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Industry Perspective on CER and the impact of HTA in Europe

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- The views expressed herein represent those of the presenter and do not necessarily represent the views or practices of Amgen.

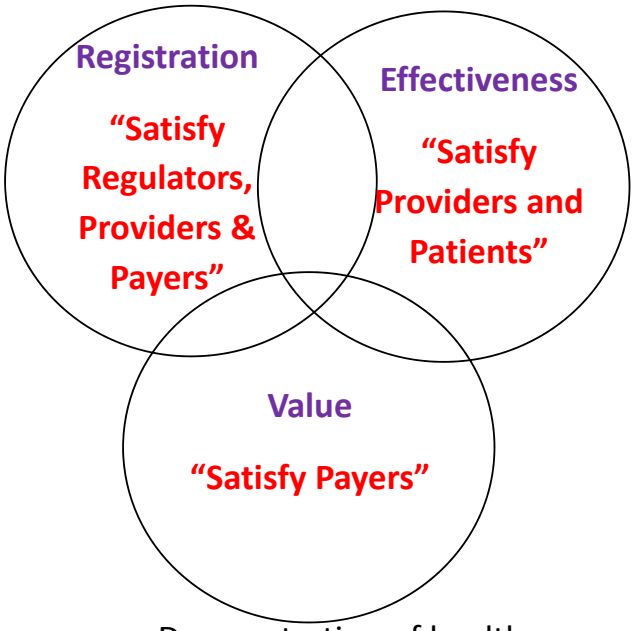
Agenda

- Evidence needs for regulators and payers
- Optimising product development programs for reimbursement success
- Comparative effectiveness research / relative effectiveness
- Impact of HTA in Europe
- Conclusions

EVIDENCE NEEDS FOR REGULATORS AND PAYERS

Three distinct sources of evidence

- Demonstration of safety and efficacy generated in randomized, controlled, and tightly monitored studies



- Demonstration of effectiveness in "real world" situations as well as additional endpoints of interest to providers
- Demonstration of health economic benefits of a drug, including quality of life

