L’ÉCONOMIE DE LA SANTÉ

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La pharmaco-économie dans le cycle de développement des médicaments : opportunités et défis

Lieven Annemans

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The innovation cycle

Value deficit

The market usage challenge

Provide Value for money

Add value

The development challenge

The market access challenge
Key problems in the innovation cycle

- Value deficit
  - Overuse
  - Lack of transparency

- Slow, rigid and expensive processes

- Add value
  - Provide Value for money

- High prices
  - Lack of consistency
  - Lack of transparency
The difficult exercise:

Sustainability of the healthcare system  
Sustainability of the innovative industry

Health for all
What should we aim for?

“We need to **make available** and **stimulate** innovative technologies/medicines that offer a **therapeutic or societal benefit at an acceptable cost** (i.e. are **cost-effective**), and **fill unmet medical needs**”

Report of the Belgian EU Presidency, 2010
The problem with innovative medicines

• “these prices are too high”
• “the budgets will explode”

• “these medicines offer huge benefits on survival and QoL”
• “the medical need is very high”
How is a price for a new medicine set by pharma?

1. The costs of manufacturing, R&D (including failures), marketing and promotion, overheads, distribution
2. The expected market size
3. The costs of current treatment
4. Price elasticity of demand
5. Price regulations and pricing policies
6. The value of the benefits of the product
Pricing = basically two options

• OPTION 1 : “cost+” price → price justified by costing structure.
  😊 acceptable mark-up as compensation for the costs of investment in R&D
  – difficult to assess the true cost of R&D (what about failures?)
  – wrong incentives (‘spend a lot on R&D’)
  – added value not sufficiently recognized
We want to know your R&D costs

That’s impossible to calculate
COST+ in practice

“We still want it; otherwise no funding”

“OK we’ll see what we can do”
COST+ in practice

“I don’t believe you. Just give us a discount”

“It is XYZ millions of Euros”
Pricing = basically two options (2)

- **OPTION 2 : Value based pricing**
  - Better added value is recognized by better rewarding
  - Profit margin may not be in reasonable proportion to the cost structure → risk for “unlimited” prices
  - Evidence often not sufficiently convincing at launch
Value for money

Cost

Health effect (QALYs)

Current care

C-EFF

Not C-EFF

Threshold

New 1

New 2

New 3

dominant
PROBLEM: where is the threshold?

- Desaigues et al (2007): willingness to pay method: €40,000 per Healthy Life Year (for EU25 countries)?
  - BUT average for EU, 10 years ago, willingness to pay depends on ability to pay

- BENCHMARKING
  - e.g. cost-effectiveness of caring for a dialysis patient
  - historically 50,000 $ per QALY
  - BUT now 100,000 $ per QALY

- WHO: 1 to 3 times GDP per capita (e.g. Belgium = +/- €37000) http://www.who.int/choice/costs/CER_thresholds/en/
  BUT RECENTLY CHALLENGED BY THE WHO ITSELF
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost per QALY gained (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive cardiovascular rehabilitation in CHD</td>
<td>dominant</td>
</tr>
<tr>
<td>Procoralan Chronic Heart Failure</td>
<td>6,000</td>
</tr>
<tr>
<td>Total Hip Replacement</td>
<td>10,000</td>
</tr>
<tr>
<td>Brillique Acute Coronary Syndrome</td>
<td>14,000</td>
</tr>
<tr>
<td>Prezista HIV</td>
<td>16,000</td>
</tr>
<tr>
<td>Sovaldi HCV</td>
<td>18,000</td>
</tr>
<tr>
<td>Velcade multiple myeloma</td>
<td>30,000</td>
</tr>
<tr>
<td>Tysabri MS</td>
<td>47,000</td>
</tr>
<tr>
<td>Annual mammography for women aged 60-70yr</td>
<td>70,000</td>
</tr>
<tr>
<td>Annual CT for 60 year-old heavy smokers</td>
<td>130,000</td>
</tr>
</tbody>
</table>

