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dukte

Key Issues Regarding the EU-Review and Enlargement

Prof. Dr. rer. nat. habil. Harald G. Schweim
President of the Federal Institut
for Drugs and Medical Devices
(BfArM), Bonn

Agencies

- Are part of different social systems
- Are involed in the effective and secure use of drugs
- Are – besides industry and universities - the third independent collumn of drug-development
- Are in discussion and critisised :
- Approval too slow
- Approval too fast
- Hurdles too high
- Hurdles too low

Non German Examples :

- 1995: The Republican speaker of the House of Representatives, Newt Gingrich referred to the FDA as "job killers: its excessive reviews, he claimed, delayed the launch of new drugs and thereby forestalled growth for the pharmaceutical industry.
- 1998 Kleinke, J.D. : Is the FDA approving drugs too fast? Probably not - but drug recalls have sparked debate. BMJ (317), 899.
- 2003 Singh, D. : Medicines Control Agency slated by Commons committee: "... ...", (BMJ (327), 10.

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Drugs in Europe (Selection)

DE	UK	SE	DK
~ 82,4 million*	~ 59 million*	~ 8,9 million*	~ 5,4 million*
~ 57 000** marketable drugs *within the competence of the BfArM 94%; PEI 6%* *incl. Parallelimports* *incl. registrated homeopathic products*	~ 26 000 marketable drugs *incl. Parallelimports* *incl. registrated homeopathic products*	~ 6400 marketable drugs *without Parallelimports* *without homeopathic/herbal products*	~ 4650 marketable drugs *incl. Parallelimports*

*Inhabitants

** human AM

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Drugs in Germany

- big (German-speaking) market (~ 100 Mio. people)

- 60,000 approved drugs with :
- ~ 1000 usable approvals with standardised master texts ("Muster")
- ~ 10,000 "freshly" appr. "old products" ("Nachzulassung")
- ~ 20,000 MRP-ready approvals (Assessment Reports)

- big market for homeophatics and herbals

- important medium-sized (and cooperative !) companies

- all global players in the market

- no pricing negotiations within approval procedure

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Tasks of the BfArM

Licensing and Registration of Medicinal Products

- Marketing Authorization of finished medicinal products on the basis of the German Drug Law and 2001/38/EC
- Registration of homeopathic medicinal products acc. to Art. 14 of 2001/83/EC

Research

Monitoring of Risks from Medicinal Products

- collects/evaluates reports on side effects of licensed products
- takes corresponding measures of risk prevention

Narcotics and Precursors

Federal Opium Agency

- grants licences for participation in legal traffic
- controls manufacture, trade, import, export and cultivation

Medical Devices

- collects serious risks occurring during use
- recommends measures of risk prevention

Organisation and Hierarchy - Abstract

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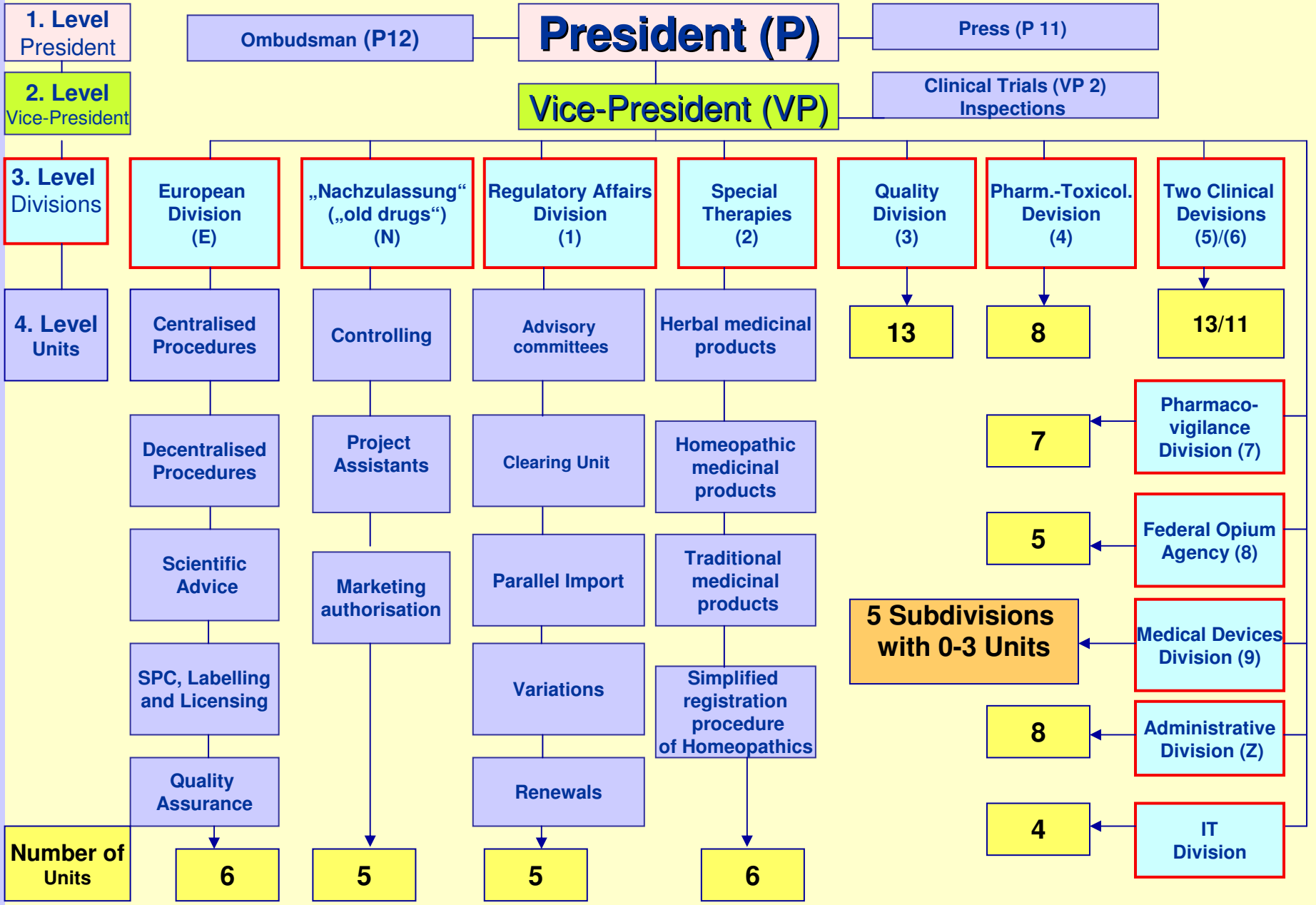

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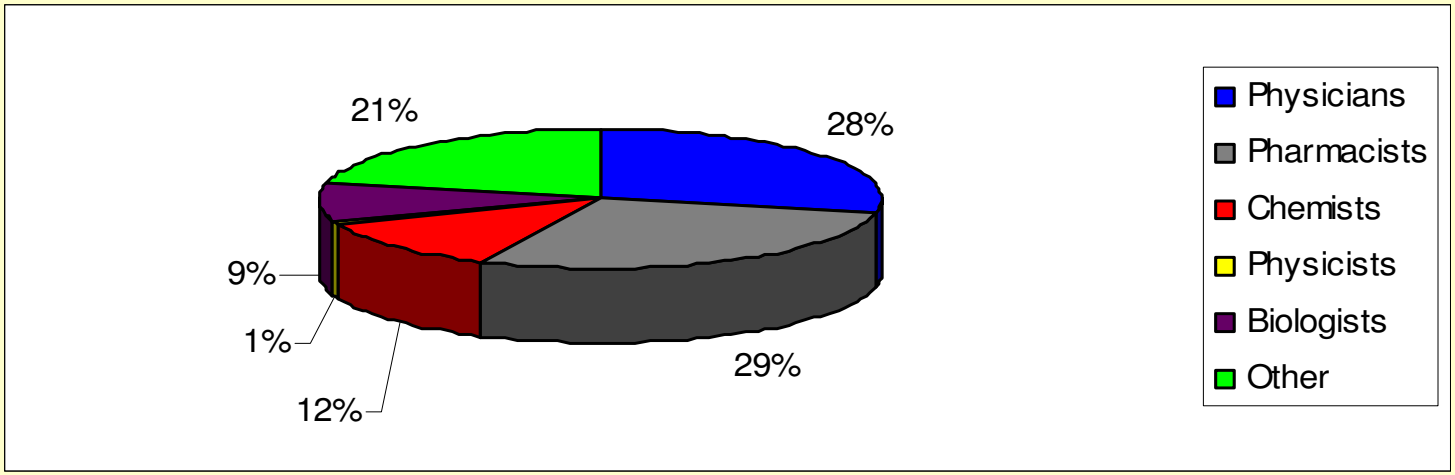
BfArM Staff

1046 employees (including part-time employees); thereof

684 females, 362 males

817 permanent positions;

342 thereof scientists



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Staffing levels in BfArM divisions

Division	P/VP	Z	E	IT	N	1	2	3	4	5	6	7	8	9
Employees *														
Total	21	225	36	56	64	96	84	134	49	56	43	65	58	43
Scientists**	8	15	18	16	7	30	50	90	34	39	33	23	10	24
Other***	13	210	18	40	57	66	34	44	15	17	10	42	48	19

* including part-time employees
** including Jurists etc.
*** including adminstrative/technical staff etc.

41.4 % of all positions for Tasks concerning Marketing Authorisation
152 Scientists
233 Adminstrative staff members
27.6 % of all positions for Tasks concerning „Nachzulassung“
125 Scientists
132 Administrative staff members

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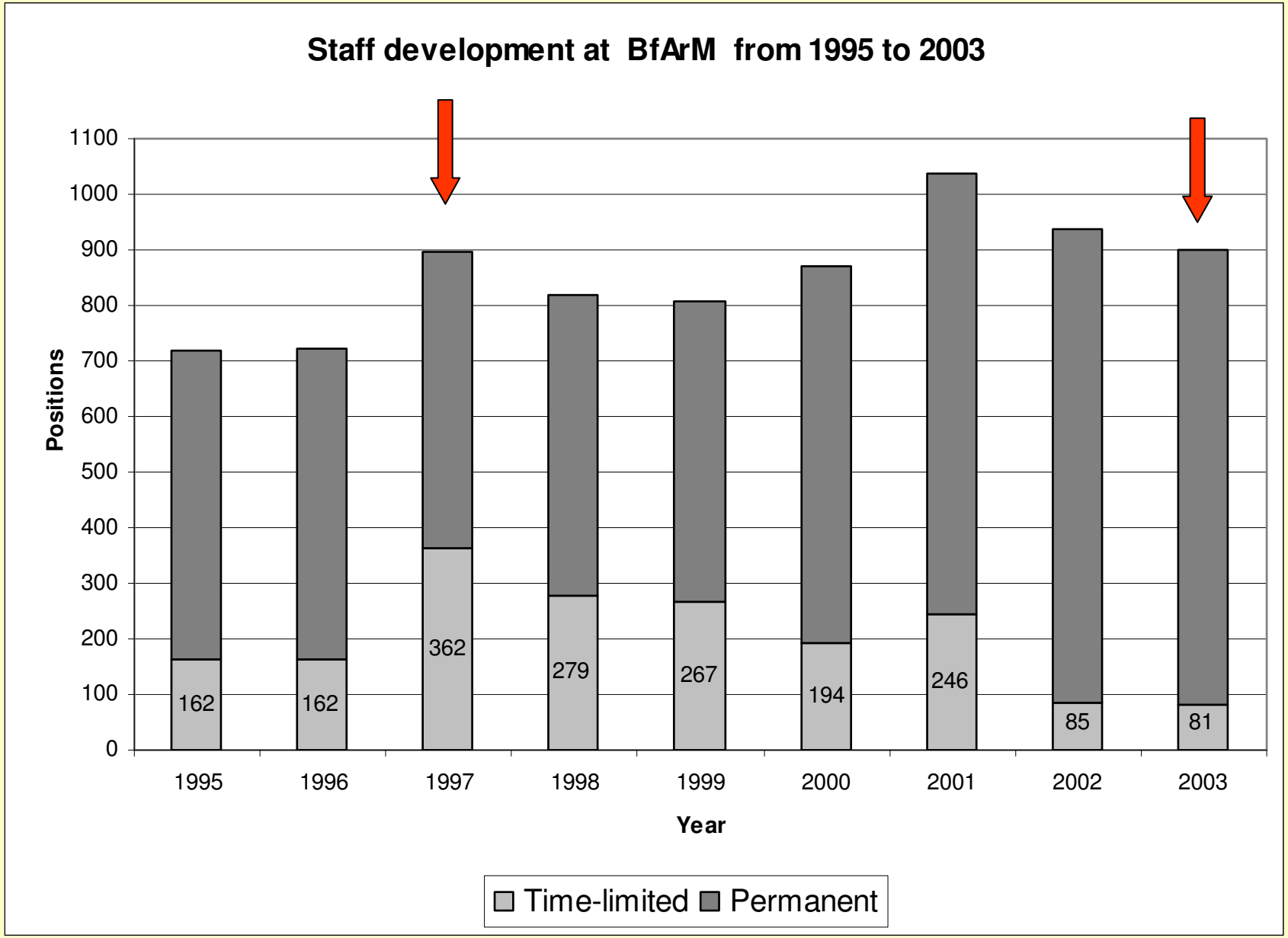

