BfArM
Bundesinstitut für Arzneimittel und Medizinprodukte

Pharmacovigilance in Germany

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Federal Institute for Drugs and Medical Devices (BfArM)

Istambul, 24.10.2003

Authorised Medicinal Products for Human Use in Germany (excl. Blood Products and Vaccines)

Total = 53 882 Medicinal Products

Of these authorised through community procedures:

1. Mutual Recognition = 2 856 Med Prod

with Germany as Reference Member State (RMS) = 409 Med Prod

e.g. Aggrastat®(Tirofiban-hcl), Codiovan® (Valsartan+Hydrochlorothiaz.) , Euthyrox® (Levothyroxin), Propofol® (Narcofol), Xusal® (Levocetirizin-hcl)

(cont.)

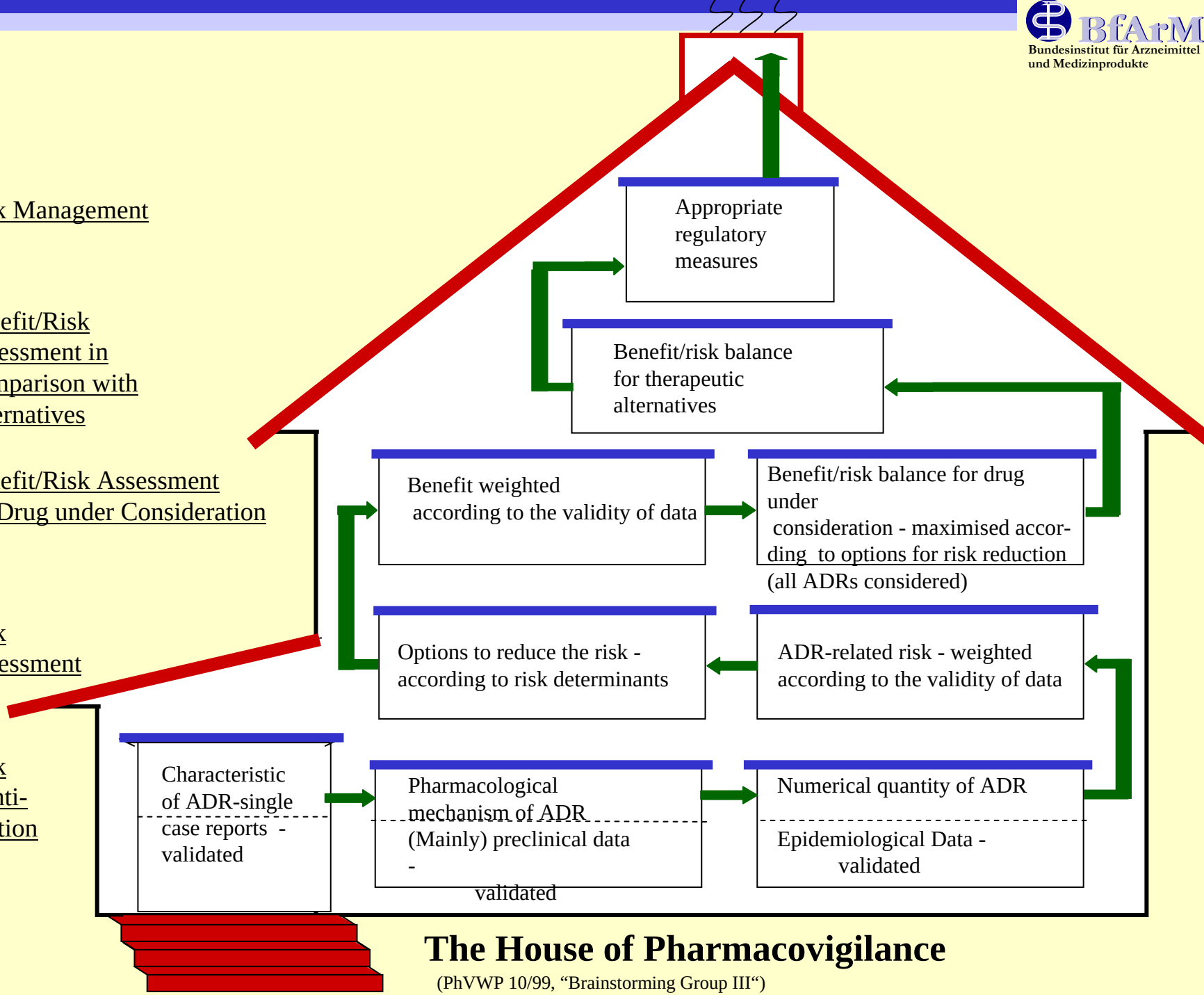
2. And authorised via the Centralised (EMEA-) Procedure = 2 757 Med Prod*

with a German Rapporteur = 193 Med Prod*

or Co-rapporteur = 301 Med Prod*

z.B. Aranesp®(Darbepoetin alfa), Neorecormon®(Epoetin beta), Xeloda®(Capecitabin)
and e.g. Ovitrelle® (Choriogonadotropin alfa) , Pegintron® (Peginterferon alfa2b) , Micardis®(Telmisartan) resp.

* with central authorisations each individual package size is counted as one Med Prod



The House of Pharmacovigilance

(PhVWP 10/99, "Brainstorming Group III")

Observe !
Measure !
Explain !

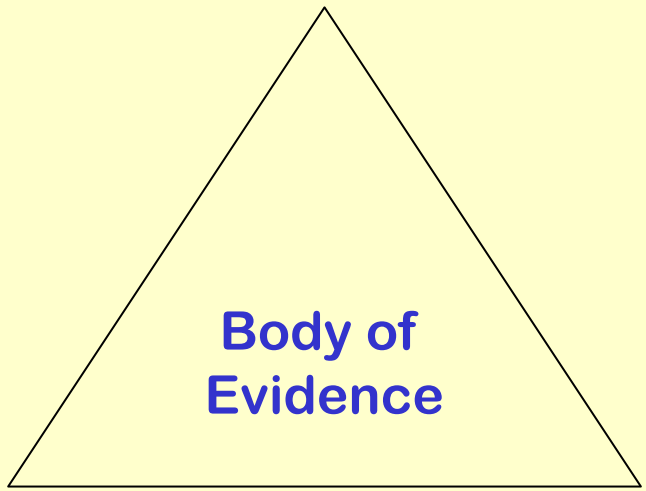
Galileo Galilei

"This telescope has the advantage of discovering the ships of the enemy two hours before they can be seen with the natural vision."

Sources of Information on ADRs, General

Single Case Reports:

Quality + Causality



Epidem. Studies:

Frequency + Causality

Pharmacol. Studies:

Mechanism + Causality

Sources of Information on Drug-related Risks, Specific (1)

- I <u>ADR-Cases, absolute</u>
  - Spontaneously reported ADR cases
    - Single cases
    - Case series in “Line Listings“
  - “Solicited“ ADR cases
    - from Intensive Observation Projects
    - from systematic complete surveillance (e.g. skin reactions)

- II Sales Figures

Sources of Information on Drug-Related Risks, Specific (2)

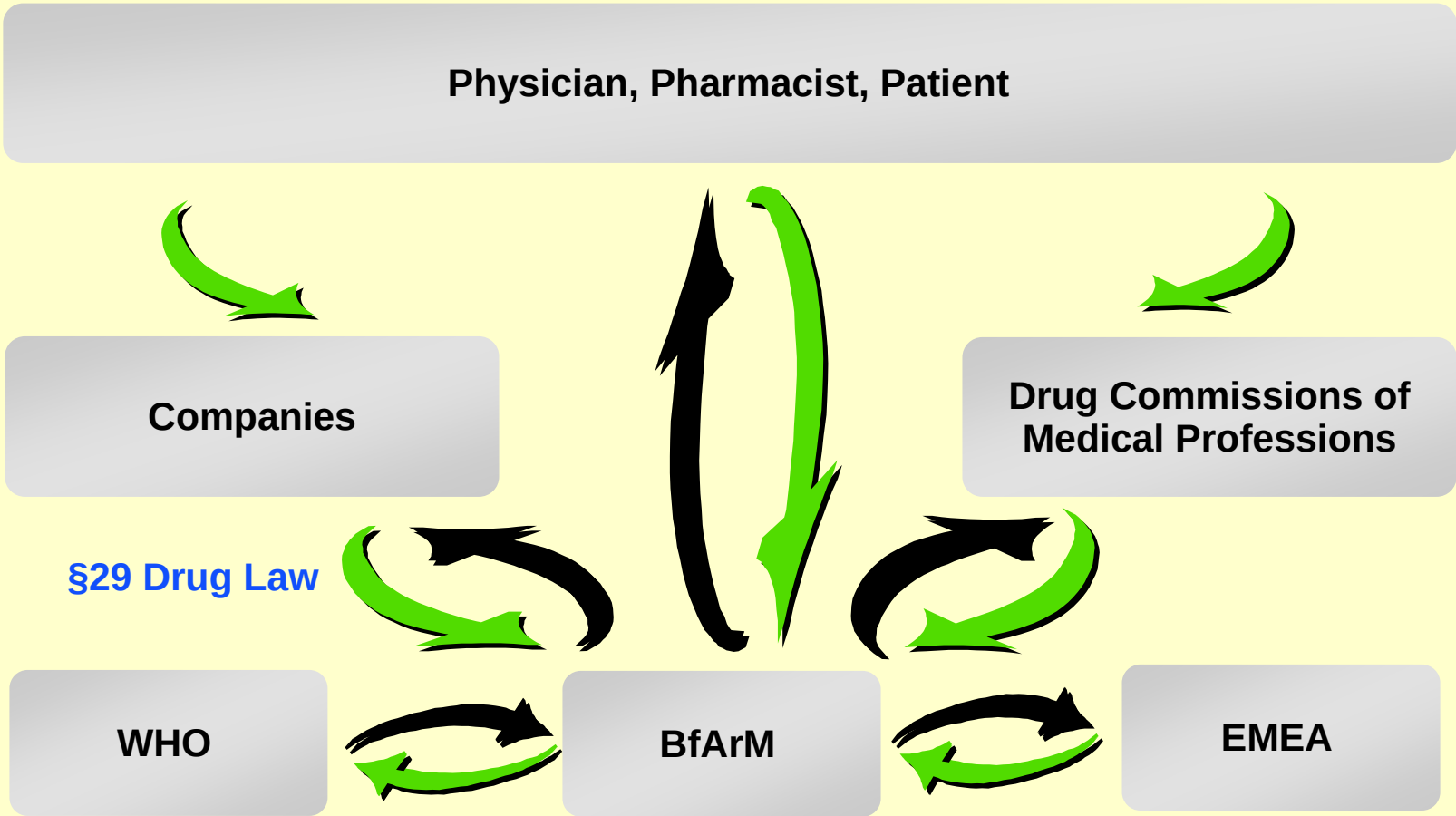
- III Studies investigating the relation ADR-Cases / Exposition
  - Controlled Clinical Studies with intervention
  - Observational (epidemiological) studies without intervention

