Pharmacoepidemiology, benefit/risk assessment and comparative effectiveness

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Chair, Belgian Committee for Reimbursement of Medicines (**CTG-CRM, INAMI-RIZIV**)

Professor of Physiology & Pharmacology, **FUNDP Namur**, Belgium

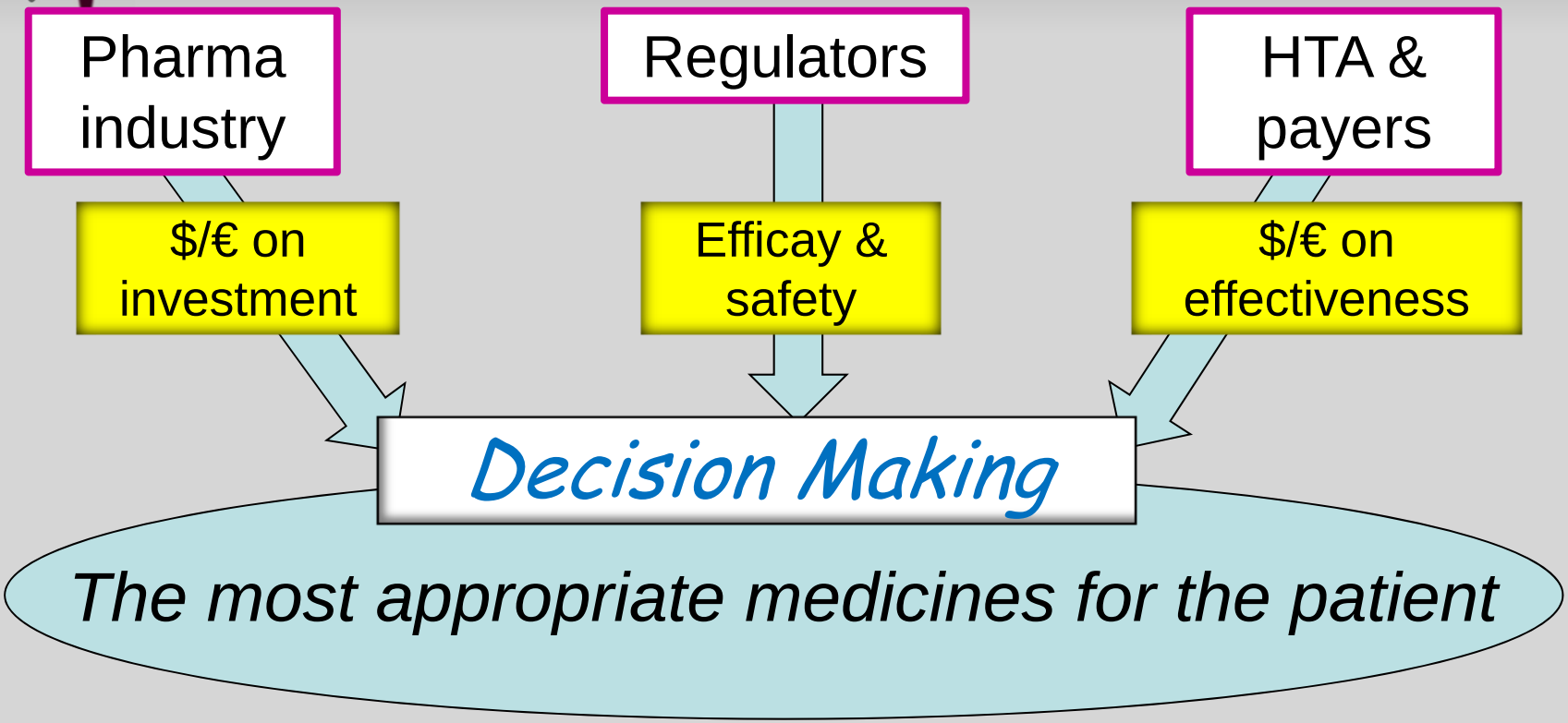
Disclaimer

My presentation might not be the view of the organisations I am working for.

My presentation is a personal viewpoint and binds in no way the organisations mentioned above.

I have no financial interest to disclose.

The process of decision making for drugs



IRRECONCILABLE?

The traditional approach

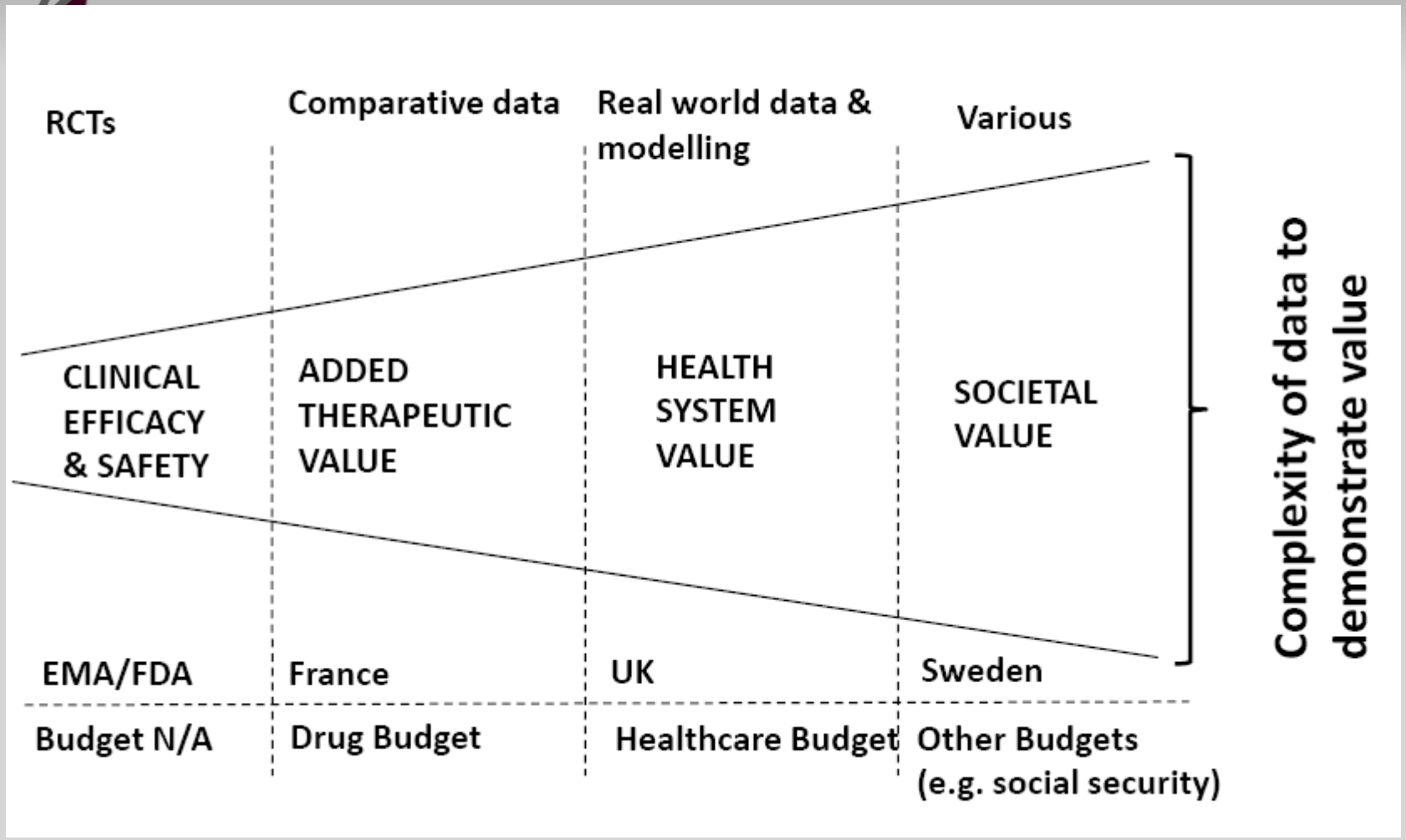
Pharma industry

$/€ on investment

- Short term clinical studies
  - Drug *vs* placebo
  - Surrogate if accepted (HbA1c, BP, PFS)
  - SAE and AE reports
- Submit package to regulators
- Promote and market the drug

The most appropriate medicines for the patient

The need to demonstrate (added) value



From: Murray Stuart (GSK), Geneva 2011

Final Conclusions and Recommendations of the High Level Pharmaceutical Forum

European Commission, Member States, members of the European Parliament, & multiple stakeholders

- *Efficacy:* is the extent to which an intervention does more good than harm under ideal circumstances.
- *Relative efficacy:* can be defined as the extent to which an intervention does more good than harm, under ideal circumstances, compared to one or more alternative interventions.
- *Effectiveness* is the extent to which an intervention does more good than harm when provided under the usual circumstances of health care practice.
- *Relative effectiveness* can be defined as the extent to which an intervention does more good than harm compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of health care practice.

