Joint Scientific Advice
Interaction of BfArM and G-BA

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BfArM



Agenda

- Responsibilities of Regulators
- Study design and it‘s implications
- Clinical trials and scientific advice
- Biomarkers / Surrogate endpoints
- Orphans
- Previous and current experience in the „learning system“
- Outlook




Medicinal Products are approved for …

- **Distinct disease entities**
- **Positive benefit-risk assessment based on**
  - Therapeutic efficacy,
  - Safe and without serious risks
  - Sufficient pharmaceutical quality

- **Procedures highly harmonized throughout EU**

Legislation SGB V

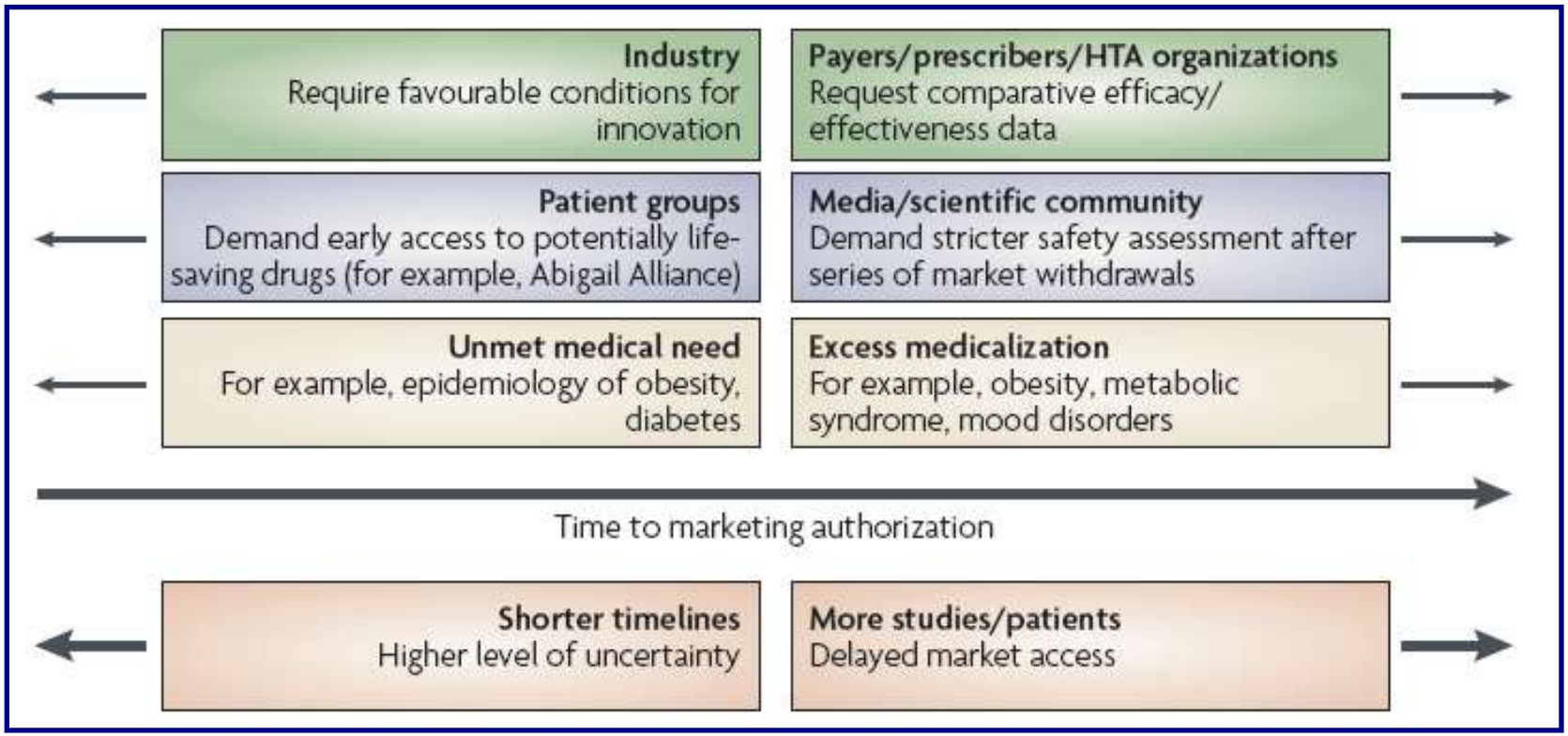
*Patient relevant (additional) benefit**

