Challenges in medicines funding for rare diseases

Josep Torrent-Farnell
Director, Medicines Area. Catalan Health Service (CatSalut)
Autonomous University of Barcelona

ISPOR Europe 2018
12th November 2018
Milestones of European Regulation: Increasing number of Orphan Medicinal Products in Europe

- Up to 145 different OMP authorised in Europe till 2017
- Higher number of OMP authorised last 4 years (57 OMP, representing 39% out of all OMP)
- Up to date, in 2018, 17 new orphan medicines have been approved in Europe
**Innovation success**

- EMA 2015, 2016, 2017
  - 93, 81, 92 positive opinions
  - 39, 27, 35 NCE
    - 13, 8, 11 oncology (~30%)

**Uncertainty**

- Conditional and exceptional approvals

<table>
<thead>
<tr>
<th></th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive</strong></td>
<td>93</td>
<td>81</td>
<td>92</td>
</tr>
<tr>
<td><strong>CA</strong></td>
<td>3</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td><strong>Exceptional</strong></td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Accelerated</strong></td>
<td>5</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>
PRIME program

Applications and eligibility decisions

Type of applicant

SME 23 86
Other 23 61
Academic 3

Therapeutic areas

Oncology 13 54
Neurology 4 14
Haematology-haemostaseology 8 9
Infectious diseases 2 12
Immunology-rheumatology-transplantation 3 7

36 products eligible to PRIME since launch

30 in rare diseases 16 for paediatric patients 15 advanced therapy medicinal products


* Out of scope applications are not included in the detailed charts.
PRIME/early access ... Some potential concerns...

- PRIME should not compromise the generation of appropriate evidence-based data.
- Otherwise the PRIME is in risk to become a questionable shortcut.
- A reasonable compromise of patients and professionals expectations needs to be guaranteed.
- Connecting initial E data with RWD
- Minimizing tensions through HTA appraisals and early and equitable access.
Challenges to face up rare diseases uncertainties

- Scientific evidence not comprehensive
- High cost of orphan drugs
- Affordability and sustainability
- Risk of access inequities
- High unmet medical needs
- Serious diseases
- Reconciling patients/professionals expectations and needs
Access to orphan drugs despite poor quality of clinical evidence

Alain G. Dupont1,2 & Philippe B. Van Wilder2

The problems of clinical trials and registries in rare diseases

Maurizio Luisetti*, Ilaria Campo, Roberta Scabini, Michele Zorzetto, Zamir Kadija, Francesca Mariani, Ilaria Ferrarotti

Development and validation of COMPASS: clinical evidence of orphan medicinal products – an assessment tool

Eline Picavet1, David Cassiman2, Bert Aertgeerts3,4 and Steven Simoens1

Pricing and reimbursement of orphan drugs: the need for more transparency

Picavet et al. Orphanet Journal of Rare Diseases 2013, 8:164
http://www.ojrd.com/content/8/1/164

Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries

Thomas Morei1, Francis Arickx2, Gustaf Befris3, Paola Silviero4, Caroline van der Meijden2, Emtla Xoo5 and Steven Simoens1

Clinical evidence for orphan medicinal products - a cause for concern?

Eline Picavet1, David Cassiman2, Carla E Hollak3, Johan A Maertens4 and Steven Simoens1
Lower robustness in scientific evidence generated with orphan medicines


<table>
<thead>
<tr>
<th>Table 4 Study design of the pivotal studies (n = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control arm</strong></td>
</tr>
<tr>
<td>No control</td>
</tr>
<tr>
<td>Controlled</td>
</tr>
<tr>
<td>Historical control</td>
</tr>
<tr>
<td>Different dosages of the OMP</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Active comparator (or standard of care)</td>
</tr>
<tr>
<td><strong>Similarity at baseline</strong></td>
</tr>
<tr>
<td>Yes, statistically verified</td>
</tr>
<tr>
<td>Likely, but not statistically verifiable</td>
</tr>
<tr>
<td>Not likely, but not statistically verifiable</td>
</tr>
<tr>
<td>No, statistically verified</td>
</tr>
<tr>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Randomized allocation</strong></td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Valid method of randomization</td>
</tr>
<tr>
<td>Invalid method of randomization</td>
</tr>
<tr>
<td>Not reported</td>
</tr>
<tr>
<td><strong>Blinding</strong></td>
</tr>
<tr>
<td>No (open-label)</td>
</tr>
<tr>
<td>No, but justified</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Blinding of the care provider</td>
</tr>
<tr>
<td>Blinding of the outcomes assessor</td>
</tr>
<tr>
<td>Blinding of the patient</td>
</tr>
</tbody>
</table>
Accurate estimation of effects pre-authorization?

