European perspectives: 
Real world outcome needs of payers, 
current and anticipated

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• Emma Medin is an employee of PAREXEL International, a global CRO with pharmaceutical clients
• Emma Medin is presenting her own views and are not speaking on behalf of PAREXEL International
Agenda

1. Evolving environment
2. RWE – current & future importance
3. Developing RWE
Health care systems in Europe—quick recap

- High share of public health expenditures
- Tax based vs social health insurance funded systems
- Market value: EUR 163b (of which EUR 120b publicly funded)
- Countries spend 1.4% of GDP on pharmaceuticals (variations across countries)
- Affected by economic crisis, leading to a decrease in annual growth
- Market authorization harmonized at the EU level, reimbursement at the national level

Before market authorization
- Horizon scanning
  - HTA
  - Reimbursement (positive list)
  - Pricing

During market authorization
- Real-life effectiveness

After market authorization
The regulatory hurdle is decreasing

Regulatory has traditionally been the main hurdle to patient access, but this is changing...

Regulators

- Quality
- Efficacy
- Safety

Study design
Accepting of benefits from a highly controlled clinical study setting

Endpoints
Accepting of shorter-term surrogate endpoints (eg, PFS, ORR, HbA1c, LDL)

New Expedited Access Pathways

Driven by

- FDA Breakthrough Status
- EMA Adaptive Pathways

In cases of high unmet medical need:
1. Iterative development (approval in stages),
2. Gathering data in real life,
3. Early involvement of patients and payers
The regulatory hurdle is decreasing

... and the payer hurdle is now increasing.

**Payers**

**Value**

- **Study design**: Want to know that study benefits will be reflected in the real-world population to be treated
- **Endpoints**: Demanding of benefits in patient relevant “final” endpoints (eg, morbidity, mortality, QoL)

**Driven by**

- Escalating costs
- Budgetary pressures

Reimbursement authorities have become **more demanding** of the patient value of new healthcare technologies
Transformative therapies amplify divergent evidence requirements of regulators and HTA agencies

Innovative new therapies will further widen the evidentiary gap

- **Expedited regulatory authorization**
- **Transformative benefits**
- **Single treatment**

- **Uncertainty in benefit magnitude and durability**
- **High prices demanded**
- **Substantial upfront costs**
Innovative new therapies will further widen the evidentiary gap

... with Novartis announcing their SMA gene therapy could be cost-effective at $4-5 million / patient...

**Drug**

AVXS-101

A gene therapy

**Clinical data for AVXS-101**

Phase 1: All 15 pts alive after 24 months and did not require permanent ventilation

**Indication**

Type 1 Spinal Muscular Atrophy (SMA)

- Rare progressive genetic disorder
- Characterized by severe muscle weakness
- Type 1 = most common and severe
- 68% affected newborns die before 2nd birthday

**Current SoC**

only available disease-modifying treatment

Cost over 10 years: $4.1 million

Novartis pegs its spinal muscular atrophy drug at $4M

Novartis says $4m price is reasonable for SMA gene therapy

Possible $4M Price for AVXS-101, ‘Foundational’ SMA Gene Therapy, Could Be Cost-Effective, Novartis Says
Innovative new therapies will further widen the evidentiary gap

... but some transformative healthcare innovations have been commercial failures.

Case study: GLYBERA® – first EC-approved gene therapy

- **Glybera**
- **€1.1 million** per patient
- **EC approval 25/10/2012** for hereditary LPLD

**Pricing**
- Launch price (in DE) **€1.1 million per patient**
- **No innovative reimbursement scheme**

**Commercial success?**
- May 2016 – one commercial sale reported
- Nov 2017 - UniQure did not renew their marketing authorisation

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1ScienceBusiness.net (2017) World's first gene therapy to be withdrawn from market in Europe.
The key question is how to bridge the widening payer/prescriber-regulator evidentiary divergence.

Potential solutions/tools:

1. **RCT**
   - Make RCTs more payer/prescriber relevant

2. **RWE**
   - Understand how the product performs in a real-life clinical setting
Making RCTs more payer/prescriber relevant can be associated with time, cost and risk trade-offs...
Real-world evidence is increasingly impacting how treatments are being used...

NOACs

Initially dominated market

Now market leader

Key factor

RWE safety data
Real-world evidence utilization for payer interaction

...but most product-specific RWE is developed post-launch; it can be challenging to use this data for reimbursement applications...
... however, Early Access Programs can potentially be leveraged as a source of local RWE for reimbursement decisions at launch.

Real-world evidence utilization for payer interaction

NICE dupilumab (Aug 2018)
Post-approval submission of RCT and RWE data

...and in conditional reimbursement schemes RCT and RWE may be submitted post-reimbursement approval ...

