Reimbursement Systems for Pharmaceuticals in Europe
Concept Mechanism and Perspective

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Part I. Reimbursement Concepts and Definitions

Health as a Good

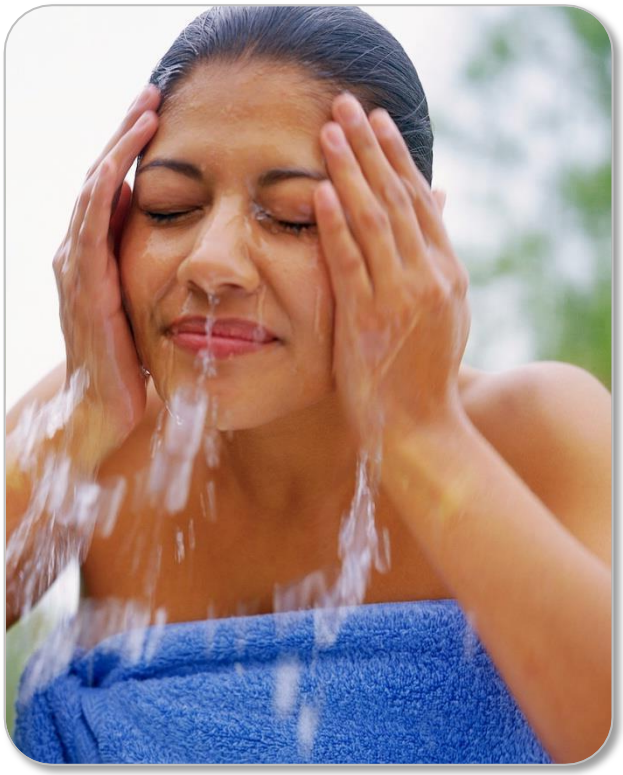
Healthcare Market Specificities

- We need health but we buy a proxy: healthcare
- We can't share health
- Health is not well regulated by the market
  - Buyer
  - Consumer
  - Payer

- Medicines are intended to produce health
- When funding medicines, payers intend to buy health production
  - There is *uncertainty* about the actual health produced by a medicine
  - There is *no uncertainty* about the cost of medicine

Determinants of Health

- Clean fresh water and hygiene
- Life style
- Environment Pollution
- Quality of food
- Genetic
- Education
- Social services
- Primary care



Pharmaceutical Spending in Europe

Widening the Gap?

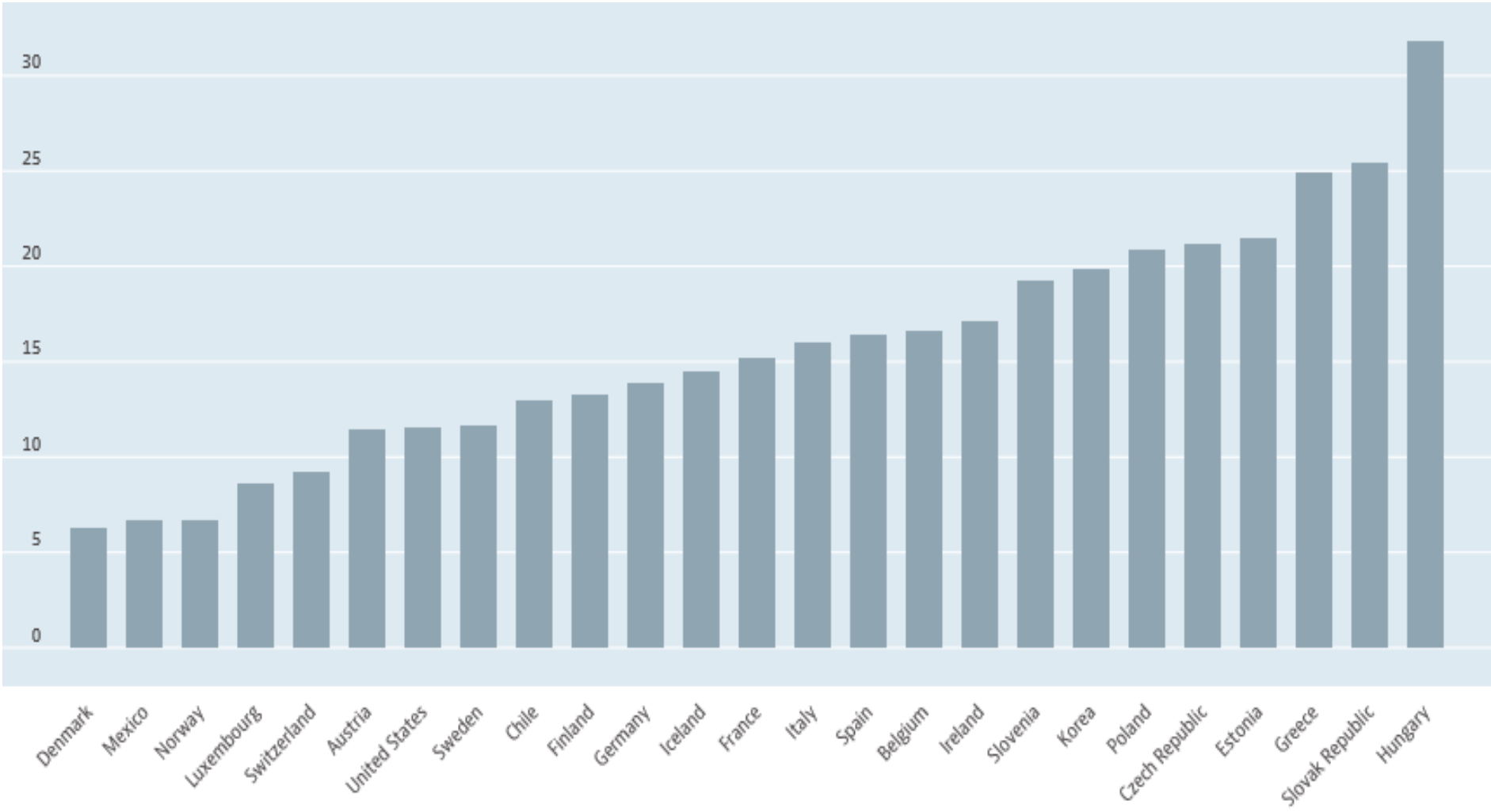
Unsustainable gap between healthcare expenditure level on one side and , affordability and demand on the other side

Current Situation

While the healthcare budget is decreasing

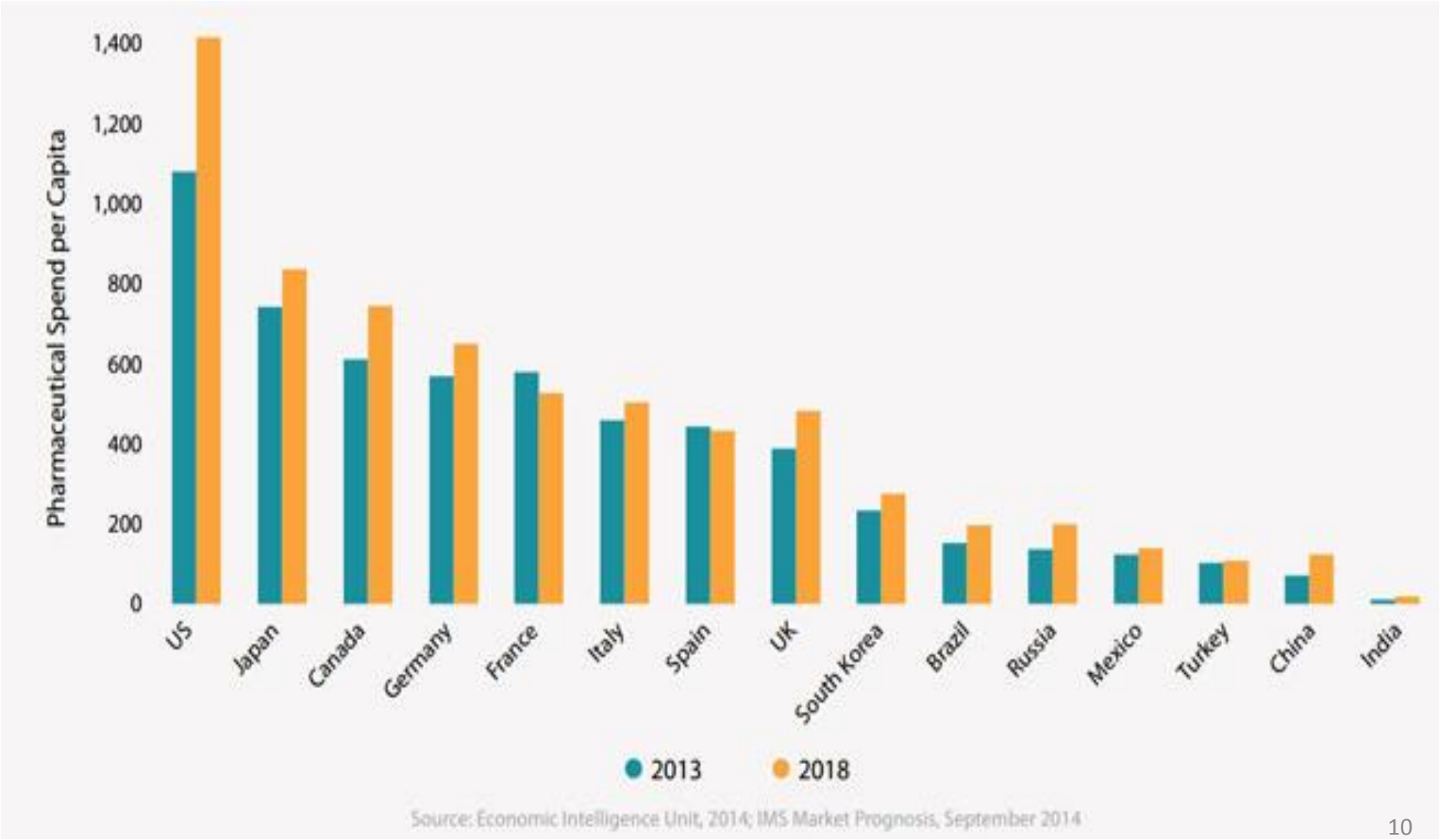
The number of very promising molecules in development is increasing

Pharmaceutical Spending
Total, % of health Spending (2012)

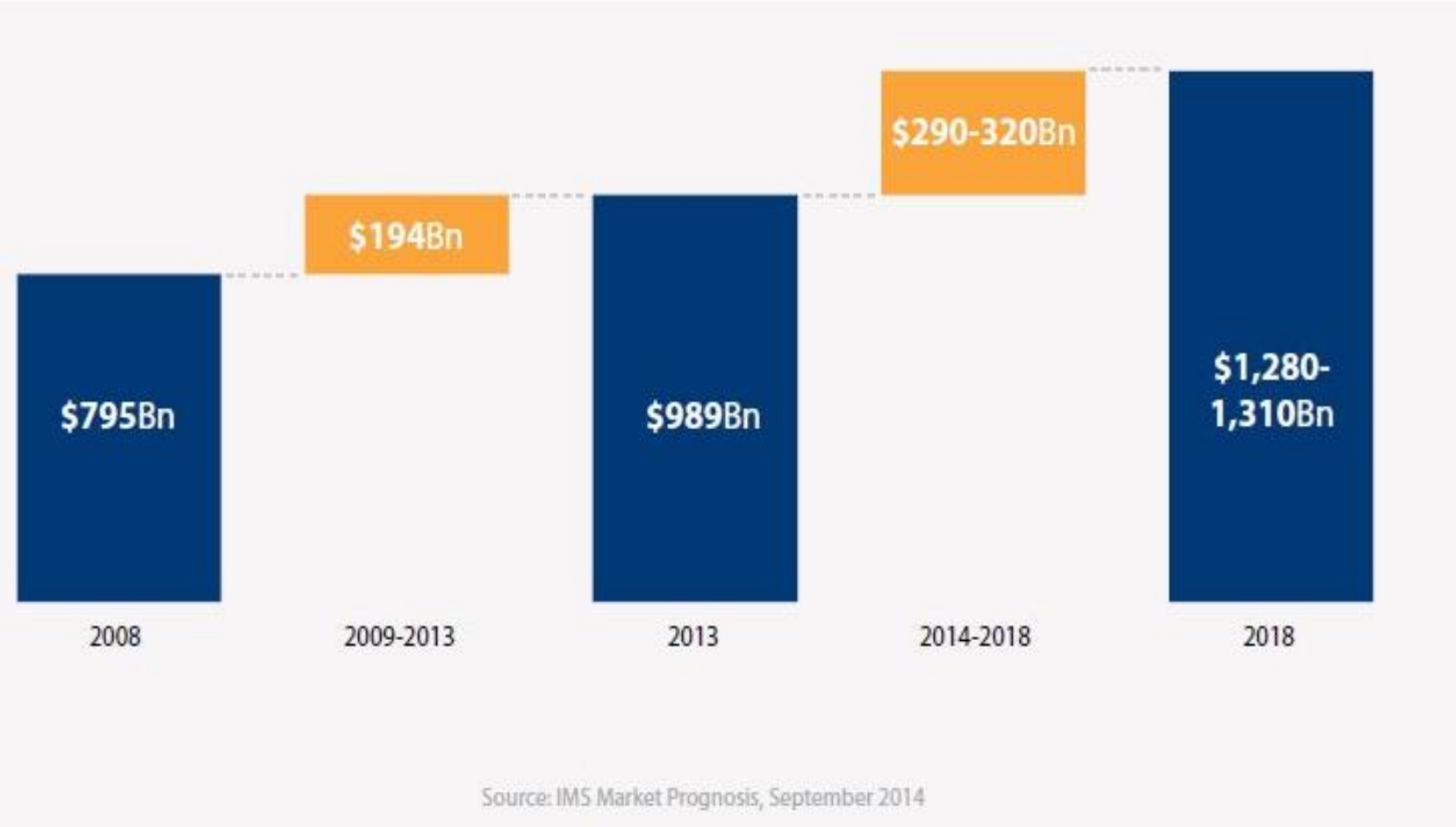


Source: OECD; https://data.oecd.org/healthres/pharmaceutical-spending.htm

Pharmaceutical Spending per Capita, 2013 vs 2018



Global Pharmaceutical Spending and Growth

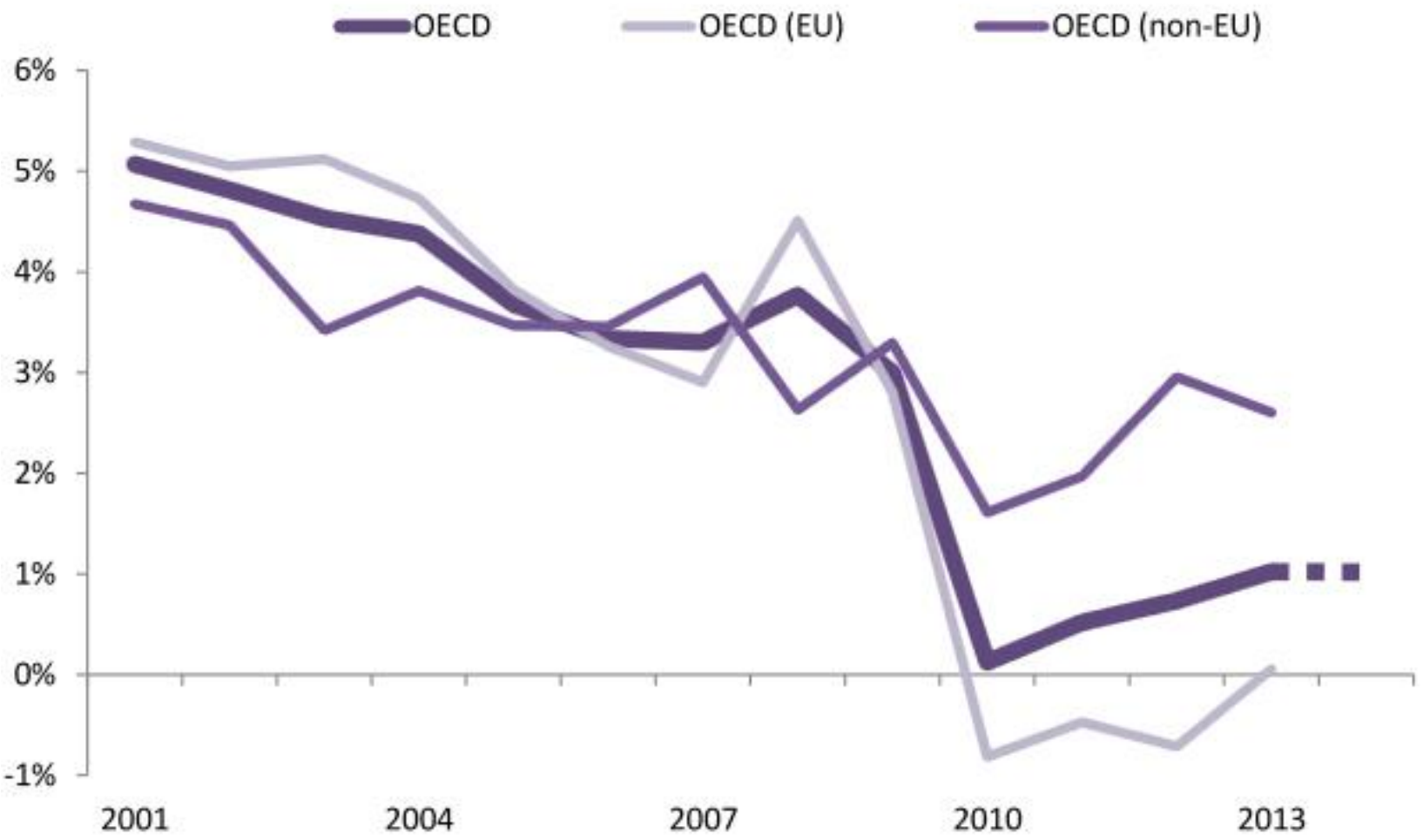


The Global Pharmaceutical Market is Expected to Grow to Nearly $1.3 Trillion by 2018

Geographic Distribution of Medicine Spending

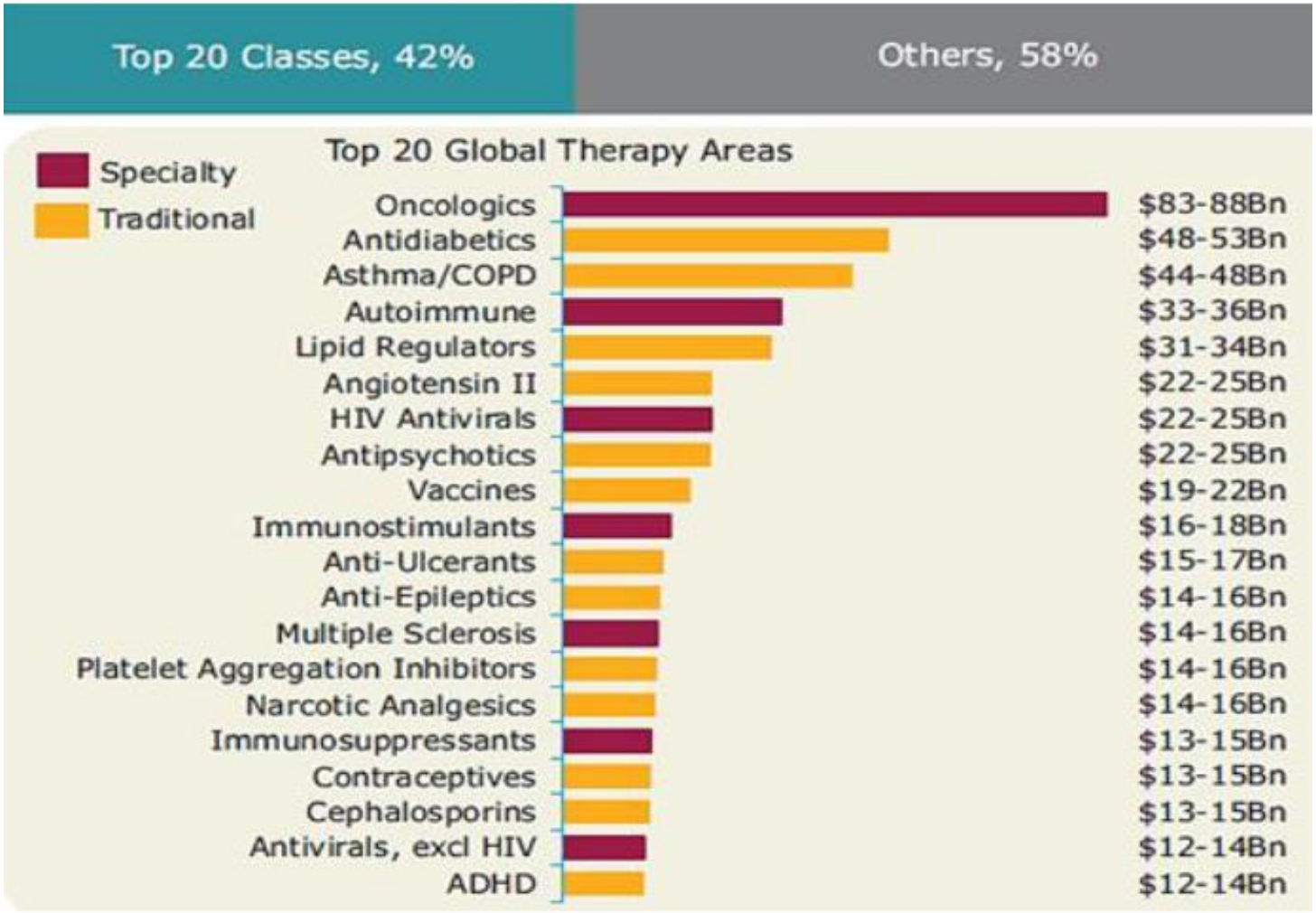
North America Continues to Contribute the Largest Proportion to Growth, but Asia is Gaining

