EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Pharmaceutical Policy and Legislation

Regulators and Industry shared responsibility

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Executive Director

Contents

- Market specificities & EU regulatory framework
- EMA and centralised procedure
- Benefit/Risk assessment and future scenario
- Benefit/Risk communication

WHY to regulate a market?

- Legislation is often "disaster driven"

  and

- Who use medicinal product neither pay nor decide
- Who decide the use of medicinal products neither use nor pay
- Who pay medicinal products neither decide nor use them

1. EU regulatory framework for pharmaceuticals

EU Marketing Authorisation (MA)

A medicinal product may only be placed on the market in the EU, when a **marketing authorisation** has been issued

by the competent authority of a EU Member State

or

by the European Commission (via EMA)

STANDARDS/REQUIREMENTS

Principles:

Based on Assessment of:

- Quality: Manufacturing aspects & GMP
- Safety: Preclinical tests & GLP
- Clinical: Efficacy + Clinical Safety & GCP

And inspections of manufacturing sites and clinical trial sites

Sources:

- Pharmaceutical law: Directives and Regulations
- ICH: International Conference on Harmonisation since 1987

  EU – US – Japan – + Switzerland, Canada and WHO as observers Regulatory Authorities + Pharmaceutical Industry
- Guidelines EMA (CHMP) of which more than 40 are ICH Guidelines

Marketing Authorisation procedures in EU

3 EU procedures

- Centralised Procedure (CP)
- Mutual Recognition Procedure (MRP)
- Decentralised Procedure (DCP)

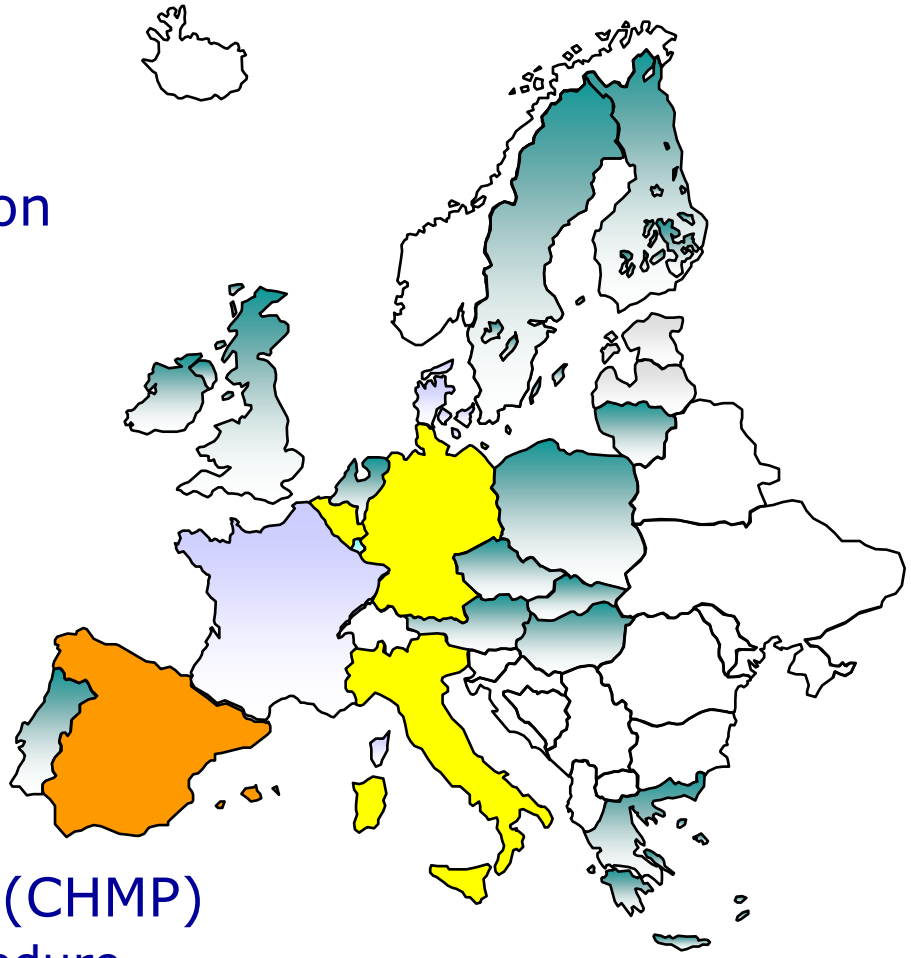
National Procedure

Application in 1 Member State only
e.g. Spain

→National marketing authorisation in 1 Member State

Mutual Recognition Procedure (since Jan 95)

1 Member State (e.g. Spain)
performs assessment of application
→ 1 National MA



Subsequent application to *n* MSs.
Other Member States to
"mutually recognise" (90 days)
the Spanish assessment
→ *n* National MAs