Trias	Criteria
Mortality	Overall survival
Morbidity	Shortage of disease duration Improvement of health status Reduction of side effects
Quality of Life	Improvement of QoL

Standards and procedures not harmonized in EU !!!

***Arzneimittelnutzenverordnung; Bundesgesetzblatt 2010; Teil 1 Nr 68/ Verfahrensordnung; Verfahrensordnung § 35a des GBA: www.gba.de**

Principal Considerations and „regulatory dilemma“



from: Eichler HG et al., NRDD 2008

Benefit-Risk-Assessment

- **Benefit**
  - Optimized for proof of efficacy
  - Uncertainties/Limits:
    -- possible differences between populations and age groups
    -- differential individual response

- **Risk**
  - Side effects, interactions, toxicity, potential for misuse
  - Uncertainties/Limits:
    -- limited number of study patients
    -- possible differences between populations and age groups
    -- limited time of active treatment

- **In comparison to identical / similar / comparable medicinal products**

http://www.ema.europa.eu/ema/

BfArM

Human medicines
Pre-authorisation
Post-opinion
Post-authorisation
Product information
Scientific advice and protocol assistance
Scientific guidelines
Search guidelines
Quality
Q&A on quality
Biologicals
Non-clinical
Clinical efficacy and safety
Clinical pharmacology and pharmacokinetics
Alimentary tract and metabolism
Blood and blood-forming organs
Blood products
Cardiovascular system
Dermatologicals
Genito-urinary system and sex hormones

Clinical efficacy and safety: Nervous system

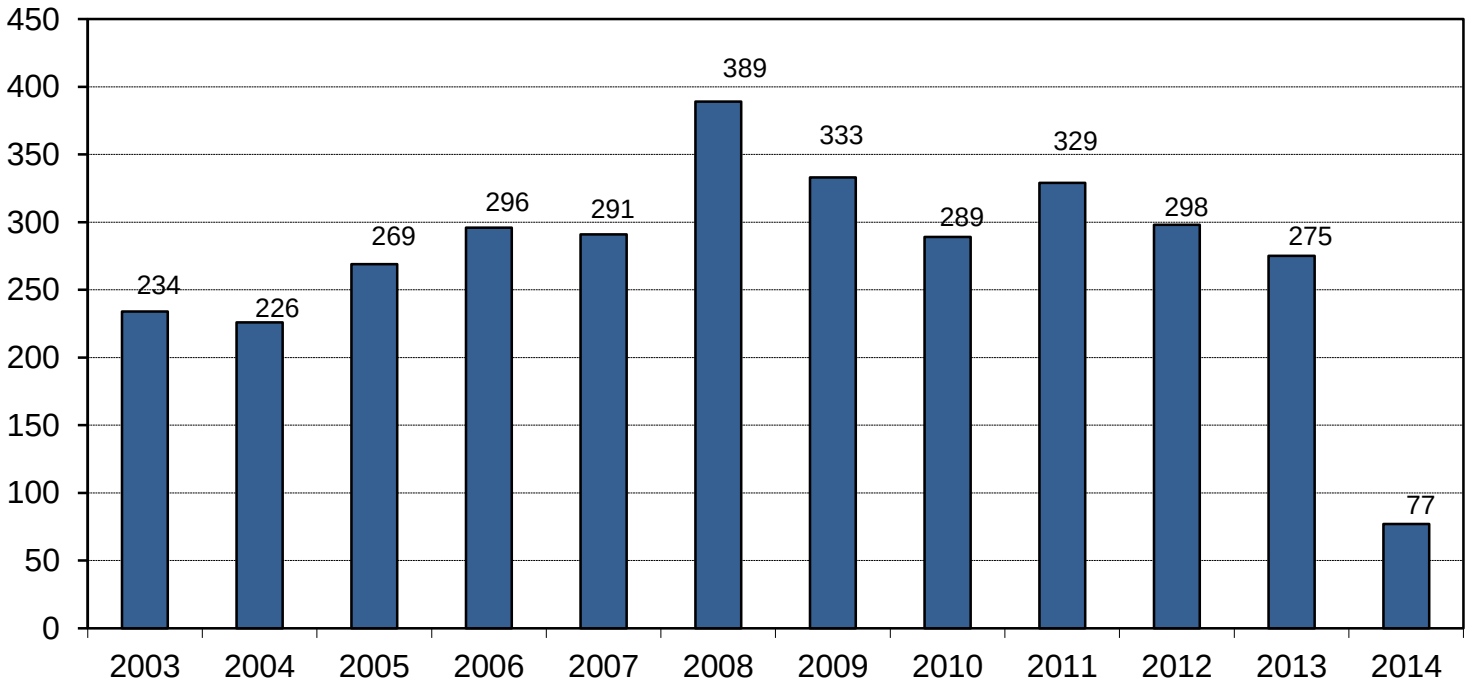
This page lists the European Medicines Agency's scientific guidelines on the clinical safety and efficacy of medicines used in nervous-system disorders.