CTG/CRM (RIZIV) (at official prices)
Cost-effectiveness of some orphan drugs

Table 1. Preliminary cost per quality-adjusted life year incremental cost–effectiveness ratio estimates by NICE (2008).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence (England)</th>
<th>Product</th>
<th>ICER (preliminary estimated £ per QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. Gaucher type I and III</td>
<td>270</td>
<td>Imiglucerase (Ceredase®)</td>
<td>391,200</td>
</tr>
<tr>
<td>MPS type 1</td>
<td>130</td>
<td>Laronidase (Aldurazyme®)</td>
<td>334,900</td>
</tr>
<tr>
<td>M. Fabry</td>
<td>200</td>
<td>Agalsidase beta (Fabrazyme®)</td>
<td>203,000</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>350</td>
<td>Nonacog alpha (BeneFIX®)</td>
<td>172,500</td>
</tr>
<tr>
<td>M. Gaucher type I</td>
<td>270</td>
<td>Miglustat (Zavesca®)</td>
<td>116,800</td>
</tr>
</tbody>
</table>

These examples from England illustrate the mismatch between ultra-orphan drug cost and conventional cost–effectiveness benchmarks as adopted by NICE (i.e., £20,000 to £30,000 per QALY gained) [8].


Medical/therapeutic Need
(Scitovsky)

Low need → no funding

High need → more solidarity
→ invest more

Acceptable health
So maybe this plane is more relevant?
The Australian criteria (PBAC)

- Comparative health gain (effectiveness, safety)
- Comparative cost effectiveness
- Patient affordability in absence of PBS/MBS subsidy
- Financial implications for PBS, MBS and government health budgets
- Severity of medical condition treated
- Presence of effective alternatives
- Ability to target therapy to those likely to benefit most
- Uncertainty
- Equity (including affordable access and equity assumptions implicit in the economic evaluation)

Plus rule of rescue
Zorginstituut NL (ZIN): variable threshold

- €80,000 per QALY for severe condition, even up to €100,000 at end-of-life
- €50,000 per QALY for moderate burden
- €20,000 per QALY for mild burden
Budget impact

“The economic and equity rationale for carrying out budget impact analyses is opportunity cost, or benefits forgone by using resources in one way rather than another”

Need for estimates at population level!

BUT: not only budget impact !!!!

Birch and Gafni (2006); Cohen et al (2008)
Cost–effectiveness information should be used alongside other considerations – e.g. budget impact and feasibility considerations – in a transparent decision-making process, rather than in isolation based on a single threshold value.
How to link all of this?
Value Informed & Affordable Prices

Willingness to pay

Burden/therapeutical need

Very low budget impact
Low budget impact
Moderate budget impact
High budget impact
... and what about uncertainty?
Uncertainty in practice

“Give us more evidence that your medicine is value for money”

“Allow us first to the market (reimburse the medicine) and then we will be able to show real life evidence”
Example ipilimumab
2 key types of outcomes based contracts

1. Coverage upon evidence development
   - *Temporary approval, then final decision*

2. Performance Linked Reimbursement (outcomes guarantee)
   - *Not as good as promised → industry pays back*
Types of agreements (Toumi et al 2016; n = 143)

- Financial agreements: 39%
- Coverage upon evidence: 37%
- Development: 24%
- Outcomes guarantee/P4P: 39%

Appl Health Econ Health Policy. 2016 Aug 31
The innovation cycle

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Threats for such schemes

- Confounders (e.g. taking other drugs)
- Case-mix
- Exceptions
- Objective measurement of indicator?
- Workload for physicians
- Administrative workload

Source: Coulton et al. 2012
When does it work?

1. Make clear what evidence is required for the next stage.
2. Match the appropriate study and research design to the uncertainties being addressed.
3. Implications of not meeting the requirements and expectations should also be agreed upon at the start of each step.
4. Ensure fast collection of high quality and accessible real life data.
5. Data governance and transparent public private partnerships between the health care system and the industry.
Which is the right attitude?

• Wa have no data, so all is lost
• We have data. What should we do with it?