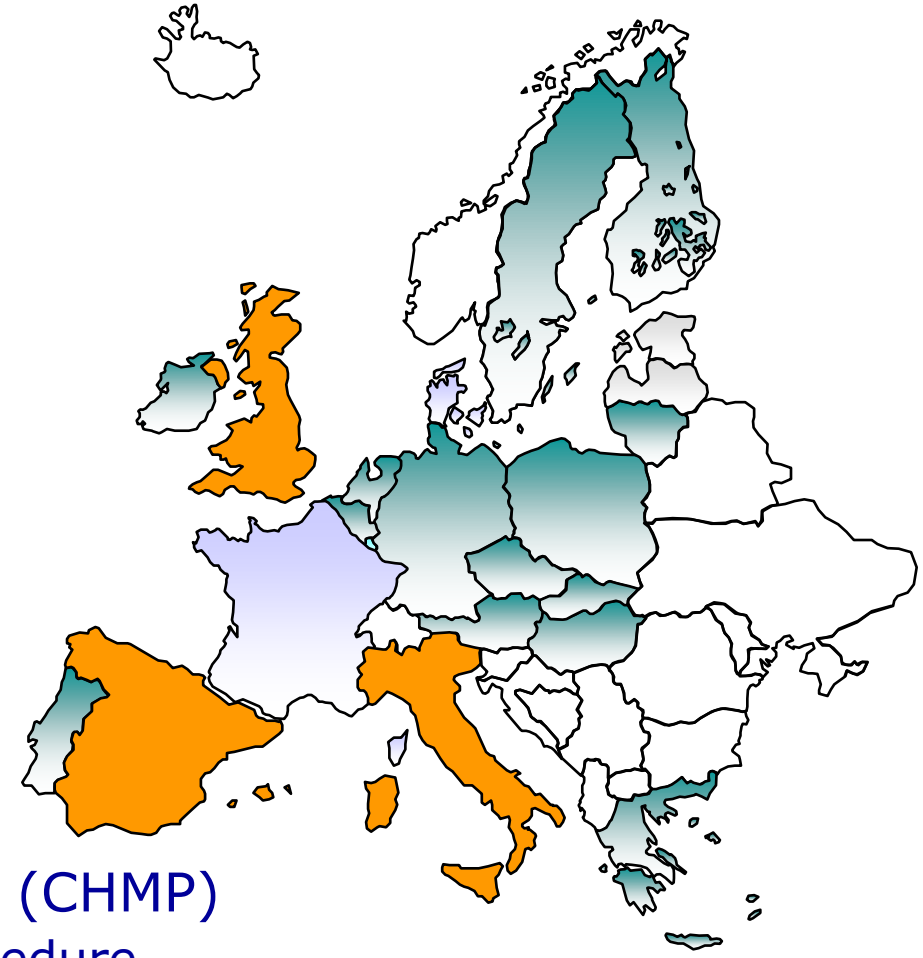
Disagreement? → referral to EMA (CHMP)
'arbitration' procedure

Decentralised Procedure (since Nov 2005)

No MA yet for the product in EU:

Parallel submissions in *n* MSs

- 'Reference' MS performs assessment
- Peer review by other MSs (concerned MSs):
  * Assessment report
  * SmPC, leaflet and labelling
- *n* MSs grant national MA after agreement (in 30 days)



Disagreement? → referral to EMA (CHMP)

'arbitration' procedure

Centralised Procedure (since Jan 95)

Opening EU Agency in London

1 Application to Agency
1 scientific evaluation --> CHMP
1 EU scientific opinion (210 days)
(EMA-CHMP Opinion)

↓

EU Commission issues
1 EU marketing authorisation
applicable in all Member States

Identical trade name and label

Summary of Product Characteristics (SmPC)
User Package Leaflet
Package Labelling

The European Union: 500 million people 27 countries

Legal Framework

- Pharmaceutical law based on the concept of refusal of a marketing authorisation if the applicant has not properly or sufficiently demonstrated the quality, safety or efficacy
- In general, clinical trials shall be done as controlled clinical trials randomised versus placebo and an established product of proven therapeutic value
- The balance of benefits and risks should be positive for any marketing authorisation

Regulation (EC) No 726/2004, Directive 2003/83 (EC)

2. EMA and the ‘Centralised Procedure’

Centralised Procedure = “reserved” procedure

Not open to all products: dedicated to **innovative** products (some legally obliged to use CP)

Not for ‘old’ substances in established indications
e.g. aspirin for headache

EMA = A Networking Agency

- Agency is an interface of co-operation and co-ordination of Member States' activities with respect to medicinal products
- National competent authorities in 27 Member States (more than 45 agencies)
- European **experts' network** underpins the work of EMA's Committees and working parties
- Expert list of **> 4,500 experts in EU**, nominated by the MSs Available for scientific work / assessments for EMA
- Scientific competence is guaranteed by their nominating authority, independence and integrity assured through public declaration of interests
- All parties linked by a secure IT network (EudraNet)

