EvaluatePharma®

Orphan Drug
Report 2019

Evaluate

Welcome to the EvaluatePharma® Orphan Drug Report 2019

The sixth edition of EvaluatePharma's Orphan Drug Report provides top-level insight from the world's financial markets into the expected performance of the orphan drug market between now and 2024. Based on EvaluatePharma's coverage of over 7,000 of the world's leading pharmaceutical and biotech companies, the Orphan Drug Report 2019 highlights trends in prescription sales of orphan drugs, US cost of treatment, leading products with an orphan drug designation, key companies in the rare diseases landscape and orphan drug designation analysis by region and therapy area.

Additional copies are available at:

www.evaluate.com/OrphanDrug2019

Overview

An orphan drug is a pharmaceutical product that treats a rare condition or disease. The development of orphan drugs has been financially incentivised through US law via the Orphan Drug Act of 1983. The National Organization for Rare Disorders (NORD), which was instrumental in establishing the Act, currently estimates that there are as many as 7,000 rare diseases and that up to 30 million Americans suffer from a rare disease. Prior to the 1983 Act, 38 orphan drugs were approved in the United States. The success of the original Orphan Drug Act in the US led to it being adopted in other key markets, most notably in Japan in 1993 and in the European Union in 2000.

Rare disease patient populations are defined in law as:

- **US:** <200,000 patients (<6.37 in 10,000, based on US population of 325m)
- **EU:** <5 in 10,000 (<256,000 patients, based on EU population of 512m)
- **Japan:** <50,000 patients (<4 in 10,000 based on Japan population of 126m)

Financial incentives by law include:

Orphan drug exclusivity

During the period of marketing exclusivity, the regulatory bodies are barred from approving the same product for the same orphan indication. A product holding several separate orphan designations for different indications can have several separate market exclusivities, which can run concurrently.

- **US:** Seven years of marketing exclusivity from approval.
- **EU:** Ten years of marketing exclusivity from approval.
- **Japan:** Ten years registration validity period (also known as re-examination period).

Reduced R&D costs, tax credits, and fees

- **US:** 50% Tax Credit on R&D Cost (owing to new tax legislation, likely to decrease to 25%).
- **US:** R&D Grants for Phase I to Phase III Clinical Trials.
- **US:** User fees waived (FFDCA Section 526: Company WW Revenues <$50m).
- **EU:** EMA protocol assistance at a reduced charge.
- **EU:** Administrative and procedural assistance at a reduced fee for small and medium sized enterprises.
- **EU:** The EMA does not offer research grants but funding is available for the European Commission (EC) and other sources, such as Horizon 2020 and E-Rare.
- **Japan:** Orphan products can be subsidised, for up to 50% of Japan development costs, through the National Institute of Biomedical Innovation (NIBIO).
- **Japan:** Guidance and consultations from the Pharmaceuticals and Medical Devices Agency (PMDA) at a lower user fee.
- **Japan:** 12% of study expenses (not including grant subsidies) incurred during the NIBIO payment period can be reported as a tax credit.

Overview

Orphan drug classification methodology

Using publically available sources, EvaluatePharma® identify products that have been granted orphan drug designations in the US, EU or Japan.
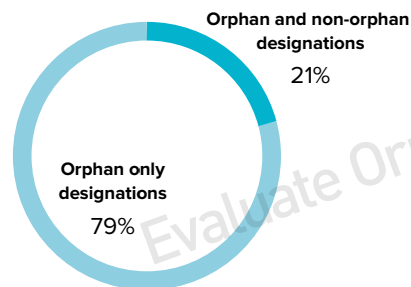
These products are then classified as 'EvaluatePharma® orphan drugs' if:

- The product is approved only for use in the indication/s for which it was awarded orphan designation and these indications are covered by Evaluate Pharma®.

- Approximately one-fifth of products have designations in orphan and non-orphan indications (see Figure 1a, for FDA orphan designated products). Products that have orphan and non-orphan drug designations and are expected to generate less than 50% of their sales in 2018 and 2024 from their orphan-designated indication/s, are excluded from this analysis. This has led to the exclusion of therapies such as Avastin, Opdivo, Enbrel, Herceptin, Humira and Remicade. Overall, 13% of therapies classified as orphan by EvaluatePharma®, are also expected to garner sales from non-orphan designated indication in 2018-2024 (see Figure 1b).

