



Accelerating Pharma time-to-market, cost effectively



Asia



Europe



Americas

How to Conduct Clinical Trials in Germany as a Mid-Size Player – landscape, requirements and opportunities

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Germany as a R&D location in a nutshell

- More than 350 years of successful drug development
- Largest pharma market in Europe, attractive price level
- BioRegions playing a driving role
- Strong academic research, KOLs, Max Planck-Institutes, Fraunhofer Institutes, established links to industry
- Assessible and respected competent authorities
- One of the most mature and established provider markets worldwide (e.g. CROs in DE 77 , US 185, UK 87)



Clinical Trial Situation Worldwide

Germany is number 2 worldwide on the basis of number of sites in clinical trials, number 3 in number of trials (FDA database)

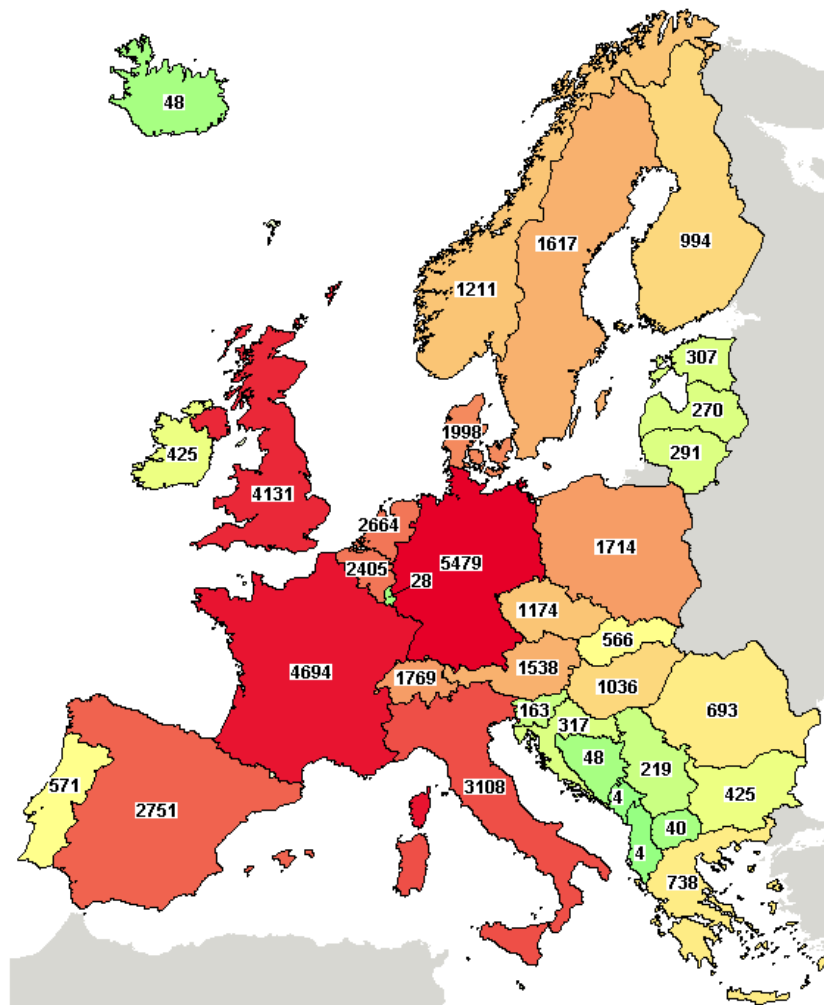
Country	No. of clinical trials
United States	44031
Canada	6521
Germany	5479
France	4694
United Kingdom	4131