EMA Scientific Committees

CHMP

(Committee for Human Medicinal Products) Chair : Dr E. Abadie

CVMP

(Committee for Veternary Medicinal Products): Chair Dr. A. Holm

HMPC

(Committee for Herbal Medicinal Products) Chair: Dr W. Knoss

COMP

(Committee for Orphan Medicinal Products) Chair : Prof K. Westermark

CAT

(Committee for Advanced Therapy Medicinal Products) Chair: Dr C. Schneider

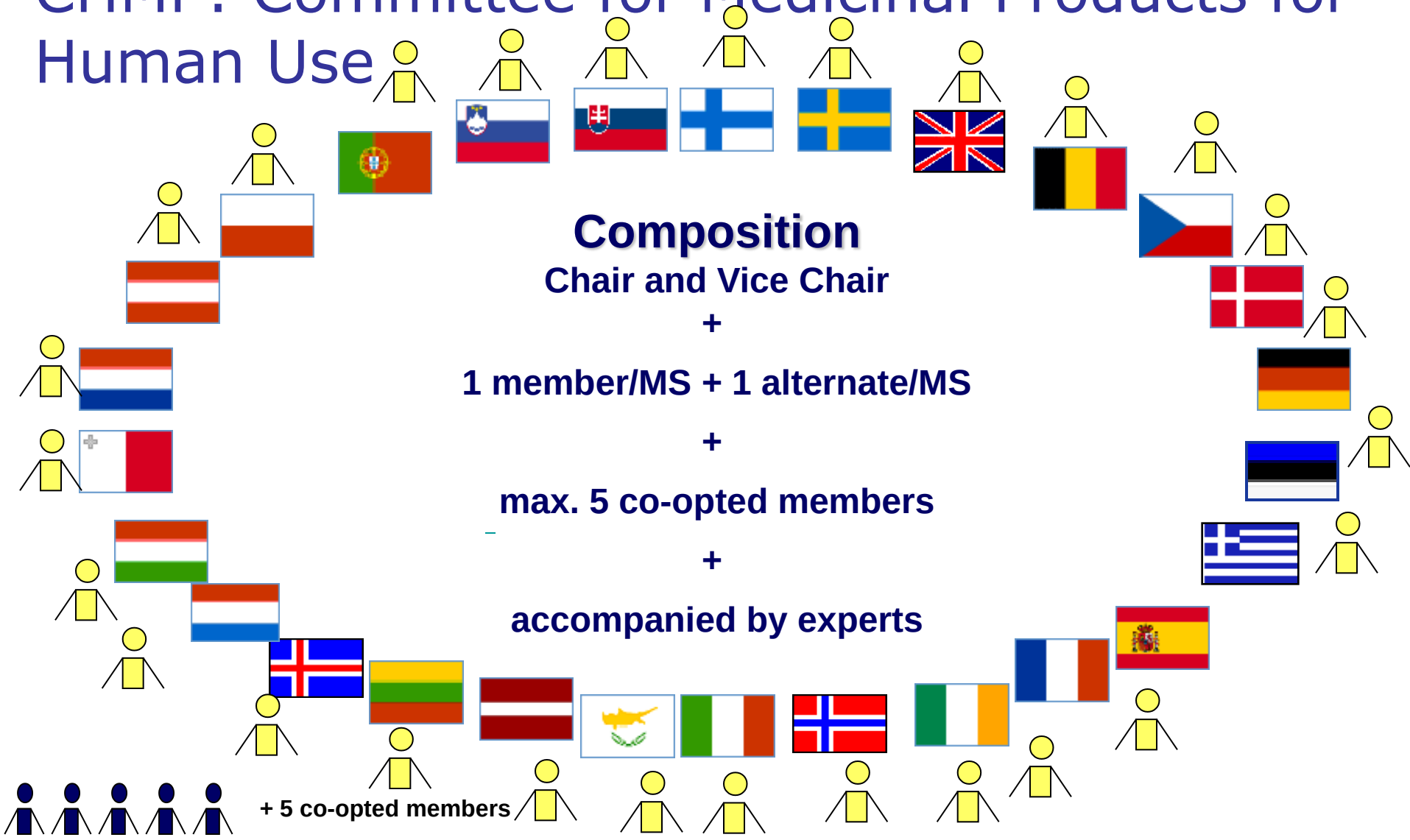
PDCO

(Paediatric Committee) Chair: Dr D. Brasseur

+ PRAC (July 2012)

(PhVig Risk Assessment Committee) Chair: xxx

CHMP: Committee for Medicinal Products for Human Use



CHMP Plenary Meeting: 4 days per month (Mon-Thur), at EMA

Role of (Co-)Rapporteurs

Support & guide CHMP in its decision-making

- Appointment of Rapporteurs and their assessment teams based on objective criteria
  → Use of best available expertise in EU in relevant scientific area
- **Lead reviewers** of the application on behalf of CHMP
  Full multi-disciplinary assessment team in 'home' agency
- Co-ordinate input from external experts/ad-hoc groups
- Propose objections and List of Questions + inspection
- Propose scientifically justifiable SmPC and final Opinion
- CHMP 'Spokesman' towards the applicant

Companies gather data...