Questions of relevance for today

1. What is the basis of benefit-risk assessment by regulatory authorities?
2. Should it become more structured, more quantitative?
3. Should it incorporate epidemiology data?
4. Should it merge into the evaluation of relative/comparative effectiveness?

Rules of Marketing Autorisation (MA) in the EU

- *Article 26 of Directive 2001/83/EC*: MA will be refused if benefit/risk (B/R) balance is not favourable (a value judgment!), or therapeutic efficacy is insufficiently substantiated, or qualitative and quantitative composition is not as declared
  → overall, this is « **QSE** »

- There is no requirement to demonstrate a medical need, no mention that B/R should not be inferior to already existing products

- However…

Rules of MA in the EU (2)

** Section 5.2.5.1 of Annex I to Directive 2001/83/EC states:

"*In general, clinical trials shall be done as 'controlled clinical trials' if possible, randomised and as appropriate versus placebo* ***and versus an established medicinal product of proven therapeutic value****; any other design shall be justified. The treatment of the control groups will vary from case to case and also will depend on ethical considerations and therapeutic area; thus* ***it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value*** *rather than with the effect of a placebo*."

The need for an active control (1)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 November 2010
2 EMA/759784/2010
3 Committee for Medicinal Products for Human Use

4 **Reflection paper on the need for active control in**
5 **therapeutic areas where use of placebo is deemed ethical**
6 **and one or more established medicines are available**
7 Draft

Adoption by CHMP for release for consultation	November 2010
End of consultation (deadline for comments)	31 March 2011

The need for an active control (2)

- When feasible, **3-arm trials** including experimental medicine, placebo and active control represent a **scientific gold standard**

- **When ethical and feasible, a placebo arm should be included in the pivotal trials to support MAA**

- Direct comparison with an **active control** is important where:
  - The experimental medicine may be associated with **safety concerns** (mortality, morbidity, QoL, discontinuations or delay in treatment leading to irreversible harm…)
  - Treatment with **a medicine of inferior efficacy** might conceivably lead to significant, long-term or irreversible harm for the patient

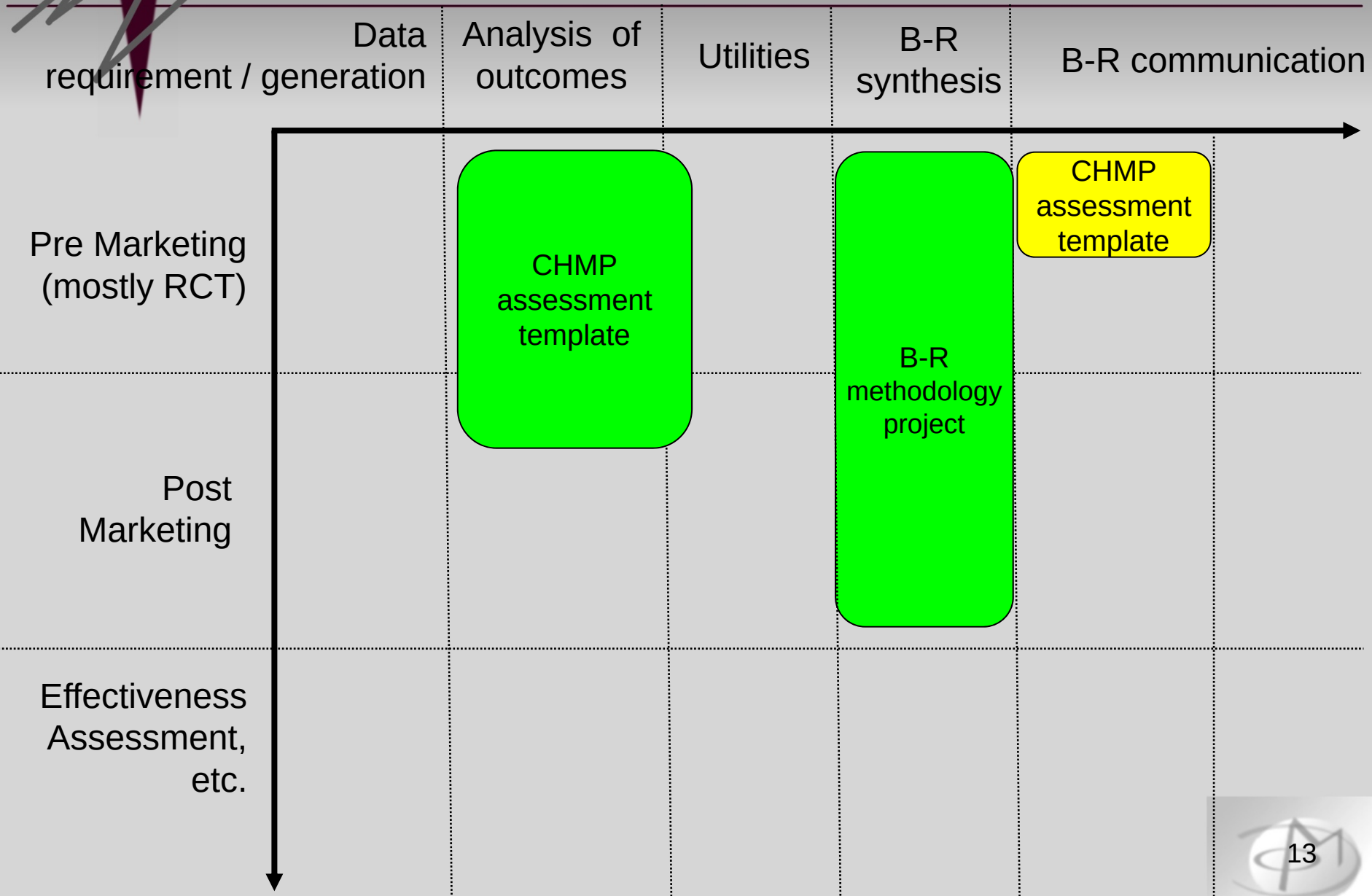
2008 Conclusions of the CHMP Working Group

- Expert judgment will remain the cornerstone of B/R evaluation
- Existing models for decision-making are not (yet) fit for use
- The current **CHMP Assessment Report Guidance** should be revised, incorporating a structured list of B & R criteria and guidance
- Methodologies for B/R assessment **should be further explored**

2009

- The Template/Guidance was revised
- Start of the BR Methodology Project (EMA sponsor: Xavier Luria):
  - London School of Economics (Prof. Larry Philipps), University of Groningen
  - CHMP/EMA Steering Group

EMA project map on B-R assessment and communication



The EMA report on Work Package 1 (1)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 March 2010
EMA/213482/2010
Human Medicines Development and Evaluation

Work Package 1

European Medicines Agency Benefit-Risk methodology project

Description of the current practice of benefit-risk assessment for centralised procedure products in the EU regulatory network