If you have comments on a document which is open for consultation, use the form for submission of comments on scientific guidelines.

Please note that the Efficacy Working Party secretariat e-mail address (ewpsecretariat@ema.europa.eu) no longer exists. Therefore, please submit your comments from now on to the following e-mail address: cnswpsecretariat@ema.europa.eu.

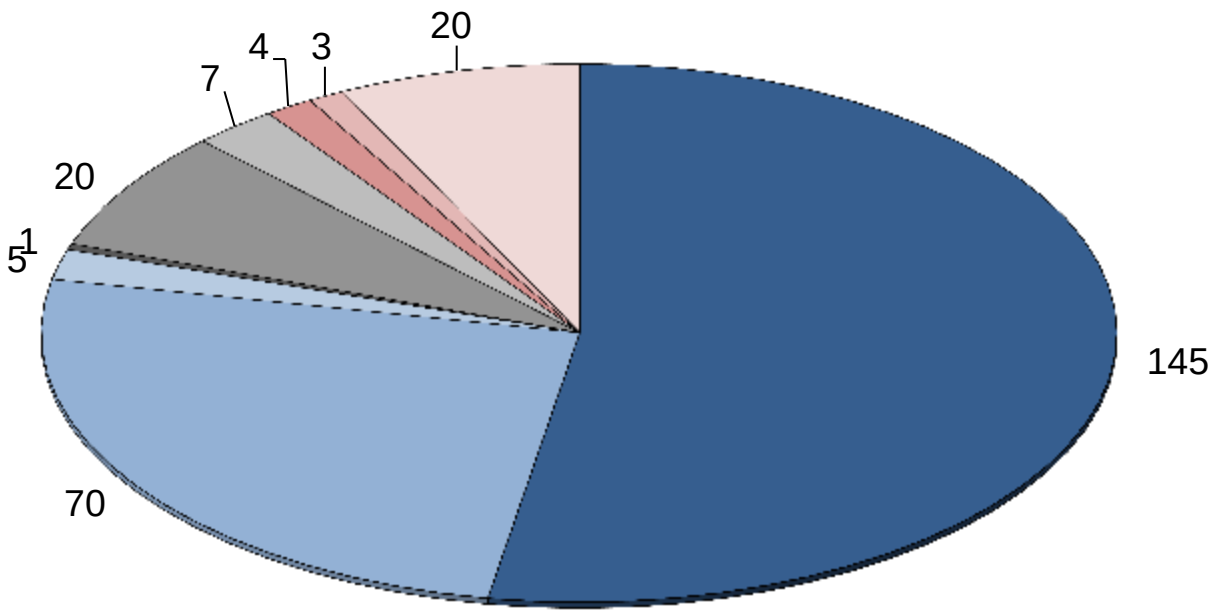
Topic	Documents	Reference number	Publication date	Effective date	Remarks
Need for revision of the guideline on medicinal products for the treatment of Alzheimer's disease and other dementias	Draft concept paper	EMA/CHMP/617734/2013	Released for consultation 31 Oct 2013		Deadline for comments 31 Jan 2014
Clinical development of medicinal products intended for the treatment of pain	Draft guideline	EMA/CHMP/970057/2011	Released for consultation May 2013		Deadline for comments 30 November 2013
Development of medicinal products for the treatment of autism-spectrum disorder	Concept paper	EMA/CHMP/40896/2013	Released for consultation April 2013		Deadline for comments 4 July 2013
Clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy	Draft guideline Concept paper	EMA/CHMP/236981/2011	Released for consultation March 2013		Deadline for comments 31 August 2013
Clinical investigation of medicinal products for the treatment of multiple sclerosis	Draft guideline	CHMP/771815/2011 Rev. 2	Released for consultation October 2012		Deadline for comments 9 April 2013
Clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia	Overview of comments Adopted guideline Draft guideline Concept paper	CHMP/40072/2010 Rev. 1	October 2012	1 April 2013	