EvaluatePharma® will also classify R&D products as 'orphan drugs – prior to the products receiving this status from regulatory bodies – in the following cases:

- The product is being developed in an indication that is classified by regulatory bodies as an orphan disease, and other products for this disease were granted orphan drug designation.

- The company developing the product states it is seeking orphan drug designation for the product's lead indication.

Figure 1a: FDA orphan drugs by designation

Orphan and non-orphan designations **21%**

Orphan only designations **79%**

Figure 1b: EvaluatePharma® orphan drugs by designation

Orphan and non-orphan designations **13%**

Orphan only designations **87%**
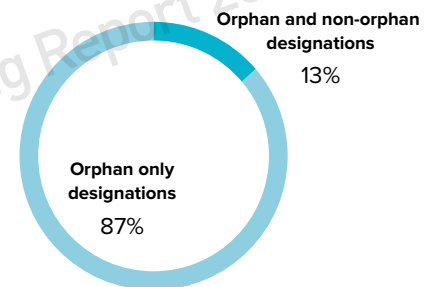
Note: Data in figure 1a is based on FDA data (https://www.accessdata.fda.gov/scripts/opdlisting/oopd/); accessed March 4th, 2019.

All data analysis in the report are based on EvaluatePharma®'s orphan drug definition. Product sales represent total brand sales.

Prices for products in the US are sourced from Medicare Part B, National Average Drug Acquisition Cost (NADAC), Federal Supply Schedule (FSS) and Medicaid.

Availability of a price point determines choice of source. The source is kept consistent across years to reflect a clear trend in pricing.

Foreword

This year's Orphan Drug report from EvaluatePharma comes at one of the most exciting points of the industry's development. Not only has the first US-approved gene therapy been launched onto the market, a whole host of other 'one and done' rare disease cures are queuing up behind it.

Spark Therapeutic's Luxturna, a treatment for a rare inherited eye disorder, could soon be joined by Novartis's Zolgensma and bluebird bio's Lentiglobin. The advent of these cutting edge treatments and the advances in cell-therapy that have seen CAR-T product Yescarta approved in orphan indications are some of the reasons why this year's report is predicting worldwide orphan drug sales to grow by 12% a year between now and 2024.

However, it might be wise to temper some of the excitement around these products and the related growth of the orphan drug market. The promise of these new therapies will only become reality if the innovation of drug companies is matched by innovation in the drug pricing and reimbursement systems.

The recent explosion in cell and gene therapies has not come cheap. Luxturna's list price is currently $425,000 per eye. And while Spark, soon to be part of Roche, has done much to relieve the burden on patients by first agreeing to a value-based price with payers and offering to fund patients co-pays, it is not clear if other drug developers will do the same.

Even with these measures taken by Spark there are still those in the market who believe the cost of the drug should be cut in half.

And while the scrutiny from US politicians over drug pricing might not have materialised into meaningful action, there remains a focus on healthcare costs that will only ramp up as the 2020 presidential election draw close.

> The fact that this year's report shows that orphan drugs will make up one-fifth of worldwide prescription sales, amounting to $242bn in spend in 2024 – with much of it going to either big pharma or big biotech – will only focus the minds of those calling for reforms to the Orphan Drug Act.

Foreword

Proof of big pharma's growing dominance within rare disease products is that while Celgene might have toppled Novartis as the world's biggest orphan drug developer, the big biotech company will soon be absorbed into Bristol-Myers Squibb.

This and the take outs of Spark by Roche for $4.8bn and Novartis's payment of $8.7bn to Avexis for Zolgensma will do nothing to silence those who believe that big pharma groups should not be benefiting from the regulatory and tax benefits offered to orphan drug developers.

But the willingness of big pharma groups to pay substantial premiums to get their hands on orphan drug products demonstrates the promise these companies see in the orphan drug space.
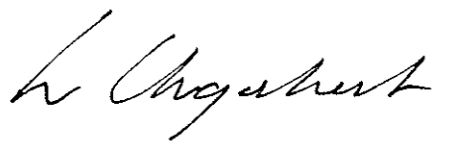
Growth rates approximately double those of the overall prescription drugs market and the mean cost per patient per year of the top 100 orphan products in the US hitting $150,854 in 2018 versus $33,654 for a non-orphan drug, explain much of the allure.

And with increasing complexity surrounding reimbursement of some of the industry's most innovative drugs, big pharma's regulatory expertise means it is arguably better placed to – if not develop orphan drugs – buy and market them.

