



Orphan drug trials accelerating in Asia Pacific

2019 review



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Introduction and Executive Summary

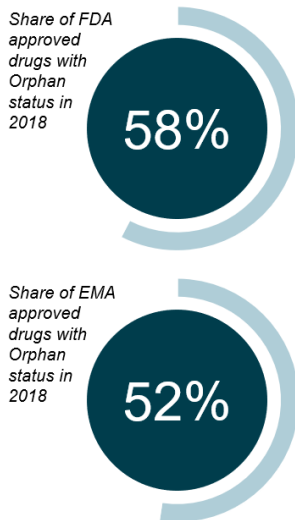
We have observed an unprecedented effort in the clinical development of Orphan drugs in the recent years. In fact, in 2018, the majority of new drugs approved by the FDA and EMA were Orphan medicines.

The objective of this report is to describe the Orphan drug development landscape and explain how the positioning of the Asia region has been evolving in the global picture. In Asia, we recently saw an acceleration in the development of legal frameworks in many locations including South Korea, Taiwan, Singapore and The Philippines. These frameworks set forth general criteria to accelerate the registration and approvals of drugs for the treatment of rare diseases and established new rules concerning health insurance coverage, expedited registration, and marketing exclusivity periods for biopharma companies.

Furthermore, the Action Plan on Rare Diseases launched in late 2018 by the Asia-Pacific Economic Cooperation is expected to accelerate supportive actions to develop public actions, disease registries, and patient access to clinical trials, and to reduce enrolment durations.

1. Market Trends in Orphan drugs trials

There may be as many as 8,000 rare diseases, affecting between 6% and 8% of the worldwide population in total. It is estimated there are about 30 million affected people in the EU and in North America, while over 45 million people may be suffering from a rare condition in Asia, with 10 million people in China alone^{1,2}.

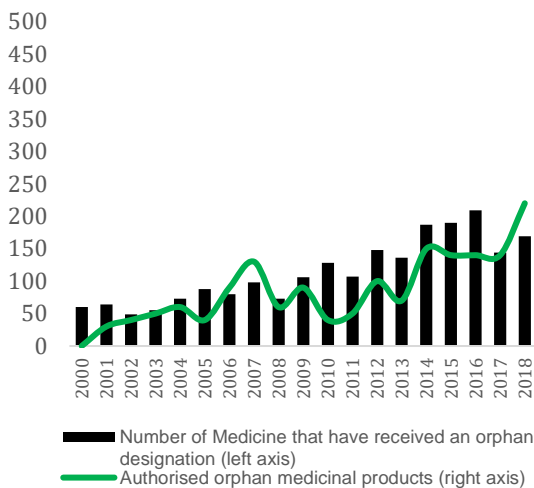


It is estimated that biological patents worth \$67 billion are due to expire by 2020. With many blockbuster drugs losing protection, big pharma companies have now gravitated towards specialty and Orphan drugs. In fact, most of the drugs approved by the FDA and EMA in 2018 were Orphan medicines³. Moreover, Orphan designations have been booming in the last 5 years.

Despite the large number of known Orphan diseases, it is estimated only about 5% of rare diseases have an approved treatment.

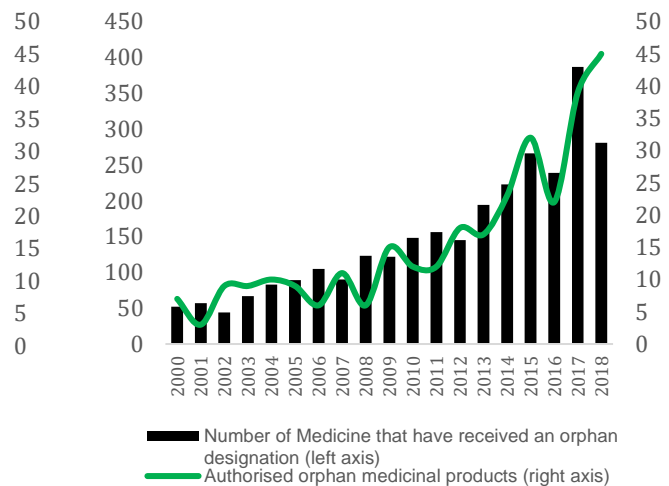
Worldwide sales for Orphan drugs are projected to be \$176 billion by the year 2020, which will comprise almost 20% of total drug sales⁴.

Number of medicines with an Orphan designation and authorized by the EMA



Source EMA

...and by the FDA (2000 – 2018)



Source FDA

¹ State of rare disease management in Southeast Asia. Shafie et al. Orphanet Journal of Rare Diseases (2016) 11:107. DOI 10.1186/s13023-016-0460-6
² Challenges in orphan drug development and regulatory policy in China. Cheng and Xie Orphanet Journal of Rare Diseases (2017) 12:13. DOI 10.1186/s13023-017-0568-6
³ Source EMA, FDA
⁴ <https://www.biospectrumasia.com/analysis/34/10293/asia-needs-a-legal-framework-to-combat-rare-diseases.html> - accessed June 3rd 2019

While the volume of Orphan drugs in development has increased significantly, recent statistics showed a sharper acceleration in the number of indications classified as Orphan.