Scientific Advice by BfArM



Stand: 31. März 2014

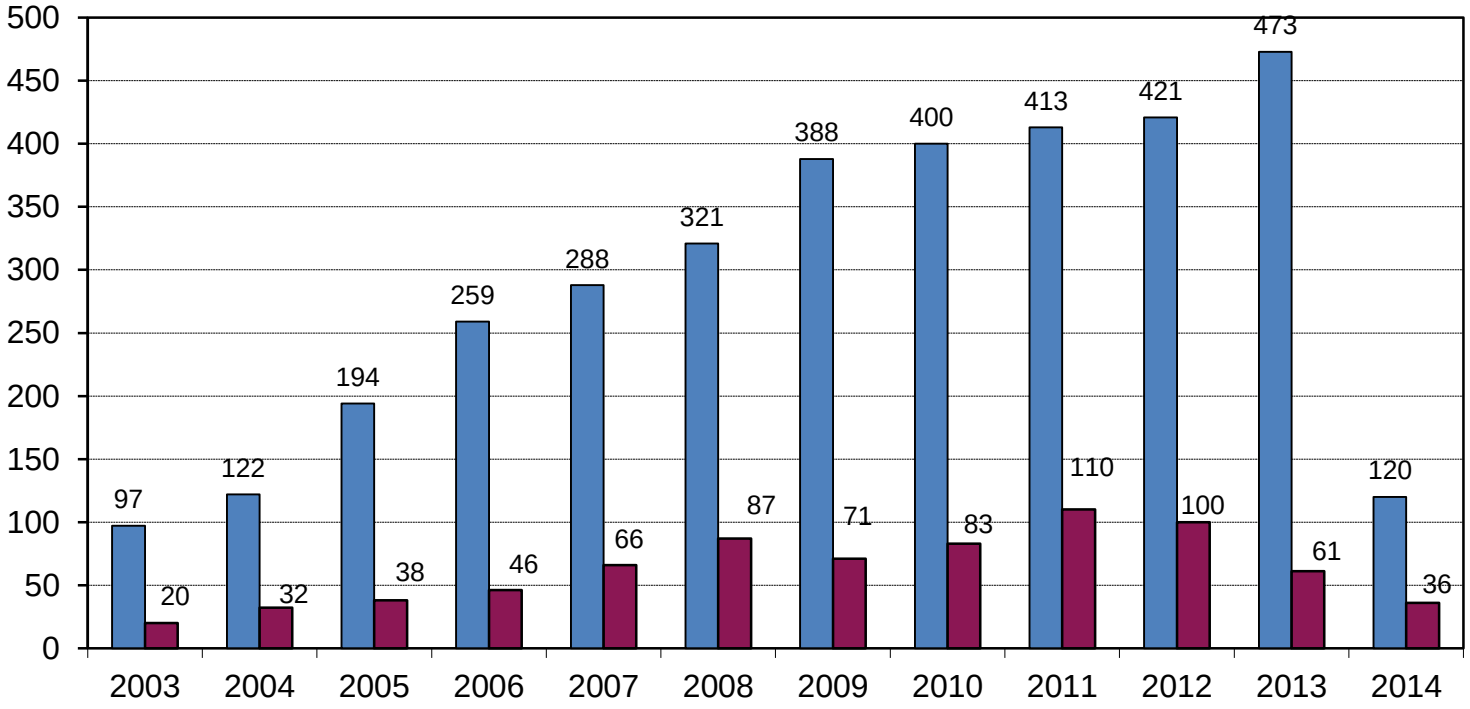
Finalized Scientific Advice in 2013 (n=275)