- **Pharmaceutical development**

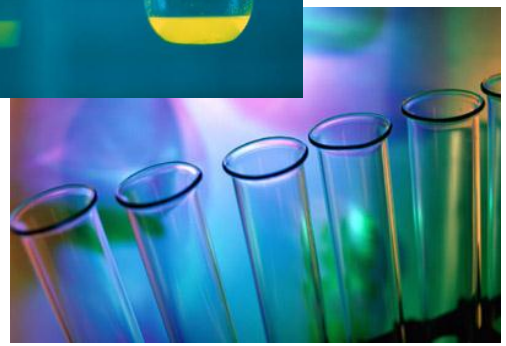
  Establish the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions

- **Non-clinical development**

  Pharmacology - Pharmaco-kinetics – Toxicology (Genotoxicity, Carcinogenicity, Reproductive and Developmental Toxicity)

- **Clinical development**

  Human Pharmaco-kinetic Studies, Human Pharmaco-dynamic Studies, Efficacy and Safety Studies



Overview of centralised procedure

MA Application submission

Start D.1

D.120

D.121

Opinion D.210

EU MA D.277

Pre-submissio → **Primary Evaluation** → **Clock Stop** → **Secondary Evaluation** → **Opinion / Decision** → **Post Authorisation**

Questions **Answers**

Scientific Advice

Paediatrics (PIP)

Rap/Co-Rap Assessment Reports (Day 80)

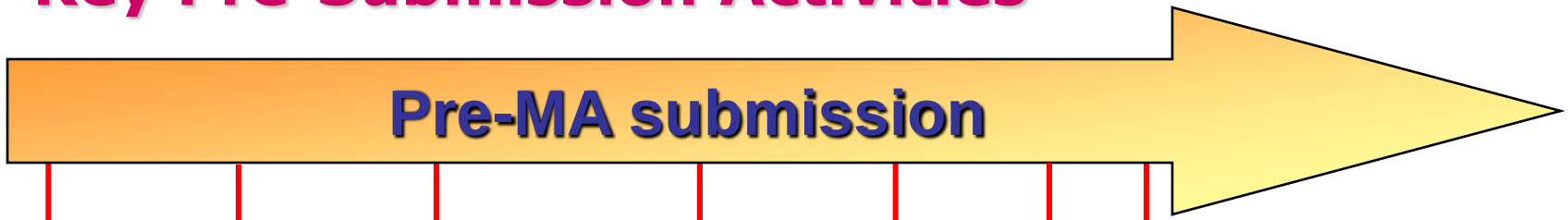
Comments CHMP (Day 100)

Joint Assessment Report on answers (Day 150)

Hearing (Day 180)

Ph.Vigilance
Variations
Extensions
Renewal

Key Pre-Submission Activities



-1 m
Request for accelerated review

Rapporteur meeting

-7 m
Letter of intent to submit
Appointment Rapporteur
Pre-submission meeting

-18m/-12m
Request **Eligibility for Centralised Procedure**
Request Invented name review
Start Rapporteur appointment process

-12m to -36m
Scientific Advice
Pipeline information

SME designation

ITF
Orphan Drug Designation
Paediatric Investigation Plan

EMA (CHMP) Assessment Report

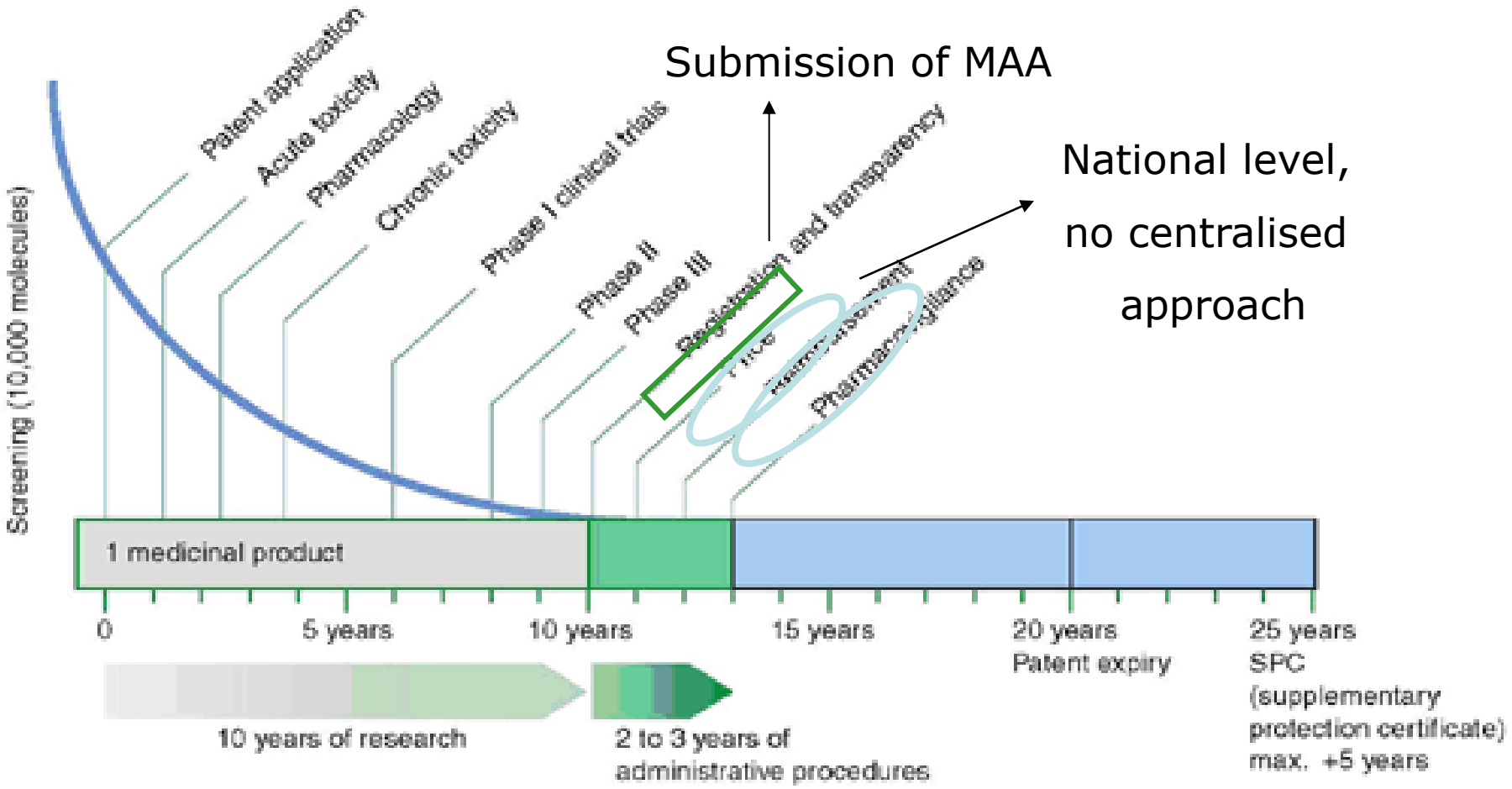
- Comprehensive **summary** of the Quality, Safety & Efficacy **data** submitted by the applicant

