

Contribution of National Agencies Internal and External Experts

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Approval of Drugs in Germany

regulatory framework

**Directive 2001/83/EEC = Codification (65/65/EEC;
75/319/EEC; 92/27/EEC) Title II Article 2 and
German Drug Law (AMG)**

how to gain marketing authorisation in Germany :

centralised procedure according to 2309/93/EEC

decentralised procedure according to 75/319/EEC

national procedure for new and known substances

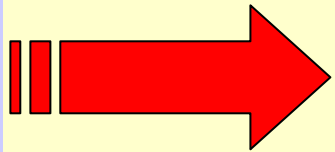
according to §§ 21, 25, 48, 49 etc. AMG

homoeopathics etc. according to §§ 34

standard approvals according to § 36 AMG

parallel import approval

old drugs ("Nachzulassung") according to § 105 AMG



Changes in the Regulation

Proposals of the Commission

- Centralised or decentralised - balance
- Mutual Recognition Committee
- Empowerment of the Mutual Recognition Procedure
- **Abolishment of renewals ???**
- **Postmarketing pharmacovigilance ?**
- **"Better regulation" ?**
- **However, lacking definitions on:**
 - NCE
 - Public health
 - **Serious risk to public health**

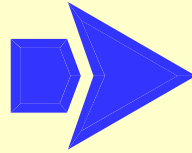
Most Important Aspects of the Review : German position

- **Streamlining of Committees**
- **Scope for centralised / decentralised procedures**
- **Renewal versus pharmacovigilance**
- **Importance of clear definitions (e.g. serious risk to public health; pharmacovigilance experts)**

Need for Definition: "Serious Risk to Public Health"

- national views / definitions differ from case to case and from country to country ?
- are national views always objective?
- maybe national views are "historical" ?
- are national views applicable to European harmonisation / single market ?
- are national views "for home use" only
 - or a "mission" to other countries?
 - Conclusion: A European definition is highly necessary.
- Already on the commission agenda ?

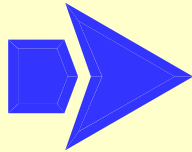
centralised



**Council Regulation (EEC) No. 2309/93 - Annex
new drugs **obligatorily (?)****

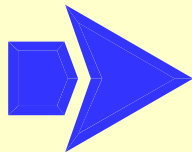
CENTRALISED

decentralised



Generics
centralised and decentralised
line-extension

national



FOR ONE MEMBER STATE ONLY;
bibliographic approval;

Future of national procedures ?

- **abolishment of the EU – "uncommon" § 49 AMG ?**
- **abolishment of renewal procedure ?**
- **and then what about outdated claims ?**

"Eurotasks" for BfArM

- present: 10 - 15%
- future: 20 - 30% (after finishing "Nachzulassung")

EU from BfArM:

innovation,
orphans,
biotechs

BfArM from EU:

generics,
OTCs,
"bread-and-butter products"

Deficits due to Centralisation/Globalisation of Product Development + Maintenance

- Loss of national identification
 - academic research
 - product development
 - licensing system
 - marketing/product maintenance
 - drug safety

Deficits due to Centralisation of Licensing Procedures

- Medium-sized companies' development of innovative products is inhibited by
 - in-house bundling of capacities for processing of centralised procedures
 - in-house costs for pursuing centralised procedures
 - fees for centralised procedures

Development I

- Shift from national + decentralised procedures to centralised procedures
- Increase in monopolisation of licensing systems
- Decrease in competition
- Decrease in national identification with products
- Shifting of decisions from national to centralised anonymous EU authorities

Development II

- Common market
- Quality of supply with medicinal products of a consistently high European standard
- Uniform regulatory system
- Transparency
- Orientation for consumer and patient

Self - defined Future Position of BfArM

- **Team leader and opinion leader**
 - according to approvals :
MRFG – RMS
Centralised - Rapporteur
 - according to projects / indications (e.g. antibiotics, HIV)
 - according to topics(Notes for Guidance, Points to Consider, Working Parties)
- **Team player in all other cases**

BfArM's Contribution I

- "Full-provider"
- Scientific expertise
- Effective and efficient licensing system
- Customer orientation
- Scientific co-operation with other regulatory authorities
- Fulfilment of European and international standards
- Development of a worldwide pharmacovigilance network

