Variations in cell therapy reimbursement across the Big5EU

Panos Kefalas

Head of Health Economics & Market Access

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Presentation focus

- Variation in pricing and reimbursement (P&R) frameworks for cell-therapies by:

  A. Geography across Big5EU (France, Germany, Italy, Spain and UK)

  A. Therapy features:

    - magnitude of incremental benefit vs alternative therapeutic approaches
    - size of target population
    - regulatory status

- Scope:

  - Hospital setting (in- and out-patient)
  - The public payers

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Unlike the US, the Big5EU healthcare expenditure is largely driven by public health insurance.

Source: OECD Health Statistics 2014

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In terms of formulary inclusion of innovative therapies, private insurance does not provide significant advantage over public

<table>
<thead>
<tr>
<th>Country</th>
<th>Main features of private insurance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>Typically cover same treatments as public; added-value from:</td>
</tr>
<tr>
<td></td>
<td>shorter waiting time</td>
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<tr>
<td></td>
<td>greater choice of providers</td>
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<tr>
<td></td>
<td>access to private hospitals</td>
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<tr>
<td></td>
<td>UK: excludes chronic disease</td>
</tr>
<tr>
<td>Italy</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>Covers patient co-payments only</td>
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<tr>
<td></td>
<td>The non-profit insurers (Mutuelles) have little impact on P&amp;R</td>
</tr>
<tr>
<td>UK</td>
<td></td>
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<tr>
<td>France</td>
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</tbody>
</table>

The priority for cell therapies in Big5EU is to pursue public reimbursement
Licensed ATMP category
There are differences in data requirements between EMA approval and HTA across the Big5EU; the latter commands evidence of comparative effectiveness vs SOC/BSC

- Quality
- Safety
- Efficacy
- Comparative clinical and economic effectiveness

REGULATORY APPROVAL

HTA/REIMBURSEMENT

Insufficient comparative effectiveness evidence penalised ChondroCelect, MACI, Provenge
- Protracted MA negotiations
- Conditional or NO reimbursement

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In Big5EU, the assessment of reimbursed price for innovative licensed therapies has shifted towards value-based models.

<table>
<thead>
<tr>
<th>What is it?</th>
<th>Cost-based</th>
<th>Competitor-based</th>
<th>Value-based</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Price based on costs, expected sales and margins</td>
<td>Price driven by competition</td>
<td>Price based on comparative effectiveness</td>
</tr>
<tr>
<td>Examples</td>
<td>Cost-plus pricing</td>
<td>Penetration pricing</td>
<td>Cost-utility based pricing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reference group pricing</td>
<td></td>
</tr>
<tr>
<td>Comments</td>
<td>Becoming obsolete</td>
<td>Enforced for undifferentiated products</td>
<td>Typical for differentiated products</td>
</tr>
<tr>
<td></td>
<td><em>Exception:</em> unlicensed ATMPs</td>
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Value-based assessments link price potential to the novel therapy’s added-value

**PRINCIPLES OF VALUE-BASED ASSESSMENTS**

\[ V = RV + PDV - NDV \]

**Differentiating Value**

- Includes:
  - Clinical effectiveness
  - Economic effectiveness: budget impact, cost-effectiveness, cost-consequence

- Comparative data against the SOC/BSC **per country** is required:
  - Gold-standard: H2H RCT
  - Indirect comparisons can be leveraged
  - Comparisons can be based on modelled data to address:
    - Trial imbalance (observational vs RCT)
    - Treatment switching/cross-over
    - Extrapolations

- For a given indication, “V” varies depending on therapeutic positioning

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How differentiating value is captured and translated to reimbursed price varies by geography