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<thead>
<tr>
<th>Country</th>
<th>Scheme</th>
<th>Examples</th>
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<tbody>
<tr>
<td>🇩🇪</td>
<td>2011 <em>Time-limited G-BA resolutions</em> are becoming increasingly common</td>
<td><img src="image" alt="ZYKADIA" /></td>
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<tr>
<td>🇬🇧</td>
<td>2016 <em>Cancer Drugs Fund/MAA</em> form a temporary reimbursement fund to collect RWE</td>
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<td>🇦🇺</td>
<td>Since 2011, <em>Managed Entry Schemes</em> allow dynamic pricing based on future RWE or future RCT</td>
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Pay for performance based pricing

... and performance-based pricing ties reimbursement to real-world evidence patient outcomes

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<tr>
<th>Country</th>
<th>Performance-based pricing</th>
<th>Examples</th>
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<tr>
<td></td>
<td><strong>2005 AIFA-Onco Registry</strong> Performance-based reimbursement of gene therapy</td>
<td><img src="image" alt="Tasigna" /> <img src="image" alt="Strimvelis" /></td>
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<td>Full refund to payer if drug is not performing as expected</td>
<td><img src="image" alt="VELCADE" /></td>
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<td></td>
<td>Full refund to payer if drug is not performing as expected</td>
<td><img src="image" alt="Zytiga" /></td>
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<td>England</td>
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<td>Sweden</td>
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<tr>
<td>Country</td>
<td>Drug</td>
<td>Disease</td>
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<tr>
<td>Germany</td>
<td>Glybera</td>
<td>Lipoprotein lipase deficiency (ultra orphan indication)</td>
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<tr>
<td>England</td>
<td>translarna</td>
<td>nm Duchenne muscular dystrophy (ultra-orphan indication)</td>
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<tr>
<td>England</td>
<td>OPDIVO (nivolumab)</td>
<td>2L non small cell lung cancer</td>
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<tr>
<td>England</td>
<td>Repatha (evolocumab)</td>
<td>Hypercholesterolemia</td>
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<tr>
<td>England</td>
<td>Abraxane (nanoparticle albumin bound paclitaxel)</td>
<td>Pancreatic cancer</td>
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<tr>
<td>England</td>
<td>VELCADE (velcade)</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>France</td>
<td>Xolair</td>
<td>Moderate to severe persistent asthma</td>
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Country | Agency | Assessments using RWE | First submission | Resubmissions/reassessment |
---|---|---|---|---|
France | HAS | 70 | 14 (20%) | 56 (80%) |
Scotland | SMC | 23 | 12 (52%) | 11 (48%) |
Australia | PBAC | 26 | 18 (69%) | 8 (31%) |
England | NICE | 18 | 15 (83%) | 3 (17%) |
Germany | G-BA | 3 | 3 (100%) | 0 |
Germany | IWQIG | 1 | 1 (100%) | 0 |
Japan | HIRA | 1 | 1 (100%) | 0 |
Canada | pCODR | 2 | 2 (100%) | 0 |
TOTAL | TOTAL | 144 | 66 (46%) | 78 (54%) |

Source: Jao, R; Pontynen A; Wang X, Health Technology Assessment Agencies’ Consideration of Real-World Evidence, presented at the 23rd Annual Meeting of ISPOR, 2018, Baltimore, MD, USA
Key opportunities and research priorities for RWE

...but RWE offer important opportunities in the near term for expanded application

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<th>Research priorities</th>
<th>Description</th>
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| Clinical outcomes               | ▪ Describe clinical and patient characteristics  
▪ Understand **real-world effectiveness** of treatments  
▪ Investigate impact of alternative treatment patterns on clinical outcomes  
▪ Explore **patient subpopulations** and associated outcomes |
| Treatment patterns              | ▪ Explore context for usage and duration of therapy treatment  
▪ **Understand use of (soft/hard) endpoints** and role in treatment decisions  
▪ Document current and emerging clinical care pathway and treatment patterns |
| Frequency of AEs                | ▪ Understand the **frequency and management of AEs** for different treatments and for different patient sub-groups  
▪ Evaluate how AEs impact treatment duration |
| Health resource utilisation    | ▪ Understand costs of treatment, care, and patient management  
▪ **Assess economic value and any other benefits** of new treatments |
| Patient reported outcomes       | ▪ Explore **patient quality of life**  
▪ Understand physical and psychological impact on patients |
So companies have to do ‘more and earlier RWE’ – but what does this mean?

Different types of RWE generating studies

PRAGMATIC CLINICAL TRIAL ‘SPECTRUM’

Interventional

Primary Interventional Studies

Minimally Interventional Studies

Observational

Primary NIS / Observational Studies / Registries

Retrospective Chart Reviews

EMR Data Analysis

Secondary Database Analyses

Hybrid Studies
The Salford lung studies- a state of the art pragmatic clinical trial

Pre-launch randomized Pragmatic Clinical Trial undertaken by a collaboration of eight UK NHS organizations, sponsored by GSK

Evaluated the use of an investigational drug for the treatment of chronic obstructive pulmonary disease (Vestbo et al., 2016), and asthma (Woodcock et al., 2017)

Larger, broader, more inclusive and representative population than is typical of a standard pre-launch RCT.

The study was able to show benefits in moderate/severe COPD exacerbations (p=0.02) and similar adverse events.

CHMP positive opinion was rendered in April 2017

“allowed important factors in usual clinical care, such as adherence, frequency of dosing, and persistence of good inhaler technique, to come into play”

“results need careful interpretation”

“challenge the automatic transfer of findings from efficacy studies to clinical guidelines”
The regulator-payer/prescriber evidentiary divergence is growing and reimbursement & prescribing will become an increasingly distinct and critical hurdle for pharmaceutical companies to overcome.

Real World Evidence can be utilized to bridge this gap and translate regulatory approval into reimbursement.

A strategic evidence generation and publication plan, building in the RWE generation plan, is key to ensure that the right data is generated and disseminated for optimal payer interest.
Thank you!