- Comprehensive **summary** of the **assessment** and CHMP conclusion to support the recommendation for granting MA
  → based on all Assessment Reports and CHMP discussions

- Prepared jointly by EMEA & (Co-)Rapporteur
  Average 50 – 100+ pages
  Reflects outcome of SAG / WP consultation, inspections etc.

- Basis for the EPAR published on the Agency's website

Medicinal Product Development



EMA's legal basis for marketing authorisation:

"authorisation decisions […] should be taken on the basis of the objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations".

Recital 13, REGULATION (EC) No 726/2004

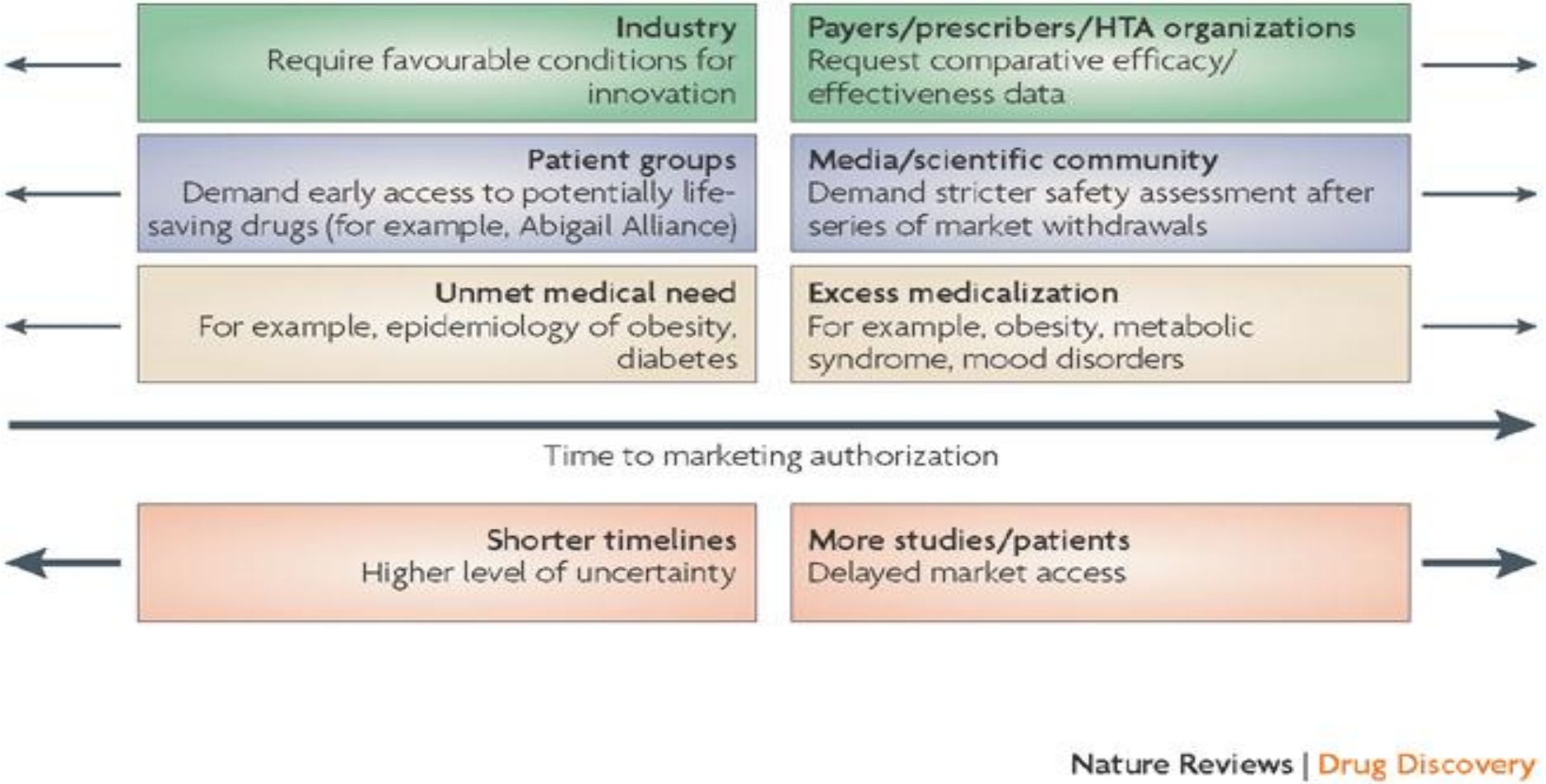
- Benefit-Risk: more good than harm
- each application on its own merit
- relative efficacy *prima facie* not a priority