As such the dominance of big pharma in the orphan drug market, excluding substantially policy reforms, is only likely to increase.

Report Author:
Karen Pomeranz, PhD
Managing Analyst, Evaluate
karen.pomeranz@evaluate.com

Foreword by:
Lisa Urquhart
Editor, Vantage
lisau@vantageanalysis.com

Analysis Highlights

- Worldwide orphan drug sales are forecast to grow at a CAGR of 12.3% from 2019 to 2024, which is approximately double the rate forecast for the non-orphan drug market.

- By 2024, orphan drugs are expected to reach $242bn and capture one-fifth of worldwide prescription sales.

- The mean orphan drug cost per patient of the top 100 US orphan drugs was almost 4.5 times greater than the non-orphan drug cost in 2018, with the median price differential decreasing between orphan and non-orphan drugs by almost 50% in the last four years.

- Naglazyme (galsulfase) and Soliris (eculizumab) achieved the highest revenue per patient per year, in 2018.

- Blood, central nervous system and respiratory are the leading orphan drug therapeutic areas in both 2018 and 2024, accounting for more than 50% of the non-oncology orphan drug market.

- Celgene will continue to be the leading company by worldwide orphan drug sales in 2024, with an estimated 73% of the company's total prescription sales coming from orphan drugs.

- In 2024, the three leading companies by sales in the oncology orphan drug market — Celgene, Abbvie and Johnson & Johnson — will account for approximately 30% of worldwide sales in this segment.

- By 2024, Imbruvica (ibrutinib) is forecast to become the top selling orphan drug worldwide.

- Pipeline orphan drugs account for over a third of total R&D pipeline sales through to 2024, with the annual growth rate from sales forecast to be 163% compared to 146% for non-orphan R&D products.

- Vertex's triple combination for cystic fibrosis (using VX669 or VX445) is the most valuable R&D orphan product with an estimated NPV of $24bn.

- Drugs being developed for oncology indications dominate the orphan drug pipeline landscape, as do cell- and gene-based therapeutics.

- Worldwide, non-Hodgkin lymphoma (NHL) was granted the most orphan drug designations in the last 35 years, followed by acute myeloid leukaemia (AML) and pancreatic cancer.

- Worldwide, the number of products granted an orphan drug designation in 2018 compared to 2017, decreased by 27% in the US, 16% in the EU and 27% in Japan.

Table of Contents

Contents

Worldwide Orphan Drug Sales (2010-2024)

Worldwide orphan drug sales forecast to total $242bn in 2024. The CAGR of orphan drugs between 2018 and 2024 is forecast to be +12.3%, approximately double that of the non-orphan drug market. Orphan drugs forecast to be 20.3% of worldwide prescription sales by 2024.

EvaluatePharma® finds that sales of drugs designated as orphans will grow by 12.3% per year, reaching $242bn in 2024 (see Figure 2 and Table 1). The growth of the orphan drug market is anticipated to be approximately double that of the overall prescription drug market, with orphan drugs set to account for a little over a fifth of all prescription drug sales by 2024. This strong growth showcases the industry's continued commitment to investing in these niche patient populations suffering from rare diseases. Additionally, despite increasing pricing pressures in key markets like the US, these products are still able to command lucrative pricing premiums over non-orphan drugs as illustrated in Figures 3a and 3b.