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Budget

2001			
	Debits	**Actual**	**Difference**
Income	25,635 T€	27,093 T€	+ 1,458 T€
Expense	100,592 T€	86,435 T€	-14,157 T€
2002			
Income	32,442 T€	35,567 T€	+ 3,125 T€
Expense	91,378 T€	83,694 T€	- 7,684 T€

- Cost-recovery for Approval and „Nachzulassung“ in 2002: 83.5 %
- Estimated Income in 2003: ~ 36,700 T€

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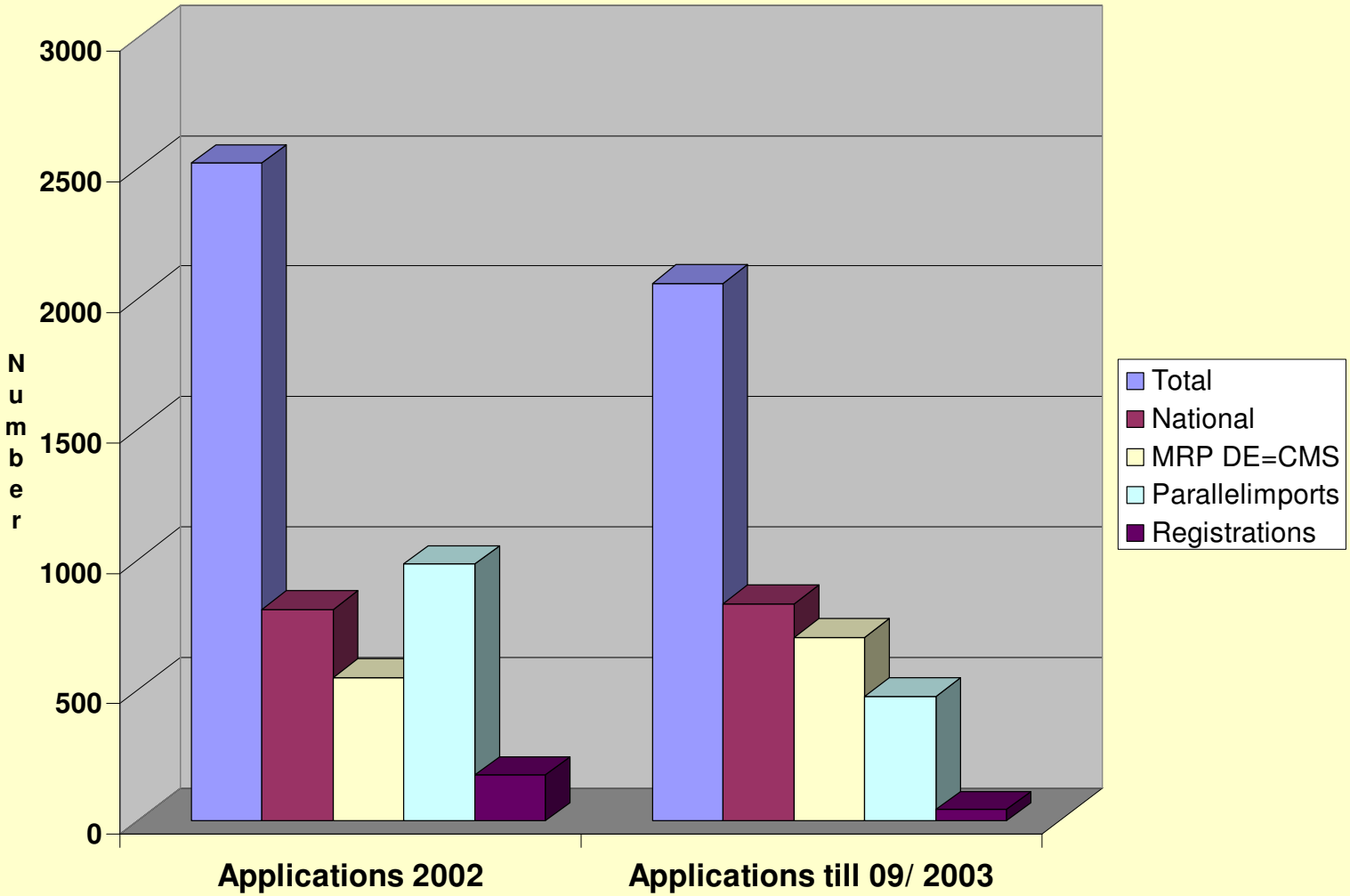
Workload - New Applications



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Workload “Nachzulassung”

Original “old market”	140 000* (notification 1978)	
Applications for post-marketing approval	32 000* (long application 1990)	
Submitted by 02.02.2001	12 500* (2001)	
7300* Processing of content (EU verdict);	open 4080**	(- 3220)
3500* Homeopath. with indication;	open 2242**	(- 1258)
4700* Homeopath. without indication;	open 3159**	(- 1541)
5200* Withdrawals, formal processing;	open 0**, ***	(- 5200)
5300* Deletions, formal processing;	open 0**,***	(- 5300)
26.000 Total load	open 9481	

* rounded; **01.11.03, precise; ***apart from cost notices

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Quality Management: Activities at BfArM

Current situation:

- Harmonisation of SOP format
- SOPs in all divisions
- Comprehensive collection of processes (flow charts) for medicinal product approval (supported by external experts)
- first steps to build-up QMS according to DIN EN ISO 9001 in several divisions

Future:

- Exchange of experience based on the ‘best practice’ examples in the BfArM

- to achieve broad acceptance of QM
- Implementation of QM system according to DIN EN ISO 9000 etc. seqq. in all divisions and units of the BfArM

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Important Aspects of the Review

- Streamlining of EU-Committees (number of members; selection process; responsibility)
- Importance of clear definitions
- Scope for centralised / decentralised procedures
- Renewal versus pharmacovigilance

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Need for Definition: "Serious Risk to Public Health"

- do national views / definitions differ from case to case and from country to country ?
- are national views always objective?
- are national views potentially "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 Commission agenda

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Scope for Centralised / Decentralised Procedure

centralised

Council Regulation (EEC) No. 2309/93 - Annex

new drugs for: AIDS, oncology & neuro-

vegetative diseases (e.g. Alzheimer's), diabetes: obligatorily CENTRALISED

…. and in the future more ?

decentralised

Generics
centralised and decentralised
line-extension

national

FOR ONE MEMBER STATE ONLY;
bibliographic approval;

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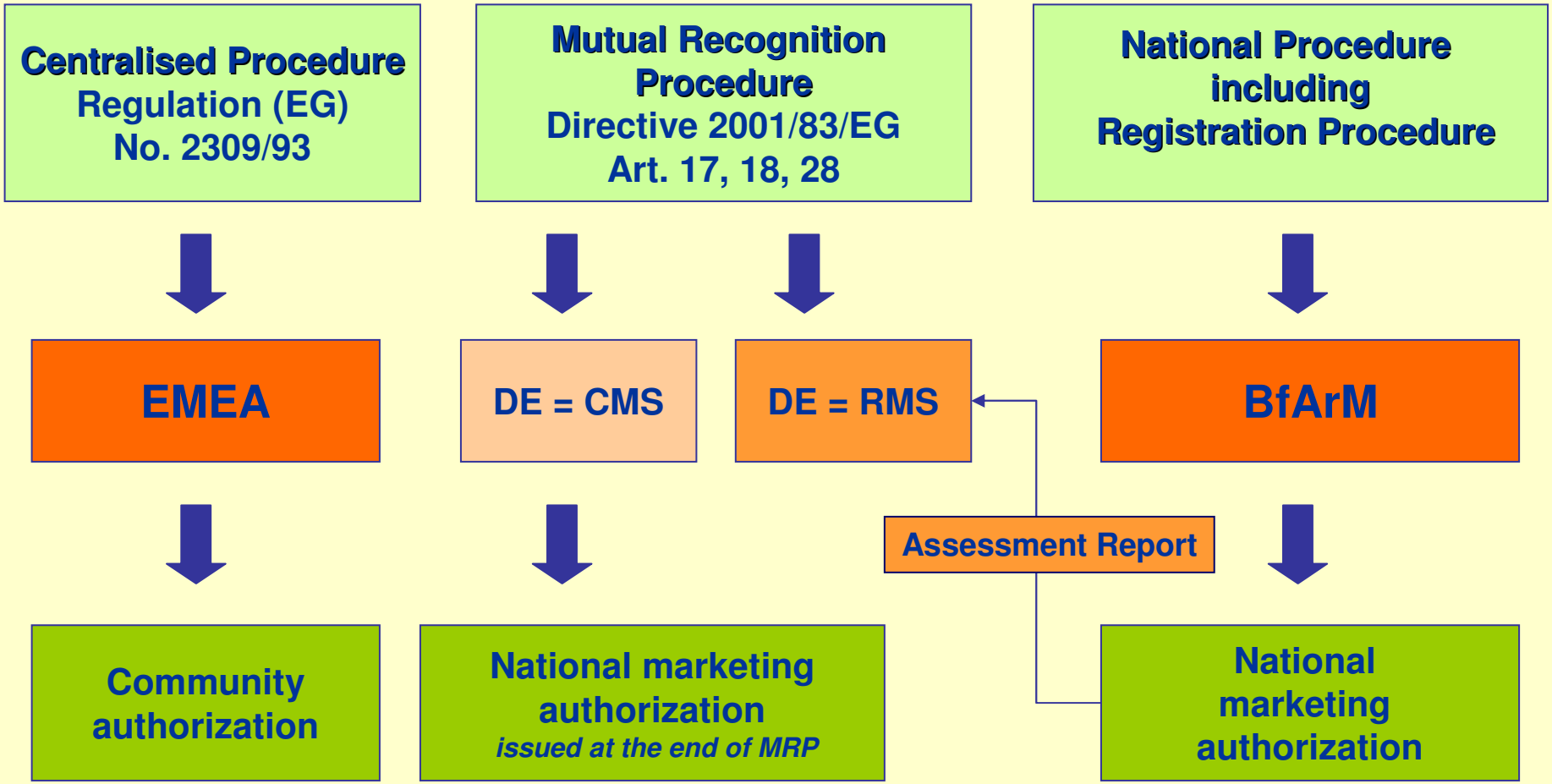
Different Types of Marketing Authorization Procedures



