What Do Payers Think the Future Holds for Orphan Drugs?

Webinar Presentation
RTI-HS Integrated Support

Supporting your brands throughout their entire lifecycle.

- Biometrics
- Epidemiology
- Clinical and Safety

- Health Economics
- Health Preference Assessment
- Market Access and Outcomes Strategy

Your brands
Contents

- What is an orphan indication/drug?
- Orphan Drug Act (ODA)
- Events occurring since ODA passage
- Challenges in developing orphan drugs
- Reimbursement hurdles
  - Orphan disease case studies
  - Payer findings from Australia, France, Germany, Italy, Spain, the UK, and the US
- Strategic recommendations
What is an orphan disease?

Orphan diseases “occur so infrequently that the cost of developing a medicinal product to treat the condition would not be recovered by the expected sales of the medicinal product” – European regulation definition

**Orphan diseases**
- Limit of prevalence 1.2 to 7.5 cases per 10,000
  - Australia: 1.2 per 10,000
  - Europe: 5 per 10,000
  - Japan: 4 per 10,000
  - US: 7.5 per 10,000
  - WHO: 6.5 per 10,000

**Ultra-orphan diseases**
- Constitute an informal subcategory
- Frequency is not well defined
- Term was first used by NICE for a rare disease affecting less than 1,000 cases in England and Wales
  - Corresponds to prevalence of < 1 case per 50,000
  - For instance, for aHUS, that corresponds to 1 physician treating 10 patients in all of Scotland

aHUS = atypical haemolytic-uremic syndrome.
Orphan indications are rare conditions or subgroups of larger indications

- Hemophilia
- Chronic myeloid leukemia (CML)
- Cystic fibrosis
- Phenylketonuria
- Acquired hemophilia
- Philadelphia chromosome-positive CML
- Cystic fibrosis with certain mutations in CFTR gene
- Melanoma with BRAF V600 mutation
- Non–small cell lung cancer with EGFR mutation

In 2013, the largest proportion of orphan drug designations were in oncology in the US

Since 1983, several ODAs were introduced to encourage orphan drug development

- Prior to the ODA, ~1 orphan drug was approved per year
  - The ODA brought about by lobbying from patient advocacy groups
- On January 4, 1983, the ODA was passed to encourage orphan drug development
  - Patent benefits (7 years marketing exclusivity)
  - Tax credits ($\leq 50\%$ clinical trial costs)
  - Waiver of user fees ($1.8$ million)
- Similar acts then passed in other countries

Opportunities and challenges in orphan drug development

**Challenges**

- Highly heterogeneous group of disorders (~7,000 rare diseases)
- Natural history of disease may not be well understood\(^a\)
- Small patient population
  - Difficult to enroll patients
  - Challenging to achieve meaningful results (statistical benefit), particularly in small subgroups
  - Competing drugs/trials may focus on same small patient population
- Lack of product availability, e.g., factor shortage for hemophiliacs due to manufacturing difficulties

**Opportunities**

- **Cost advantages:**
  - Reduced clinical trial costs (smaller patient population)
  - Tax incentives
- **Regulatory advantages:** Lack of alternatives gives orphans an advantage in terms of regulatory review
- **Pricing potential:** Cost per patient can be up to six times that of nonorphans
  - Can be a double-edged argument

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\(^a\) Also, with global migration, ethnic/regional diseases may arise in unexpected places.

Since the ODA in the US, 395+ orphan drugs have been brought to market

Since the introduction of the ODA in the US:
- 3,660+ designation requests
- 2,550+ products have received orphan designation
- 395+ drugs brought to market