Figure 2: Worldwide Orphan Drug Sales & Share of Prescription Drug Market (2016-2024)
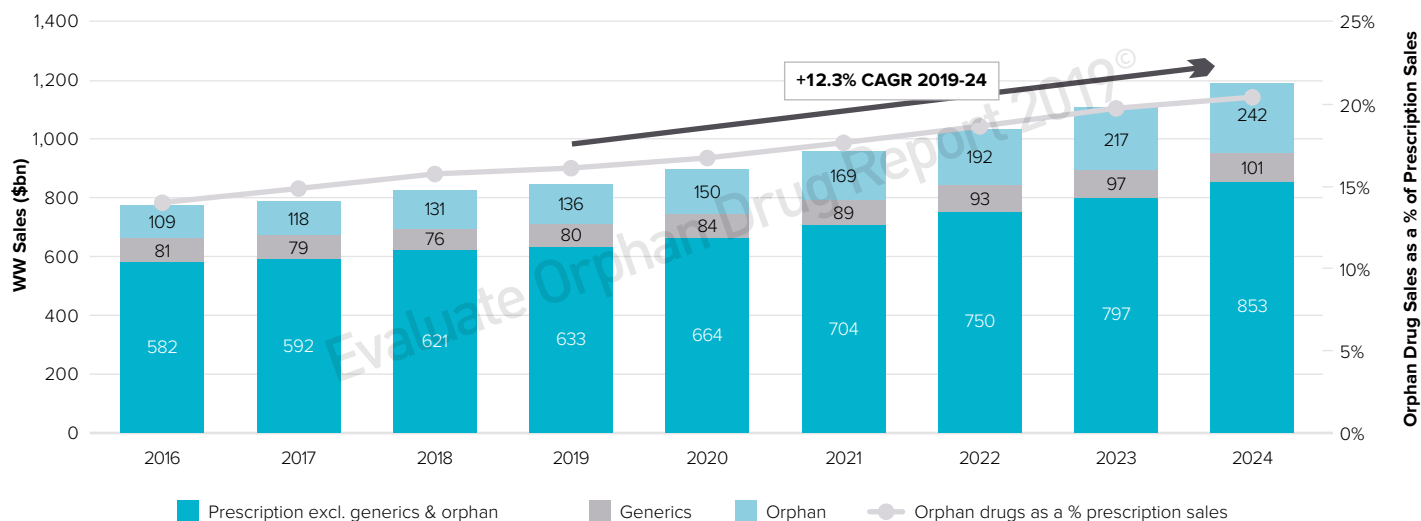
Table 1: Worldwide Orphan & Prescription Drug Sales (2010-2024)

Year	Worldwide Sales ($bn)														
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Orphan drug sales	72	80	84	91	96	100	109	118	131	136	150	169	192	217	242
Growth per year		+10.4%	+5.5%	+7.9%	+6.4%	+3.7%	+8.6%	+8.3%	+11.1%	+4.1%	+10.4%	+12.9%	+13.6%	+13.0%	+11.5%
Orphan drug sales as a % of presciption sales	10.5%	10.8%	11.6%	12.4%	12.8%	13.4%	14.1%	14.9%	15.8%	16.0%	16.7%	17.6%	18.6%	19.6%	20.3%
Non-Orphan Drug Prescription Sales	617	655	637	640	659	647	663	671	697	712	748	792	843	894	954
Growth per year		+6.2%	-2.6%	+0.4%	+3.0%	-1.7%	+2.4%	+1.2%	+3.8%	+2.2%	+5.0%	+6.0%	+6.3%	+6.1%	+6.8%
Prescription (excluding generics)	629	668	655	661	680	670	691	710	752	769	814	873	942	1,014	1,096
Growth per year		+6.3%	-2.0%	+0.9%	+2.9%	-1.4%	+3.1%	+2.7%	+5.9%	+2.3%	+5.9%	+7.3%	+7.9%	+7.6%	+8.0%

- WW Orphan Drug Market CAGR 19-24 +12.3%
- WW Non-Orphan Drug Market CAGR 19-24 +6.0%
- WW Prescription (Rx) Excluding Generics CAGR 19-24 +7.4%

Note: Industry sales based on Top 500 pharmaceutical and biotech companies.

Sales for 2018 based on available company reported sales data. Sales forecasts to 2024 based on a consensus of leading equity analysts' estimates for company product sales and segmental sales.

All sales analysis based on EvaluatePharma®'s definition of orphan products, See 'Overview' section.

