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Title **Policies for Orphan Diseases and Orphan Drugs**

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Aim

To describe the regulatory processes for orphan drugs from orphan designation to reimbursement and explore whether and how to improve the policy on orphan drugs.

Conclusions and results

European legislation defines a rare disease as a life-threatening or chronically debilitating condition with a prevalence of 5 patients per 10 000 people or less. EU has created incentives for development of orphan drugs, eg, fee reductions, protocol assistance, and 10 years of market exclusivity.

The European Medicines Agency (EMEA) grants the orphan designation, after which marketing authorization can be requested. Upon authorization, a European Public Assessment Report (EPAR) is prepared and published on the EMEA website. The EPARs generally reflect the information from clinical files submitted to EMEA, but more could be done to improve the utility of the EPARs for national drug reimbursement committees (DRCs).

To obtain product reimbursement, companies must send the DRC a budget impact analysis and evidence on the drug's efficacy, preferably, and effectiveness.

Recommendations

Some of the recommendations formulated for the European and national levels include:

- For high priority orphan diseases, Europe should set up registries as early as possible; preferably before a drug is being developed for the disease.
- HTA agencies could help design patient registries to ensure that useful data are collected on the effectiveness and cost effectiveness of novel drugs.
- Aggregated data from the registries should publicly available.
- Registries should be funded and governed independently from the company developing an orphan drug.
- Evidence from RCTs with clinically relevant endpoints should remain the standard for granting marketing authorization.
- HTA agencies may provide valuable input at the EMEA level to define the endpoints and level of clinical improvement needed in phase-3 studies to qualify the product for reimbursement.

Methods

Definitions for orphan diseases and orphan drugs were based on a narrative review of regulatory documents and published articles. Descriptions of regulatory processes were based on regulatory documents and interviews with experts, key actors, and stakeholders involved at the national and European levels.

We compared the clinical files submitted to EMEA for marketing authorization, the resulting EPARs, and clinical evidence submitted to the Belgian National Institute for Health and Disability Insurance as part of a drug reimbursement request for 15 specific, drug-indication combinations.

Clinical and economic evidence submitted to the Belgian DRC was critically appraised for 8 cases, looking at the type and level of evidence and the methodological standards applied to drug reimbursement files for orphan drugs.

Six countries were included in comparing orphan drug reimbursement procedures: Belgium, France, Italy, the Netherlands, Sweden and the United Kingdom.

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