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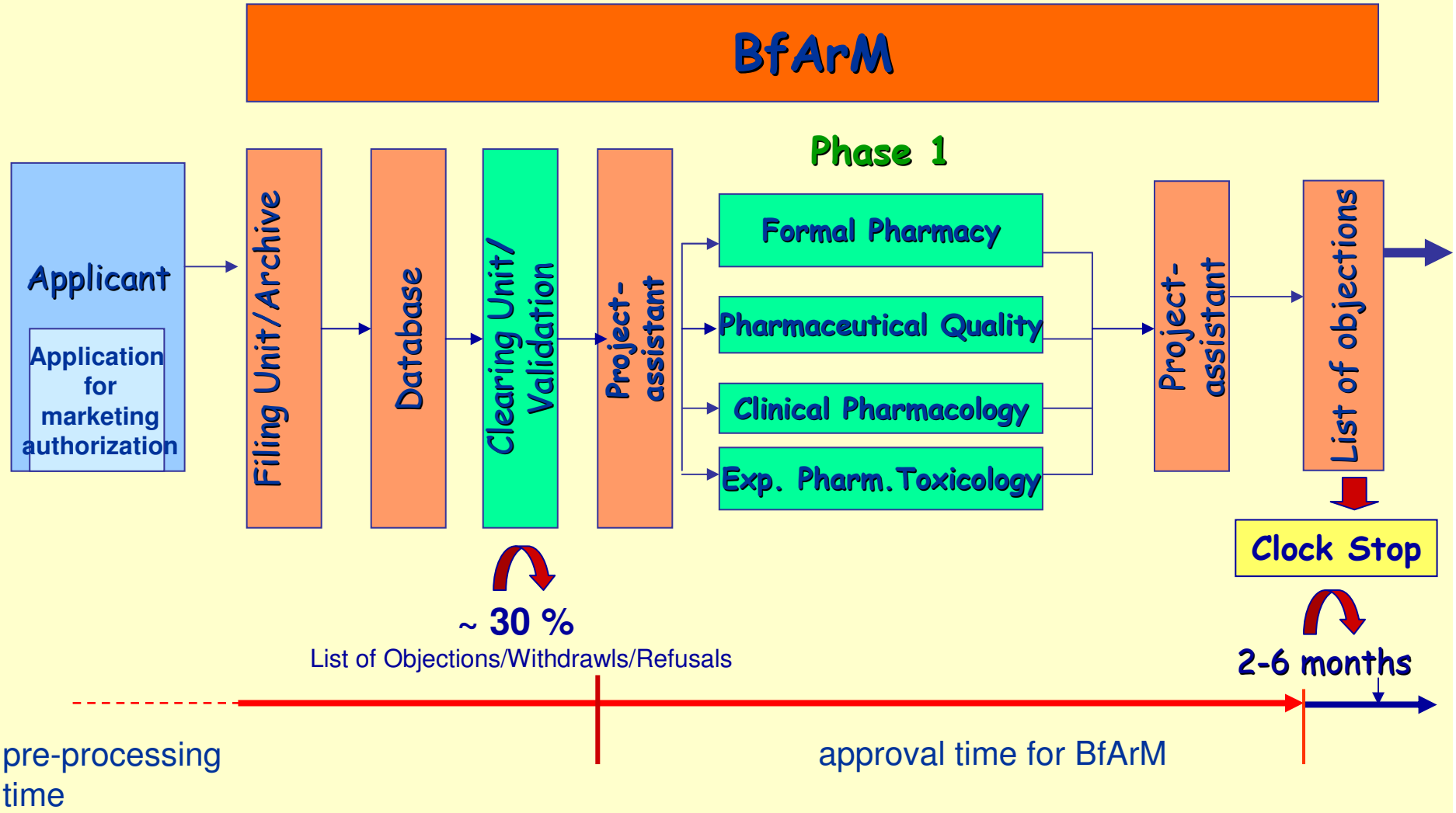
Marketing Authorization Procedure



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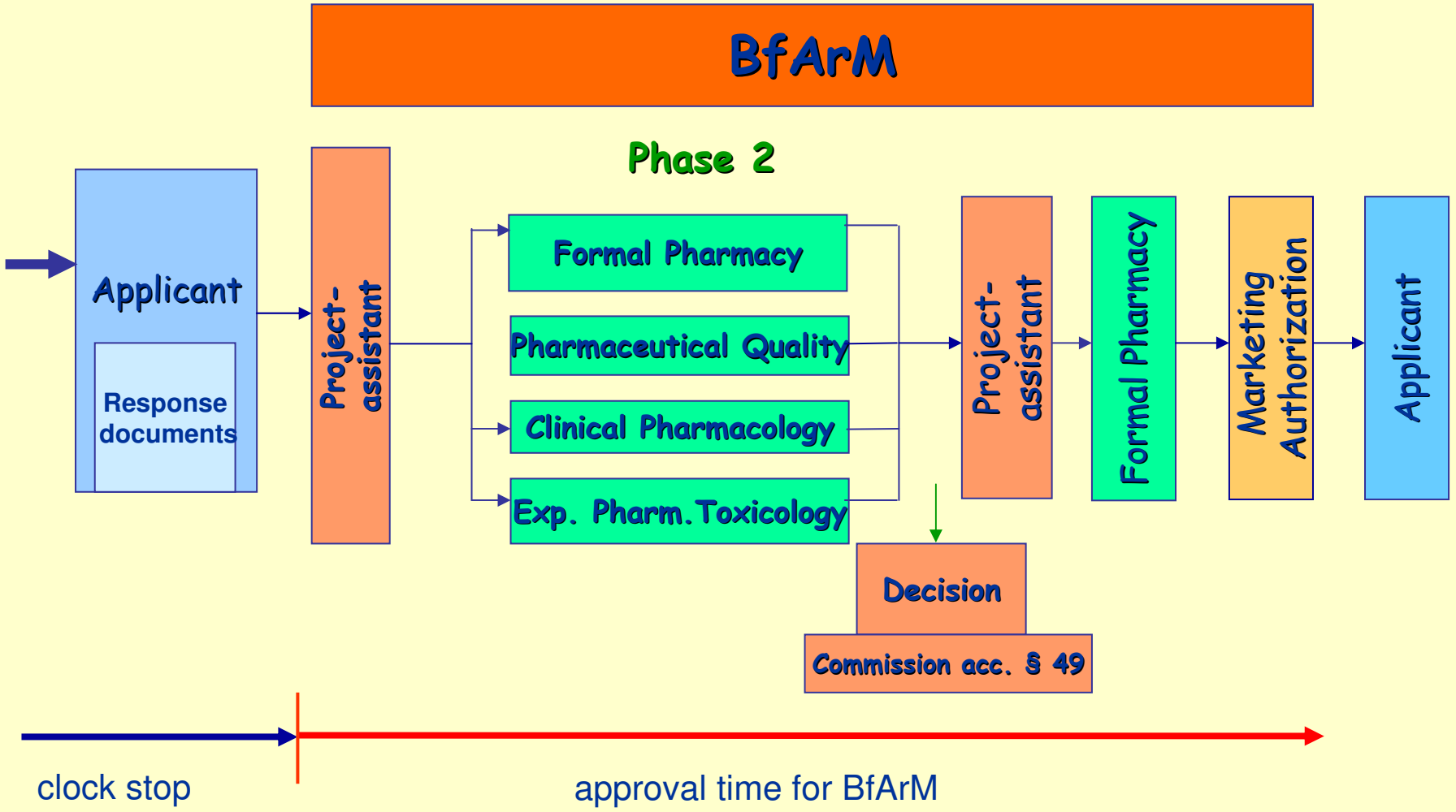
Marketing Authorization Procedure



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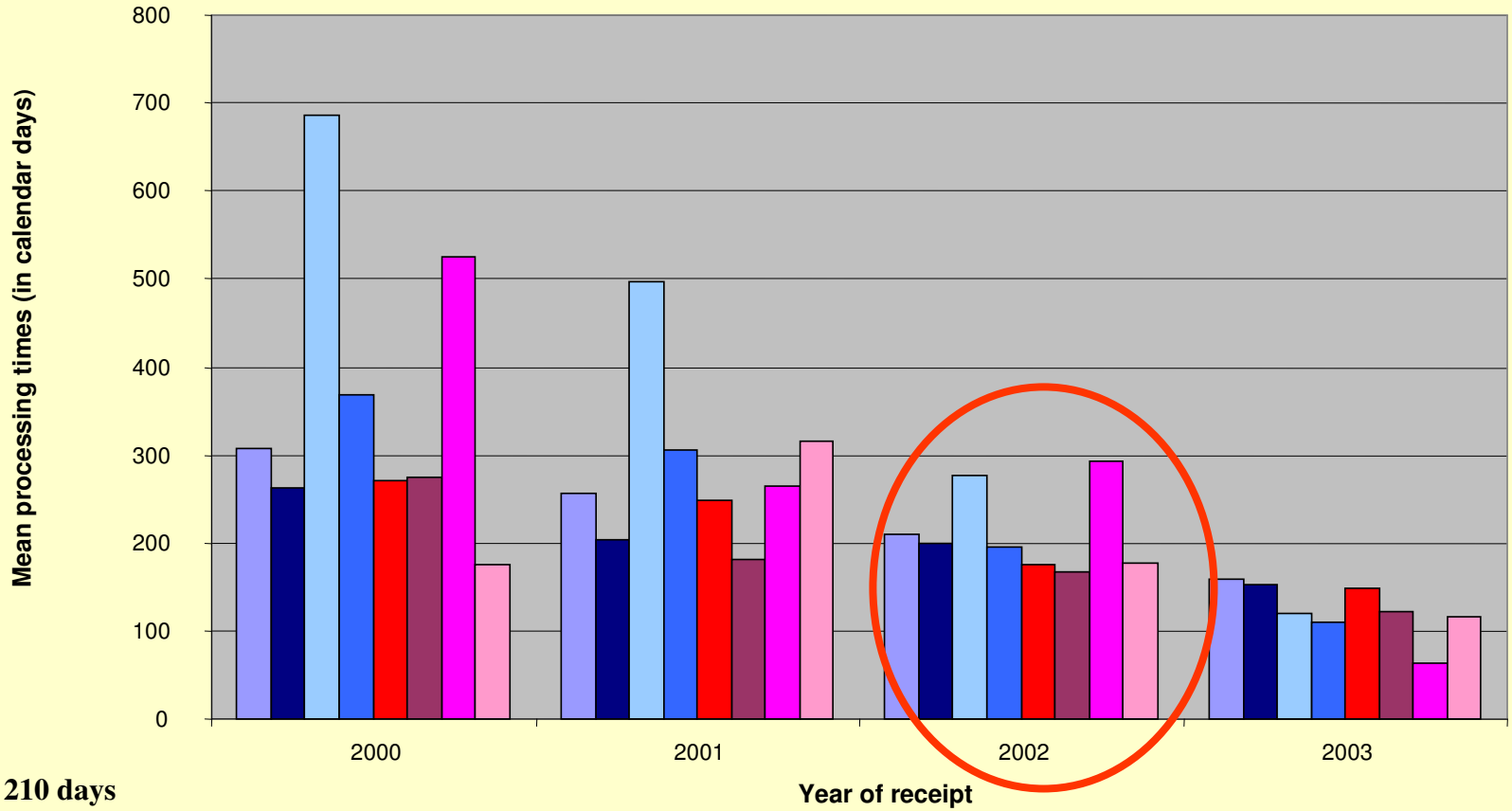
Deadlines are kept in European procedures. Approval times have been improved in national procedures; e.g., in 2002 decisions were taken in approx. 72 % of all applications (national* and European).