BfArM's Contribution II

- Co-operation in detecting counterfeit medicinal products
- Co-operation in the field of inspections
- Development of a European strategy for consumer information
- "Off-label use", "orphan drugs", "fast-track drug development"

BfArM – European Workload 1995 to 2002

<ul style="list-style-type: none"> • Centralised Procedure (incl. line extension) • Mutual Recognition 	<p>Number</p> <p>368</p> <p>Number</p> <p>Projects: 1877</p> <p>Single: 3562</p>	<p>BfArM as (Co)Rapp</p> <p>54 (ca. 16 %)</p> <p>as RMS</p> <p>Projects: 258</p> <p>Single: 466</p> <p>as CMS 1362</p>
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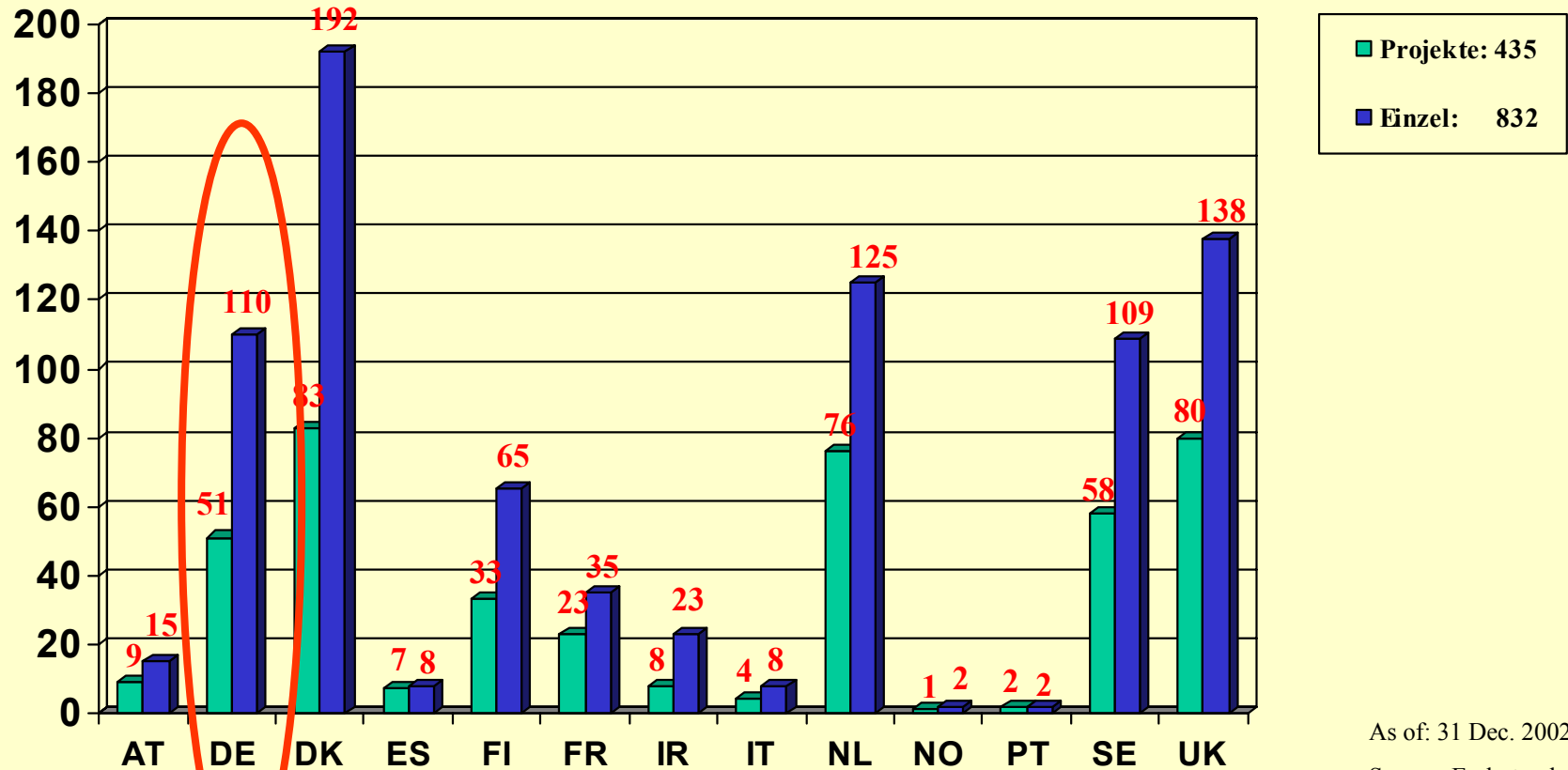
DE holds rank 4 of RMS countries (2002)

