Orphan Drugs in a Budget Constraint Healthcare System

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Pr. Mondher Toumi
Aix Marseille University
The demand is growing fast in an increasingly constraint environment
Around 10% of GDP is spend on healthcare in Europe

Source: OECD 2017
Pharmaceutical and total health expenditures grew at a higher rate than the mean annual growth rate of GDP for the OECD countries between 2000 and 2015.

Source: OECD data
GDP: Gross Domestic Product
Notes: values are average value for total OECD countries
Year 2000 was considered 100%
Sustainability Gap of the Healthcare System by Country

A positive healthcare sustainability gap is identified. Each year a larger part of the GDP of these countries is allocated to health care.

The graph shows the difference between average real growth rate per capita total health care spending and real per capita GDP growth rate 2000-2008.

Widening the gap?

Unsustainable gap between healthcare expenditure level on one side and affordability and demand on the other side.
Current Situation

While governments are trying to cut the healthcare expenditure growth

The number of very promising molecules in development is increasing
Rapid Pace of Therapeutic Innovation

Dramatic advances in technology

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

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
High Prices of Orphan Drugs
USA, EU & Japan Orphan Designations
Cumulative Total: Fast Increase

Source: EvaluatePharma® 30 September 2015
Innovation High Prices
Some approved Cell and Gene therapies

- **Glybera®**
  - Lipoprotein lipase deficiency
  - Gene therapy
  - Price per patient: €1,1M
  - Withdrawn recently

- **Strimvelis**
  - Adenosine deaminase deficiency
  - Gene therapy
  - Price per patient: 594 000€

- **KYMRIAH™**
  - Cell-based gene therapy
  - Acute lymphoblastic leukemia
  - Price per patient: 475 000$  

- **YESCARTA™**
  - CAR-T cell therapies
  - Diffuse large B-cell lymphoma
  - Price per patient: 373 000$

- **Online Consultation**: Sustainable access to innovative therapies
# Number of Orphan Drugs with Available Prices

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of orphan drugs with available price</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>67 (exclude hospital products)</td>
</tr>
<tr>
<td>Germany</td>
<td>68</td>
</tr>
<tr>
<td>Italy</td>
<td>83</td>
</tr>
<tr>
<td>Norway</td>
<td>67</td>
</tr>
<tr>
<td>Spain</td>
<td>42</td>
</tr>
<tr>
<td>Sweden</td>
<td>35</td>
</tr>
</tbody>
</table>

## Orphan Drugs Annual Treatment Costs in Seven EU Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Minimum annual cost</th>
<th>Maximum annual cost</th>
<th>Mean annual cost</th>
<th>Median annual cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>€1 500</td>
<td>€912 600</td>
<td>€103 744</td>
<td>€32 100</td>
</tr>
<tr>
<td>Germany</td>
<td>€3 285</td>
<td>€1 051 956</td>
<td>€142 194</td>
<td>€51 598</td>
</tr>
<tr>
<td>Italy</td>
<td>€755</td>
<td>€823 617</td>
<td>€80 457</td>
<td>€31 294</td>
</tr>
<tr>
<td>Spain</td>
<td>€980</td>
<td>€912 600</td>
<td>€75 035</td>
<td>€37 986</td>
</tr>
<tr>
<td>UK</td>
<td>€937</td>
<td>€1 012 677</td>
<td>€95 533</td>
<td>€42 085</td>
</tr>
<tr>
<td>Sweden</td>
<td>€1 906</td>
<td>€469 513</td>
<td>€72 802</td>
<td>€46 044</td>
</tr>
<tr>
<td>Norway</td>
<td>€803</td>
<td>€927 706</td>
<td>€113 770</td>
<td>€36 600</td>
</tr>
</tbody>
</table>

France Annual Treatment Cost Per Prevalence (0–1 Per 10,000)

When the annual costs were adjusted using GDP per capita, EU-5 and the Nordics maintained the minimal differences in median cost ratios. However, the lower GDP countries Bulgaria, Romania, Poland, and Hungary showed higher median costs than high-GDP countries, and 3 to 6 times higher costs than the UK.
Launch Prices of New Drugs are Increasing at a High Pace

Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval 1965-2016

Source: Peter B. Bach, MD, Memorial Sloan Kettering Cancer Center
Cost & Return on Investment for Orphan vs Non-orphan Drugs
The graphs show the mean results over the period 2007–2011 for five baskets of six to seven companies, drawn from 33 publicly traded companies. The following financial indicators for each basket were analysed: gross margin; spending on research and development (R&D) as a percentage of sales; EBITDA margin (a measurement of a company’s operating profitability), equal to earnings before interest, tax, depreciation and amortisation (EBITDA) divided by total revenue; return on accounting equity; and return on equity (ROE) on market capitalization.

Mrel, T, Popa C, Simoens S, Market watch: Are orphan drug companies the pick of the pharmaceutical industry? Nature Reviews Drug Discovery 13, 10(2014)
Influence of Orphan Designation Status on Price

• Picavet E et al, demonstrated that awarding orphan designation status in itself is associated with higher prices for drugs for rare disease indications
• Prices for 28 designated orphan drugs and 16 comparable non-designated drugs for rare disease indications were compared.
• Sensitivity analysis confirmed the robustness of the results

Median price per DDD for designated orphan drugs:
138.56 €
Interquartile range
406.57 €

Median price per DDD for Non-designated orphan drugs:
16.55 €
Interquartile range
28.05 €

p < 0.01

Average Cost per Patient per Year 2010-2014

Source: EvaluatePharma® 30 September 2015
Median Cost per Patient per Year 2010-2014

Source: EvaluatePharma® 30 September 2015
## R&D Costs (Phase III/Filed) & Expected Investment Returns (NPV)

