



**Notes on Access to**

# **Orphan Medicinal Products**

**(Focus on Germany, as at February 2017)**

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EURORDIS 2nd Multi-Stakeholder Symposium on Improving Patient Access to Rare Disease Therapies



## International Orphan Drug Legislation

- USA: Orphan Drug Act (1983); Orphan Drug Regulation (1993)
- Japan: Orphan Drug Regulation (1993)
- Australia: Orphan Drug Policy (1997)
- European Union: Regulation CE No. 141/2000 (2000)

### Some Measures:

- R&D grants, tax credits, protocol assistance, accelerated review, market exclusivity (USA, 7y; Japan and EU, 10y; Australia, 5y)

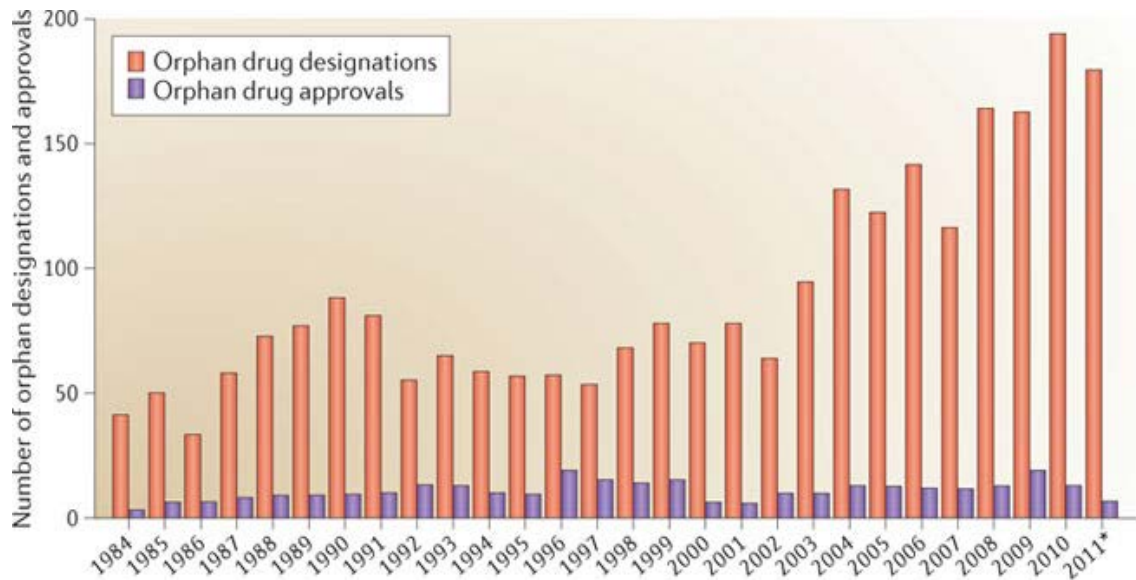
### Some Definitions:

- USA: prevalence  $< 7.5/10,000$  (i.e.,  $< 200,000$ )
- Japan: prevalence  $< 4/10,000$
- Australia: prevalence  $< 1.1/10,000$
- European Union: prevalence  $< 5/10,000$
- England / Wales: “ultra-orphan” disorders, prevalence  $< 1/50,000$