DE (together with SE) leading in the licensing of new substances in MR-Procedures

DE is concerned in more than 50% of all procedures and thus has the most MR licenses in Europe

Overview of Reference Member States in Decentralised Procedures

- completed procedures (Day 90) 1 January 2002 until 31 December 2002 -

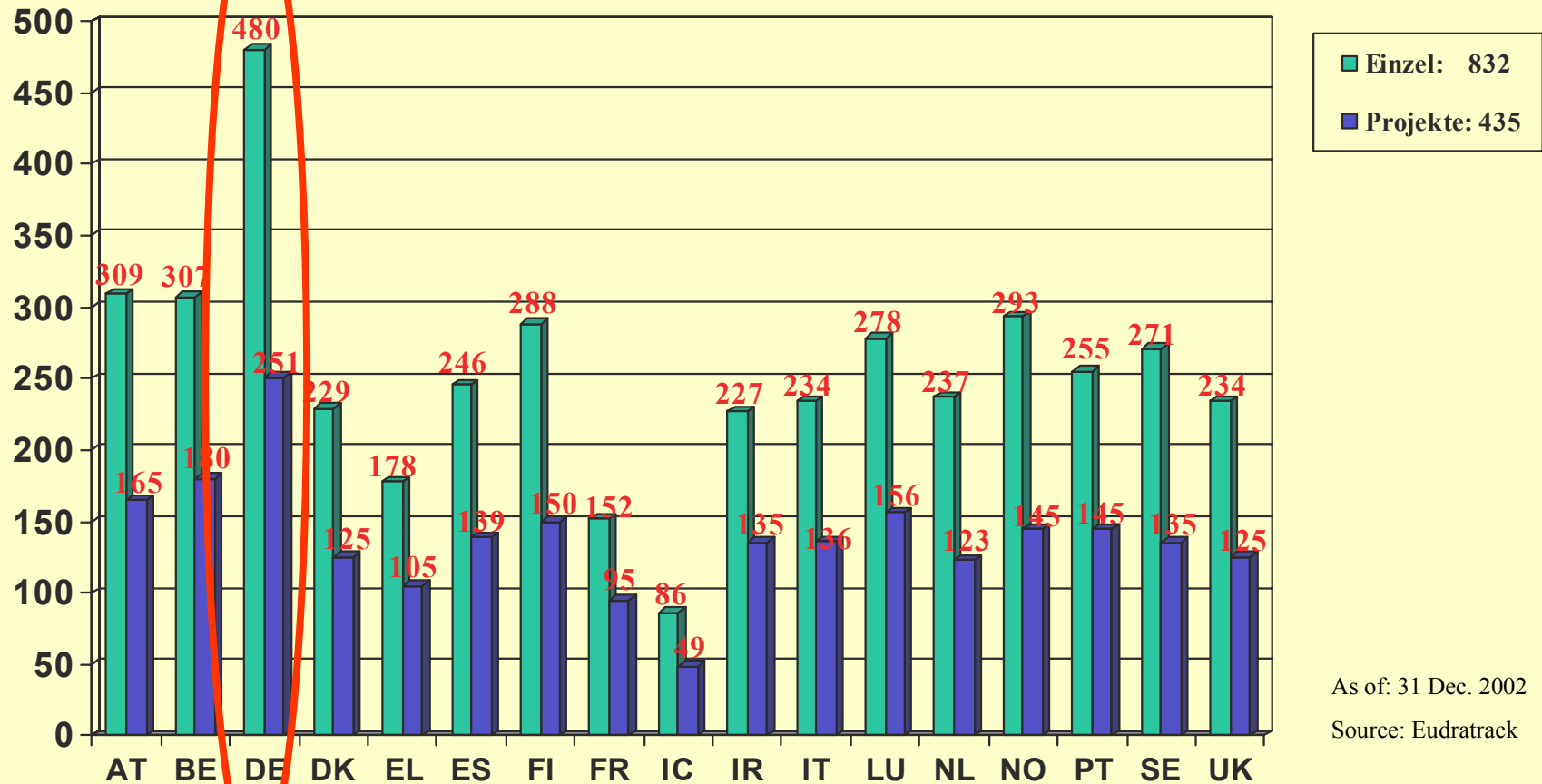


As of: 31 Dec. 2002

Source: Eudratrack

Overview of Concerned Member States in Decentralised Procedures

- completed procedures (Day 90) 1 January 2002 until 31 December 2002 -



As of: 31 Dec. 2002

Source: Eudratrack

Optimisation of European Procedures at BfArM

- **Excellent national and EU scientific advice**
- **High scientific level expertise**
- **Bridging of national / EU advice**
- **Contribution to European pharmaceuticals market :**
 - **"Nachzulassung" Candidate Countries ?**
- **Quality / quality assurance**



Importance of European Procedures - Future

Need for clarification

- Regulation of access to Centralised/Mutual Recognition Procedures
- Balance between Centralised and Mutual Recognition Procedures
- For 2003, only few (22+16 orphans*) new substances can be expected within the Centralised Procedure. What is the EMEA's future?
(costs ? , fees ? , 240 employees must be paid!)
 - Centres of excellence for agencies ??
 - Therapeutic advisory groups as "European FDA starting point"??
 - Variations Type IA (and some Type IB) to be handled by EMEA

"An open door may tempt a saint"

Our Proposal for the Future European System

- "Premium products" (innovative)  centralised
 - "Bread-and-butter products"  mutual recogn.
 - "me too"
 - "former" innovative classes of products
 - OTC's
 - generics
 - "important" herbals
-
- the balanced status (centralised/decentralised) must survive :
 - fast access for innovations, not overloading CP
 - but some NCE need the MRP

"Diamonds are forever ! (Premiums are not !)"

Windows of Opportunity - Vision