    Cohort studies (prospective, starting with actually treated women)

    –- comparative, I.e. two- oder more arms

    –- non-compartive, i.e. one arm

Routes of Information

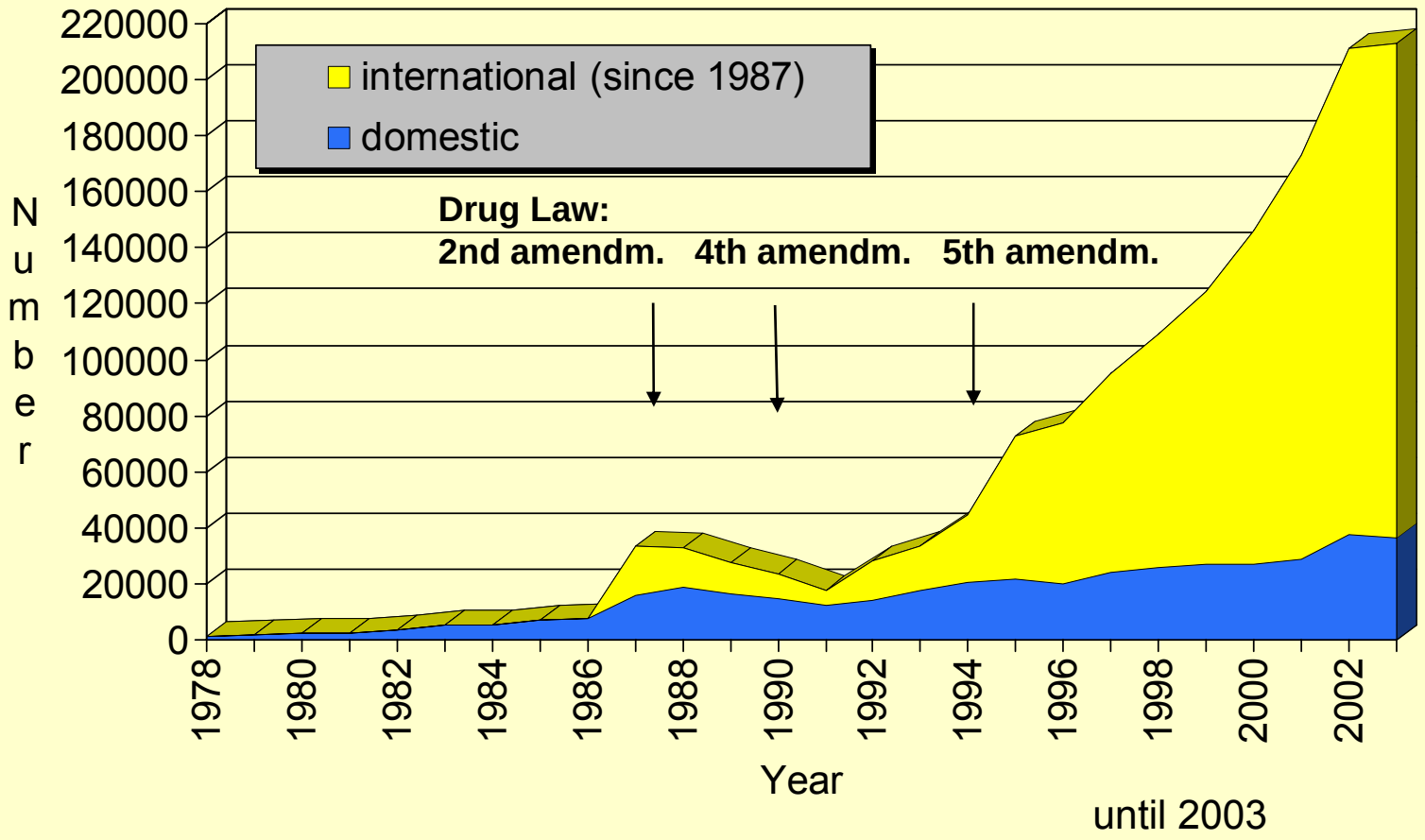


BfArM´s ADR-Reporting Requirements

German Drug Law (AMG) §29, 5th amendment

- **The Marketing Authorisation Holder has to**
  - **report without delay any change in the scientific background relevant to approval of a drug**
  - **report within 15 days any suspected case of serious ADR or serious interaction or serious misuse**
  - **record and report after first approval of a drug all non-serious cases of ADR or interaction, which have to be reported every six months for two years, yearly for next three years, then every five years together with the five yearly reports the application for renewal of authorisation**
  - **provide a scientific assessment**
  - **continue to report even when the drug is no longer on the market**

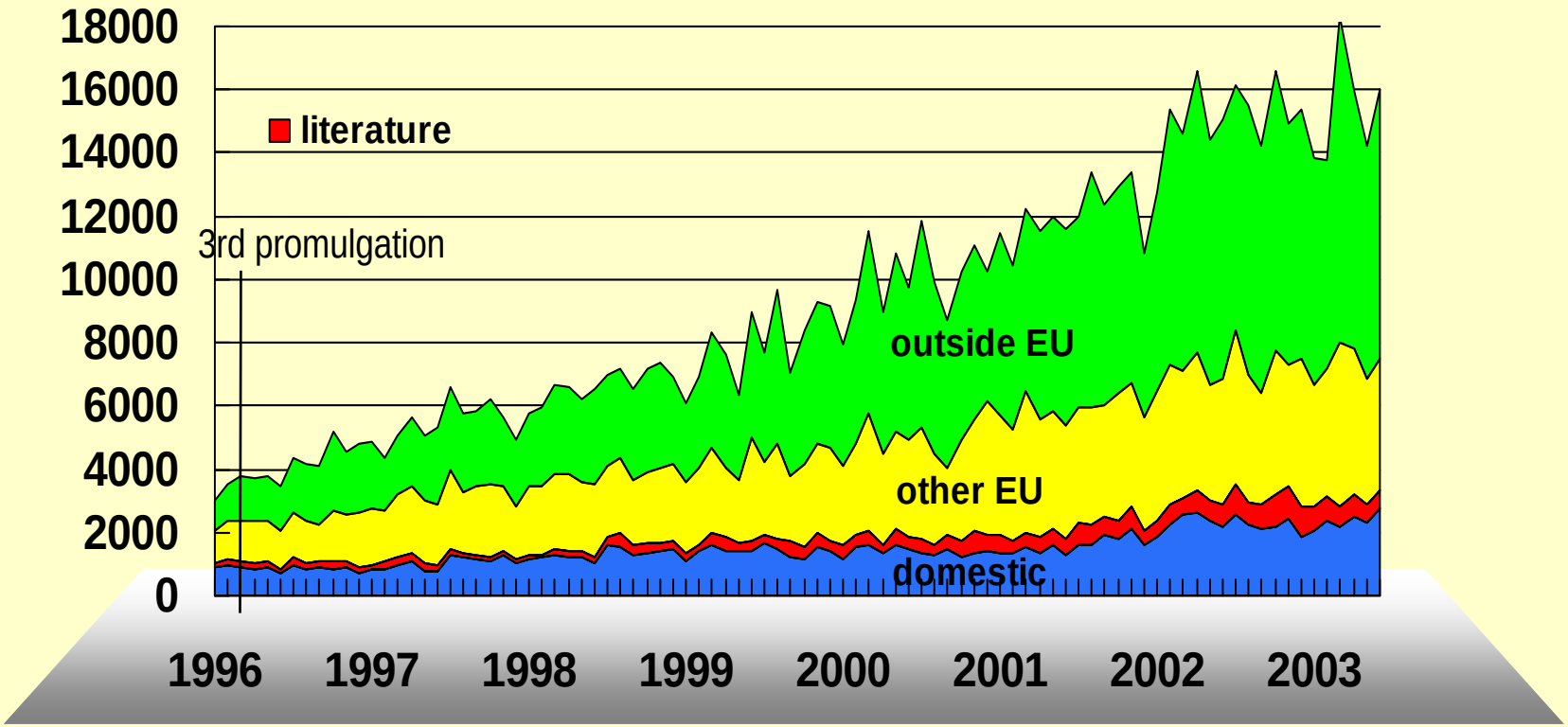
Number of Reports per Year (1978 - 2003, ICSRs incl. follow-ups and Reports in PSURs)



until 2003

Number of ADR-Reports (1996 - 2003, ICSRs incl. follow-ups)

