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Rare Disease Policies and Orphan Drug Designation Processes in European and Asia-Pacific (APAC) Countries

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INTRODUCTION

More than 7,000 rare diseases have been identified, with a recent study estimating more than 10,000 rare diseases globally.[1] While these diseases are uncommon individually, as a group they affect over 4% of the global population.[2] Rare diseases mostly affect children, most of whom have an underlying genetic cause.[3] Treatments are necessary to improve the burden of rare diseases not only for the patients, but also for parents and caregivers.

The lack of available and accessible treatments for rare diseases is a major public health issue.

To improve availability and accessibility of rare disease treatments, we must first understand the associated barriers. For example, manufacturers of orphan drugs face difficulties throughout regulatory and reimbursement processes due to high prices and insufficient clinical trial data. In addition, orphan drug policies may differ across jurisdictions, posing additional hurdles.

OBJECTIVES

We aimed to understand the market access landscape for orphan drugs by comparing regulatory, health technology assessment (HTA), and reimbursement-related policies for rare disease and orphan drugs across nine major markets in the European Union (EU) and the APAC region.

METHODS

- We reviewed publicly available policy, legislative, and regulatory documents regarding rare diseases and orphan drugs in England, France, Germany, Australia, China, Japan, Singapore, South Korea, and Taiwan. In addition, we examined documents describing HTA and reimbursement processes for rare disease and orphan drugs among the nine jurisdictions
- Documents were sourced from government agency websites (published as of June 2023) and supplemented with peer-reviewed literature from 2014–2023.

RESULTS

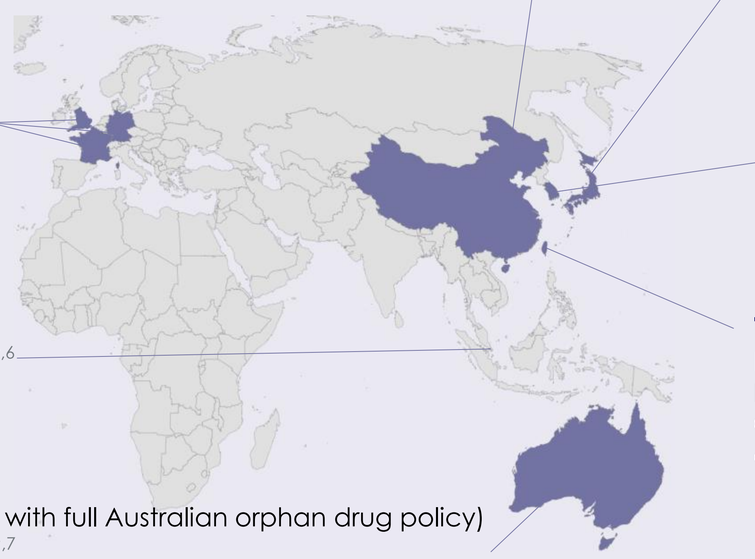
Figure 1. Rare disease definitions and orphan designation criteria across the EU, Australia, China, Japan, South Korea, Singapore, and Taiwan

European Union
(European Medicines Agency [EMA] covers the EU, including England, France, Germany)
Legislation: Regulation EC No. 141/2000
Rare disease: condition affecting ≤ 5 in 10,000 people[4]
Orphan designation: a life-threatening or chronically debilitating condition affecting no more than 5 in 10,000 persons in the community; or life-threatening, seriously debilitating or serious chronic condition in EU and without incentives the Sponsor would develop the medicine; and there are no other satisfactory method of diagnostic, prevention or treatment of the condition[5]

Singapore
Legislation: Medicines Act (Chapter 176, section 9)
Rare disease: condition affecting ≤ 5 in 10,000 people†,[6]
Orphan designation: doctor or dentist identifies and designates orphan diseases[7]

Australia
Legislation: Therapeutic Goods Act (amended in 1997 with full Australian orphan drug policy)
Rare disease: condition affecting ≤ 5 in 10,000 people†,[7]
Orphan designation: A life-threatening or chronically debilitating condition affecting no more than 5 in 10,000 persons in the community; and there are no existing therapeutic goods for the diagnosis, prevention or treatment of the condition[8]

China*
Regulation: China's First National List of Rare Diseases
Rare disease: condition affecting ≤ 1 in 10,000 people†. Disease is only recognized as rare if it is on China's First National List of Rare Diseases[9]



Japan
Legislation: Amendment of the Pharmaceutical Affairs Act and Drug Fund for Adverse Reaction Relief and Research Promotion Act (1993)
Rare disease: condition affecting <50,000 people in Japan[6]
Orphan designation: intended for use in less than 50 000 patients in Japan and for which there is a high medical need[10]