Average Annual Growth in Per Capita Health Spending, in Real Terms, 2001-2014



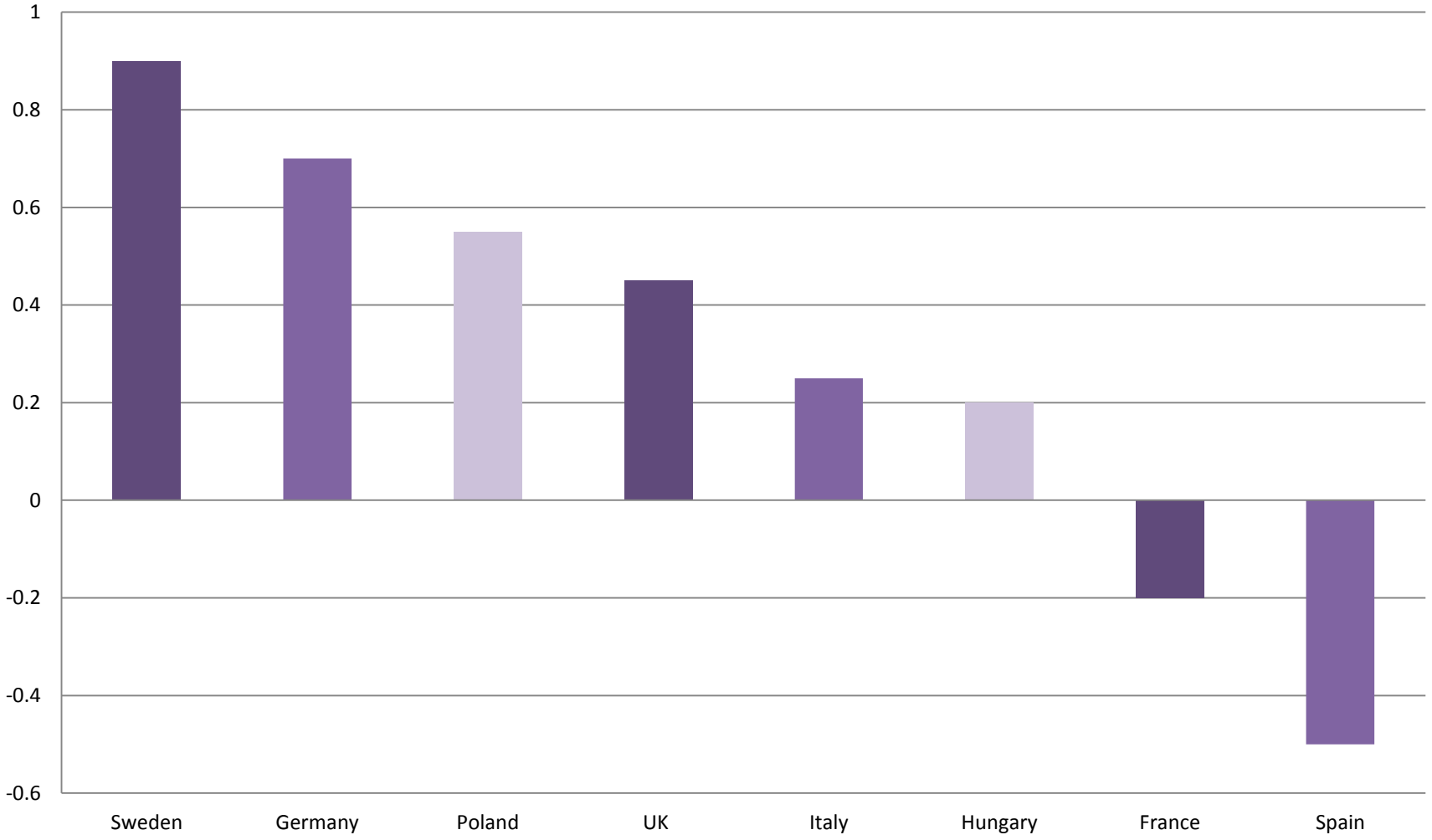
OECD; Organisation for Economic Co-operation and Development
Source: OECD Health Statistics 2015

Global Project Spending on Medicines by 2016



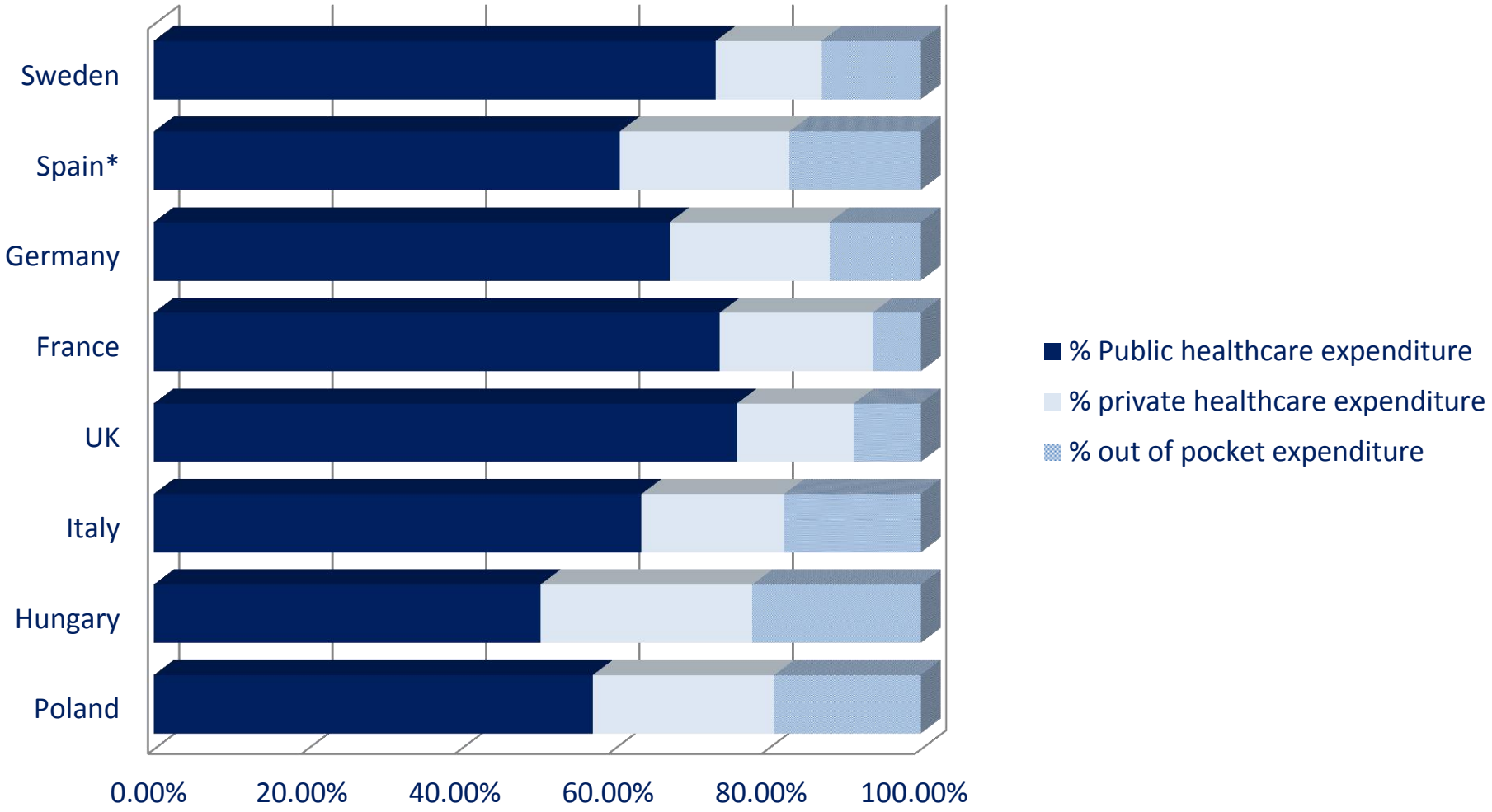
Source:Vogler S, Zimmermann N, Habl C, Piessnegger J, Bucsics A. Discounts and rebates granted to public payers for medicines in European countries. South Med Rev. 2012;5(1):38–46

Change in public spending on health as a share of total public (government) spending, 2007–2011



Source: Thomson S, Figueras J, Evetovits T, Jowett M,Mladovsky P, Maresso A et al., eds (2014). Economic crisis, health systems and health in Europe: impact and implications for policy. Maidenhead: Open University Press.

Healthcare expenditure in 2013 (US$ per capita)



*Spain healthcare expenditure in 2011

Source: OECD data on healthcare expenditure in 2013

Resource Allocation under Budget Constraint is the Issue

All is About Affordability

- US society accept to pay increase in life expectancy of 1.2 months $80,000
- By extrapolation survival of 1 year is valued at $800,000
- 550,000 Americans die of cancer annually
- To extend their life by one year 440 billion would be needed
- Even US will not afford it

The Oncology Tsunami

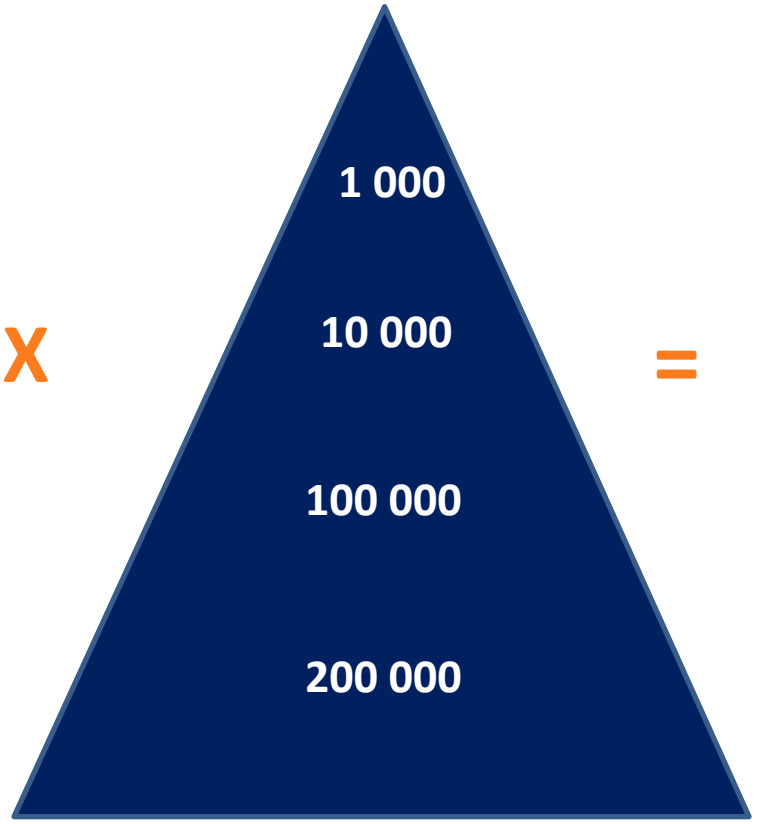
- 10 years ago, they were one blockbuster cancer drug; today more than a dozen
- Pipeline is filled with hundreds of targeted cancer drugs that will reach the market like a tsunami
- Targeted cancer drugs systematically expand indication

Investing in oncology means depriving patients suffering from other diseases access to effective medicine and prevent channeling public funding to other critical area that affect population health (social, education, environment, etc)

The Reverse Blockbuster Pyramides

GP Product	1 00 000
Specialist product	100 000
Orphan	10 000
Ultra-orphan	5 000

X



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BLOCKBUSTER

Orphan drug is the other pending tsunami with a couple of thousand of designated orphan drugs

EBM used by HTA Will NOT Help Containing the Cost

"Some fear that evidence based medicine will be hijacked by purchasers and managers to cut the costs of health care. This would not only be a misuse of evidence based medicine, but suggests a fundamental misunderstanding of its financial consequences. Doctors practicing evidence based medicine will identify and apply the most efficacious interventions to maximize the quality and quantity of life for individual patients; this may raise rather than lower the cost of their care."

(Sackett et al, BMJ, 1996)

Is Incremental Cost Effectiveness Ratio The Solution?

Could Cost Effectiveness Resources Allocation?

Drug	ICER ($ / QALY)
A	40,000
B	53,300
C	57,100
D	125,000

Could Cost Effectiveness Help Allocating Resources?

Drug	Health Gain (QALY)	ICER ($ / QALY)
A	250	40,000
B	300	53,300
C	70	57,100
D	80	125,000

Need for Budget Impact?

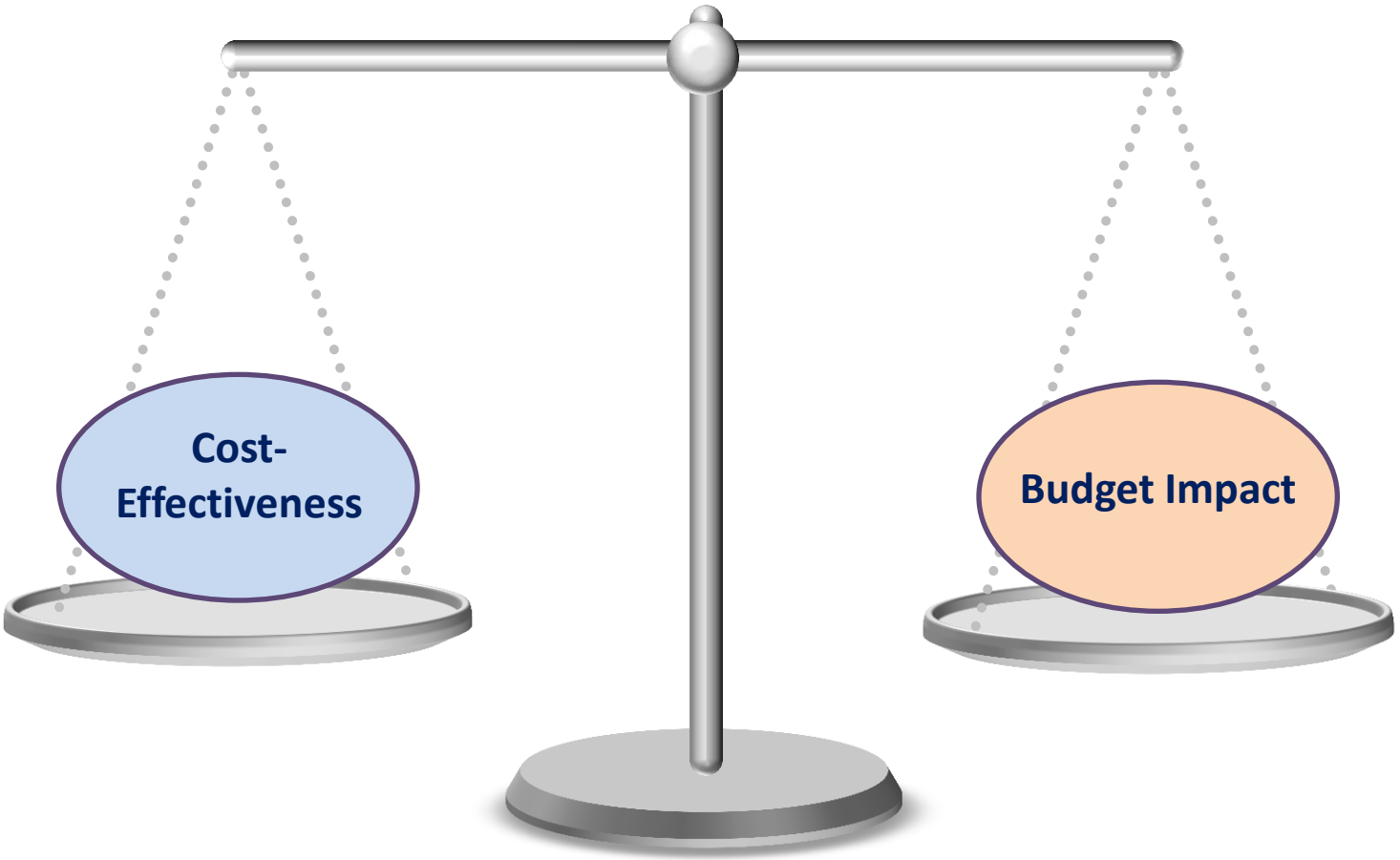
Drug	Health Gain (QALY)	Cost (m$)	ICER ($ / QALY)
A	250	10	40,000
B	300	16	53,300
C	70	4	57,100
D	80	10	125,000

Affordability Drive the Decision

Drug	Health Gain (QALY)	Cost (m$)	ICER ($ / QALY)
A	250	10	40,000
B	300	16	53,300
C	70	4	57,100
D	80	10	125,000

Assume your budget is 20 m$

From Cost-Effectiveness to Budget Impact



From Price to Value and Incremental Value

Innovation Pillars for Pharmaceuticals

1. Prevent copy cat
   - Patent
   - Data protection

2. Value-based pricing
   - Often unknown and source of multiple confusion

Value-Based Pricing

Value-Based Pricing or Value optimized pricing is a business strategy. It sets selling prices on the perceived value to the custumer, rather than on the actual cost of the product, the market price, competitors prices, or the historical price."

Consequences

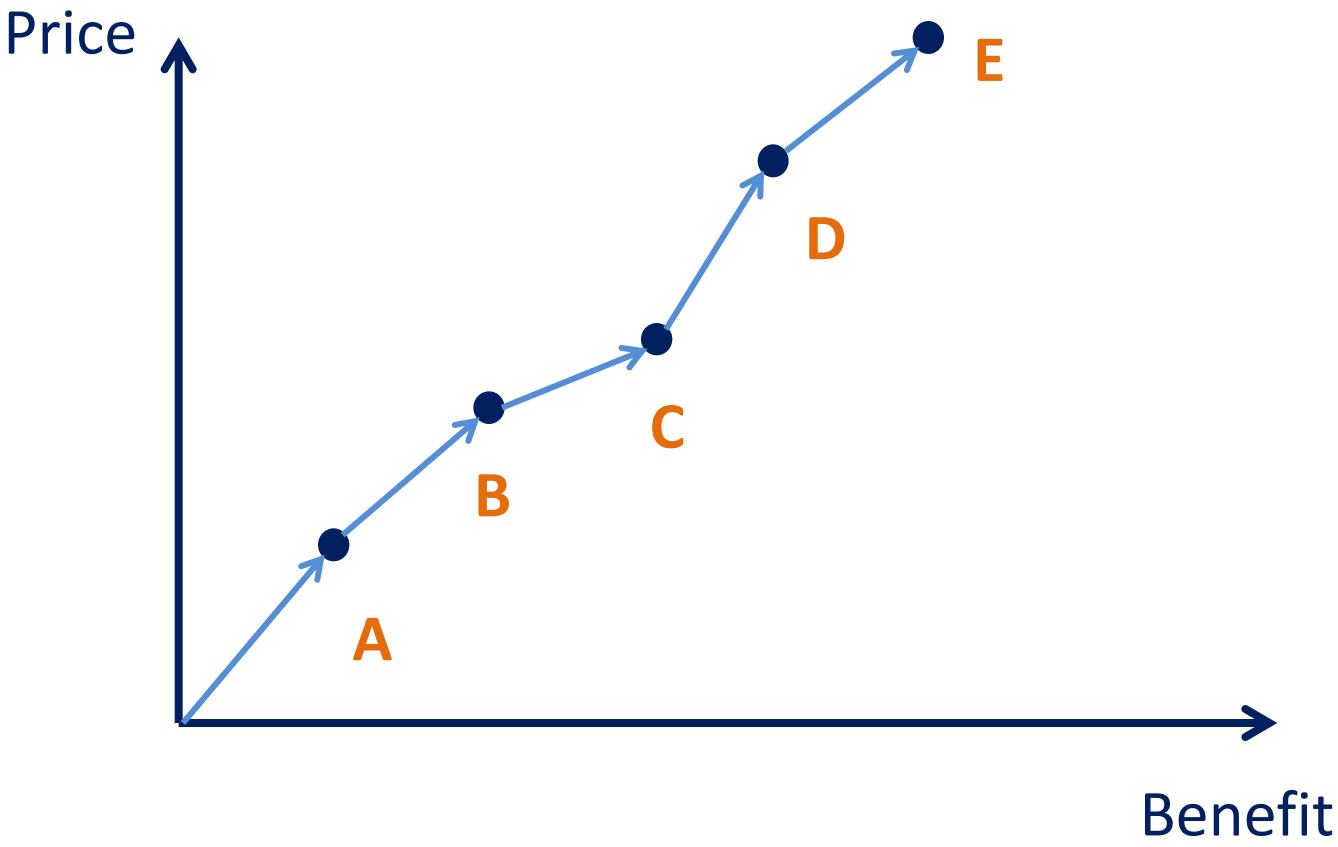
1. How to link value perceived and value delivered?
2. Value depends on how customers appreciate it
3. Value appreciation may evolve over time

What is Value?

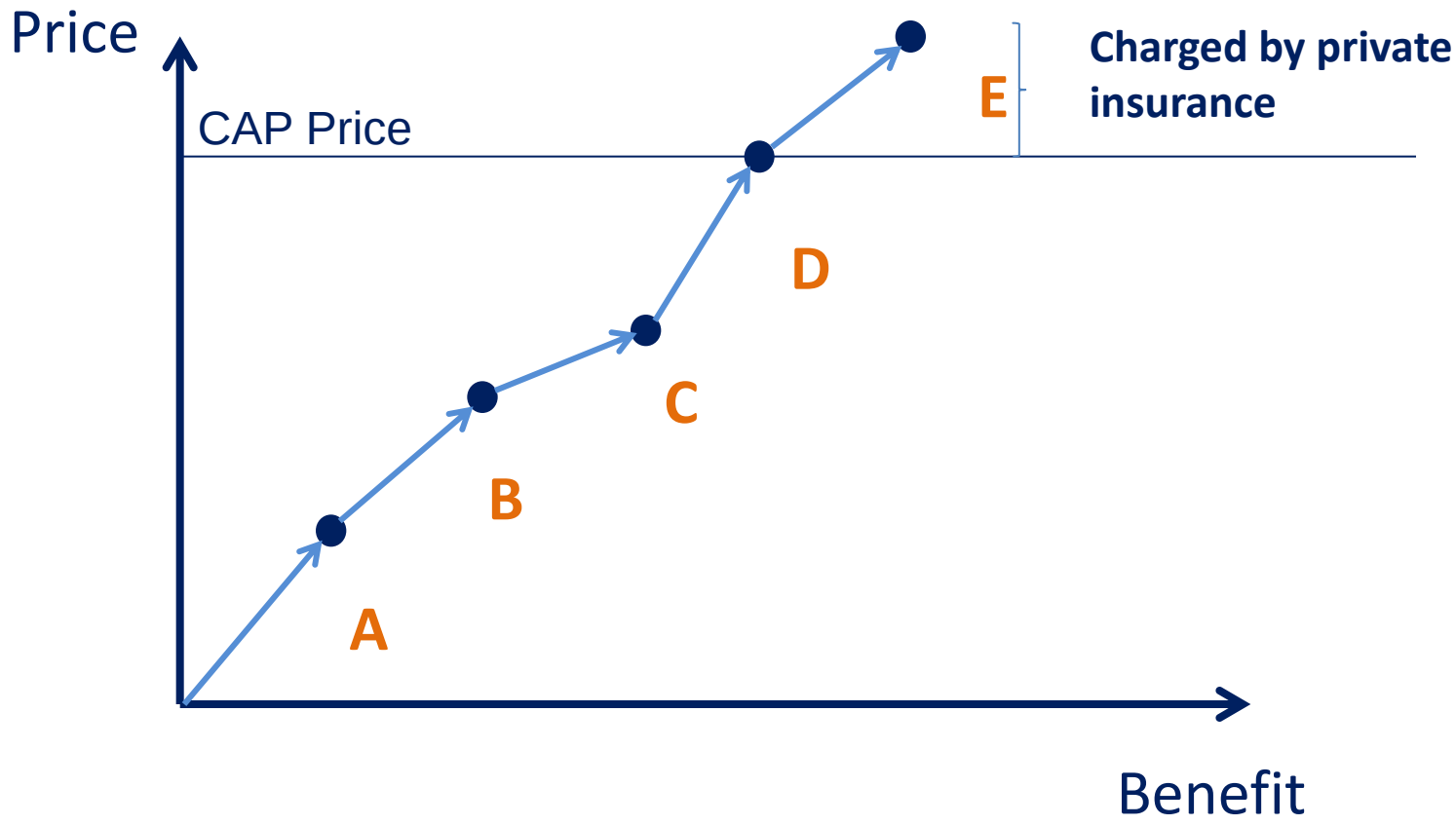
"**Price**
is what you pay
and **value**
is what you get"

Warren Edward Buffett is an American business magnate, investor and philanthropist. He is the most successful investor of the 20th century.