*** 210 days**

Stand 22.10.2003

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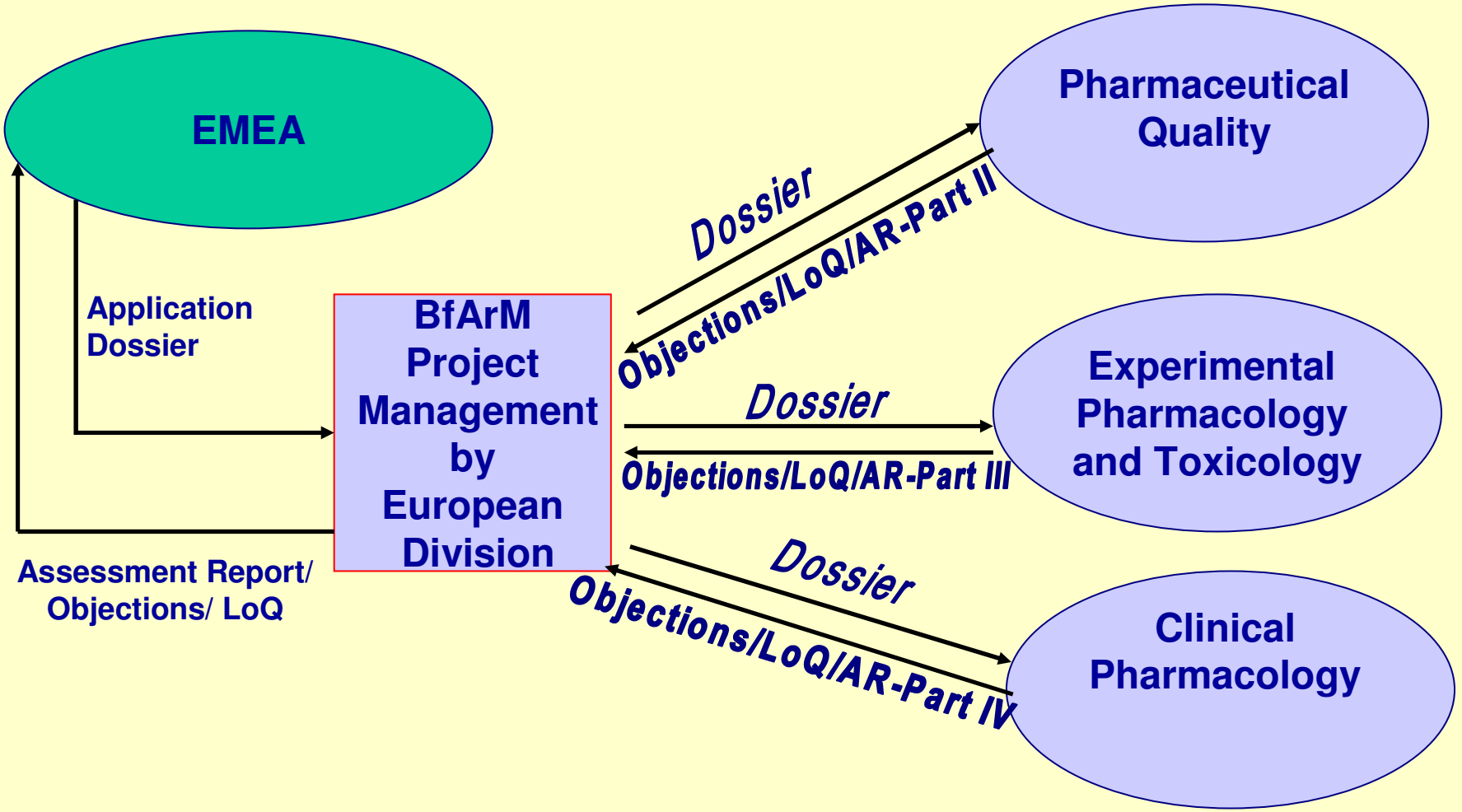
Organisation of Review Process – Centralised Procedures



BfArM – Europ. Workload
Centralised Procedure 1995 bis 2003

Centralised Procedure*	total number	BfArM as (Co)Rapp	
(without line extension)	394	52	ca. 13 %
(including line extension)	458	57	ca. 12 %

21 Applications from native German Companies:

	Applications	BfArM Rapp	BfArM Co-Rapp	BfArM total
Boehringer Ingelheim	10	3	4	7
Bayer AG	4	-	-	-
Merz	2	-	-	-
Schwarz Pharma	2	-	2	2
Behringwerke	1	-	-	-
Grünenthal	1	-	-	-
Medac	1	1	-	1
total number:	21			10

Conclusion: out of 21 applications within it's legal responsibility the BfArM has acted in nearly 50 % as (Co)Rapporteur

*Date: 15. 11. 2003

Importance of European Procedures - Future

For 2004*, 33 new substances are expected within the Centralised Procedure but 200 „orphans“ are „on the horizon“ in the next few years.

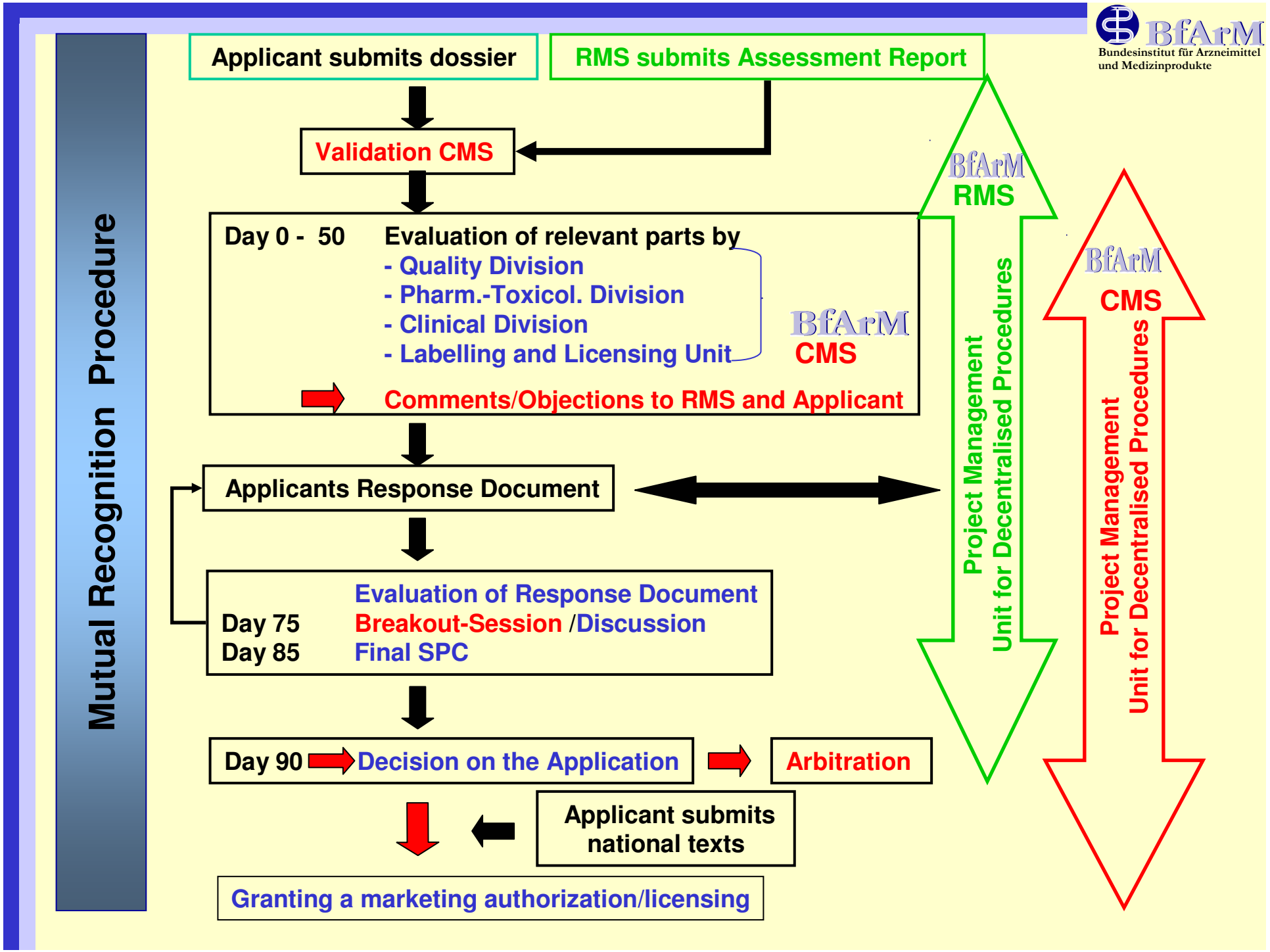
What is the future ??

How to get a rapporteurship from a smaler „cake“ ??

What‘s about the new members and their „slice“ ??

(costs ? , fees ?, 240 EMEA - employees must be paid!)

* source: T. Lönngren, Rome 27.11.03


Mutual Recognition Procedure
Applicant submits dossier
RMS submits Assessment Report
Validation CMS
Day 0 - 50
Evaluation of relevant parts by
- Quality Division
- Pharm.-Toxicol. Division
- Clinical Division
- Labelling and Licensing Unit
BfArM
CMS
Comments/Objections to RMS and Applicant
Applicants Response Document
Day 75
Day 85
Evaluation of Response Document
Breakout-Session /Discussion
Final SPC
Day 90
Decision on the Application
Arbitration
Applicant submits national texts
Granting a marketing authorization/licensing
BfArM
RMS
Project Management
Unit for Decentralised Procedures
BfArM
CMS
Project Management
Unit for Decentralised Procedures
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BfArM – Europ. Workload
Mutual Recognition 1995 bis 2003

Mutual Recognition*

	EU	BfArM RMS	BfArM CMS	BfArM total
Procedures:	2325	290	1334	1624
Applications:	4605	528	2721	3249

DE has taken 2002 the 4th position of all MSs acting as RMS.

DE - together with SE - took the leading position in the approval of new substances in the MRP.

DE has participated in more than 50 % of all MRPs including 2/3 of all applications submitted in the EU.

DE has the biggest share of marketing authorisations through the MRP in Europe.

