Significant benefit of OMPs

Industry views

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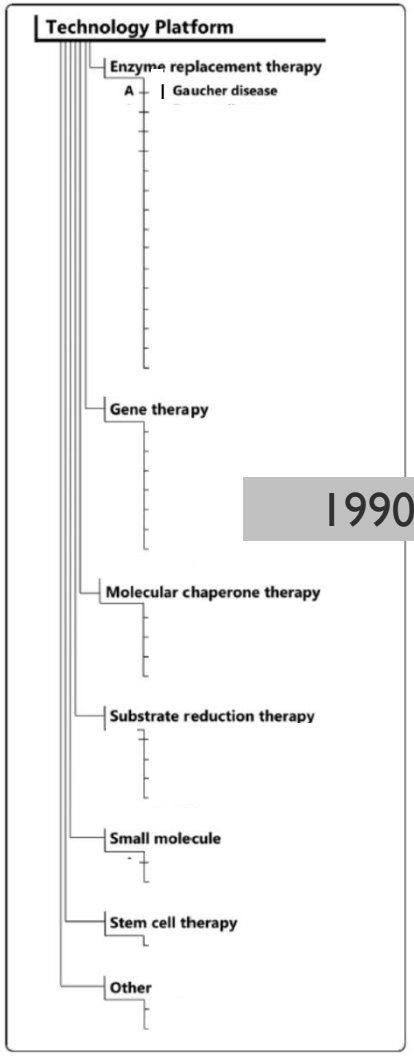
Positive benefits of Orphan Medicines regulation in the EU

- Industry values the Orphan Medicinal Product Regulation (EC) 141/2000
- Incentives have corrected a market failure and allowed industry to develop over 100 OMPs in 81 conditions
- The current framework has:
  - Incentivised research in exceptional cases and outliers from which a lot of scientific knowledge has emerged
  - Facilitated breakthrough advances in care and in novel technology platforms
  - Enabled applications of novel technology platforms in other rare diseases
  - Encouraged continued innovation in rare diseases with an approved therapy with long-term improvements in patient care

Lysosomal storage disorders

Enzyme replacement therapy for fatal genetic diseases

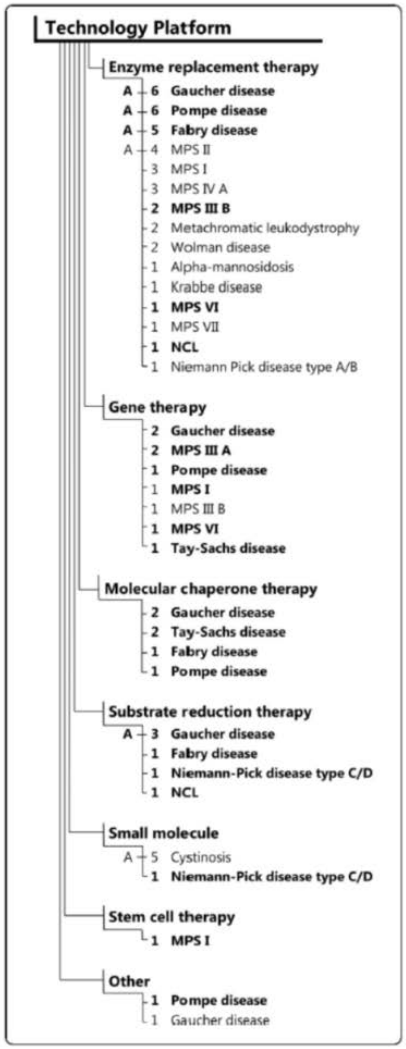


A group of 40 diseases

14 approved treatments for 7 diseases

7 different technological platforms

1990 2000 2010 2012 2013



Mechler K , Mountford W, Hoffman G, Ries M. Pressure for drug development in lysosomal storage disorders – a quantitative analysis thirty years beyond the orphan drug act. Orphanet (2015) 10:46

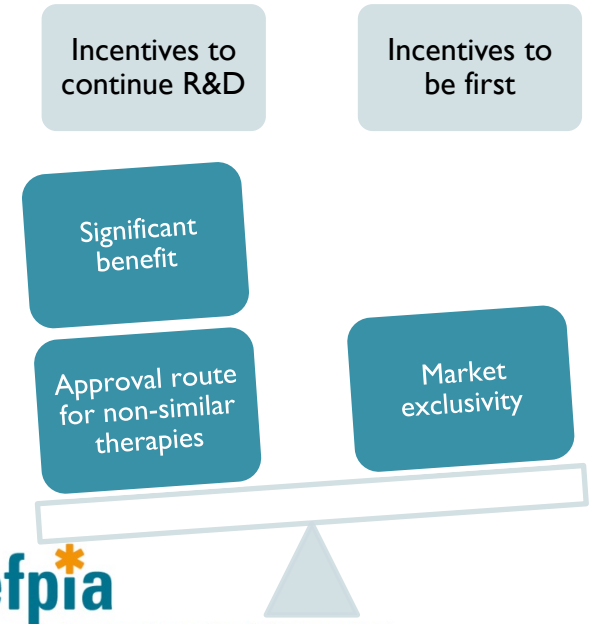
What does significant benefit mean to companies developing orphan medicines?