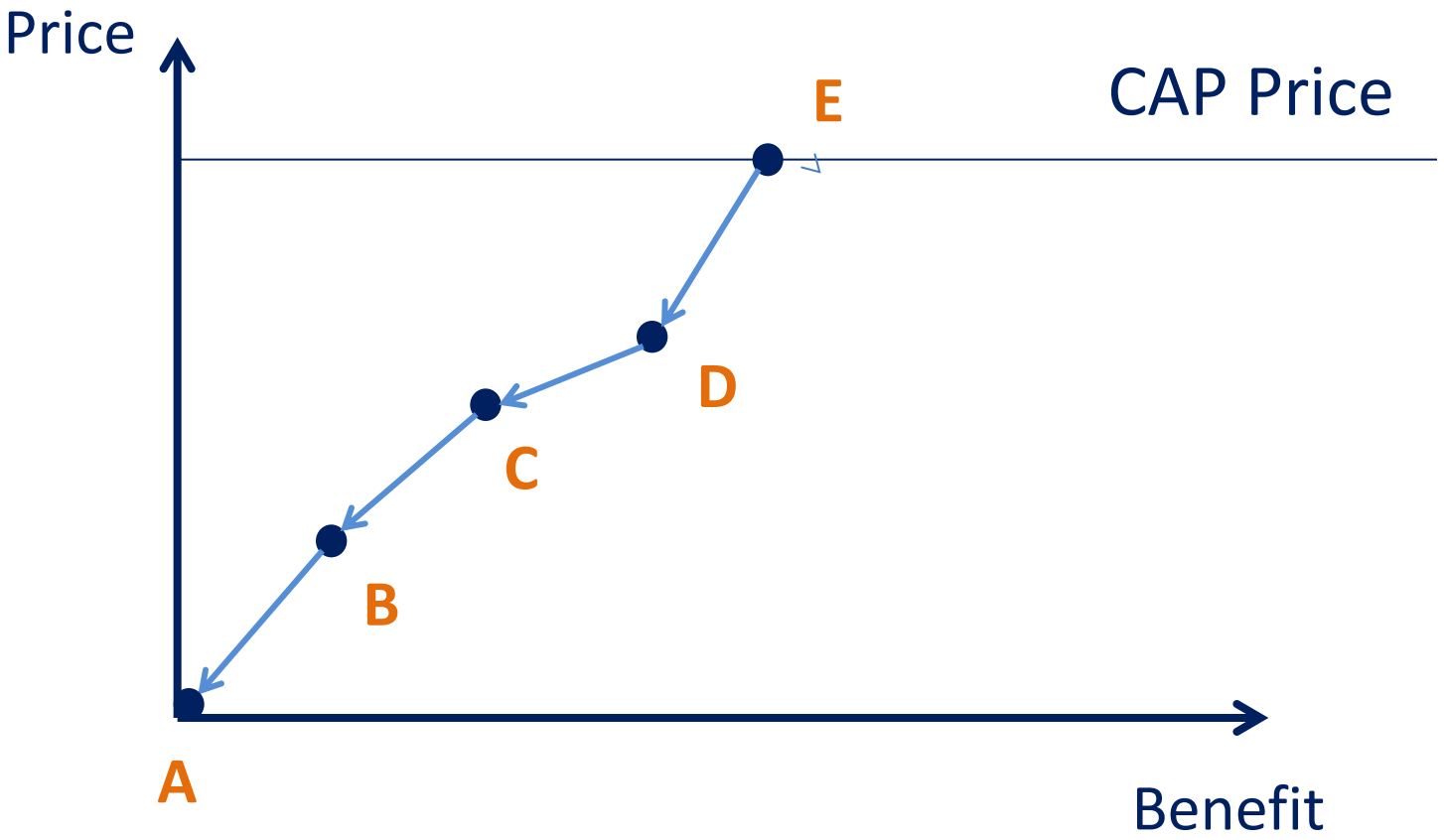
VBP With No CAP Price



VBP with CAP Price, Over Costs Charged by Private Insurance



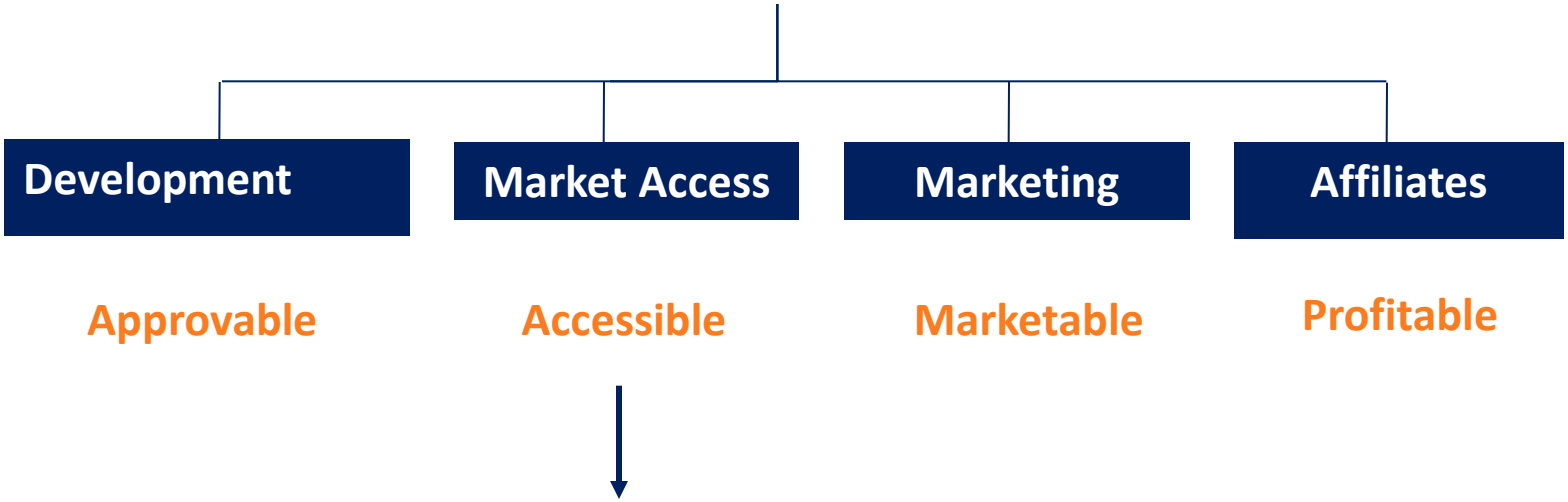
VBP with CAP Price Managed by NHS



Market Access Paradigm

Pharmaceutical Business Environment

Drug Value Chain



Market Access is becoming more and more a crucial element of the value chain

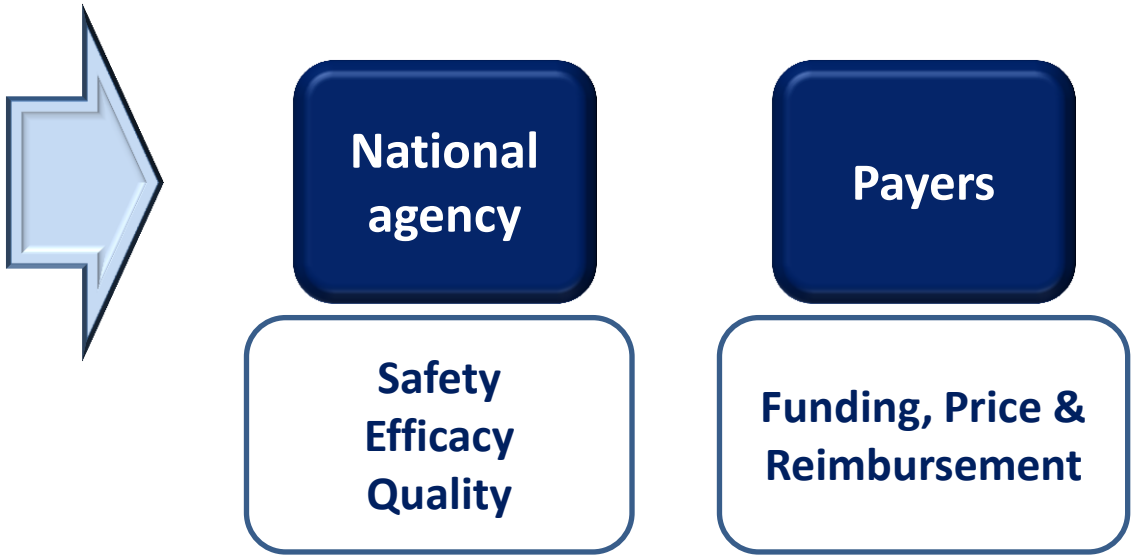
Market Access is Different From Regulatory

Regulatory		Market Access
Fulfil the requirements of market authorisation	⇔	Negotiate with payers
Meet criteria for efficacy, safety and quality	⇔	Determine trade-offs between price and market access to achieve optimal return on investment
Deal with certainty	⇔	Deal with uncertainty
Transparent regulation	⇔	Not transparent, fast changing rules
Global	⇔	National to local

Market Access Is Different From Marketing

Marketing		Market Access
Perception based	⟺	Evidence based
Audience not accountable	⟺	Price sensitive audiences
Opinion leaders are Key	⟺	Multiple stakeholders influence
Innocent until proved guilty	⟺	Guilty until proved innocent

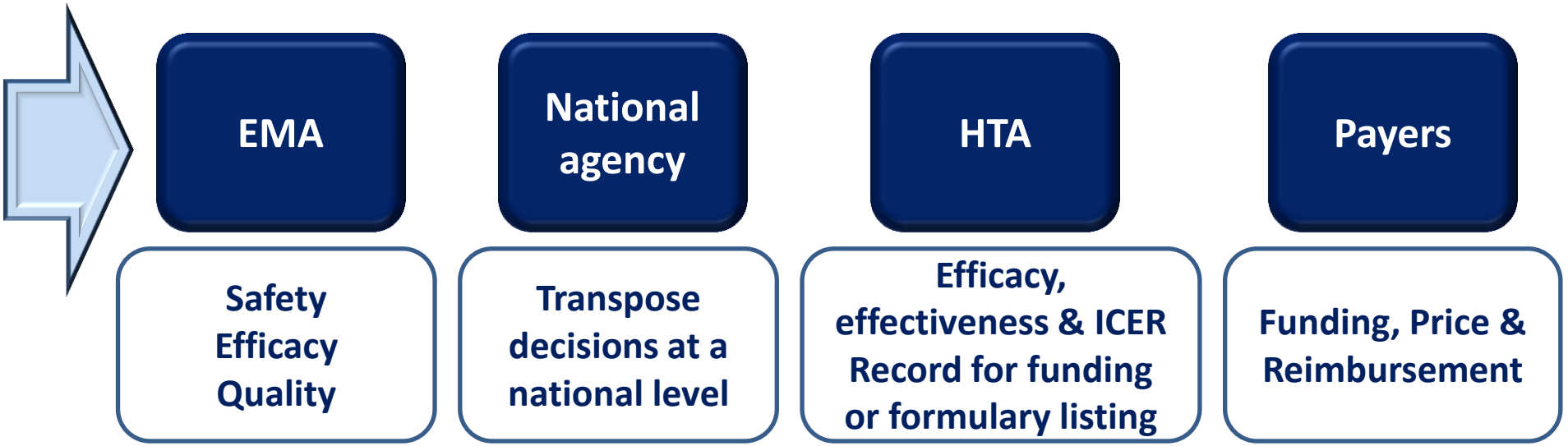
From Approval to Funding



From Approval to Funding

National agency	HTA	Payers
Safety Efficacy Quality	Efficacy, effectiveness & ICER Evaluation for funding or formulary listing	Funding, Price & Reimbursement

From Approval to Funding



Payers are Heterogeneous

Who are the Payers? (1/3)

Any price sensitive audience who impacts price, reimbursement, access or adoption is a payer

- Could be directly or indirectly incentivised
- Could be decision maker or not
- Could be a prescriber or not
- Acting for his own organization or not

Who are the Payers? (2/3)

Who are the Payers? (3/3)

The Payer's audience is:

- Growing fast
- Heterogeneous
- With diverse perspectives

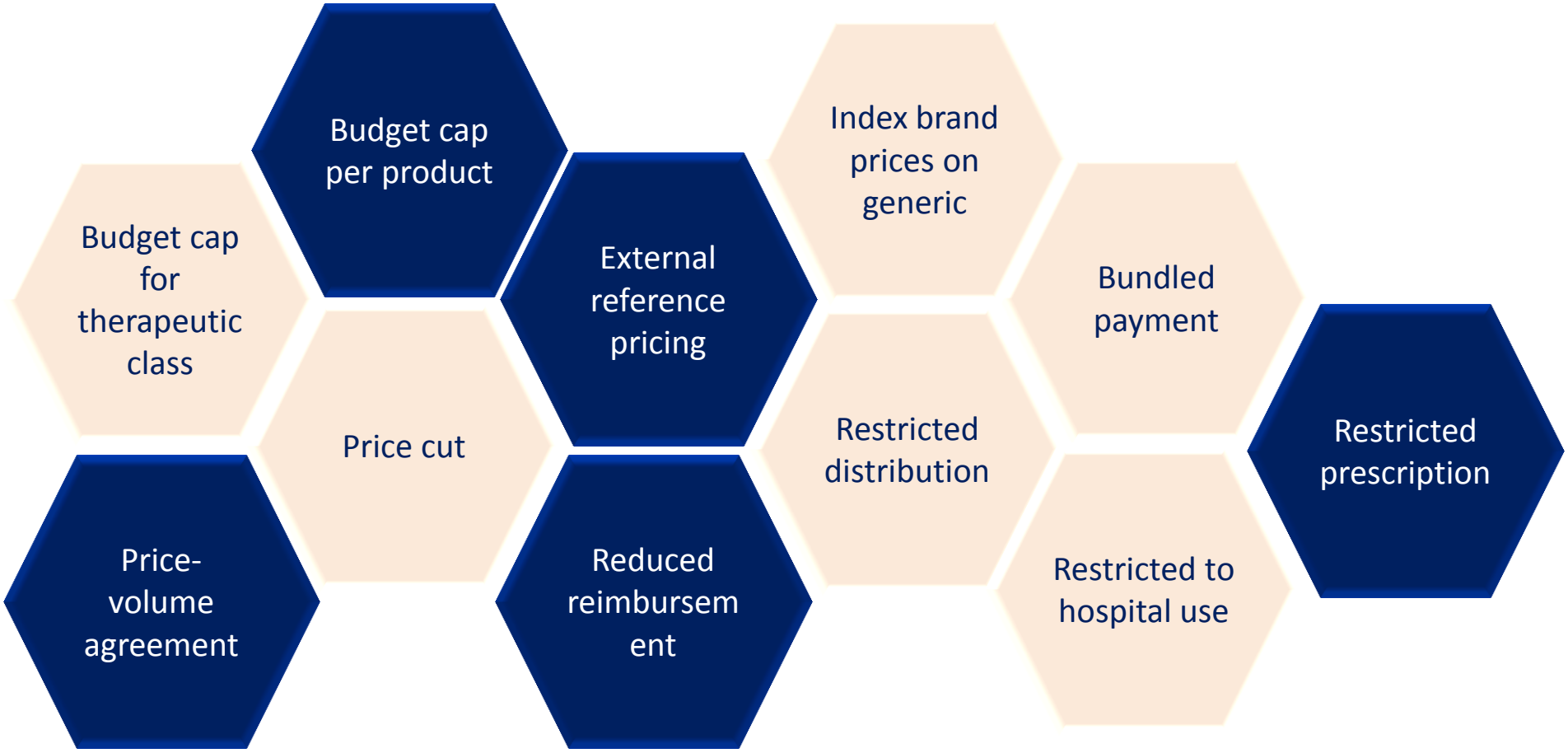
Approach and value proposition needs to be adapted to the type of payer

What are the Payers Doing?

- Because affordability is the issue
- Because payers have limited resources
- Because the demand increases very fast
- Because the offer increases fast

Payers spend their time containing costs through increasingly complex and irrational but sometimes (very) effective measures

Cost-Containment Measures



General P&R Policies

Drug Reimbursement Policies

Health Technology Assessment (HTA)

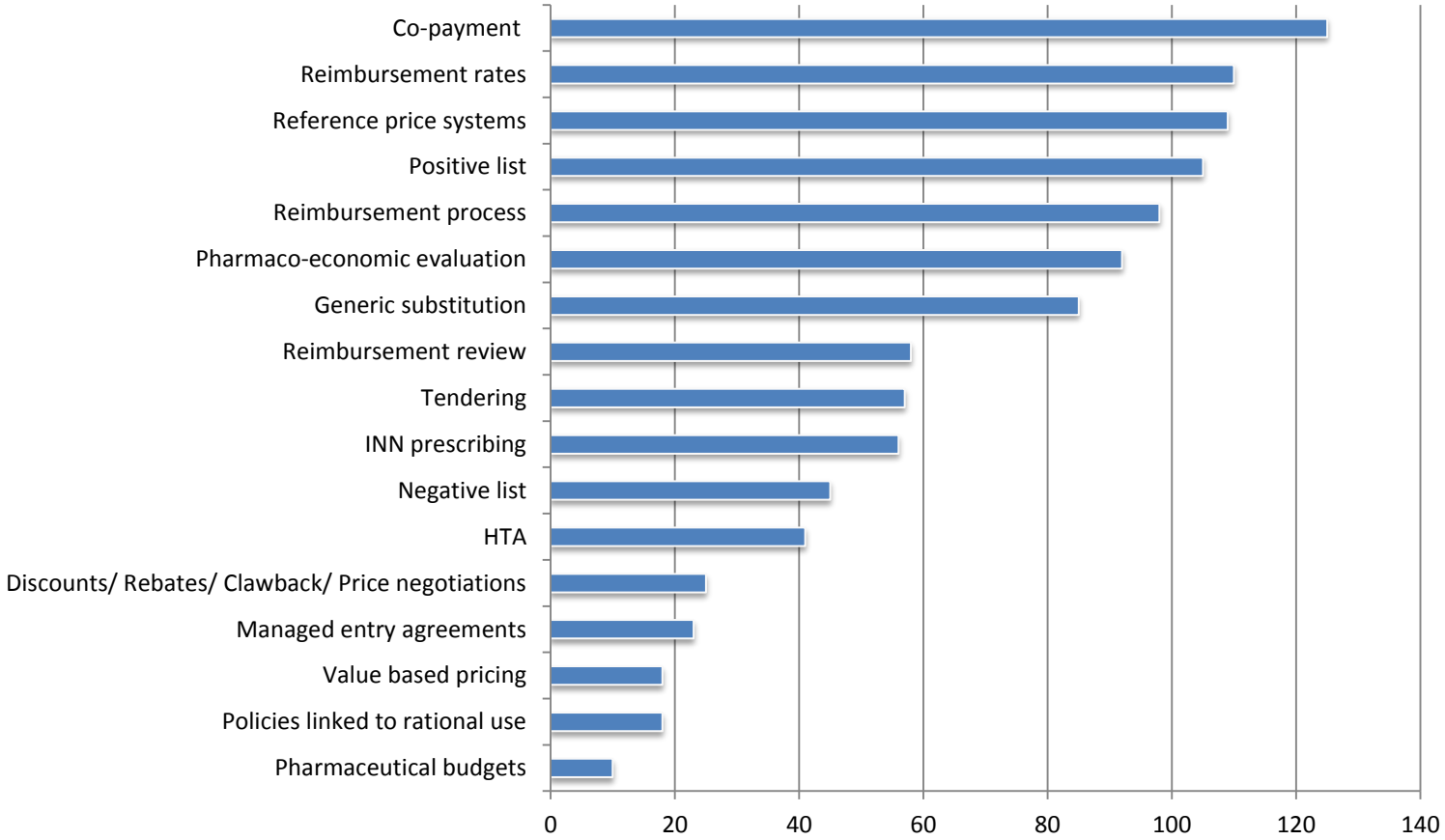
- Conditional reimbursement on meeting specific clinical and/or economic (cost-) effectiveness criteria

Positive/ negative lists

- All EU Member States have positive lists specifying which specific pharmaceuticals are reimbursed
- A few countries have negative lists, excluding specific pharmaceuticals from reimbursement

Reimbursement Policies in EU Countries

Systematic literature review identified policy measures related to pharmaceutical reimbursement in EU Member States (including Croatia) and the EEA countries (Iceland, Lichtenstein, Norway) from 1995-2013



Source: Vogler S, Zimmermann N, Habimana K, Study of the policy mix for the reimbursement of medicinal products,january 2014, Vienna

Price Regulation Policies

International reference pricing

- Applied in 26 EU Member States (except Sweden and UK)
- Benchmarks product prices in one country against prices of the same product in a selected basket of other countries

National reference pricing

- 20 EU Member States set the price to be paid by the public payers by comparing prices of equivalent or similar products in a chemical, pharmacological or therapeutic group
- The patient pays the difference between the retail price and the "reference price", in addition to any co-payment arrangement

Price updates

- Regularly according to pricing regulations

Expenditure Control Policies

Discounts/ rebates	• Imposed upon manufacturers and pharmacists, such that they have to return a part of their revenue
Clawback	• Applied to pharmacies, requiring them to pass a part of their turnover to third party payers
Payback	• Requires manufacturers to pay back a share of their revenue, if a pre-specified budget ceiling for public pharmaceutical expenditures is exceeded
Risk-sharing arrangements	• Financial or performance-based schemes which trigger lower prices or refunds from the manufactures if pre-agreed targets are not reached.
Price freezes and cuts	• Prices are frozen or cut by law or as an outcome of a negotiated agreement
Public tendering	• Currently, the Netherlands and Germany are well known examples for ample use of public tendering

A Matter of Culture Across Countries

France

- **Objective**
  - Secure all products gain access at the right price
- **Process**
  - Driver: Public health relevance of benefit over the next best alternative
  - Method: Single double blind reference randomized clinical trial
    - Effect size
- **Impact**
  - Gate-keeper for price and reimbursement

United Kingdom

- **Objective**
  - Obtain rational allocation of resources
- **Process**
  - Driver: Maximization of efficiency of the health care output
  - Method: Cost utility
  - Threshold is £ 20,000/QALY
- **Impact**
  - Recommendation for prescriber
  - Formulary listing

Germany

- **Objective**
  - Obtain savings on drug spending with no impact on safety/efficacy
- **Process**
  - Driver: Same effect same price (Jumbo group)
  - Method:
    - Meta-analysis
    - Efficiency frontier
- **Impact**
  - Reimbursement decreased

Other Countries Fall in Between

- Sweden
  - Between UK and Germany
- Canada
  - Between France and UK
- Etc.