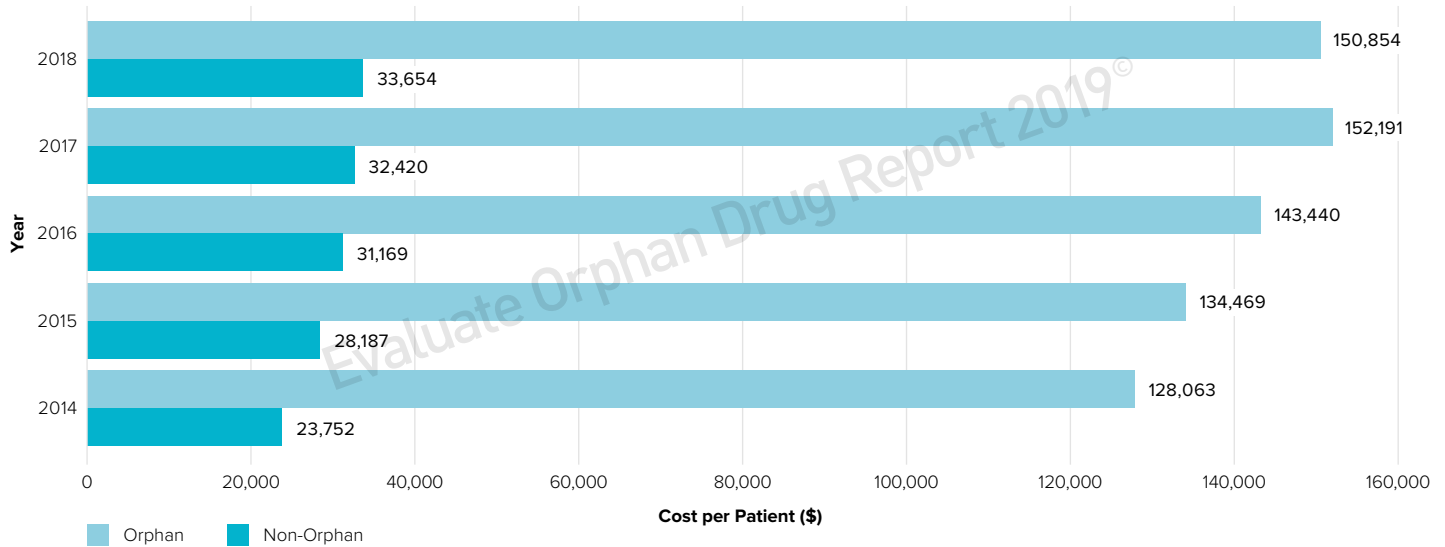# US Drug Cost per Patient per Year 2014-2018: Top 100 Products

Mean orphan drug cost per patient in the US is almost 4.5 times greater than non-orphan drug cost. The median price differential between orphan and non-orphan decreased by almost 50% during the course of the last four years, suggesting that the difference in cost between an orphan and non-orphan drug is diminishing.
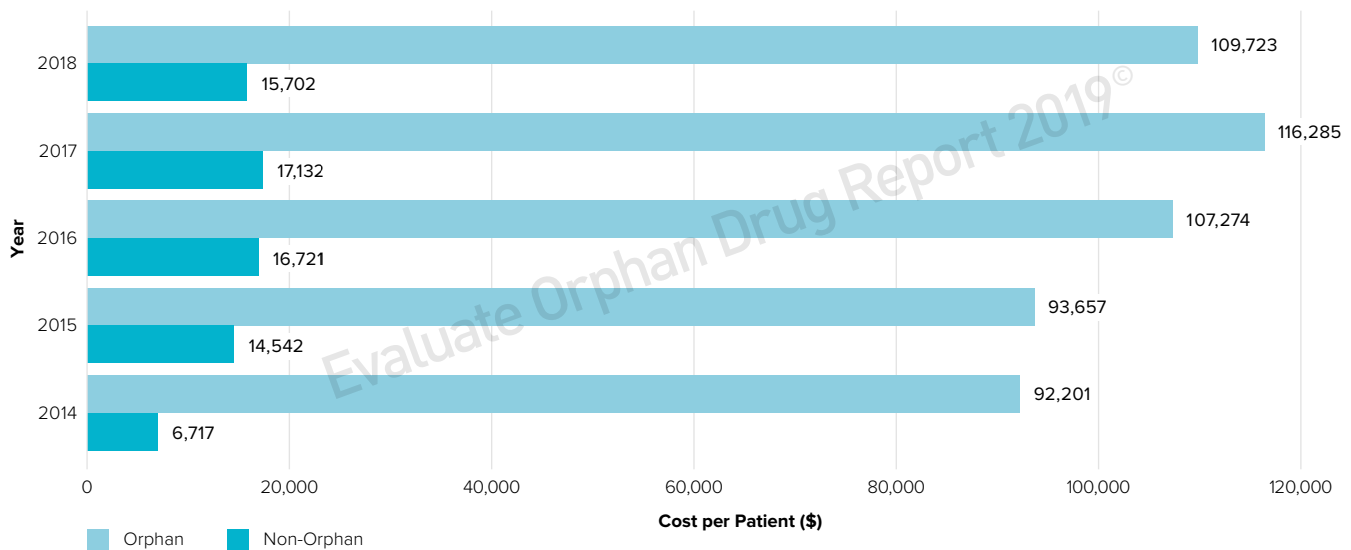
EvaluatePharma® estimates that the mean cost per patient per year of an orphan drug was $150,854 versus $33,654 for a non-orphan drug (analysis based on the top 100 drugs in the US in 2018), as shown in