1996: 48500, 1997: 66000, 1998: 80000, 1999: 95000,
2000:119000, 2001: 144000, 2002 : 181000, 2003 estimate: 184000



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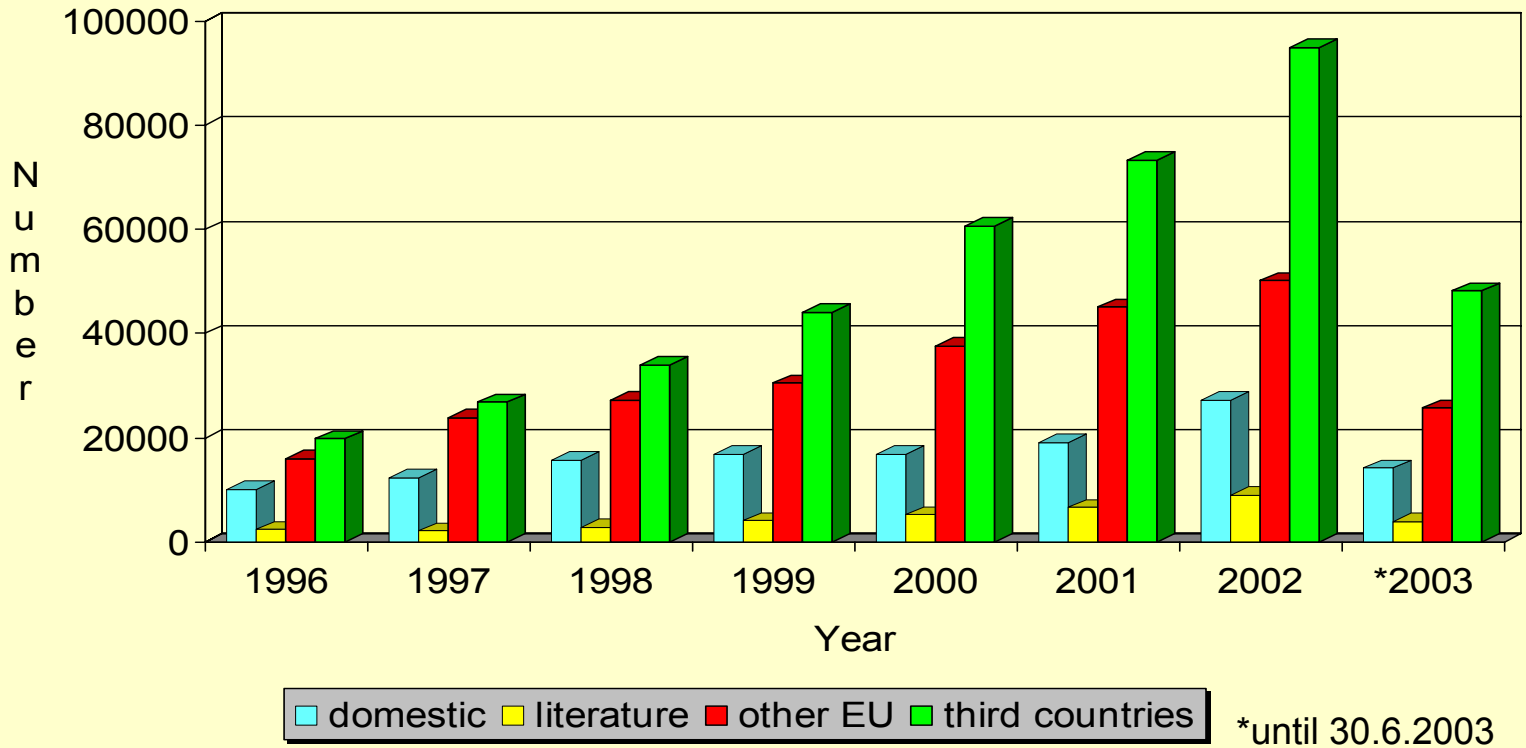
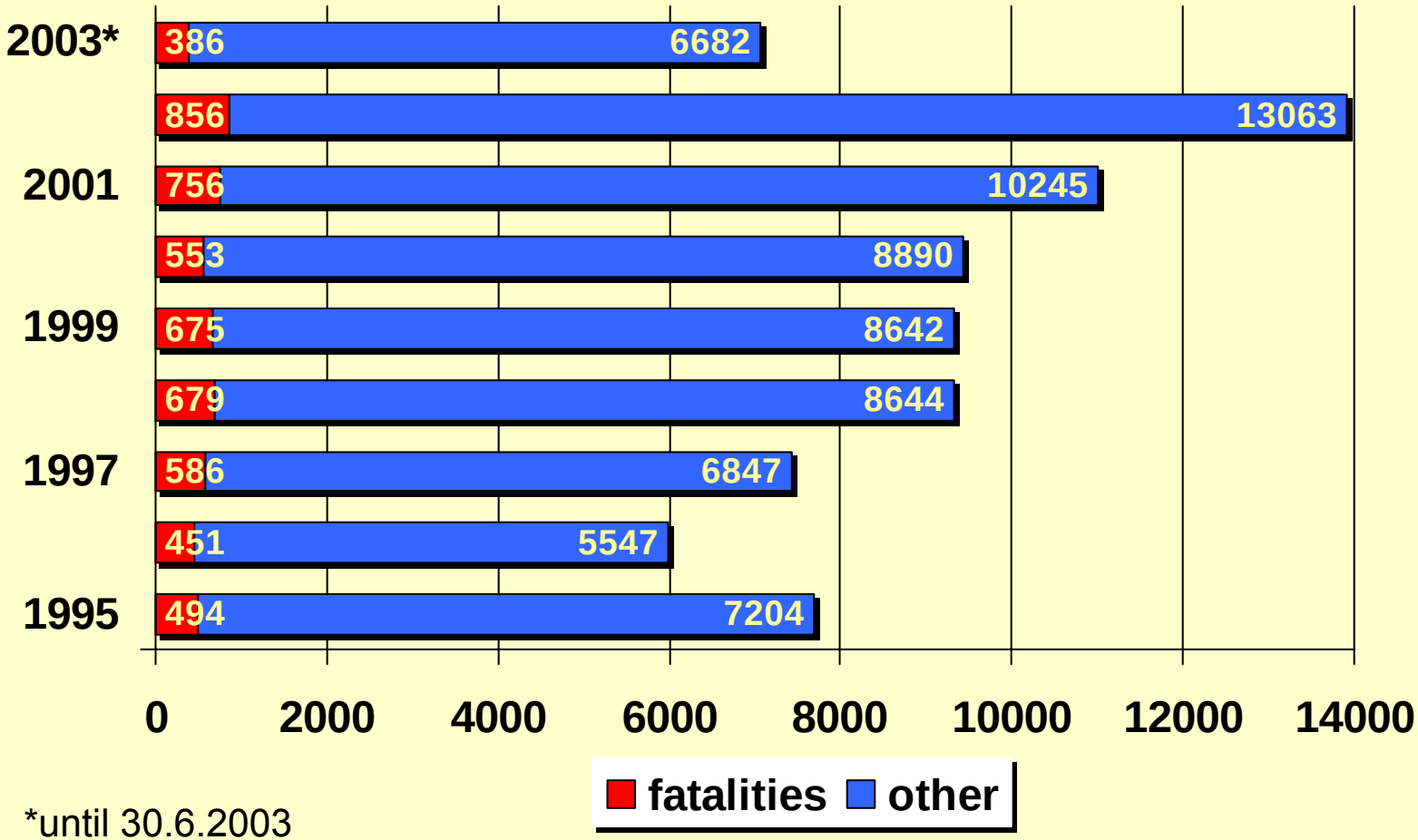


*until 30.6.2003

Number of ICSRs (Domestic)

Distinguishable Cases since 1995 (n=81.200)