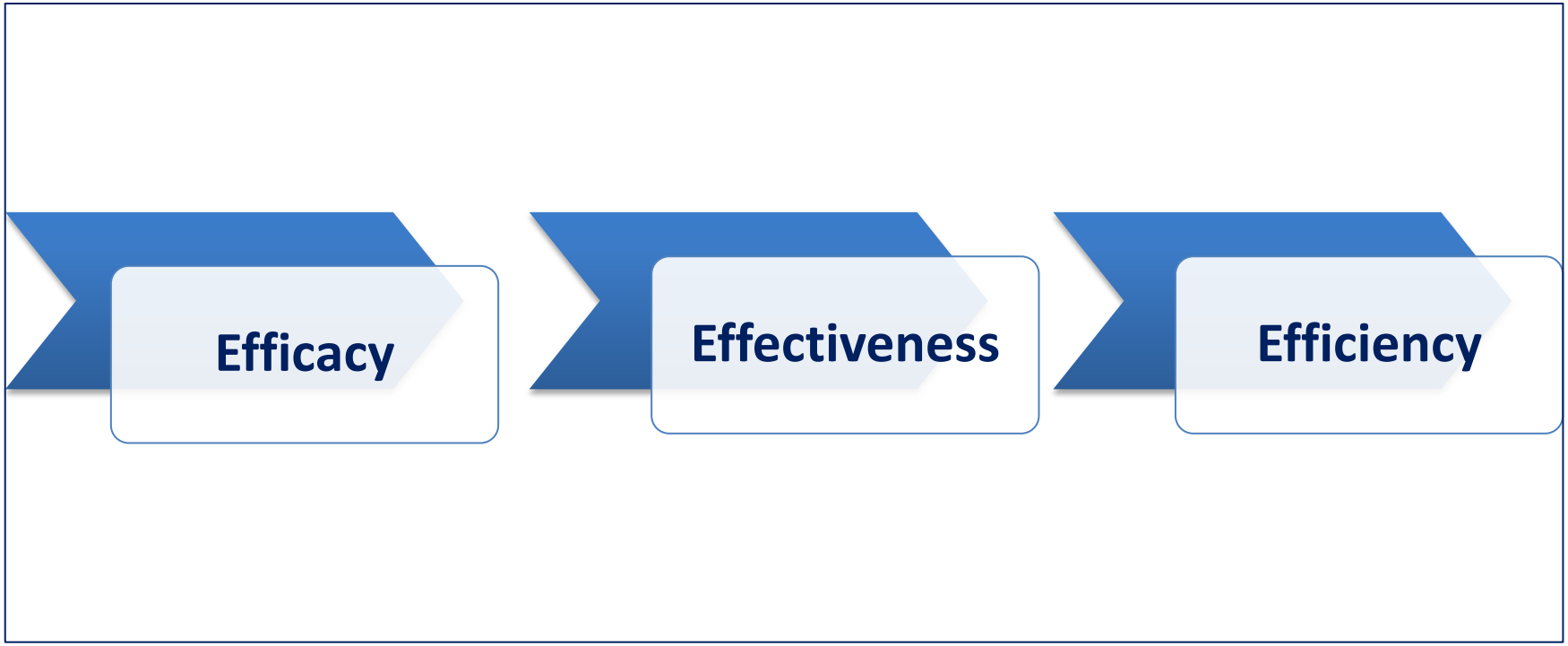
HTA & Payers resistance is driven by real life transferability and generalisability

Major Source of Uncertainty/Risk

Major uncertainty:

Transferability of the clinical trial results to the real world setting;

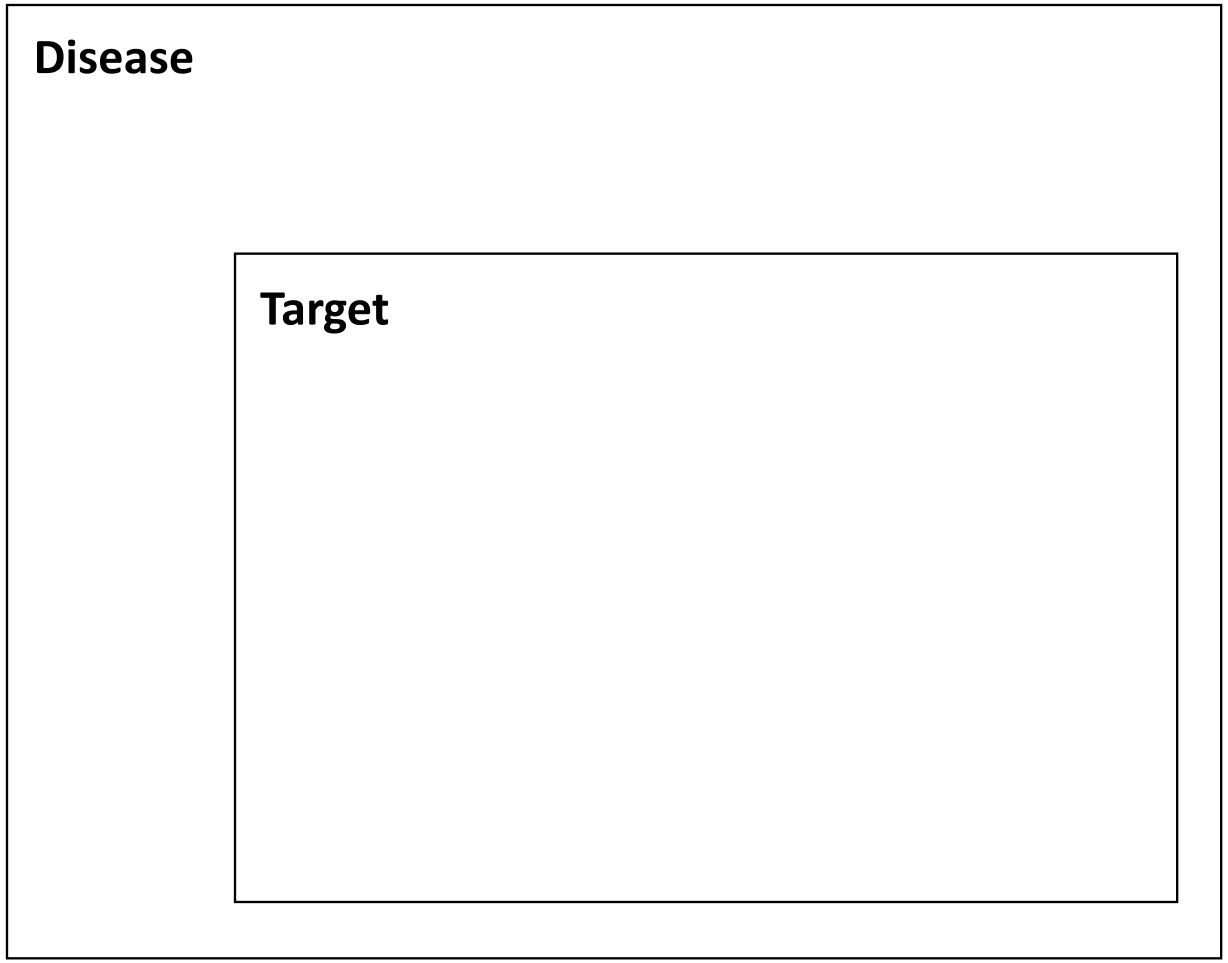
It is not new but has become critical and ubiquitous