In 2013, 33% of all NMEs approved in the US had orphan status

<table>
<thead>
<tr>
<th>FDA approved orphan drugs in 2013</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imbruvica (ibrutinib)</td>
<td>Mantle cell lymphoma</td>
</tr>
<tr>
<td>Gazyva (obinutuzumab)</td>
<td>Chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>Gilotrif (afatinib)</td>
<td>NSCLC – tumors that express specific types of EGFR gene mutations</td>
</tr>
<tr>
<td>Mekinist (trametinib)</td>
<td>Melanoma – tumors that express the BRAF V600E or V600K gene mutations</td>
</tr>
<tr>
<td>Tafinlar (dabrafenib)</td>
<td>Melanoma – tumors that express the BRAF V600E gene mutation</td>
</tr>
<tr>
<td>Pomalyst (pomalidomide)</td>
<td>Multiple myeloma – after disease progression on other drugs</td>
</tr>
<tr>
<td>Adempas (riociguat)</td>
<td>PAH and chronic thromboembolic pulmonary hypertension</td>
</tr>
<tr>
<td>Opsumit (macitentan)</td>
<td>Pulmonary arterial hypertension</td>
</tr>
<tr>
<td>Kynamro (mipomersen sodium)</td>
<td>Homozygous familial hypercholesterolemia</td>
</tr>
</tbody>
</table>

The ODA has helped to bring drugs for rare diseases to millions of patients and continues to stimulate research and development of orphan drugs

NME = new molecular entity; NSCLC = non–small cell lung cancer; PAH = pulmonary arterial hypertension
Some orphans have faced reimbursement and access hurdles

Overview

- First drug to treat underlying molecular defect in cystic fibrosis
- Application of personalized medicine
- Costs approximately $311,000 (US) / £180,000 (UK) per patient per year
- Long-term treatment

Examples of funding/access challenges

- Australia (~250 eligible patients):
  - PBAC initially deferred decision because of cost
  - Government then allocated PBS funding on pay-for-performance basis
- England (~320 eligible patients):
  - Cost per QALY originally estimated to be between £335,000 and £1,274,000
  - Discounted price remains confidential; however, cost per QALY reduced to between £285,000 and £1,077,000 (~15% reduction)
  - Specialized Commissioning Group subsequently agreed to fund Kalydeco
- Scotland (~70 eligible patients):
  - Rejected by SMC
  - Subsequently funded by new government fund for orphan drugs

PBAC = Pharmaceutical Benefits Advisory Committee; PBS = pharmaceutical benefits scheme; QALY: quality-adjusted life-year; SMC = Scottish Medicines Consortium.

Sources:
Some orphans have faced reimbursement and access hurdles

**Soliris (eculizumab) for aHUS**

**Overview**
- First in class; step-change in treatment; addresses high unmet need
- Rare disease that damages vital organs
- Costs up to $400,000 (US) / £340,200 (UK) per patient per year; world's most expensive drug
- Long-term treatment

**Examples of funding/access challenges**
- **Australia** (~70 patients):
  - Initially rejected by PBAC for inclusion on life-saving drug program (unacceptable cost-effectiveness was one reason)
  - PBAC approved the drug with **payment for performance** and government allocated PBS funding for Soliris
- **England** (~200 eligible patients):
  - NICE asked manufacturer to justify price by providing information on research and development costs
  - Approved **conditional** on coordination through expert center, monitoring to record number of aHUS patients, development of a protocol for starting/stopping treatment, and a research program that evaluates when to stop treatment or adjust dosage
  - Budget impact is uncertain but will be considerable. NHS and manufacturer should consider what opportunities might exist to reduce the cost of Soliris to the NHS

NHS = National Health Service.
Note: Soliris for aHUS was not submitted to the Scottish Medicines Consortium.
With so many orphan drugs launching, payers face new challenges

Examples include:
- Cerezyme (Gaucher disease)
- Elaprase (Hunter syndrome)
- Kalydeco (cystic fibrosis)
- Remodulin (pulmonary arterial hypertension)
- Soliris (paroxysmal nocturnal hemoglobinuria and aHUS)