The EMA report on Work Package 1 (2)

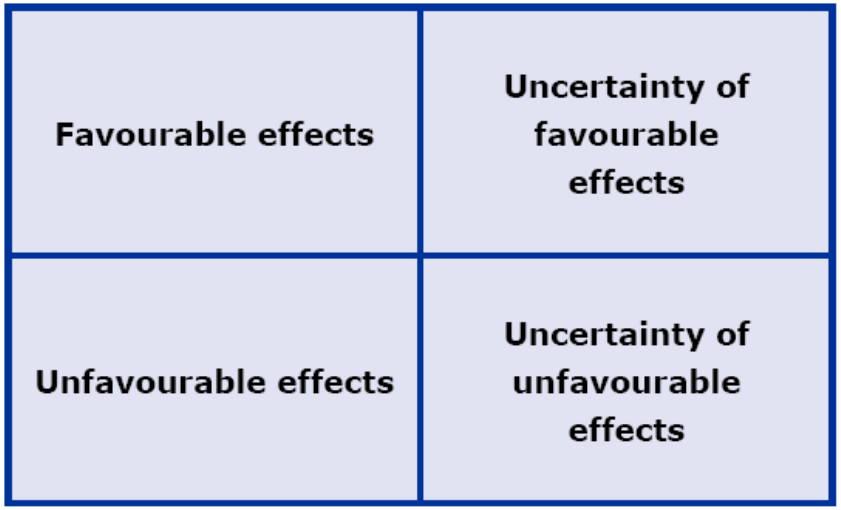
Interview protocol

1) Agency's history and purpose
2) Agency's relationships with governmental and non-governmental organisations
3) Agency's organisational structure
4) Information flow
5) Meaning of "benefits" and "risks"
6) Benefit-risk assessment process
7) Consistency
8) Existence of models

6 participating agencies:

- FR
- NL
- SE
- ES
- UK
- DE (PEI)

Figure 1. The EMA's four-fold model of 'benefits' and 'risks'



The EMA report on Work Package 2 (1)

31 August 2010
EMA/549682/2010 - Revision 1
Human Medicines Development and Evaluation

Benefit-risk methodology project

Work package 2 report: Applicability of current tools and processes for regulatory benefit-risk assessment

The EMA report on Work Package 2 (2)

- Judgment plays an important role in regulatory decision making
- Research findings in cognitive psychology show that models can assist […]
- We evaluated 18 quantitative approaches and came to the following conclusions:…

The EMA report on Work Package 2 (3)

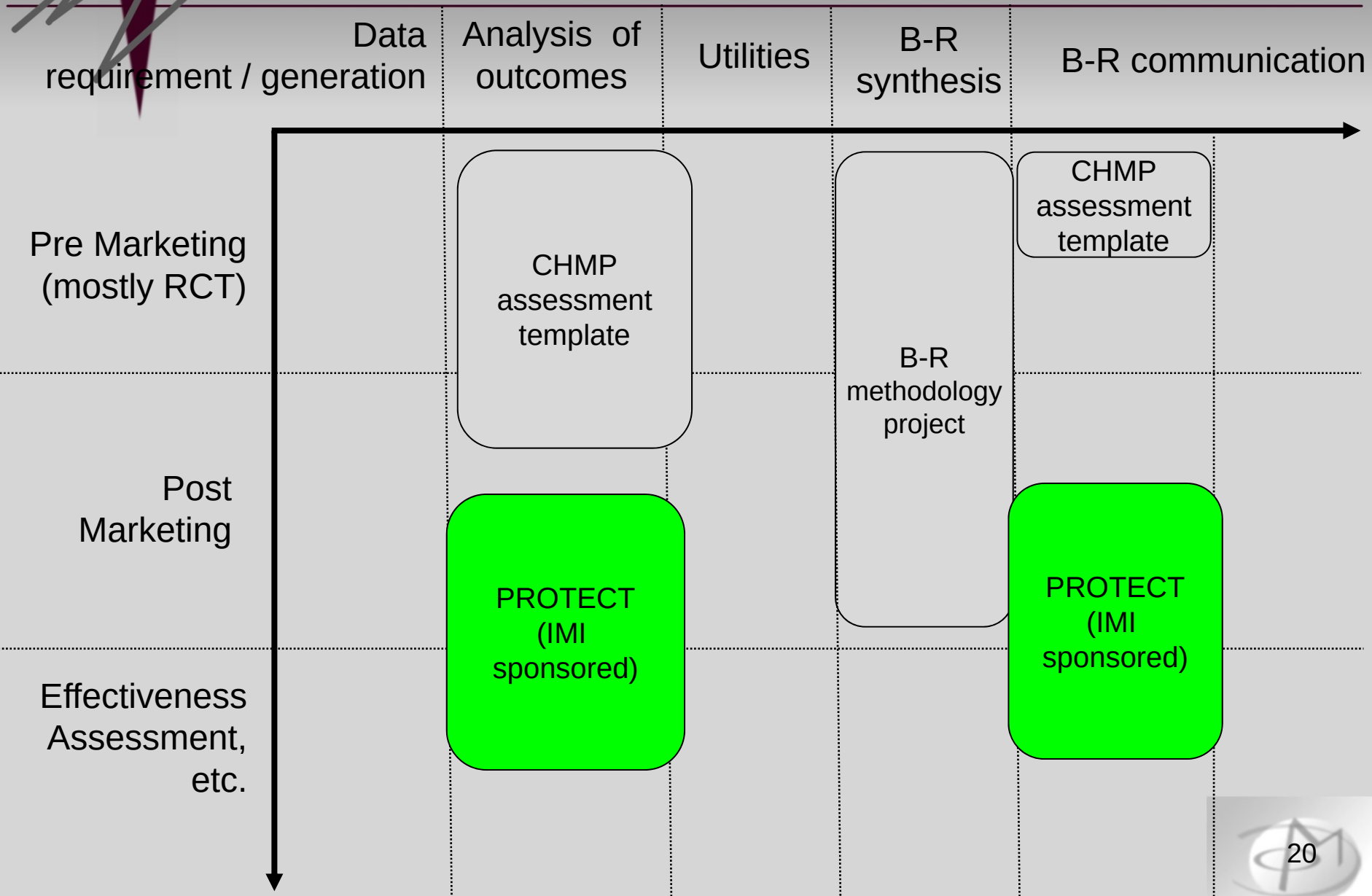
1. Any quantitative method **requires a qualitative framework** within which the model can be effectively developed. The qualitative approach may be sufficient for simpler B/R decisions.
2. Only **3 quantitative approaches** are sufficiently comprehensive for a numerical representation of the B/R (as a difference or a ratio) along with its uncertainties:
   - Bayesian statistics
   - Decision trees and influence/relevance diagrams
   - Multi-criteria decision analysis (MCDA)

The EMA report on Work Package 2 (4)

3. Five other approaches, while more restricted in scope, **may well prove useful** for particular cases:
   - Probabilistic simulation
   - Markov processes
   - Kaplan-Meier

     (both for estimating changes in health states over time)
   - QALYS for modelling multiple health outcomes
   - Conjoint analysis to explicate trade-offs among effects, especially for eliciting patient preferences
4. Combination of approaches will prove useful in some situations