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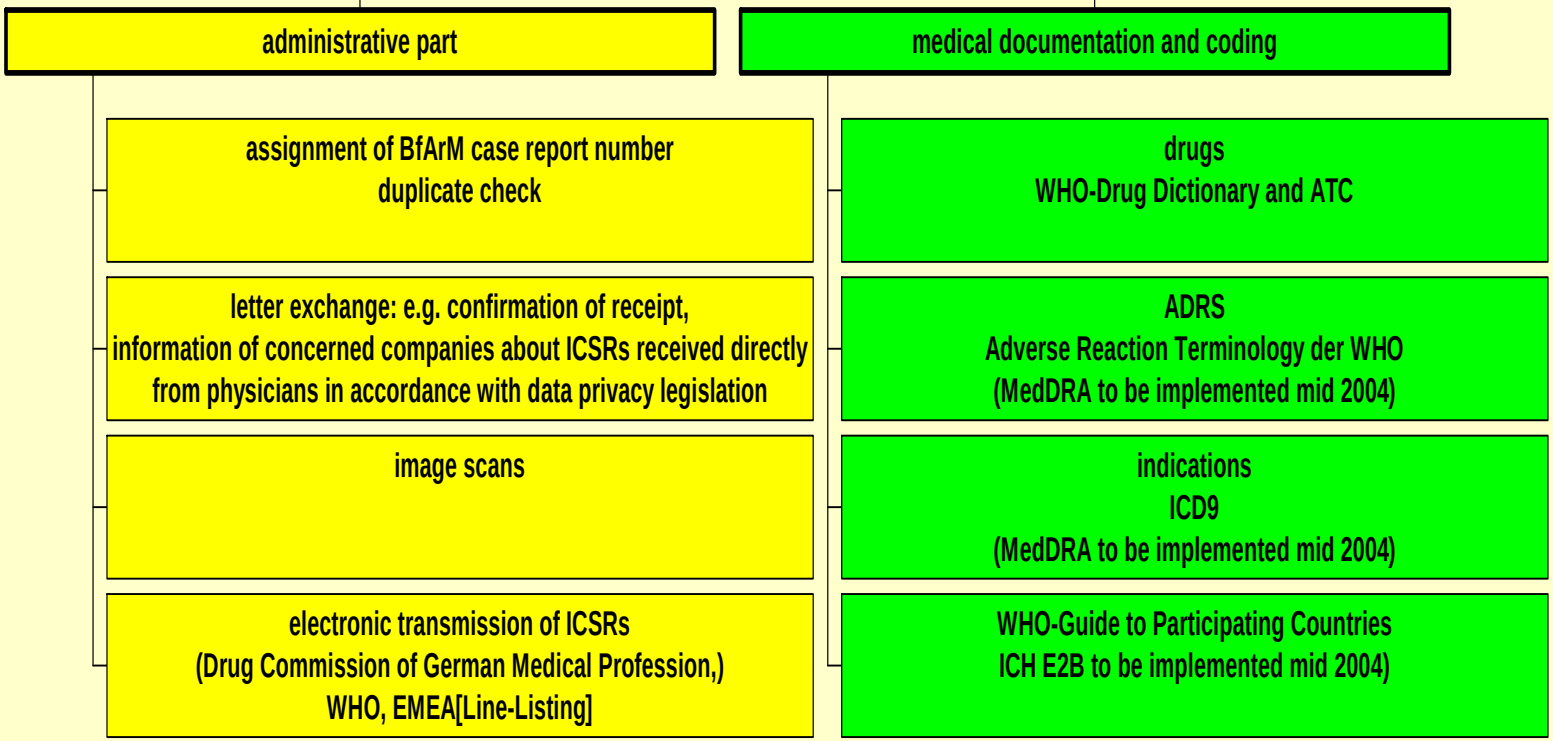
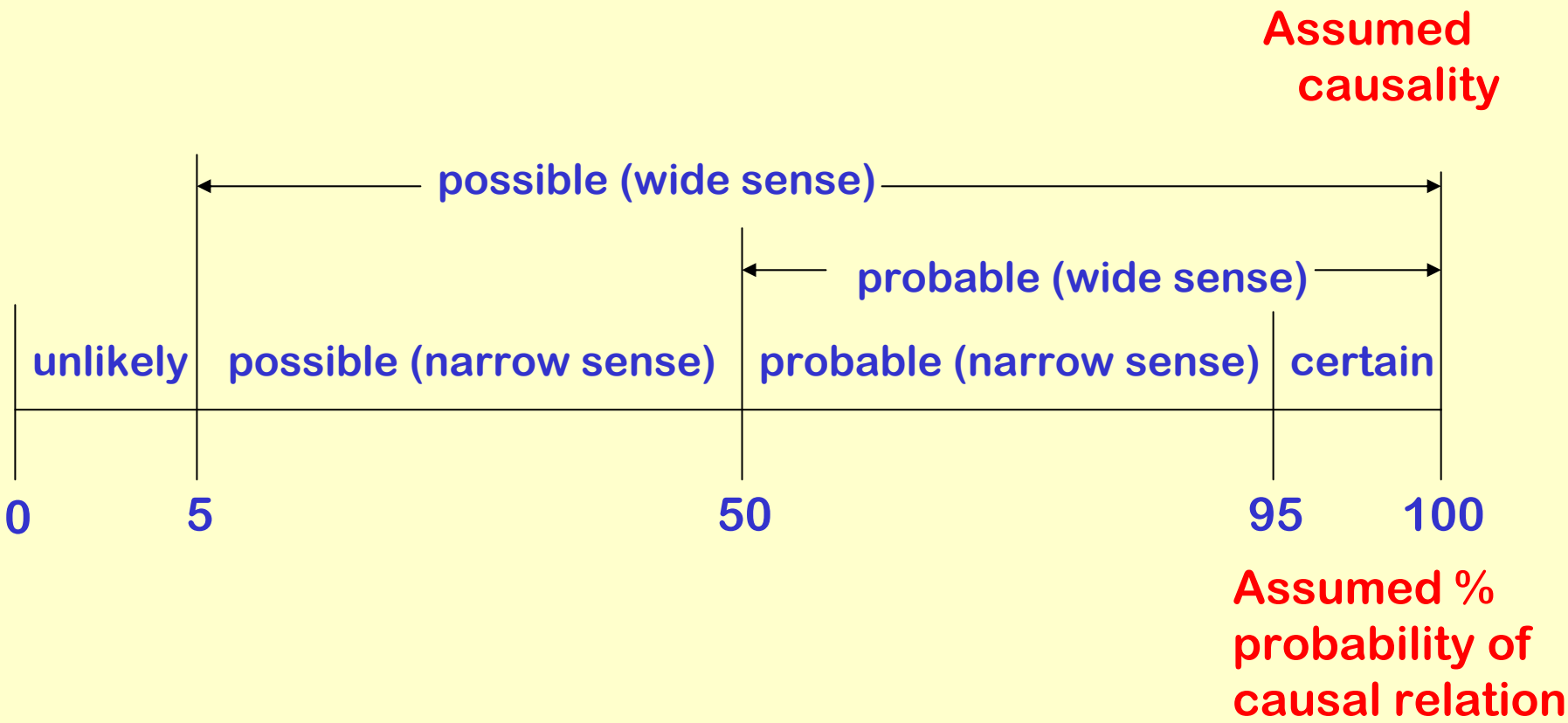
Management and Documentation of ICSRs

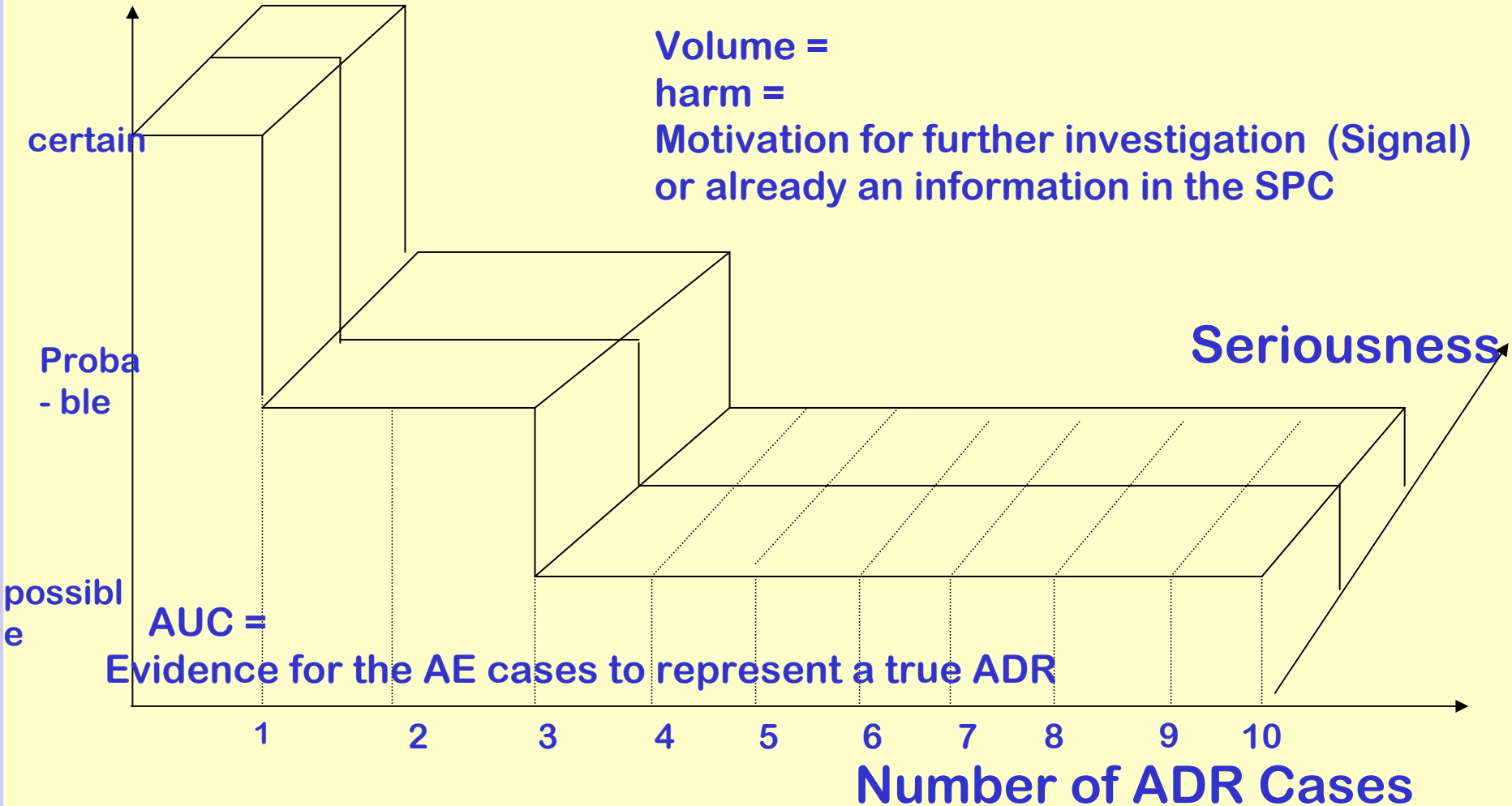


Degrees of Assumed Causality and their Meanings in Terms of Probability of Causal Relation in the Assessment of Adverse Events / Drug Reactions



Number of Reported Cases, Causality and Seriousness of an ADR

as Components for a "Signal" or the Motivation to Take Actions in Terms of Informing about the Risik



Under-Reporting from the Viewpoint of the Chairman of the Pharmacovigilance Working Party of the CPMP

(Sue Wood Symposium)

Myths about Under-Reporting

- Level is fixed at 90%
  i.e. 10% of reactions are reported
- Level of reporting has a linear relationship with the effectiveness of a scheme
- Under-reporting undermines the concept of ADR reporting

What can ADRs Inform about?