source: clinicaltrials.gov, 30th Nov 2009



Clinical Trial Situation Europe

Number of registered clinical trials by country

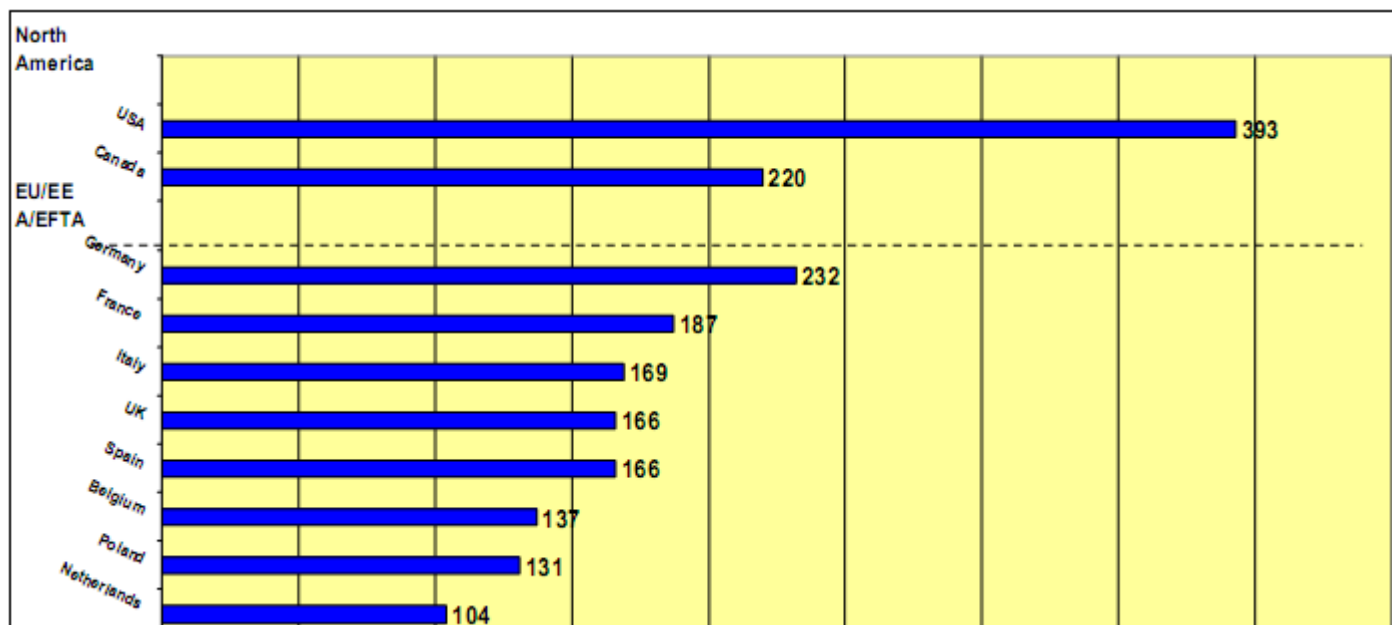


30th November 2009, clinicaltrials.gov



Clinical Trial Situation Worldwide

Number of pivotal clinical trials by country submitted in MAA to EMEA during 2005-2008



source: EMEA/INS/GCP/58632/2009

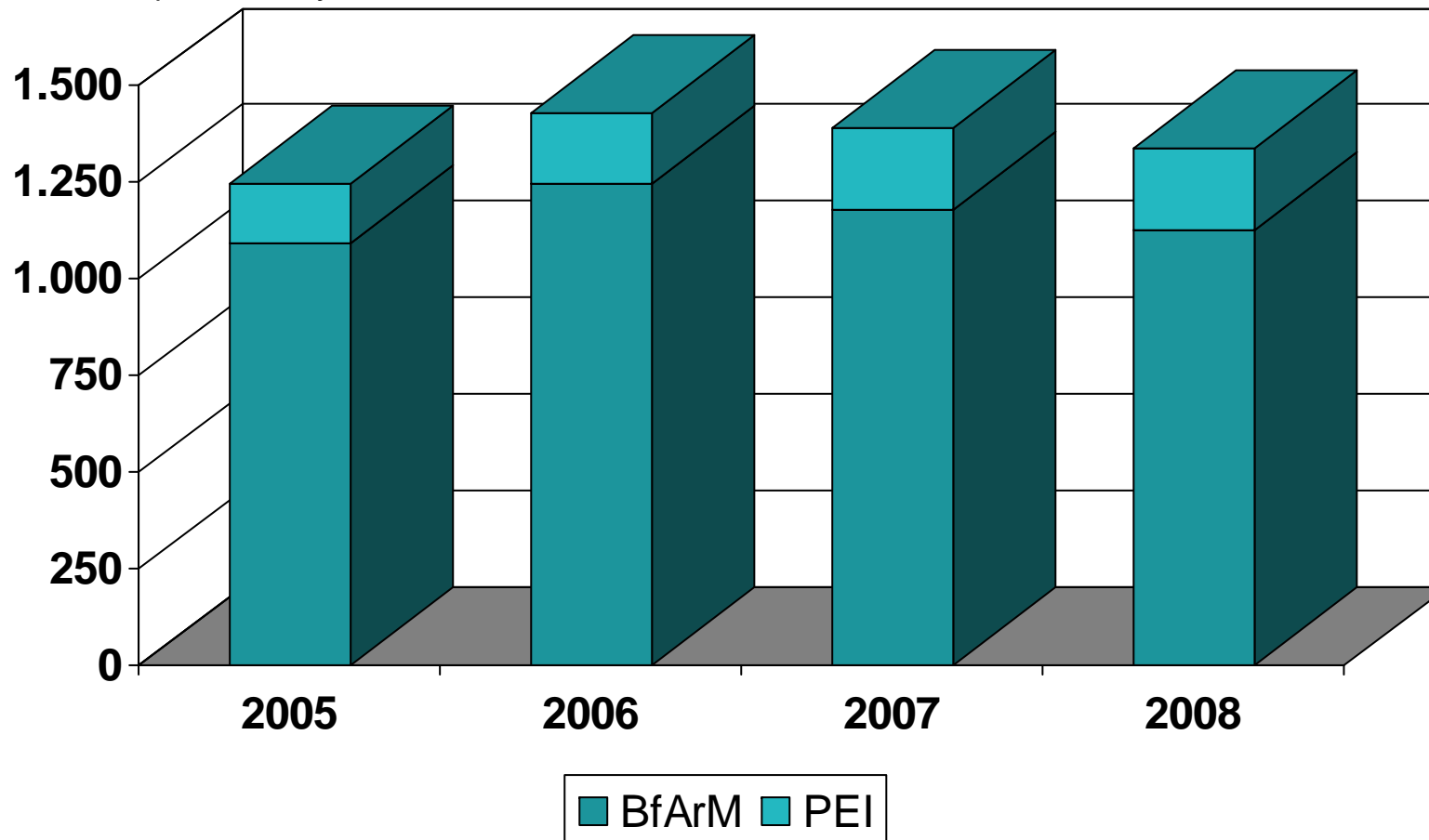
Germany is number 2 worldwide on the basis of number of pivotal clinical trials, submitted to EMEA