Comparison of treatment effect sizes from pivotal and post-approval trials of novel therapeutics approved by the FDA based on surrogate markers of disease: a meta-epidemiological study

- FDA often approves new drugs based on trials using surrogate markers, which may risk making erroneous inferences about the medical product's actual clinical effect.
- All novel drugs initially approved by the FDA between 2005 and 2012 based on surrogate markers as primary endpoints.
  - Comparison of treatment effects among pivotal trials vs post-approval trials for the same indication

- 88 novel drugs (90 indications) based on => 1 pivotal trials using surrogates.
  - Many post-approval trials not directly comparable to pivots, particularly due to endpoint selection.
  - 27/88 novel drugs for 27/90 indications could be matched to at least one postapproval trial, total of 43 matches.

  - Non-continuous surrogates:
    - 9/12 (75.0%) pivotal trials showed effects larger than post-approval trials (average 50% larger, significant differences)
  - Continuous surrogates:
    - 17/31 (54.8%) pivotal trials showed effects larger than post-approval trials (no significant average differences)

26/43 (60%) pivotal trials showed effects larger than post-approval trials

Wallach JD et al. BMC Medicine 2018 16:45
Gathering evidence during early commercialization?


- From 2009 to 2013, the EMA approved the use of 48 cancer drugs for 68 indications:
  - 12% indications based on a single arm study
  - Survival data not available in 35%.
  - Benefit on OS 1 to 5.8 months, median 2.7
  - QoL data available in 10%

- Post-marketing results:
  - 3/44 indications without OS data in MA showed OS gain.
  - 5/44 showed benefit in QoL.

- Follow-up: 3.3 to 8.1 years, median 5.4 years after MA:
  - 35 (51%) indications had shown significant improvement in OS or QoL,
  - 23 scored by ESMO: 11 (48%) had meaningful improvement,
  - 33 (49%) remained uncertain.

33/68 (49%) of authorised oncological indications remained uncertain after a mean of 5.4 years post-approval.

High cost and budget impact of orphan drugs

“Most expensive drugs in the world”

Table 1 – The most expensive drugs in the world [1].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Annual cost</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soliris (eculizumab)</td>
<td>Paroxysmal nocturnal hemoglobinuria</td>
<td>$409,500</td>
<td>Alexion</td>
</tr>
<tr>
<td>Elaprase (idursulfase)</td>
<td>Hunter’s syndrome</td>
<td>$375,000</td>
<td>Shire</td>
</tr>
<tr>
<td>Naglazyme (galsulfase)</td>
<td>Maroteaux-Lamy syndrome</td>
<td>$365,000</td>
<td>BioMarin</td>
</tr>
<tr>
<td>Cinryze (C1 esterase inhibitor)</td>
<td>Hereditary angioedema</td>
<td>$350,000</td>
<td>ViroPharma</td>
</tr>
<tr>
<td>Myozyme (agalactosidase alpha)</td>
<td>Pompe disease</td>
<td>$300,000</td>
<td>Genzyme</td>
</tr>
<tr>
<td>Arcylast (rilonacept)</td>
<td>Cryopyrin-associated periodic syndromes</td>
<td>$250,000</td>
<td>Regeneron</td>
</tr>
<tr>
<td>Fabrazyme (agalactosidase beta)</td>
<td>Fabry disease</td>
<td>$200,000</td>
<td>Genzyme</td>
</tr>
<tr>
<td>Cerezyme (imiglucerase)</td>
<td>Gaucher disease</td>
<td>$200,000</td>
<td>Genzyme</td>
</tr>
<tr>
<td>Aldurazyme (larionidase)</td>
<td>Hurler syndrome</td>
<td>$200,000</td>
<td>Genzyme, BioMarin Pharmaceutical</td>
</tr>
</tbody>
</table>

Note. From 2010 data provided by Forbes and Pharmaceutical Commerce (all prices in US dollars).

All of them intended to treat Rare diseases

Key considerations: Managing uncertainty with MEA

Limiting budgetary uncertainty
- Financial agreements can be useful
  - Relatively simple tools, such as caps or price-volume agreements
  - Only control budget impact, does not address uncertainty on value

Limiting uncertainty on evidence
- Performance-based agreements can be useful
  - Implementation of studies or registries may be complex and costly in practice
  - Reliability of data, missingness
  - Definition of effectiveness based on surrogates of unknown clinical relevance as in trials – uncertainty may persist
  - Results available late – useful to reverse decisions?

<table>
<thead>
<tr>
<th>Management of stakeholders’ expectations</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Unfeasibility to conduct further controlled clinical trials</td>
</tr>
<tr>
<td>- Physicians’ and patients’ reluctance to enrolment into randomized controlled studies if product is commercially available</td>
</tr>
<tr>
<td>- Thus, difficult to gather robust risk/benefit evidence</td>
</tr>
<tr>
<td>- Bias of observational data (RWD), overestimation of effects</td>
</tr>
<tr>
<td>- Authorization reversal may be not feasible</td>
</tr>
<tr>
<td>- Patients on treatment requiring continuation</td>
</tr>
<tr>
<td>- Treatment availability becomes SOC</td>
</tr>
<tr>
<td>- Difficulties for pricing revisiting</td>
</tr>
<tr>
<td>- Negotiation with MAH difficult since most eligible population already treated and product considered SOC</td>
</tr>
</tbody>
</table>
Exploring new solving-pathways

