Reimbursement Systems for Pharmaceuticals in Europe
Concept Mechanism and Perspective

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Part I. Reimbursement Concepts and Definitions
Health as a Good
• 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
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

Source: Economic Intelligence Unit, 2014; IMS Market Prognosis, September 2014
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

Source: OECD Health Statistics 2015
Global Project Spending on Medicines by 2016

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

Healthcare expenditure in 2013 (US$ per capita)

- **Sweden**
- **Spain***
- **Germany**
- **France**
- **UK**
- **Italy**
- **Hungary**
- **Poland**

Source: OECD data on healthcare expenditure in 2013

*Spain healthcare expenditure in 2011
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
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)
Orphan drug is the other pending tsunami with a couple of thousand of designated orphan drugs.
“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?
<table>
<thead>
<tr>
<th>Drug</th>
<th>ICER ($ / QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>40,000</td>
</tr>
<tr>
<td>B</td>
<td>53,300</td>
</tr>
<tr>
<td>C</td>
<td>57,100</td>
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<tr>
<td>D</td>
<td>125,000</td>
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</tbody>
</table>

Could Cost Effectiveness Resources Allocation?
<table>
<thead>
<tr>
<th>Drug</th>
<th>Health Gain (QALY)</th>
<th>ICER ($ / QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>250</td>
<td>40,000</td>
</tr>
<tr>
<td>B</td>
<td>300</td>
<td>53,300</td>
</tr>
<tr>
<td>C</td>
<td>70</td>
<td>57,100</td>
</tr>
<tr>
<td>D</td>
<td>80</td>
<td>125,000</td>
</tr>
</tbody>
</table>
## Need for Budget Impact?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Health Gain (QALY)</th>
<th>Cost (m$)</th>
<th>ICER ($ / QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>250</td>
<td>10</td>
<td>40,000</td>
</tr>
<tr>
<td>B</td>
<td>300</td>
<td>16</td>
<td>53,300</td>
</tr>
<tr>
<td>C</td>
<td>70</td>
<td>4</td>
<td>57,100</td>
</tr>
<tr>
<td>D</td>
<td>80</td>
<td>10</td>
<td>125,000</td>
</tr>
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<td>Cost (m$)</td>
<td>ICER ($ / QALY)</td>
</tr>
<tr>
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<tr>
<td>D</td>
<td>80</td>
<td>10</td>
<td>125,000</td>
</tr>
</tbody>
</table>

Assume your budget is 20 m$
From Cost-Effectiveness to Budget Impact
From Price to Value and Incremental Value
1. Prevent copy cat
   - Patent
   - Data protection

2. Value-based pricing
   - Often unknown and source of multiple confusion
Value-Based Pricing or Value optimized pricing is a business strategy. It sets selling prices on the *perceived* value to the customer, 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

Price

Benefit

A
B
C
D
E
VBP with CAP Price, Over Costs Charged by Private Insurance

Price

CAP Price

Benefit

Charged by private insurance
VBP with CAP Price
Managed by NHS

Price

CAP Price

Benefit

A

B

C

D

E
Market Access Paradigm
Market Access is becoming more and more a crucial element of the value chain
### Market Access is Different From Regulatory

<table>
<thead>
<tr>
<th>Regulatory</th>
<th>Market Access</th>
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</thead>
<tbody>
<tr>
<td>Fulfil the requirements of market authorisation</td>
<td>Negotiate with payers</td>
</tr>
<tr>
<td>Meet criteria for efficacy, safety and quality</td>
<td>Determine trade-offs between price and market access to achieve optimal return on investment</td>
</tr>
<tr>
<td>Deal with certainty</td>
<td>Deal with uncertainty</td>
</tr>
<tr>
<td>Transparent regulation</td>
<td>Not transparent, fast changing rules</td>
</tr>
<tr>
<td>Global</td>
<td>National to local</td>
</tr>
<tr>
<td>Marketing</td>
<td>Market Access</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>--------------------------------</td>
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<tr>
<td>Perception based</td>
<td>Evidence based</td>
</tr>
<tr>
<td>Audience not accountable</td>
<td>Price sensitive audiences</td>
</tr>
<tr>
<td>Opinion leaders are Key</td>
<td>Multiple stakeholders influence</td>
</tr>
<tr>
<td>Innocent until proved guilty</td>
<td>Guilty until proved innocent</td>
</tr>
</tbody>
</table>
From Approval to Funding

