Analysis of Health Technology Assessment Procedures and Outcomes for Orphan Drugs

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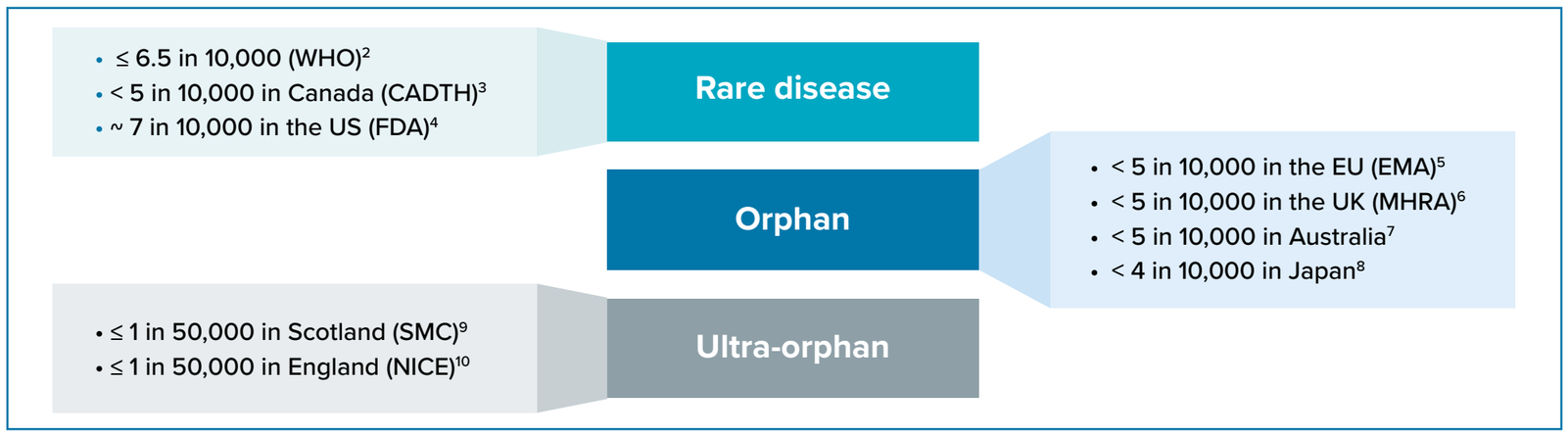
BACKGROUND

- Various agencies perform health technology assessment (HTA), and although the aims of HTA are similar across agencies (e.g., to provide information to help decision-makers with the potential value of a health technology), the procedures used and outcomes for orphan drugs may vary.
- Orphan drugs are those that treat rare diseases, but definitions differ by country (Figure 1). Ritcher et al.[1] identified 296 definitions related to rare diseases from 32 international jurisdictions.

OBJECTIVE

- To research how orphan drugs are evaluated by agencies performing HTA in England, Scotland, France, Germany, Sweden, Australia, Canada, and the United States, and to compare decisions taken on orphan drugs across 3 key European agencies

Figure 1. Variation in Orphan Drug Definitions



CADTH = Canadian Agency for Drugs and Technologies in Health; EMA = European Medicines Agency; MHRA = Medicines and Healthcare Products Regulatory Agency; NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicines Consortium; UK = United Kingdom; WHO = World Health Organisation.

METHODS

- Publicly available information on each agency's procedures for orphan drug evaluation were identified, categorised, and compared. The procedures used by the agencies were qualitatively assessed to establish whether procedures for assessing orphan and non-orphan drugs were the same or different.
- Drugs with an EMA orphan designation that had been assessed by NICE between June 2021 and June 2022 were identified, and HTA outcomes for the identified drugs were analysed and compared across 3 European agencies that each used a different category of HTA procedure.

RESULTS

- Overall, 3 categories of HTA procedures were identified (Table 1):
  - **Standard:** procedures for orphan and non-orphan drugs are identical
  - **Standard with flexibilities:** procedures are the same as standard but with some flexibilities allowed that may benefit orphan drugs, such as accepting greater uncertainty in the evidence, accepting higher prices, using higher willingness-to-pay thresholds, or using managed entry or risk-sharing agreements
  - **Specialised:** different procedures that may benefit orphan drugs compared with standard procedures, such as exempting orphan drugs from HTA
- For some agencies (such as NICE, SMC, and G-BA), more than 1 HTA procedure is available to assess orphan drugs.
- In total, 29 drugs that had an EMA orphan drug designation and that had been considered by NICE were identified. A European agency from each of the 3 identified categories of HTA procedures was selected so that outcomes relevant to the procedure could be compared. The 3 selected agencies were HAS (standard procedure), NICE (flexible procedure), and G-BA (specialised procedure).
- Of the 29 identified orphan drugs, 15 had an HTA decision published by all 3 of the selected agencies and were included in the analysis. Drugs that were terminated, in progress, had unclear decisions, and that were not assessed by all 3 agencies were excluded. Because each agency has different procedures that inform different types of decisions, HTA outcomes were broadly classified as:
  - **Positive:** best possible outcome (e.g., full recommendation or full reimbursement)
  - **Restrictive:** broadly positive outcome (e.g., partial recommendation, restricted reimbursement)
  - **Negative:** worst outcome (e.g., not recommended, not reimbursed)
- The outcome for each drug is summarised in Table 2. Overall, the number of orphan drugs that received positive outcomes was 0 (HAS, standard procedure), 0 (NICE, flexible procedure), and 9 (G-BA, specialised procedure). The remaining drugs achieved HTA outcomes that were restrictive or negative. HTA outcomes were considered consistent across all 3 agencies for only 3 (20%) orphan drugs.