Figure 3a. In 2018, there was a fall in both the mean and median price per patient for orphan drugs, while non-orphan drugs saw the mean price increase by almost 4% (see Figures 3a and 3b). While orphan drugs target smaller patient populations and are priced at a premium to non-orphan drugs, data in Table 2 clearly indicates that the US market is becoming more price sensitive, irrespective of whether the drug is orphan or non-orphan, with a significant slowdown in cost per patient growth rates since 2014.

Figure 3a: Mean US Cost per Patient per Year for Top 100 Products, 2014-2018

Year	Orphan	Non-Orphan
2018	150,854	33,654
2017	152,191	32,420
2016	143,440	31,169
2015	134,469	28,187
2014	128,063	23,752

Cost per Patient ($)

Orphan   Non-Orphan

Figure 3b: Median US Cost per Patient per Year for Top 100 Products, 2014-2018

Year	Orphan	Non-Orphan
2018	109,723	15,702
2017	116,285	17,132
2016	107,274	16,721
2015	93,657	14,542
2014	92,201	6,717

Cost per Patient ($)

Orphan   Non-Orphan

Table 2: US Drug Cost per Patient per Year 2014-18 for the Top 100 Products

Cost per Patient ($) per Year		2014	2015	2016	2017	2018	CAGR
Orphan	Mean price	128,063	134,469	143,440	152,191	150,854	4.2%
	Growth per year		5.0%	6.7%	6.1%	-0.9%	
	Median price	92,201	93,657	107,274	116,285	109,723	
Non-Orphan	Mean price	23,752	28,187	31,169	32,420	33,654	9.1%
	Growth per year		18.7%	10.6%	4.0%	3.8%	
	Median price	6,717	14,542	16,721	17,132	15,702	
Median price differential (orphan/non-orphan)		13.7	6.4	6.4	6.8	7.0	
				Median price increase 2014/18:			
				Orphan:	1.19		
				Non-Orphan:	2.34		

Note: All sales analysis based on EvaluatePharma®'s definition of orphan products, See 'Overview' section.

Cost per patient is an estimate for the retail cost of a drug to a patient, for a given year, based on a 100% compliance to the treatment guidelines outlined in the FDA label. Does not include off-invoice discounts. The Top 100 orphan and non orphan drugs were ranked by US sales for 2017.

Prices for products in the US are sourced from Medicare Part B, NADAC, FSS and Medicaid. Availability of a price point determines choice of source. The source is kept consistent across years to reflect a clear trend in pricing.
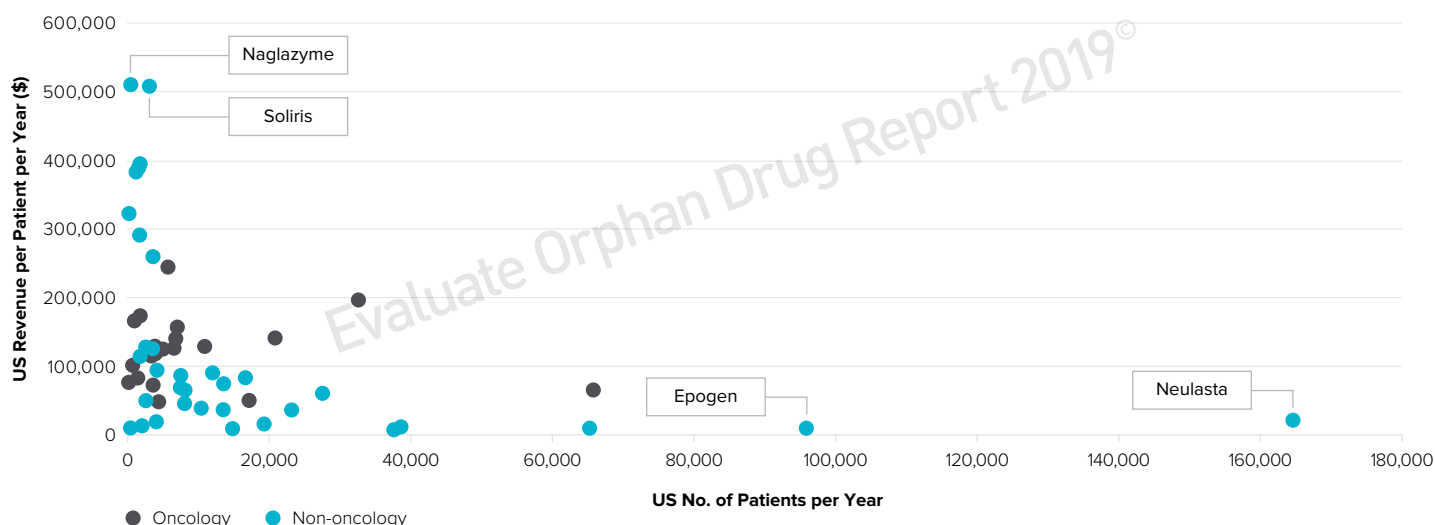
US Revenue per Patient in 2018