- meetings in person
- written procedures
- complex written procedure
- advice by phone
- withdrawal
- refused (incomplete)
- not applicable to BfArM
- portfolio meeting
- pre-submission meeting

Stand: 31. Dezember 2013

BfArM activities in EMA scientific advice



Stand: 31. März 2014

Use of active comparator

- **Comparison of results**
  - positive effects in comparison
  - Unwanted effects / risks in comparison

- **Assessment of Benefit-Risk**
  - Overall comparison of benefit-risk
  - Contrasting juxtaposition and interpretation

- **Critical discussion of relative benefit-risk-balance**
  - Balancing of uncertainties
  - Results in view of different stakeholders
  - Need for additional clinical trials

European Public Assessment Report (EPAR)

- *This document is a summary of the European Public Assessment Report (EPAR). It explains how the Committee for Medicinal products for Human Use (CHMP) assessed the studies performed, to reach their recommendations on how to use the medicine.*
- *If you need more information about your medical condition or your treatment, read the Package Leaflet (also part of the EPAR) or contact your doctor or pharmacist. If you want more information on the basis of the CHMP recommendations, read the Scientific Discussion (also part of the EPAR).*

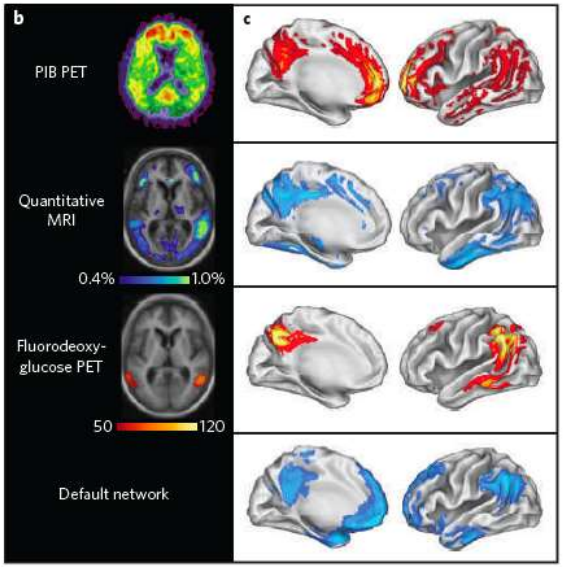
- **clear structure, improved templates**
- **all pivotal studies**
- **precise statements on active comparator**

- **precise statements on benefit-risk-assessment (quantitative and qualitative)**

- **access to and transparency of data**

Biomarker can be used to …

- Understand the biology of a disease
- Understand the effects of medicinal products
- Provide information on sub-populations of patients that might respond to treatment or be susceptible to side effects (individualized medicine)
- Developing better diagnostics and medicinal products
- Improve methodology of clinical trials