Clinical Trial Situation Germany

Submissions to Competent Authorities in Germany

medicinal products only

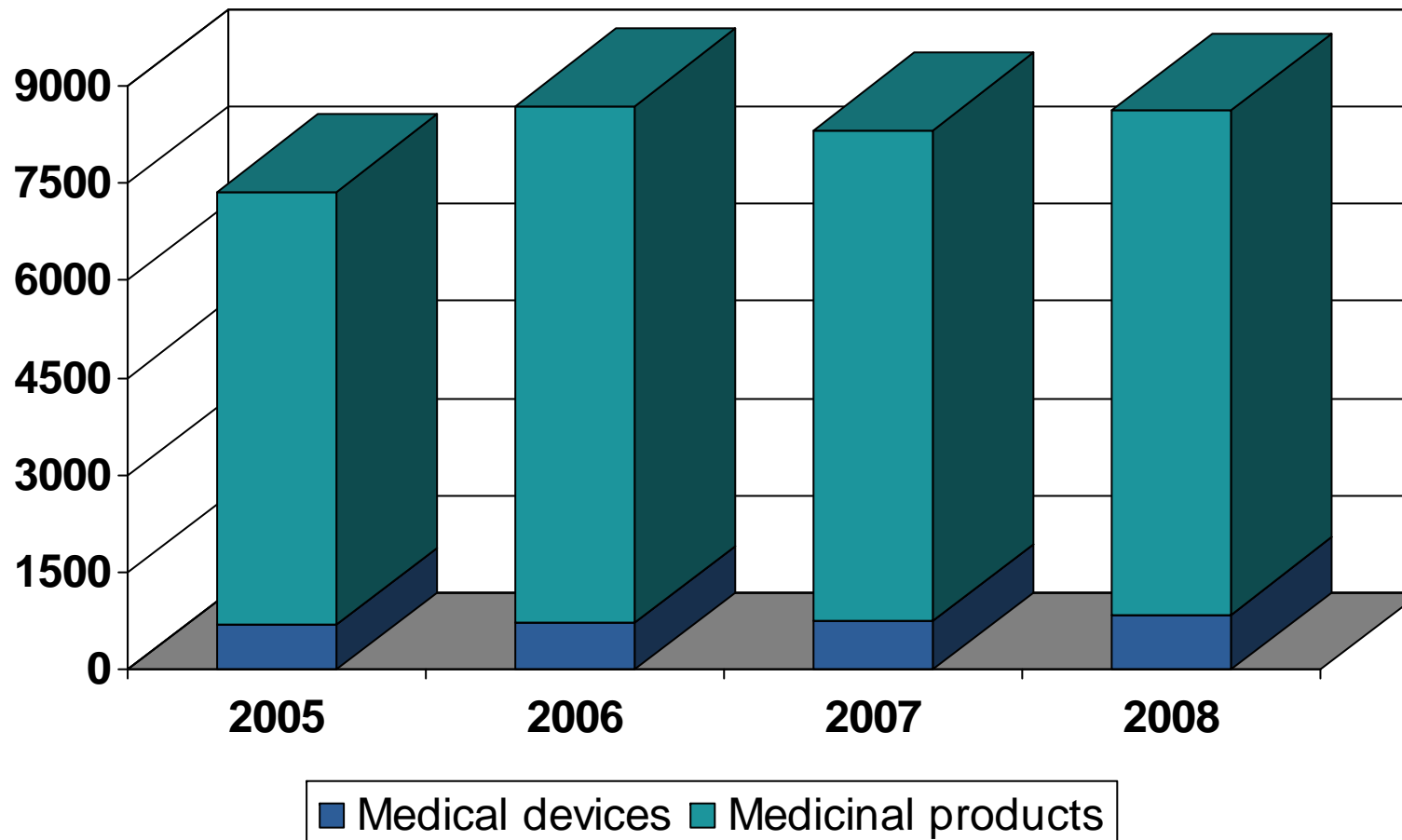


source: www.pei.de, www.bfarm.de, 25th Nov 2009



Clinical Trial Situation Germany

Submissions to ECs in Germany



Numbers are calculated based on the total number of submissions to leading and local ECs

source: www.ak-med-ethik-komm.de



Clinical Trial Application in Germany

Detailed timelines (CAs and EC) for the approval

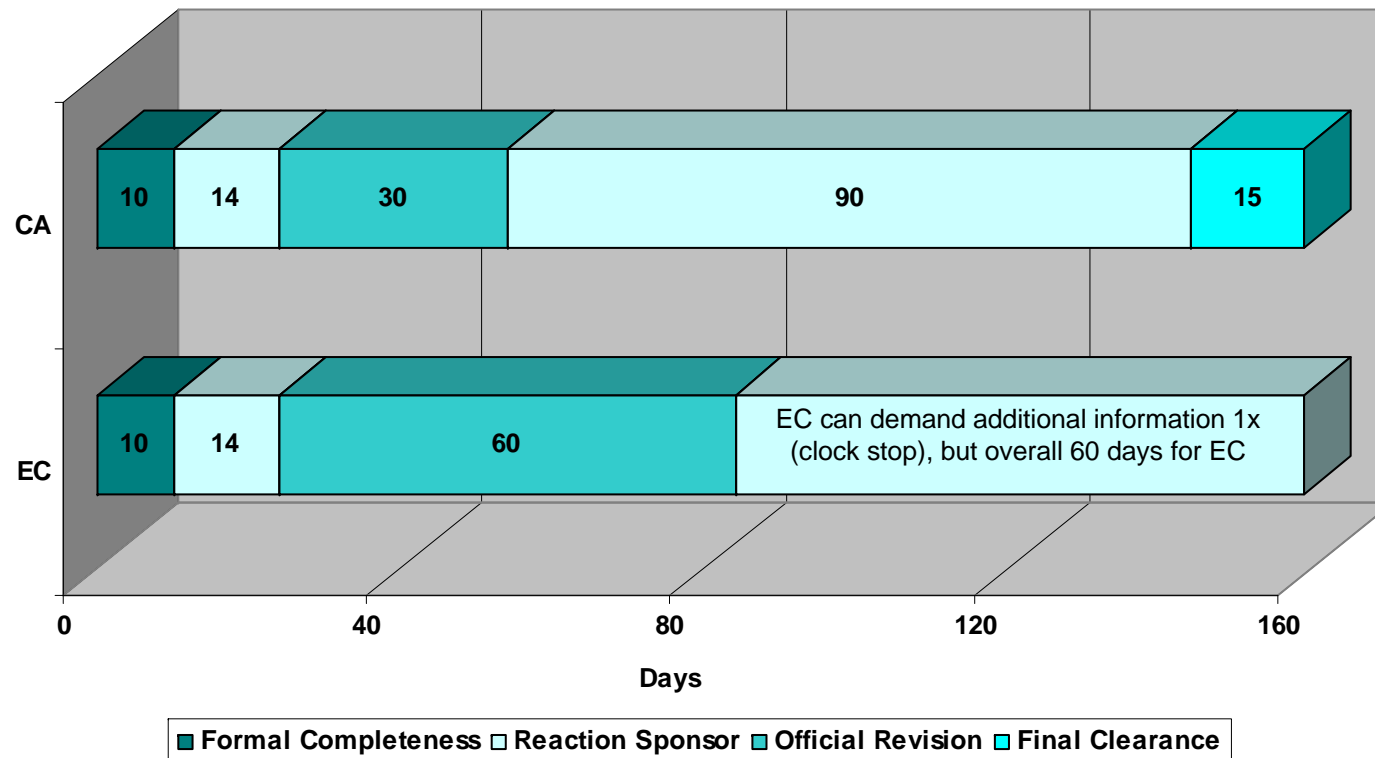
- Multi centre drug trials – 30 (CA)/60 (ECs) days
- Single centre studies and phase I trials (drug)– 30 days
- Sequential phase I drug trial – 30 days (initial), 14 days (further trials in planned sequence)
- Other timelines: Biologics – 60 days; somatic cell therapeutics – 90 days; IMPs for gene transfer – 90 days; IMP with genetically modifies organisms 90 days; Xenogenic cell therapeutics – no time limit
- medical device trials (mono and multicenter) – 60 days



Clinical Trial Application in Germany

Approval Process in Germany

Key regulated timelines according to German drug law (AMG)



Timelines relevant for the majority of multi-centre trials.



