MODELS FOR HEALTH ECONOMIC EVALUATION – A EUROPEAN PERSPECTIVE

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Agenda

- **Context**

- Selected European models of economic evaluation

- Some final remarks
The Pharmaceutical Market

Virtuous Cycle

- Investors (VC)
  - Public / Charitable sector
  - Bio Pharma companies

- Collaborations / Alliances

- Capital

- Discovery
  - (internal or external)

- Profits

- Returns

- Development

- NME

- Capital

- Drug

- Licensing

- Product

- Market

- Failure

- Costs

- Failure risk

- Failure

- Regulator demands

- Failure

- Costs

- Failure risk

- Failure

- Returns

- Cheap generics
  - Patent expiry

- Price/Volume controls
  - HTA
  - Competition
Overview – Five Global Challenges

Challenge 1: Increasing importance of specialised and stratified medicines

Challenge 2: Rising drug development costs

Challenge 3: Closer benefit-risk monitoring by regulators over a medicines’ life cycle

Challenge 4: Increase in demand for real world evidence of relative effectiveness by HTA, payers and regulators

Challenge 5: Disconnect between regulators’ and payers’/HTA bodies’ evidence needs

Key variables: Price * Volume * Time (and “VALUE”!)
Europe – Some Basic Facts

• European pharmaceutical market = US$243bn (25% of world) [Source: IMS World Review 2013]
• Large number of individual national markets which display differing characteristics
• Pricing and reimbursement (P&R) policies and economic evaluation models are likely to remain matters of national competence within EU for foreseeable future
• Range of possible policies is large and varied. The vigour with which they may be applied in different EU markets also varies
• Need a logical structure in order to analyse developments over time
Europe has primarily focused on prices e.g. price cuts and price freezes combined with product-focused policies

Plus use of HTA expanding – albeit with significant differences across countries
Agenda

• Context

• Selected European models of economic evaluation

• Some final remarks
1. What does the payer **value**?

2. How does the payer decide if sufficient value is present?
   - a) How is value **measured**?
   - b) What **evidence** is used to measure value?
   - c) How is the evidence **aggregated** in arriving at a decision?

Framework to assess different economic evaluation models
Approaches to “Value”

Two approaches by decision makers:

1. The use of formal Cost Effectiveness Analysis
2. “Therapeutic added value” approach
   - Both involve a comparison with other drugs or the standard of care (SoC) to link price to value
   - Price (P) can therefore be thought of as a function of the decision maker’s perception of value (V)
   - \( P = f(V) \)

Two definitions:

- Relative efficacy: how treatments work compared with existing alternatives in target narrow populations under closely controlled environments
- Relative effectiveness: how treatments work compared with existing alternatives under circumstances of usual care
Framework

EX-ANTE

Relative efficacy → Relative effectiveness → Added therapeutic value

EX-POST

Launch

Post-launch studies

P&R

Relative effectiveness, Cost-effectiveness

Guidance

Revise price/Rx decision (?)

Source: Mestre-Ferrandiz et al., 2010
England and Wales

Source: Mestre-Ferrandiz et al., 2010
Sources of value

Health gains measured as QALYs, cost against comparator, some aspects of severity, and other factors including equity

Measures of value

Incremental cost effectiveness ratio as compared to threshold value

End of life, paediatric or orphan patient population
The English System (Current)

Evidence of value

Incremental cost effectiveness ratio (ICER) established based on RCT data against comparator via an explicit economic model

Cost = NHS and personal social services costs (tax funded)

Effectiveness = quality adjusted life years (QALYs) – usually measured by EQ-5D instrument

End of life and orphan patients identified explicitly, implicit consideration of other evidence of patient disadvantage

Aggregation of value

Decisions heavily influenced, but not dictated, by comparing ICERs against £/QALY threshold range

Manufacturer sets price then NICE accepts or rejects for reimbursement

Possibility of Patient Access Schemes giving companies a 'second chance' to find an acceptable price

End of life modelled as a range of QALY multipliers

Other considerations weighed deliberatively by committees
NICE has become more binary in its decisions

Note: the multiple assessments that analyse a non-medicine health technology and a medicine health technology are counted only once.
Source: OHE analysis. Data from htain site.com. Until April 2014
Effect of Thresholds

Figure 4. Impact of ICER ranking on recommendations

Cost-effectiveness alone correctly predicted 82% of decisions;

recommendation, there is currently no evidence that the threshold has changed over time. The model with highest prediction accuracy suggested that a technology costing £40,000/quality-adjusted life year (QALY) would have a 50% chance of NICE rejection (75% at £52,000/QALY; 25% at £27,000/QALY).