*Date: 15. 11. 2003

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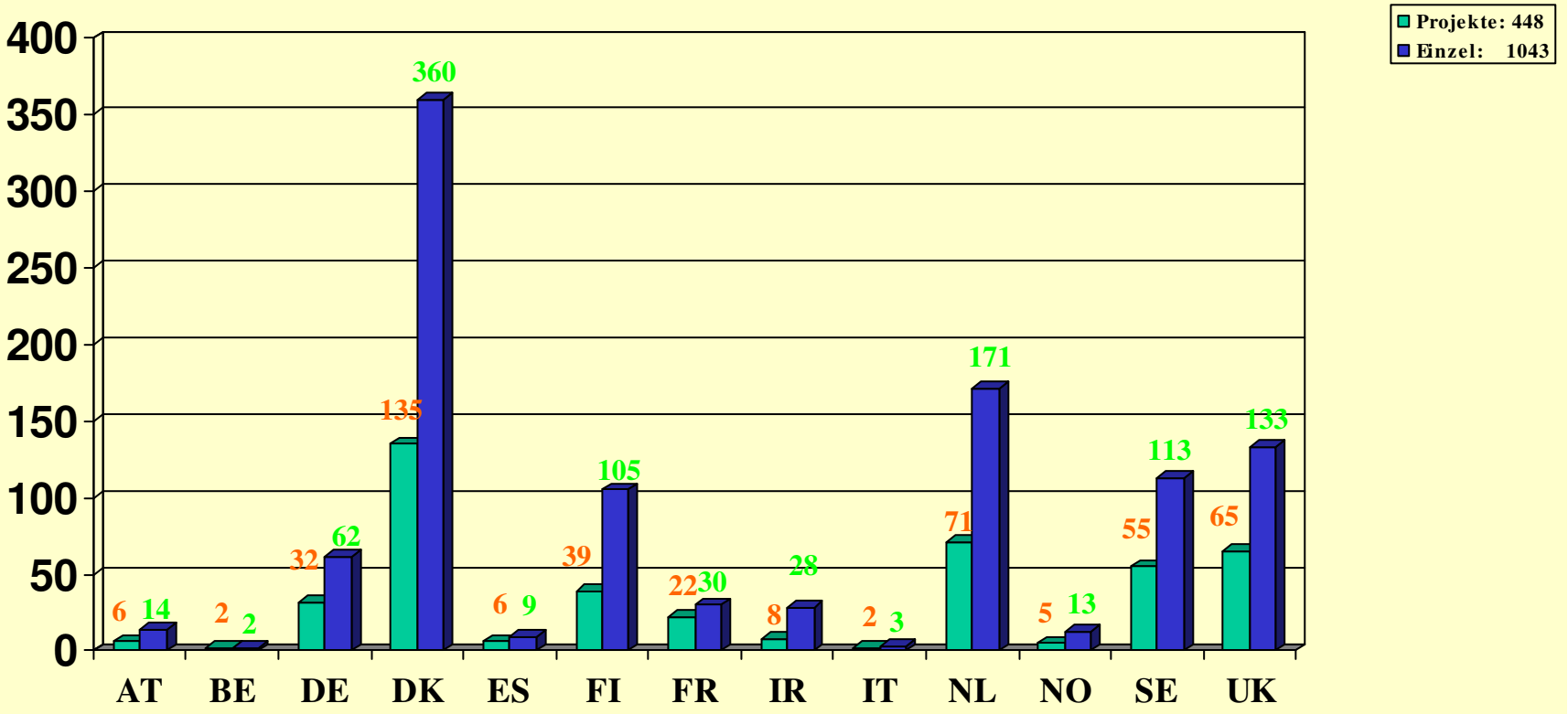
Overview
Reference Member States in MRP
- Finished Procedures (Day 90)
01.01.2003 till 15.11.2003 -



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Reference Member State

Timetable for the Mutual Recognition Procedure

- Nationale Authorisation with Assessment Report
- Start of Procedure in compliance with the Best Practice Guide (MRFG)
- Day 1 - 50 ⇨ Receive comments (RMS/MAH) of CMS
- Day 51 - 60 ⇨ Agreement on Response Document (MAH and RMS)
- Day 61 ⇨ Distribution of Response Document by MAH to RMS/CMS
- Day 75 ⇨ “Break-out Session" parallel to MRFG-Meeting
- Day 85-89 ⇨ "final position" CMSs
- Day 90 ⇨ End of Procedure

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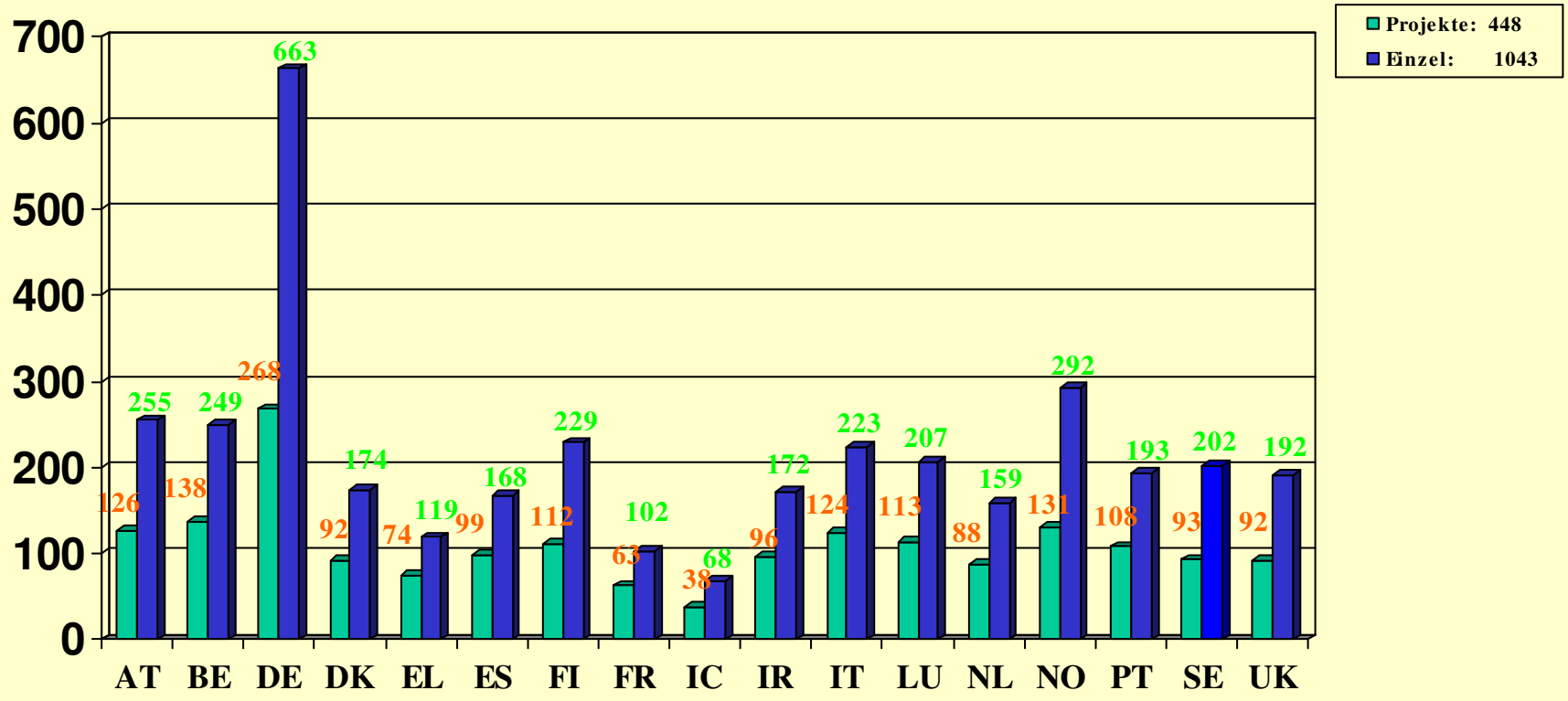
Overview
Concerned Member States in MRP
- Finished Procedures (Day 90)
01.01.2003 till 15.11.2003 -



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Concerned Member State

REALIZATION OF THE REQUIREMENTS OF THE BEST PRACTICE GUIDE

- **CHECK IN PROCEDURE**
  - AUTOMATIC VALIDATION TIME → **10 WORKING DAYS**

- **POTENTIAL SERIOUS HEALTH ISSUE** → **NOT LATER THAN DAY 50**
  ALWAYS BEFORE DAY 50

- **OBJECTIONS AND ANY ISSUES OF CLARIFICATION SHOULD CAREFULLY SCREENED WITHIN THE NATIONAL AGENCIES**

- **AGREEMENT ON THE SPC BEFORE** → **DAY 90**

- **NATIONAL AUTHORISATIONS TO BE ISSUED WITHIN** → **30 CALENDAR DAYS**

Granting of National Marketing Authorisation after MRP

EFPIA survey July 2001- Sep. 2002

30 - 60 Tage = 3 MS

60 - 90 Tage = 7 MS ⟸ DE (BfArM)

90 - 120 Tage = 6 MS

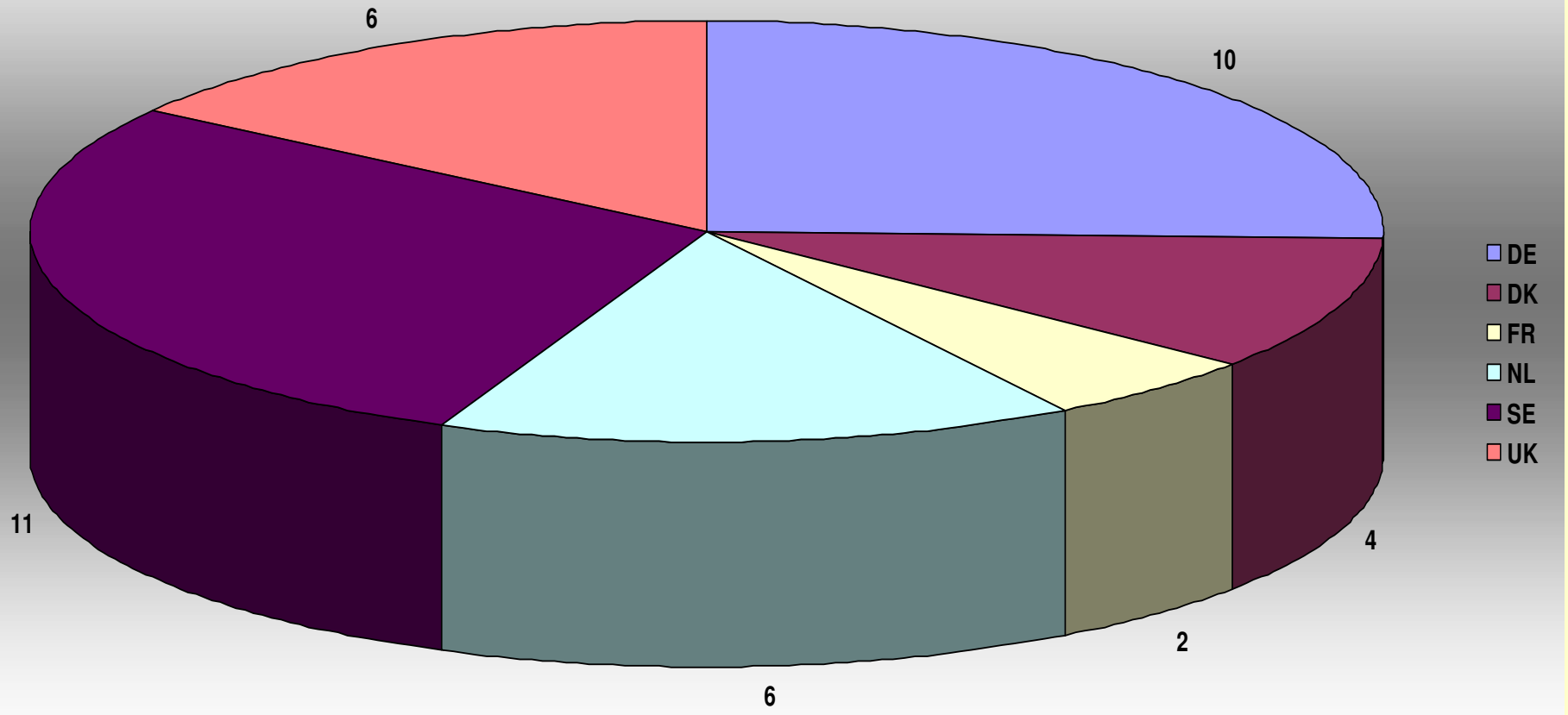
> 200 Tage = 1 MS

Time within the responsiblity of the BfArM:

2002 80 Days (mean value)

2003 **60** Days (mean value)

New Active Substances by RMS
Mutual Recognition New Applications
finalised in 2002



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Variations

Mutual Recognition Procedure
Commission Regulation (EC) No 1084/2003

Type IA	Type IB	Type II
Example: name/address of MAH or manufacturer, name of active substance,	Example: name of medicinal product, manufacturer of active substance, shelf life	Example: change of SPC (indications, Contraindications, Interaction or Side Effects, ...)
Notification Procedure	Notification Procedure	Approval Procedure
CMS: Validity RMS: Validity, Plausibility	CMS: Validity RMS: Validity, Plausibility (Quality and/or Clinical Assessment)	CMS: Quality and/or Clinical Assessment RMS: Quality and/or Clinical Assessment + Assessment Report