Clinical Trial Application in Germany

Ethics Committees

All clinical studies (including medical device studies) need a favourable opinion of the respective EC

ECs are constituted by regional Medical Chambers for office based medical practitioners and by academic institutions or hospitals for their investigative sites

EC Application

- Application to lead EC (EC of the coordinating investigator) which formulates an opinion on the study in consultation with the local ECs
- Copies of the application to be sent to all local ECs who formulate opinions on the suitability of the local investigational sites

For a medical device study only application to one EC (EC of the coordinating investigator) is necessary



Clinical Trial Application in Germany

Applicants' Perspective on ECs in Germany

- Heterogeneity of requirements and assessments due to the federal structure and the number of ECs in Germany
- Approach to unify the requests of the different ECs in Germany (Working group of ECs; "Arbeitskreis medizinischer Ethikkommissionen") has already resulted in positive outcomes.
- Objections mainly focus on patient information and the wording of the informed consent
- The timelines given for the total authorisation process at the ECs are kept, or below the given maximum timelines

"The overall situation regarding the application process at the ECs is seen as reliable, scientifically sound and in support of the assurance of a high scientific quality."



Clinical Trial Application in Germany

Competent Authorities in Germany

Federal Institute for Drugs and Medical Devices (BfArM)

The CA for all medicinal products except the ones handled by PEI, but not medical devices

Paul Ehrlich Institute (PEI)

The CA for sera, vaccines, blood preparations, bone marrow products, tissue preparations, test allergens, test sera, test antigens, gene transfer medicinal products, somatic cell therapy medicinal products, xenogenic cell therapy medicinal products and genetically engineered blood components.

DIMDI

Online notification system for medical device studies. Regional Competent Authorities are responsible for certain kinds of medical devices (implants, active, non-active)



Clinical Trial Application in Germany

Most common substantive objections of the CAs

- Criteria for early termination of the trial
- Inclusion/exclusion criteria
- Methods of contraception
- Additional medical examinations
- PEI more frequently comments on safety monitoring with regard to “Targeted Adverse Events”
- PEI also focuses more on the role and the competence of Data Safety Monitoring Boards (DSMB)

The applicants mainly had to adapt the trial protocol, the investigator brochure, but also the Investigational Medicinal Product Dossier (IMPD) or the labelling

Due to the competence focus of the PEI on biomedical medicinal products special precautions are justified and needed



Clinical Trial Application in Germany

Applicants' Perspective on CAs in Germany

- The statutory deadlines are met – total authorization process at the CAs clearly falls below the given maximum timelines
- Extremely good and open dialog and discussion opportunities with the CAs, e.g., telephone conferences with the CAs in English are possible.

“The overall situation regarding the application process at the CAs is seen as reliable, adequate in its focus on regulatory aspects and in support of the assurance of a high scientific quality”



