Orphan Drug Exclusivity: A Lifeline for Rare Disease Patients

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RAVI RAVIKANT, Associate Manager, Ark Patent Intelligence, IQVIA
ARPIT JAIN, Senior Insight Assoc, Ark Patent Intelligence, IQVIA

Diseases that affect a small number of individuals are known as rare or orphan diseases. The exact criteria for the number of patients required for a disease to qualify as an orphan disease differ across jurisdictions. There are more than 10,000 types of rare diseases in existence. As per reports, 400 million people are suffering from rare diseases globally, where 80% have a genetic origin, and 50% of the patients diagnosed with a rare disease are children. A pharmaceutical agent intended for use in orphan indications is called an orphan drug. In some cases, these medicines may also have additional non-orphan indications approved by the regulatory authorities. However, a single market authorization (MA) can be granted for either orphan or non-orphan indications.[1,2]

There is an exclusive market protection provided by the regulatory authorities to orphan drugs, known as orphan drug exclusivity (ODE). It prevents regulatory authorities from approving any other application for the same drug for the same orphan indication for a specific period. The ODE operates concurrently with other exclusivities like reference product exclusivity (RPE) and market protection and will expire independently. RPE is a form of exclusivity that occurs in the US, where the US FDA cannot approve any 351(k) application[3] for a biosimilar or interchangeable product that relies on a previously approved product as a reference for biosimilarity for a 12-year period (submissions can be filed after 4 years). The 12-year period is further divided into a 4-year biosimilar

application submission exclusivity (BASE) and an 8-year biosimilar application approval exclusivity (BAAE). On the other hand, market protection (MP) is a type of exclusivity that occurs in the EU, in which the sponsor gets a 10-year period[4] after the initial marketing authorization of a medicine during which a generic or biosimilar cannot be placed on the market (submissions can be filed after 8 years).

ODE may also be combined with other exclusivities such as pediatric (PED) exclusivity and generating antibiotic incentives now (GAIN) (Table 1). PED is a form of exclusivity that encourages the development of treatment plans for pediatric patients and serves as an add-on to current marketing exclusivity or patent protection, and GAIN is an exclusivity available only in the US for the development of new antibacterial or antifungal drugs for human use to treat serious or life-threatening infections.[5,6]

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Table 1: Major key features related to orphan drugs of US and EU[7]

PARTICULARS	US	EU
Act	Orphan Drug Act[8]	Regulation EC n°141/2000[9]
Administrative authorities	Office of Orphan Products Development (OOPD)	Committee for Orphan Medicinal Products (COMP)
Review period	Typically, 90 days	Maximum of 90 days
Marketing exclusivity	7 years	10 years
ODE + PED	7 years + 6 months	10 years + 2 years
ODE + GAIN	7 years + 5 years	–

Benefits associated with orphan drugs

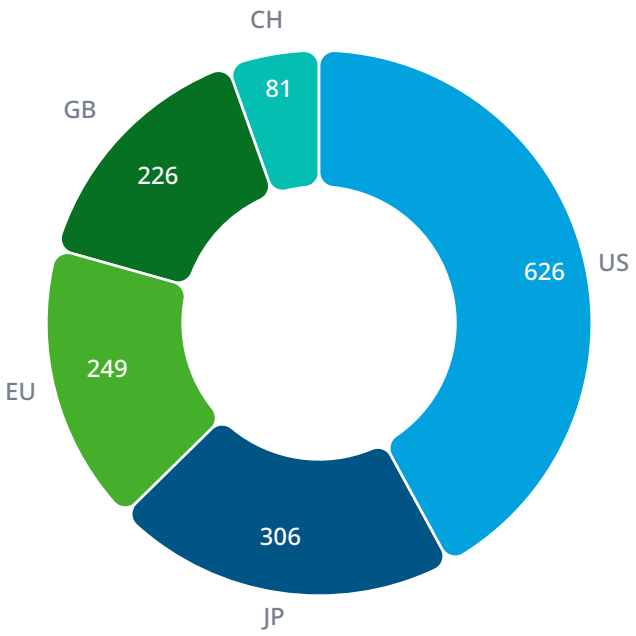
- Significant opportunity to address the public's unmet health needs.
- Several grants for orphan drug research and development.
- Sponsors get protocol assistance which helps streamline the drug development process.
- Regulatory authorities waive the fees associated with orphan drugs, which vary according to respective jurisdictions.
- Sponsors can receive significant tax credits for clinical drug testing expenses.
- Once orphan drug status is granted, ODE is granted that has a broader scope of protection.
- Untapped market potentials include market expansion, surge in investment, increase in diagnoses, and a global impact.[10,11]

Significant opportunity to address the public's unmet health needs and several grants for orphan drug research and development are available.

