

HTA and Reimbursement Considerations for Rare Diseases in European Markets: What Are the Implications for Manufacturers?

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BACKGROUND

- According to the European Medicines Agency definition, orphan drugs are intended for diagnosis, prevention, or treatment of rare diseases whose conditions affect no more than 5 in 10,000 persons.¹
- Currently, no official definition of “ultra-orphan disorders” has been adopted globally. This informal subcategory was introduced by the National Institute for Health and Care Excellence (NICE), which applied it to drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons.²
- Approximately 60 million people in the United States and European Union are affected by a rare disease.³
- Despite orphan drugs’ association with high drug prices, their number is expected to grow at double the rate of the rest of the pharmaceutical industry over the next 6 years.⁴

OBJECTIVES

- Orphan drug studies often have lower-quality evidence compared with nonorphan drugs, and economic evaluations are associated with greater uncertainty, making application of general health technology assessment (HTA) rules challenging.
 - Limited efficacy and safety profile evidence at launch (small studies reflect small recruitment pool).
 - Limited natural history and epidemiology data.
 - Clinical studies are usually noncontrolled, and many are single-arm studies.
 - Many rare diseases affect children, thus impacting parents and caregivers; therefore, the full benefits of a new drug may not be captured using traditional HTA methods.
- This review identified special HTA and reimbursement considerations introduced for the assessment of orphan drugs and implications for manufacturers.

METHODS

- We conducted a targeted literature search in the PubMed database from January 1, 2016, to April 25, 2018, in the English language.
- We supplemented the literature search by conducting desktop research of HTA websites and third-party websites to identify recent information on HTA considerations and conditions for new drugs for the treatment of rare diseases.
- We searched bibliographies of selected articles for further details.
- Countries included in the search were England, France, Germany, the Netherlands, Sweden, Scotland, and Wales.

RESULTS

Special HTA Considerations

- Three countries (Germany, France, and Scotland) have special HTA considerations for orphan drugs as presented in Table 1. These include:
 - Flexibility regarding level of evidence (Scotland and Germany)
 - Acceptance of proven additional benefit if the annual budget impact is below a threshold (€30 million for France and €50 million/year for Germany)

Table 1. Countries With Special HTA Considerations for Orphan Drugs

Country	Overview of Special HTA Considerations
France	Certain special HTA criteria are applied to orphan drugs: <ul style="list-style-type: none"> • Additional benefit is considered proven at marketing authorisation if the annual budget impact is less than €30 million per year for a particular indication • An accelerated HTA procedure is available for all innovative drugs (this can also apply to nonorphans)⁵
Germany	Certain special HTA criteria are applied to orphan drugs ⁶ : <ul style="list-style-type: none"> • Higher <i>P</i> values for small sample sizes • Use of surrogate endpoints • Additional benefit is considered proven if the budget impact is less than €50 million per year for a particular indication Higher therapeutic benefit is automatically recognised for orphan drugs (Section 35a, para. 1 clause 10 of the German Social Code Book V) because these drugs had to prove significant additional therapeutic benefit compared with other possibly already approved drugs as part of the European marketing authorisation procedure. ⁷
Scotland	The PACE is part of the SMC assessment process for new medicines. It can be used to allow a more flexible approach to considering new orphan or ultra-orphan drugs. ⁸ <p>The PACE process involves engagement with patient groups, clinical experts, and pharmaceutical companies and allows the gathering of evidence that will allow a discussion on the benefits of a new drug, including how it can impact the quality of the patient’s life and of their carers and wider family. This information may not always be captured fully in the conventional assessment process.</p> <p>In October 2018, a process will be introduced to allow faster access to ultra-orphan drugs⁹:</p> <ul style="list-style-type: none"> • The Scottish government will introduce a new definition of ultra-orphan medicines that can treat very rare conditions affecting fewer than 1 in 50,000 people—approximately 100 people or fewer in Scotland. • This new definition also allows the SMC to treat some medicines for rare orphan diseases as ultra-orphan medicines. If SMC deems the new drug to be clinically effective, it will be made available on the NHS for at least 3 years while information on its effectiveness is gathered. The SMC will then review the evidence and may make a final decision on its routine use in NHS Scotland. • Furthermore, medicines that fall under the new definition and which have been recently reviewed by SMC but not recommended for routine use will be admitted to the new pathway.

NHS = National Health Service; PACE = Patient and Clinician Engagement Process; SMC = Scottish Medicines Consortium.

Special Reimbursement Conditions

- Four countries (England, Germany, The Netherlands, and Sweden) have special reimbursement conditions for orphan drugs and are presented in Table 2.