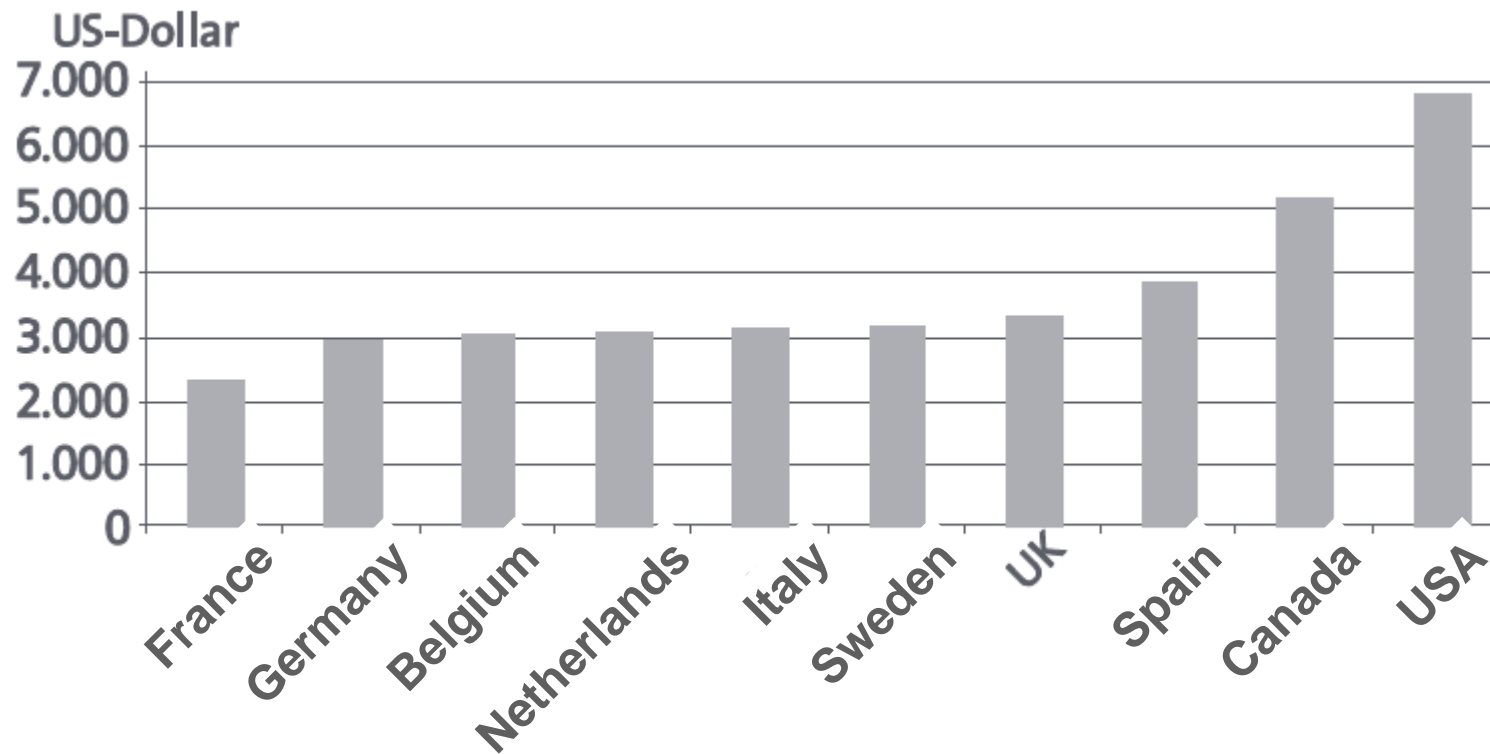
On opportunity costs in clinical development

- **In the end it is not about costs or speed (alone)**
- **It is about getting quality data in a reasonable time frame, or at all,**
- **...that allow for a founded decision making of initiating the next, usually even more costly step.**



Clinical Trial Conditions

Cost per Patient (Phase III) - an International Comparison



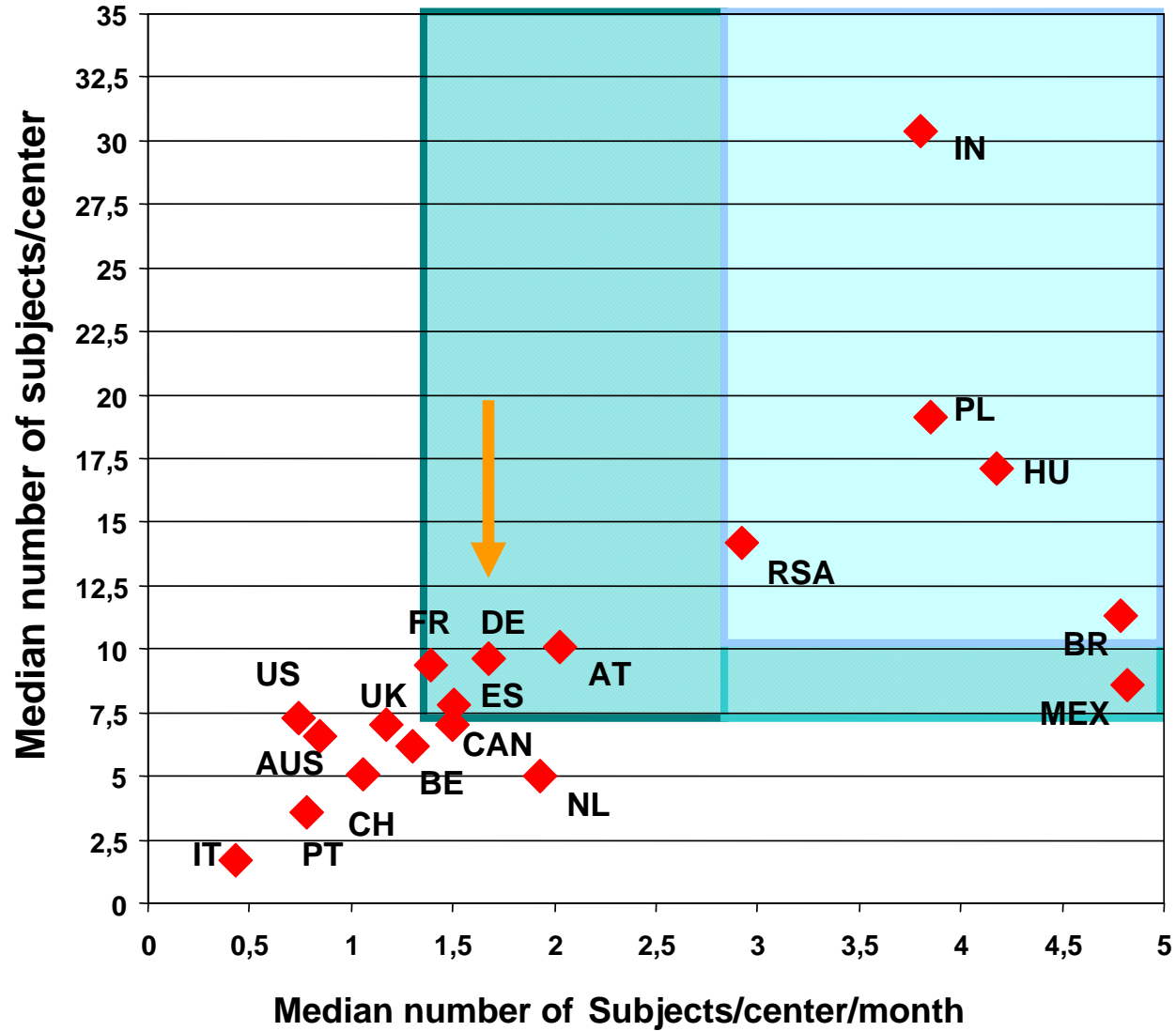
source: Deutscher Bundestag, Drucksache 16/14146, based on Charles River Associates, 2004