## Impact of Orphan Drug Legislation

### Orphan Drug Designations and Approvals, U.S.A., 1984-2011

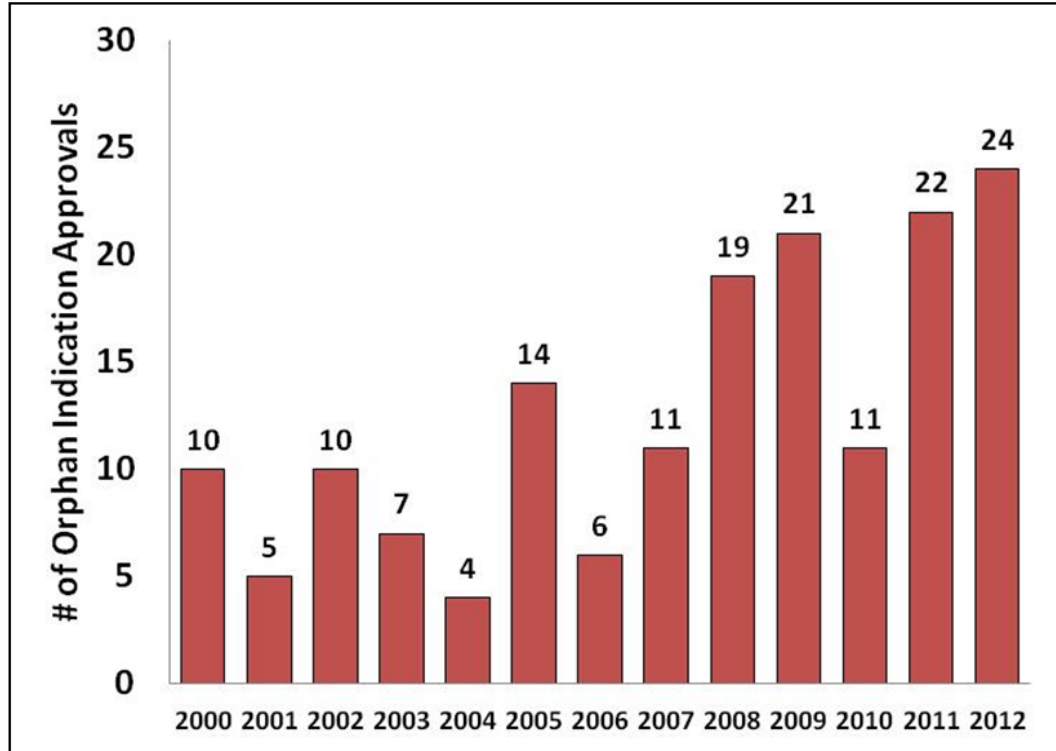


Nature Reviews | Drug Discovery

Source: I. Melnikova: Rare Diseases and Orphan Drugs.  
*Nature Reviews Drug Discovery* 2012, 11 (4): 267-268, Fig. 1 (© Macmillan Publishers Ltd.)



## Impact of Orphan Drug Legislation

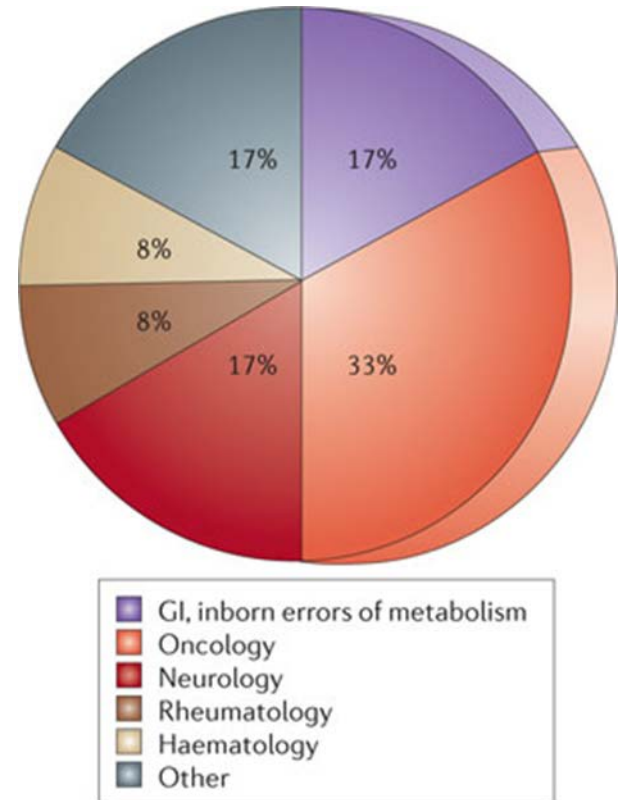


Source: <http://www.biotech-now.org/wp-content/uploads/2013/03/Historic-Orphan-Drug-Approvals.png>



## Impact of Orphan Drug Legislation

**Orphan  
New Drug Approvals  
by Therapeutic Area  
U.S.A., 2006-2011**



Source: I. Melnikova: Rare Diseases and Orphan Drugs.  
*Nature Reviews Drug Discovery* 2012, 11 (4): 267-268, Fig. 1  
(© Macmillan Publishers Ltd.)



## Health Economic Evaluation Principles

### The Logic of Cost-Effectiveness – Questions Asked:

1.



#### Safety

- Does it harm?  
(controlled conditions)

2.