All of these are priced at more than $100,000 per year

# Payers in key markets viewed things differently about orphan drugs

<table>
<thead>
<tr>
<th>Country</th>
<th>Respondents Interviewed</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>AU</td>
<td>▪ Health economics professor and HTA advisor to Medical Services Advisory Committee (MSAC) and Pharmaceutical Benefits Advisory Committee (PBAC)</td>
<td>1</td>
</tr>
<tr>
<td>FR</td>
<td>▪ Health economics professor and advisor to Haute Autorité de Santé (HAS) and working group on economic evaluation of rare diseases</td>
<td>1</td>
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<tr>
<td>DE</td>
<td>▪ Health economics professor and member of arbitration board for drug pricing</td>
<td>1</td>
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<tr>
<td>IT</td>
<td>▪ Health economics professor and regional HTA advisor, member of committee for modernization of high-cost medicines</td>
<td>1</td>
</tr>
<tr>
<td>ES</td>
<td>▪ Health economics professor, regional HTA advisor, member of committee for modernization of high-cost medicines</td>
<td>1</td>
</tr>
<tr>
<td>UK</td>
<td>▪ Health economics professor and HTA advisor to Scottish Medicines Consortium (SMC) and National Institute for Health and Care Excellence (NICE)</td>
<td>1</td>
</tr>
</tbody>
</table>
| US      | ▪ Medical director for national health plan – 11 million lives  
▪ Medical director for integrated health plan – 1.1 million lives  
▪ Pharmacy director for national Pharmacy Benefit Management (PBM) – 35 million lives                                                                 | 3      |
| Total   |                                                                                                                                                                                                                      | 9      |
However, all payers expected expenditure on orphans to increase

<table>
<thead>
<tr>
<th>Country</th>
<th>How do you expect expenditure on orphans to change over the next 5 years?</th>
</tr>
</thead>
<tbody>
<tr>
<td>AU</td>
<td>↑</td>
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<td>FR</td>
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<td>ES</td>
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<tr>
<td>UK</td>
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<tr>
<td>US</td>
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</tr>
</tbody>
</table>

Payers gave the following examples of orphans/disease states that “keep them awake at night” and are a concern in terms of budget impact:

- Cancer
- Cystic fibrosis
- Hemophilia
- Hepatitis C
- Intravenous immunoglobulin\(^a\)
- Pulmonary arterial hypertension

\(^a\) Which is used to treat a variety of immune disorders

“I expect it to continue to grow.”

“Increasing ... more orphan drugs and broadening orphan class.”
Understanding comparative efficacy remains one of the biggest challenges

<table>
<thead>
<tr>
<th>What is your biggest challenge in reviewing orphan drugs?</th>
<th>AU</th>
<th>FR</th>
<th>DE</th>
<th>IT</th>
<th>ES</th>
<th>UK</th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited clinical evidence/including comparative efficacy benefits&lt;sup&gt;a&lt;/sup&gt;</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
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<tr>
<td>Uncertainty in treatment sequencing</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
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<td>●</td>
</tr>
<tr>
<td>Cost/CE, and trade-off between CE and orphan drug objectives</td>
<td>●</td>
<td>●</td>
<td>●</td>
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<td>●</td>
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<tr>
<td>Pressure from advocacy groups</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Differentiating real orphan/ultra-orphan indications</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

CE = cost-effectiveness; RCT = randomized controlled trial.

<sup>a</sup> Due to small patient population, noncomparative clinical trials, no standards of care.

“RCT has no comparator, no standard of care. Small RCT” – Spanish payer

“Difficulty in understanding factoring into the greater treatment paradigm” – US payer

“Orphans have high cost/QALY. Ultra-orphans are astronomically high cost/QALY” – UK payer

“Advocacy groups and legislation ties our hands” – US payer

“Everything is classified as orphan” – US payer
When clinical evidence is limited, what else can support P&MA for orphans?

### Evidence
- Demonstrate clear survival improvements – ES, US, UK
- Underscore impact the drug has – AUS
- Conduct postmarketing/real-world validation – US
- Extend RCT with real-world study to extend time points for benefit – UK
- Conduct comparative clinical studies vs. current practice, wherever feasible – UK, DE

### Costs
- Demonstrate any clear cost offsets and associated budget impact – IT, US, FR
- Consider risk-sharing agreements – IT, AUS

### Guidelines
- Develop clear guidelines – US
- Include start and stop rules for the new drug – US

### Burden of disease
- Develop thorough definition of disease burden – FR
- Underscore the difficulty and rarity of the disease – AUS
- Include the patient perspective – IT
- Leverage advocacy group support – IT, FR, US
- Clearly define the patient population and provide robust evidence regarding patient numbers – UK