National agency
- Safety
- Efficacy
- Quality

Payers
- Funding, Price & Reimbursement
From Approval to Funding

- National agency
  - Safety
  - Efficacy
  - Quality

- HTA
  - Efficacy, effectiveness
  - & ICER
  - Evaluation for funding
  - or formulary listing

- Payers
  - Funding, Price &
  - Reimbursement
From Approval to Funding

- EMA
  - Safety
  - Efficacy
  - Quality

- National agency
  - Transpose decisions at a national level

- HTA
  - Efficacy, effectiveness & ICER Record for funding or formulary listing

- Payers
  - Funding, Price & Reimbursement
Payers are Heterogeneous
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)

- Private health insurance
- Member of HTA committees
- GPs in UK and Germany
- Employers
- Patients
- Hospital managers, Doctors
- Pharmacists in some countries
- Member of pricing committees

Payers
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

- Budget cap per product
- External reference pricing
- Index brand prices on generic
- Bundled payment
- Restricted prescription
- Budget cap for therapeutic class
- Price cut
- Reduced reimbursement
- Restricted distribution
- Restricted to hospital use
- Price-volume agreement
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
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.

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
Currently, the Netherlands and Germany are well known examples for ample use of public tendering.

- 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
A Matter of Culture Across Countries
• **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
• **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
• **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 uncertainty:**
Transferability of the clinical trial results to the real world setting;
It is not new but has become critical and ubiquitous.
Disease
Disease

Target
Disease
Disease

Specialists

GPs
Disease
<table>
<thead>
<tr>
<th>Disease</th>
<th>Mild</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
</tr>
</tbody>
</table>
This is real world!

- Disease
  - Mild
    - Treatment
  - Moderate
    - GPs
    - Failure
    - Efficacy
    - Disease 2 ± treatments
  - Severe
    - Hospital ± treatments
  - Specialist
    - Target
  - Pharmacists
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 where 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.
Behaviour is artificial and may not exist in real life
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
Pragmatic studies
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 models 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

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)**
- **Economic and Public Health Assessment Committee (CEESP)**

#### Reimbursement Rate
- **National Union of Health Insurance Funds (UNCAM)**

#### Pricing
- **Economic Committee for Healthcare Products (CEPS)**

#### Final Decision
- **Ministry of Health (MoH)**
Marketing Authorisation

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

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

Health Technology Assessment

French National Authority for Health (HAS)

Transparency Committee (CT)
Assessment of actual benefit (AB), improvement in actual benefit (IAB), target population

Economic and Public Health Assessment Committee (CEESP)
Health economic assessment

Pricing & Reimbursement Decision

National Union of Health Insurance Funds (UNCAM)
Reimbursement rate

Economic Committee for Healthcare Products (CEPS)
Price negotiation with pharmaceutical company*

Ministry of Health (MoH)
Inclusion in hospital list and reimbursement list

Publication in the Official Journal

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

Timelines (Months)**

~3.5
~3-4.5
~1-3

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

*Price notification for hospital drugs outside performance-based costing system (T2A)
### Medical Assessment by CT

#### Key Decision Drivers

<table>
<thead>
<tr>
<th>Actual benefit (AB)</th>
<th>Improvement in actual benefit (IAB)</th>
<th>Target population</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Disease severity</td>
<td>• Assessment by indication vs. comparators or therapeutic strategy</td>
<td>• Quantitative estimation of prevalence/incidence in France of the population who might benefit from the product in claimed indications</td>
</tr>
<tr>
<td>• Efficacy/safety</td>
<td>• Benefit mainly driven by the effect size of the incremental clinical efficacy benefit</td>
<td></td>
</tr>
<tr>
<td>• Position in the therapeutic strategy</td>
<td>• Safety and QoL considered if substantial burden</td>
<td></td>
</tr>
<tr>
<td>• Impact on public health</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Type of treatment (preventive, curative or symptomatic)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Driver of reimbursement rate