Notes: Decisions are ranked by ICER, with NICE decisions to “recommend” shown in blue and to “reject” shown in red. For clarity, only the first five datasets of randomly-sampled ICERs are shown.

Source: Dakin et al., 2013 (available at www.ohe.org)
Distribution of NICE decisions for cancer medicines: before and after introduction of EoL criteria (2009)

Post-EoL era is associated with more cancer medicines rejections (Note: not all cancer medicines quality for EoL criteria)
NB Until April 2014

Source: OHE analysis. Data from htainsite.com
Cancer Drugs Fund

- For oncology medicines specifically, a “Cancer Drugs Fund” (CDF) was introduced in England in 2010
- Originally announced to run until 2014, it has now been given extra money and extended until 2016
- The CDF provides a means of improving patient access to cancer drugs, and is used to fund drug treatments, including radiopharmaceuticals, for patients who have been unable to access a drug recommended by their oncologist
- This includes drugs that are either not routinely available on the NHS or have not been approved or appraised by NICE. It also provides fast track access to cancer drugs that are awaiting NICE guidance as well as access to drugs for less common cancers
- There have been notifications for 41 medicines under the CDF (August 2014)
  - Four drugs – Bevacizumab, Abiraterone, Bendamustine and Cetuximab – account for nearly 53 per cent of all patient notifications (requests) to the CDF (http://www.kingsfund.org.uk/blog/2014/09/cancer-drugs-fund-inequitable-and-inefficient)
Cancer Drugs Fund associated with increase in NICE rejections and fall in restricted recommendations for cancer medicines
NICE’s Current Approach

- Certainty of the ICER: £20,000 per QALY
- HRQoL inadequately captured
- Innovative nature of technology
- Non-health objectives of the NHS
- Life extending treatment at the end of life: £50,000 per QALY

Source: NICE Consultation Paper – Value Based Assessment of Health Technologies
Proposed “Modifiers”

- Burden of illness
- Wider societal impact
- Certainty of the ICER
- HRQoL inadequately captured
- Innovative nature of technology
- Non-health objectives of the NHS

Source: NICE Consultation Paper – Value Based Assessment of Health Technologies
“Following a consultation, the Institute has decided to undertake further work before making changes to the way it appraises new medicines and other technologies for use by the NHS. It argues that any changes to NICE’s methods need to be made as part of a wider review of the innovation, evaluation and adoption of new treatments (including those for cancers) involving patients, people working in or with the NHS, the life sciences industries and health researchers” (18 September)

France

EX-ANTE

Relative efficacy
Relative effectiveness
Added therapeutic value (ASMR)

EX-POST

Launch

P&R

Post-launch studies

Relative effectiveness
Cost-effectiveness
Guidance

Revise price/Rx decision (?)

Source: Mestre-Ferrandiz et al., 2010
France - Overview

• Long history of SMR/ASMR rating
  • Determines copayments (SMR) and pricing (ASMR)
• SMR: absolute medical value
• ASMR: relative medical value
• Two key decision bodies:
  • “Haute Autorité de Santé” (HAS)
  • “Comité Economique des Produits de Sante” (CEPS) – sets prices
The “Medical Value” (Service Médical Rendu - SMR) rating is based on the following factors:

- efficacy/tolerance
- severity of the disease
- existence of therapeutic alternatives
- place in the therapeutic strategy (first line, second line, etc.); and
- public health impact

### Relationship between SMR rating, severity of disease and patient co-payment rate

<table>
<thead>
<tr>
<th>SMR</th>
<th>Disease</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Severe</td>
</tr>
<tr>
<td>Major or important</td>
<td>35%</td>
</tr>
<tr>
<td>Modest or low</td>
<td>65%</td>
</tr>
<tr>
<td>Insufficient</td>
<td>100%</td>
</tr>
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</table>
Price of new drugs determined by the level of therapeutic improvement relative to existing treatments is assessed using the ASMR (Amélioration du Service Médical Rendu)

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Major therapeutic progress</td>
</tr>
<tr>
<td>II</td>
<td>Significant progress in terms of therapeutic efficacy and/or reduction in side effects</td>
</tr>
<tr>
<td>III</td>
<td>Modest progress in terms of therapeutic efficacy and/or reduction in side effects</td>
</tr>
<tr>
<td>IV</td>
<td>Minor progress in terms of efficacy/usefulness (improved compliance, value added formulation, improved pharmacokinetic properties e.g. reduced risk of interactions)</td>
</tr>
<tr>
<td>V</td>
<td>No therapeutic progress</td>
</tr>
</tbody>
</table>

“Free” pricing – in line with prices in Germany, Italy, Spain and UK
France: SMR/ASMR Ratings (2008)
• Current reforms being implemented in France are part of an on-going discussion around pharmaceutical regulation, prompted by what has been termed the “Mediator scandal”