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P&MA = pricing and market access.
# Future indication expansion for Kalydeco could erode price in some markets

## Kalydeco (ivacaftor) for cystic fibrosis

### Current situation – high price achieved based on high incremental clinical benefit (step change in treatment of cystic fibrosis)
- No restrictions on access across most markets (risk sharing in Australia)
- In Spain, available but not used (not recommended by GENESIS group of hospital pharmacists as there are cheaper alternatives)
- In Scotland, “Kalydeco fund” granted

### Future perspectives if indication is expanded\(^a\)
- **Australia:** Rule of rescue applied on a case-by-case basis; TGA may not assign as orphan anymore\(^b\)
- **France:** Could be clawbacks based on increased patient population and new ASMR
- **Germany:** If the revenue threshold exceeds €50 million, the manufacturer will need to submit a full dossier with a G-BA approved comparator (if appropriate) and undergo full assessment
- **Italy:** Price renegotiation; will be high on payers’ radar due to budget-impact concerns
- **Spain:** Price renegotiation; may be recommended by GENESIS group?
- **UK:** “Kalydeco fund”—will it continue if the indication expands?
- **US:** Prior authorization to label; confirmation of mutation testing

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TGA = Therapeutic Goods Administration; ASMR = amélioration du service médical rendu (improvement in medical benefit); G-BA = Gemeinsamer Bundesausschuss [Federal Joint Committee]; GENESIS = Group for Innovation Assessment, Standardisation and Research in the Selection of Drugs.

\(^a\) Ivacaftor is being examined for additional label expansion to include additional mutations to the CFTR gene and patient populations in additional age ranges; also for combination therapies.  
\(^b\) Depends on patient numbers.
Payers mentioned the same for Soliris

**Soliris (eculizumab) for aHUS**

<table>
<thead>
<tr>
<th>Current situation – high price achieved based on high incremental clinical benefit in indication with high unmet need</th>
</tr>
</thead>
<tbody>
<tr>
<td>- No restrictions on access across markets (risk sharing in Australia)</td>
</tr>
</tbody>
</table>

**Future perspectives if indication is expanded**

- **Australia:** Rule of rescue applied on a case-by-case basis; TGA may not assign as orphan anymore (depending on patient numbers)
- **France:** Adjust price/volume agreement accordingly
- **Germany:** If the revenue threshold exceeds €50 million, the manufacturer will need to submit a full dossier with a G-BA approved comparator (if appropriate) and undergo full assessment
- **Italy:** Price renegotiation; will be high on payers’ radar
- **Spain:** Price renegotiation; strict guidelines and approval by higher authority before use
- **UK:** Health economic evaluation and will depend on cost/QALY; local health board may make exceptions
- **US:** Payers are becoming increasingly cost conscious and may look for ways to manage (e.g., risk sharing)

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*Eculizumab is being examined for additional orphan indications in various phases of the late-stage development.*
Possible restrictions that payers may impose in the future on orphans

- Risk-sharing and increased monitoring – to mitigate some of the risk based on limited clinical evidence
- Requirement to determine appropriate comparator (if applicable) – single-arm studies may no longer be acceptable in certain indications if an appropriate comparator is available
- If indication gets crowded, there could be preferences for specific drugs
- More closed formularies and more cost to patient
  Payers are unlikely to cover a new drug if a low-cost alternative has similar efficacy
Final comments from the payers

UK
"There is not a blank cheque. Questions are going to be increasingly asked about justification for price. More and more resistance in the future."

ES
"Payers really worry about orphan drugs, particularly pricing."