- Driver of price negotiation

- Driver of price-volume agreements
### Medical Assessment by CT

**AB and IAB**

**Actual benefit (AB)**
Service Médical Rendu (SMR)

**Improvement in actual benefit (IAB)**
Amélioration du Service Médical Rendu (ASMR)

<table>
<thead>
<tr>
<th>5 levels of AB</th>
<th>5 levels of reimbursement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>100%* or 65%</td>
</tr>
<tr>
<td>Important</td>
<td>65%</td>
</tr>
<tr>
<td>Moderate</td>
<td>30%</td>
</tr>
<tr>
<td>Weak</td>
<td>15%</td>
</tr>
<tr>
<td>Insufficient</td>
<td>0%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>IAB I</th>
<th>Therapeutic breakthrough</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAB II</td>
<td>Important improvement in terms of efficacy or safety</td>
</tr>
<tr>
<td>IAB III</td>
<td>Modest improvement in terms of efficacy or safety</td>
</tr>
<tr>
<td>IAB IV</td>
<td>Minor improvement in terms of efficacy or safety</td>
</tr>
<tr>
<td>IAB V</td>
<td>No improvement</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Channel</th>
<th>Retail</th>
<th>Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Listing of medicines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not reimbursed</td>
<td>Reimbursed</td>
<td>Retrocession</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Outpatient</td>
<td>Inpatient</td>
</tr>
<tr>
<td><strong>Reimbursement rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>15%-100%</td>
<td>65-100%</td>
</tr>
<tr>
<td><strong>Price setting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free pricing</td>
<td>Price negotiation with CEPS based on:</td>
<td>Ceiling price for reimbursement (price notification to CEPS)</td>
</tr>
<tr>
<td></td>
<td>• IAB level</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IRP (Germany, Italy, Spain, UK for IAB I-III)</td>
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<tr>
<td></td>
<td>• Competitors price</td>
<td></td>
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<tr>
<td></td>
<td>• Target population</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Budget impact</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Health economics evaluation (for innovative drugs)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• French financial context/situation of pharmaceutical industries</td>
<td></td>
</tr>
</tbody>
</table>

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

European Medicines Agency (EMA)/European Commission (European Level)

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

Institute for Quality and Efficiency in Healthcare (IQWiG)

Federal Joint Committee (G-BA)

Federal Association of Health Insurance Funds (GKV-SV)
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 2\textsuperscript{nd} 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**

<table>
<thead>
<tr>
<th>Timelines (Months)</th>
<th>Marketing Authorisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU Level: <strong>European Medicines Agency (EMA)/European Commission</strong></td>
<td></td>
</tr>
<tr>
<td>National Level: <strong>Federal Institute for Drugs and Medical Devices (BfArM)/Paul-Ehrlich-Institut (PEI)</strong></td>
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</tbody>
</table>

**Early Benefit Assessment**
- Manufacturer submits dossier to initiate AMNOG process

**G-BA Early Benefit Assessment (decision & publication)**
- **Additional benefit**
  - Eligible for premium price
- **Manufacturer/GKV-SV Reimbursement price negotiation**
  - (List price minus a negotiated discount)
- **Arbitration board**
  - (Neutral, manufacturer and GKV-SV)
  - Reimbursement price negotiation
  - (applies retroactively from the first day of the 13th month after product launch)
- **Manufacturer/GKV-SV Reimbursement price negotiation**
  - (Not exceeding the cost of comparative therapy)
- **Reference price**
  - Not eligible for reference price
  - **IQWiG Advice on level of benefit**
  - Recommendation
  - Reference price possible or possibility to create a reference group