1. Quality of ADRs
2. Interactions
3. Additional determinants of the risk
4. Possible mechanisms (hypothesis generation)
5. Habits an trends in prescription and use of a drug
6. Profils of reporting and (to a limited degree) occurrence of ADRs
7. Signifikantly excessive numbers of reports of certain ADRs of certain drugs in the whole data base (creating a signal)
8. (Possibly) relative differences in the frequency of a specific ADR of two or more drugs
9. Minimum occurrence of an ADR in an exposed population (if population exposure can be estimated)

ADR-Database Analysis

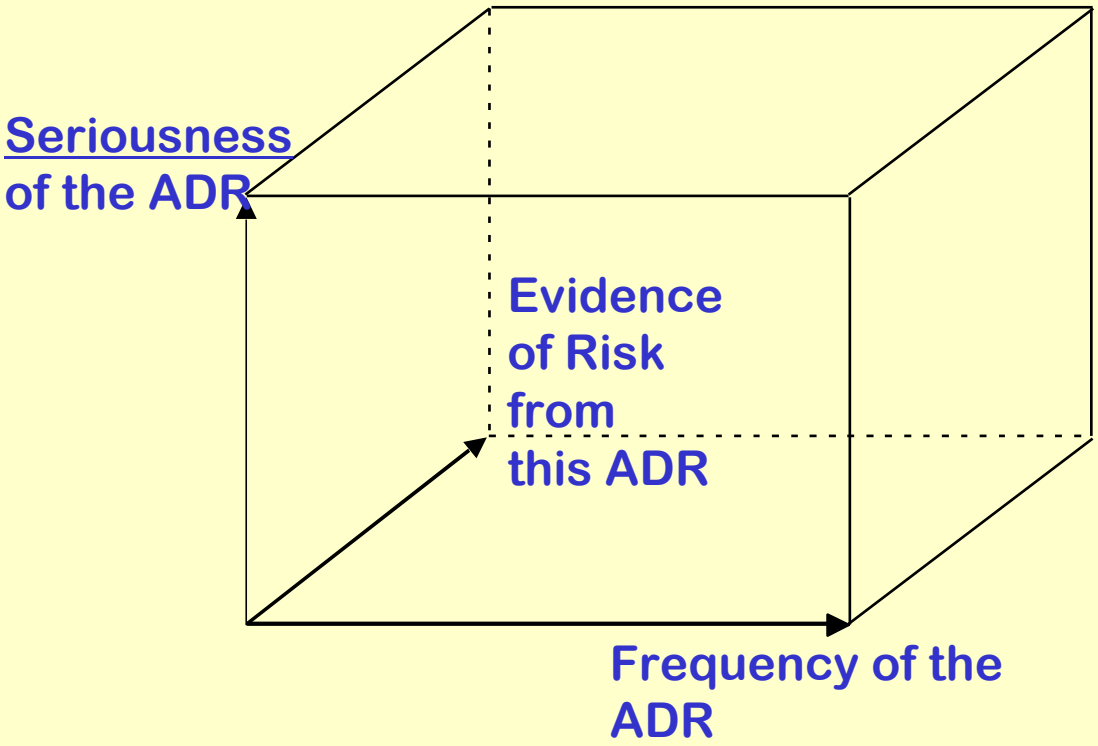
by Calculation of "Proportional Reporting Ratios"

	Drug under consideration	All other drugs
ADR under Consideration	a	b
All other ADRs	c	d

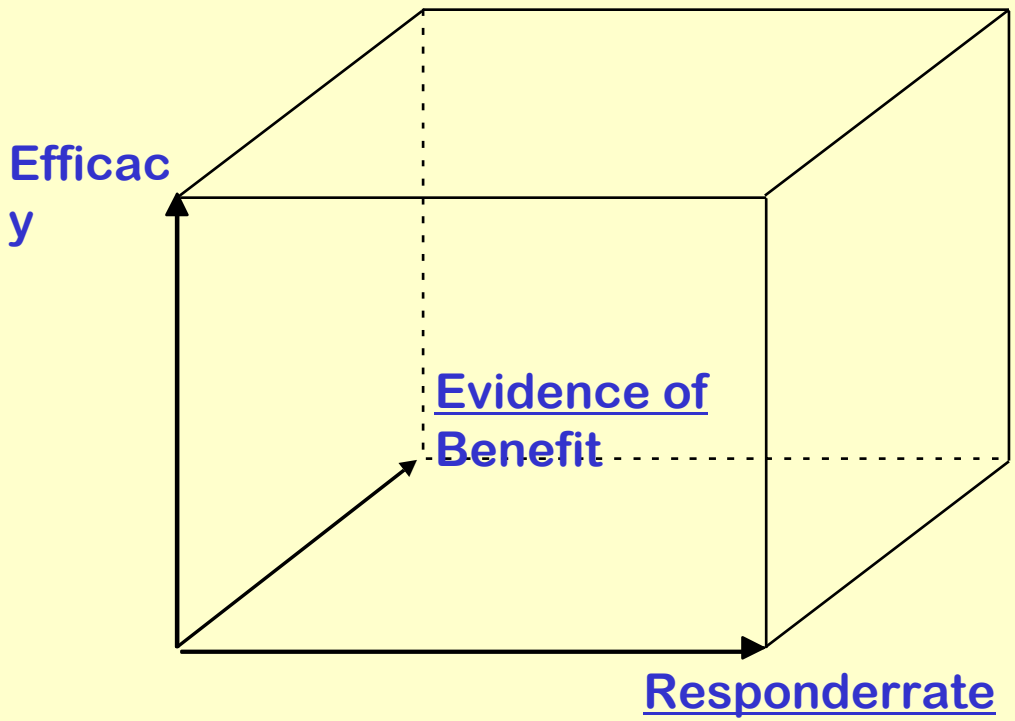
1. Calculation of PRR = $\frac{a / a+c}{b / b+d}$

2. Calculation of χ^2
   as a measure of the reliability of the assumption that the PRR
   indicates
   a true peculiarity of the reporting frequency for the drug/ADR under consideration

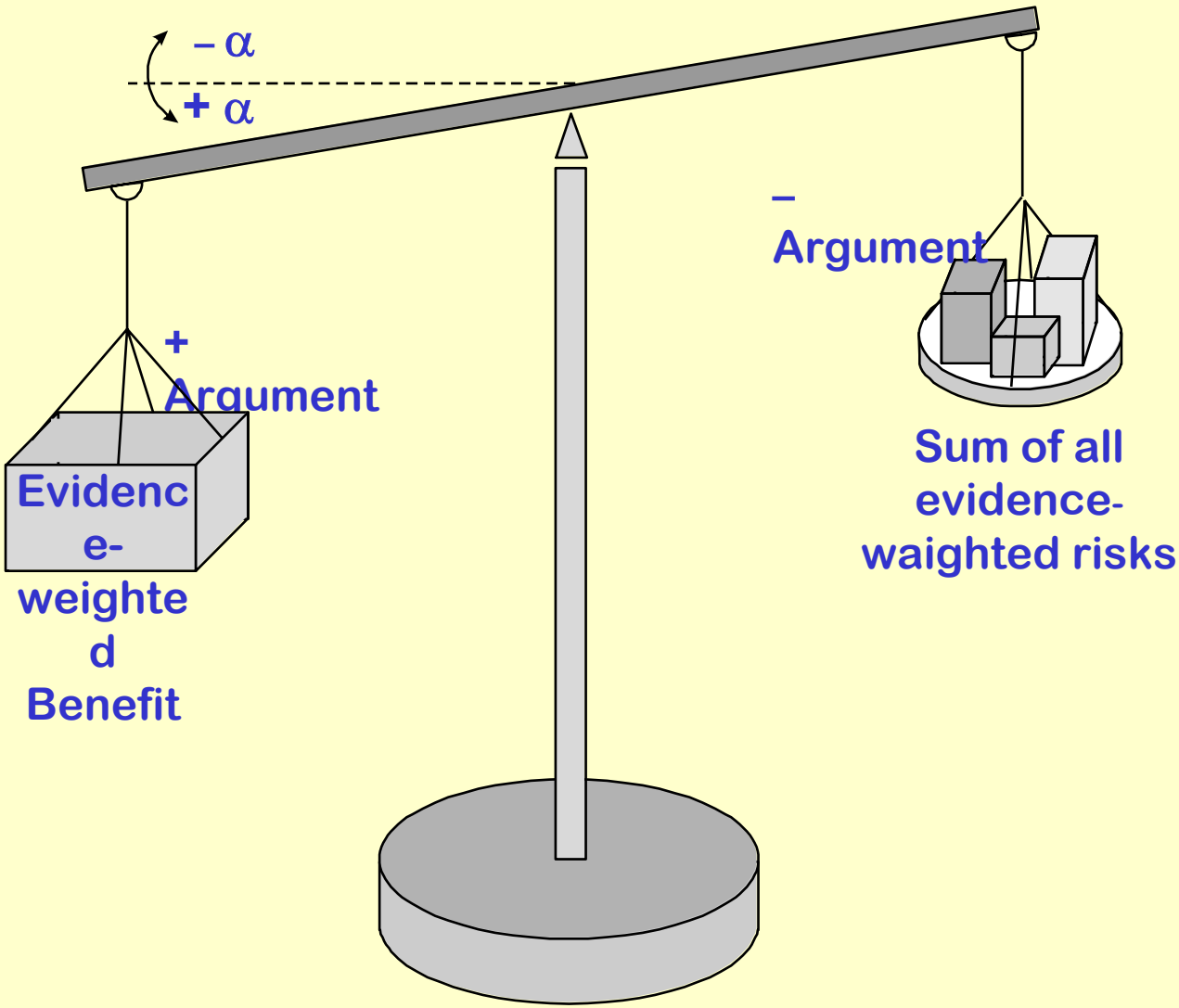
"Evidence-Weighted" Risk of a Certain ADR = Weight/Importance of the Aspect of this ADR in Making Pharmacovigilance Decisions