Table 1. Agencies and Type of Procedure Used to Perform HTA

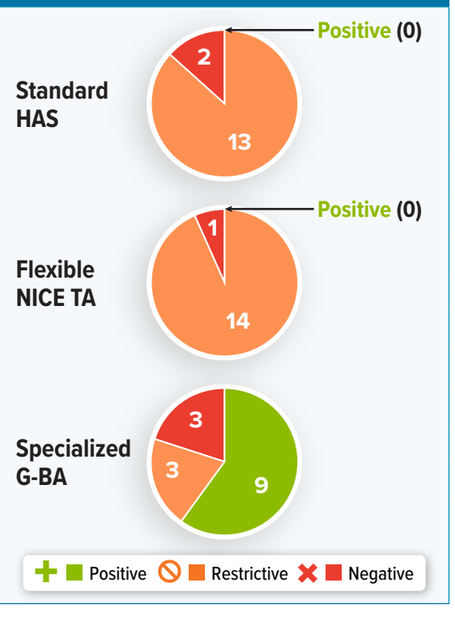
Agency (country)	Classification of procedure (procedure name, if applicable)	Criteria
PBAC (Australia)	Standard (Pharmaceutical Benefits Scheme)	Any drug. Drugs going through standard procedures may be eligible for rule of rescue or the Life Saving Drugs Program.
CADTH (Canada)	Standard	Any drug
NICE (England)	Standard with flexibilities (technology appraisal)	Any drug that does not meet the HST criteria
	Specialised (highly specialised technology)	Any drug that meets the HST criteria: • The disease is very rare: < 1 in 50,000 (< 1,100 people in England). • The number of people in England eligible for the drug is < 300 (single indications) or < 500 (across all its indications). • The very rare disease significantly shortens life or severely impairs QOL. • There are no other satisfactory treatment options, or it will offer significant benefit over existing options.
HAS (France)	Standard	Any drug
G-BA (Germany)	Standard	Any drug that does not meet the orphan drug criteria
	Specialised (orphan drug exemption)	EMA orphan designation Sales must not exceed €50 million per year
SMC (Scotland)	Standard with flexibilities	Any drug that does not meet the ultra-orphan drug criteria
	Specialised (ultra-orphan pathway)	• The condition has a prevalence of < 1 in 50,000 in Scotland. • The medicine has a Great Britain orphan marketing authorisation from the MHRA. • The condition is chronic and severely disabling. • The condition requires highly specialised management.
TLV (Sweden)	Standard with flexibilities	Orphan and non-orphan drugs
ICER (US)	Standard with flexibilities	Orphan and non-orphan drugs
	Specialised (ultra-rare diseases)	Any drug that meets the criteria: • < 10,000 patients in the US • Future expansion of the indication to > 20,000 patients is unlikely • Offers major gains in quality and/or length of life

G-BA = Gemeinsame Bundesausschuss; HAS = Haute Autorité de Santé; HST = highly specialised technology; ICER = Institute for Clinical and Economic Review; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; QOL = quality of life; SMC = Scottish Medicines Consortium; TLV = Tandvårds-och läkemedelsförmånsverket.

Table 2. Orphan Drug HTA Outcomes

Orphan drug (indication)	Standard HAS	Flexible NICE TA	Specialised G-BA
Selumetinib (type 1 neurofibromatosis in children)	⊘	⊘	+
Elosulfase alfa (mucopolysaccharidosis type 4A)	⊘	⊘	+
Atidarsagene autotemcel (metachromatic leukodystrophy)	⊘	⊘	+
Pitolisant hydrochloride (obstructive sleep apnoea)	⊘	✖	✖
Odevixibat (progressive familial intrahepatic cholestasis)	⊘	⊘	+
Daratumumab in combination (multiple myeloma)	⊘	⊘	⊘
Venetoclax with azacitidine (acute myeloid leukaemia)	⊘	⊘	⊘
Risdiplam (spinal muscular atrophy)	⊘	⊘	⊘
Givosiran (acute hepatic porphyria)	⊘	⊘	+
Crizanlizumab (sickle cell disease)	⊘	⊘	+
Berotralstat (hereditary angioedema)	⊘	⊘	✖
Midostaurin (systemic mastocytosis)	⊘	⊘	+
Pemigatinib (advanced cholangiocarcinoma)	⊘	⊘	+
Chlormethine gel (mycosis fungoides-type cutaneous T-cell lymphoma)	✖	⊘	+
Ravulizumab (atypical haemolytic uraemic syndrome)	✖	⊘	✖

Summary



CONCLUSIONS

- HTA procedures and outcomes for orphan drug HTA vary widely.
- Drug benefits are considered differently by agencies, and drugs considered beneficial by 1 agency may not be considered the same in another. This creates a complex and unpredictable market access environment that ultimately affects patient access.

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