#### Efficacy

- *Can* it work?<sup>1</sup>  
(controlled conditions)

3.



#### Effectiveness

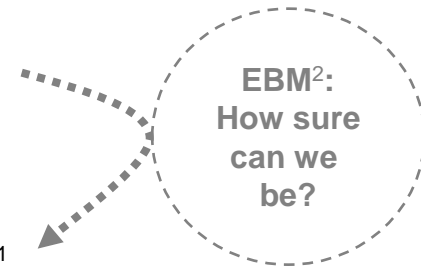
- Does it work and is it safe?<sup>1</sup>  
(normal practice)

4.



#### Efficiency

- Do its benefits outweigh its costs?  
*(frequently: “Is it cost-effective”?)*



<sup>1</sup>cf. D. Schwartz and J. Lellouch (1967); <sup>2</sup>EBM: “evidence-based medicine”



## Early Benefit Assessments in Germany

### AMNOG: The Logic of Comparative Effectiveness

1.



#### Safety

- Does it harm?  
(controlled conditions)

2.



#### Efficacy

- *Can* it work?<sup>1</sup>  
(controlled conditions)

3.



#### Effectiveness

- Does it work and is it safe?<sup>1</sup>  
(normal practice)

4.



#### Comparative Effectiveness

- Does it outperform current standard therapy?  
(**Germany: “Is it more effective”?**)

<sup>1</sup>cf. D. Schwartz and J. Lellouch (1967); <sup>2</sup>EBM: “evidence-based medicine”



## Early Benefit Assessments and OMPs

### AMNOG: Orphan Medicinal Product Reimbursement

- ↪ OMP Designation by EMA
- ↪ Immediate Market Access
  - ↪ reimbursement at price asked for by manufacturer
- ↪ Additional Benefit Assumed
- ↪ Early Appraisal by GBA: Size of Additional Benefit
  - ↪ mostly “unquantifiable”
- ↪ Revenue Threshold: max. €50m p.a.
  - ↪ once exceeded,  
OMP will be subject to standard Early Benefit Assessment





## Early Benefit Assessments and OMPs

### AMNOG: Orphan Medicinal Product Reimbursement

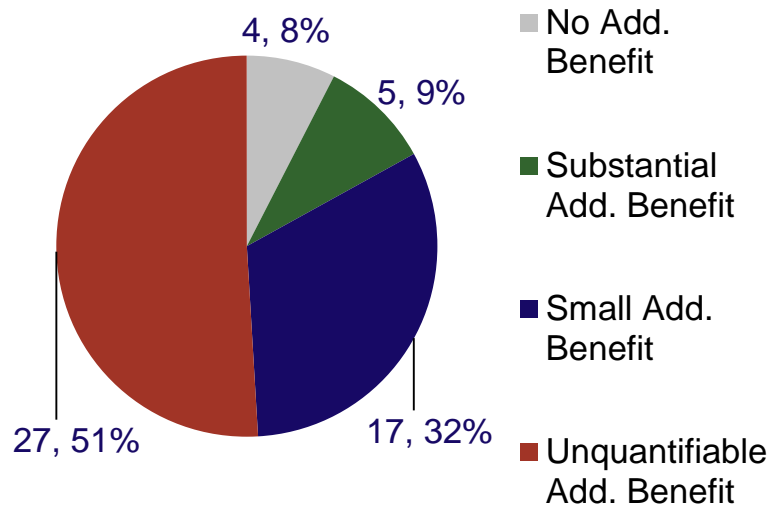
- **Sustainable?**
  - 26% of all newly launched drugs had OMP status in 2010
  - 32% of all newly launched drugs had OMP status in 2015
  - Additional Benefit mostly “unquantifiable” (10/12 in 2015)
  - Health Care and Drug Spending growing faster than GDP
- **Controversial:**
  - Marginal Benefit *only* (at sometimes extreme acquisition costs?)
  - Immediate Market Access (at manufacturer’s price?)
  - Revenue Threshold (too high?)
  - Adaptive Pathways (shifting R&D risk and cost to payers?)



## Early Benefit Assessments and OMPs

### AMNOG: Orphan Medicinal Product Reimbursement

#### Orphan Drugs



OMP Early Benefit Appraisals:

Size of additional benefit;  
reference: patient (sub)groups.