OR

• We have a research question. What data do we need to answer that question?
Post Launch real world evidence (RWE)

a) Collection of data to validate earlier made assumptions (non comparative)

= Extended follow up to assess effectiveness and safety
  1) Prospective $\rightarrow$ more complete, but more expensive and ‘participation bias’
  2) Retrospective $\rightarrow$ really real, but data gaps

b) Real life comparison of technologies (real patients, real treatment setting, ...)
  1) Prospective (see above)
  2) Retrospective (see above, PLUS selection bias)
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A typical process

TARGET PRODUCT PROFILE

TPP

- Preclinical
  - Phase I
  - Phase II
  - Phase III

- Early Models
  - 2b Models
  - Cost of Illness studies
  - QoL & Utility measurement

- 2b Models
  - Piggy back
  - Reimbursement Models

- Phase III
  - Launch Date
  - Real life data post marketing
Early models: simple example

Key questions in this example:

→ What is the incidence of failure in real life? Is it 20%? Everywhere? ...
→ What is the health burden of failure/disease? QALY loss?
→ How is failure managed in real life? Differences between settings?
→ What is the cost of failure?
→ ....
The purposes of Early Health economic modelling

– input into go/nogo and in priority setting decisions
– guide the decision on further development, ...
  • in specific indications/patient groups, ...
    – only in high risk, only if already N relapses, ...
  • to be positioned in comparison with specific competitors, ...
    – Not competitive against drug A in 1st line, but against drugs B or C after failure of A
  • with a given time horizon, ...
    – Key driver is sustainability of effect → longer trial needed
  • focussing on a given very sensitive parameter (the management of a given adverse event, the level of compliance, ...)
Example of a result: TORNADO

Cost of treatment (10€ - 30€ per day) (basecase = 20)
Prob of treatment success (50-70%) (basecase = 60)
Utility value of event (0.3-0.6) (basecase = 0.45)
Prob of treatment success for Comparator
Cost of treating Adverse Event for Comparator
Cost of Comparator treatment
Prob of Adverse Event for Comparator
...
Phase II, III

• Product team with clinical, marketing, regulatory and health economics/pricing, and some country affiliates represented
• Early model is a *continuously evolving tool* for decision making on Positioning; Pricing; Clinical development
• Use trial endpoints and design that meet requirements of EMA and payers
EFFICIENCY GAINS VIA PUBLIC PRIVATE PARTNERSHIPS?

Introducing IMI

IMI's goals

The Innovative Medicines Initiative (IMI) is working to improve health by speeding up the development of, and patient access to, innovative medicines, particularly in areas where there is an unmet medical or social need. It does this by facilitating collaboration between the key players involved in healthcare research, including universities, the pharmaceutical and other industries, small and medium-sized enterprises (SMEs), patient organisations, and medicines regulators. IMI is a partnership between the European Union (represented by the European Commission) and the European pharmaceutical industry (represented by EFPIA, the European Federation of Pharmaceutical Industries and Associations).

The budget

IMI is the world's biggest public-private partnership (PPP) in the life sciences. Through the IMI 2 programme, it has a €3.3 billion budget for the period 2014-2024. Of this:
Aligning clinical trials and market access

WELL DESIGNED Clinical trials

Safety
Efficacy
HE outcomes

(Modeling)

(Morbidity)
(Mortality)
(PRO/HRQoL)
(Resources use)

Authorisation

“Real-world” modeled effectiveness and cost-effectiveness

Databases
Literature
Cohorts
Local unit costs

Into Modeling

Into Modeling

Market access
Introduction of HPV vaccines in European Union countries – an update
Value Informed and Affordable Prices – model to be completed with evidence of reasonable profits
10 recommendations for a joint solution

1. Public Private Partnerships (IMI) to facilitate development of innovations
2. Early economic evaluations (based on TPP)
3. More efficient development processes
   → Faster and more efficient development in line with what we need
4. **Value based pricing**
5. Importance of **medical need** (involve citizens and patients!) and **budget impact** to review/modulate the cost/QALY thresholds
6. **Explicit societal limits** & value for money benchmarks
7. **Price competition** between similar products
8. Outcomes based agreements
9. Industry to show reasonable profit margins
10 recommendations

10. Stimulate the right usage of the innovations, monitor their use (contracts)
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