• Focuses on improving pharmacovigilance and pharmaceutical regulation

• But also new requirements around comparators
France: On-going Reforms

• But also includes a decree changing the comparator requirement for new medicines introduced to the French market – this can be viewed as part of an on-going trend in France
  • Manufacturers are required to provide evidence demonstrating that the new drug has an additional benefit against an active comparator as well as a placebo
  • The Transparency Committee (TC) is becoming more strict in its application of the SMR and ASMR criteria
  • Some uncertainties still exist around how comparator requirements will be implemented in practice
France: On-going Reforms

- Integration of SMR/ASMR rating into one index (relative therapeutic index; Index Thérapeutique Relatif, ITR)
- The generation of the ITR will be a sequential, semi-quantitative process
- The TC will first validate the primary and secondary efficacy endpoints and the comparator used by the sponsor, followed by an assessment of relative efficacy, primarily based on a product’s primary clinical endpoint and, if needed, also based on secondary criteria. The product’s tolerance and its administration will then be considered in setting the ITR in one of the five classes: Inferior, Identical, Slightly Superior, Moderately Superior, Very Superior
- HAS will then recommend to the Ministry of Health the reimbursement and pricing be applied as follows:
  - Inferior: No reimbursement
  - Identical: No reimbursement or reimbursement at a reduced price (vs. comparator)
  - Slightly superior: Reimbursement at same price of comparator
  - Moderately superior: Reimbursement at a negotiated price
  - Very superior: European price
France: On-going Reforms

• By law, an economic assessment will be required for products that either are viewed as having a significant impact on health economics or that will change the management of a disease

• At least two assessments:

  1. “Flash study” performed by reviewing the sponsor’s submission to verify validity and compliance with the HAS’s guidelines and to estimate the preliminary drug’s cost/efficacy ratio – this will be based on clinical data

  2. A study will then be designed and agreed with the firm to collect “real world” data and determine the incremental cost-effectiveness versus the comparator that is representative of standard practice. Timelines between the two assessments is presently unclear but is expected to be two to three years. Such cost/effectiveness assessment will lead to review and, if need be, to revise reimbursement, conditions of use and pricing of that drug
France: On-going Reforms

- Future role of economic evaluations – Methods guideline published in October 2012
  - QALYs are to be measured in cost utility analyses, where it is possible to get QALY data at reasonable cost
  - This has signalled a move to a more formalised economic evaluation process based on cost effectiveness
  - However, the methodology and processes recommended are much less formal than in the UK, for instance
AMNOG represents a paradigm shift in the way new drugs launched in Germany are assessed and priced

- It came into effect on 1 January 2011

The main difference pre- and post-AMNOG is the lack of free pricing

After more than 3 years of AMNOG, some tweaks to the system – see later
Fig. 1. The timeline of the dossier assessment according to the new bill in effect 1 January 2011. Shaded boxes display where and how the Institute for Quality and Efficiency in Health Care (IQWiG) comes in with regard to health economic criteria in the decision-making process on drug prices in Germany. AMNOG = Act to Reorganize the Pharmaceuticals’ Market in the SHI System; FJC = Federal Joint Committee; SHI = statutory health insurance.
AMNOG - Timelines

1. The manufacturer submits a comprehensive value dossier to the decision-making body, the Federal Joint Committee (GBA) – focusing on clinical / health gain and added value

2. The GBA, the IQWiG, (or another commissioned third party), has three months to determine the additional clinical benefit of the new drug relative to appropriate therapeutic alternatives (Early Benefit Assessment)

3. The manufacturer can then comment on the review in a hearing process. GBA analyses the hearing comments received, and, after another three months, passes a resolution as to whether or not the new drug does or does not have an additional benefit

4. If a drug is categorised as having ‘no additional benefit’, it is priced according to similar drugs in the same therapeutic reference group

5. If the drug provides an additional benefit, the GBA (or the IQWiG) assess the extent of additional benefit proven, by patient group. The size of the additional benefit is categorised on a six point scale (a “major” improvement corresponds to a score of 1 while a “smaller benefit” corresponds to a score of 6)

6. The manufacturer and the National Association of the Statutory Health Insurance Funds (GKV-SV) then negotiate a reimbursement price

7. If no agreement is reached, an arbitration board has three months to come up with a price
The German System

Sources of value

The German system is a search for efficacy. A valuable medicine is one with a proven and high efficacy, based on available RCT results.

Societal perspective is mentioned in the IQWiG methodology guide, but it is completely ignored in practice.