US
"Be very attentive to price because the day is coming. Price concerns are #1 oncology/specialty drugs, #2 orphan ... the well is not infinitely deep"
## Market-specific expectations for orphan drugs

<table>
<thead>
<tr>
<th>Expectations / possible scenarios</th>
<th>AU</th>
<th>FR</th>
<th>DE</th>
<th>IT</th>
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<th>US</th>
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</thead>
<tbody>
<tr>
<td>Risk-sharing agreement likely</td>
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<tr>
<td>Local-level purchasing hurdles likely</td>
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<td>●</td>
<td>●</td>
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<td>●</td>
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<tr>
<td>Specific orphan drug criteria for reimbursement exception</td>
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<td>●</td>
<td></td>
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<td>●</td>
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<tr>
<td>Prior authorization likely</td>
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<td></td>
<td></td>
<td>●</td>
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<tr>
<td>Confirmation of diagnostic testing likely, if applicable</td>
<td>●</td>
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<td>●</td>
<td>●</td>
<td>●</td>
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<td>●</td>
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<tr>
<td>Additional pricing justification possible (Soliris example)</td>
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<td>●</td>
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<tr>
<td>Budget-impact threshold triggers/clawbacks</td>
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<td>●</td>
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<tr>
<td>Additional indications treated as new drug evaluation</td>
<td>●</td>
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</table>
### Key considerations to support successful P&MA for orphans

**Early engagement with payers**

- Develop the product’s value proposition and understand supporting evidence requirements
- Qualitative payer and payer influencer research for value drivers
- Pricing research
- Price-value mapping

**Understand and define the unmet needs**

- What is the burden to the patient and/or any caregiver?
- What is the cost of the disease?
- Literature reviews
- Patient/caregiver surveys
- Retrospective data analyses (claims, chart reviews, etc.)

**Comparator**

- Where appropriate, conduct comparative trials

**Managing budget impact**

- Define the eligible patient population using the most robust data possible
- Clearly define treatment start/stop rules, with supporting evidence
- Provide robust evidence to support any relevant cost offsets
- Develop budget-impact model
- Validate model with payers and payer influencers
# Key considerations to support successful P&MA for orphans

<table>
<thead>
<tr>
<th>Details</th>
<th>How to achieve this</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Consider risk-sharing/managed entry schemes in countries where already in place (e.g., Italy, Australia)</td>
<td>• Packaging observational and clinical data and actively engaging with the stakeholders on risk-sharing/ managed-entry schemes</td>
</tr>
<tr>
<td>• To fast track orphan drug review</td>
<td>• From observational studies/registries</td>
</tr>
<tr>
<td>• Obtain longer-term data for decision makers to understand the drug’s efficacy and safety profile in the longer term</td>
<td>• Engage with practicing key opinion leaders</td>
</tr>
<tr>
<td>• Any relevant patient-centric information can be useful to add to the evidence base and for prescriber pull-through</td>
<td>• Engage with patient advocacy</td>
</tr>
<tr>
<td></td>
<td>• Engage with the patients</td>
</tr>
<tr>
<td></td>
<td>• Social media/blogs</td>
</tr>
</tbody>
</table>

Great need to “package” all of the evidence into a customizable communications platform to accurately and consistently communicate to the decision makers
Australia Rule of Rescue Criteria for funding under the Life-Saving Drugs Program

- No alternative exists in Australia to treat patients with the specific circumstances of the medical condition meeting the criteria of the restriction. This means that there are no nonpharmacological or pharmacological interventions for these patients.
- The medical condition defined by the requested restriction is severe, progressive, and expected to lead to premature death. The more severe the condition, or the younger the age at which a person with the condition might die, or the closer a person with the condition is to death, the more influential the rule of rescue might be in the consideration by PBAC.
- The medical condition defined by the requested restriction applies to only a very small number of patients. Again, the fewer the patients, the more influential the rule of rescue might be in the consideration by PBAC. However, PBAC is also mindful that the PBS is a community-based scheme and cannot cater for individual circumstances.
- The proposed medicine provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition. The greater the rescue, the more influential the rule of rescue might be in the consideration by PBAC.

Learn More

- Poster presented at the ISPOR 18\textsuperscript{th} Annual European Congress: 
  \textit{Orphan and ultra-orphan technologies: European and Australian payer perceptions}.

- Poster presented at the ISPOR 20\textsuperscript{th} Annual International Meeting: 
  \textit{Orphan and ultra-orphan technologies in the new era of payment reform: United States payer perceptions}.

- Visit \url{rtihs.org} to find out how we can support you.

- Contact \textit{Susan Hogue} for additional information about our orphan drug project experience.