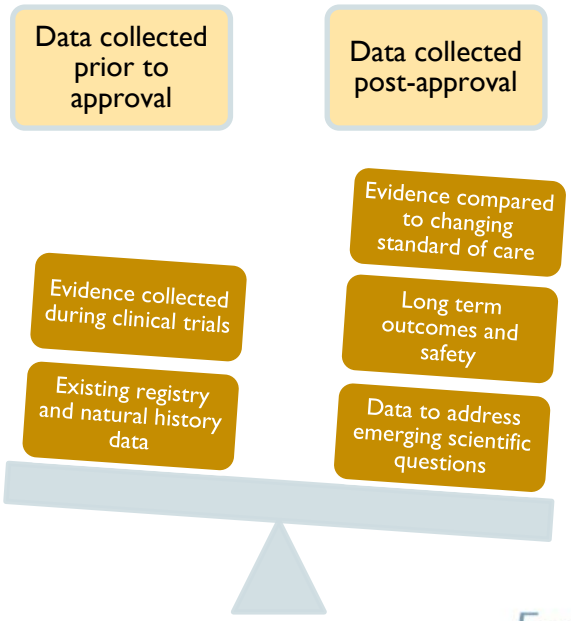
- We are looking for an environment that properly balances two sets of issues:

1. Incentives to be first vs incentives to continue to advance knowledge and care

AND

2. Data collected prior to approval vs data to be collected post-launch





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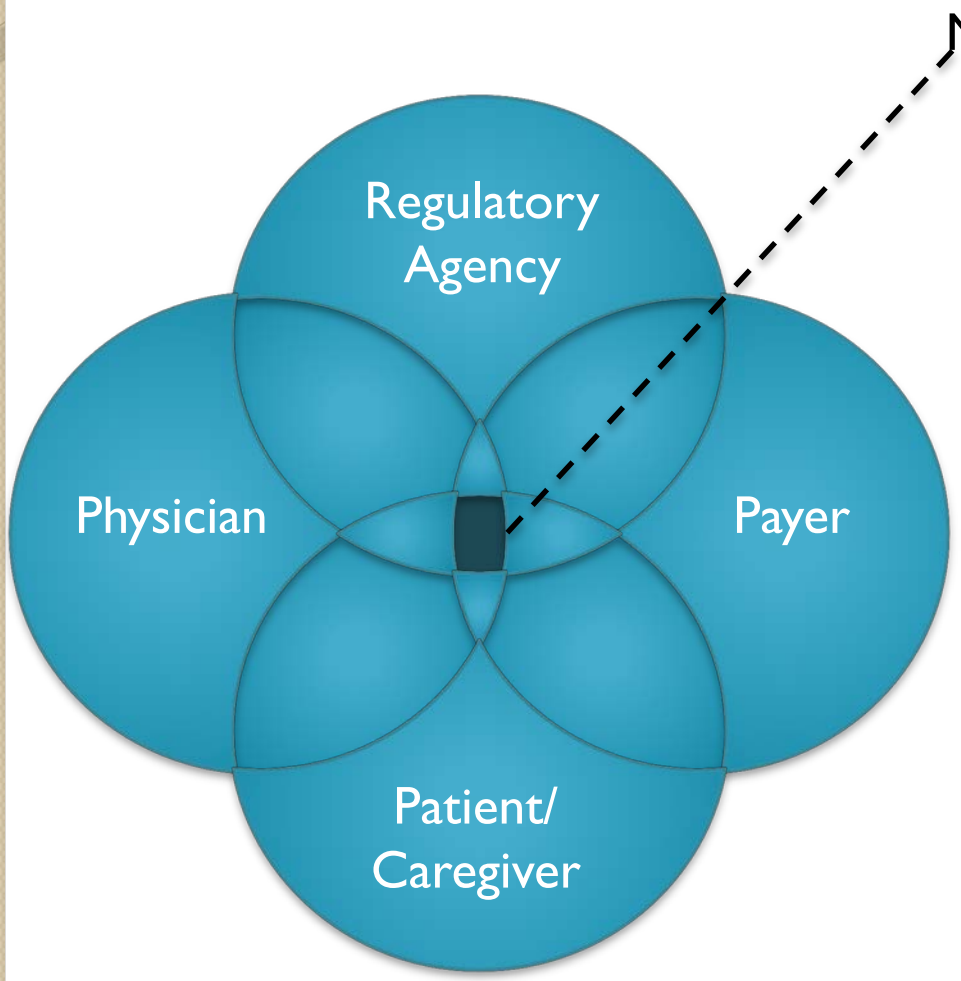
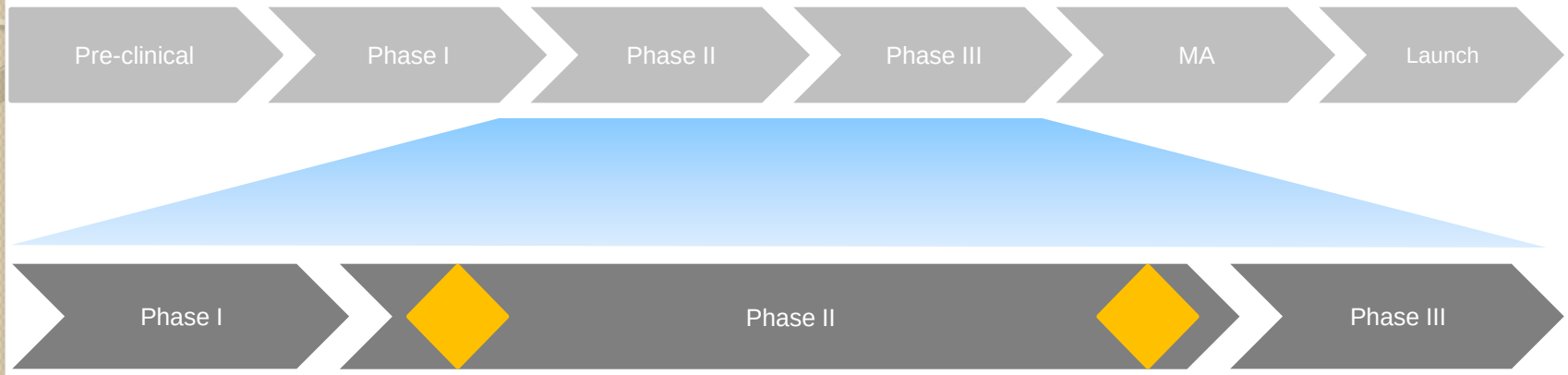
Delivering data that is meaningful to everyone can be far from easy