Soliris and Naglazyme have the highest revenue per patient, per year.

EvaluatePharma® finds that, as highlighted in Figure 4, the revenue per patient increases as the patient population size decreases. In 2018 there were 10 drugs which generated revenues per patient in excess of $200,000, four of which were for blood disorders and two of which were for respiratory disorders. As shown in Table 3, Soliris (eculizumab) and Naglazyme (galsulfase) were the two highest revenue-generating orphan drugs in 2018, with both earning sales

of over $500,000 per patient per year, despite treating the lowest number of patients per year. Naglazyme, marketed by BioMarin Pharmaceuticals, is indicated for Maroteaux-Lamy disease and was used to treat fewer than 200 patients in 2018. While Soliris, marketed by Alexion Pharmaceuticals and indicated for Paroxysmal nocturnal haemoglobinuria (PNH), was used to treat just under 3,000 patients. Conversely, Neulasta (pegfilgrastim), marketed by Amgen for the treatment of Neutropaenia, was used to treat over 160,000 patients in 2018 but only generated revenue of around $24,000 per patient.

Figure 4: 2018 US Revenue per Patient vs. Number of Patients Treated

Table 3: Examples of US Orphan Products and Their Respective Lead Indication by Revenues per Patient, in 2018

US Revenues per patient ($)	Product	Lead indication
0 - 50,000	Letairis	Pulmonary hypertension
	Ampyra	Multiple sclerosis
50,000 - 100,000	Rituxan	Non-Hodgkin lymphoma (NHL)
	Copaxone	Multiple sclerosis
100,000 - 200,000	Revlimid	Multiple myeloma
	Imbruvica	Leukaemia, chronic lymphocytic (CLL)
200,000 - 400,000	Pomalyst	Multiple myeloma
	Orkambi	Cystic fibrosis (CF)
400,000 +	Soliris	Paroxysmal nocturnal haemoglobinuria (PNH)
	Naglazyme	Maroteaux-Lamy disease (Mucopolysaccharidosis VI or MPS VI)

Note: Sales represent company reported sales where available, otherwise based on an average of equity analyst estimates.

US sales represent sales for all indications. All sales analysis based on EvaluatePharma®'s definition of orphan products, See 'Overview' section.

*Revenues per patient: An estimate of the dollar ($) revenues per year received, by a company, per patient for a drug in the US market. This takes into account the cost per patient (average mg per year multiplied by the cost per mg), off-invoice discount and patient compliance.

Prices for products in the US are sourced from Medicare Part B, NADAC, FSS and Medicaid. Availability of a price point determines choice of source. The source is kept consistent across years to reflect a clear trend in pricing.