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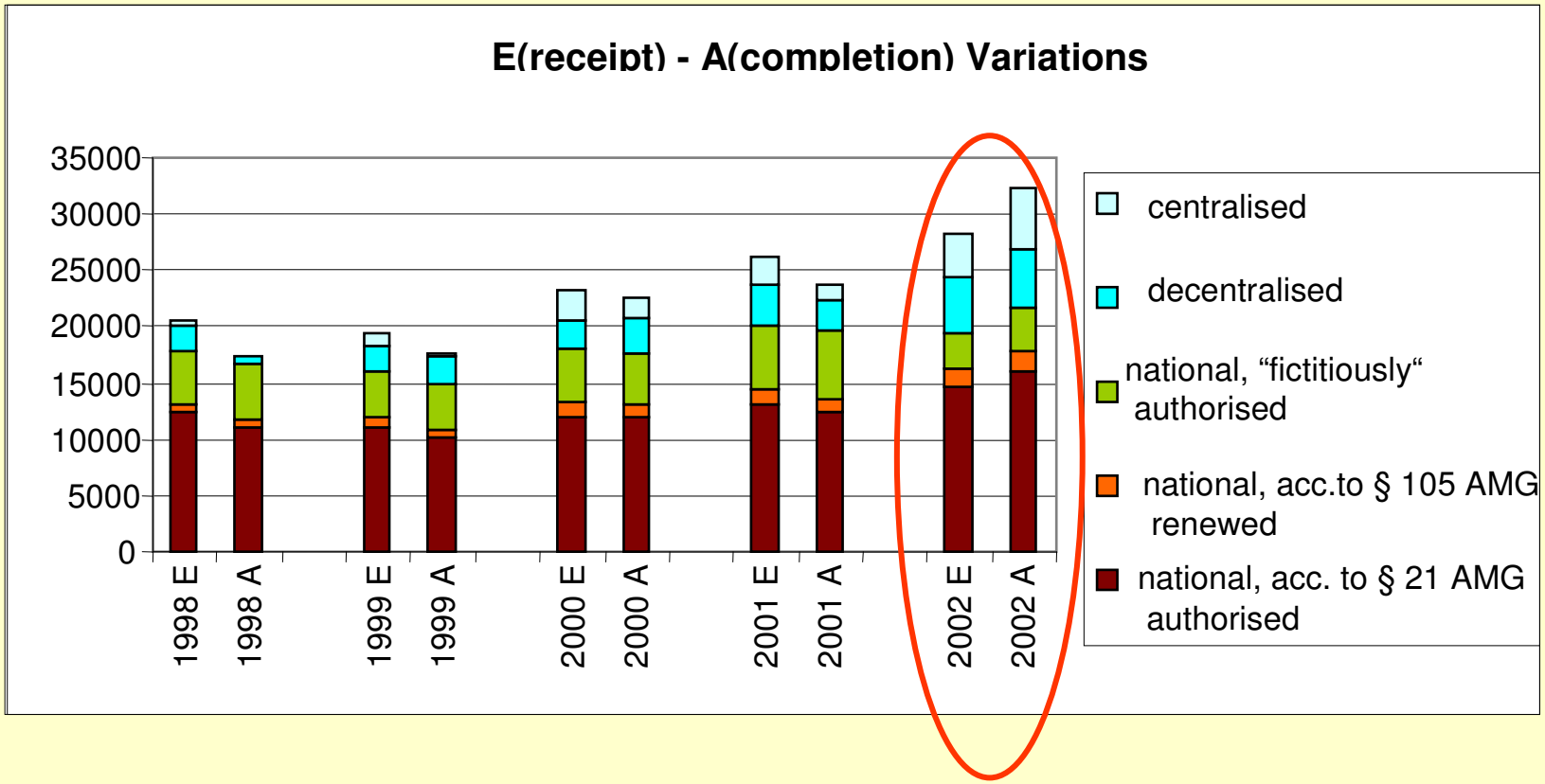
Variations

Receipt (E) + Completion (A)



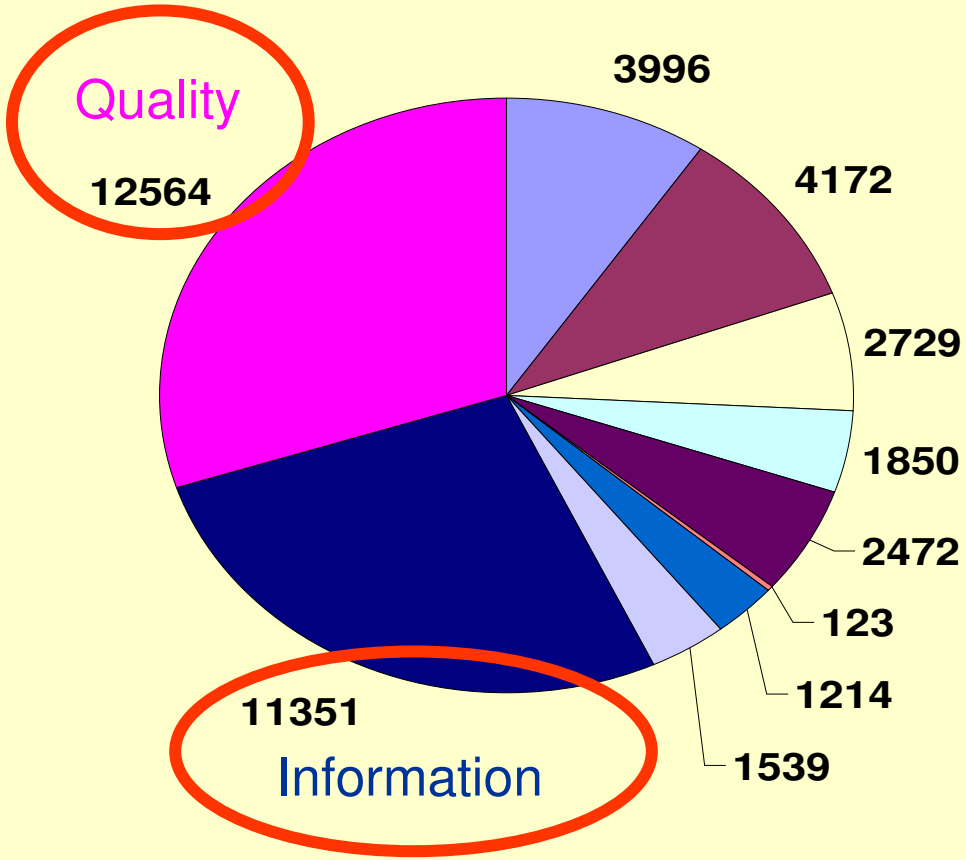
2002 Number of completed procedures higher than number of receipts

Variations 2002/ 1. Hj. 2003

Eingang 2002	nur B113	Qualität	Medizin	sonst.	gesamt
Coordination of Assessment in Scientific Divisions by the Variation Unit of the Regulatory Affairs Division			97	178	2630
			19	804	17250
dezentral, RMS, Type I	304	268	2	2	575
dezentral, RMS, Type II	1	34	59	5	90
dezentral, CMS, Type I	3293	24	4	2	3323
dezentral, CMS, Type II	4	568	410	29	983
zentral, RMS, Type I	96	167	0	0	263

Eingang 1. Hj. 2003	nur B113	Qualität	Medizin	sonst.	gesamt	383
national, zustimmungspflichtig	342	209	652	64	1134	374
national, nicht zustimmungspflichtig	4091	2124	750	472	7320	2480
dezentral, CMS, Type I	110	143	6	0	259	
dezentral, CMS, Type II	0	42	25	7	67	
zentral, CMS, Type I	1703	45	7	0	1755	
zentral, CMS, Type II	0	175	408	9	536	
dezentral, RMS, Type I	12	71	0	0	83	
dezentral, RMS, Type II	0	93	76	12	169	
zentral, RMS, Type I	0	8	0	0	8	
zentral, RMS, Type II	0	380	1033	0	1406	

Variations 2002



- Zulassungsinhaber
- Hersteller
- Bezeichnung
- Packunsgrößen
- Mitvertreiber
- Darreichungsform
- Parallelimporte (zugelassen)
- Zusammensetzung
- Informationstexte
- Qualität ohne Darreichungsform und Zusammensetzung

Possible Development I (Risks)

- 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 (Advantages)

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

But Pharmacovigilance always stays a national responsibility !!

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Agencies Have to Define Their Position for the Future:

- **Team leader and/or opinion leader ?**
- **Centres of excellence for agencies or "full provider" ??**
  - **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 ! (The Network-System !)**

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Role and Tasks of the Agencies in the Future

to be clarified :

- **How to survive ?**

- **Centre of excellence or "full provider" ?**

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My Proposed Solution

- Cooperation on a network-basis
- Promotion of research and development via scientific expertise
- Some agencies as "full providers"
- Other agencies as centers of excellence
- Cooperation within the procedures

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BfArM's possible Contribution

- "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

Aspects of the Enlargement

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Where are the Problems to be found?

- **Potentially everywhere:**
  - Centralised Procedure
  - Article Procedures
  - Mutual Recognition (less for the „new“ Decentralised Procedure)
  - National Procedure
    - Full Applications, Generics, WEU, Herbal Pharmaceuticals
    - Any „Old“ and „New“ Member State
- **Potentially at any time:**
  - Before Accession (transitional observation)
  - During Transition (transitional behaviour)
  - After Accession (transitional arrangement?)

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Contributions Provided by the BfArM

- Participation and Contribution to the EU-System (at the Eur. Commission and EMEA level)
- Participation and Contribution to the PHARE Programmes:
  - PERF I, II, and III
  - Twinning (ongoing with Poland [official start: 1-3.12.03])
  - scheduled with Latvia (start approx. 01.09.04))
- HoA-East Programme: platform for discussion among HoA-E, and also with HoA-W and with Industry Provision of relevant data bases
- Organisation of Participation in Training Programmes (example: BfArM: biostatistics for non-mathematics)

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European Bodies Executing Medicines Regulation

- **Eur. Commission** — **EMEA**
- Pharmaceutical or Standing Committee — CPMP, Working Parties, ad hoc Groups, TAG‘s

Controlling approx. 10% of Pharmaceuticals via Centralised and Article Procedures

- **Competent Authorities of the Member States**
- **Mutual Recognition** — **National Procedures**

Controlling approx. 20% — **approx. 70%**

of Pharmaceuticals on the EU-Member States Markets

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European Bodies Executing Medicines Regulation: Responsibilities ?

Eur. Commission

Guardian acquis Communautaire

- hard law / soft law
- Transitional arrangements

Member States

Facilitator to Accession

- transparency
- provision of experience

EMEA

- simplification
- logistic support

New Member States

- responsible for assessment
- competent for decisions
  (throughout the product lifetime)

Pharmaceutical Industry (trade associations, MAH's - „old" / „new" EU)

- „Old" generics (without dossier?)
- Upgrading effort
- Use of simplified procedures
- Provision of dosisiers on time

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Partnership of National competent Agencies: Current and New Member States

Current EU Member State	New EU Member State
Centrally authorised product (CAP)	Simplified procedure available
Mutually recognised authorised Product (MAP) Referral/Arbitration harmonised product (RAP)	Simplified procedure available Early, on-time or no implementation?
Solely nationally authorised product (NAP)	Simplified procedure(s) available?
Originator authorised product Self-Standing Dossier (WEU) Essentially Similar Product (consented) Essentially Similar Product (generic) BE with local product?	Current or Future EU-MS product? Current or Future EU-MS dossier? Consent to a Future EU-MS product Claim to be based on MA of Originator BE with European product?
Module 3 (Part II) to be submitted	Module 3 (Part II) to be submitted

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European Bodies Executing Medicines Regulation: Where are the Problems to be found?