- Multi-stakeholder dialogue (e.g. **parallel scientific advice**) to agree what is achievable
- Opportunities to discuss evolution of evidence over time (e.g. **adaptive pathways**)

Collecting evidence to substantiate significant benefit at time of MA



- Promising early data can accelerate launch plans e.g. PhII data
- With a more complete programme, it can easily be 3-4 years from scientific advice/finalising data collection plan to MA
  - Other products being developed for the same disease may succeed (or fail)
  - New end points or patient relevant outcome measures may be developed/agreed
  - Standard of care (based on reimbursed practice in Europe) may change

Sources of evidence for significant benefit

- RCTs are undertaken in rare diseases, but not always appropriate or achievable:

Feasibility challenges to randomisation and control groups in trials*
Small patient population
Poor prognosis/no alternative treatment
Lack of equipoise
Outcomes occur in the distant future
Small adaptation of an intervention
Extension of the indication

- Problems where multiple therapies are being in developed in parallel
- Hard to quantify or compare outcomes in therapies with long duration of treatment effect (cell and gene therapy)

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*From De Groot et al., BMJ Open, 2015

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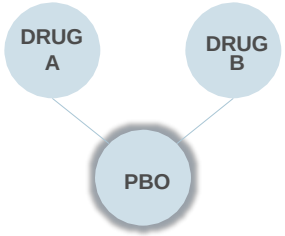
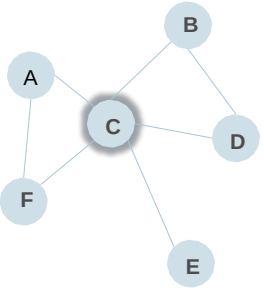
Sources of evidence for clinical benefit - indirect comparisons

- Publications and experience of anchor-based indirect comparisons:





- For rare diseases, fewer studies and single-arm studies more likely:

- Even here, simulated treatment comparisons and matching adjusted indirect comparisons have sometimes been used successfully