Validation of „Surrogat-Endpoints“

Bucher HC et al., JAMA (1999) 282, 771-778

(1) Plausible connection between basic science and clinical trials

(2) Is there a strong, independent, consistent association between surrogate endpoint and clinical outcome (necessary, not sufficient)

(3) Evidence from randomized trials that improvements in the surrogate endpoint leads consistently to improvement of the target outcome

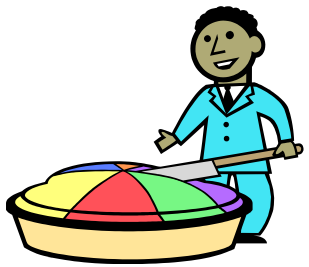
(4) Large, precise, and lasting treatment effects

(5) Are the likely benefits worth the potential harms and costs

Continuous Evidence after MA

- **Regular and continuous benefit-risk-assessment by MAH and BfArM (§ 29 AMG)**
- **Pharmacovigilance**
  - Spontaneous reporting, PSURs, registries, epidemiological studies,…
  - **Since 2012:**
    - targeted trials on safety (PASS) and efficacy (PAES) of aproved products
- **“Adaptive Licensing”**
  - “staggered approval” (EMA)
  - “progressive licensing” (Health Canada)
  - “progressive authorisation scheme” (NEWDIGS)

Orphan Drugs



- **No evidence of „orphanisation“**
- **„Orphan Drug Designation“**
  - Rare, severe or life-threatening disease
  - No satisfactory / unmet medical need
  - Probably significant („erheblich“) therapeutic benefit
- **Approval of an „Orphan“**
  - Reexamination and confirmation of significant („erheblich“) therapeutic benefit
- **Dossier for G-BA necessary**
  - Quantification of benefit
  - Negotiation of reimbursement

Advice of BfArM to G-BA and IQWiG April 2011 – April 2014

- **Total of 48 procedures**
  - 15 regular advices based on § 8 AM-NutzenV with involvement of BfArM
  - 9 requests by MAH in relation to additional benefit, active comparator, study design
  - 9 general requests of G-BA to BfArM
  - 15 requests of IQWIG to BfArM

Options for improvement

- BfArM not involved on a regular basis
- No knowledge of complete dossier of MAH
- No dialogue in person between G-BA and BfArM, in general written procedure
- Invitation to internal discussions only exception
- No joined scientific advice