CPMP as a trend-setter for pharmaceutical science

- centralised procedure focussed on
 - therapeutic innovations, technologies,
 - new therapeutic principles

national authorities ("better regulation") in MR-Procedures

- known biotechnological products (e.g. insulins)
- known chemical substances and combinations thereof
- other new substances

**Implementation and surveillance of consolidated opinions within the MRFG
outside the complex and elaborate Centralised Procedure**

Fulfilment of EMEA Tasks

- + Co-ordination, project management
- (+) Platform for decision making
(still possible after Court of Justice on OCs-3, anorectics, Capoten?)
- Transparency, websites etc.
- Archiving, documentation, **data-bases (pending)**
- EUDRA xxx products (**deficitary**)
- (+) Success monitoring, cost-performance accounting, quality assurance
- Personnel required per application (**too much administration?**)

Fulfilment of National Tasks

- + Scientific evaluation (**professional work = service for EMEA**)
- + Experts in a stand-by mode
- + Implementation of the European idea in MR-Procedures
- (+) Translation of recognition into national licenses
- ! Avoidance of double offers / double work

WHAT ? WHERE ?

- **Expertise, co-ordination** -- at home
- **Co-operation** -- on site (London, Brussels)
 - HoA, MRFG, MB, Ph-Com
 - CPMP, COMP, SciARG, ORGAM, WP's, ad hoc groups
 - “Topic Leader” of the BfArM at ICH:
 - eCTD; Quality; BIOTEC; SAFTEY; VIGILANCE
- **Delegation**
 - to Commission
 - to EMEA

Role and Tasks of the Agencies in the Future

to be clarified :

- **How to survive ?? (Especially small ones)**
- **Centre of excellence (EU and CEEC) ??
or "full provider" ??**

Further European Interests of the BfArM

- **Promotion of research and development via scientific advice**
- **Acceleration of procedures / licenses, if applicable under specific conditions**
- **Regulations for "orphans", paediatrics, etc.**
- **Precursor in the field of technology**