EMA project map on B-R assessment and communication



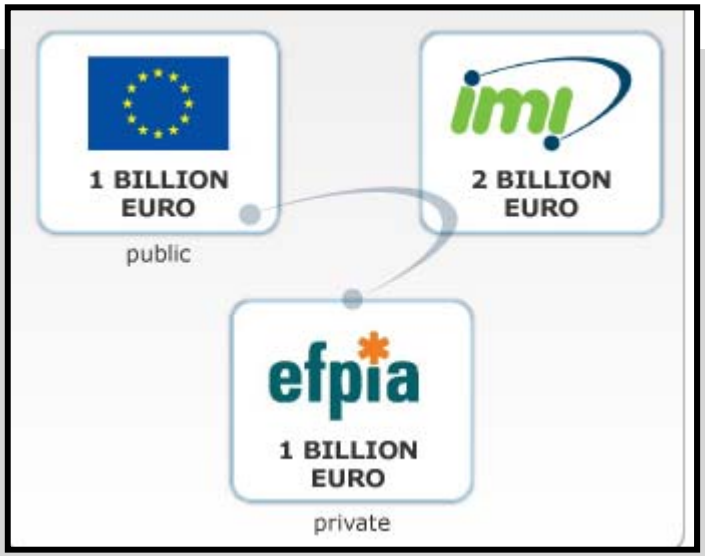
Innovative Medicines Initiative

PRESS RELEASE

IMI announces a new total of 23 unique projects to boost drug innovation

Brussels, March 8, 2011 -

http://www.imi.europa.eu/



The IMI PROTECT program (1)

IMI 1ST CALL PROJECTS: SAFETY

Innovative Medicines Initiative

PROTECT

PHARMACOEPIDEMIIOLOGICAL RESEARCH ON OUTCOMES OF THERAPEUTICS BY A EUROPEAN CONSORTIUM

[…] PROTECT will look at limitations of current methods used in pharmacovigilance and pharmacoepidemiology in order to strengthen the monitoring of the B/R balance of medicines marketed in Europe.

A set of innovative tools and methods will be developed […]:

- modern ways of collecting data on medications, lifestyle, risk factors directly from consumers
- improved tools for early and proactive detection of signals
- modeling approaches
- graphical methods to display B/R profiles

The IMI PROTECT program (2)

PARTICIPANTS:

EFPIA:

- GlaxoSmithKline Research and Development LTD, Brentford, UK
- Amgen NV, Brussels, Belgium
- Bayer Schering Pharma AG, Berlin, Germany
- AstraZeneca AB, Södertälje, Sweden
- Genzyme Europe B.V., Naarden, The Netherlands
- H. Lundbeck A/S, Valby, Denmark
- Merck KGaA, Darmstadt, Germany
- Novartis Pharma AG, Basel, Switzerland
- Novo Nordisk A/S, Bagsvaerd, Denmark
- Pfizer Limited, Sandwich, United Kingdom
- F. Hoffmann-La Roche AG, Basel, Switzerland
- Sanofi-Aventis Research and Development, Chilly-Mazarin, France

UNIVERSITIES, RESEARCH ORGANISATIONS, PUBLIC BODIES & NON-PROFIT:

- European Medicines Agency *(Project Coordinator)*
- Lægemiddelstyrelsen (Danish Medicines Agency, Copenhagen, Denmark
- Agencia Española de Medicamentos y Productos Sanitarios, Madrid, Spain
- Fundación Centro Español de Investigación Farmacoepidemiológica, Madrid, Spain
- Fundació Institut Català de Farmacologia, Barcelona, Spain
- International Alliance of Patients' Organizations, London, UK
- Imperial College of Science, Technology & Medicine, London, UK
- Institut National de la Santé et de la Recherche Médicale, Paris, France
- Ludwig-Maximilians-Universität München, München, Germany
- Mario Negri Institute for Pharmacological Research, Milan, Italy
- Medicines and Healthcare products Regulatory Agency, London, UK
- Rijksuniversiteit Groningen, Groningen, The Netherlands
- Stiftelsen WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden
- University of Newcastle upon Tyne, Newcastle upon Tyne, UK
- Universiteit Utrecht, Utrecht, The Netherlands

SME's:

- LA Santé Épidémiologie Evaluation Recherche, Paris, France
- Outcome Europe Sarl, St. Prex, Switzerland

STARTING DATE:	01.09.2009
DURATION:	60 months

FINANCING:	
IMI funding:	€ 11.009.715
Other contributions:	€ 8.816.164
EFPIA in kind contribution:	€ 9.984.734
TOTAL PROJECT COST:	**€ 29.810.613**

Eu2P, an IMI educational program (1)

IMI 1ST CALL PROJECTS: EDUCATION & TRAINING

Innovative Medicines Initiative

EU2P

EUROPEAN PROGRAMME IN PHARMACOVIGILANCE AND PHARMACOEPIDEMIOLOGY

Eu2P, an IMI educational program (2)

PARTICIPANTS:

EFPIA:

- F. Hoffmann-La Roche AG, Basel, Switzerland *(Project Coordinator)*
- Amgen NV, Brussels, Belgium
- AstraZeneca AB, Södertälje, Sweden
- Bayer Schering Pharma AG, Berlin, Germany
- Boehringer Ingelheim International GmbH, Ingelheim, Germany
- Eli Lilly And Company Limited, Basingstoke, United Kingdom
- GlaxoSmithKline Research and Development LTD, Brentford, UK
- H. Lundbeck A/S, Valby, Denmark
- Janssen Pharmaceutica NV, Beerse, Belgium
- Laboratorios Almirall S.A., Barcelona, Spain
- Novartis Pharma AG, Basel, Switzerland
- Novo Nordisk A/S, Bagsvaerd, Denmark
- Orion Corporation, Espoo, Finland
- Sanofi-Aventis Recherche & Developpement, Chilly Mazarin, France
- UCB Pharma SA, Brussels, Belgium

UNIVERSITIES, RESEARCH ORGANISATIONS, PUBLIC BODIES & NON-PROFIT:

- Université Victor Segalen Bordeaux II, Bordeaux Cedex, France
- Agence Française de Sécurité Sanitaire des Produits de Santé, Saint-Denis Cedex, France
- Erasmus Universitair Medisch Centrum Rotterdam, Rotterdam, The Netherlands
- European Medicines Agency, London, United Kingdom
- Fundació Institut Català De Farmacologia, Barcelona, Spain
- Karolinska Institutet, Stockholm, Sweden
- The University of Hertfordshire, Higher Education Corporation, Hatfield, United Kingdom
- Universiteit Utrecht, Utrecht, The Netherlands
- Universita degli Studi di Verona, Verona, Italy

- Includes EMA, AFSSAPS (FR)