Orphan drug exclusivity via Ark Patent Intelligence

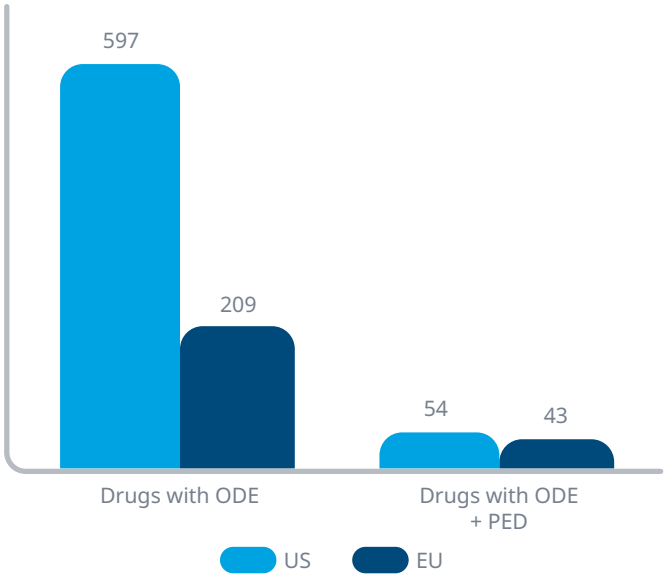
According to Ark Patent Intelligence data, a total of 763 distinct drugs have received orphan drug designation across various jurisdictions such as the US, JP, EU, GB, and CH (Figure 1). The same drug might receive orphan drug status in various countries. Since the US was the first country to implement the Orphan Drug Act, it has approved the highest number of orphan drugs and indications, followed by other countries.

Figure 1: Orphan drugs in US and EU



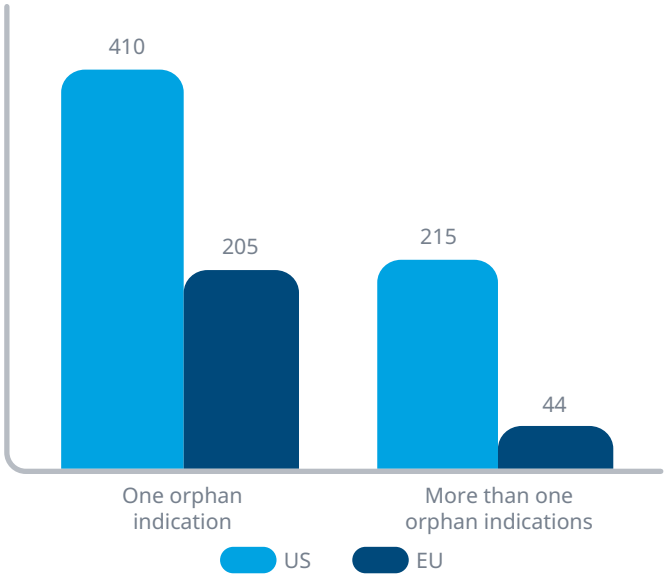
Source: Ark Patent Intelligence

Figure 2: Drugs with ODE and ODE+PED



Source: Ark Patent Intelligence

Figure 3: Drugs with multiple orphan indications



Source: Ark Patent Intelligence

Additionally, the Ark data set also showcases the total number of orphan drugs listed with PED exclusivity. (Figure 2). In the EU, PED is granted upon compliance of a pediatric investigation plan (PIP) and for ODs, the applicant must decide whether to have a 2-year extension to the ODE or a 6-month extension to the supplementary protection certificate (SPC) — it is not possible to have both.

A single orphan drug can be approved for one or more orphan indications, and for each indication, the drug will receive separate orphan exclusivities, which are not cumulative. For a drug with multiple approved orphan indications, the various ODEs associated with the same drug will expire individually after the completion of the respective term approved by regulatory authorities (Figure 3).

Daratumumab case study

Daratumumab (Darzalex) is a CD38-directed cytolytic antibody (immunoglobulin G1 kappa monoclonal antibody) used alone or in combination with other drugs in the treatment of multiple myeloma and light chain amyloidosis. Developed by Janssen Biotech, it received US FDA approval in November 2015, and centralized EU marketing authorization in May 2016. The approved orphan designations associated with daratumumab are presented below (Table 2).