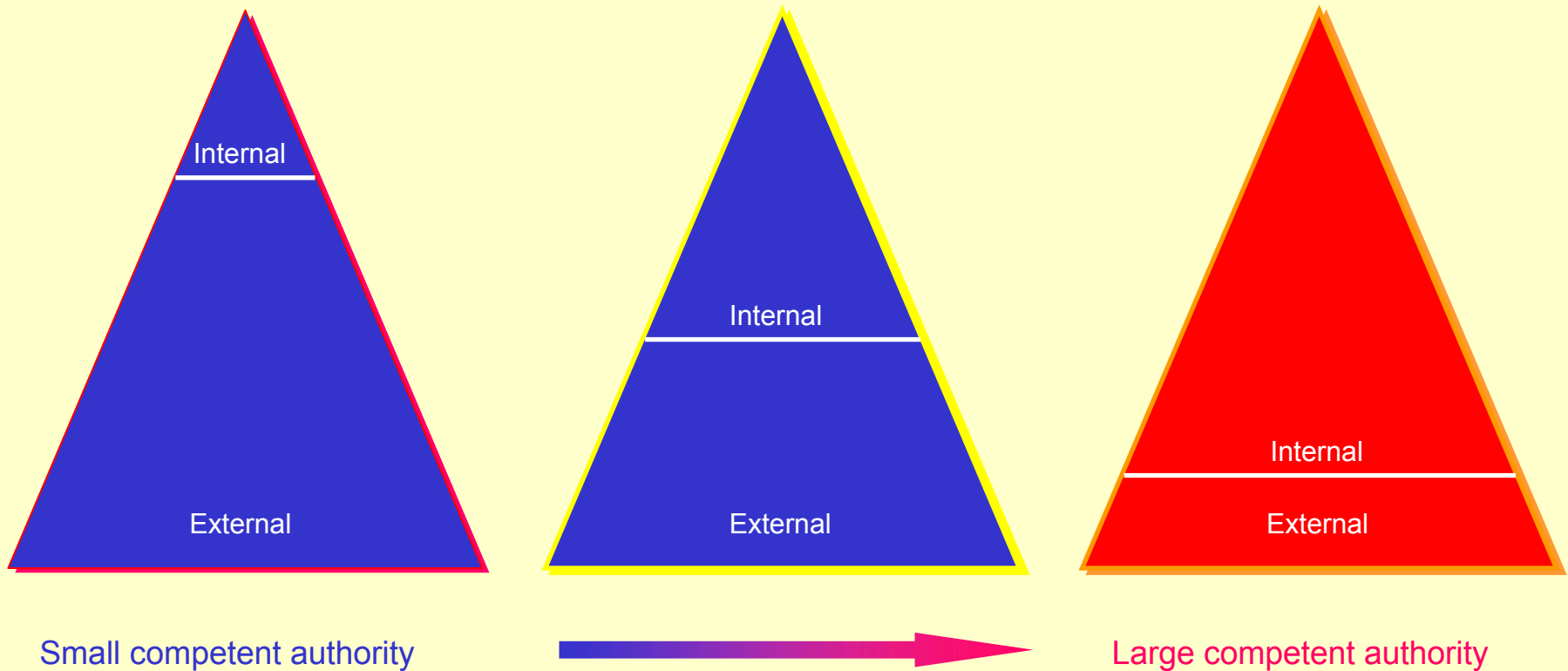
Prejudice about the Use of Experts in National Competent Authorities

- Assessment reports are only written by internal assessors
- External experts are
 - only very rarely used
 - and not systematically used
- There is a lack of transparency