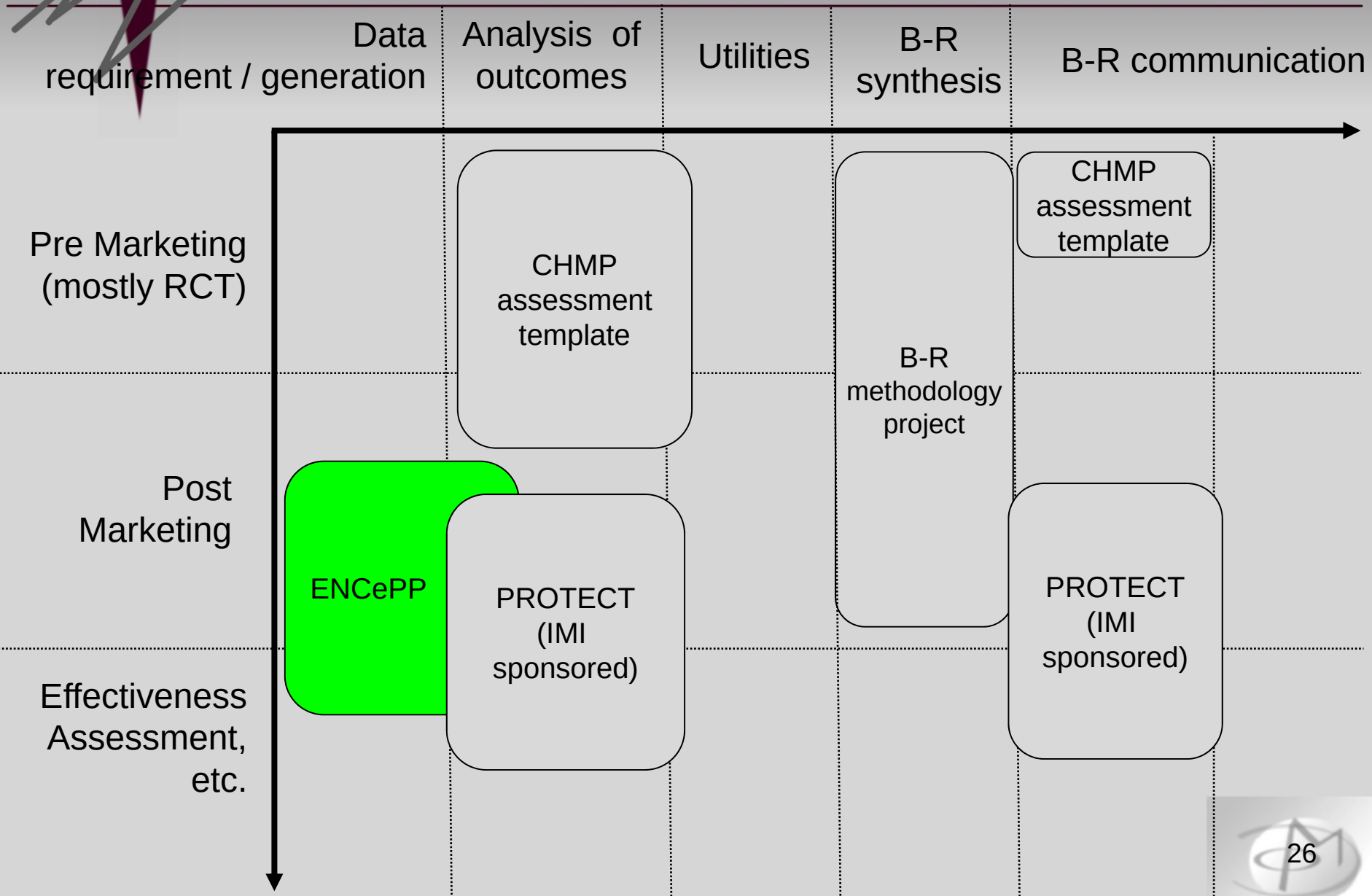
Eu2P
EUROPEAN PROGRAMME IN
PHARMACOVIGILANCE AND PHARMACOEPIDEMIOLOGY

http://www.eu2p.org

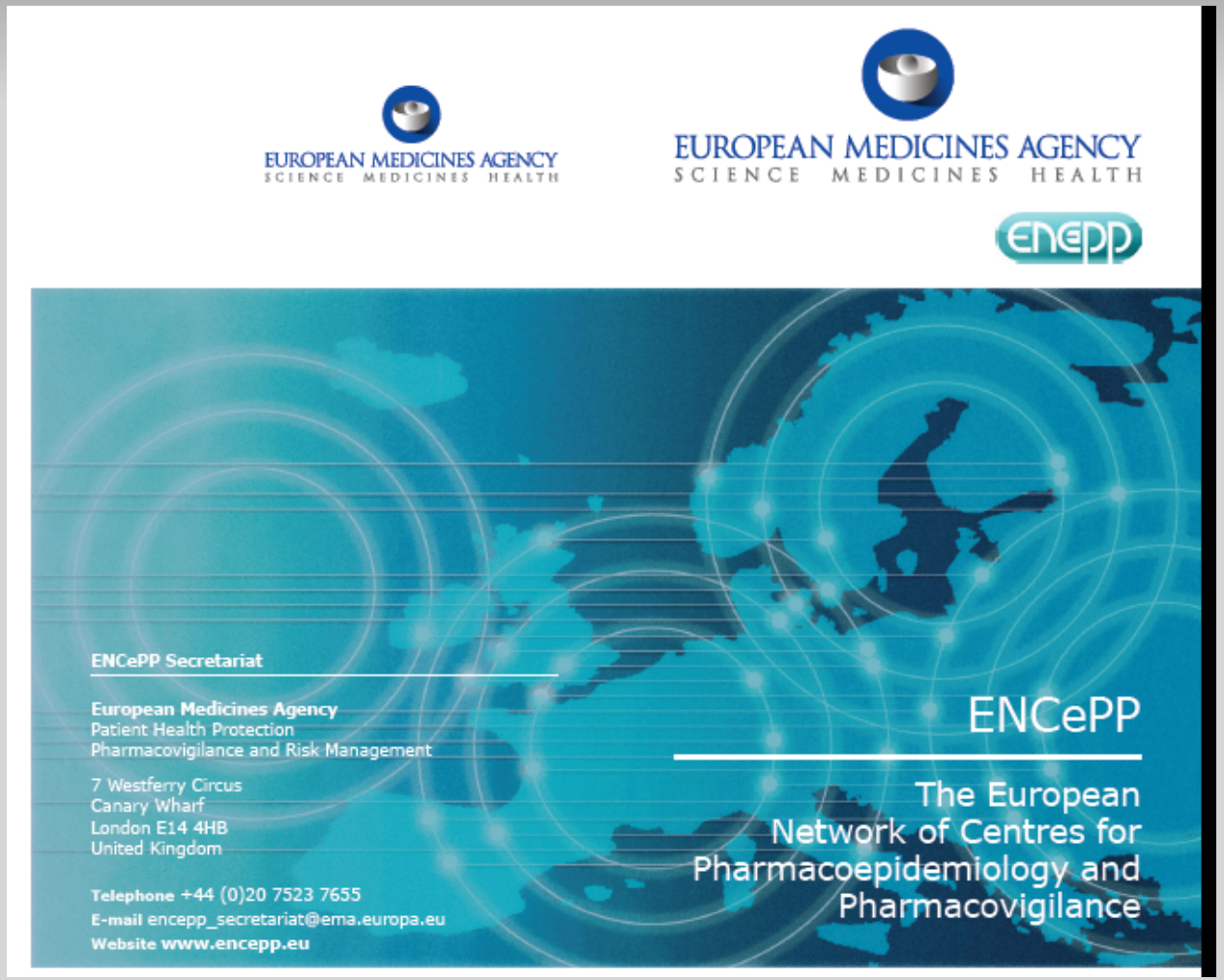
STARTING DATE:	01.09.2009
DURATION:	60 months

FINANCING:	
IMI funding:	€ 3.479.725
EFPIA in kind contribution:	€ 3.791.161
TOTAL PROJECT COST:	**€ 7.270.886**

EMA project map on B-R assessment and communication



The ENCePP (1)



http://www.encepp.eu

The ENCePP (2)

To this end the concept of '**ENCePP Study**' was introduced. In short, all pharmacovigilance and pharmacoepidemiological studies can qualify as an ENCePP study provided that the (primary) lead investigator belongs to an entity that is included in the ENCePP Inventory of resources and that the '**CoRe requirements**' are met:

- **C**ode of conduct for scientific independence and transparency in the conduct of pharmaco-epidemiological & pharmacovigilance studies *(signed declaration and checklist)*
- checklist of meth**o**dological standards *(signed checklist)*

The signed declaration and checklists must be provided to the ENCePP Secretariat before the study commences. The original and final versions of the protocol will be made publicly available after the final study report.

- e-**Re**gister of studies

The study must be included in the electronic ENCePP register of studies before it commences.