"Evidence-Weighted“ Benefit = Weight/Importance of the Benefit Argument (for one Indication)

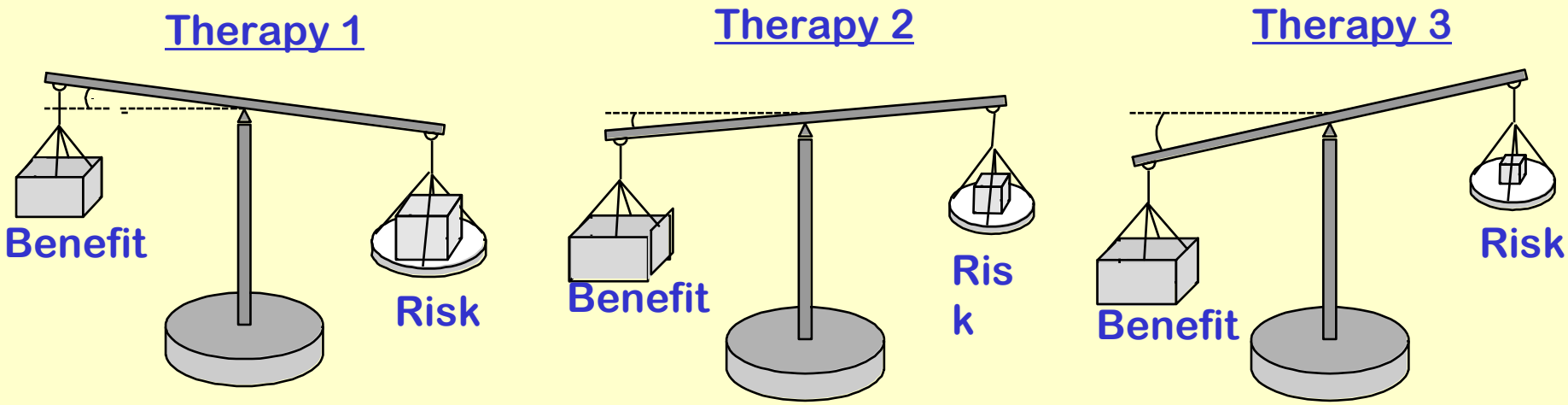


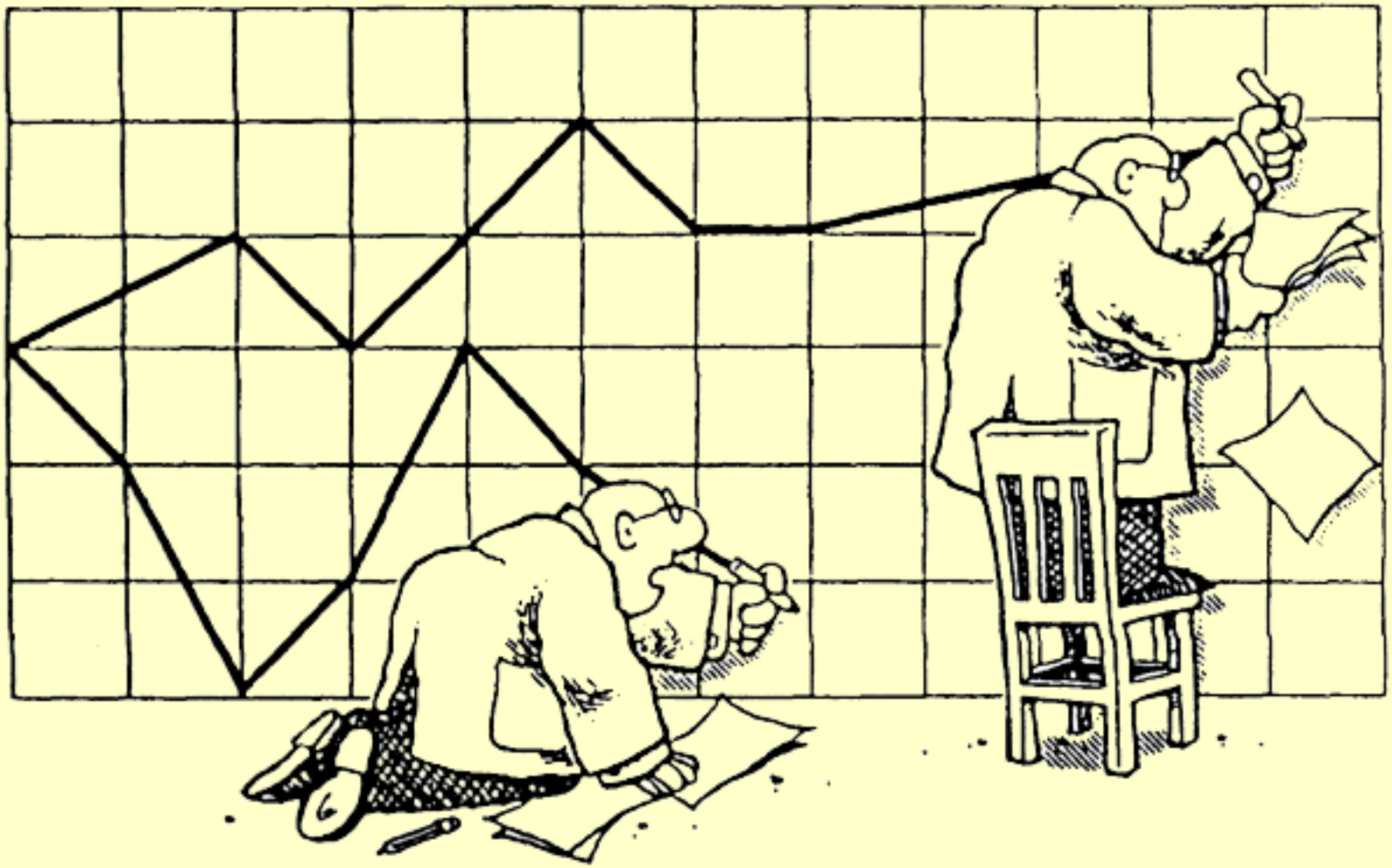
Weighing Positive Benefit- versus Negative Risk-Arguments in the Assessment of a Drug



Comparing the Benefit / Risik-Balance between Therapies

(Risik associated with several ADRs are combined in single cubes)





"HEY, I THOUGHT WE WERE WORKING WITH THE SAME DATA..."

Pharmacovigilance Working Party and Germany‘s Role

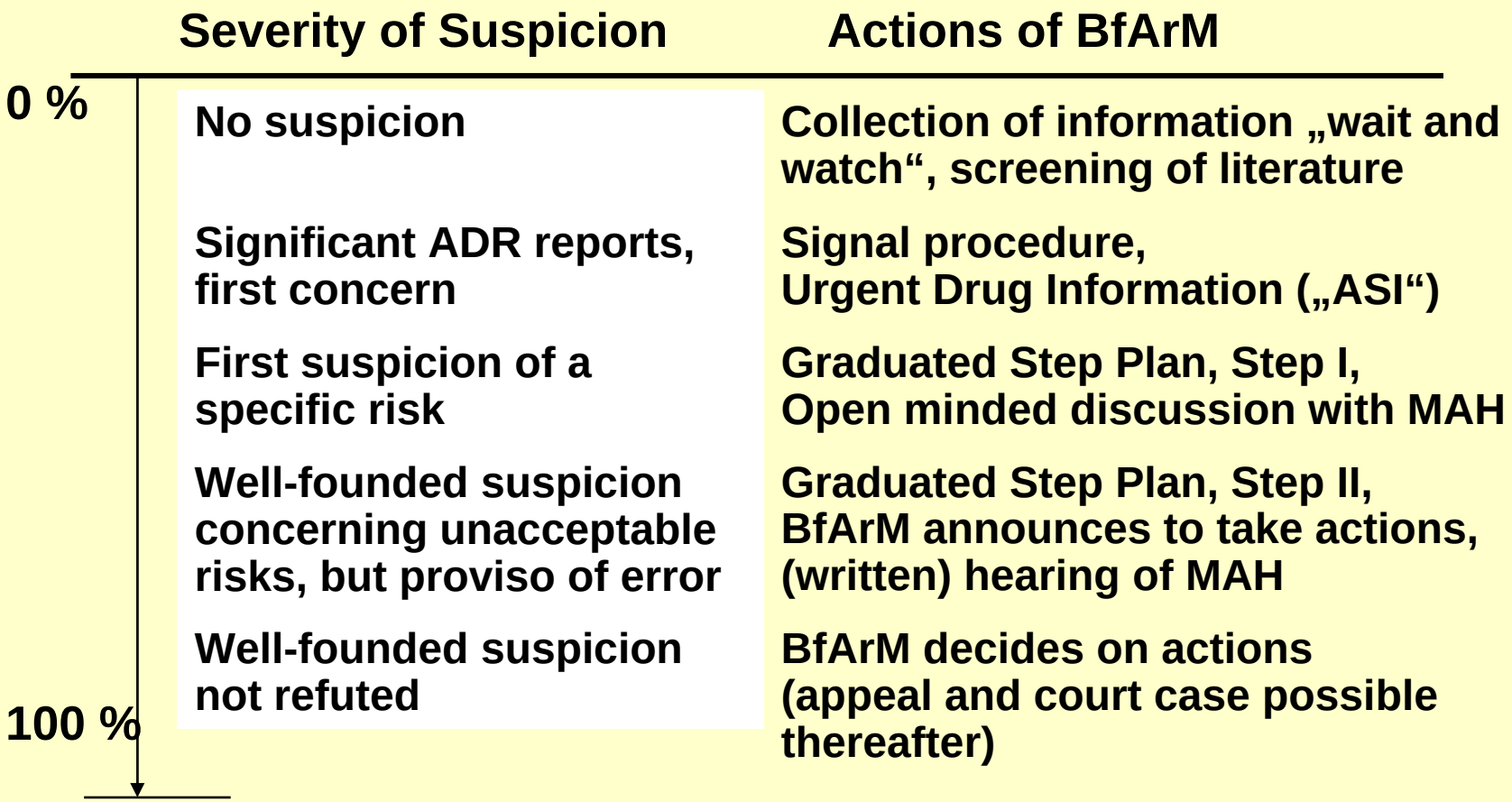
	Drugs on behalf of CPMP	Drugs with only national competence	Organisational
Total No. of issues per CPMP meeting	15	15	3
No. with Germany's contribution	5	4	0.3
Contribution of Germany [%]	34	29	10