Table 2: Daratumumab approved orphan indication in US and EU, MM (Multiple Myeloma), AL (Amyloidosis)

TRADE NAME (ACTIVE SUBSTANCE)	JURISDICTION	APPROVED ORPHAN EXCLUSIVITY-PROTECTED LABELLED INDICATION (EPLI)	MA DATE	EXCLUSIVITY EXPIRY DATE
Darzalex (Daratumumab)	EU	Treatment of plasma-cell myeloma	May 2016	May 2026
		Treatment of light-chain amyloidosis	Jun 2021	Jun 2031
	US	Treatment of multiple myeloma (EPLI-1)	Nov 2015	Nov 2022
		Treatment of multiple myeloma (EPLI-2)	Nov 2016	Nov 2023
		Treatment of multiple myeloma (EPLI-3)	Jun 2017	Jun 2024
		Treatment of multiple myeloma (EPLI-4)	May 2018	May 2025
		Treatment of multiple myeloma (EPLI-5)	Jun 2019	Jun 2026
		Treatment of multiple myeloma (EPLI-6)	Sep 2019	Sep 2026
		Treatment of multiple myeloma (EPLI-7)	Aug 2020	Aug 2027
Darzalex Faspro (Daratumumab and hyaluronidase-fihj)	US	Treatment of light-chain amyloidosis	Jan 2021	Jan 2028

Table 3: Regulatory Timelines for Daratumumab in US and EU for Multiple Myeloma, ODE (Orphan Drug Exclusivity), RPE (Reference Product Exclusivity)

DARATUMUMAB	US	EU
Market Authorization Date	Nov 2015	May 2016
General Exclusivity Rule	4+8 (BASE + BAAE)	8+2+1 (NCE + MP + MP-I)
Biosimilar Filing Date	Nov 2019	May 2026
RPE/market protection Expiry	Nov 2027	May 2027
Last ODE Expiry	Aug 2027	May 2026
Constraining Patent Expiry	May 2029	Mar 2031
Possible Biosimilar Entry	After May 2029	After Mar 2031

Source: Ark Patent Intelligence

In the US, when a drug holds RPE and ODE exclusivities, the competitive effects of each differ. RPE will prevent a biosimilar using Darzalex as a reference product but does not prevent a new biologics license application (BLA) submission for daratumumab by another sponsor if they provided their own data. ODE bars any sponsor from making the same drug for the same disease, even if the sponsor does not rely on the innovator's data. Exclusivities cannot be considered in isolation — patent protection from US patent US7829673 limits the market entry of any biosimilar daratumumab until at least May 2029 (Table 3).

In the EU, under the MP exclusivity, the 8+2+1 rule allows generics to apply after 8 years but bars them from marketing until after 10 or 11 years. If patent protection extends beyond this period, generics may enter the market immediately after the protection ends. However, for drugs with ODE as the last protection, generic applications are only accepted post-ODE expiration, and with the EMA's evaluation process taking approximately 277 days, the entry of generics will not be immediate post-protection.

Darzalex has regular MP and ODE for the treatment of multiple myeloma, both of which will expire in May 2026. Furthermore, it was granted an additional year of MP (MP-I), which will end in May 2027. Thus, the filing of a generic will be possible from May 2026 (10 years after approval under the 8+2+1 rule) for the treatment of plasma-cell myeloma, however, once again, patent protection will prevent the entry of the generic beyond the MP expiry of May 2027, because SPCs on European patent EP2567976 do not expire until around March 2031. There is an additional ODE for the treatment of light-chain (AL) amyloidosis, which expires later than the SPCs, in June 2031.

Summary

In the last ten years, there has been a notable increase in the approval of Orphan Drug Exclusivities (ODEs) across different regions. The future of ODEs looks promising, with continuous progress in treatments for rare diseases and possible enhancements in regulatory frameworks to optimize patient advantages. Employing multiple ODEs for a single product is yielding benefits for innovators and is further stimulating innovation in the pharmaceutical sector.

Regarding protection, the influence of ODE on the expiration of protection dates and the expected entry of generics or biosimilars depends on how many indications are covered by the ODEs and any concurrent patent protection. When older drugs are repurposed for orphan indications and no new patent protection is available, ODE can offer significant protection against competition.

Given the numerous advantages of ODEs, it is anticipated that pharmaceutical firms will escalate their investment in research and development for rare diseases, which will benefit a broader patient base. In the coming years, we might witness more rigorous regulatory policies surrounding orphan drugs to overcome the hurdles related to rare disease treatments.

Authors

ARPIT JAIN
Senior Insight Assoc,
Ark Patent Intelligence,
IQVIA

RAVI RAVIKANT
Assoc Manager,
Ark Patent Intelligence,
IQVIA

Arpit Jain holds a post-graduation degree in Pharmaceutical Sciences from Bharati Vidyapeeth Deemed University, Pune, India. He is Senior Insight Associate at IQVIA and has over 3 years of experience in patent searches, FTO and patent analytics. He has been a part of patent intelligence team since 2022.

Ravikant holds a master's degrees in Medicinal Chemistry from national Institute of Pharmaceutical Research and Education (NIPER) Mohali, and has 9 years of experience in Technology scouting, Innovation support, patent analytics and competitive intelligence. He has been associated with the patent intelligence team for 6 months.

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