1. Code of conduct
2. Checklist
3. e-Register

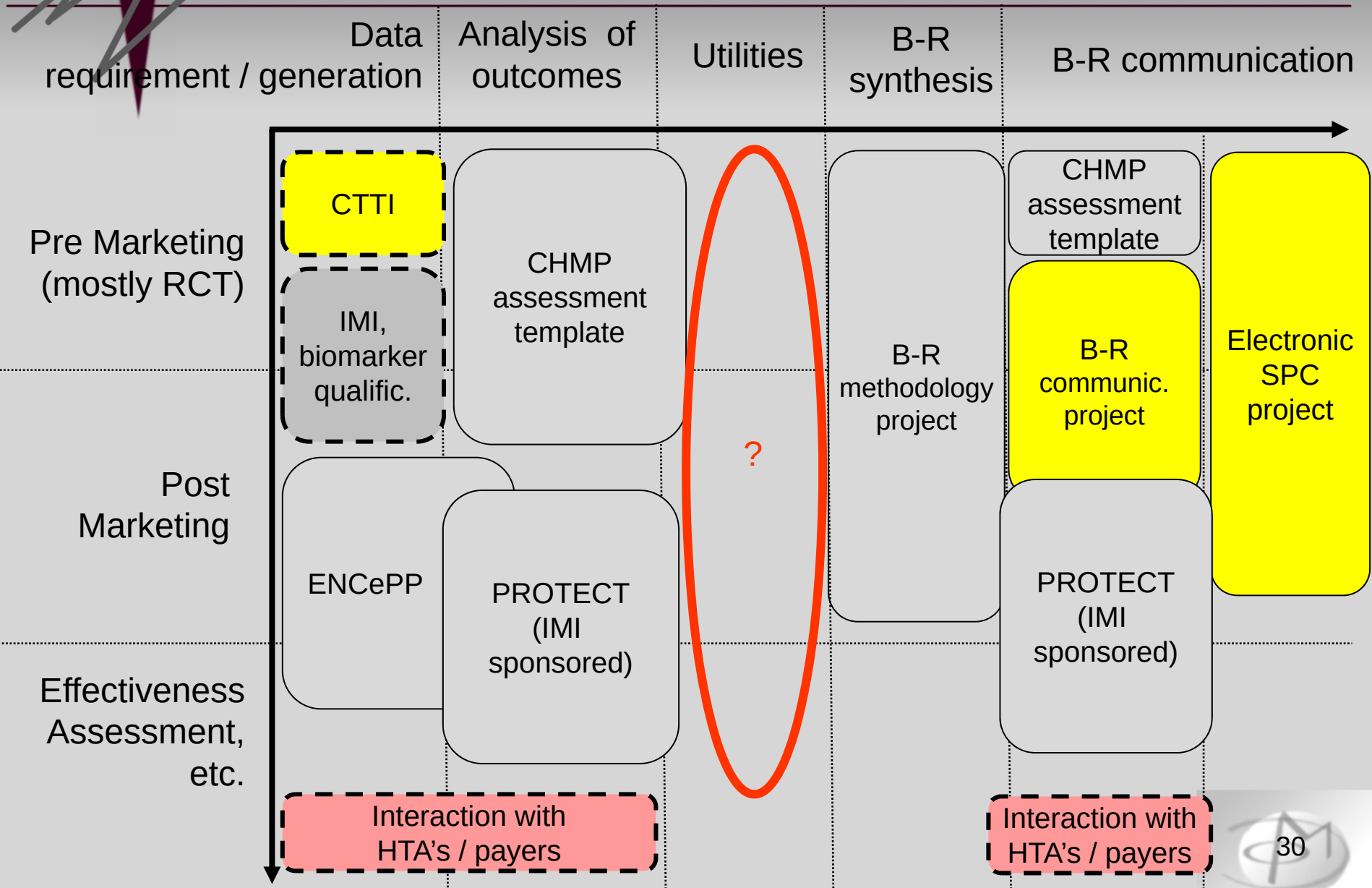
The ENCePP (3)

1. Core research values

2. Public, fully searchable database of the available EU research resources in the field of pharmacoepidemiology and pharmacovigilance:
   - Inventory of ENCePP research centres and networks
   - Registry of EU data sources

3. Electronic register of studies

EMA project map on B-R assessment and communication



The 2009 EMA Transparency Policy

Examples of Key Transparency Initiatives

- Proactively publish agendas/minutes scientific committees
- Improve the EPARs and better describe the rationale for opinion-making
- Progress with the project on methodology for benefit/risk analysis
- Redefine the notion of commercially confidential information
- Assess the completeness of information outlined in the EPARs for orphan drugs (in collaboration with KCE, Belgium)
- Implement the EMA Access to Documents Policy
- Get ready for public hearings in the field of pharmacovigilance (upcoming new legislation)
- Improve the interaction with patients/consumers and healthcare professionals organisations
- Organise workshops and training with external stakeholders
- Explore, through a dialogue with EU Health Technology Assessment (HTA) bodies, how the EPARs could further contribute to the cost/effectiveness assessment performed by HTA bodies

The EMA Roadmap to 2015 (1)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 January 2010
EMA/299895/2009

The European Medicines Agency Road Map to 2015:
The Agency's Contribution to Science, Medicines, Health
Draft for Public Consultation

The EMA Roadmap to 2015 (5)

Strategic Area 3: Optimising the Safe Use of Medicines

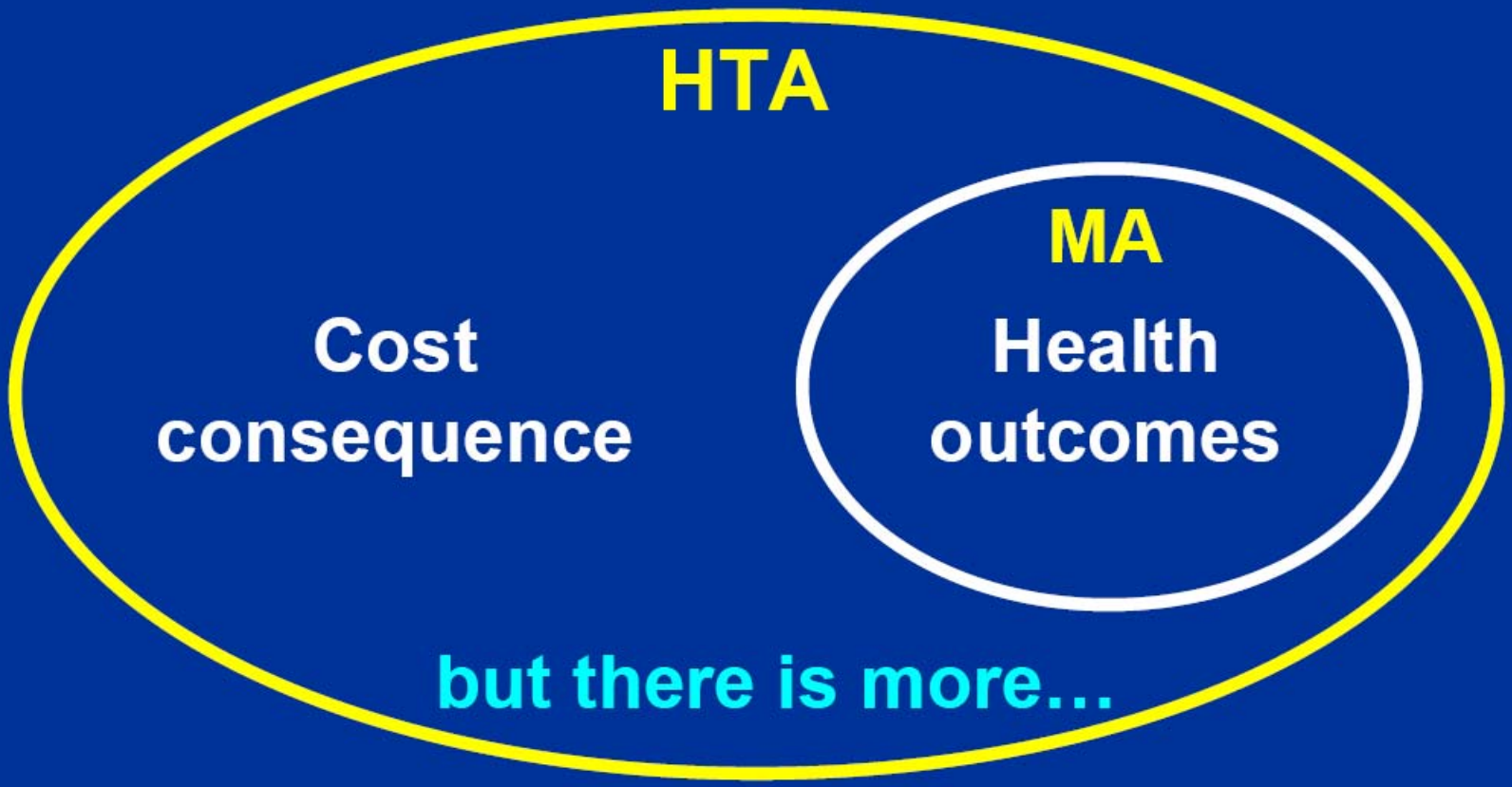
Objectives	Impact/Result Indicators
Strengthen the evidence base in the post-authorisation phase to enable better regulatory decision-making.	A regulatory model which facilitates the post-authorisation collection of data on benefits and risks of medicinal products is put at the disposal of the Regulatory System.
Enhance patient safety by avoiding unnecessary risks to patients as a result of the use of medicines.	A revised risk management concept, which targets both novel pharmacovigilance methodologies as well as a risk minimisation toolbox better adapted to reduce harm, is available.
Become a reference point on information for medicines evaluated by the Agency.	A high-quality, informative and targeted set of information on medicines, falling within the sphere of the Agency's responsibilities, is proactively put at the disposal of the EU Regulatory System Network at the moment of licensing/updating of the marketing authorisation.
Improve the decision-making process by taking due account of patient experience, hence contributing to the rational use of medicines.	Conclusions from outcome research projects analysing the impact of the regulatory decisions on public health are used to provide input in future regulatory policy decision-making.