Concept…n°1

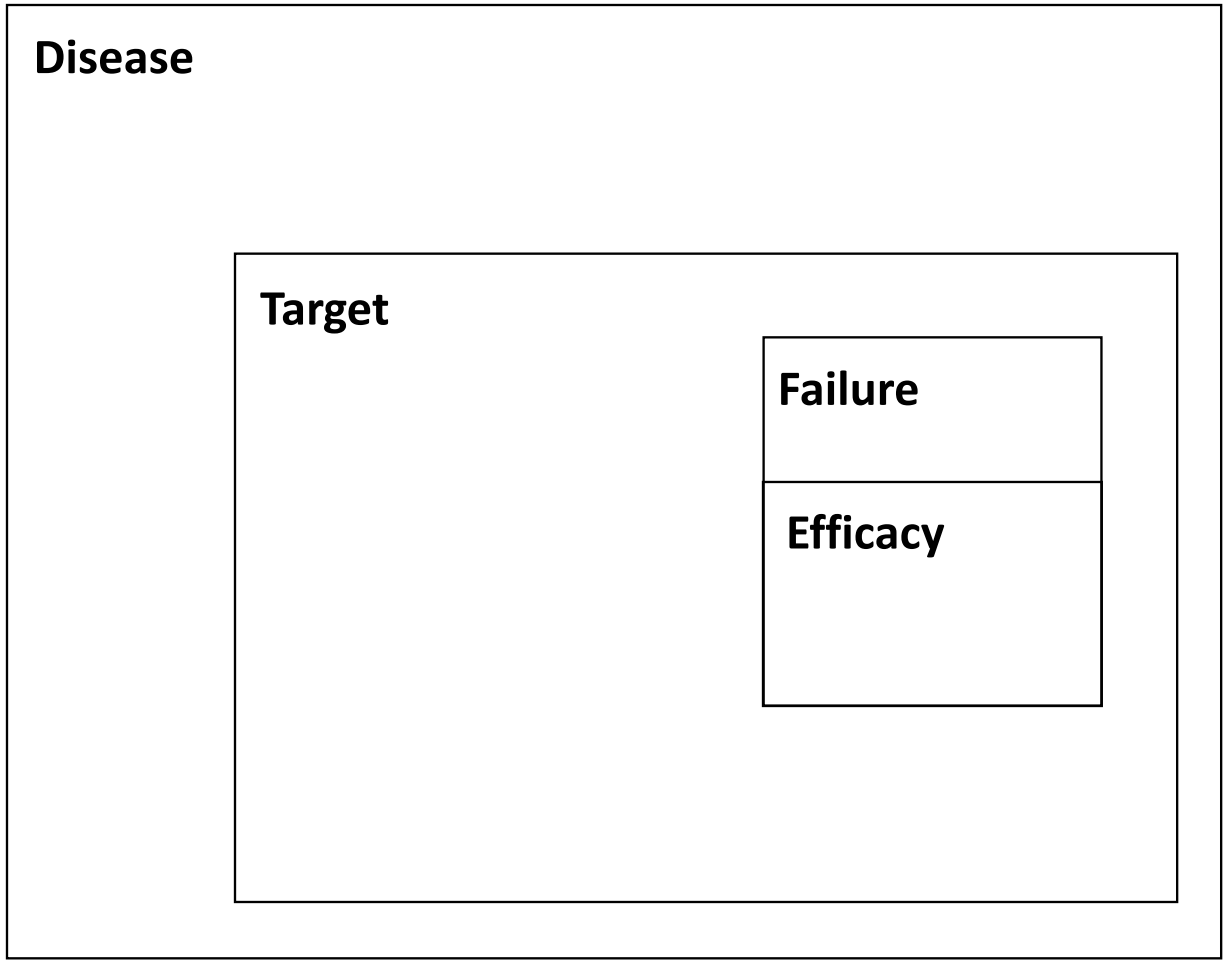
Disease

Concept…n°1

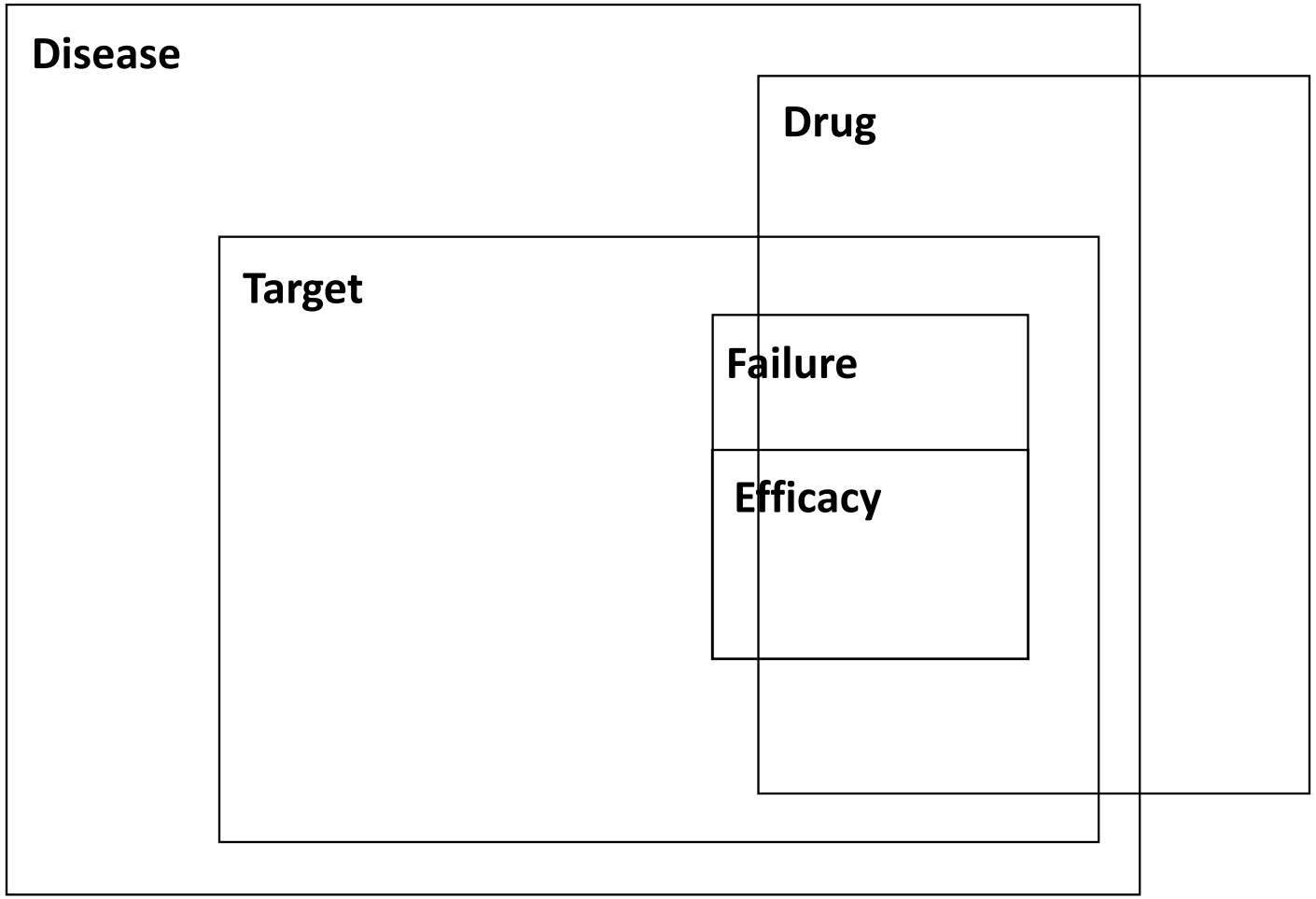


Concept…n°1

Concept…n°1



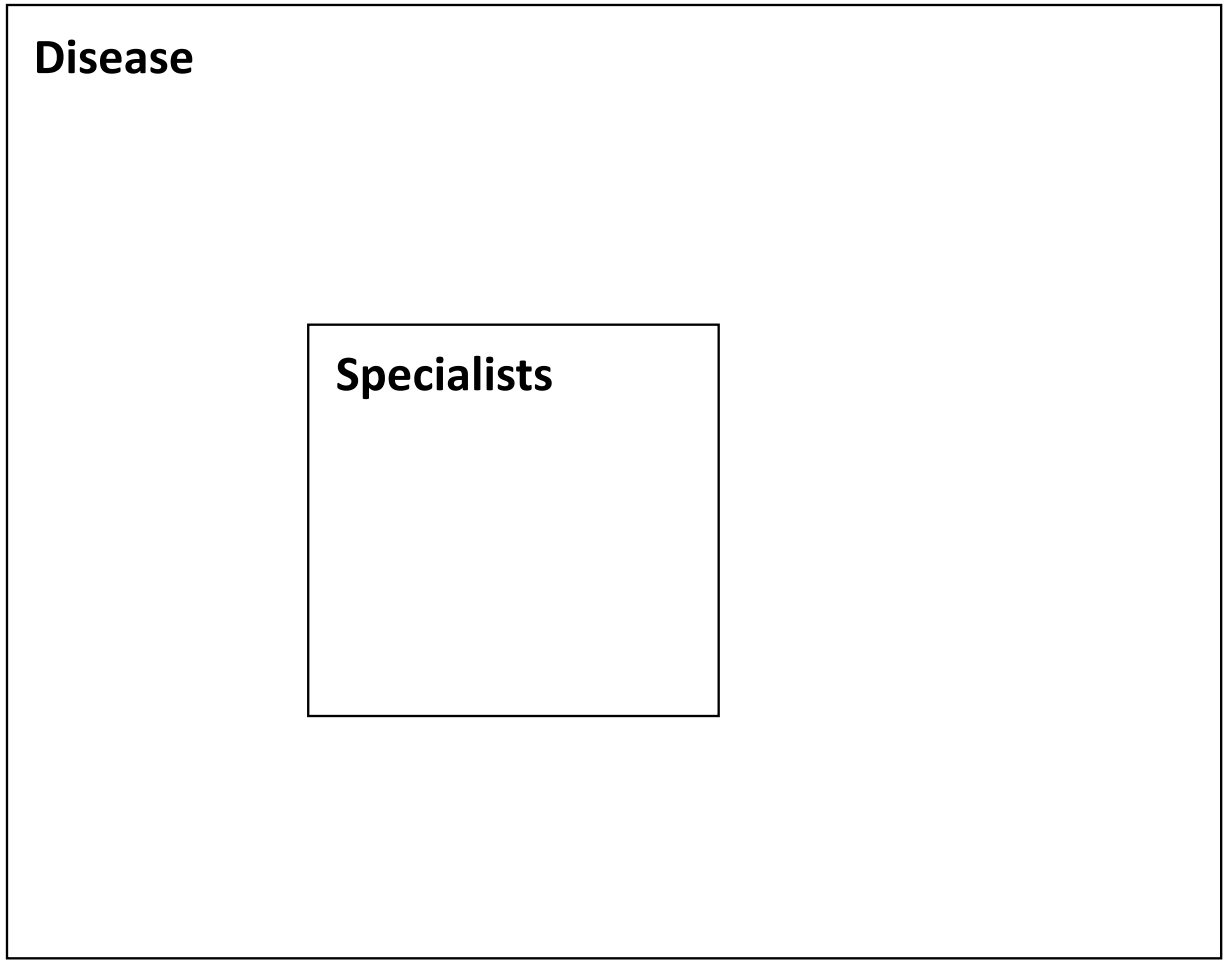
Concept…n°1



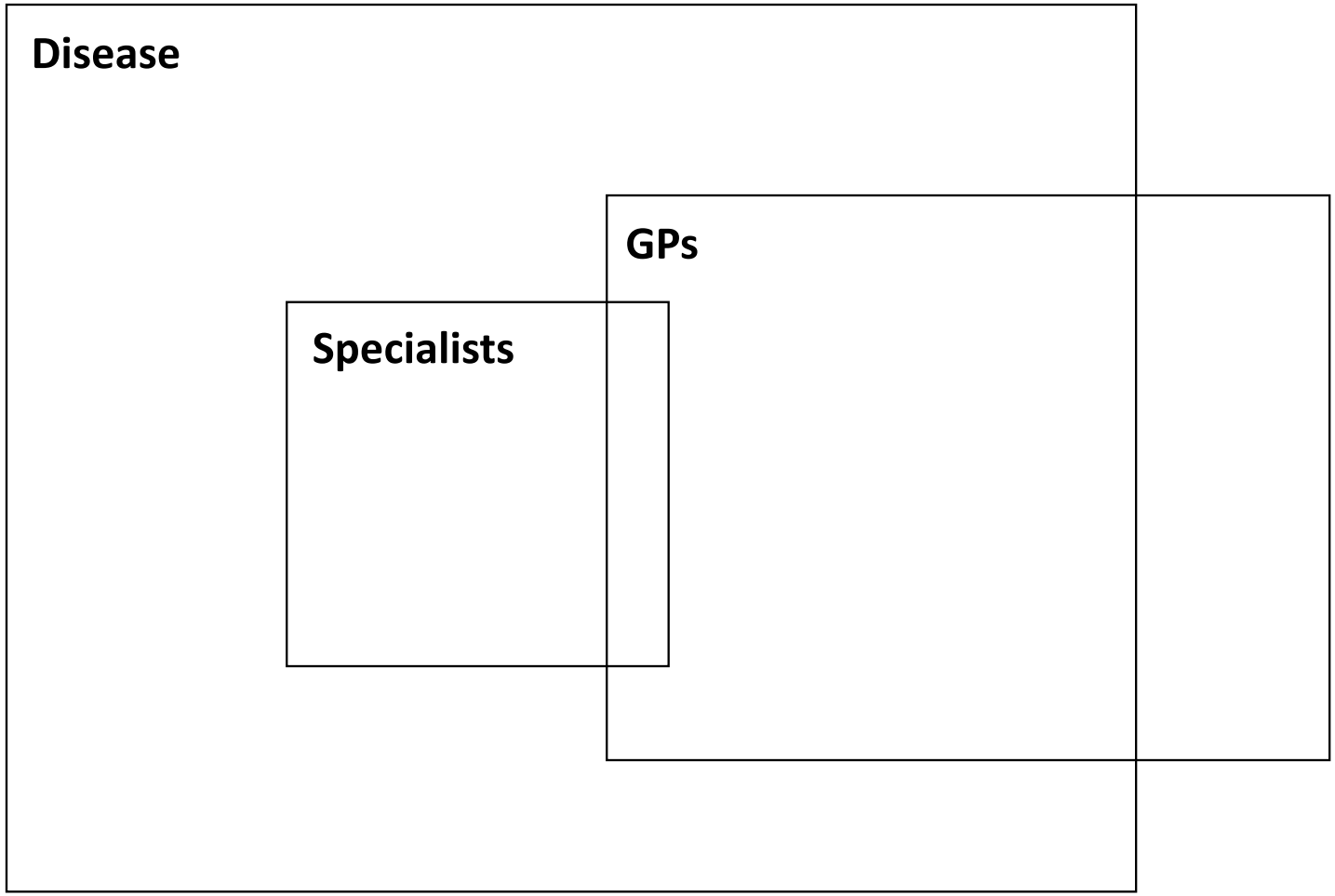
Concept…n°2

Disease

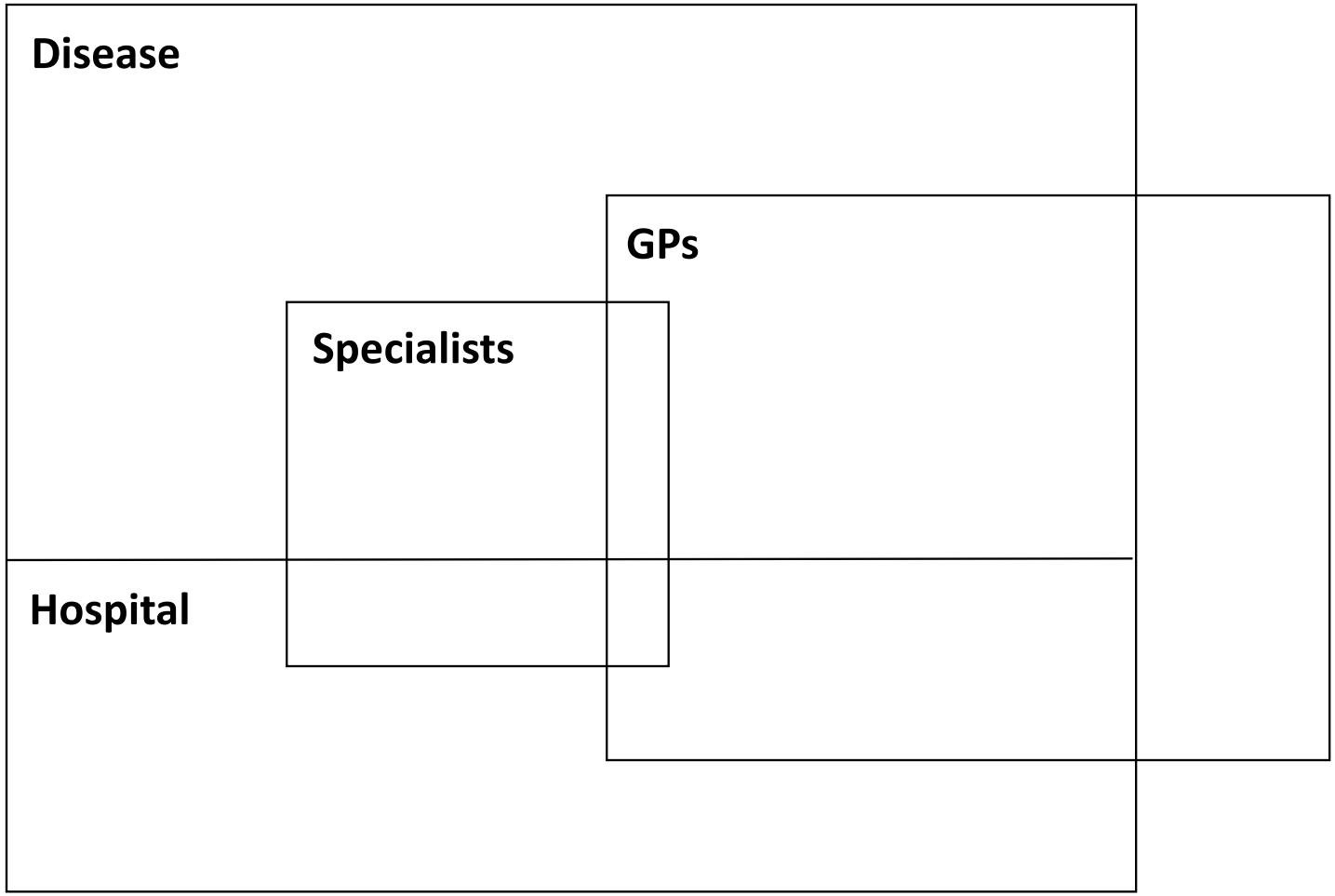
Concept…n°2



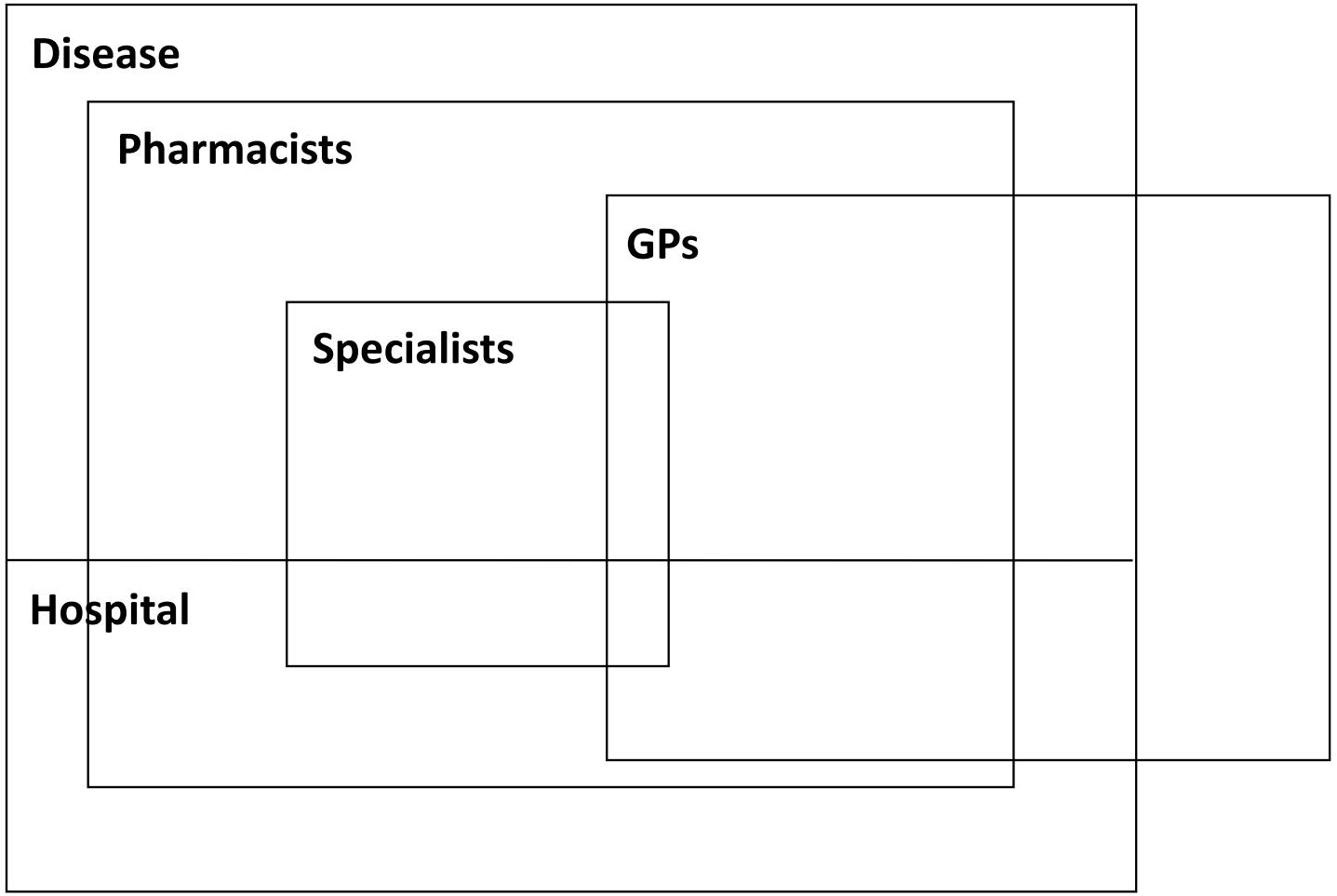
Concept…n°2



Concept…n°2



Concept…n°2



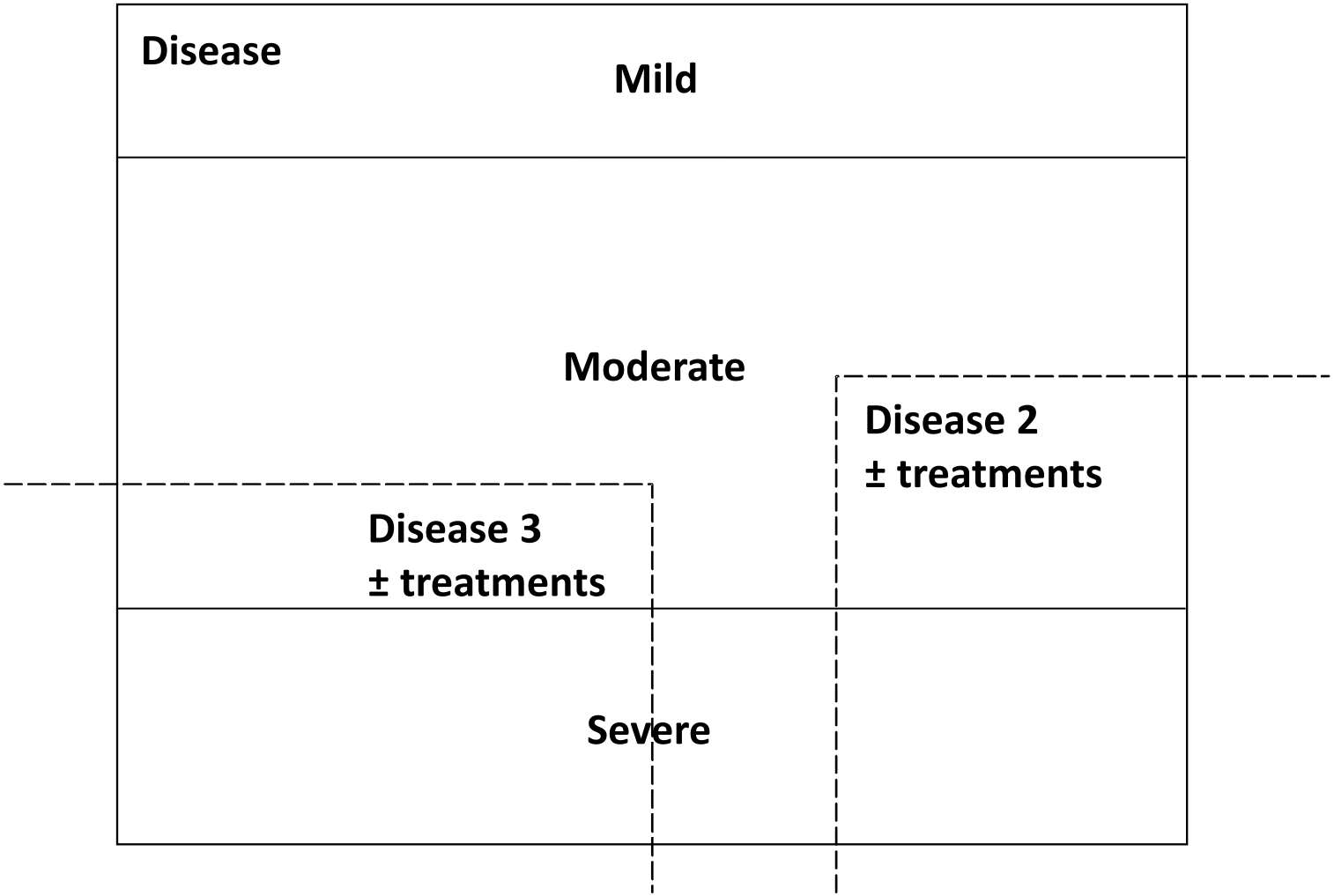
Concept…n°3

Disease

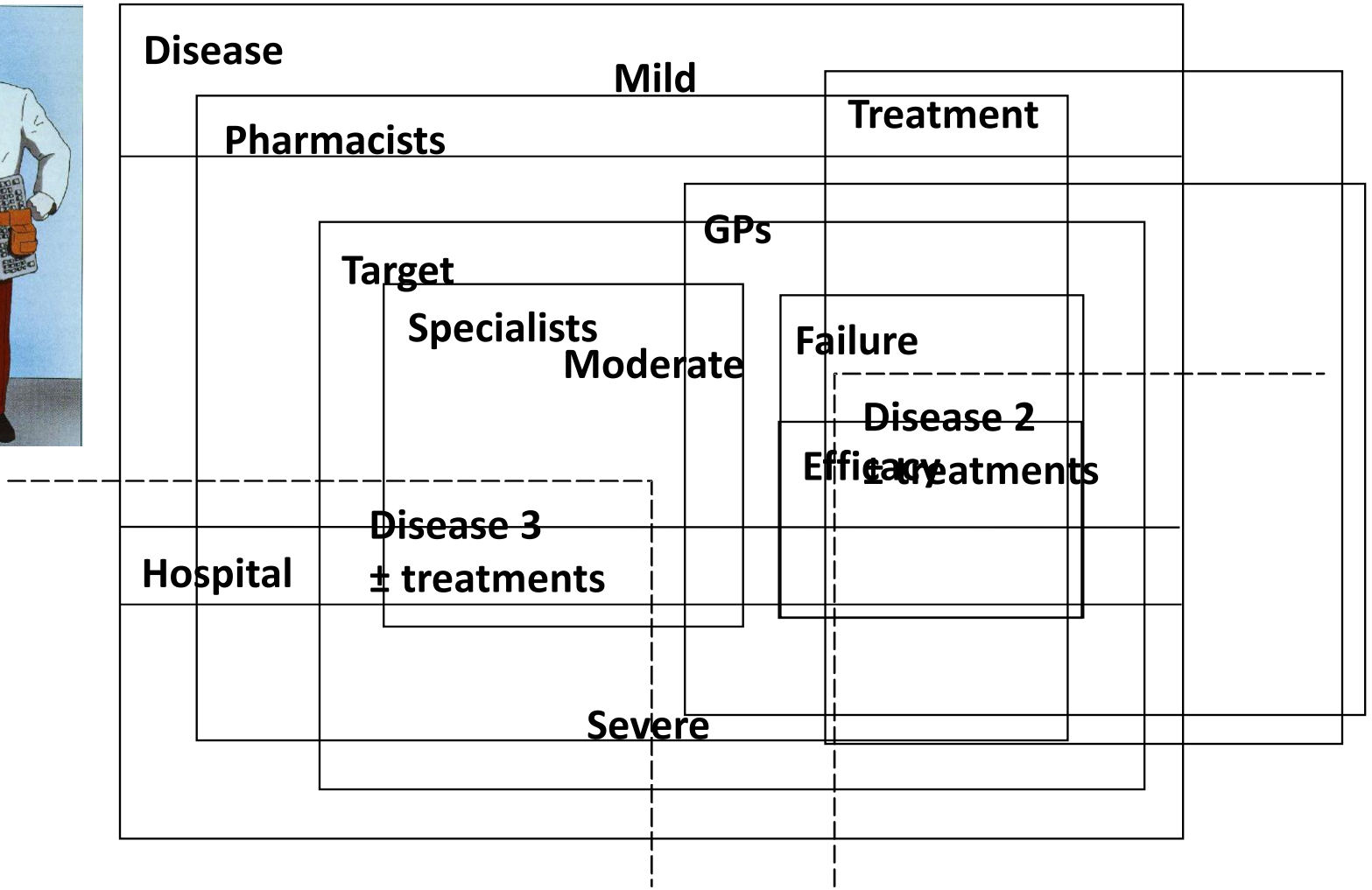
Concept…n°3

Disease	Mild
	Moderate
	Severe

Concept…n°3


Disease
Mild
Moderate
Disease 2
± treatments
Disease 3
± treatments
Severe

This is real world!



Two questions and a framework to analyze them

Transferability

Address how condition of use,
the population profile,
the health care services,
patients management in the target countries which RCT were conducted may impact the results of the trial if it was conducted in my country

Generalisability

How the study design, population selection including sampling,

the trial's centres,

the study drug administration may restrict the generalization of the outcomes to the overall population in my country.

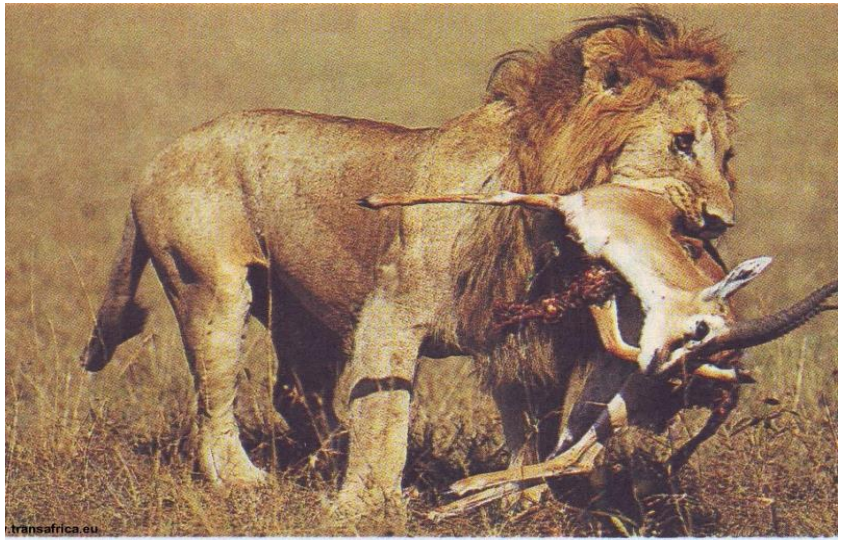
Randomized double blind two arms clinical study

Behaviour is articificial and may not exist in real life

Pragmatic/observational study

Try to mirror natural behaviour but still some control

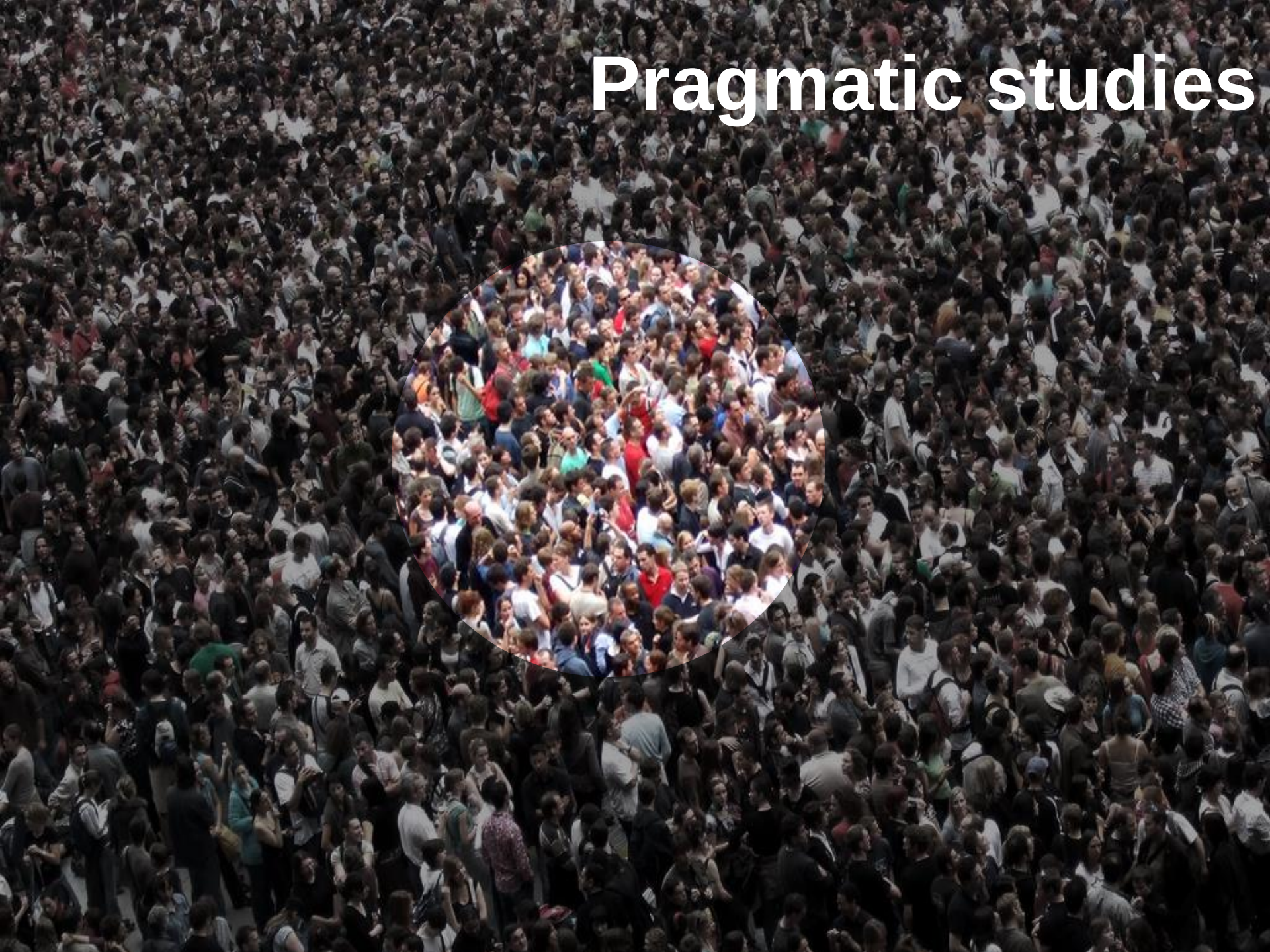
Real life clinical study Requested by HTA and Payers



Only databases capture the actual behaviour in real life as the observation is totally unbiased,
But there are limitation on what could be collected
Modelling provide the closest information to reality

RCT

Pragmatic studies



Observational studies


REALITY

Our message to payers: RCT is reality

Who will trust you?

- You want to convince me that the picture on the left inform properly the picture on the right
  - If you do not spend effort to reassure me how this may work, I won't trust you!
  - If you do not generate the requested data to be credible you will have no chance!

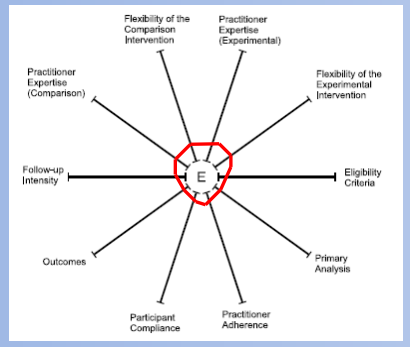
- This is why observational data are generated to inform generalisability and transferability
- This is why model are developed to simulate real life and inform decision makers!


There is a major gap to bridge
Clinical trials
Real Life

Pragmatic trials are part of a continuum of study design

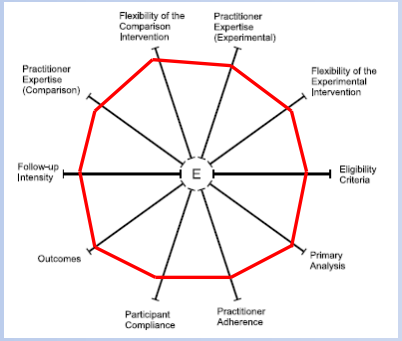
Dimensions of pragmatic vs explanatory trial design: PRECIS

Explanatory



Does it work?

Pragmatic



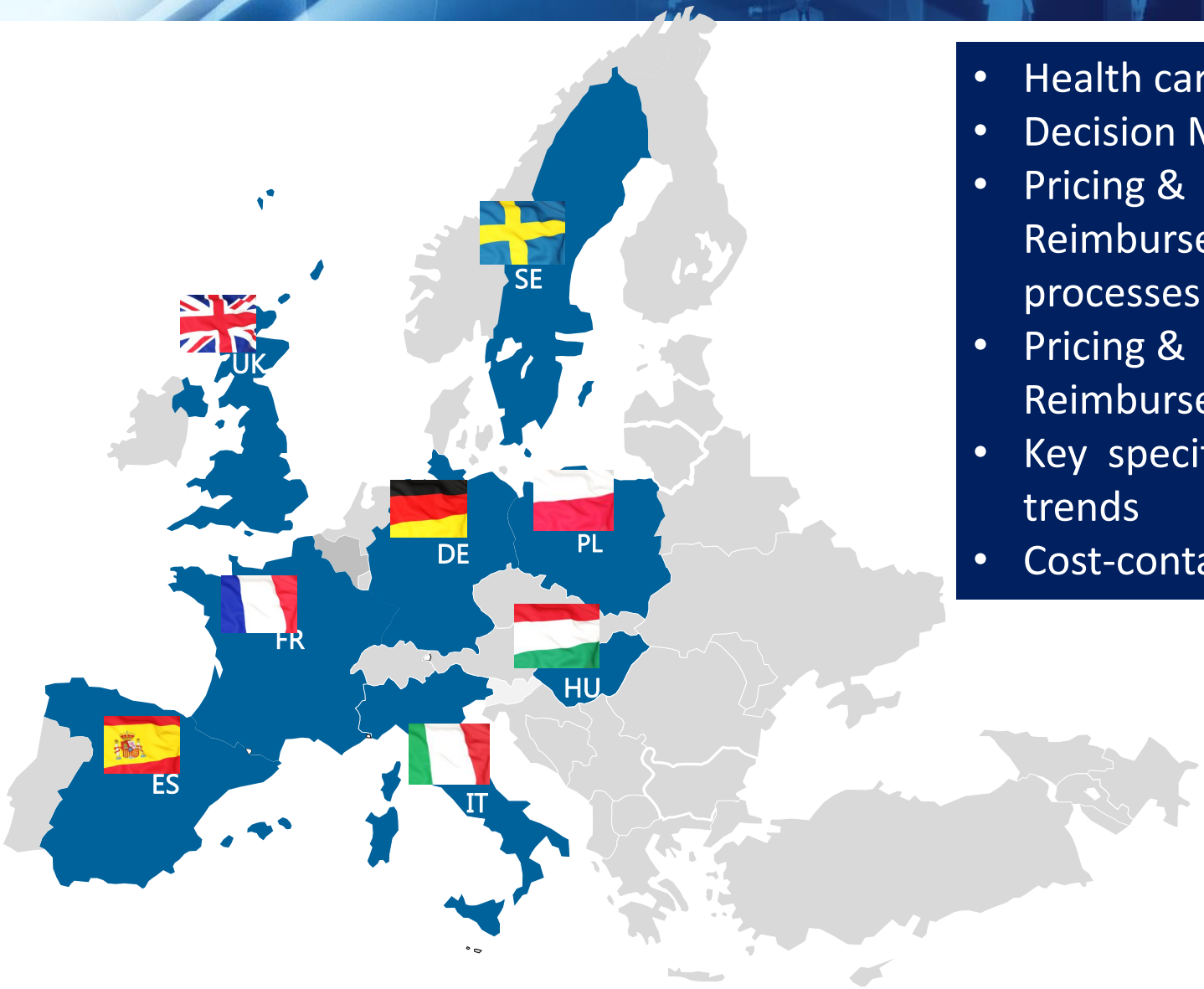
Does it work in real world conditions?