Evolution of the number of Orphan indications and Orphan drugs (1983 – 2018)



Source: FDA Orphan Drug Database; Drugs@FDA Database, FDA websites; IQVIA Institute, Sep 2018

About 25% of drugs granted with an Orphan designation since 2015 were concentrated on 10 major indications. For most of these indications, clinical studies involving sites from Asia-Pacific outperformed median patient enrolment duration.

Top 10 indications granted Orphan designation from the FDA, and trial recruitment rates

Indications	# of medicines granted Orphan designation *	Recruitment rates (p/s/m) and median enrolment duration – Globally **	Recruitment rates (p/s/m) and median enrolment duration – Asia-Pacific **
Acute myeloid leukemia	54	0.75 (17.7 months)	1.1 (11.5 months)
Pancreatic cancer	48	1.18 (20.0 months)	1.52 (15.2 months)
Multiple myeloma	34	1.2 (21.5 months)	0.88 (15.2 months)
Amyotrophic lateral sclerosis	32	0.69 (10.5 months)	0.36 (17.1 months)
Ovarian cancer	23	1.56 (14.1 months)	2.00 (12.4 months)
Idiopathic Pulmonary Fibrosis	21	0.96 (14.0 months)	1.88 (14.7 months)
Duchenne muscular dystrophy	17	0.31 (15.0 months)	0.31 (13.6 months)
Diffuse large B-cell lymphoma	16	0.62 (23.1 months)	0.27 (26.8 months)
Hepatocellular carcinoma	16	1.13 (20.3 months)	0.66 (20.3 months)
Cystic fibrosis	15	1.04 (6.0 months)	0.62 (5.4 months)

Source FDA, GlobalData

* between 2015 – 2019 as of June 1st

** Trials initiated between Jan-2018 and May 2019

psm = patient per site per month

2. Understanding regulatory pathways

An increasing number of Asian countries have implemented a legal framework similar to the Orphan Drug Act in the US in recent years. Although the current regulations only set forth general criteria to accelerate registration and approval of Orphan drugs, these frameworks established new rules concerning health insurance, expedited registration, and marketing exclusivity periods for biopharma companies. Recently, China's FDA is offering to grant conditional approvals for Orphan meds already approved abroad, even without in-China trial data. China is also actively promoting the regulation of rare diseases and Orphan drugs⁵.

Comparison of Orphan drug regulation across the US, Europe and a selection of locations in Asia-pacific^{6,7,8}

Location	Rare disease definition	Market Exclusivity	Financial Incentive	Legal Framework
United States	Prevalence <200,000	7 years	The tax credit was reduced from 50% to 25% in 2017.	Orphan Drug Act of 1983
Europe	Prevalence <5/100,000	10 years	Various administrative fee reductions	Regulation (EC) No 1411/2000
China	Prevalence <500,000	N/A	NSFC research grant and fast track approval	None nation-wide
Australia	Prevalence <5/10,000	5 years	Regulatory fee waivers, protocol assistance, and priority review. The R&D cash refund scheme may apply	Orphan Drug Program (1998)
Japan	Prevalence <50,000	Up to 10 years	Regulatory fee waivers, clinical and non-clinical study grants, 15% tax credits. Protocol assistance and fast track approval	Pharmaceutical Affairs Law (1993)
South Korea	Prevalence <20,000	6 years	50% subsidized application fee	Orphan Drugs Guideline (2003)
Taiwan	Prevalence <2,300	10 years	Grants, copay can be waived, fast track approval, protocol assistance, and medical reimbursement	Rare Disease and Orphan Drug Act (2000)
Singapore	Prevalence <20,000	10 years	N/A	Medicines Act (Chapter 176, Section 9) (1991)
The Philippines	Prevalence <1/20,000	N/A	N/A	Rare Disease Act of the Philippines (2016)

⁵ Source <https://www.biospectrumasia.com/analysis/34/10293/asia-needs-a-legal-framework-to-combat-rare-diseases.html> - accessed June 3rd 2019

⁶ A compilation of national plans, policies and government actions for rare diseases in 23 countries, Neil Khosla, Rodolfo Valdez. *Intractable & Rare Diseases Research*. 2018; 7(4):213-222. DOI: 10.5582/irdr.2018.01085Review

⁷ Shafie et al. *Orphanet Journal of Rare Diseases* (2016) 11:107. DOI 10.1186/s13023-016-0460-9