3. BENEFIT/RISK ASSESMENT

Benefit-Risk Assessment Template

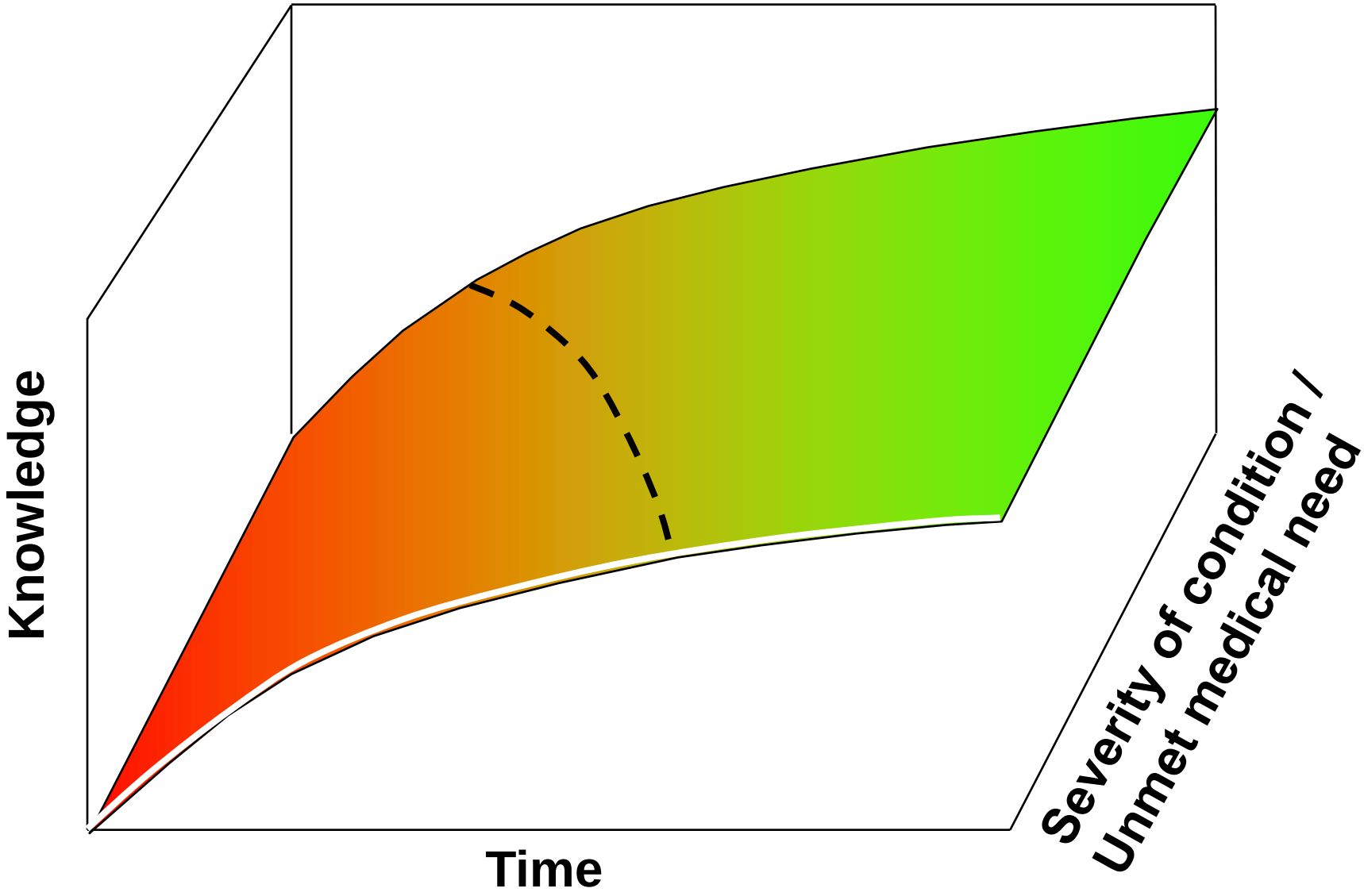
- Benefits
  - Beneficial effects
  - Uncertainty in the knowledge about the benefits
- Risks
  - Unfavourable effects
  - Uncertainty in the knowledge about the risks
- Balance
  - Importance of favourable and unfavourable effects
  - Benefit-risk balance
- Discussion on the benefit-risk assessment
- Conclusions