South Korea
Legislation: Rare Disease Management Act (2015), amendment to the Pharmaceutical Affairs Act (2001).
Rare disease: condition affecting <20,000 people in Korea or unknown prevalence due to diagnostic difficulties[6]
Orphan designation: for rare diseases and no available treatments in the market, or the new drug offers significantly better safety/efficacy compared to existing alternatives[6]

Taiwan
Legislation: Rare Disease and Orphan Drug Act (amended in 2015)
Rare disease: condition affecting ≤ 1 in 10,000 people†,[6]
Orphan designation: drugs with major indications for the prevention, diagnosis and treatment of rare diseases[11]

* There is no legislated policy on orphan drugs in China
† There is no legislated quantitative definition of rare diseases in China, Singapore, Taiwan, or Australia. The generally accepted quantitative definition for each of these countries has been provided.

Table 1. Summary of market authorization policies for rare disease treatments and orphan drugs

		EU	France	Australia	China	Japan	Singapore	South Korea	Taiwan
Unique market authorization process		X	Early access authorization (AAP) for innovative drugs‡,[12,13]	X	X	X	X	X	X
Common Incentives	**Accelerated procedure**	Centralized review through the EMA[14]	AAP considered accelerated[12,13]	X	Priority approval[6]	Priority review[6]	X	Accelerated approval[6]	X
	Lower fees	✓[14]	✓[12,13]	✓[15]	X	✓[6]	X	✓[6]	✓[6]
	Market Exclusivity	10 years + 2 for paediatric[14]	NA	X	X	10 years[6]	X	10 years + 1 for paediatric[6]	10 years data exclusivity[6]

‡In France, the AAP for innovative drugs may apply for treatments of rare diseases (for criteria, see Table 2). The AAP facilitates pre-market authorization in France, as assessed by HAS (*Haute Autorité de Santé*). Thus, this process would precede market authorization by the EMA.[12,13]

Unique reimbursement processes & subsidies for orphan drugs

- In **Australia**, orphan drugs for very rare, life-threatening conditions that receive a negative reimbursement decision following standard review process may be considered by the LSDP (Life Saving Drugs Program)[6]
- In **Japan, Singapore** and **Taiwan**, orphan drugs may qualify for **subsidized payment**[6]
- In **Singapore**, drugs for rare disease that is chronically debilitating or life-threatening can be supported under the RDF (Rare Disease Fund)[6]
- In **South Korea**, patients with specific rare diseases incur **reduced co-payments**[6]

Table 2. Specialized HTA processes for rare disease & orphan drugs

Country (agency)	Classification of procedure	Criteria
England (NICE)	Highly Specialized Technologies (HST) programme[16,17]	• Very rare disease (<1 in 50,000) that significantly shortens life or severely impairs quality of life (QoL) • Eligible population <300 (single indication) or <500 (for all indications) • No satisfactory treatments, or new drug with offer significant benefit over existing options
France (HAS)	Early Access Authorization programme[12,13]	Presumed innovative product • New treatment modality for the serious, rare, or disabling disease, brings substantial change to patients' QoL • Appropriate development plan with strong presumption that product is effective and safe based on results of therapeutic trials
Germany (G-BA)	Specialised – exemption[18]	EMA orphan designated drug, unless annual budget impact exceeds €50 million. If so, G-BA accepts lower levels of statistical significance for clinical outcomes
Japan	Specialised – exemption[6]	Rare disease treatments, unless annual budget impact exceeds ¥35 billion (or high unit prices, though threshold not explicitly defined)
South Korea (NECA)	Standard – adjusted ICER[6]	ICER of rare disease drugs is higher than for standard drugs (₩40.3 million/QALY vs. ₩10.8/QALY)
	Exemption of economic evaluation[6,19]	Oncologic or orphan designated drugs • Severe disease with no alternative intervention • Patient population too small to generate evidence • Drug is reimbursed by at least 3 of 7 pre-specified countries

Abbreviations not defined in this table or elsewhere: G-BA: Gemeinsamer Bundesausschuss; ICER: incremental cost-effectiveness ratio; NECA: National Evidence-based healthcare Collaborating Agency; NICE: National Institute for Health and Care Excellence; QALY: quality adjusted life years

CONCLUSIONS

- There is a wide variety of requirements and processes related to orphan drugs across European and APAC countries. In most countries, there is no difference in the requirements for regulatory assessment of orphan drugs compared to non-orphan drugs, though some provide incentives, such as priority review or 10-year market exclusivity. Some countries have implemented modified HTA processes for orphan drugs and may provide subsidies.
- Developing policies and procedures specific for rare disease and orphan drugs, and standardizing these across jurisdictions may improve equitable access to treatments for patients with rare diseases.

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