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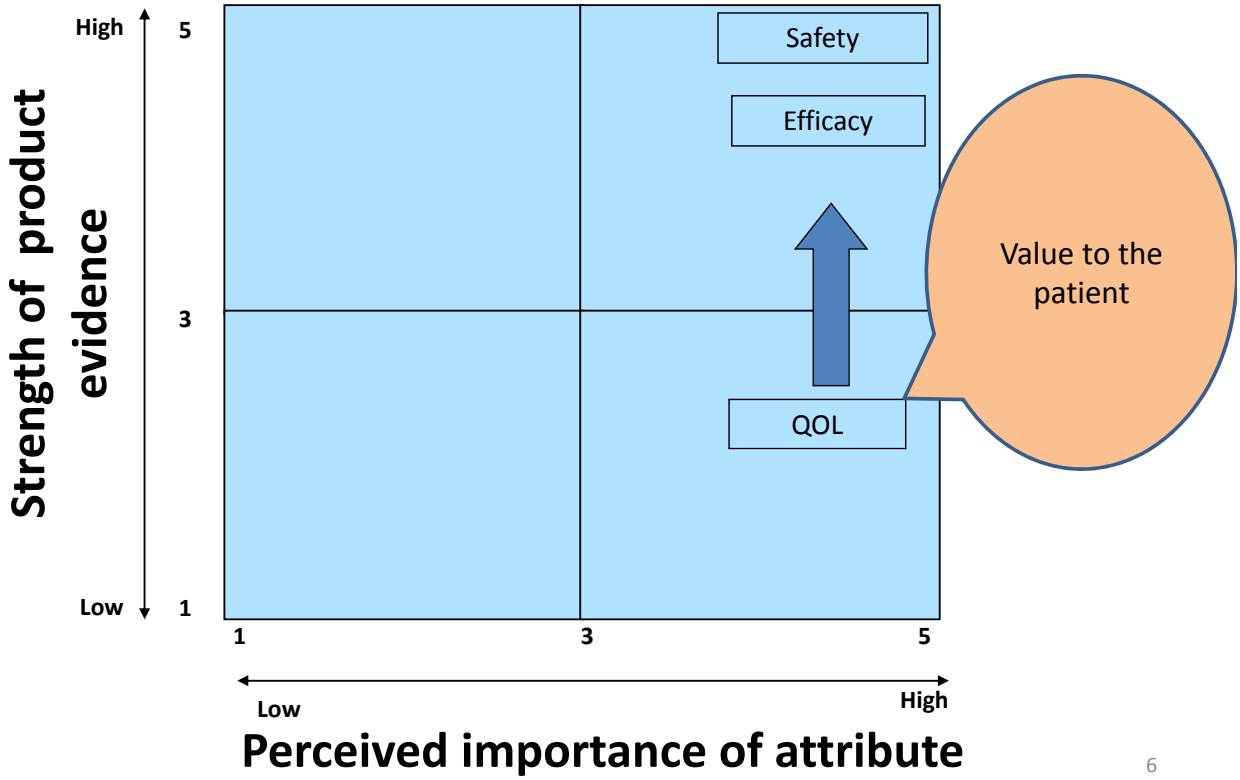
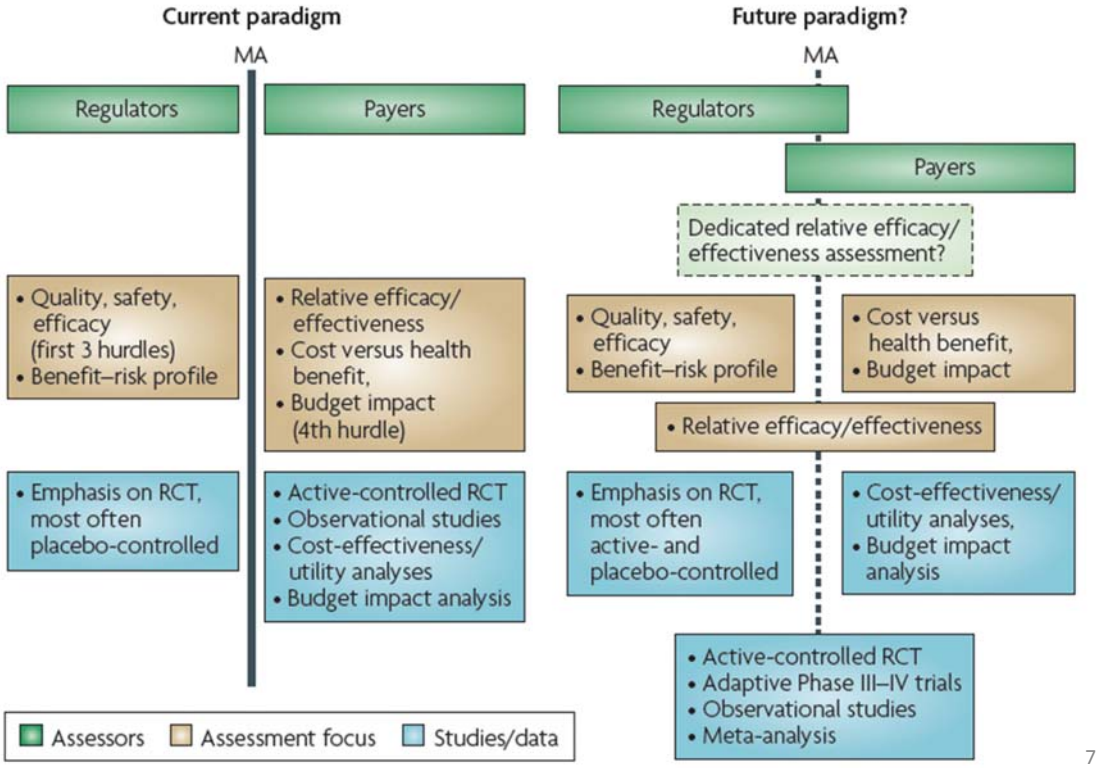
Source: "Medical Affairs Recommendations for the Commercialization Process" Oct 2006, Interviews Wes Daniels, Oct 2006, Synthesis Nov 2006