Early Joined Advice and Communication I

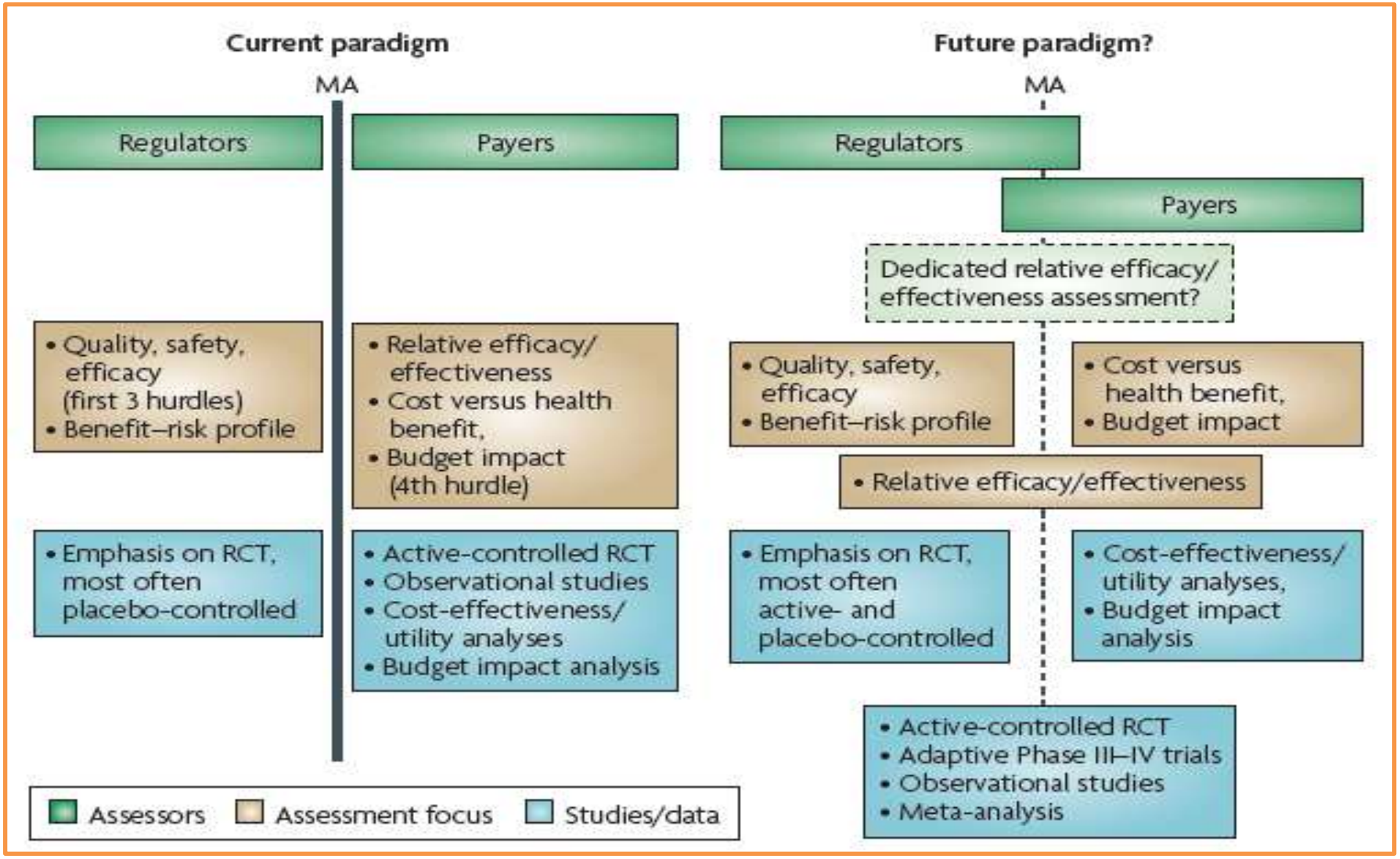
- **Advantages / Chances**
  - **Marketing Authorisation Holders:**
    - predictability, targeted use of ressources
    - Consideration of multinational, multicenter programs
  - **Regulators:**
    - Relevant endpoints, study designs, patient related outcomes
  - **Payers:**
    - Improved database/results for decision-making
  - **Physicians / Patients:**
    - Clinical practice consistent with regulatory and HTA-decision making, higher transparency

Early Joined Advice and Communication II

- **Requirements**
  - Early joined advice before phase III on a regular basis
    - Precondition for reasonable and feasible development programs
    - Ethically required to avoid unnecessary studies
    - Need for transparency / full dossier
    - Legally fixed (§35a Abs. 7 SGB V)
  - Real dialogue / trialogue necessary
    - BfArM / PEI have the competence and experience
    - Avoidance of double competence
    - Safeguarding for endpoints relevant to BfArM/PEI and G-BA/IQWiG
      - Active comparators helpful with regard to „zweckmäßige Vergleichstherapie“
      - Patient related outcomes, „hard“ primary endpoints and rigorous interpretation

Possible Challenges ...

from: Eichler HG et al., NRDD 2010



Summary

- **Experience for joint advice between BfArM and PEI is still limited – interactions are no exception, but far away from routine**
- **BfArM offers competence and experience for early and joint advice**
- **„Adaptive Licensing“ and „early access programs“ (e.g. EAMS in UK) or issues around individualized medicine will make assessments even more complex**
- **BfArM is prepared to play a proactive role in national and EU procedures**

Vielen Dank für Ihre Aufmerksamkeit!