Observational (non-randomised)

Thorpe KE et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *Journal of Clinical Epidemiology* 62 (2009) 464e475

Overview and Comparison of Reimbursement Processes of Pharmaceuticals in a Selection of European Markets

Content



- Health care funding
- Decision Makers
- Pricing & Reimbursement processes
- Pricing & Reimbursement drivers
- Key specificities and trends
- Cost-containment tools

FRANCE

Decision Making Bodies

Marketing authorization	European Medicines Agency (EMA)/European Commission	European Level	
	National Agency for the Safety of Medicine and Health Products (ANSM)	National Level	
Health Technology Assessment	French National Authority for Health (HAS)	Transparency Committee (CT)	Opinion
		Economic and Public Health Assessment Committee (CEESP)	
Reimbursement Rate	National Union of Health Insurance Funds (UNCAM)		Decision
Pricing	Economic Committee for Healthcare Products (CEPS)		
Final Decision	Ministry of Health (MoH)		

ANSM, Agence Nationale de Sécurité du Médicament et des Produits de Santé; HAS, Haute Autorité de Santé ; CEESP, Commission Evaluation Economique et de Santé Publique ; CT, Commission de la Transparence; CEPS, Comité Economique des Produits de Santé ; UNCAM, Union Nationale des Caisses d'Assurance Maladie

P&R Process

Timelines *(Months)***

Marketing Authorisation

EU Level: **European Medicines Agency (EMA)/European Commission**

National Level: **National Agency for the Safety of Medicine and Health Products (ANSM)**

~3.5

Health Technology Assessment

French National Authority for Health (HAS)

Transparency Committee (CT)	**Economic and Public Health Assessment Committee (CEESP)**
Assessment of actual benefit (AB), improvement in actual benefit (IAB), target population	Health economic assessment

~3-4.5

Pricing & Reimbursement Decision

National Union of Health Insurance Funds (UNCAM)	**Economic Committee for Healthcare Products (CEPS)**	**Ministry of Health (MoH)**
Reimbursement rate	Price negotiation with pharmaceutical company*	Inclusion in hospital list and reimbursement list

~1-3

Publication in the Official Journal

**P&R decision timelines about 1-2 months for hospital drugs

*Price notification for hospital drugs outside performance-based costing system (T2A)

Reimbursement and pricing decisions are endorsed by the Ministry of Health and published in the official journal

Medical Assessment by CT
Key Decision Drivers

Actual benefit (AB)

Service Médical Rendu (SMR)

- Disease severity
- Efficacy /safety
- Position in the therapeutic strategy
- Impact on public health
- Type of treatment (preventive, curative or symptomatic)

Driver of reimbursement rate

Improvement in actual benefit (IAB)

Amélioration du Service Médical Rendu (ASMR)

- Assessment by indication vs. comparators or therapeutic strategy
- Benefit mainly driven by the effect size of the incremental clinical efficacy benefit
- Safety and QoL considered if substantial burden

Driver of price negotiation

Target population

- Quantitative estimation of prevalence/incidence in France of the population who might benefit from the product in claimed indications

Driver of price-volume agreements

Medical Assessment by CT AB and IAB

Actual benefit (AB)

Service Médical Rendu (SMR)

5 levels of AB	5 levels of reimbursement
Major	100%* or 65%
Important	65%
Moderate	30%
Weak	15%
Insufficient	0%

** Can be 100% for specific drugs, such as drugs in oncology or transplantation*

Improvement in actual benefit (IAB)

Amélioration du Service Médical Rendu (ASMR)

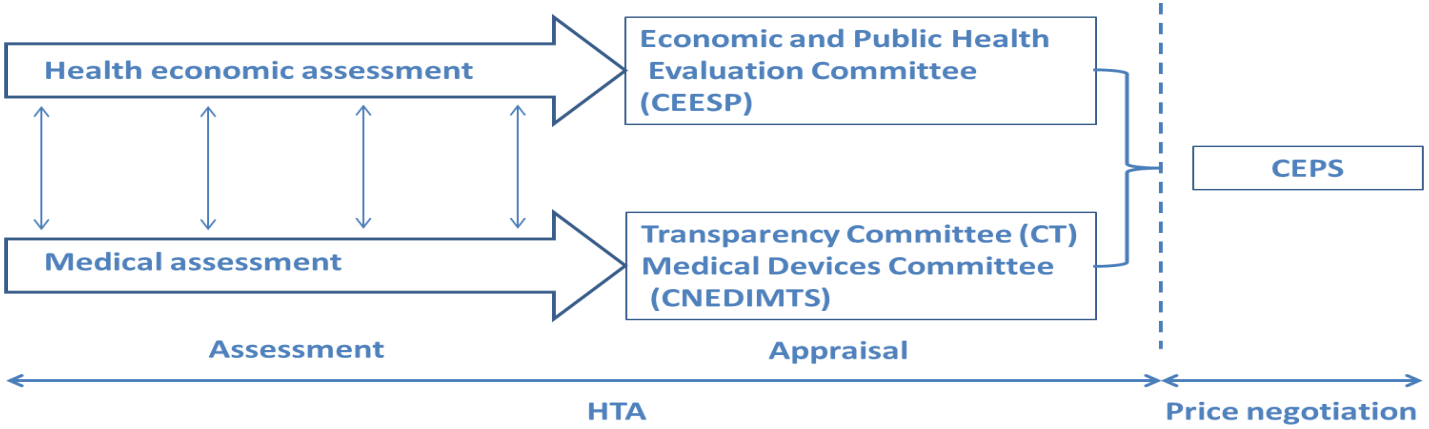
IAB I	Therapeutic breakthrough
IAB II	Important improvement in terms of efficacy or safety
IAB III	Modest improvement in terms of efficacy or safety
IAB IV	Minor improvement in terms of efficacy or safety
IAB V	No improvement

Health Economic Assessment by CEESP

First Listing/Relisting of Drugs

IAB claimed by the company: I, II, or III **+** Significant impact on health insurance budget (> €20 million)

Health Economic Assessment



- Data submitted by the manufacturer to CEESP and CEPS, along with the request for inclusion/renewal of inclusion of the product on the reimbursable drugs formulary
- No publication of CEESP opinions until the end of price negotiation

➢ **Expected to inform on the compliance of health economic evaluations with the HAS guidelines, but not to inform on whether the intervention is cost-effective or not**

Pricing & Reimbursement per Channel

Channel	Retail		Hospital		
	Some retail medicines used for hospital care				
Listing of medicines	Not reimbursed	Reimbursed	Retrocession	Supplementary list*	DRG
Distribution	Outpatient		Inpatient		
Reimburs-ement rate	0%	15%-100%	65-100%	100%	
Price setting	Free pricing	Price negotiation with CEPS based on: •IAB level •IRP (Germany, Italy, Spain, UK for IAB I-III) •Competitors price •Target population •Budget impact •Health economics evaluation (for innovative drugs) •French financial context/situation of pharmaceutical industries	Ceiling price for reimbursement (price notification to CEPS)		Free pricing (Commercial discounts)

*« *Liste en sus* » for costly medicines funded on top of DRG tariff

GERMANY

Decision Making Bodies

Marketing authorization	European Medicines Agency (EMA)/European Commission	European Level
	Federal Institute for Drugs and Medical Devices (BfArM)/ Paul-Ehrlich-Institut (PEI)	National Level
Health Technology Assessment	Institute for Quality and Efficiency in Healthcare (IQWiG)	Opinion
Early Benefit Assessment	Federal Joint Committee (G-BA)	Decision
Pricing	Federal Association of Health Insurance Funds (GKV-SV)	Decision

BfArM, Bundesinstitut für Arzneimittel und Medizinprodukte; G-BA, Gemeinsamer Bundesausschuss; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; GKV-SV, Gesetzliche Krankenversicherung-Spitzenverband

Market Access Process Overview

Reimbursement

Automatic reimbursement following marketing autorisation (some exceptions: non-prescription drugs, lifestyle drugs)

Pricing

- Early benefit assessment (EBA) for newly launched active substance, new combination, new indication
  - Free price up to 12 months after launch
  - EBA dossier to be submitted by manufacturer to G-BA
  - From 2nd year onwards, reimbursement price is based on a discount negotiation or reference pricing following EBA
- EBA exemptions and free pricing: non reimbursed drugs, hospital-only medicines, generics

P&R Process for New Drugs, EBA

Timelines *(Months)*

- 3 — Early Benefit Assessment
- 3 — Early Benefit Assessment
- 6 — Discount negotiation/arbitration
- 3 — Discount negotiation/arbitration

Marketing Authorisation

EU Level: **European Medicines Agency (EMA)/European Commission**

National Level: **Federal Institute for Drugs and Medical Devices (BfArM)// Paul-Ehrlich-Institut (PEI)**

Manufacturer submits dossier to initiate AMNOG process

G-BA
Early Benefit Assessment (decision & publication)

Can commission preliminary EBA

Recommen-dation

IQWiG
Advice on level of benefit

Additional benefit

Eligible for premium price

Manufacturer/GKV-SV
Reimbursement price negotiation
(List price minus a negotiated discount)

No agreement

No additional benefit

Not eligible for reference price

Reference price possible or possibility to create a reference group

Manufacturer/GKV-SV
Reimbursement price negotiation
(Not exceeding the cost of comparative therapy)

No agreement

Reference price

Arbitration board
(Neutral, manufacturer and GKV-SV)
Reimbursement price negotiation
(applies retroactively from the first day of the 13th month after product launch)

Manufacturer and GKV-SV can request a cost-benefit assessment prepared by the IQWiG if not satisfied with the arbitration board's decision; price discount may be renegotiated

EBA: Methodology and Decision Drivers (1/2)

Drug benefit and drug additional benefit

Importance of robust comparison vs. appropriate comparative therapy to gain positive additional benefit assessment

Drug benefit

- The patient-relevant therapeutic effect in regards to:
  - Improved state of health
  - Shorter duration of the disease
  - Increased survival
  - Fewer side effects
  - Improved quality of life

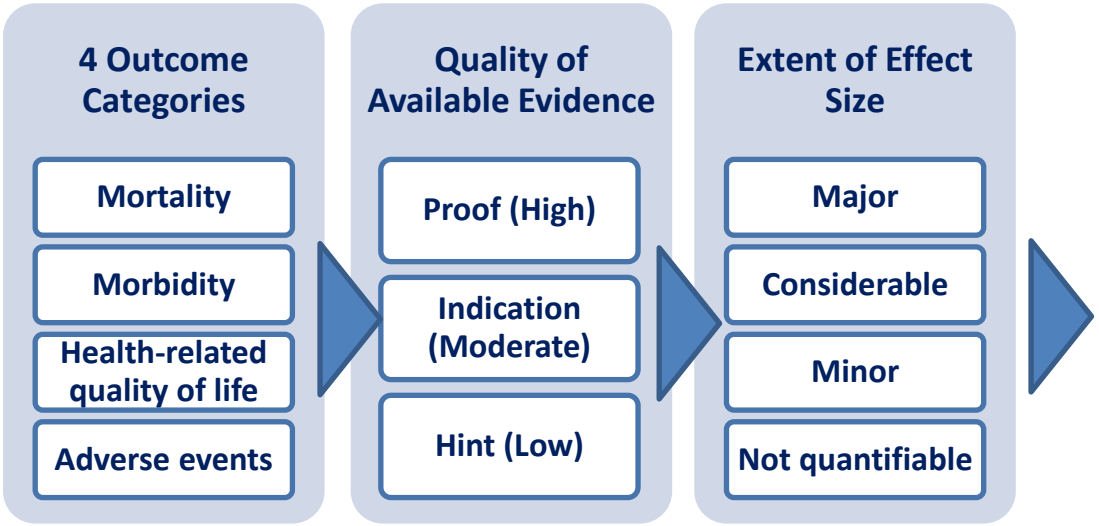
Drug additional benefit

- The quantitative or qualitative added benefit for patients compared to the appropriate comparative therapy in different subpopulations

Appropriate comparative therapy

- Set out by the G-BA
- Can be a non-/pharmaceutical treatment or best supportive care
  - If pharmaceutical: must have a market authorisation in the therapeutic indication
- Preferably already assessed by G-BA
- Should be appropriate therapy based on current medical knowledge

EBA: Methodology and Decision Drivers (2/2)



6 levels of additional benefit

1	**Major**	Sustained and large improvement in outcome not previously achieved with the appropriate comparator
2	**Considerable**	Significant improvement in outcome not previously achieved with the appropriate comparator
3	**Minor**	Moderate and not just small benefit not previously achieved with the appropriate comparator
4	**Not quantifiable**	There is evidence that additional benefit exists, however the scientific information is not sufficient to estimate the size of the additional benefit
5	**None**	No additional benefit demonstrated
6	**Inferior**	Less benefit than the appropriate comparator

No additional benefit

Specific Considerations in EBA

Extent of benefit based on the 95% upper limit of the confidence interval of the relative risk ratio

- Mortality:
  - Major : UL CI95% < 0.85; Considerable : UL CI95% < 0.95; Minor : UL CI95% <1
- Morbidity/QoL
  - Major : UL CI95%< 0.75; Considerable : UL CI95%< 0.90; Minor : UL CI95%< 1
- Adverse events or minor symptoms
  - Major: Not possible; Considerable : UL CI95%< 0.80; Minor : UL CI95%< 0.90

Additional benefit rated at sub-population level

- Definition of sub-populations can differ between IQWiG/G-BA and manufacturer

Importance of head-to-head trials

- Indirect comparisons may be used if well justified and with robust methodology

Hard endpoints preferred/required vs surrogate endpoints

- Solid validation required for surrogate endpoints

Increased number of conditional decisions

- About 30%
- Time limited decisions between 1 to 5 years

Pricing

Channel	Retail		Hospital*
EBA eligibility	Non eligible for EBA	Eligible for EBA	Hospital-only drugs
Reimburs-ement rate	0%	100%	
Price setting	Free pricing	Reimbursement price: ➢ No additional benefit : reference pricing (if eligible) ➢ Additional benefit/No additional benefit (if not eligible for reference pricing): price negotiation with GKV-SV based on: • EBA vs comparator • IRP (15 EU countries) • Prices of comparators • Affected GKV-target population • Budget impact	Free pricing

*Hospital drugs funded through DRG; Costly medicines can be funded on top of DRG tariff

ITALY

Decision Making Bodies

Marketing authorization	European Medicines Agency (EMA)/European Commission	European Level	
	Italian Medicines Agency (AIFA)	National Level	
Central			
Pricing & Reimbursement	Italian Medicines Agency (AIFA)	Technical-Scientific Commission (CTS)	Decision
		Pricing & Reimbursement Committee (CPR)	
		AIFA Board of Directors	
Regional			
Drug regional access	Regional HTA Bodies		Opinion
	Regional authorities		Decision

AIFA, Italiana del Farmaco; CTS, Commissione Tecnico Scientifica; CPR, Comitato Prezzi e Rimborso

P&R Process

Timelines* ***(Months)***

Marketing Authorisation

EU Level: **European Medicines Agency (EMA)/European Commission**

National Level: **Italian Medicines Agency (AIFA)**

Pricing & Reimbursement Decision

Italian Medicines Agency (AIFA)

Technical-Scientific Commission (CTS)
Clinical evaluation and advice on reimbursement classifications

Pricing & Reimbursement Committee (CPR)
Price negotiation with pharmaceutical company

AIFA Board of Directors
Ratification of pricing and reimbursement decision

Inclusion in National Pharmaceutical Formulary (PFN) and Publication in the Official Journal (Gazzetta Ufficiale)

** In theory, the pricing and reimbursement process should take 6 months, while in practice it often takes longer*

CTS Reimbursement Criteria

3 key drivers for inclusion on reimbursement list

Disease criteria	Product profile	Economic criteria
• Disease severity and burden • Unmet needs	• Therapeutic value • Level of innovation • Therapeutic alternatives	• Price of therapeutic alternatives • Budget impact

Reimbursement class	Reimbursement rate	Description
A	100%	Essential pharmaceuticals
A with notes	100%	Prescription-only pharmaceuticals reimbursed only under specific conditions
H	100%	Prescription-only pharmaceuticals reimbursed only when used in hospitals under specialist supervision
C	0%	Prescription-only pharmaceuticals which are not reimbursed
C bis	0%	Over-the-counter pharmaceuticals (non-prescription drugs)
C nn	0%	Temporary class for new drugs with marketing approval but not yet assessed by AIFA

Reimbursed drugs are included into the National Pharmaceutical Formulary (Prontuario Farmaceutico Nazionale, PFN)

CPR Pricing Negotiation Criteria

- **CTS assessment of degree of innovation & therapeutic value**
- **Drug prices in other EU countries**
- **Price of comparable existing therapies in Italy**
- **Budget impact**
- **Sales forecast**
- **Cost-effectiveness**
  - Not a main driver in pricing decisions but can be provided by companies for innovative products and be used for pricing negotiations

- For non-reimbursed medicines (Class C), prices are freely determined (with some limitations: price declaration) by manufacturers and monitored by AIFA
- For hospital drugs, regional/local negotiations or tenders to set drug prices (max. price sets by AIFA)

Key Market Access Specificities

Whole P&R process is not completely transparent

- No publication of assessments at national and few at regional level
- Uncertainty on impact of cost-effectiveness analyses in reimbursement decisions
- Level of innovation criteria unclear

Highly decentralised system

- Disparities in drug access and cost-containment policies across regions with disparities in terms of:
  - Hospital formulary listings
  - Prescribing guidelines/incentives
  - Tenders
  - Patient co-payments: Regions are legally allowed to implement co-payment fees for retail drugs (varying between regions)
- Market access hurdles for hospital drugs: regional dossier for inclusion of the drug in the regional hospital formularies (process can take 6-7 months up to 50 months)
  - Mandatory inclusion of drugs recognised as innovative by AIFA

Hospital drug funding

- DRG used by regions
- Costly drugs funded on top of DRG tariff and listed in file F (regional level decision)

112

Decision Making Bodies

Marketing authorization	European Medicines Agency (EMA)/European Commission	European Level	
	Spanish Medicines Agency (AEMPS)	National Level	
Central			
Health Technology Assessment	National health Technology Assessment Agency (AETS)		Opinion
Pricing & Reimbursement	Ministry of Health (MSSSI)	General Subdirectorate of Quality of Medicines and Health Products (SGCMPS)	Decision
		Interministerial Commission for Pricing of Medicinal Products (CIPM)	
Regional			
Drug regional access	Regional HTA Bodies		Opinion
	Regional authorities		Decision

AEMPS, Agencia Española del Medicamento y Productos Sanitarios; CIPM, Comisión Interministerial de Precios de los Medicamentos ; MSSSI, Ministerio de Sanidad, Servicios Sociales e Igualdad; SGCMPS, Subdirección General de Calidad de Medicamentos y Productos Sanitarios; AETS, Agencia de Evaluación de Tecnologías Sanitarias

P&R Process

Timelines* ***(Months)***

6

Marketing Authorisation

EU Level: **European Medicines Agency (EMA)/European Commission**

National Level: **Spanish Medicines Agency (AEMPS)**

Pricing & Reimbursement Decision

Ministry of Health (MSSSI)

General Subdirectorate of Quality of Medicines and Health Products (SGCMPS), part of the Directorate General of the Basic Services Portfolio of the National Health System and Pharmacy (DGCBSF)
Pricing & reimbursement recommendations

Interministerial Commission for Pricing of Medicinal Products (CIPM)
Final pricing decision

National health technology assessment agency (AETS)
Support for P&R decisions

Final pricing and reimbursement decision

** In theory, the pricing and reimbursement process should take 6 months, while in practice it often takes longer*

SGCMPS Reimbursement Criteria

3 key drivers for inclusion on reimbursement list

Disease criteria

- Disease severity and burden
- Unmet needs

Product profile

- Therapeutic value
- Level of innovation
- Therapeutic alternatives

Economic criteria

- Price of therapeutic alternatives
- Budget impact

Reimbursement conditions

- Negative list for products excluded from reimbursement
- Hospital drugs reimbursed at 100%
- Co-payment for retail drugs:
  - Based on patient's income for drugs indicated for non chronic/severe diseases:
    - **Workers**: 0% co-payment for long-term unenmployed, 40%, 50% or 60% co-payment based on income with no maximum co-payment
    - **Pensioners**: 0% co-payment for underpriviledged pensioners, 10% or 60% co-payment based on income with a maximum co-payment
  - Fixed co-payment system for drugs indicated for chronic/severe diseases:
    - 10% co-payment with a maximum co-payment per prescription

CIPM Pricing Negotiation Criteria

- Degree of therapeutic innovation
- Drug prices in other EU countries
- Price of comparable existing therapies in Spain
- Budget impact
- Total cost of the drug
- Company profit
- R&D activity and manufacturing investment in Spain

- Confidential rebates negotiated between CIPM and manufacturers
- For hospital drugs, maximum prices are set at national level and actual prices negotiated between hospitals/groups of hospitals and manufacturers or determined at central level through regional/national purchasing

Key Market Access Specificities

Whole P&R process is not completely transparent

- No publication of assessments at national and few at regional level

Highly decentralised system

- Disparities in drug access and cost-containment policies across regions with disparities in terms of:
  - Formulary listings
  - Prescribing guidelines/incentives
  - Use of market access agreements
- Drug assessment performed by numerous healthcare department (7regional HTA agencies and drud evaluation committees in each region)

Hospital drug funding

- Annual global funding system for hospitals by regional authorities
- There is no provision for Spanish hospitals to return to the regions for extra funding should a new drug exceed their total budget

117

Key Trends in Market Access

Health Economic Assessment

- To date, no formal health economic assessment BUT expected since Decree-Laws 9/2011 and 16/2012
  - A new committee composed by health economics experts would be responsible for cost-effectiveness and budget impact evaluation
  - Its recommendations would support the CIPM pricing decisions
  - At this time, no details on the implementation have been released