Consequences?

- Cooperation
- Collaboration
- Networking
  - Bilaterally (between Agencies, Twinning)
  - Multilaterally (between Agencies, PERF)
  - Specific Groups (CPMP, QRD, „HoA-East“)

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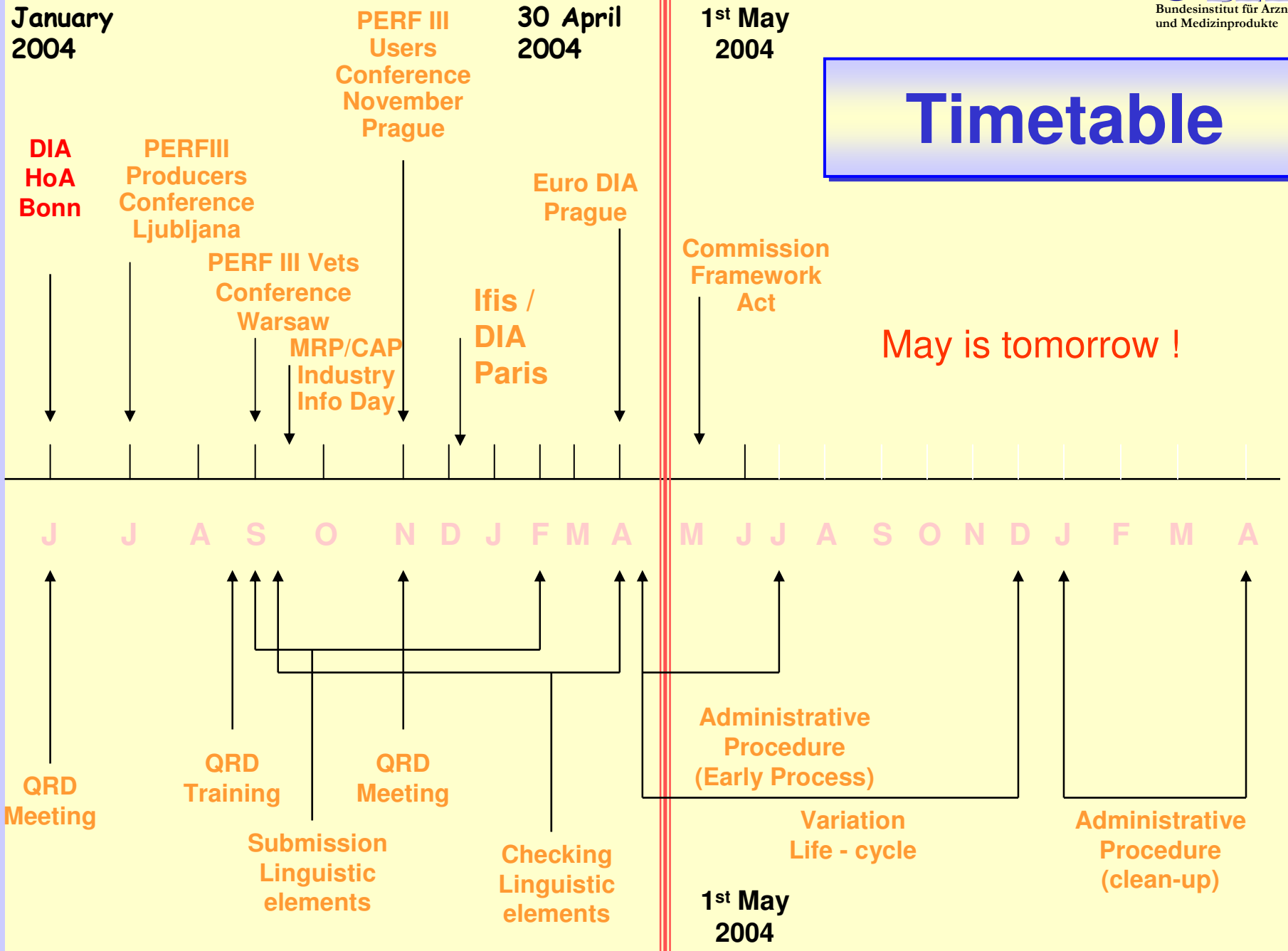
Timetable



As an example :
The great challenge
"Harmonis/zation
of Summary of Product
Characteristics"

E.G. : Article 11

75/319/EEC Procedure for originator

- **When?**

  Different national decisions on the drug

- **Why?**

  Harmoniz/sation of national decisions

- **Who starts ?**

  Member States, EU Commission, applicant/holder of author.

- **Who is concerned ?**

  the drug

  applicant/holder of authorisation

  the reference drug

  Member States with existing authorisations

  Member States with withdrawn/suspended authorisations

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Follow-up after Community Referral
Article 11

How ? „ nis/za “ (If we even not agree on the spelling ?)

The procedure harmoniz/ses the "Summary of Product Characteristics" especially Parts III and IV of the Dossier (pharm-tox, clinical)

Not Part II, Quality. This part of the SPC can remain unharmonised

However, the authorisation holder is seriously advised to harmoniz/se voluntarily or to file the Quality Dossier as a 'European Dossier'

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CTS- Steps 2003 – 2004

10/04/03 Specialized Specification of the new Variations

10/04 Feature-definition completed by the CTS Usergroup

10/04 New Data-Model finished

12/05 CTS NextGen Server finished

30/06 CTS NextGen Client with new Variations finished

15/08 Interaction between 5.3.9 and NextGen-Client finished

30/08 Beta-Test with CTS Usergroup-Members

15/09 Testing Phase at all European Sites

01/10 Going Live with new Variations

May/2004 CTS NextGen completely replaces EMR 5.3.9

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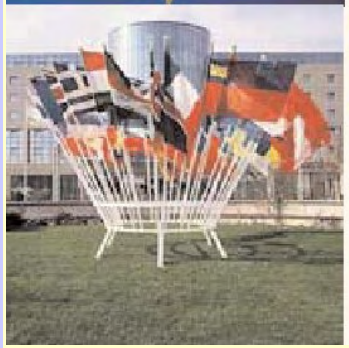
DIA®
DRUG INFORMATION ASSOCIATION

Dedicated to Your Information & Advancement

….. 4th Meeting with HoA-East

January 12-13, 2004 - Maritim Hotel, Bonn, Germany



Enlargement Summit

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DIA/BfArM JOINT CONFERENCE

THIS DIA CONFERENCE IS BEING ORGANISED IN COOPERATION WITH THE FEDERAL INSTITUTE FOR DRUGS AND MEDICAL DEVICES (BfArM), GERMANY

Programme Committee

Rolf Bass, Federal Institute for Drugs and Medical Devices (BfArM), Germany
Roger Grase, Federal Institute for Drugs and Medical Devices (BfArM), Germany
Brenton James, GlaxoSmithKline R&D, UK
Ingrid Klingmann, Pharmaplex, Belgium
Jacques Mascaro, Johnson & Johnson Pharmaceutical R&D, UK
Anu Tummavuori-Liemann, F. Hoffmann-La Roche Ltd, Switzerland

Programme Advisor

Harald Schweim, Federal Institute for Drugs and Medical Devices (BfArM), Germany

Faculty Members

CYPRUS
George Antoniou, Pharmaceutical Services, Ministry of Health
CZECH REPUBLIC
Milan Smid, State Institute for Drug Control
ESTONIA
Kristin Raudsepp, State Agency of Medicines
HUNGARY
Tamas L. Paal, National Institute of Pharmacy
LATVIA
Janis Ozolins, State Agency of Medicines
LITHUANIA
Vytautas Basys, State Medicines Control Agency
MALTA
Maria Ellul, Medicines Authority, Operations and Regulatory Affairs
POLAND
Michal Pirozynski, Office for Registration of Medicinal Products, Medical Devices and Biocides
SLOVAK REPUBLIC
Ludevit Martinec, State Institute for Drug Control
SLOVENIA
Agency for Medicinal Products*

BULGARIA
Borislav Borissov, Bulgarian
CROATIA
Sinisa Tomic, Croatian Agen

EMEA, UK
Anthony Humphreys
Hans-Georg Wagner

EUROPEAN COMMISSION, BELGIUM
Irene Sacristan Sanchez

* Invited

more meetings planned…… ?

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my home – country :
EUROPE*

Thank You for Your kind Attention !

*Intermediate stage 2004/7

and Turkey ?

Procedure of the Ethics committee

Situation according to the current legislation

56 Ethics committees formed according to ´Länder-Law`:

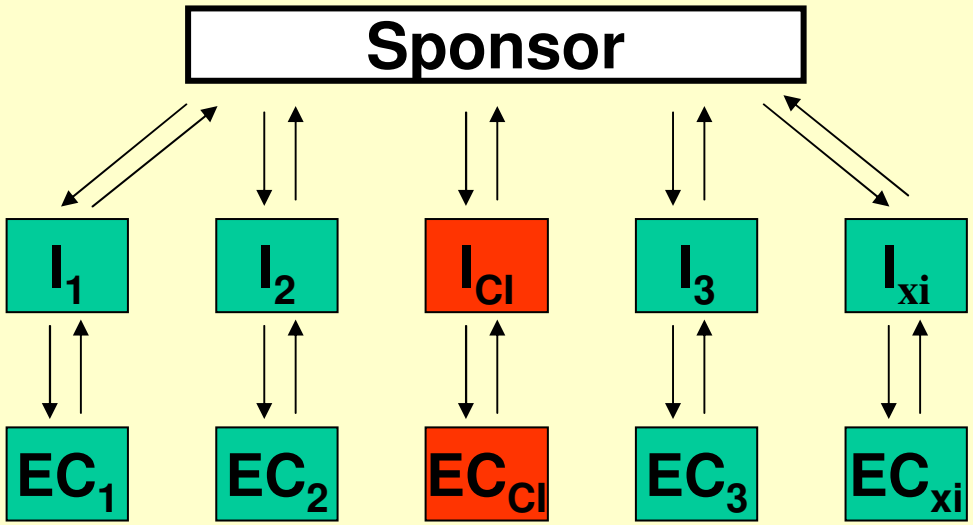
- 20 ECs of the Medical Practioner Association in the ´Bundesländer´
- 36 ECs of the Medical Faculties of Universities and Medical High Schools

Requirements according to GML

Favourable Opinion of EC competent for the coordinating investigator

***Requirements according to professional law for MDs*:**

Each investigator should to be consulted by the concerned EC.