**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**
**Drug benefit and drug additional benefit**

**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

Importance of robust comparison vs. appropriate comparative therapy to gain positive additional benefit assessment
**EBA: Methodology and Decision Drivers (2/2)**

### 4 Outcome Categories
- Mortality
- Morbidity
- Health-related quality of life
- Adverse events

### Quality of Available Evidence
- Proof (High)
- Indication (Moderate)
- Hint (Low)

### Extent of Effect Size
- Major
- Considerable
- Minor
- Not quantifiable

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**6 levels of additional benefit**

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

---

Additional benefit assessment based on available evidence, assessment of quality of available evidence and extent of effect size at outcome level.
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

<table>
<thead>
<tr>
<th>Retail</th>
<th>Hospital*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non eligible for EBA</td>
<td>Eligible for EBA</td>
</tr>
<tr>
<td>0%</td>
<td>100%</td>
</tr>
</tbody>
</table>

EBA eligibility

- Non eligible for EBA
- Eligible for EBA
- Hospital-only drugs

Reimbursement rate

- 0%
- 100%

Price setting

- Free pricing
- 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

*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
- Technical-Scientific Commission (CTS)
- Pricing & Reimbursement Committee (CPR)
- AIFA Board of Directors

Pricing & Reimbursement
- Italian Medicines Agency (AIFA)
- AIFA Board of Directors

Regional
- Regional HTA Bodies
- Regional authorities

Drug regional access

AIFA, Italiana del Farmaco; CTS, Commissione Tecnico Scientifica; CPR, Comitato Prezzi e Rimborso
P&R Process

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
### 3 key drivers for inclusion on reimbursement list

<table>
<thead>
<tr>
<th>Disease criteria</th>
<th>Product profile</th>
<th>Economic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Disease severity and burden</td>
<td>• Therapeutic value</td>
<td>• Price of therapeutic alternatives</td>
</tr>
<tr>
<td>• Unmet needs</td>
<td>• Level of innovation</td>
<td>• Budget impact</td>
</tr>
<tr>
<td></td>
<td>• Therapeutic alternatives</td>
<td></td>
</tr>
</tbody>
</table>

### Reimbursement classes and rates

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

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

**Criteria**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTS assessment of degree of innovation &amp; therapeutic value</td>
<td></td>
</tr>
<tr>
<td>Drug prices in other EU countries</td>
<td></td>
</tr>
<tr>
<td>Price of comparable existing therapies in Italy</td>
<td></td>
</tr>
<tr>
<td>Budget impact</td>
<td></td>
</tr>
<tr>
<td>Sales forecast</td>
<td></td>
</tr>
<tr>
<td><strong>Cost-effectiveness</strong></td>
<td></td>
</tr>
<tr>
<td>• Not a main driver in pricing decisions but can be provided by companies for innovative products and be used for pricing negotiations</td>
<td></td>
</tr>
</tbody>
</table>

- 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)
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)
Decision Making Bodies

**Marketing authorization**
- European Medicines Agency (EMA)/European Commission
- Spanish Medicines Agency (AEMPS)

**Central**
- Health Technology Assessment
  - National health Technology Assessment Agency (AETS)
  - General Subdirectorate of Quality of Medicines and Health Products (SGCMPS)
  - Interministerial Commission for Pricing of Medicinal Products (CIPM)

**Pricing & Reimbursement**
- Ministry of Health (MSSSI)

**Regional**
- Drug regional access
  - Regional HTA Bodies
  - Regional authorities
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

Final pricing and reimbursement decision

* In theory, the pricing and reimbursement process should take 6 months, while in practice it often takes longer
### 3 key drivers for inclusion on reimbursement list

<table>
<thead>
<tr>
<th>Disease criteria</th>
<th>Product profile</th>
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<td>• Budget impact</td>
</tr>
<tr>
<td>• Therapeutic alternatives</td>
<td>• Therapeutic alternatives</td>
<td></td>
</tr>
</tbody>
</table>