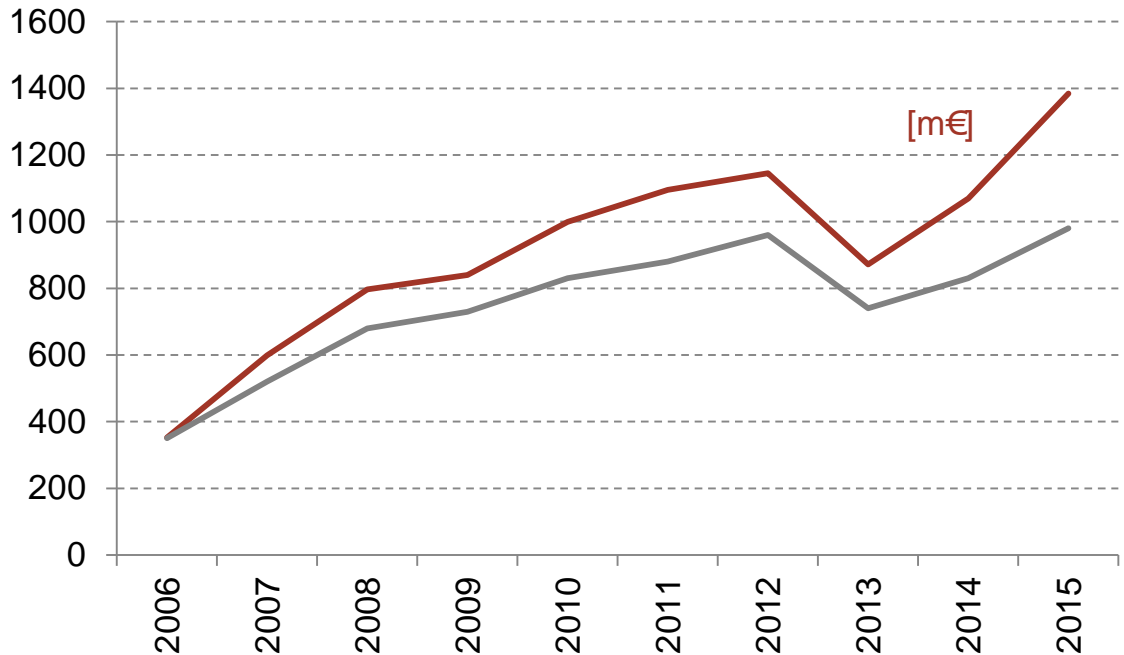
Status as at Aug. 01, 2016

Data source:  
U. Schwabe, D. Paffrath (2016),  
p. 161



## Early Benefit Assessments and OMPs

### Outpatient Orphan Drug Revenues, 2006-2015



#### OMP Outpatient Revenues Germany:

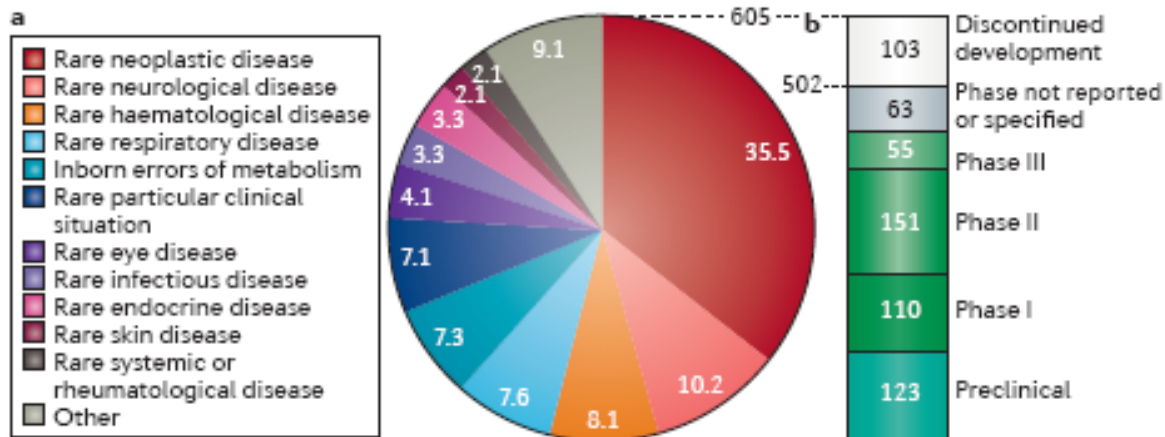
2006-2015, data source: U. Schwabe,  
D. Paffrath (2016), p. 17