Market Access process harmonisation

- Therapeutic Positioning Reports (IPT) were introduced in 2013 to harmonise market access process through a single national report
  - In the long term, expected to facilitate market access by avoiding re-assessment at regional or local level
- Reports developed by AEMPS and reviewed by 2 assigned regions (publicly available on AEMPS website)
- Assessment of the added therapeutic value of new drugs in the current therapeutic strategy

118

United Kingdom

Decision Making Bodies

Marketing authorization	European Medicines Agency (EMA)/European Commission	European Level
	Medicines and Healthcare Products Regulatory Agency (MHRA)	National Level
Health Technology Assessment	National Institute for Health and Care Excellence (NICE)	Opinion
	Scottish Medicines Consortium (SMC)	
	All Wales Medicines Strategy Group (AWMSG)	
Pricing	UK Department of Health (DH)	Decision
Funding	Regional authorities	

P&R Process

Marketing Authorisation

EU Level: **European Medicines Agency (EMA)/European Commission**

National Level: **Medicines and Healthcare Products Regulatory Agency (MHRA)**

Pricing (Retail/Hospital*)

UK Department of Health (DoH)
Acknowledgment of branded medicine launch notification including the proposed NHS list price and SmPC

Branded Drugs (including branded generics)

2 different schemes chosen by pharma companies

1. Pharmaceutical Price Regulation Scheme (PPRS)
- Free pricing for new active substances and price negotiation for other products
- Indirect profit control

2. Statutory Price Regulation Scheme
- Statutory price limits on sales of prescription drugs

Generics

- Free pricing (price to be below off-patent original price)

*Actual prices negotiated between hospital and manufacturer, or via tenders

Funding & Access

- Generally automatic full reimbursement of drugs upon marketing authorisation, however funding will depend on health technology assessment (HTA)

Central UK Government
Central funding

National HTA agencies assess the efficient use of NHS resources

NHS England	NHS Wales	NHS Scotland	NHS Northern Ireland
NICE	NICE/ AWMSG**	SMC	NICE***

Regional authorities
Responsible for drugs funding

**AWMSG normally considers appraising a product if not/not yet appraised by NICE
*** Northern Ireland adapts as appropriate determinations by NICE to be endorsed by Department of Health, Social Services and Public Safety (DHSSPS) of Northern Ireland

HTA Process
Cost-Effectiveness Evaluation

Funding Decisions by Regional Authorities based on Cost-Effectiveness Assessment from HTA Agencies

- Comparison of healthcare interventions using Incremental Cost-Effectiveness Ratio (ICER) which quantifies the cost per unit of benefit gained from using one treatment versus another
- Quality-Adjusted Life Years (QALYs) is the preferred outcome of benefit gained

ICER (Cost/QALY) is a key driver of the decision, but no formal threshold

ICER < £20,000	£20,000 < ICER < £30,000	ICER > £30,000
Recommendation likely to be positive	Recommendation not predictable	Recommendation likely to be negative

- NICE adopts a more flexible approach for life-extending treatment at the end of life
  - Short life expectancy<24 months
  - Life extension with drugs>3 months vs current NHS treatment
  - Small patient populations
- Drugs which meet end-of-life criteria can potentially be recommended at higher ICER threshold (usually between £30,000 and £50,000)

NICE & SMC Process

	NICE in England	SMC in Scotland
Scope	• Binding guidance in England and Wales	• Binding guidance in Scotland
Assessments	• Limited number of drugs identified though specific criteria: • Patient clinical benefit, public health interest, potential cost to the NHS	• All new medicines • New formulations of existing medicines • New indications for existing medicines
Remit	• Excludes vaccines and HIV therapies	• Excludes vaccines, generics, non-prescription-only medicines, blood products, plasma substitutes and diagnostic drugs
Methodology	• Two different technology appraisal processes 1. Single-technology assessment (timelines: 6 months): Appraisal of a single treatment for a single indication 2. Multiple-technology assessment (timelines: 12 months): Appraisal of more than one treatment, or one technology, for more than one indication	• Two-stage process to decision-making 1. New Drugs Committee (NDC) makes recommendations on basis of clinical and economic evidence submitted by the manufacturer 2. Deliberative process and final advice by SMC committee
Impact	A drug can either be recommended, recommended with restrictions, or not recommended • If a drug received a positive appraisal , regional authorities are required to fund the drug • If a drug received a negative appraisal (or not assessed), regional authorities are not required to fund the drug	

NICE & SMC Decision Drivers

NICE: 4 main decision drivers	SMC: 3 main decision drivers
1. Appropriateness and relevance of comparator technologies 2. Clinical effectiveness and health-related factors 3. Cost-effectiveness analysis (ICER, cost/QALY) 4. Non-health factors: that are considered socially valuable but not directly related to health and not easily captured in a cost per QALY analysis	1. Clinical efficacy/safety 2. Cost-effectiveness analysis (ICER, cost/QALY) 3. Budget impact

Key Market Access Specificities

Cancer Drugs Fund in England

- Managed by NHS England
- Additional funding source for cancer drugs established in 2010 and will run until the end of March 2016 (funding of £560 million in 2014-16)
- Cancer drug fund is for additional drugs/indications that would not otherwise be funded by the NHS (not recommended by NICE/not yet reviewed by NICE)

Orphan Drugs Fund in Scotland

- £21million fund launched in 2013 for one year to cover the cost of medicines not available for routine prescription for rare diseases (not recommended by SMC) and extended until 2016

Hospital drug funding

- Hospital drugs in England are funded by the CCGs through Diagnosis-Related Group (DRG) system called Payment by Results (PbR) (do not apply to Scotland, Wales or Northern Ireland)
- Some high-cost medicines may be excluded from PbR and directly funded by the CCGs

125

POLAND

Decision Making Bodies

Marketing authorization	European Medicines Agency (EMA)/European Commission	European Level	
	Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (URPL)	National Level	
Health Technology Assessment	Agency for Health Technology Assessment and Tariff System (AOTMiT)	Transparency Council	Opinion
Reimbursement & Pricing	Economic Committee (representatives of Ministry of Health and NFZ)		Decision
Final Decision	Ministry of Health		

AOTMiT, Agencji Oceny Technologii Medycznych i Taryfikacji ; URPL, Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych

P&R Process

Marketing Authorisation

EU Level: **European Medicines Agency (EMA)/European Commission**

National Level: **Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (URPL)**

Timelines *(Months)*

6

Pricing & Reimbursement Decision

Ministry of Health

Economic Committee (representatives of Ministry of Health and NFZ)
Pricing negotiations & reimbursement recommendations

Ministry of Health
Final pricing & reimbursement decision

If positive decision, publication of P&R conditions

Agency for Health Technology Assessment and Tariff System (AOTMiT)

Assessment of pricing & reimbursement applications when no reimbursed therapeutic alternatives available in Poland

AOTMiT
Initial verification and methodological assessment of application

Transparency Council
Appraisal of the application

Opinion

AOTMiT President
Reimbursement recommendation

Reimbursement Criteria

Multiple criteria

Recommendations
- Economic Committee
- AOTMiT

Disease criteria
- Disease severity and burden

Public health impact
- Public healthcare priorities
- Organizational implications
- Ethical and social aspects

Product profile
- Effectiveness & safety (importance of transferability of clinical trial data)
- Therapeutic alternatives

Economic criteria
- Cost (vs therapeutic alternatives)
- Price competitiveness
- Budget impact*
- Cost-effectiveness (CUA preferred, or CEA alternatively)

Reimbursement Levels

100%	Proven efficacy in the treatment of malignant cancers, psychotic disorder, mental impairment, developmental disorder or infectious disease that constitutes serious threat to the population
100%+fixed co-payment (PLN 3.20)	Use >30 days + high monthly cost with 30% co-payment (exceeds 5% of minimum wage) Use ≤30 days + high monthly cost with 50% co-payment (exceeds 30% of minimum wage)
70%	Use >30 days but do not meet criteria for 100% reimbursement
50%	Use ≤30 days but do not meet criteria for 100% reimbursement

*Rationalization analysis (if budget impact demonstrates increase in reimbursement expenditure)

Pricing Criteria

Pricing decision drivers

The following criteria are considered:

- AOTMiT recommendations
- Drug prices and any price agreements in other EU/EFTA countries where the drug is reimbursed
- Treatment cost of the new drug versus therapies already available
- Budget impact
- Cost-effectiveness (cost/QALY or cost/life-year gained)

No reimbursed therapeutic alternatives	•Price negotiation between the manufacturer and the Economic Committee
Reimbursed therapeutic alternatives	•**One alternative**: maximum ex-factory price≤75% ex-factory price of alternative •**More than one alternative**: maximum ex-factory price≤reference price

- "Ex-officio" pricing procedure allow the Ministry of Health to set the drug price without the manufacturer (notification and request for information about drug) for generally highly expensive medicines under specific conditions
- Free prices for non-reimbursed drugs
- For hospital drugs, maximum prices set as defined above and actual prices negotiated with hospitals

SWEDEN

Decision Making Bodies

Marketing authorization	European Medicines Agency (EMA)/European Commission	European Level
	Medical Products Agency (MPA) Läkemedelsverket	National Level
Health Technology Assessment & Reimbursement Decisions	Dental and Pharmaceutical Benefits Agency (TLV)	Decision
Regional Access	20 County councils Pharmaceutical Committées	Opinion

P&R Process Retail drugs

Timelines
(Months)

3-6

Marketing Authorisation

EU Level: **European Medicines Agency (EMA)/European Commission**

National Level: **Medical Products Agency (MPA)**

Health Technology Assessment

Dental and Pharmaceutical Benefits Agency (TLV)

Department for Value based Pricing
Evaluation of the submission to be included in the pharmaceutical benefit scheme

Scientific committee
Can contribute to the evaluation with clinical expertise

Pharmaceutical Benefits Group for County Councils
Requested to comment on the evaluation before decision

Company
Possibility to comment (but not submit new data) if decision is not general reimbursement

Pricing & Reimbursement Decision

Dental and Pharmaceutical Benefits Agency (TLV)

Pharmaceutical Benefits Board
Decides if the pharmaceutical is to be included in the pharmaceutical benefit scheme, and if any restrictions or conditions should be applied

Publication of decision on TLV website

SBU
- Swedish Agency for Health Technology Assessment

- Do not directly influence P&R decisions
- Source of knowledge for decision-making bodies in general
- Evaluate medical products without manufacturers' submission

Pricing of hospital drugs is free

TLV Reimbursement Criteria

The TLV's Pharmaceutical Benefits Board meets once every month to make decisions about inclusion of drugs in the pharmaceutical benefit scheme

Fundamental principles

- **The cost-effectiveness principle** - the cost of using a medicinal product should be reasonable from a medical, humanitarian and socioeconomic perspective
- **The need and solidarity principle** - those with the most pressing medical needs should have more of the health care system's resources than other patient groups
- **The human value principle** - the health care system should respect the equal value of all human life

Reimbursement decision drivers

The following criteria are considered:

- Cost-effectiveness versus SoC
- Similar benefit and less expensive than SoC
- Need for alternative treatments
- Severity of the disease
- Vulnerable patient group with high need

Decision

- General Reimbursement
- Reimbursement with restrictions
  - Specific indication or population or duration
- Reimbursement with conditions
  - Manufacturer must take additional steps such as submission of additional data, etc.
- No reimbursement

There are no price negotiations and the board does not suggest any price level
If the submission is rejected the company can resumbit with more data or lower price

Reimbursement System

- The annual spending for products included in the pharmaceutical benefit scheme is limited for the patient
- During a 12 month period a patient can pay maximum 2200 SEK
- The level of co-payment decreases with increasing overall spending.

Cost up to 1100 SEK
The patient pays 100% of the cost

Cost of 1101 to 2100 SEK
The patient pays 50% of the cost

Cost of 2101 to 3900 SEK
The patient pays 25% of the cost

Cost of 3901 to 5400 SEK
The patient pays 10% of the cost

Cost of more than 5400 SEK
100% Reimbursed - Patient do not pay any co-payment

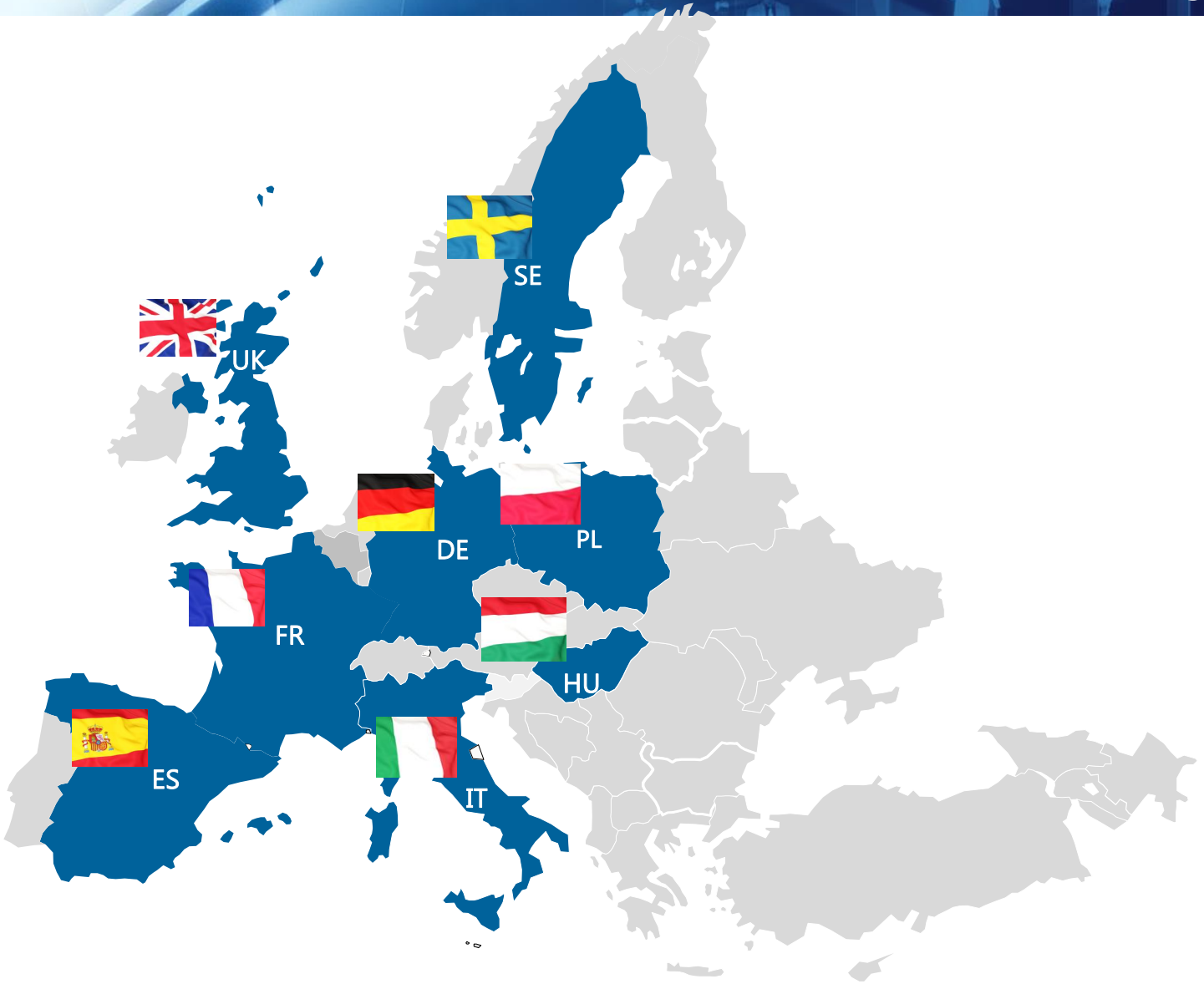
TLV Cost-Effectiveness Assessment

TLV uses a value-based pricing system to decide to reimburse a drug

Requirements of pharmacoeconomic analysis according to TLV guidelines (May 2003)

- Be performed from a **societal perspective** and should use Swedish data where possible
- Cover the entire **patient population** for which reimbursement is being sought
- Use quality-adjusted life-years (**QALY**) as well as other metrics where appropriate
- Include data on benefits and cost versus the most **appropriate comparator** (typically the moste widely used treatment in Sweden)
- Set out costs in terms of the drug's proposed **pharmacy sales price** (AUP)

Cross-Country Comparison of MA Pathways



Formal vs Informal HTA

Formal HTA	• A term and mission are set • Transparent decision framework process • Meeting agenda available • Decisions are publicly available and argued based on evidence submitted by manufacturer
Informal HTA	• Do not meet formal HTA criteria • No decision report is published

	Formal	Informal
 France	✓	✗
 Germany	✓	✗
 Hungary*	✗	✓
 Italy	✗	✓
 Poland	✓	✗
 Spain	✗	✓
 Sweden	✓	✗
 UK	✓	✗

*Available decision framework but not transparent (no publication of assessments)

HTA Ex Ante vs Ex Post Reimbursement

	Ex-ante	Ex-post
France	✓	✗
Germany	✗	✓
Hungary	✓	✓
Italy	✓ (National)	✓ (Regional)
Poland	✓	✗
Spain	✓ (National)	✓ (Regional)
Sweden	✓ (National)	✓ (Regional)
UK	✗	✓

HTA Key Decision Criteria

	Absolute therapeutic value*	Relative therapeutic value**	Budget impact	Cost-effectiveness
 France	✓✓✓	✓	✗	✓ (innovative products)
 Germany	✓	✓✓✓	✓	✗
 Hungary	✓	✓✓	✓✓✓	✓✓
 Italy	✓✓✓	✓✓✓	✓✓✓	✓
 Poland	✓✓	✓✓	✓✓✓	✓✓
Spain	✓✓✓	✓✓✓	✓✓✓	✗
 Sweden	✓✓✓	✓✓✓	✗	✓✓✓
 UK	✓	✓	✗	✓✓✓

*Disease severity and burden, unmet needs, efficacy/safety of the product
**Incremental efficacy/safety versus available comparators

Pricing Rules for Reimbursed Prescription Drugs

	Free pricing	International reference pricing	National reference pricing	Price negotiations	Managed entry agreements
 **France**	✗	✓ (main criteria for innovative drugs)	✓ (by active substance)	✓	✓
 **Germany**	✓ • Drugs eligible to EBA: up to 12 months after launch • Drugs non eligible to EBA	✓ (supportive criteria)	✓ (By active substance, pharmacological class, therapeutic class)	✓ (drugs eligible to EBA with added benefit or no reference price groups)	✓
 **Hungary**	✗	✓ (main criteria)	✓ (By active substance, pharmacological class, therapeutic class)	✓ (informal)	✓
 **Italy**	✗	✓ (supportive criteria)	✓ (by active substance)	✓	✓
 **Poland**	✗	✓ (supportive criteria)	✓ (By active substance, pharmacological class, therapeutic class)	✓	✓
 **Spain**	✗	✓ (supportive criteria)	✓ (by active substance)	✓	✓
 **Sweden**	✗	✗	✗	✗ (acceptance of rejection)	✓
 **UK**	✓ (indirect profit control through PPRS)	✗	✗	✗(indirect profit control through PPRS)	✓

Managed Entry Agreements

	Price-volume agreement	P4P individual	CED	Price discount	Cap volume/dose
France	✓✓✓✓	✗	✓✓	✓✓✓	✓
Germany	✓	✓	✗	✓✓✓✓	✗
Hungary	✓✓	✓✓	✓	✓✓✓	✓
Italy	✓✓	✓✓✓✓	✗	✓✓✓	✓✓✓✓
Poland	✓✓	✓✓	✓	✓✓✓	✓✓
Spain	✓✓	✓✓	✓	✓✓✓	✓✓
Sweden	✓	✓	✓✓✓✓	✗	✗
UK	✗	✗	✓	✓✓✓✓	✓✓

Conclusion

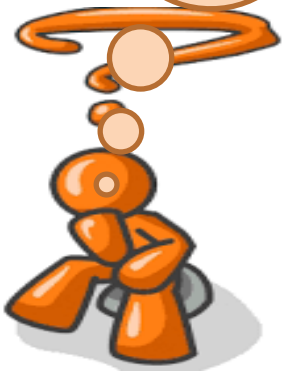
Future Trends and Coming Challenges

Cost-contrained Environment

Unprecedent increase demand

Decrease funding

Affordability?