### 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 unemployed, 40%, 50% or 60% co-payment based on income with no maximum co-payment
    - **Pensioners**: 0% co-payment for underprivileged 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 (7 regional HTA agencies and drug 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
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
United Kingdom
## Decision Making Bodies

### Marketing authorization
- **European Level**: European Medicines Agency (EMA)/European Commission
- **National Level**: Medicines and Healthcare Products Regulatory Agency (MHRA)

### Health Technology Assessment
- **Opinion**: National Institute for Health and Care Excellence (NICE)
- **Decision**: Scottish Medicines Consortium (SMC), All Wales Medicines Strategy Group (AWMSG)

### Pricing
- UK Department of Health (DH)

### Funding
- Regional authorities
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)

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

<table>
<thead>
<tr>
<th>NHS England</th>
<th>NHS Wales</th>
<th>NHS Scotland</th>
<th>NHS Northern Ireland</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICE</td>
<td>NICE/AWMSG**</td>
<td>SMC</td>
<td>NICE***</td>
</tr>
</tbody>
</table>

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
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

<table>
<thead>
<tr>
<th>ICER &lt; £20,000</th>
<th>£20,000 &lt; ICER &lt; £30,000</th>
<th>ICER &gt; £30,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation likely to be positive</td>
<td>Recommendation not predictable</td>
<td>Recommendation likely to be negative</td>
</tr>
</tbody>
</table>

- 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

<table>
<thead>
<tr>
<th>NICE in England</th>
<th>SMC in Scotland</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scope</strong></td>
<td><strong>Scope</strong></td>
</tr>
<tr>
<td>• Binding guidance in England and Wales</td>
<td>• Binding guidance in Scotland</td>
</tr>
<tr>
<td><strong>Assessments</strong></td>
<td><strong>Assessments</strong></td>
</tr>
</tbody>
</table>
| • 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**       | **Remit**       |
| • Excludes vaccines and HIV therapies | • Excludes vaccines, generics, non-prescription-only medicines, blood products, plasma substitutes and diagnostic drugs |
| **Methodology** | **Methodology** |
| • Two different technology appraisal processes  
  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**      | **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: 4 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

## SMC: 3 main decision drivers

1. Clinical efficacy/safety
2. Cost-effectiveness analysis (ICER, cost/QALY)
3. Budget impact
**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**

- £21 million 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
POLAND
Decision Making Bodies

**Marketing authorization**
- European Medicines Agency (EMA)/European Commission
- Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (URPL)

**Health Technology Assessment**
- Agency for Health Technology Assessment and Tariff System (AOTMiT)

**Reimbursement & Pricing**
- Economic Committee (representatives of Ministry of Health and NFZ)

**Final Decision**
- Ministry of Health

**Transparency Council**
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)

**Pricing & Reimbursement Decision**

- **Ministry of Health:** Final pricing & reimbursement decision
- **Economic Committee (representatives of Ministry of Health and NFZ):** Pricing negotiations & reimbursement recommendations
- **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

**Timelines (Months):**

- **9** months

If positive decision, publication of P&R conditions
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

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>Proven efficacy in the treatment of malignant cancers, psychotic disorder, mental impairment, developmental disorder or infectious disease that constitutes serious threat to the population</td>
</tr>
<tr>
<td>100%+fixed co-payment (PLN 3.20)</td>
<td>Use &gt;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)</td>
</tr>
<tr>
<td>70%</td>
<td>Use &gt;30 days but do not meet criteria for 100% reimbursement</td>
</tr>
<tr>
<td>50%</td>
<td>Use ≤30 days but do not meet criteria for 100% reimbursement</td>
</tr>
</tbody>
</table>

*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
- Medical Products Agency (MPA) Läkemedelsverket

Health Technology Assessment & Reimbursement Decisions
- Dental and Pharmaceutical Benefits Agency (TLV)

Regional Access
- 20 County councils Pharmaceutical Comités
P&R Process Retail drugs

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
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 resubmit 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

The annual spending for products included in the pharmaceutical benefit scheme is limited for the patient.