Recruitment: Speed and quantity

(A. Hajos, own 2002-2004 data)

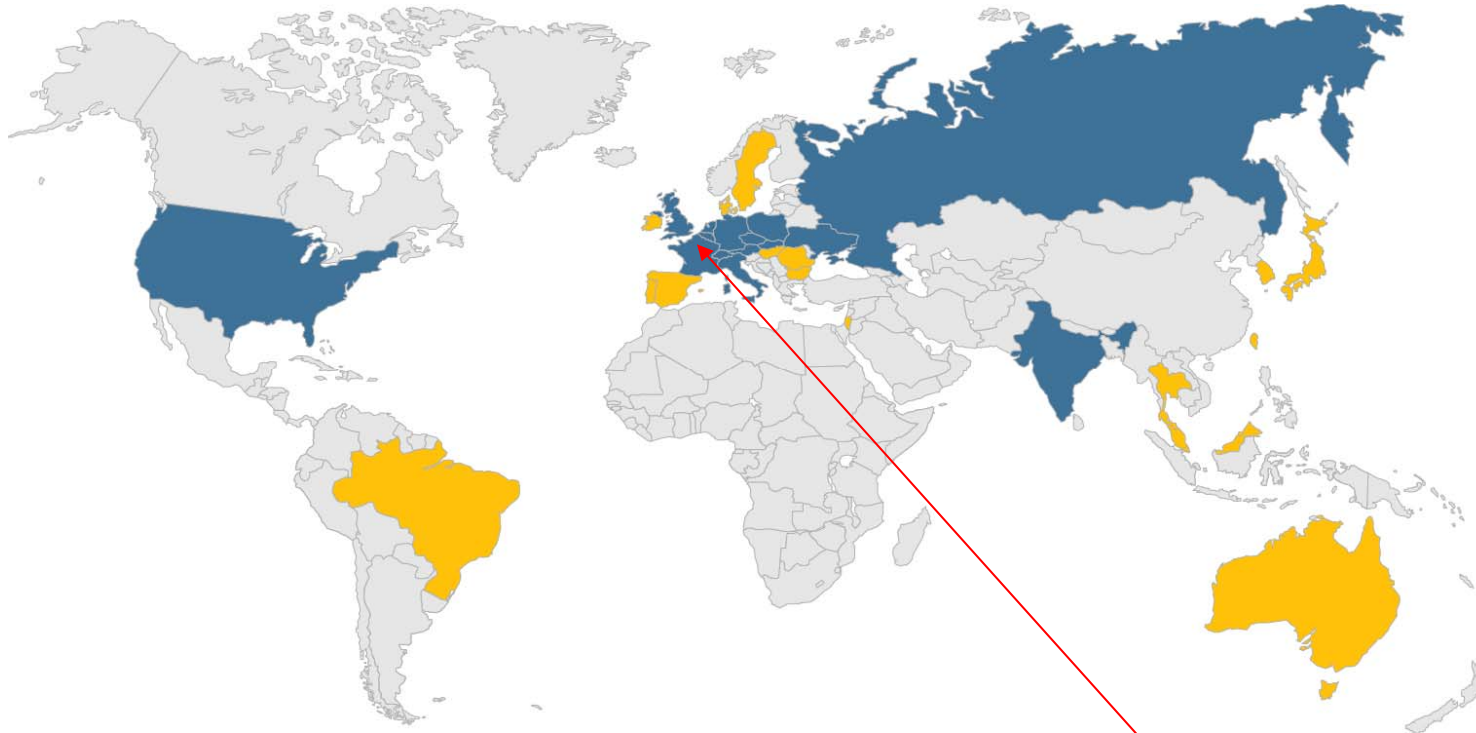
Quantity/Speed: Subjects/Center vs. Subjects/Center/Month