Obstacles for Use of External Experts

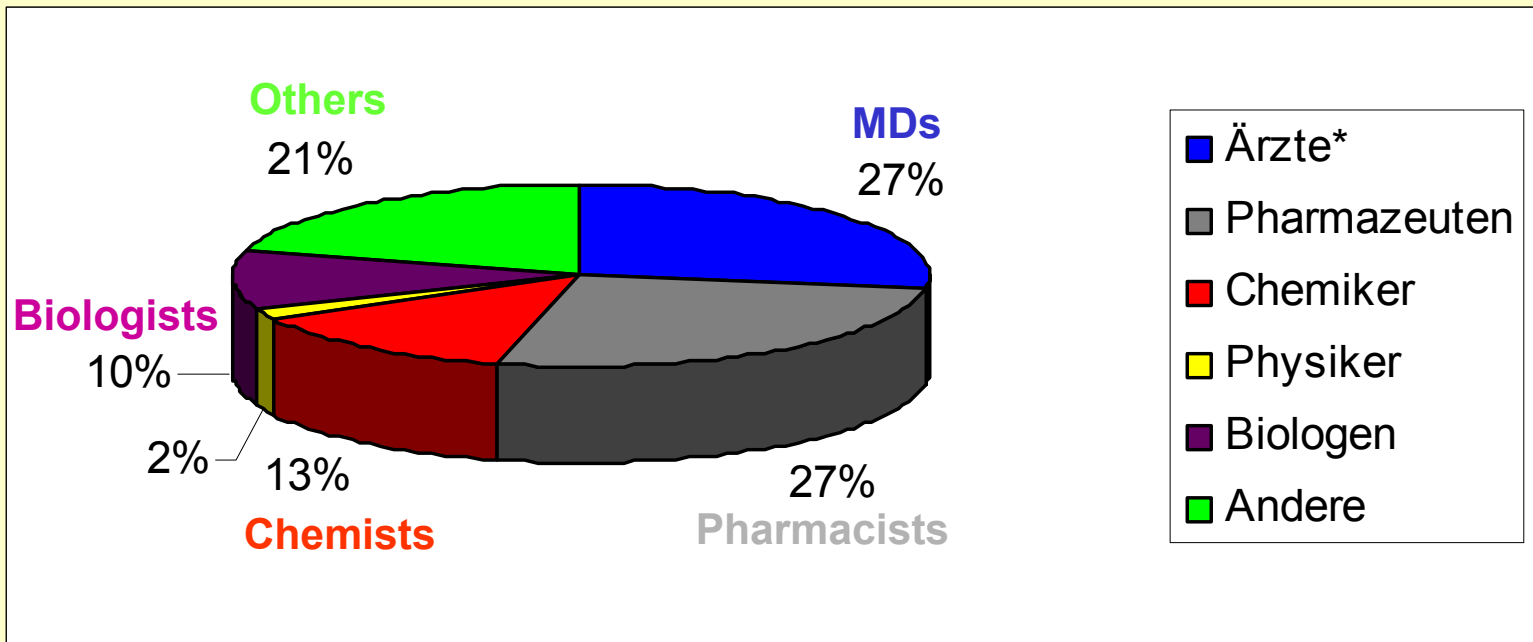
- Budget constraints
- Conflict of interest
- Creation of registries of experts in specialised therapeutic areas and in transversal areas
- Confidentiality
- Efforts for education and training

The Truth about Internal and External Expertise in NCA's



Staff at BfArM (05/01/02)

965 Employees;
 630 thereof female and 335 male;
 695 thereof in scientific Dep./270 in administrative Dep.;
 342 thereof scientists;
 184 thereof female and 158 male



Use of Experts in BfArM

- 1 -

- BfArM as a large competent authority has many internal experts in the fields of
 - Regulatory affairs
 - Pharmaceutical quality
 - Non-clinical issues
 - Clinical issues
 - Pharmacovigilance
- Use of external experts from candidate countries
- External expertise is also available to BfArM but is not used as frequently

Use of Experts in BfArM

- 2 -

- National procedures
(Internal and external experts)
- Mutual recognition procedures
(Internal experts, external experts only in exceptional cases)
- Centralised procedures
(Internal experts with the exception of CADREAC colleagues)