Need of
adoption of cost-containment measures, to reduce expenditure growth for public health

Rapid Pace of Therapeutic Innovation

Dramatic advances in technology

Advanced-Therapy Medicinal Products	Personalized Medicines	Digitised medicine and big data
• Gene therapy medicinal product • Somatic cell therapy medicinal product • Tissue engineered product	• Medicines tailored to the specific characteristics of a patient (e.g. targeted therapies in oncology)	• Electronic-health-records • Computer based medical decision • Lost of clinical power in Rx decision

Therapies that might substantially extend survival times, even cure chronic and/or severe diseases

Easier analysis and utilization of rapidly growing, large repositories of health information

New Challenges in Drug Development

Development of companion diagnostic

Genomics leading to slicing population and combining innovative expensive treatment

Large benefit in small trials leading to early approval with limited evidence

- Uncertainty to be addressed post-launch

Shift of life-threatening disease to chronic diseases

- Validation of new surrogate endpoints to be considered

Fast development of available therapeutic alternatives, often making obsolete the comparator used in the drug development program

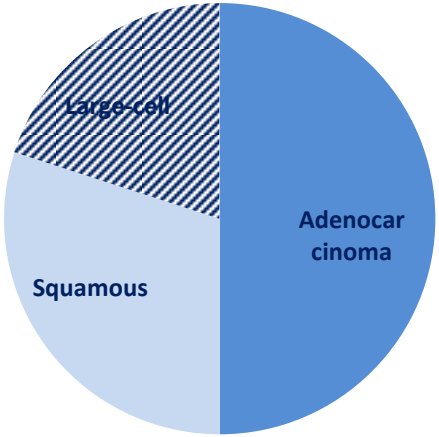
- Indirect comparison becoming unavoidable

New types of clinical trials emerging , known as clinical trials using genomic profiling

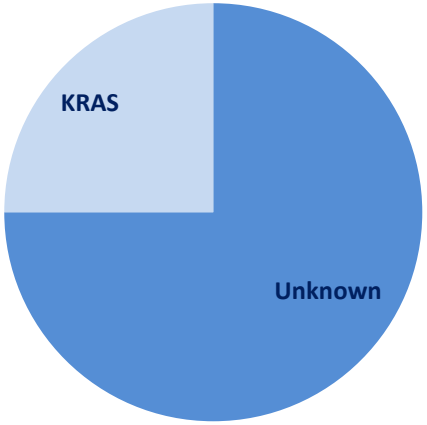
- Imply new methodologies such as integrated protocols (several phases in only one trial), use and comparisons of several treatments without marketing authorisation, new endpoints and adaptive designs

Genomics is a Moving Target

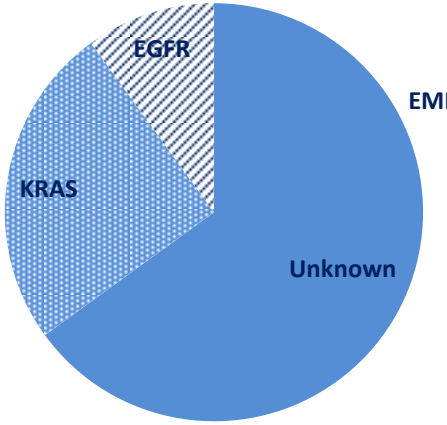
Traditional view



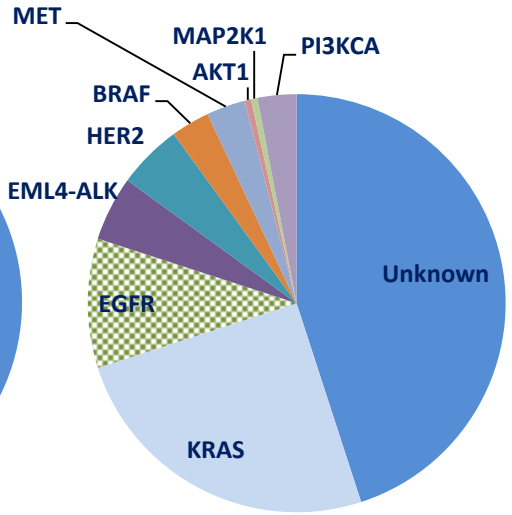
1987



2004

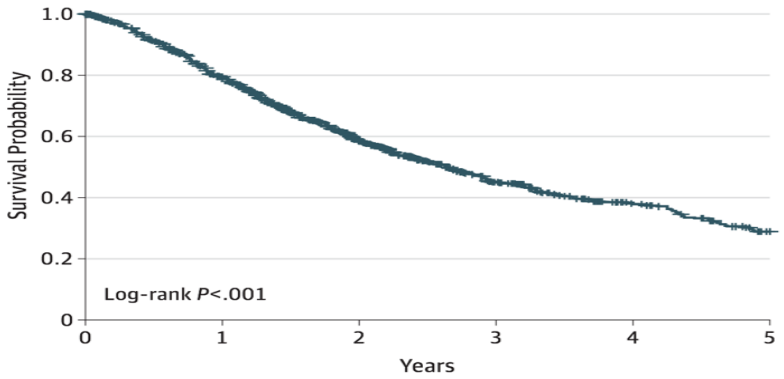


2009



Pao, Lancet 2011 Kris et al, JAMA 2014

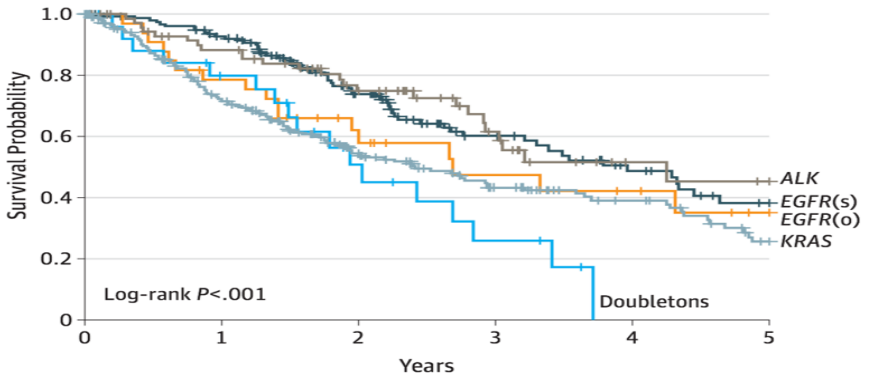
A All patients with adenocarcinoma, genotyping, and follow-up



No. at risk

All patients	938	680	375	195	115	66

B Patients with the 5 most frequent oncogenic driver mutations



No. at risk by oncogenic driver

EGFR(s)	158	137	80	41	26	16
EGFR(o)	33	25	15	9	7	3
ALK	74	59	41	21	8	6
KRAS	232	152	88	52	33	16
Doubletons	26	18	9	4		

Shift in Payer Model

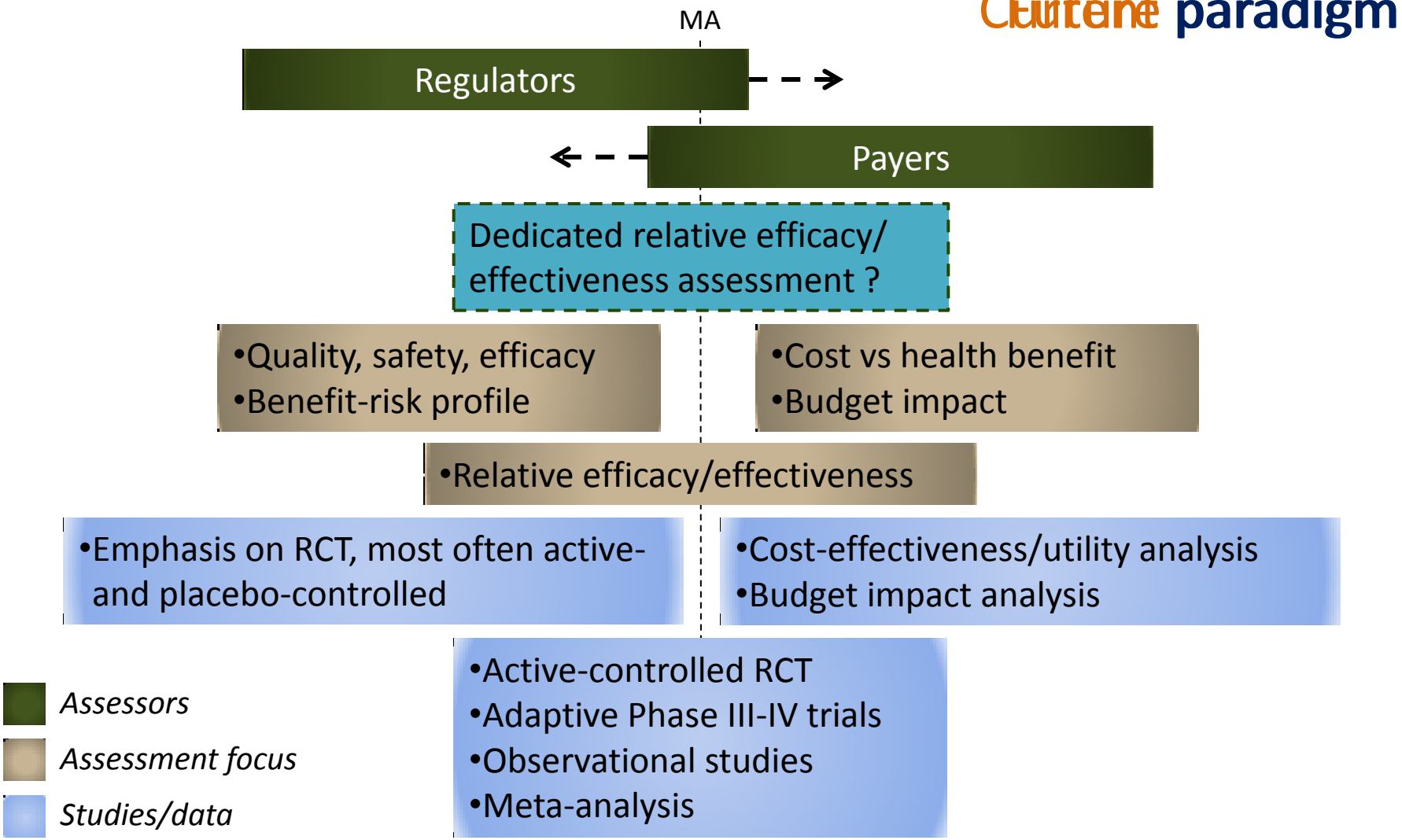
- The promised benefit must be evidenced in real life clinical practice
- Outcomes must be shown in well designed real world studies with limited or no intervention on the field or within databases
- The internal validity will be the door entry outcome
- The external validity will be the value acquired by payers

Clinical trials revolution will be challenging for payers

Recent international concept of “Adaptive Pathways” defined as a prospective planned and flexible approach to licensing and coverage of drugs and learning from real-world data

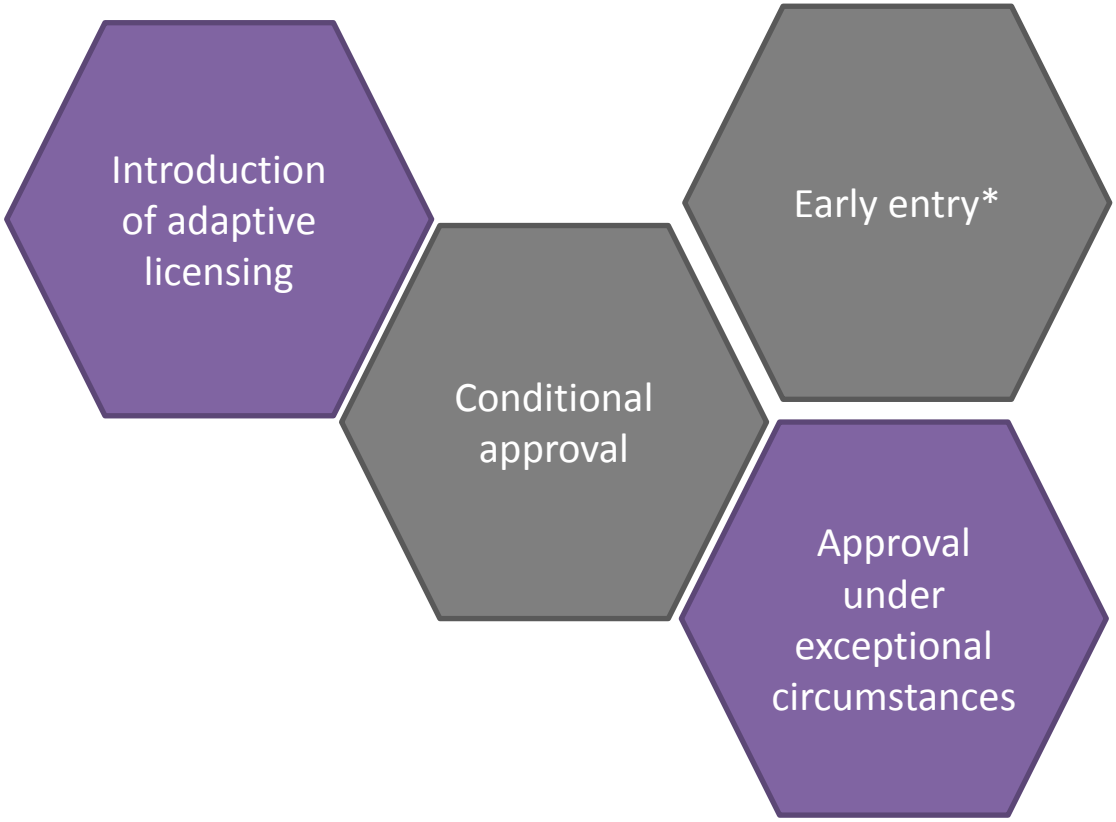
From a Trend to Reality

Current paradigm



Source: Eichler H.-G., Bloechl-Daum B., Abadie E., Barnett D., König F. and PearsonS. Outlook: Relative efficacy of drugs: an emerging issue between regulatory agencies and third-party payers *Nature Reviews Drug Discovery* 9, 277-291 (April 2010)

New Regulatory Processes is widening the gap with payers



- **Regulators impact**: earlier availability for patients
- **Payers impact**: level of evidence is lower

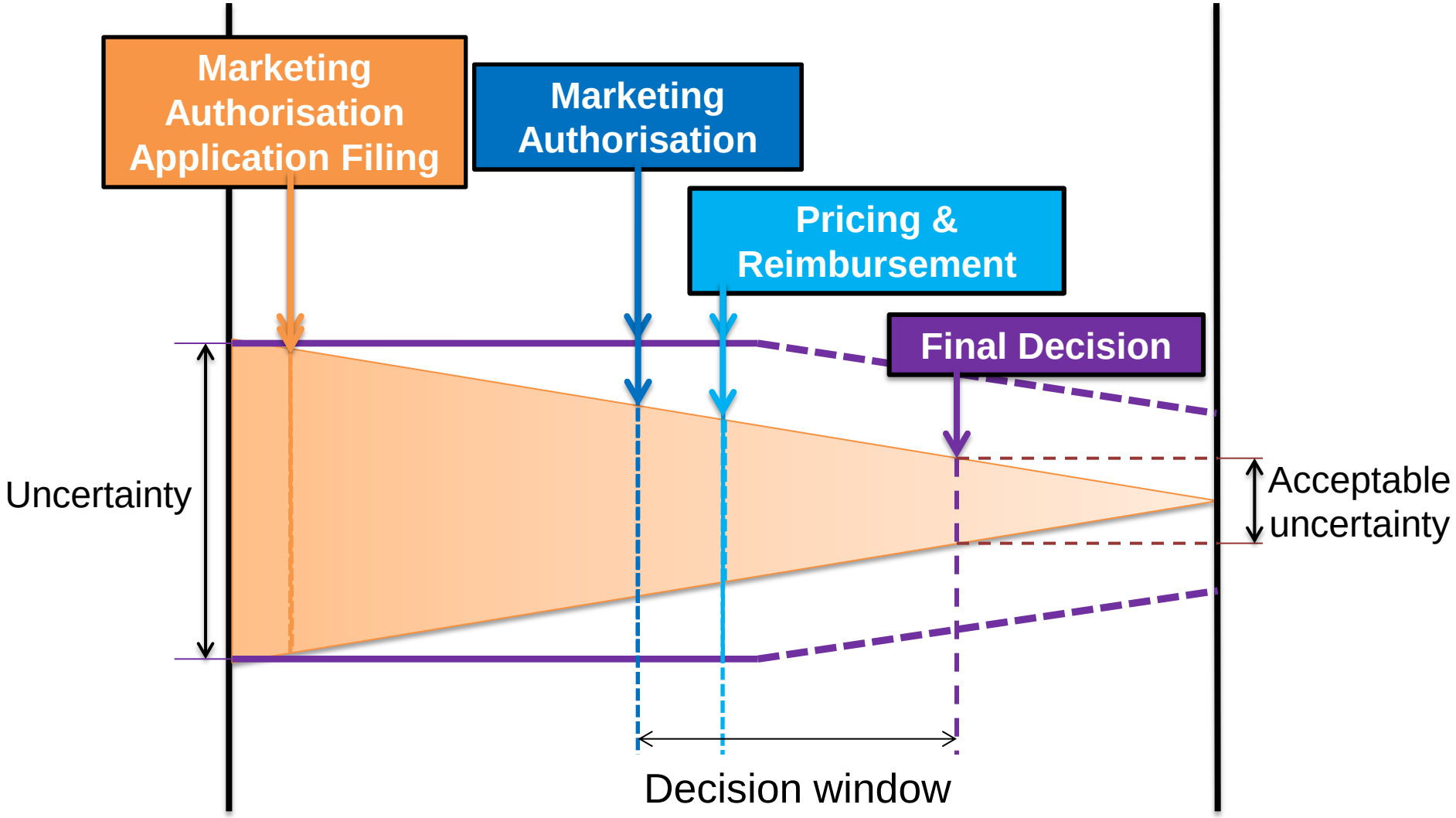
**access before marketing authorisation is granted*

Yesterday

no interest in managing post-launch uncertainty

Today

Management of uncertainty



The Window is Already Here

Some examples are well known and widely communicated in literature

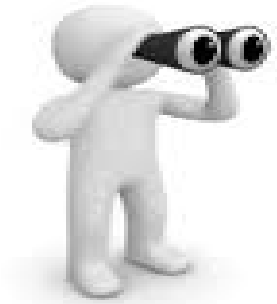
	Country	MA	CP	Final	Window
Risperdalconsta	France	07/01/2003	10/02/2005	End 2010	7 years
Sitagliptin	France	21/03/2007	03/2008	2010 (End of CED)	5years
	Scotland	03/2007	09/2007	06/2010	3.25 years
Duodopa	Sweden	2002	2003	2008	6 years

Time Limit G-BA Resolutions

Example of GBA decision window

Vemurafenib (1 y)	Sitagliptin (2 y)	Vandetanib (3 y)
Crizotinib (2 y)	Sitagliptin/metf (2 y)	Axitinib (4 y)
Eribulin (2 y)	Belatacept (3 y)	Ipilimumab (5 y)
Saxagliptin (2 y)	Cannabis sativa (3 y)	Pertuzumab (5 y)
Saxagliptin/metf. (2 y)	Fingolimod (3 y)	Bosutinib (5 y)

Window from 1 to 5 years



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Changes in Health Care Services Organisation

Integrated healthcare systems

Hospitals, multispecialty care delivery, other services, and coverage integrated into a comprehensive system for delivering care

- New funding model: from fee to services to outpatient service and all other related ancillary services included into a lump-sum payment
  - **Shift of decision-making from payers to healthcare providers**

Changes in Health Care Services Organisation

Integrated healthcare systems

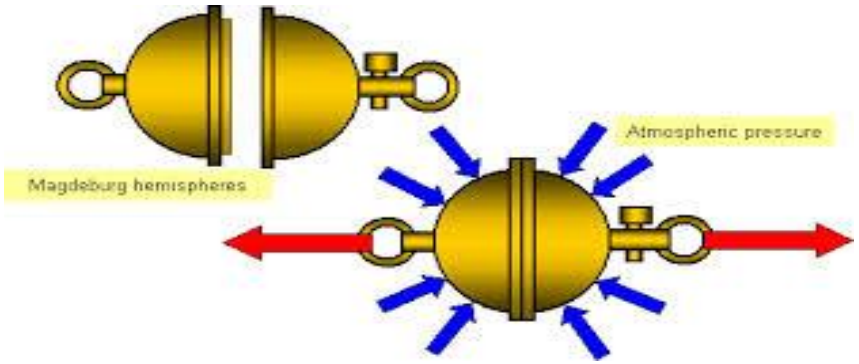
The client is changing but the client requirement and perspective are also changing

- New health economics model perspective:
- Move from from micro-economic assessment to a more macro-economic assessment

Systemic models identify impact on health care organization the entry of a new intervention

Bundled Payment

- Bundling payment of drugs to procedures, *(mirror Hospital DRG)*
- Example of ESA bundled to dialysis
  - Tenders become systematic
  - Competition driven by prices
  - Price discount up to 80%
- Shift of power negotiation from payers to healthcare providers

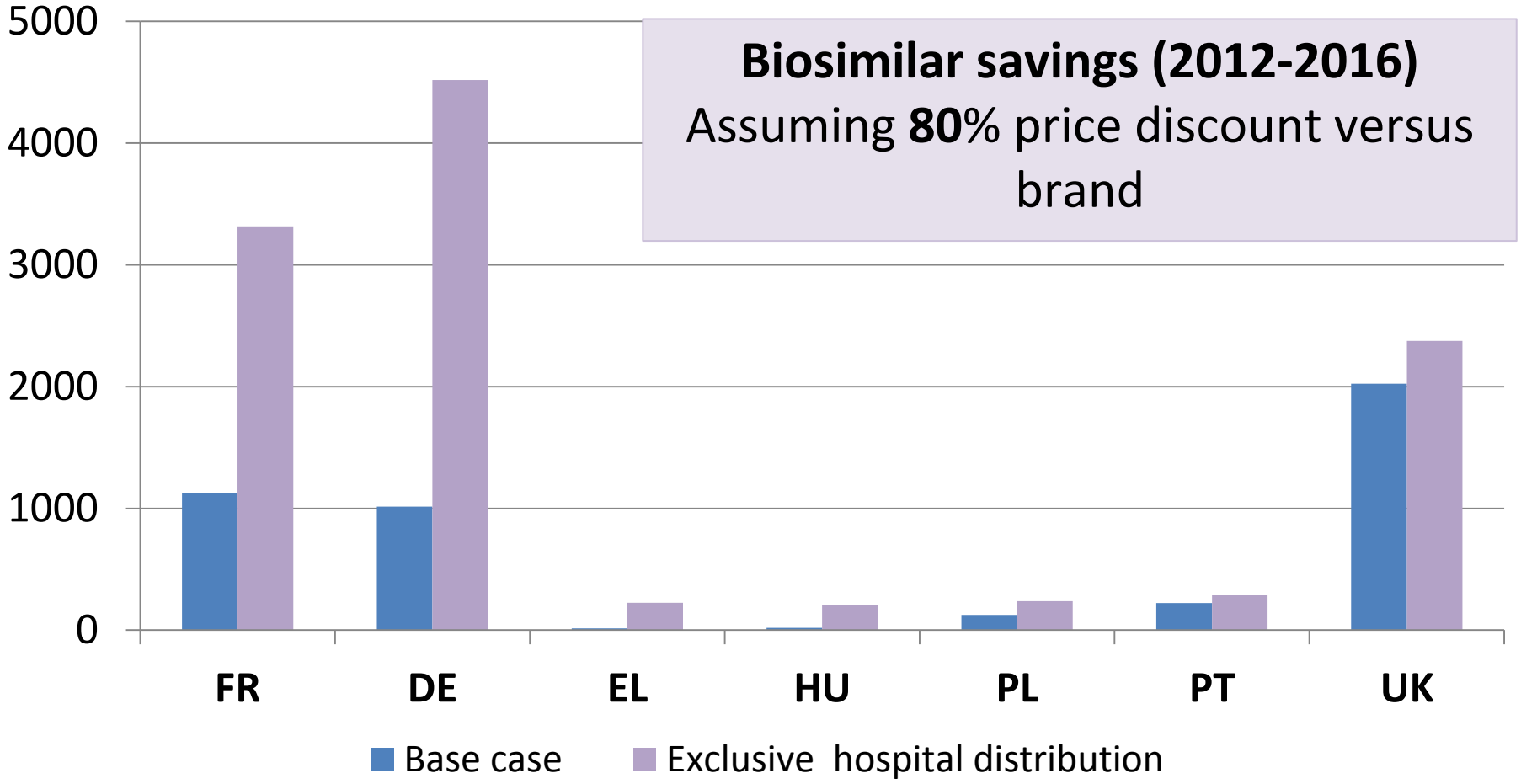


DRGs for outpatient services

- **Ambulatory Patient Group (APG)** is a classification system for outpatient services reimbursement developed for the American Medicare service by the Health Care Financing Administration (since 2010)
- APG reimbursement system does not recognize units of service.
  - nutrition counselling
  - crisis management
  - patient education including diabetes
  - asthma self management services
  - health/behavioral assessments

HOSPITAL RESTRICTED

Impact of Distribution of Biosimilars through Hospital (million €)*



Biosimilar savings (2012-2016)
Assuming **80**% price discount versus brand

*Health care public payer perspective

PRICE AS A POWERFUL OPTIMISATION TOOL BUT MAY BE DANGEROUS TOO

B

The Pricing Lock

25 years after GSK tritherapy we are back with Gilead.

Financial toxicity: An elephant in the room

- Discussion with patients about financial concerns represents a clear unmet need
- Many patients who are insured do not have adequate drug plan coverage and end up in bankruptcy.
- This has become socially unacceptable

"I'm right there in the room, and no one even acknowledges me."

Key Trends and Future Perspectives in P&R of Drugs in Europe

Greater pan-European coordination of HTA, and greater dialogue between regulatory and HTA bodies

More pragmatic approaches to clinical trial design pre- and post-launch

Increasing number of post-launch observational studies

- To meet outstanding regulator and HTA body requirements for relative effectiveness evidence

New funding mechanisms for high costs medicines

More adaptive approach to pricing and reimbursement

Openings to biosimilar substitution

Increasing use of managed entry agreements

Innovation is threatening sustainability of health insurance
Traditional reimbursement setting rules have to change

Traditional reimbursement setting rules will change

Thank you

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