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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 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 most 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

<table>
<thead>
<tr>
<th>Country</th>
<th>Formal</th>
<th>Informal</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>Germany</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>Hungary*</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Italy</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Poland</td>
<td>✓</td>
<td>✗</td>
</tr>
<tr>
<td>Spain</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Sweden</td>
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<td>✗</td>
</tr>
<tr>
<td>UK</td>
<td>✓</td>
<td>✗</td>
</tr>
</tbody>
</table>

*Available decision framework but not transparent (no publication of assessments)*
<table>
<thead>
<tr>
<th>Country</th>
<th>Ex-ante</th>
<th>Ex-post</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>✔️</td>
<td>❌</td>
</tr>
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<td>Germany</td>
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<td>✔️</td>
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<td>Hungary</td>
<td>✔️</td>
<td>✔️</td>
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<td>✔️ (National)</td>
<td>✔️ (Regional)</td>
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<td>✔️</td>
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<tr>
<td>Country</td>
<td>Absolute therapeutic value*</td>
<td>Relative therapeutic value**</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>France</td>
<td>✔ ✔ ✔</td>
<td>✔</td>
</tr>
<tr>
<td>Germany</td>
<td>✔</td>
<td>✔ ✔ ✔</td>
</tr>
<tr>
<td>Hungary</td>
<td>✔</td>
<td>✔ ✔</td>
</tr>
<tr>
<td>Italy</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
</tr>
<tr>
<td>Poland</td>
<td>✔ ✔</td>
<td>✔ ✔</td>
</tr>
<tr>
<td>Spain</td>
<td>✔ ✔ ✔</td>
<td>✔ ✔ ✔</td>
</tr>
<tr>
<td>Sweden</td>
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<td>✔ ✔ ✔</td>
</tr>
<tr>
<td>UK</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

*Disease severity and burden, unmet needs, efficacy/safety of the product

**Incremental efficacy/safety versus available comparators
### Pricing Rules for Reimbursed Prescription Drugs

<table>
<thead>
<tr>
<th></th>
<th>Free pricing</th>
<th>International reference pricing</th>
<th>National reference pricing</th>
<th>Price negotiations</th>
<th>Managed entry agreements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>France</strong></td>
<td>✗</td>
<td>✓ (main criteria for innovative drugs)</td>
<td>✓ (by active substance)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Germany</strong></td>
<td>✓</td>
<td>✓ (supportive criteria)</td>
<td>✓ (By active substance, pharmacological class, therapeutic class)</td>
<td>✓ (drugs eligible to EBA with added benefit or no reference price groups)</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>✓</td>
<td>(supportive criteria)</td>
<td>✓ (By active substance, pharmacological class, therapeutic class)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Hungary</strong></td>
<td>✗</td>
<td>✓ (main criteria)</td>
<td>✓ (By active substance, pharmacological class, therapeutic class)</td>
<td>✓ (informal)</td>
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<tr>
<td><strong>Italy</strong></td>
<td>✗</td>
<td>✓ (supportive criteria)</td>
<td>✓ (by active substance)</td>
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<td>✓</td>
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<tr>
<td><strong>Poland</strong></td>
<td>✗</td>
<td>✓ (supportive criteria)</td>
<td>✓ (By active substance, pharmacological class, therapeutic class)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Spain</strong></td>
<td>✗</td>
<td>✓ (supportive criteria)</td>
<td>✓ (by active substance)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Sweden</strong></td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗ (acceptance of rejection)</td>
<td>✓</td>
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<td><strong>UK</strong></td>
<td>✓ (indirect profit control through PPRS)</td>
<td>✗</td>
<td>✗</td>
<td>✗ (indirect profit control through PPRS)</td>
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## Managed Entry Agreements