Disease	Treatment evaluated	Single-arm	Method(s)	Publically-available HTA
Renal cell carcinoma	Axitinib	Y	STC, MAIC	Y
Multiple myeloma	Bortezimib	Y	MAIC	Y
Pancreatic neuroendocrine tumors	Everolimus	Y	MAIC	Y
Non-small cell lung cancer	Ceritinib	Y	MAIC	
Mantle cell lymphoma	Ibrutinib	Y	MAIC	
Cystic fibrosis	Tobramycin	Y	MAIC	

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Diagrams and table selected from Swallow et al, ISPOR 2015

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Sources of evidence for clinical benefit - indirect comparisons

- Multiple methods and growing experience. Can be very effective and best option BUT:
  - "The choice of methodology is **context specific** and should be based on an objective assessment of the quality and **quantity** of the direct and indirect evidence, the **comparability** of the selected studies, and of the fundamental assumptions in the different models"†
  - Heterogeneity is a big problem – indirect comparisons introduce less uncertainty when study populations, end points, study duration, treatment settings etc are aligned
  - What conclusions to draw if indirect comparison shows no benefit?
- More fundamentally, is relative efficacy always the right question?
  - Additional options in oncology treatment pathways
  - Dissimilar interventions or target populations within a disease (mutation-specific vs all patients)
  - HTA and regulatory perspectives and decision-contexts differ

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† EUnetHTA Guideline Comparators and Comparisons: Direct and Indirect Comparisons Feb 2013

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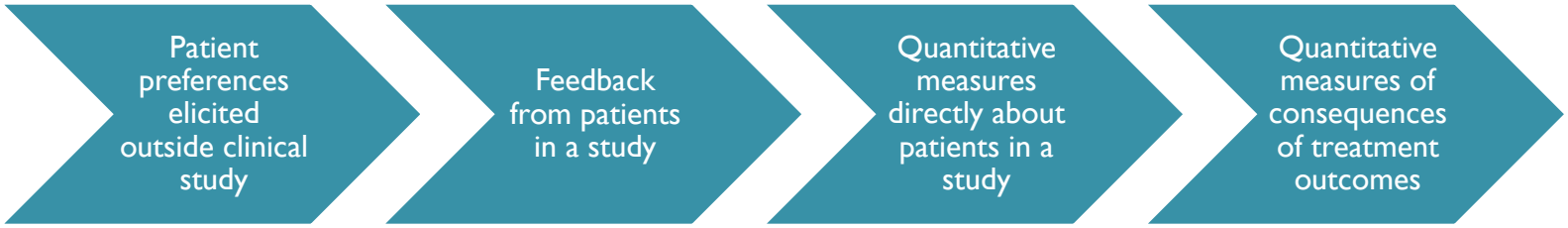
Measuring major contribution to patient care

- Positive experiences of consortium work led by patient groups and academics to develop guidelines and new measures (PPMD, Telethon, IRDiRC workshop on PROs)
- Some items may be better measured in a real world setting (e.g. adherence)
- Need evidence standards to be proportionate – depends on disease, therapy and state of knowledge
- Availability of baseline data on current treatment (esp if new)?



- E.g. Discrete choice experiments on re-formulation/oral vs IV
- E.g. Disease specific questionnaires or clinical functioning reports
- E.g. Patient-relevant outcomes measures designed for that disease; generic QoL measures (sometimes age-specific)
- E.g. Measures of carer burden, health and social care resource use, return to work

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What are companies optimistic about?

- Options to tackle some rare diseases in an even more meaningful way than we have in the past
  - Novel therapies that target specific mutations to make progress in hard-to-treat diseases
  - New therapeutic modalities (gene and cell therapy, immuno-oncology and combination therapy)
- Potential to establish continuum of evidence collection and good examples to test and try new trial design and analytical techniques to meet stakeholder needs over time
  - Opportunities for early dialogue via Parallel Scientific Advice, Adaptive Pathways
  - Collaborations on research and PRO development and registries

What are companies worried about?

- Bringing HTA questions and evidence standards into regulatory framework
  - Decision context and consequences are different
  - Problems in applying uniform standards across diverse rare diseases
- Having additional methods available ≠ having sufficient evidence to accurately apply methods to show or quantify significant benefit.
  - Higher evidence hurdles and more regulatory risk likely to limit investments in research that could deliver incremental but important benefits to patients
  - Quantifying relative effectiveness of some new therapeutics will be really challenging
- How to respond to signals?
  - Single products in a TA or competition between companies working on emerging technologies?
  - Dialogue, quality and evidence commitments over time or gamble on being first?
  - Novel therapies with long-term treatment effect or definite outcomes and statistical certainty?

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2003/C 178/02 JO 29.7.2003
Industry suggested areas for clarification

1. Flexibility for clinical trial designs and clinical development program
2. Alignment between COMP, CHMP and SAWG
3. Clarity on re-evaluation of designation criteria
4. Communication of significant benefit

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