Geographic spread – but focus on Germany

Full Service
CRO
20+
YEARS
Track Record



Covered by EA

Austria, Belgium, Czech Republic, France, Germany, India, Italy, Netherlands, Poland, Russia, Slovakia, Switzerland, UK, Ukraine, USA



Covered through Co-operations

Australia, Brazil, Bulgaria, Denmark, Hungary, Ireland, Israel, Japan, Korea, Malaysia, Portugal, Romania, Singapore, Spain, Sweden, Taiwan, Thailand

Ca. 60% of all trial subjects are recruited in Germany



Clinical Trial Requests – A Geography for Innovative Products

PEI - Requests 2008

Product group	Phase I	Phase II	Phase III	Phase IV
Allergens	2	4	6	0
Blood products	0	2	3	0
Gene-transfer medicinal products / GMO	1	4	1	0
Coagulation factors	1	2	2	0
Immunoglobulins, normal	1	2	1	0
Immunoglobulins, special	0	1	0	0
Vaccines	7	6	17	3
Monoclonal antibodies	16	57	42	7
Somatic cell therapeutics	5	5	5	0
Tumour vaccines / peptides	1	7	2	0

CTs in Germany: Why do Phase 1 there ?



Phase I Units

- Many units have been established at academic centers/university hospitals
- Excellent equipment (storage conditions including deep freeze, emergency equipment, labs for complex analyses, medical specialists)
- Close cooperation with specialist's departments guarantees patient recruitment, medical oversight
- Highly trained clinical research specialists (comprehensive knowledge of ICH-GCP, European guidelines, FDA guidelines)

Investigators

- Highly motivated pharmacologists/physicians with scientific interest
- Successful informed consent procedure based on extensive knowledge of IMP

Regulatory bodies

- Assessment at PEI and BfArM by highly specialized experts includes consideration of EMEA and FDA requirements
- Highly qualified experts and lawyers guarantee subject safety, EC opinion is well recognized by other countries



A track record of innovative clinical trials - cases

National Case Studies from Ecron Acunova experience

Product	<i>Tumor specific monoclonal antibody</i>	<i>SpineSupport (ceramic bone material substitute)</i>
Indication	<i>Advanced Gastroesophageal Cancer</i>	<i>Osteoporotic Vertebral Fractures</i>
Phase	<i>Ib, FIM</i>	<i>Medical device</i>
Study objectives	<i>MTD, safety and tolerability, pharmacokinetics profile, immunogenicity</i>	<i>Safety profile, pain relief, QoL</i>
Competent Authority	<i>Paul Ehrlich Institut</i>	<i>State Regulator Kassel</i>
Investigational Sites	<i>4 university hospitals</i>	<i>6 sites, 2 of them university units</i>
Recruitment	<i>15 patients</i>	<i>41 patients</i>
EA Services	<i>Project management, EC and CA Submission, Monitoring, Data Management, Evaluation, Reporting</i>	<i>EC and CA Submission, co- monitoring</i>



Selected Business Associations - Acknowledgement

BVMA

Federal Association of Contract Research Organizations

at present 26 companies, operating in the field of clinical research at a national as well as international level, are members of the Association. Ecron Acunova is a founding member. Only European association with voluntary self-audit of members.

<http://www.bvma.de/englisch/index.php>

VFA

German Association of Research-based Pharmaceutical Companies

50 leading research-based pharmaceutical companies are organized in the

<http://www.vfa.de/en/articles/index-en.html>

Thanks are due to Dr. Ruppert of VfA for providing statistical data.



Germany - a Competitive Location for Clinical Research

- High quality of infrastructure, personnel and hence data. Reliable and efficient recruitment of patients.
- Reliable and adequate application process at CAs and ECs
- Moderate costs, yet mature provider market
- Clinical trial conduct in Germany facilitates product development for European market and international recognition
- Established collaboration and bilateral recognition of expertise between Israel and Germany



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Lake Constance & city view of Constance, birthplace of Ecron