⁸ Rare diseases, orphan drugs, and their regulation in Asia: Current status and future perspectives. *Intractable & Rare Diseases Research*. 2012; 1(1):3-9. DOI: 10.5582/irdr.2012.v1.1.3

3. Challenges and way forward

While we observe the emergence of legal frameworks in many countries of Asia, the region still faces challenges due to the lack of a systematic structure across countries. Asia-Pacific is home to many key opinion leaders across a range of therapeutic areas but would still lack resources allowing systematic diagnostic or testing for rare conditions. Clinical trials for Orphan drugs can be accelerated through the development of patient registries. Patient registries are data repositories containing health information to facilitate patient enrolment in clinical trials, and real-time post marketing surveillance including off-label drug use. Regulatory bodies can also engage patients and caretakers in the development of relevant clinical endpoints in the evaluation of drug approval applications⁹. There are still a limited number of international registries although over 700 rare disease registries were counted in the European Union¹⁰.

The regulatory and legal framework of Orphan drugs in Asia is still recent and varies between countries. However, we have observed an acceleration of initiatives to foster the development of disease awareness and patient registries in the region in the recent years. In late 2018, the Asia-Pacific Economic Cooperation (APEC) launched an Action Plan on Rare Diseases which provides a framework for facilitating alignment of domestic policies and best practices and enhancing regional collaboration¹¹. The main goal of the plan is to improve the economic and social inclusion of those affected by rare diseases, facilitate diagnostic and nation-wide patient registries, and raise public and political awareness on Orphan diseases issues.

⁹ Source <https://www.clinicalleader.com/doc/rare-disease-patient-recruitment-and-retention-0001> - accessed on June 3rd 2019

¹⁰ Overview on State of the Art on Rare Disease Activities in Europe: <http://www.rd-action.eu/wpcontent/uploads/2018/09/Final-Overview-Report-State-of-the-Art-2018-version.pdf>

¹¹ <https://www.apec.org/rarediseases/News/APEC-Rare-Disease-Action-Plan-Sets-Precedent-to-Integrate-Rare-Disease-Care-by-2025> accessed on June 13th 2019

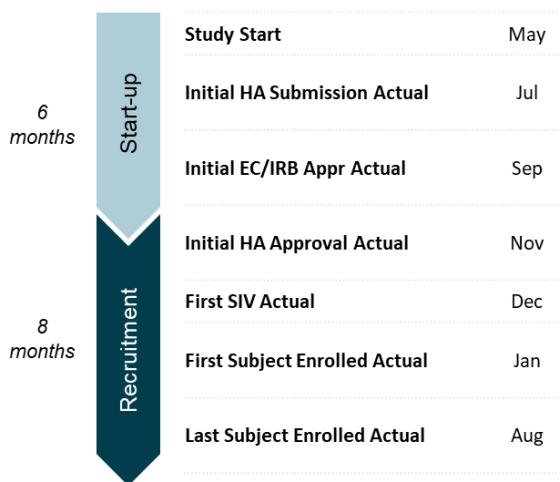
Case Study

Phase 1 for the study of Paroxysmal nocturnal hemoglobinuria

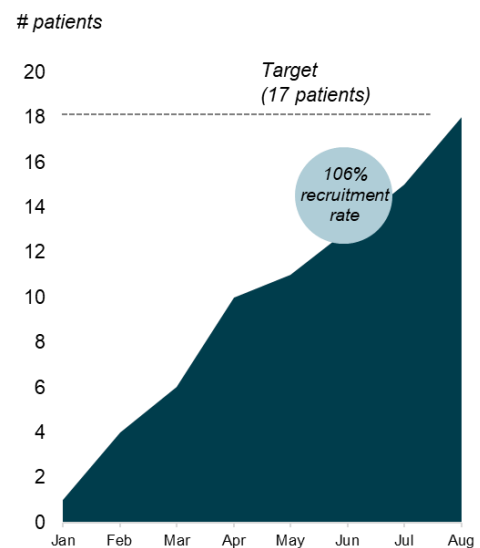
Western sponsor looking to accelerate their clinical development in an orphan indication (PNH)

Multiple sites in China, Malaysia and Thailand

Project timelines: 14 months from study start to last patient enrolled



Cumulative patient recruitment over time



Takeaways

- We have recently observed an unprecedented effort in the clinical development of Orphan drugs globally.
- More specifically in Asia, we saw an acceleration in the development of legal frameworks in many countries which set forth general criteria to foster the registration and approvals of drugs for the treatment of rare conditions.
- The regulatory and legal framework of Orphan drugs in Asia is still recent and varies between countries, with some still lacking resources allowing systematic diagnostic or testing for rare conditions.
- The Action Plan on Rare Diseases launched in late 2018 by the Asia-Pacific Economic Cooperation is expected to accelerate supportive actions to develop public actions, disease registries, and patient access to clinical trials, and to reduce enrolment durations.