Note

- no time limits for application and review procedure of EC
- risk of several discordant opinions in multi-centre trials

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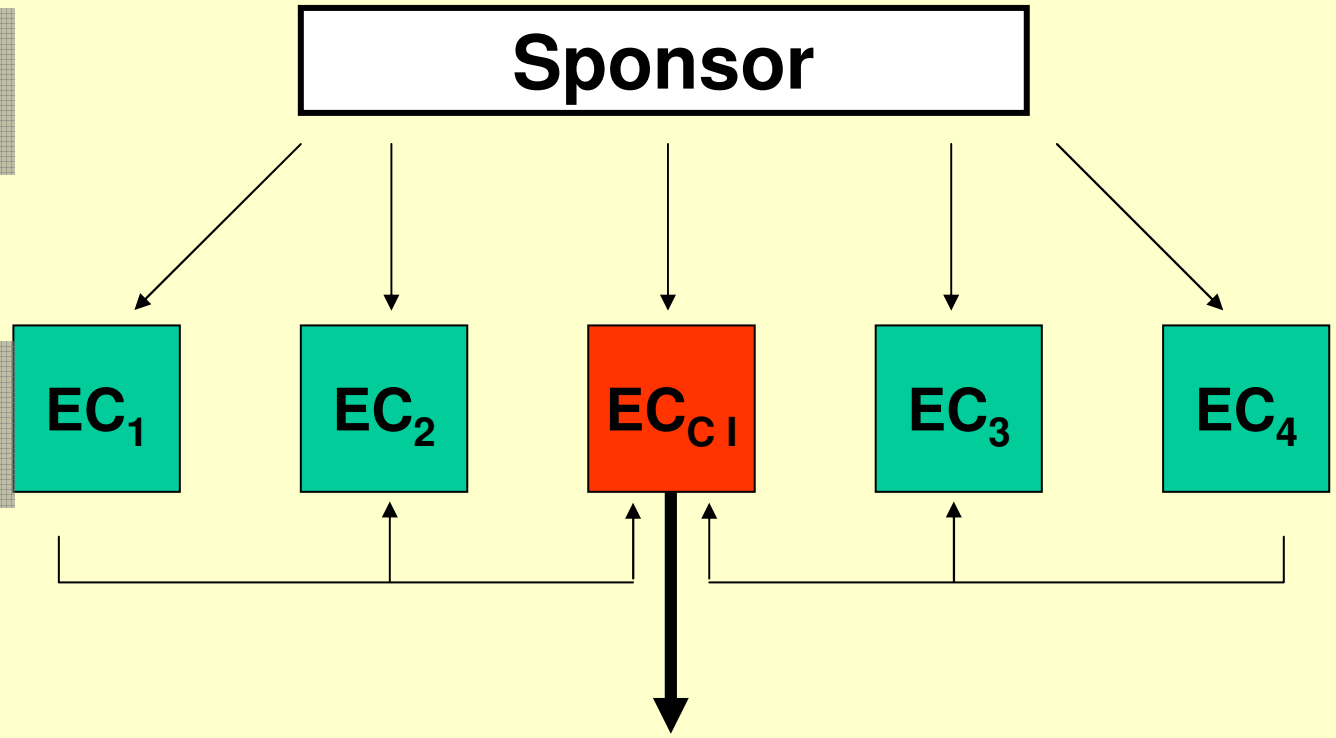
Application for an Ethics committee opinion

Procedure for single opinion in a multi-centre trial

§ 41 (2) 12. law amending GDL (draft), § 7 Ordinance on GCP (draft)

Sponsor provides a valid application to all Ethics Committees



EC1-x provide comments within 30 days to EC of coord. invest.

Single opinion provided by EC of coord. invest. within 60 days

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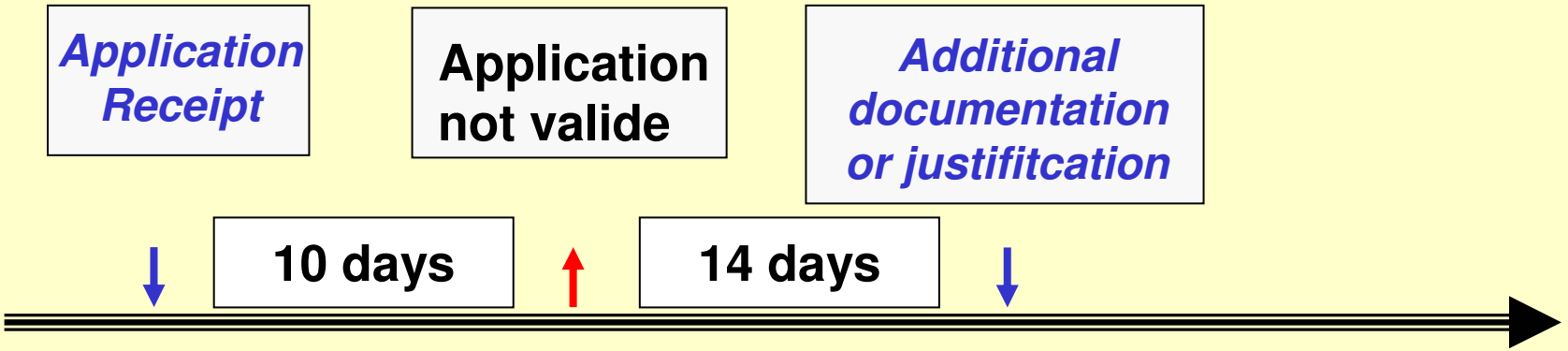
Application for an Ethics committee opinion

§ 41 (1) 12. law amending GDL (draft), § 7 (1) GCP-Ordinance (draft)



Review on completeness

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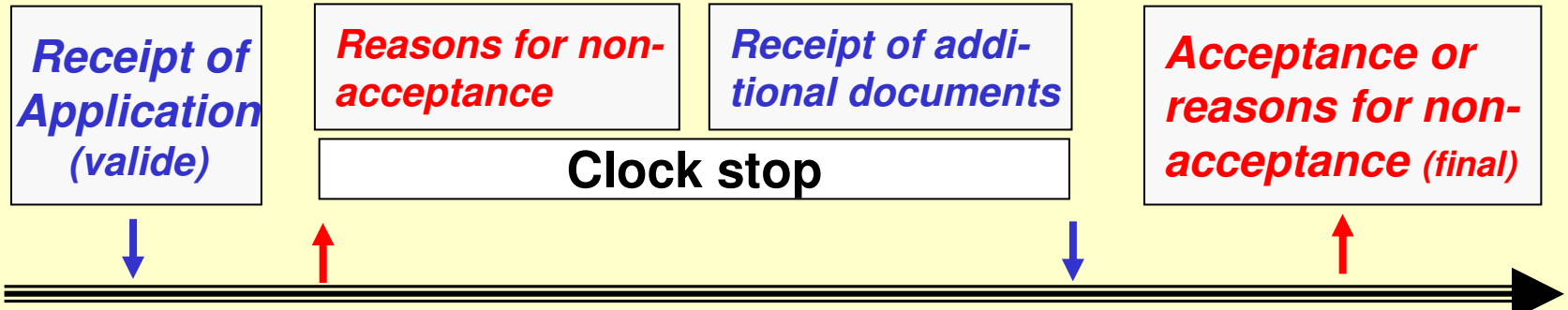
Application for an Ethics committee opinion

Procedure and time limits

§ 41 (2) 12. law amending GDL (draft), § 7 Ordinance on GCP (draft)



Multi-centre trials:	**60 days**
Single-centre trials (incl. 1. step phase I trials) :	**30 days**
Phase I trials (Second + further steps):	**14 days**

Review

According to the prevailing standard of scientific knowledge:

- **completeness of documents**
- **protocol, investigators brochure, modalities on the recruitment of trial subjects**
- **informed consent**

Note

Time limit 90 days in clinical trials investigating Gentransfer, somatic cell therapy, genetically modified organisms

Extended to 180 days if external experts are consulted

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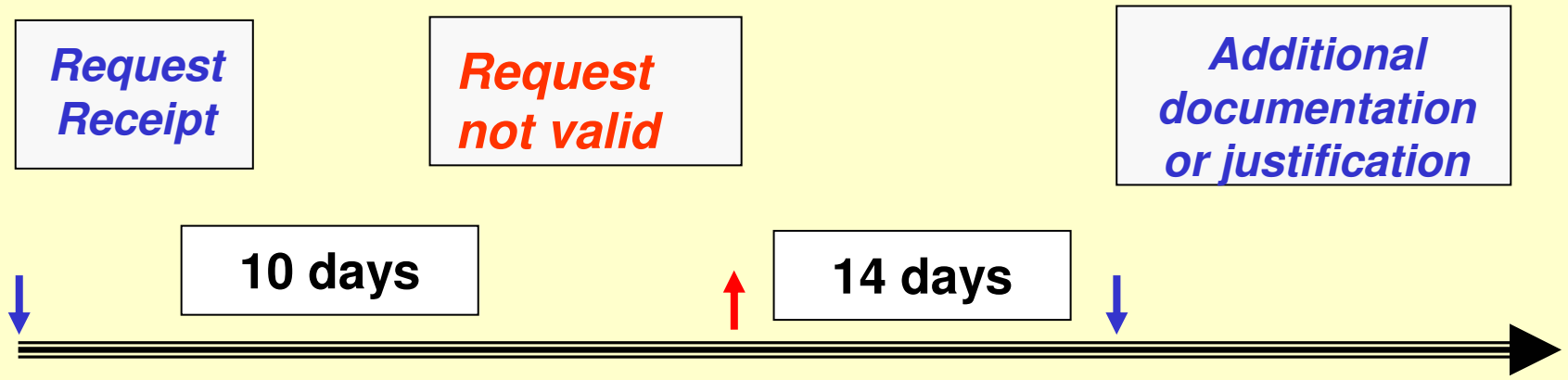
Request for Authorisation to the competent authority

§ 41 (2) 12. Revision GDL (draft), § 8 GCP-Ordinance (draft)



Review on completeness

- Covering letter
  (Eudract Nr.)
- Application form
- IMP Dossier
- Investigators brochure
- Protocol
- Certificates

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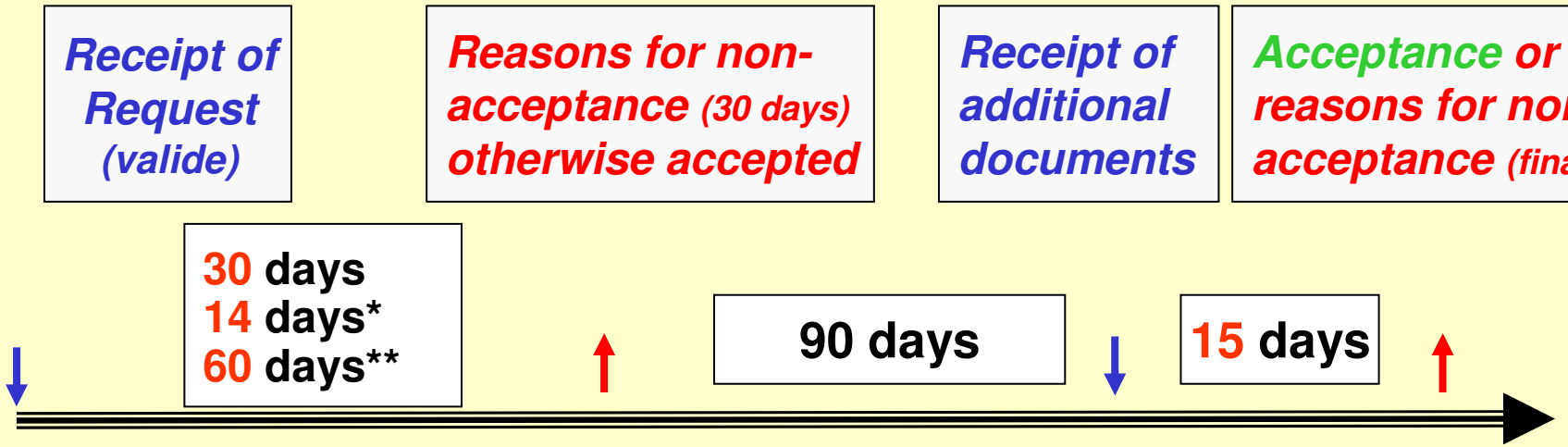
Request for Authorisation to the competent authority

§ 41 (2) 12. Revision GML (draft), § 8 Ordinance on GCP (draft)



Review

According to the prevailing standard of scientific knowledge:

- **Quality**
  - Drug substance
  - Drug product
- **pharm-tox. documentation**
- **clinical documentation**

Note

*** 14d 2nd + further trials in phase I**

*** time limit 60d in clinical trials with IMPs according to Dir. 2001/20/EC Art. 9 (5) and (6)**

Time period may be extended to max. 180d if BOB has to consult external expert groups