Red: annual revenues [m€]  
Grey: annual DDDs [10,000s]



## Early Benefit Assessments and OMPs

### Sustainability? – The Orphan Drug Pipeline in Europe<sup>1</sup>

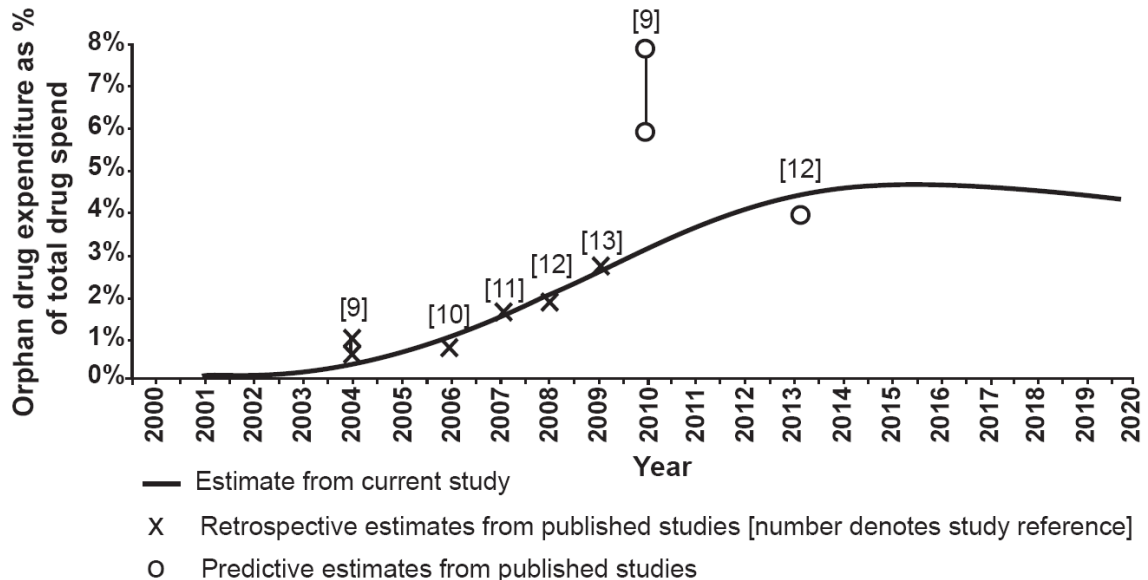


**Figure 1 | Analysis of orphan designations in the European Union.** The data are for orphan designations granted between 2002 and 2012 with annual reports filed to the European Medicines Agency in 2013 or 2014 ( $n = 605$ ). **a** | Orphan designations granted, subdivided by therapeutic area. **b** | Orphan designations granted, subdivided by development stage.