A central question is:

(How) Can we bridge marketing authorisation to reimbursement decisions?

What distinguishes regulators from HTA/payers?

EUROPEAN MEDICINES AGENCY



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Courtesy of Hans-Georg Eichler, Senior Medical Officer, EMA

EUROPEAN MEDICINES AGENCY

Evidence standards; regulators vs. HTA/payers

- Level of acceptable uncertainty
- External validity (efficacy vs. effectiveness
- Perception of clinical relevance
- Absolute vs. relative efficacy
- Methodological issues (validity of QoL instruments, composite endpoints, surrogates, Bayesian stats, …)

Courtesy of Hans-Georg Eichler, Senior Medical Officer, EMA

Different “evidentiary and analytical standards” – this is NOT about cost !

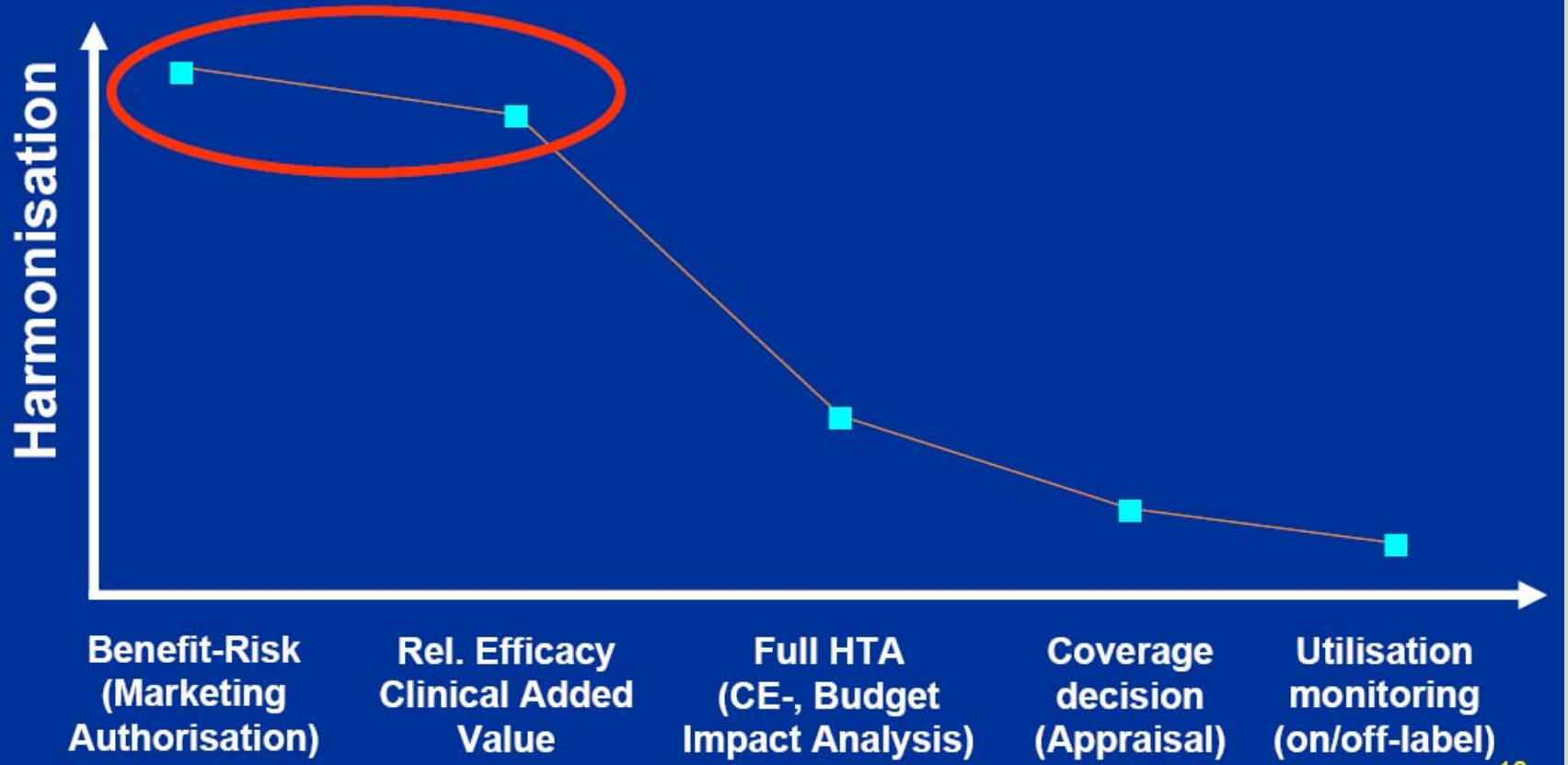
Examples

- Pulmonary art. hypertension: 6 min walk test
- Oncology: OS, PFS, ORR
- EQ-5D

Courtesy of Hans-Georg Eichler, Senior Medical Officer, EMA

EUROPEAN MEDICINES AGENCY

Drug development/Access to Drugs: What can be harmonised in the EU?



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Courtesy of Hans-Georg Eichler, Senior Medical Officer, EMA

November 2010

Tapestry Networks

Relationships • Insight • Courage ™

Pilots of multi-stakeholder consultations in early-stage drug development

The pilot initiative involves clinicians, health technology assessors (HTAs), patient representatives, payers, regulators and drug developers from France, Germany, Italy, the Netherlands, Sweden, the United Kingdom and the European Medicines Agency. Participating companies will seek early advice regarding a medicine under development for the treatment of either Breast Cancer or Type 2 diabetes, with consultations planned over the next four months. The agreed consultation process will engage all participants on issues of therapeutic value and a narrower group of HTAs and payers on questions of economic value deriving from therapeutic benefits.

AstraZeneca, GlaxoSmithKline and Johnson & Johnson support and fund this initiative that is independently led by Tapestry Networks in accordance with its principles and guidelines for public-private networks.