Value

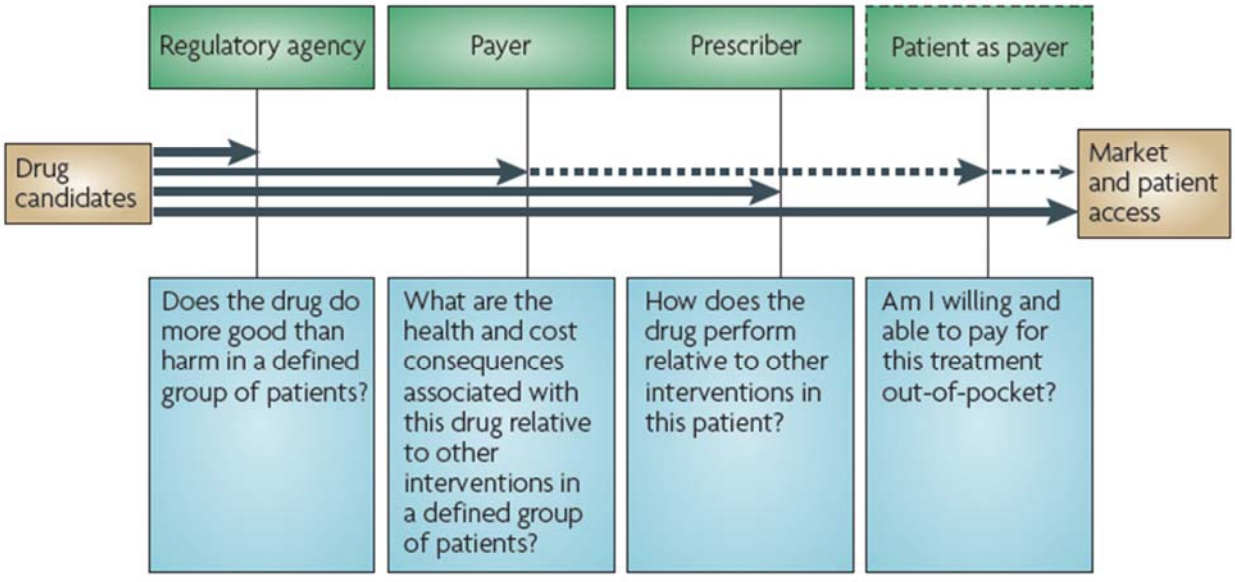


What evidence is sufficient?



Eichler et al, Nature Reviews 2010

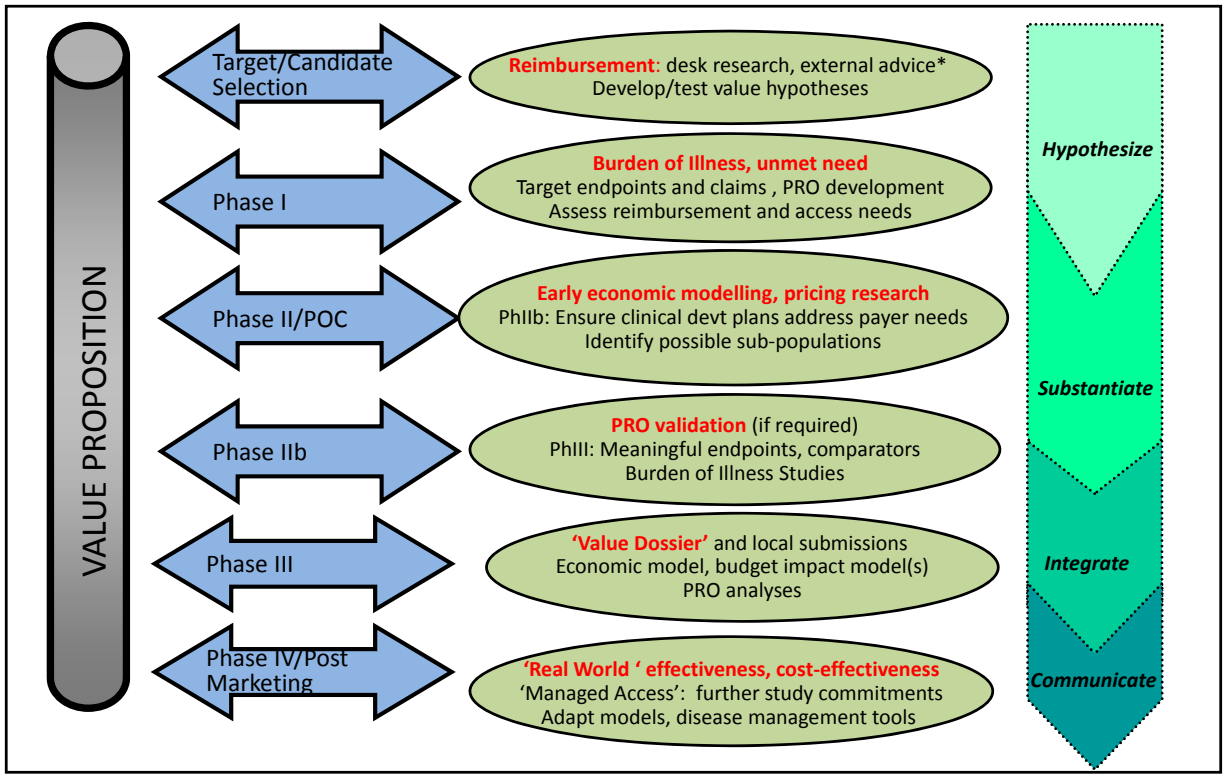
Decision makers on the road to market access