The regulator's dilemma

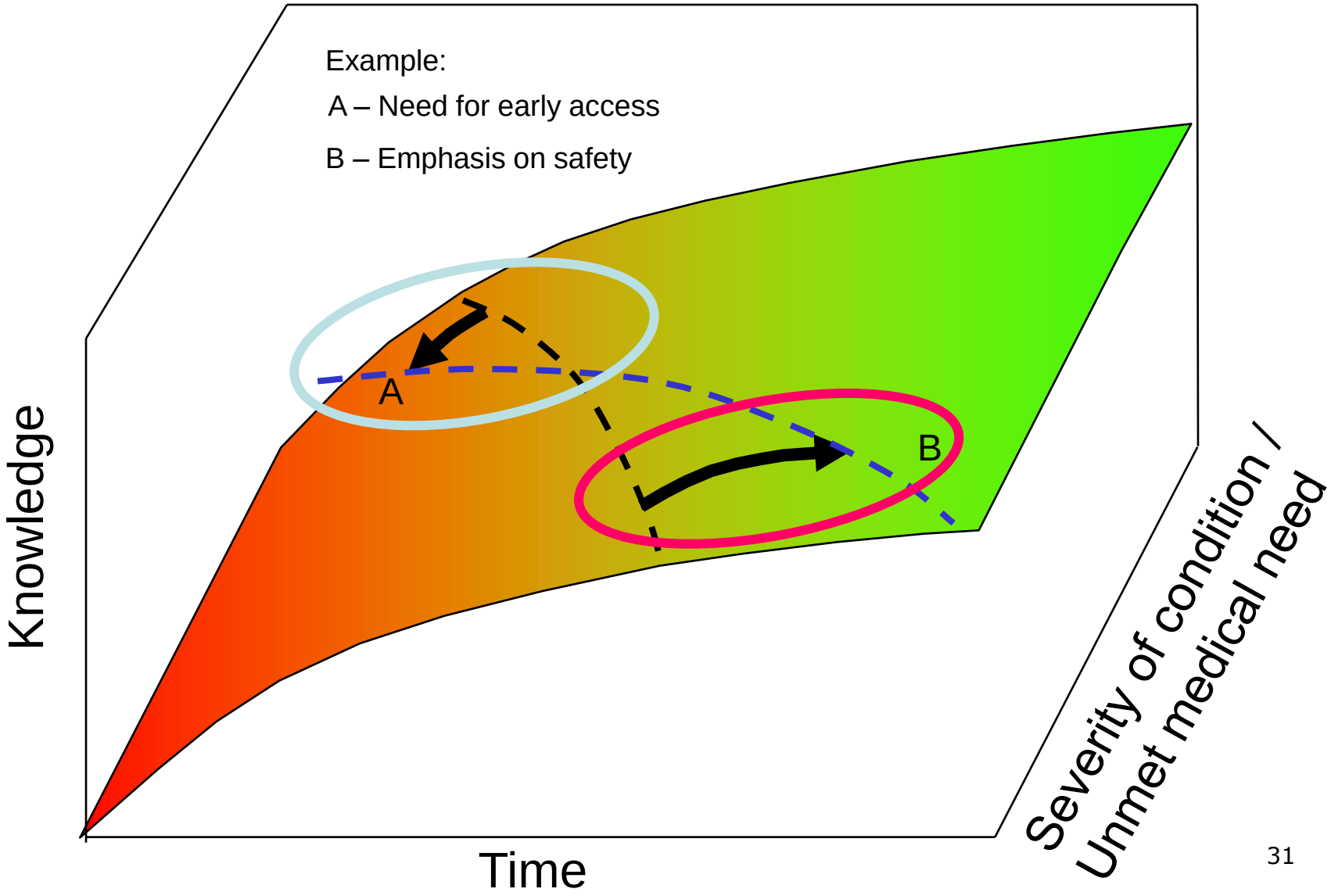


Nature Reviews | Drug Discovery

Information needs for Licensing ?



Addressing the regulator's dilemma



Efficacy versus effectiveness

Efficacy is the extent to which an intervention does more good than harm under ideal circumstances

Effectiveness is the extent to which an intervention does more good than harm when provided under the usual circumstances of health care practice

Definitions by the EU High Level Pharmaceutical Forum (Oct 2008)

Efficacy >> Effectiveness

Evolution of post-marketing research activities

Benefits

RCT's (in context of conditional approval)

Risks

Spontaneous reporting

↓

Active surveillance
RMP's:
- registers
- observational studies (eMedical Records)
- RCT's, LST's

Evolution of post-marketing research activities

Benefits	Risks
RCT's (in context of conditional approval)	Spontaneous reporting
Payers requirements: (pay-for-performance, coverage with evidence development) → relative (comparative) effectiveness	Active surveillance RMP's: registers observational studies (eMedical Records) RCT's, LST's

integrated assessment of clinical outcomes (the good and the bad) → relative effectiveness

4. Benefit–Risk Communication

Benefit communication is different from risk communication

- Patients and media are more risk adverse
- Perceptions are often more important than reality
- Difficult to communicate preventive medicine – the better you prevent a problem the less the public will understand that there was a problem in the first place
- Specific case of vaccines

"The emotional epidemiology of flu vaccination"*

Patients in summer 2009:
"When will there be a vaccine?"