- Alternative and robust methodological designs on RD clinical trials.
- Tailoring the appraisal of OMP: MCDA
- Following up real data of patient and treatment: MEA (Risk-sharing and financial agreements); Patient Outcome Registries; favouring PROMs / PREMS.
Drug access in Catalonia

- Authorization and price reimbursement at national level
  - P&R supported by national reports on therapeutic positioning
  - Reports coordinated, contributions of 17 regions
  - P&R decision binding for all regions
- Budget allocation at regional level

Catalan Harmonization Program

- Therapeutic positioning:
  - Drug technical appraisal
  - Catalan Pharmaco-therapeutic Committee
  - Prioritization and clinical criteria for use
  - Invoicing system and requirements
- Budget allocation
- Managed access
- Real world data collection and analysis
- Tools for implementation
How to balance medical needs with uncertainties
Initiatives developed in Catalonia

Steps taken to improve the assessment of **clinical added value** of orphan medicines

Steps taken for HTA appraisal to minimize the **budget impact** on OMP and reconciling the cost with the **outcomes achieved**

- MCDA methodology
- Managed entry agreements
- Patient participation in drug evaluation
- Patient registries: real world data
Catalan Pharmacotherapeutic Harmonisation Programme
Developed to improve access to innovative medicines (including OMP)

Drug evaluation → “Clinical value” → Recommendations

Pharmacoeconomics and budget impact → “Money for value” → Implementation and Patient Registry

Evaluation of health outcomes

2 (+ 2 alternates) patients out of 24 members participating in each committee
Catsalut: Real World Data collection

Ongoing for 7 years: ~200,000 treatments; ~125,000 patients; ~20,000 active; ~1,000 non-oncological OMP active

- Regional registry for high impact medicines
  - Involves OMP and non-OMP
  - Since 2011, requirement for invoicing since 2014
  - Data collected on:
    - Dates of treatment
    - Clinical indication criteria
    - Main effectiveness outcomes
    - Reasons for discontinuation
    - Invoicing
    - Linkable to other data sources

- Analyzed yearly
  - By product or indication
  - Description of treated population
    - Adherence to harmonized clinical criteria
  - Main outcomes
    - As derived from trials supporting access decisions
    - Heterogeneity across sites
  - Impact in patients and €
  - Deviation from expectations
CatSalut: examples of RWD in OMP

- HPN, Gaucher type I-III, Fabry’s disease

- Compliance with harmonised clinical criteria: in general 100% (74% pre-treated)
- Reaching of response according to main outcomes: 76%, 69%, 50%

Able to estimate effectiveness
## CatSalut: MEA in OMP (2018)

<table>
<thead>
<tr>
<th>Area</th>
<th>Type of agreement</th>
<th>Description</th>
<th>Access</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumology</td>
<td>Financial (Price – volume)</td>
<td>Subgroup of patients + Volume discounts 4 years</td>
<td>Clinical criteria + registry + Starting 2018</td>
</tr>
<tr>
<td>Nephrology</td>
<td>Financial (Cap)</td>
<td>Max regional invoicing 3 years</td>
<td>Individual authorization by expert group + registry + Starting 2018</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>Financial (National budget Cap + Regional budget Cap)</td>
<td>Max national invoicing 2 years Max regional invoicing 2 years (NA if national cap reached)</td>
<td>Clinical criteria + registry + Starting 2018</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>Financial (patient cap + National budget Cap)</td>
<td>Discount (in product) + Max patient invoicing + Max national invoicing 3 years</td>
<td>Individual authorization by expert group + registry + Starting 2018</td>
</tr>
<tr>
<td>Neurology</td>
<td>Financial (National budget Cap)</td>
<td>Max national invoicing 5 years</td>
<td>Individual authorization by expert group + registry + Starting 2018</td>
</tr>
</tbody>
</table>
6.7% of the budget assigned to medicinal products
OMP used by 0.1% Catalan population
Percentage of OMP expenditure in 2017 per ATC

- Metabolism (22.2M; 14%)
- Blood (6.6M; 4%)
- Cardiovascular system (9.9M; 6%)
- Hormones (4.1M; 3%)
- Antineoplastic and immunomodulating agents (109.14M; 69%)
- Neuromuscular (3.1M; 2%)
- Others (3.6M; 2%)

OMP - Catalonia
Lessons learned and take-home messages

• Positive 18-year-effects of the EU OMP policies on all stakeholders and for the patient’s unmet medical needs.

• OMP displays unique features that needs to be properly addressed: new tools for clinical development and new methods for pricing, HTA appraisal and patients registries and follow-up

• Independent and industry-based research should be aligned with patients and societal needs

• Empowered patient’s participation becomes a “must” in all orphan decision-making process

Dialogue-cooperation-collaboration-transparency-participation
Thank you for your attention

http://canalsalut.gencat.cat