## Early Benefit Assessments and OMPs

### Sustainability? – OMP Budget Impact Projection (2011)

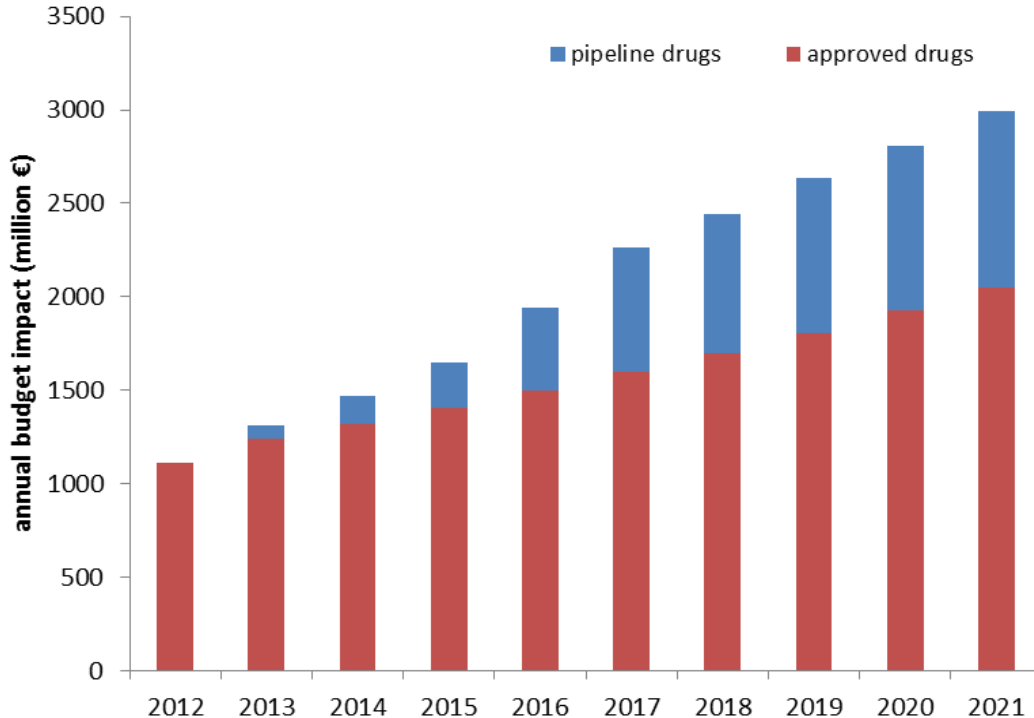


Source of graph: Schey et al. (2011), p. 6.

C. Schey et al.: Estimating the budget impact of orphan medicines in Europe: 2010 – 2020. *Orphanet Journal of Rare Diseases* 2011; 6: 62



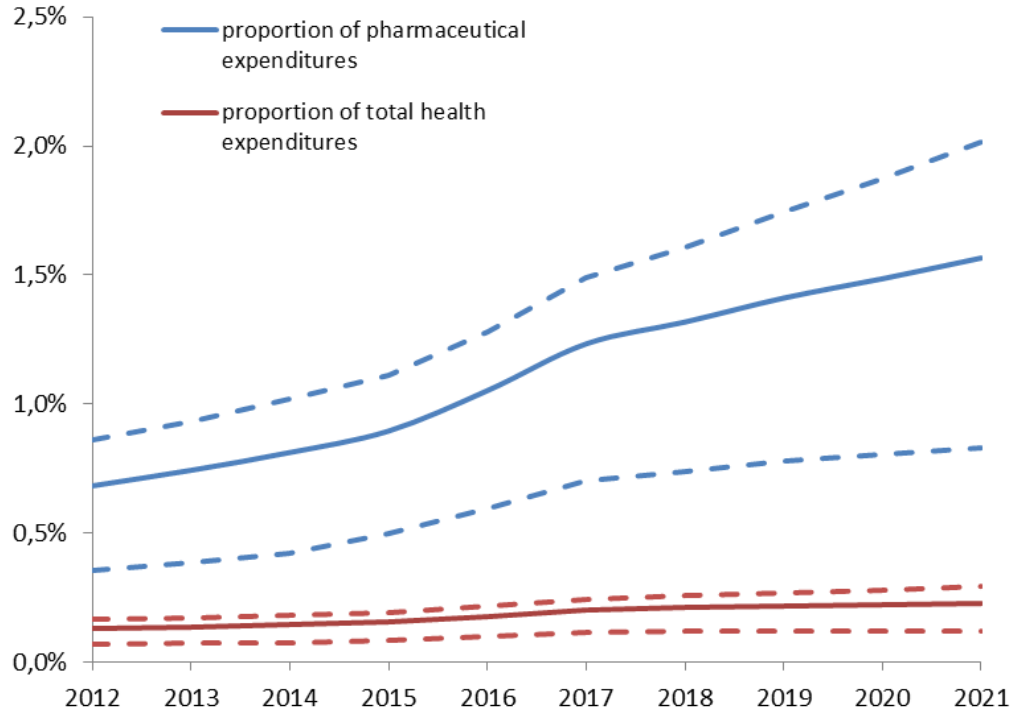
## Projected URD Budget Impact (2014)



Annual budget impact of approved and pipeline drugs for ultra-rare diseases over 10 years (2012 to 2021) in Europe from a payer's perspective. Data from M. Schlander et al.: Budget impact analysis of drugs for ultra-orphan non-oncological diseases in Europe. *Expert Review of Pharmacoeconomics & Outcomes Research*, 14 (1), 2014: 123-129.