§ 5 German Drug Law: Prohibition in respect of unsafe drugs

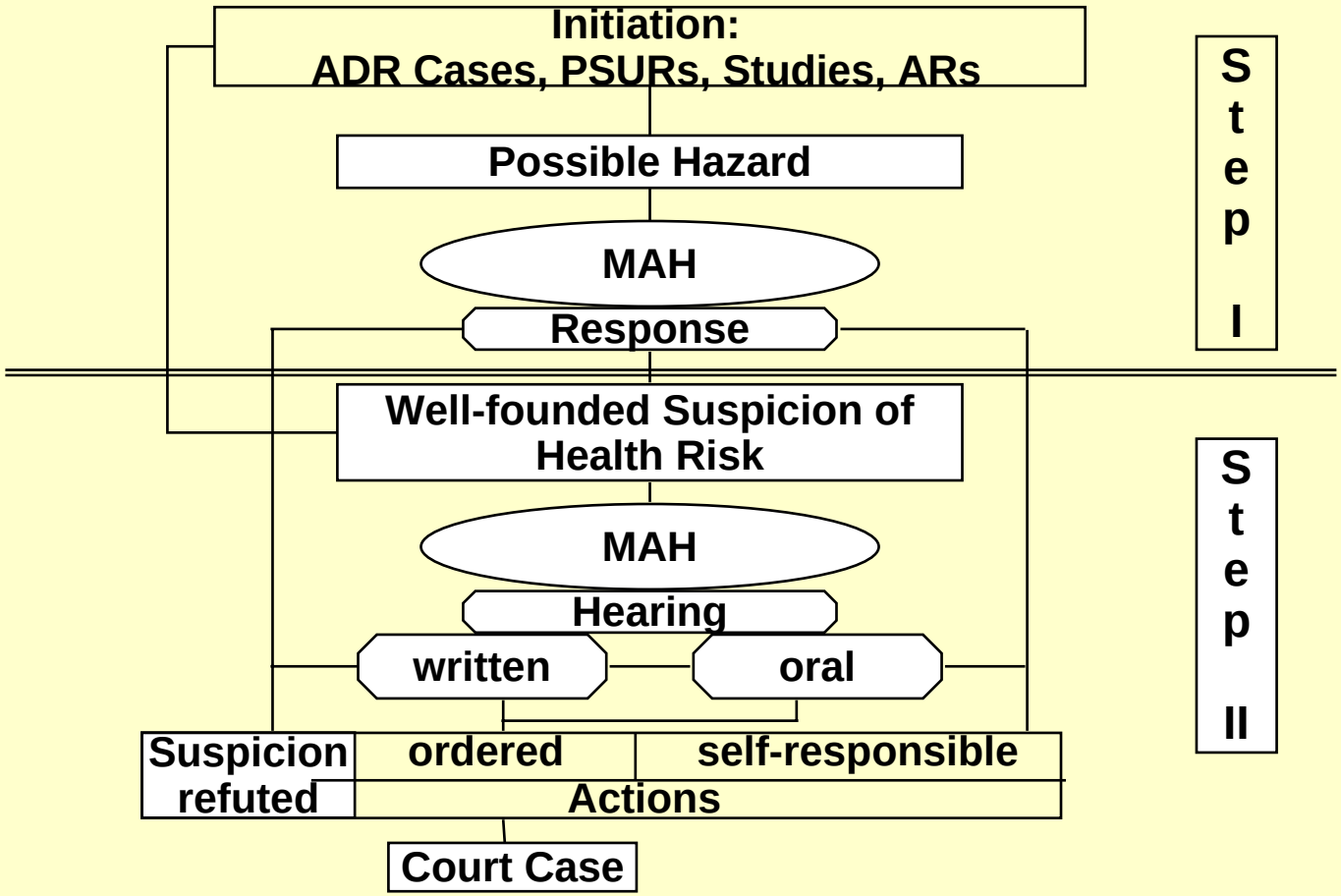
(1) The placing on the market of unsafe drugs shall be prohibited.

(2) Drugs shall be considered unsafe if, according to the current level of scientific knowledge, there is reason to suspect that, when used in accordance with their intended purpose, they have harmful effects which exceed the limits considered tolerable in the light of current medical knowledge.

Severity of Suspicion Concerning a Risk, Actions of BfArM



Graduated Step Plan



Number of Drugs during the Years 1990 - 2003

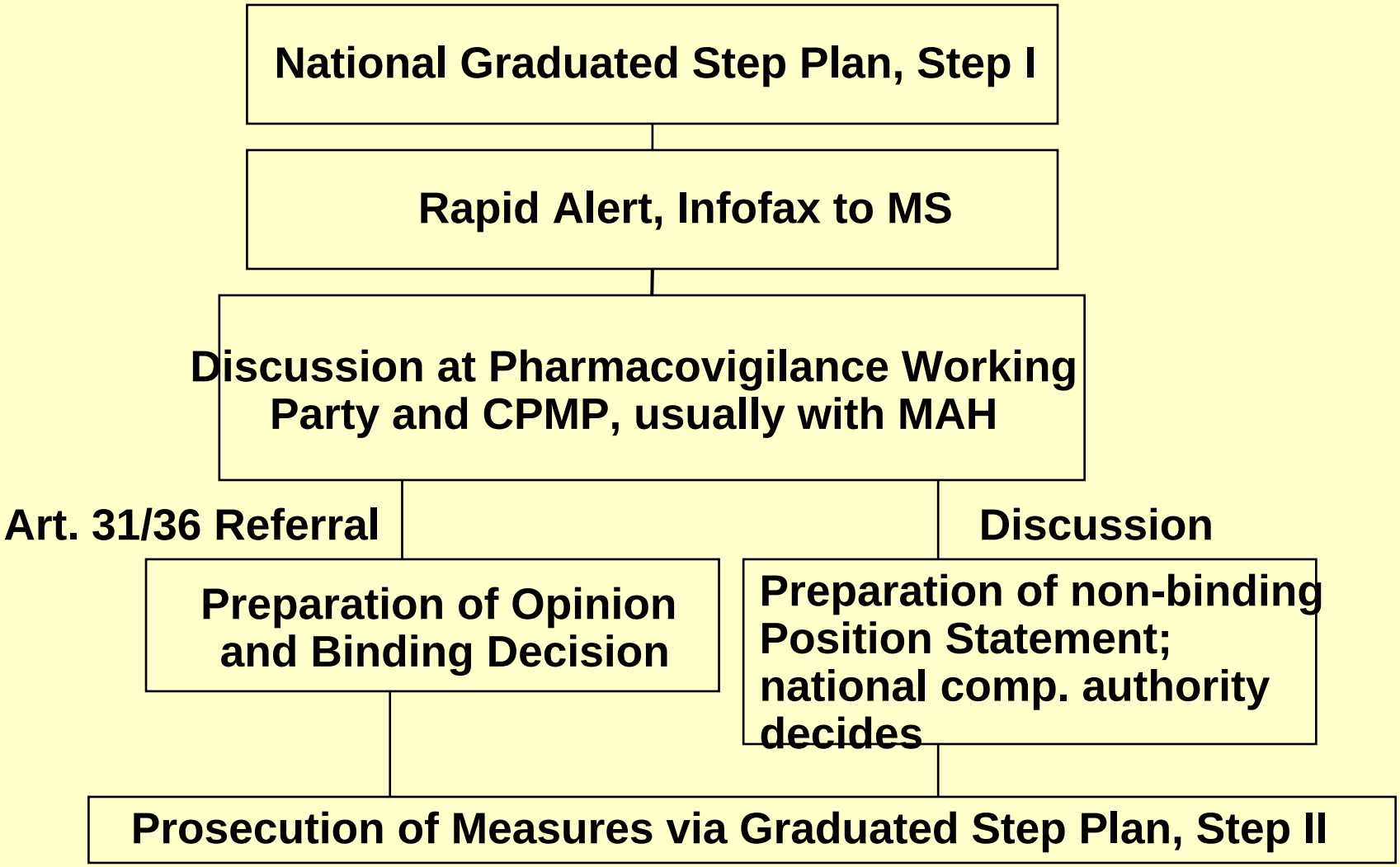
affected by Measures of a Graduated Step Plan