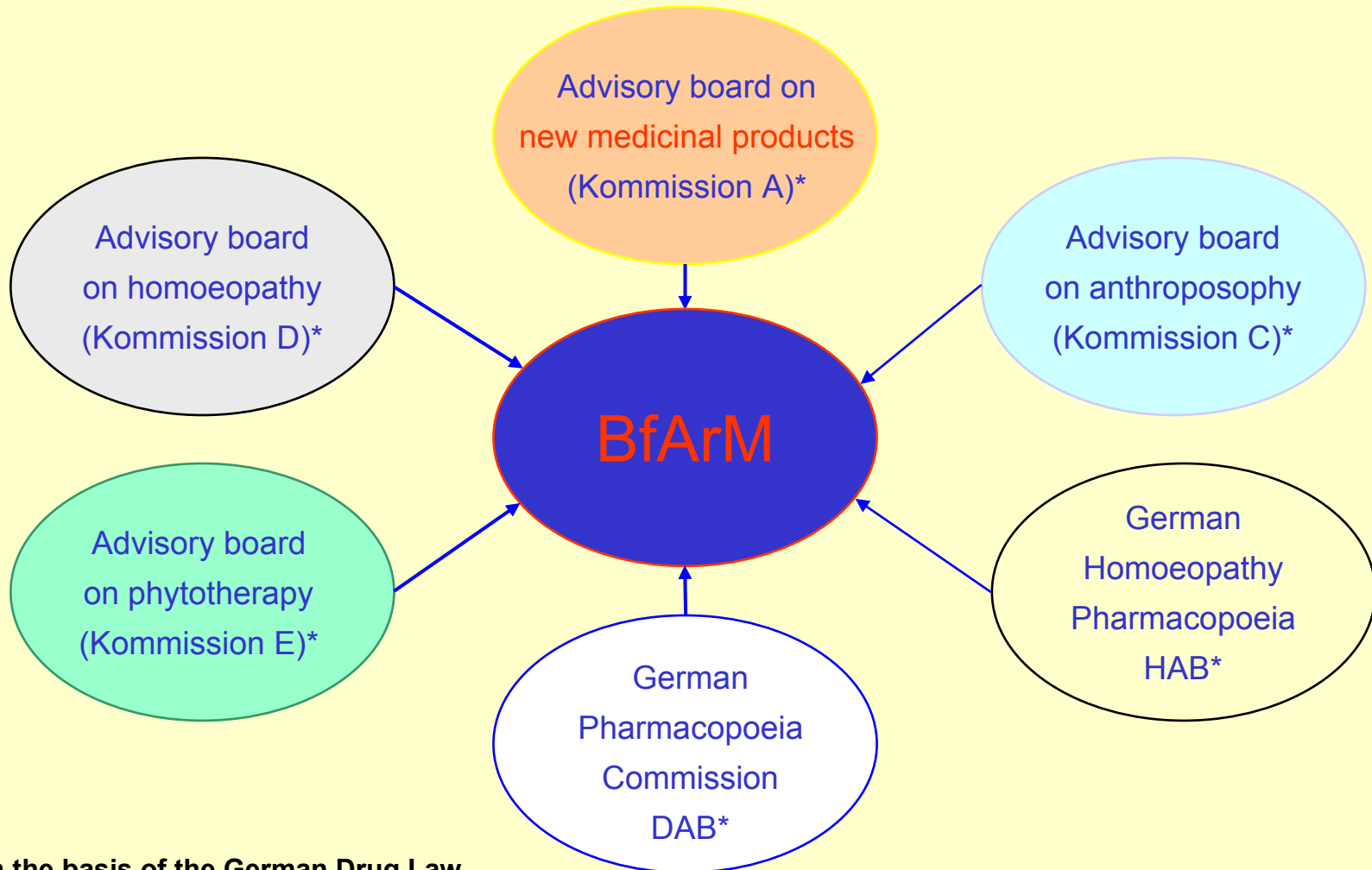
Use of External Expertise

- 1 -

- Assessment of marketing authorisation applications
 - **Limiting factors in Germany**
 - Availability of the external experts
 - Size of the documentation
 - Close contact with internal experts
 - Education and training of external experts
 - Is not considered an honour (in Germany's sci. comm.)
 - Budget
 - Conflict of interests?
- Advice on highly specific issues of drug licensing
- Advice on general scientific issues

Use of External Expertise

- 2 -



* on the basis of the German Drug Law

German Nominees in EMA Expert Database

92 Internal Experts

81 External Experts

43 Experts of Federal "Laender"

Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)



Thank you for your kind attention