<table>
<thead>
<tr>
<th>Country</th>
<th>Price-volume agreement</th>
<th>P4P individual</th>
<th>CED</th>
<th>Price discount</th>
<th>Cap volume/dose</th>
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<tr>
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<td>✔</td>
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</tr>
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<td>✗</td>
<td>✔ ✔ ✔ ✔ ✔</td>
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<tr>
<td>UK</td>
<td>✗</td>
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<td>✔</td>
<td>✔ ✔ ✔ ✔ ✔</td>
<td>✔</td>
</tr>
</tbody>
</table>
Conclusion

Future Trends and Coming Challenges
Cost-constrained Environment

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
- Gene therapy medicinal product
- Somatic cell therapy medicinal product
- Tissue engineered product

Personalized Medicines
- Medicines tailored to the specific characteristics of a patient (e.g. targeted therapies in oncology)

Digitised medicine and big data
- 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

- KRAS
- EGFR
- EML4-ALK
- HER2
- BRAF
- AKT1
- MET
- MAP2K1
- PI3KCA
- Unknown

Pao, Lancet 2011
Kris et al, JAMA 2014
• 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
NEW DEVELOPMENT PROGRAM AND REGULATORY PROCESSES WILL INCREASE PAYER UNCERTAINTY
From a Trend to Reality

Dedicated relative efficacy/effectiveness assessment?

- Quality, safety, efficacy
- Benefit-risk profile
- Cost vs health benefit
- Budget impact

Relative efficacy/effectiveness

- Emphasis on RCT, most often active- and placebo-controlled
- Cost-effectiveness/utility analysis
- Budget impact analysis

Active-controlled RCT
- Adaptive Phase III-IV trials
- Observational studies
- Meta-analysis

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*
IT IS ALREADY THERE, WE JUST HAVE NOT REALISED IT YET
Yesterday: no interest in managing post-launch uncertainty

Today: Focus on uncertainty

Acceptable uncertainty

Decision window

Marketing Authorisation Application Filing

Marketing Authorisation

Pricing & Reimbursement

Final Decision
Some examples are well known and widely communicated in literature

<table>
<thead>
<tr>
<th>Country</th>
<th>Date 1</th>
<th>Date 2</th>
<th>Date 3</th>
<th>Description</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperdalconsta</td>
<td>France</td>
<td>07/01/2003</td>
<td>10/02/2005</td>
<td>End 2010</td>
<td>7 years</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>France</td>
<td>21/03/2007</td>
<td>03/2008</td>
<td>2010 (End of CED)</td>
<td>5 years</td>
</tr>
<tr>
<td></td>
<td>Scotland</td>
<td>03/2007</td>
<td>09/2007</td>
<td>06/2010</td>
<td>3.25 years</td>
</tr>
<tr>
<td>Duodopa</td>
<td>Sweden</td>
<td>2002</td>
<td>2003</td>
<td>2008</td>
<td>6 years</td>
</tr>
</tbody>
</table>
### Example of GBA decision window

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Time Limit (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vemurafenib (1 y)</td>
<td>Sitagliptin (2 y)</td>
</tr>
<tr>
<td>Crizotinib (2 y)</td>
<td>Sitagliptin/metf (2 y)</td>
</tr>
<tr>
<td>Eribulin (2 y)</td>
<td>Belatacept (3 y)</td>
</tr>
<tr>
<td>Saxagliptin (2 y)</td>
<td>Cannabis sativa (3 y)</td>
</tr>
<tr>
<td>Saxagliptin/metf. (2 y)</td>
<td>Fingolimod (3 y)</td>
</tr>
<tr>
<td></td>
<td>Vandetanib (3 y)</td>
</tr>
<tr>
<td></td>
<td>Axitinib (4 y)</td>
</tr>
<tr>
<td></td>
<td>Ipilimumab (5 y)</td>
</tr>
<tr>
<td></td>
<td>Pertuzumab (5 y)</td>
</tr>
<tr>
<td></td>
<td>Bosutinib (5 y)</td>
</tr>
</tbody>
</table>

*Window from 1 to 5 years*
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.
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 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
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
25 years after GSK tritherapy we are back with Gilead.
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.
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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