## Projected URD Budget Impact (2014)



Proportion of pharmaceutical and total health expenditures in Europe spent on drugs for ultra-rare diseases (URDs). Dashed lines indicate ranges provided by the extreme-case scenario analyses. Source: M. Schlander et al.: Budget impact analysis of drugs for ultra-orphan non-oncological diseases in Europe. *Expert Review of Pharmacoeconomics & Outcomes Research*, 14 (1), 2014: 123-129



## Clinical Effectiveness

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

**Eline Picavet, David Cassiman, Carla E Hollak, Johan A Maertens, Steven Simoens**

[...]

We quantitatively assessed the characteristics and quality of clinical evidence of the pivotal studies of 64 OMPs as described in the European Public Assessment Report and/or the Scientific Discussion document prepared by the Committee for Human Medicinal Products of the EMA.

[...]

The 64 OMPs were altogether authorized for 78 orphan indications, for which 117 studies were identified as ‘pivotal’ or ‘main’ studies. In approximately two thirds of the studies, the allocation was randomized (64.8%) and a control arm was used (68.5%). Half of the studies applied some type of blinding. Only a minority (26.9%) of the studies included a Quality-of-Life (QoL) related endpoint, of which a third claim an improvement in QoL.

[...]

In conclusion, the pivotal studies that are the basis for marketing authorization of OMPs are a cause for concern, as they exhibit methodological flaws [...]

*Orphanet Journal of Rare Diseases 2013, 8: 164*





## Clinical Effectiveness

### Systematic review of available evidence on 11 high-priced inpatient orphan drugs

**Tim A Kanters, Caroline de Sonnevile-Koedoot, W Ken Redekop, Leona Hakkaart**  
[...]

A systematic review was performed [...] for 11 inpatient orphan drugs listed on the Dutch policy rule on orphan drugs. For included studies, we determined the type of study and various study characteristics.

[...]

A total of 338 studies met all inclusion criteria. Almost all studies (96%) focused on clinical effectiveness of the drug. Of these studies, most studies were case studies (41%) or observational studies (39%). [...] a randomized clinical trial was available for 60% of the orphan drugs. Eight studies described the cost-effectiveness of an orphan drug; an equal number described an orphan drug's budget impact.

[...]

Despite the often heard claim that RCTs are not feasible for orphan drugs, we found that an RCT was available in 60% of orphan drugs investigated. Cost-effectiveness and budget impact analyses for orphan drugs are seldom published.

*Orphanet Journal of Rare Diseases 2013, 8: 124*



## Clinical Effectiveness

### Generating health technology assessment evidence for rare diseases

**Karen Facey et al.**

[...]

Discussion with an expert panel was augmented with references and case studies to explore robust approaches for HTA evidence generation for rare disease treatments.

**Results:** Traditional RCTs can be modified using sequential, three-stage or adaptive designs to gain more power from a small patient population or to focus trial design. However, such designs need to maintain important design aspects such as randomization and blinding and be analyzed to take account of the multiple analyses per formed. N-of-1 trials [...] could be particularly valuable for rare diseases and when prospectively planned across several patients and analyzed using Bayesian techniques, a population effect can be estimated that might be of value to HTA. When the optimal outcome is unclear in a rare disease, disease specific patient reported outcomes can elucidate impacts on patients' functioning and wellbeing. Likewise, qualitative research can be used to elicit patients' perspectives, with just a small number of patients.

**Conclusions:** International consensus is needed on ways to improve evidence collection and assessment of technologies for rare diseases [...].

*International Journal of Technology Assessment in Health Care 2014, 30 (4)*



## Adaptive Licensing?

### Evidence of Clinical Effectiveness

#### Recommendations:

- Approval based on **surrogate endpoints** should be accepted as an exemption (and if and when so, as an interim solution) only.
- Conditional reimbursement to ensure rapid patient access may be linked to “**coverage with evidence development**” agreements.
- **However:** Even at prevalence rates as low as 1/50,000 (the URD qualifier), there are about 10,000 patients in Europe.
- Thus it should be **possible to set up multinational RCTs** designed to show relevant clinical endpoint benefit.
- If necessary, such trials might be supported by the not-for-profit *European Clinical Research Infrastructure Network* (ECRIN).

M. Schlander, S. Garattini et al.: Determining the Value of Medical Technologies to Treat Ultra-Rare Disorders (URDs). A Consensus Statement. *Journal of Market Access & Health Policy* 2016; 4: 33039.



# Thank You for Your Attention!

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