Table 2. Countries With Special Reimbursement Conditions for New Orphan Drugs

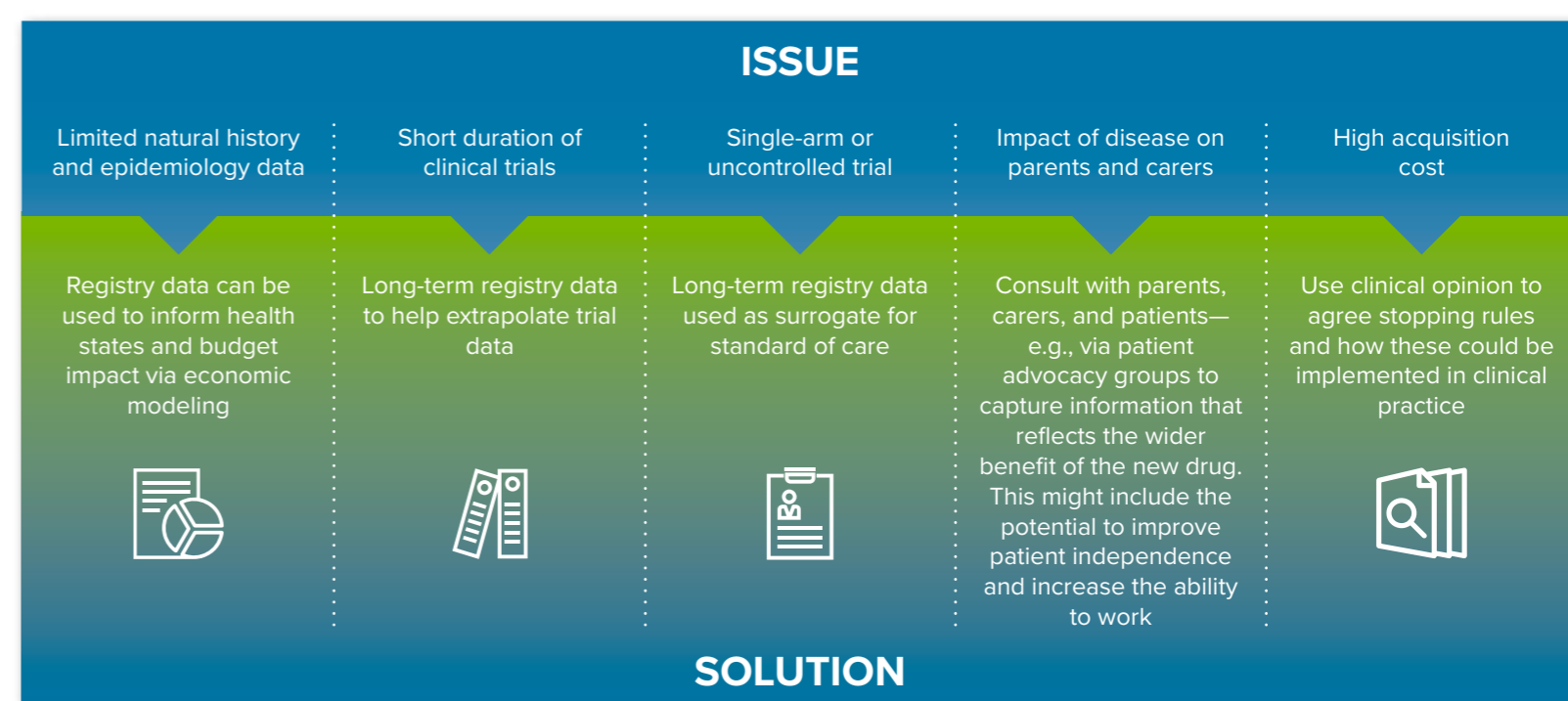
Country	Overview of Special Reimbursement Conditions
England	NICE introduced the Highly Specialised Technology Programme for ultra-orphan conditions (prevalence < 1 in 50,000). These are evaluated by an independent advisory committee. ¹⁰ This programme includes broader consideration of value including the nature of the condition, the impact of the new drug, cost to the NHS and Personal Social Services, quality-of-life impact on patients and carers, modification of the cost-per-QALY threshold, lower discount rates, and recognition of uncertainty in the data.
Germany	There are no specific pricing considerations for orphan drugs, but lack of therapeutic alternatives often results in a continued free-pricing approach. ⁷
The Netherlands	Hospitals may apply for full additional funding for orphan drugs; additional temporary funding considers therapeutic benefit, cost prognosis, and outcomes research; treatment of all patients needs to be documented in a patient registry; the therapeutic value, the severity of the disease, and the efficient prescription are important for the listing and funding decision. ⁷
Sweden	TLV can take a flexible approach to reimbursement based on the level of unmet need and uncertainty, and may consider a higher cost-effectiveness threshold for orphan drugs. Orphan diseases are considered severe conditions (conditions in which there is a greater need take precedence over others). In practice, this takes into account the small patient numbers involved, limited budget impact, and high unmet medical needs. ^{11,12}

QALY = quality-adjusted life-year; TLV = Tandvards-och Lakemedelsformansverket.

Strategies for Manufacturers to Demonstrate the Value of Orphan Drugs

- Figure 1 presents strategies that manufacturers can employ to improve the robustness of the evidence and decrease uncertainty in the value assessment of new orphan drugs.

Figure 1. Mitigation Strategies to Collate Data and Manage Uncertainty for Orphan Drugs



CONCLUSIONS

- Although several European countries have introduced special considerations for the assessment and reimbursement of drugs for rare diseases, evidence requirements for orphan versus nonorphan drugs are similar.
- Manufacturers should utilise a range of evidence sources and techniques, including comparative real-world information, to bridge data gaps and address uncertainty to enable equitable decision-making.

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