Eichler et al, Nature Reviews 2010

OPTIMISING PRODUCT DEVELOPMENT PROGRAMS FOR REIMBURSEMENT SUCCESS

Value evidence generation in development



Based on: Sollano JA, Kirsch J, Bala MV, Chambers MG et. al. Clinical Pharmacology & Therapeutics (2008); 84, 2, 263–26

**External advisors/payer input obtained iteratively throughout product development*

Value Evidence Generation during Product Development Program

- Planning a variety of studies
  - Burden of illness (observational)
    - Understanding epidemiology
  - Randomised Controlled Trials to demonstrate safety and efficacy (interventional)
    - Design considering regulatory and payer requirements
  - Chart reviews (observational)
    - E.g. Resource utilisation
  - Existing database analyses (observational)
    - E.g. Pharmacovigilance

Key clinical trial design features

- Populations/subgroups of interest
- Outcome Measures
- Comparators

COMPARATIVE EFFECTIVENESS RESEARCH / RELATIVE EFFECTIVENESS

Relative Effectiveness (RE)*

Objective

To develop principles, methodological guidance as well as functional online tools and policies for REA by identifying areas where methodological guidance is needed and by providing it, suggesting ways to integrate REA of pharmaceuticals as a special version of the Core Model. In addition to test and implement a REA of (a group) of pharmaceuticals in line with the core HTA development.

Deliverables

1) A methodological guidance that will be appropriate for the assessment of relative effectiveness of pharmaceuticals (Dec 2012)

2) A relative effectiveness assessment of a (group) of pharmaceutical(s) (Mar 2012)

*EUnetHTA [HTA network of agencies across Europe] Work Package 5 "Relative Effectiveness of Pharmaceuticals" EMA and EUnetHTA Joint Action collaboration on EPAR and RE (Feb 2010)