<table>
<thead>
<tr>
<th>Type</th>
<th>Number of patients</th>
<th>Phase III costs ($bn)</th>
<th>As a %</th>
<th>Number of products</th>
<th>NPV / Phase III Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orphan</td>
<td>44,357</td>
<td>6.9</td>
<td>23%</td>
<td>69</td>
<td>12.7</td>
</tr>
<tr>
<td>Non-orphan</td>
<td>426,951</td>
<td>23.1</td>
<td>77%</td>
<td>117</td>
<td>11.1</td>
</tr>
<tr>
<td>Total</td>
<td>471,308</td>
<td>30.1</td>
<td>100%</td>
<td>186</td>
<td>11.5</td>
</tr>
</tbody>
</table>

Source: EvaluatePharma® 30 September 2015
Orphan Drugs Budget Impact Will Not Be Sustainable
Spinal muscular atrophy (SMA) is a genetic disease affecting the part of the nervous system that controls voluntary muscle movement. The muscles closer to the center of the body (proximal muscles) are usually more affected in spinal muscular atrophy than are the muscles farther from the center (distal muscles). Spinal muscular atrophy (SMA) is a progressive genetic disorder that affects the nervous system and muscles, and is a very rare disease at that, found in an estimated 1/6000 to 1/10000 people.

<table>
<thead>
<tr>
<th>Type</th>
<th>Onset</th>
<th>Life expectancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMA type 0</td>
<td>The most severe form of the disease, takes place before birth.</td>
<td>Few live longer than six months after their birth</td>
</tr>
<tr>
<td>SMA Type 1</td>
<td>Within the first six months of life</td>
<td>68% of children die before their second birthday and 82% die before their fourth</td>
</tr>
<tr>
<td>(most common)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMA Type 2</td>
<td>between the age of 7 months and 18 months</td>
<td>majority live into early adulthood</td>
</tr>
<tr>
<td>SMA Type 3</td>
<td>After 18 months</td>
<td>the same as the rest of the population</td>
</tr>
</tbody>
</table>
Case Study

Spinal muscular atrophy (SMA)

• Gene therapy X is an innovative therapy for SMA type 1.
• Gene therapy X proved a good efficacy in clinical trials. Almost all treated patients were cured after the Gene therapy X administration.
• Life expectancy becomes normal instead of 2 years.

Life years gained: **78 years**

QALY = Life years gained x Utility = 78 years x 0.75 = **58.5 QALY gained**

The cost-effective price = QALY gained x 250 000 €

= 58.5 x 250 000

= **14 625 000€**

250g: **9100€**
If 20 orphan gene therapies for 20 diseases will reach the market successively (3 to 4 orphan drugs each year), the annual budget impact may reach €35bn.

The price of an orphan gene therapy was estimated 350,000€
Orphan Drugs will be Cost-Effective but Not Affordable
From Cost-Effectiveness to Budget Impact
Potential Solutions to Ensure Funding for High Price Orphan Drugs
Funding Solutions

Funding models

Health outcomes based agreements
- Health outcomes based agreements
  - Individual level
    - Per patient per course or overall per year
  - Populational level

- Performance linked payment
  - Annuity payment
    - Conditional to preventing predefined effect
    - Payback for non-performance
    - Payment for side effects management
    - Pay by achieved outcome

- Coverage with Evidence Development
  - Single payment

Financial agreements
- Healthcare loans
- Cost plus price
- Rebate
- Bundle
- Discounts
- Price caps/volume caps
- Price-volume agreement
- Fund based payment
- Intellectual based payment
- Per patient
- Per target population
- Pooled funding
- National condition specific fund
- International fund
- Risk adjustment
- Reinsurance
- Risk corridors
- Front loading
- Tax
- Debt reduction

Healthcoin

Hanna E, Toumi M, Dussart C, Borissov B, Dabbous O, Badora K, Auquier P, Funding breakthrough therapies: a systematic review and recommendation, Health policy journal, in press
A « Special Fund » may be a potential solution to ensure fund for innovation while maintaining the sustainability of the health insurance.
Need of Transparent HTA Decision Frameworks
1. Need to support the development of a robust and reliable methodology to implement MCDA techniques in HTA decision frameworks

   - MCDA methods appears to be the most appropriate for integrating multiple attributes, but they require additional research and shared guidelines for an appropriate use to become actionable

2. Need to support research on constraint optimisation modelling (with associated research on disease burden) to be used in HTA decision frameworks.

   - Using mathematical programming techniques to maximise population and society health gain while adhering to a predefined budget and other recognised constraints
   - This should be recognised by HTA bodies as a relevant method that could be used when a product may create a shift in the interventions mix within one specific therapeutic area and for a defined patient population, when it is possible to document the associated budget
HTA decision frameworks should encompass all attributes recommended by the EUnetHTA Core Model®

- These attributes should be integrated as modifiers of ICER threshold or as modifiers of the added clinical benefit assessment scoring

- Need to integrate all domains of attributes of EUnetHTA HTA Core Model® in a standardised and explicit way through a transparent and reproducible deliberative process
  - Explicit metrics
  - Reported in publicly available HTA reports
- For attributes which are not already included in HTA decision frameworks or informally included, it is suggested to include these attributes as modifiers of the existing HTA frameworks while respecting current HTA decision frameworks, thus preventing major revision of these frameworks
Conclusion

• The high increase of health expenditure is a threat for public health as it channel ressource off the determinant of health
• New orphan drugs will be cost effective and we will not be able to afford them
• Orphan drugs are a very good value for money for investors and RoI is high
• New HTA transparent decision analysis is needed
• New funding routes are needed based on new rules and affordable willingness to pay equations