**Most commonly used levers by market**

<table>
<thead>
<tr>
<th>Levers</th>
<th>UK</th>
<th>France</th>
<th>Germany</th>
<th>Italy &amp; Spain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st order</td>
<td>Comparative clinical effectiveness of the novel therapy vs a relevant comparator in the given market</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd order</td>
<td>Cost-effectiveness</td>
<td><strong>ASMR1-3:</strong> International price referencing (EU4) + Cost-effectiveness</td>
<td><strong>With added benefit:</strong> Budget impact Efficiency Frontier International price referencing (EU15)</td>
<td>Budget Impact + International price referencing (cost-effectiveness: minor lever)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>ASMR4-5:</strong> Domestic comparator price</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Price-volume agreements</td>
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</tbody>
</table>
Additional factors impact willingness to pay and reimbursed price potential across the Big5EU

- Willingness to pay higher in very rare diseases & small subpopulations of larger indications
  - Due to budget impact and disease burden considerations
- Where significant economic constraints exist, P&R largely influenced by budget impact (BI)
  - This limits capacity to reward upfront for long-term benefits
- Northern vs Southern Europe

**Impact on Reimbursed price**

- Incremental Clinical effectiveness
- Economic factors (Cost-effectiveness; Budget Impact)
- Disease burden & Unmet need
- International price referencing
- Contribution to GDP; Lobbying

**Factor magnitude**

**Interdependent Factors**

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Unlike BI, CUA and its reliance on modelled data provides an opportunity for cell therapies to capitalise on long-term benefit claims; however its application and impact vary across Big5EU.

- Cost-utility analysis (CUA) applicable in:
  - UK
  - France: ASMR1-3
  - Spain
  - In Italy not mandatory
  - Germany: N.A

The ICER is an indicator of price potential.

- Explicit ICER thresholds only in UK
  - ≥500 patients: £20-30K
    - For end-of-life up to £50K
  - Very rare conditions: ICER less relevant
    - e.g. Cerezyme (Gaucher’s / prevalence 270) commissioned: ICER = £391,244

\[ \text{ICER} = \frac{\text{Cost B} - \text{Cost A}}{\text{QALY B} - \text{QALY A}} \]

\[ \text{QALY} = \text{Life expectancy (life years)} \times \text{Quality of life (utility)} \]
For chronic disease, the CUA horizon can be lifetime; a therapy-specific model is used to capture time-dependent transitions across health states and outcomes.

- Health states & transitions: as per disease trajectory
- Time horizon: Up to 100 yearly cycles (discounted)
- Pay-offs: cost, utility, life years
- Sensitivity analysis to address uncertainty
  - Deterministic: univariate / multivariate
  - Probabilistic: parametric / non-parametric (bootstrapping)
  - Structural
- Model type: Decision tree, State transition Markov model, DES, Transmission model
- Analysis: Cohort simulation, Microsimulation

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Probabilistic sensitivity analysis informs price potential while accounting for uncertainty

**Incremental Cost-Effectiveness (Cell Therapy X vs SOC)**

ICER scatterplot generated through Monte Carlo simulation

Software: *TreeAge Pro 2014*

A health economically justified price results in the majority of ICER iterations falling below the WTP threshold
In Germany instead of cost-utility, a cost-benefit analysis may be applied but only as a last resort

- If added benefit is recognised but agreement on price is not reached:
  - Manufacturers can request cost-benefit analysis to avoid international price-referencing (to EU15 average)

- Costs & benefits of currently commissioned treatments (e.g. 1-3) define the efficiency frontier (blue line) i.e. the willingness to pay (WTP)
- New treatments exceeding the existing cost and benefit levels can be considered acceptable if they are above the extension of the WTP
Across Big5EU, only in UK there is clear HTA guidance on how long-term claims can be substantiated through extrapolations

- To bridge the gap between short-term data and long-term claims a regression framework is applied
  - Specified parametric and semi-parametric models are fitted
  - Optimal model selected based on statistical considerations and biological plausibility

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Fitted survivor function for an example trial

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To address uncertainty outcomes-based pricing agreements can be employed

- Types of outcomes-based pricing agreements in operation:

  - Cohort-based
    - Adjust price based on real world evidence
  - On individual patient basis
    - e.g. ChondroCelect in Spain:
      - 100% refund if failure at year one
      - 75% refund if failure at year two
      - 50% refund if failure at year three

Due to high RWE and administrative burden confidential discounts/rebates are implemented more often
There is variation across the Big5EU on degree of centralisation of P&R decision-making

<table>
<thead>
<tr>
<th>Level</th>
<th>France</th>
<th>Germany</th>
<th>UK</th>
<th>Italy</th>
<th>Spain</th>
</tr>
</thead>
<tbody>
<tr>
<td>National</td>
<td>Centralised P&amp;R at national level (HAS, CEPS)</td>
<td>Centralised P&amp;R at national level (G-BA, IQWiG, GKV)</td>
<td>-</td>
<td>Reimbursed ceiling price negotiated (AIFA)</td>
<td>Reimbursed ceiling price negotiated (AEMPS)</td>
</tr>
<tr>
<td>Regional</td>
<td>26 regional health agencies (ARS)</td>
<td>~150 sickness funds (KKs); Distribute funding to hospitals</td>
<td>Regional HTA: • NICE • SMC • AWMSG</td>
<td>Funding decision by each of the 21 regions</td>
<td>Funding decision by each of the 17 regions</td>
</tr>
<tr>
<td></td>
<td>Distribute funding to hospitals; little P&amp;R impact</td>
<td>Regional commissioning for specialised services: • England • Scotland • Wales • Northern Ireland</td>
<td></td>
<td>EXCEPTION: therapies achieving ‘innovative’ classification by AIFA must be funded</td>
<td>Can negotiate price down</td>
</tr>
<tr>
<td>Local</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Hospital funding negotiations / Discounts</td>
<td></td>
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</table>
Following reimbursement decision hospital adoption of costly therapies may be delayed due to complexity of securing funding

- Funding mechanisms:
  - Short-term: Provide supplementary funding
  - Long-term: Revise / create new DRG (diagnosis related group) tariff

<table>
<thead>
<tr>
<th>Country</th>
<th>Supplementary funding for hospital products</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>Funding <em>(Hors T2A)</em> restricted to:</td>
</tr>
<tr>
<td></td>
<td>- ASMR I-III, or ASMR IV-V against a comparator with ASMR I-III</td>
</tr>
<tr>
<td>Germany</td>
<td>Temporary funding <em>(NUB)</em> set locally; Permanent funding <em>(ZE)</em> set nationally</td>
</tr>
<tr>
<td>Italy</td>
<td>Tariff set regionally <em>(File F)</em></td>
</tr>
<tr>
<td>Spain</td>
<td>Rarely granted by regions: hospitals have to absorb costs <em>(impacting uptake!)</em></td>
</tr>
<tr>
<td>UK</td>
<td>Agreed regionally</td>
</tr>
<tr>
<td></td>
<td>Cancer Drugs Fund <em>(£340M p.a.)</em> in England for therapies without NICE endorsement</td>
</tr>
</tbody>
</table>

Launch strategy should account for meeting deadlines for supplementary funding applications
Other categories:

Minimally Manipulated Cell Therapies
Hospital Exemptions
Compassionate Use
Other regulatory categories and main differences from the P&R processes described for licensed ATMPs

Minimally manipulated cell therapies (MMCs)
- In France, Germany and UK same P&R assessments apply to MMCs and ATMPs
- In Italy and Spain, MMCs can bypass national/regional P&R assessments and be assessed by hospitals only

Hospital exemptions / Specials
- Price often determined on a cost-plus basis (rather than value-based)
  - Exception Spain: Need to be supplied on a not-for-profit basis

Compassionate use
- In Germany the manufacturer has to provide treatment free of charge
- In the other 4 markets price is set freely
  - In France, free-pricing can be penalised through post-launch rebates (ATU)
For more info visit: https://ct.catapult.org.uk/whitepapers-and-resources