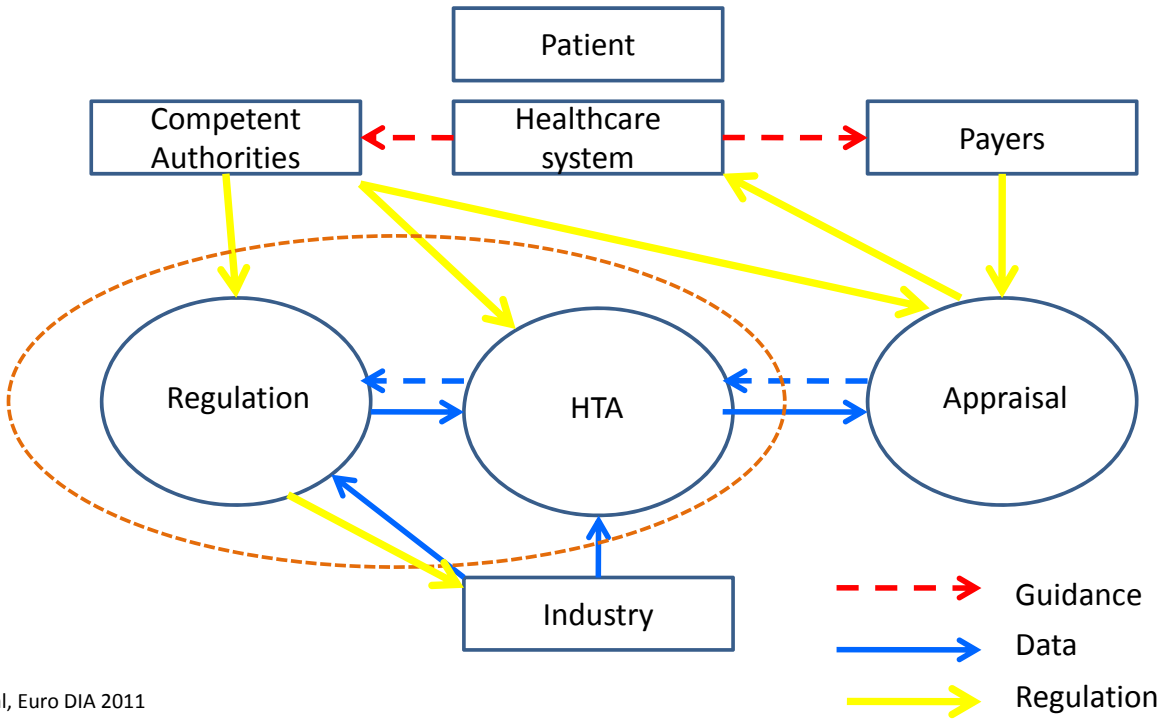
Study designs for assessing RE

Type of study	Advantages	Disadvantages
Active-controlled superiority- showing randomized controlled trial (RCT)	• High internal validity • May provide relevant relative efficacy (RE) information if comparator deemed appropriate	• Often requires large sample size • Only one comparator can usually be studied
Two-arm non-inferiority-showing RCT	• May be the only alternative available for demonstration of efficacy if placebo-controlled RCT considered unethical • Provides limited RE information	• May lack assay sensitivity and therefore internal validity
Active- and placebo-controlled RCT	• Most informative trial design • High internal validity	• Not achievable if placebo control considered unethical • Often requires large sample size
Pragmatic clinical trial	• High external validity • Demonstrates relative effectiveness	• Lower signal-to-noise ratio than conventional RCTs • Requires larger sample size • May mask small true differences between treatments
Common reference indirect comparison based on RCT information (network meta-analysis)	• Relatively easy and less expensive than RCTs • Useful in the absence of head-to-head RCTs	• Essentially non-randomized methodology • May be subject to unknown confounding variables
Observational studies	• May be conducted retrospectively or prospectively • Less expensive and time-consuming than RCTs • Large patient numbers can be observed	• Non-randomized information • Subject to high risk of confounding variables

Eichler et al, Nature Reviews 2010

IMPACT OF HTA IN EUROPE

Relationships in healthcare systems



Synthesise all available evidence

- Assessing relative effectiveness from RCT's
  - Increasing acceptance of Network Meta-Analysis - can increase uncertainty, depends upon similarity and consistency of evidence
  - Availability of data to investigate populations/subgroups of interest
- Assessing randomised vs observational evidence
  - Comparability, identification, description and reporting of biases and limitations
  - May have inconsistent results/conclusions

Understanding sources of uncertainty

- Quality of systematic review
  - Was there a pre-defined protocol, search criteria etc?
- Quality of clinical trials
  - How well were randomised trials conducted?
- Quality of observational research
  - Were confounders, selection bias and information bias minimised in design and analysis?

Quantifying uncertainty for HTA decision making

- Evidence synthesis forms basis for a 'Yes' or 'No' decision by payers
- Modelling and simulation used to
  - Consider wide range of potential scenarios
    - Vary assumptions
  - Extrapolate clinical and cost outcomes
    - Beyond clinical trial
- Uncertainty in whole evidence package must be explored and quantified to aid decision making

CONCLUSIONS

Design product development programs for regulators and payers

Include the needs of payers in clinical trial programs, essential for value evidence generation

Foster a strong collaboration between Health Economics, Clinical, Biostatistics and Regulatory

Clear roles and responsibilities ensure effective use of expertise, skills and resources

Best Practices

Effective communication of value evidence generation activities across the whole product life-cycle

Early engagement and cross-functional alignment on regulatory and market access hurdles

Being flexible and adaptable to a changing and evolving