Revocation of authorisation: 15 substances in ca. 175 drugs

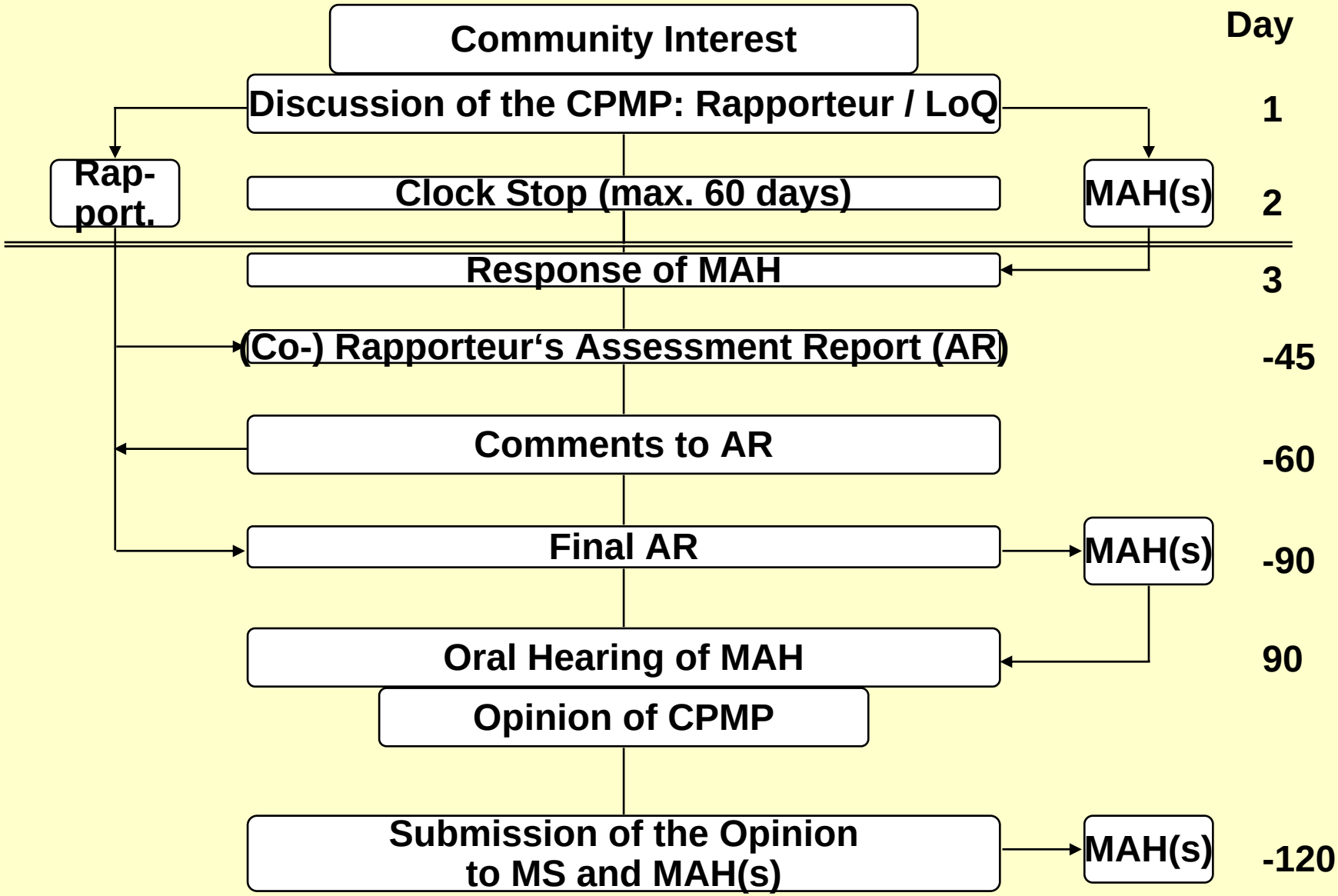
Suspension of authorisation: 5 substances in ca. 100 drugs

Changes of authorisation: several hundred substances in several thousand drugs

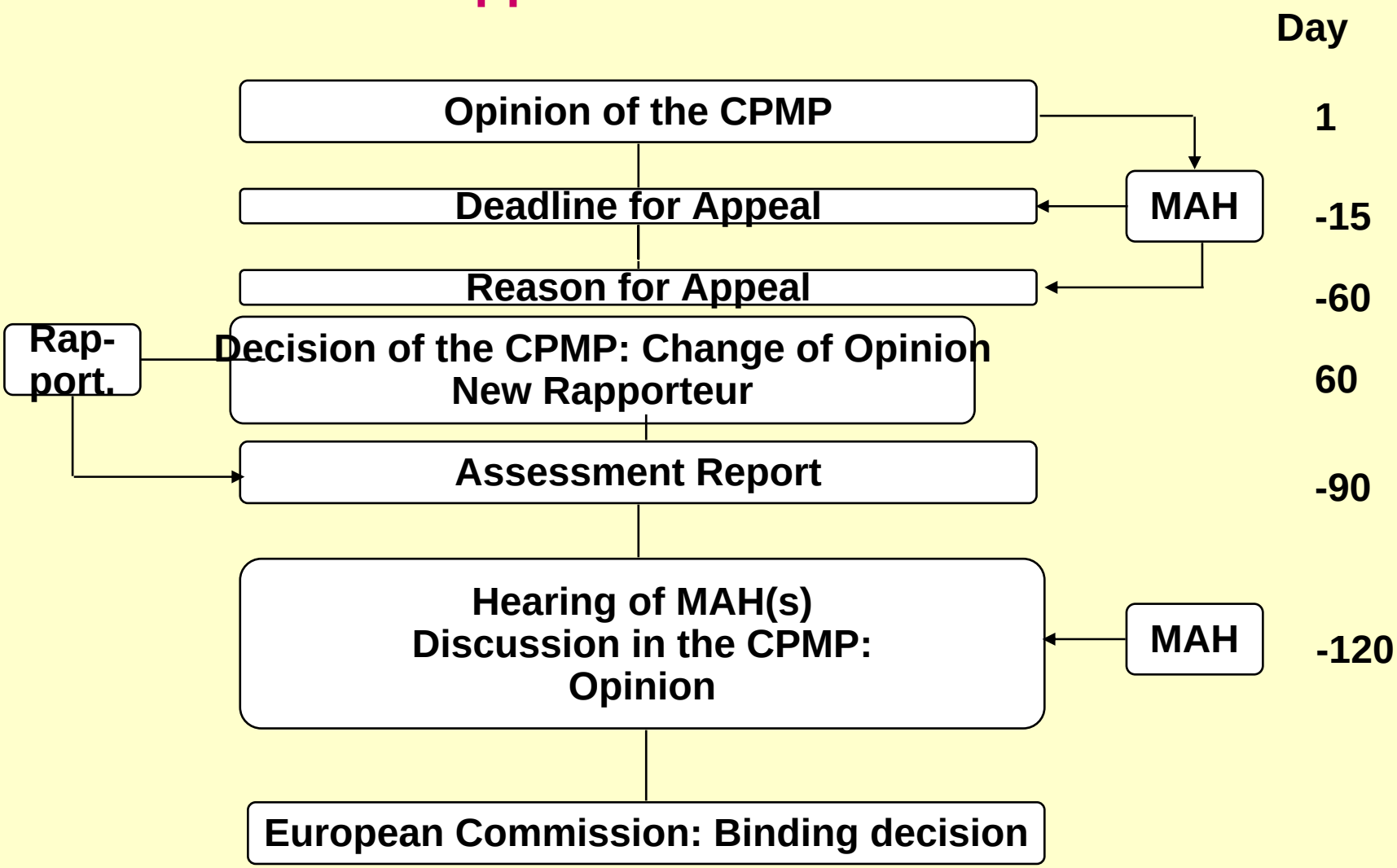
Information about Risks, Co-ordination of Assessment and - if necessary - measures in the EU



Arbitration Procedure



Appeal Procedure



Procedures to Minimise the Risk

	National	EU
Procedure	Graduated Step Plan	Referral under Art. 31, 36 or 18
Initiator	Higher federal authority (BfArM or PEI)	MS, EU, MAH
Criteria for start of procedure	1. hint for risks 2. reasonable suspicion concerning unacceptable risks	Community interest (severe risk, actions, some concerned MS)
Conduct of procedure	Higher federal authority with own or with external experts if necessary	EMEA with Rapporteur/Co-Rapporteur in discussion with all MS
Decision	Higher federal authority	Commission on the basis of CPMP Opinion

Important Recent Pharmacovigilance Activities of the BfArM (I)

Medicinal product	Procedure	Risk	Outcome
Anorectics	EU	Cardiovascular ADRs	Revocation (court case)
Medicinal products made of human materials	National	Transmission of vCJD	Measures to select donators
Medicinal products made of bovine materials	National/EU	Transmission of BSE	Varification of safety
Bupropion	EU	Cardiovascular ADRs	Changes of SPC
Cerivastatin	National/EU	Rabdomyolysis	Market withdrawl
COX 2 inhibitors	EU	Cardiovascular and gastro-intestinal ADRs	Changes of SPC (procedure ongoing)

Important Recent Pharmacovigilance Activities of the BfArM (II)

Medicinal product	Procedure	Risk	Outcome
Hormone replacement therapy (HRT)	National/EU	Breast cancer, thrombembolism	Procedure ongoing
Ionic contrast media	National	Hypersensitivity reactions	Revocation
Kava kava	National	Liver toxicity	Revocation
Oral contraceptives	National/EU	Venous thrombembolism	Changes in SPC
Plant laxantins	National	Dependancy	Restriction of use
Terfenadine	EU	Arrhythmia	Changes of SPC

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Thank you for your Attention !