Measures of value

Mortality, morbidity, improvement in disease and quality of life

A medicine which only had effects on quality of life, without a clinical measure, would be rejected – need to show, for example, pain free days, returns to work.

Reduced side effects would be a useful addition measure, but would not gain approval without proven efficacy.
Evidence of value

Evidence presented in Germany must almost always be RCT-based.

More interest in direct measures of mortality. Reduction in blood pressure wouldn’t be a good measure, relative to showing actual reduced cardiac events. There is no comparison across disease areas.

Officially quality of life improvement is important, but tends to be of poor quality, and tends not to attract much weight.

Strength of evidence is very important: for two drugs, one showing uncertain evidence of a large effect, the other showing certain evidence of a small effect, the second would be approved while the first would not.

Aggregation of value

There is no aggregation in the IQWiG process. The most important outcome will drive the decision.

The main concern is avoiding uncertainty.
The quality (or probability) of proof is based principally on whether the evidence was generated using a direct active comparator (head-to-head) trial or was generated by an indirect comparison with the comparator deemed as most appropriate by the G-BA.

Evidence produced using the recommended (by the G-BA) direct comparator constitutes “proof” whilst evidence from indirect comparisons or inconclusive evidence is classified as an “indication” or a “hint”.

### AMNOG: Quality of the Evidence

#### Decision by G-BA

<table>
<thead>
<tr>
<th>Indication 1</th>
<th>Subgroup 1: Proof - important</th>
<th>Subgroup 2: Indication - slight</th>
<th>Subgroup 3: No additional benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication n</td>
<td>Subgroup 1:</td>
<td>Subgroup 2:</td>
<td></td>
</tr>
</tbody>
</table>

#### Additional Benefit

<table>
<thead>
<tr>
<th>Uncertainty</th>
<th>Additional Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROOF</td>
<td>Sustained improvement in outcome that was previously unattained compared to the appropriate comparator</td>
</tr>
<tr>
<td>INDICATION</td>
<td>Significant improvement in outcome that was previously unattainable compared to the appropriate comparator</td>
</tr>
<tr>
<td>HINT</td>
<td>A moderate and just small benefit that was previously unattainable with appropriate comparator</td>
</tr>
<tr>
<td>MAJOR</td>
<td>Scientific basis does not allow comparison</td>
</tr>
<tr>
<td>CONSIDERABLE</td>
<td>No additional benefit demonstrated</td>
</tr>
<tr>
<td>MINOR</td>
<td>Benefit of medicinal is smaller than that of the comparator</td>
</tr>
<tr>
<td>NOT QUANTIFIABLE</td>
<td></td>
</tr>
<tr>
<td>NONE</td>
<td></td>
</tr>
<tr>
<td>INFERIOR</td>
<td></td>
</tr>
</tbody>
</table>
G-BA often ‘sliced’ the total patient population into subgroups and assigned different additional benefit scores for the identified subgroups.

Of the total number of 40 subgroups, an additional benefit was reported in only about 50%

G-BA has not assigned the category of major additional benefit to any drug evaluated so far

Disagreement between the appropriate comparator therapy (ACTs) suggested by G-BA and the manufacturers

Advice meetings usually after PIII trials have started => not possible to take G-BA advice into account
Agenda

- Context
- Selected European models of economic evaluation
- Some final remarks
Country Specific Challenges

- United Kingdom: Value based assessment
- Germany: Focus on certainty
- France: Increasing cost consciousness
“Managed Entry Arrangements” - Overall

Continued and even growing interest in PBRSAs on the part of both manufacturers and payers

Clear slowdown in the growth of outcomes-based agreements in recent years

The number of new outcomes-based agreements is still small—mostly exceptional situations

Globally, there are increasing numbers of financially-based schemes

Source: ISPOR Issues Panel, 2014
“Managed Entry Arrangements” – Country specific

**Italy and Sweden** have invested in EHRs, and **Italy** has working P4P type arrangements tracking patients in registries for most new oncology drugs and for other drugs in high areas of uncertainty.

The experience in **Sweden** has been to assess effectiveness in the patient groups who receive the treatment leading to a review.

Recent **UK** experience has been based on confidential price discounts or de facto price discounts, with only a few pay-for-performance (e.g. Velcade) or CED schemes (e.g. Votrient). The NHS was scarred by the experience of the multiple sclerosis risk-sharing scheme.

In the **Netherlands**, hospital schemes are seen as a failure: evidence was not collected.

Arguably, what we see in Europe is experimentation and then either (i) retreat (UK and Netherlands) or (ii) an established pattern of use (Italy and Sweden).
To enquire about additional information and analyses, please contact Dr. Jorge Mestre-Ferrandiz at jmestre-ferrandiz@ohe.org

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