Purpose of the multi-stakeholder consultations

Seek clarity and alignment among the stakeholders regarding what constitutes a **medicine's value**

and **the evidence required** to demonstrate that value most effectively

Key goals of the Tapestry Pilot program

For the sponsors

1. Identify the projects most likely to result in **added value** to healthcare systems

2. **Eliminate** the projects unlikely to contribute to the assessment of the drug's value

3. Consider how to generate data relevant for HTA and payers **even before MA**

The medicines involved in the three pilots

October 2010 (AstraZeneca)

- NCE for **type 2 diabetes**

December 2010 (GlaxoSmithKline)

- NCE for **type 2 diabetes**

February 2011 (Johnson & Johnson)

- NCE for **breast cancer**

Participants (besides industry)-1

Appendix A: Institutions contributing to the pilot consultations

France	▪ Agence Française de Securité Sanitaire des Produits de Santé (AFSSAPS)
	▪ Comité Economique des Produits de Santé (CEPS)
	▪ Haute autorité de santé (HAS)/Commission de la Transparence
Italy	▪ Agenzia Italiana del Farmaco (AIFA) Italian Medicines Agency
The Netherlands	▪ CVZ (College voor zorgverzekeringen) [Health Care Insurance Board]
	▪ Dutch Diabetes Association
	▪ Menzis
	▪ Netherlands Breast Cancer Association (BVN)
	▪ UVIT
Germany	• Center for HTA & Public Health

Clinical expert

HTA | Payer | Patient | Clinician | Regulator

Participants (besides industry)-2

Sweden	▪ Breast Cancer Association (BRO)
	▪ Dental and Pharmaceutical Benefits Agency (TLV)
	▪ Medical Products Agency (MPA)
	▪ SKL (Sveriges Kommuner och Landsting) Landsting County Councils
United Kingdom	▪ Medicines and Healthcare products Regulatory Agency (MHRA)
	▪ National Health Service Primary Care Trusts (Derbyshire County, Redcar & Cleveland, Stockton-on-Tees)
	▪ National Institute for Health and Clinical Excellence (NICE)
Pan-European	▪ EUnetHTA (Observer)
	▪ EUROPA DONNA (Observer)
	▪ European Medicines Agency (EMA)
United States	▪ US Food and Drug Administration (Liaison)

Clinical experts

HTA | Payer | Patient | Clinician | Regulator

Design of the pilots

- Participants within their usual legal framework
- Most of them waived their usual fees
- SAWP (CHMP) followed their usual procedure and provided written advice
- No written advice from HTA/payers
- Availability of minutes
- Non-committing process

Feedback from the participants

- Non-sponsor participants: generally positive; good interactions; increased common understanding

- Sponsor: generally positive;

  (e.g.) areas that the company would approach differently in light of the advice received:

  - Scientific basis for the medicine's mechanism of action and link to biomarkers
  - Approach to patient segmentation
  - Proof-of-concept study design

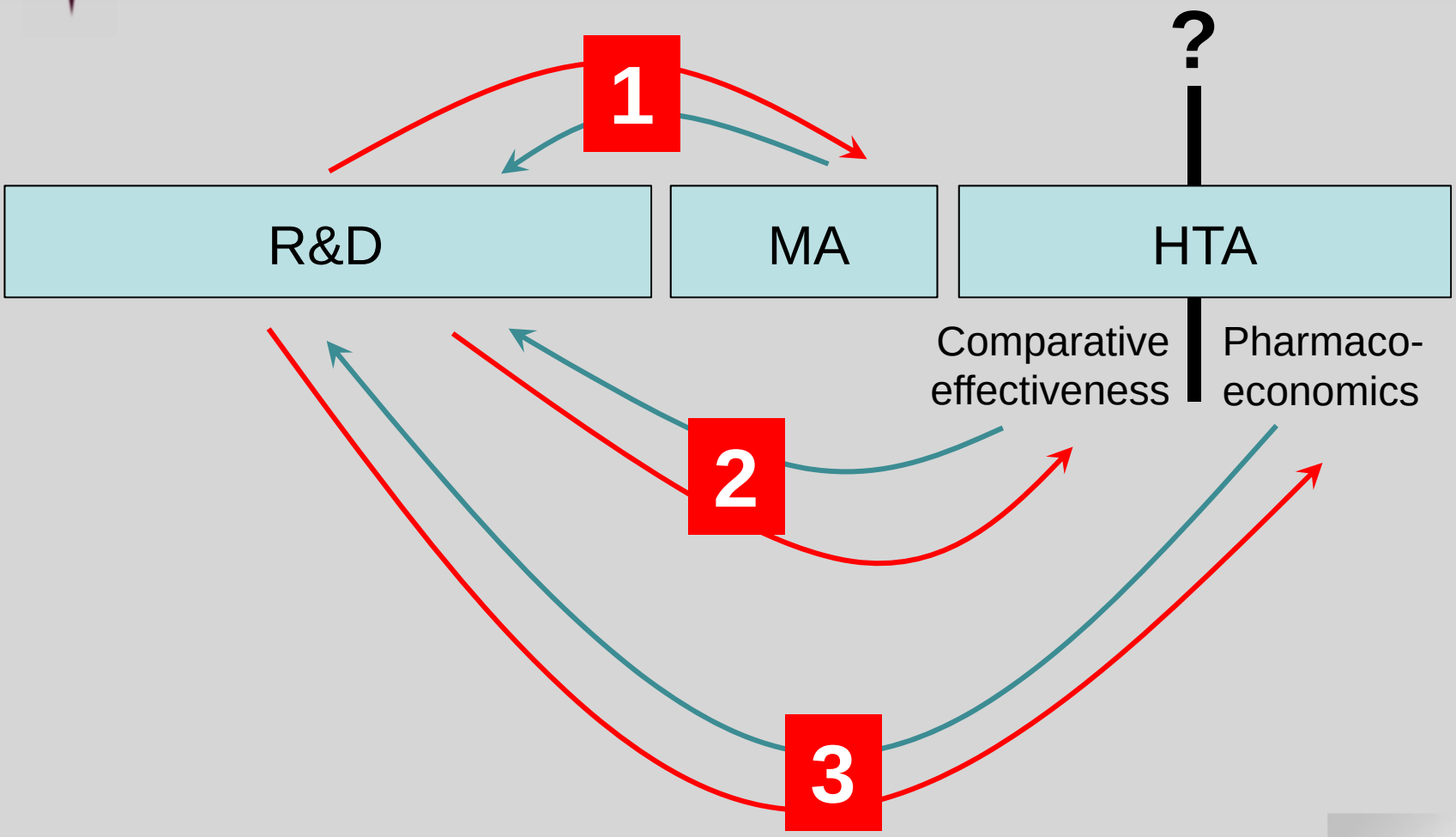
Personal views on the pilots

Problem	Consequence	Possible solutions
Early stage consultation	• High level of uncertainty • HTA/payers "out of their own comfort zones"	HTA/payers to consider the benefits of the procedure
No written advice from HTA/payers	Lack of harmonisation	HTA/payers to consider some (crossborder) commitment
No harmonised EU approach available to HTA/payers	Lack of harmonisation	• EUnetHTA initiatives • More joint advices • Direct EMA-HTA briefings
How to deal with economic aspects	(e.g.) Relevance of pharmacoeconomic models for each MS?	Different levels of involvement (SAWP - HTA - payers)

Some open questions

- Benefits to HTA/payers
- How to involve an EU-wide set of HTA/payers and expect some harmonisation
- Logistics
- Follow-ups
- Huge/increasing diversity of EU reimbursement systems

An evolving iterative process



The Future of Drug Regulations

The future of drug regulations

1. Industry, academia, regulators, payers and patients agree on the path to clinical benefit for any new drug under development: early and joint scientific advice
2. The data requirements are set out: proof-of-concept, efficacy, comparative data (as early as Phase II), relevant clinical outcomes
3. Industry commits to early no-go decisions
4. A consistent, quantitative approach to benefit-risk assessment is favoured –this is crucial in difficult cases
5. Post-marketing studies supported by governments and industry become a key part of the continuous benefit-risk assessment

Thank you !!