Same patients in late 2009:
"It's not tested", "I'm not putting that in my body"

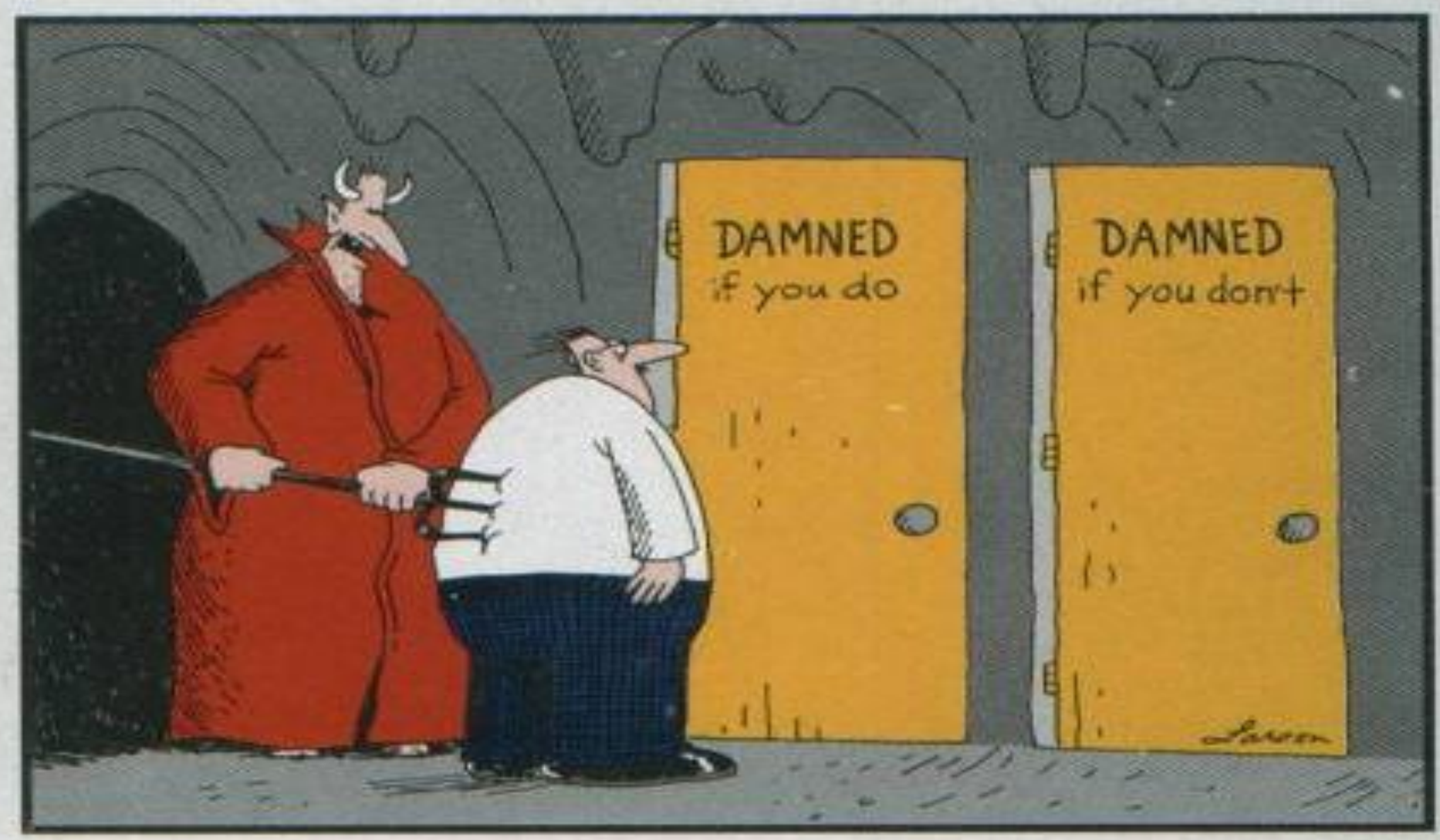
The media in summer 2009:
"What are health authorities doing to protect us?"

Same media in late 2009:
"Vaccines are unsafe, were rushed to market"

* Ofri D: N Engl J Med 361:2594, 2009

Benefit communication is different from risk communication

- "…a nine-fold increase in risk of narcolepsy"
- "…an increase from 1 to 9 cases per 100 000 vaccines"
- "…*x* n of cases of narcolepsy in every 100 000 in non vaccinated people vs 1 to 9 in 100 000 vaccines"
- "…*x* n of deaths from flu complication in non vaccinated population vs 1 to 9 narcolepsy in 100 000 vaccines in 1 single region in Europe"



"C'mon, c'mon — it's either one or the other."