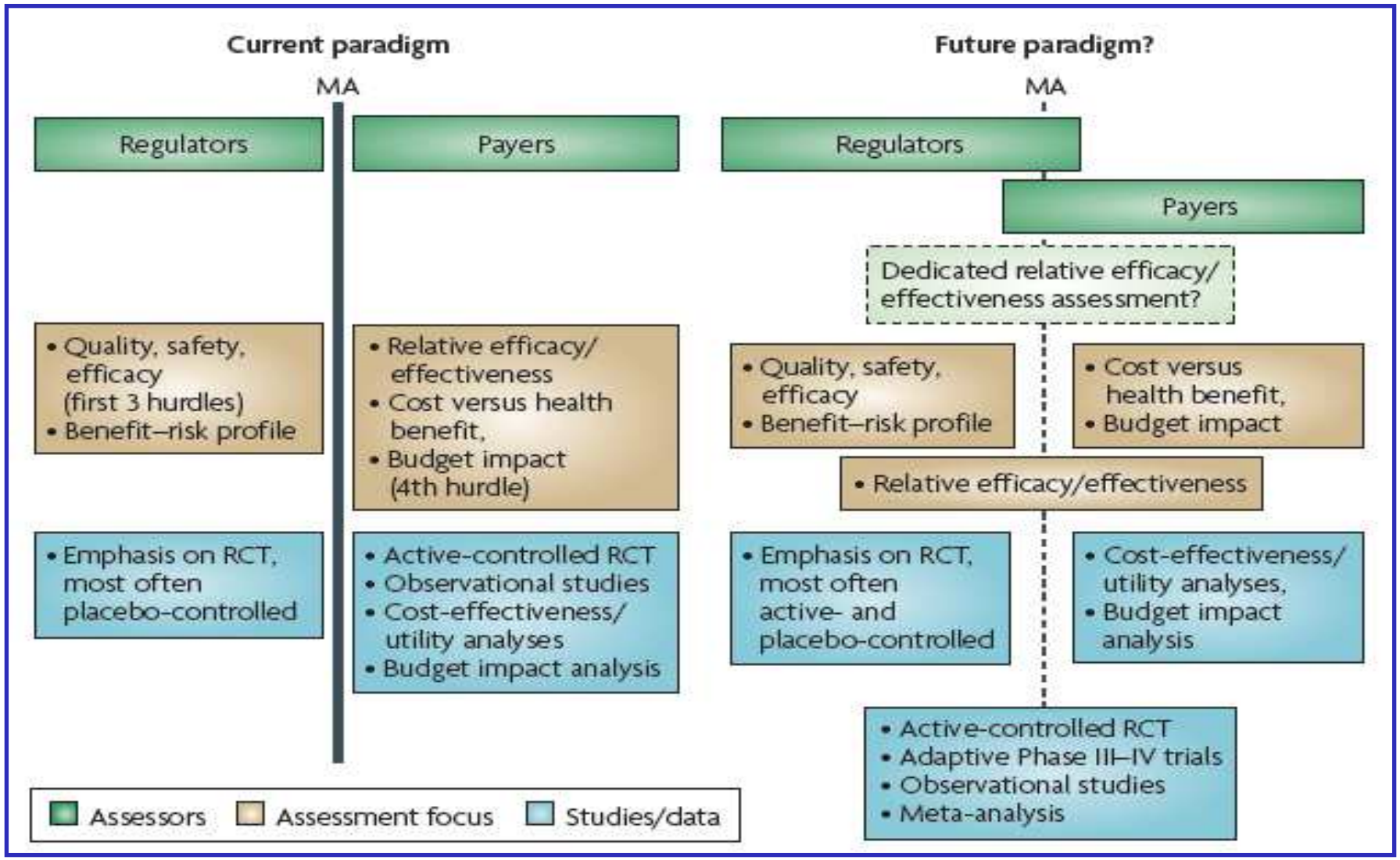


Evolution of Remicade (EU): Safety



Possible Challenges ...

from: Eichler HG et al., NRDD 2010



Conclusion

- Many new challenges ahead ...
- BfArM ...
  - is prepared to develop scientifically robust, consistent and transparent assessment systems
  - is keen to play a proactive role, both at national and European level
  - fosters strongly teamwork and cooperation within the European framework
- Research activities growing to strengthen scientific evaluation („best available expertise“)

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