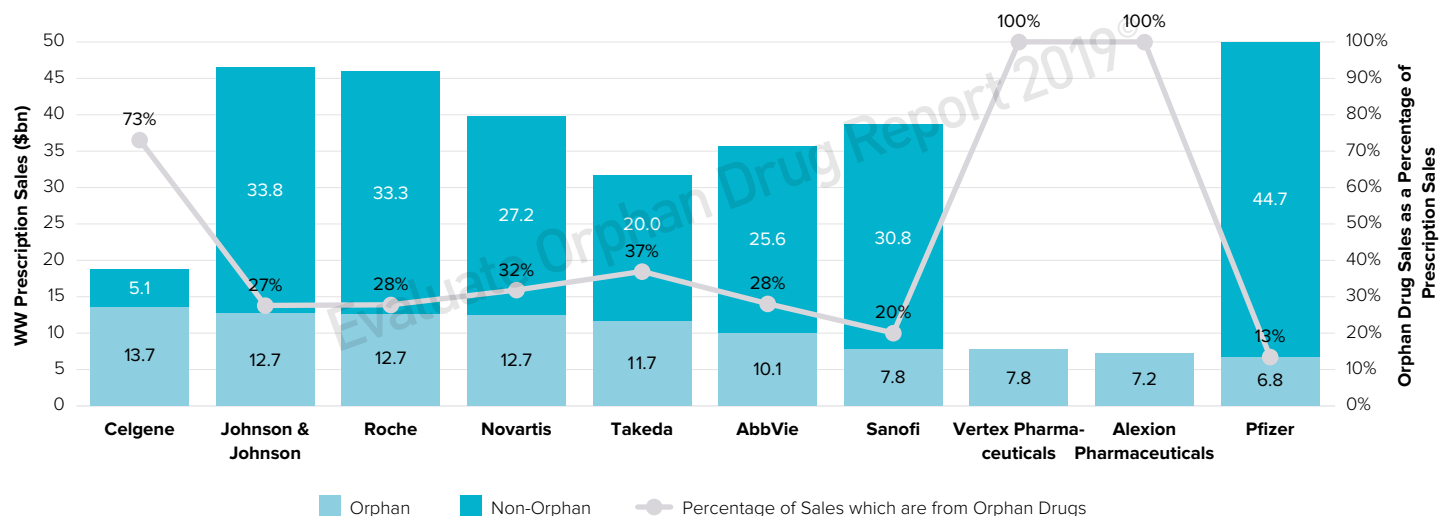# Worldwide Orphan Drug Sales in 2024: Top 20 Companies

Celgene is expected to be the leading company in the orphan drug market in 2024 with worldwide sales of $13.7bn. Revenue from orphan drugs for the Top 5 companies is forecast to exceed $60bn in 2024 and to account for 26% of the total orphan drug market.

EvaluatePharma® finds that while Celgene is expected to be the leading company in 2024, with an estimated 73% of its total prescription sales coming from orphan drug sales, the company's market share is expected to decrease by almost 40% by 2024. Additionally, while key players within the top 5 in 2018 continue to dominate the market in 2024 with their combined revenue expected to exceed $60bn, their market share decreases by about 25%.

Key movers (see Table 4) include AstraZeneca which is forecast to more than double their market share through 2024 owing to an increase in penetration and use of their PARP inhibitor Lynparza (olaparib) in ovarian cancer. Eisai is expected to almost double their market share owing to Lenvima (lenvatinib mesylate) which launched in March 2018 for the treatment of liver cancer. It is expected to generate around 63% of its total worldwide sales in 2024 for use in this indication (data not shown). Also, as highlighted in Table 4, the orphan drug market is becoming increasingly fragmented with more companies choosing to focus development efforts on fewer indications and drugs. Examples of this include Vertex Pharmaceuticals, who focus solely on cystic fibrosis, and Alexion Pharmaceuticals, who focus mainly on blood disorders (see Figure 6). Both companies are expected to generate all their 2024 prescription sales from the orphan drug market.

Figure 5: Worldwide Orphan Drug Prescription Sales & Share in 2024 for the Top 10 Companies

Table 4: Worldwide Orphan Drug Sales (2018-2024), Lead Product & Total Market Share for the Top 20 Companies

Rank	Company	2024 Leading Orphan Product	WW Orphan Drug Sales ($bn)			WW Orphan Drug Market Share	
			2018	2024	% CAGR 18-24	2018	2024
1.	Celgene	Revlimid	12.6	13.7	+1.4%	9.6%	5.6%
2.	Johnson & Johnson	Darzalex	8.4	12.7	+7.2%	6.4%	5.2%
3.	Roche	Hemlibra	10.3	12.7	+3.6%	7.9%	5.2%
4.	Novartis	Tafinlar	10.2	12.7	+3.7%	7.8%	5.2%
5.	Takeda	Ninlaro	3.8	11.7	+20.4%	2.9%	4.8%
6.	AbbVie	Imbruvica	3.7	10.1	+17.9%	2.9%	4.2%
7.	Sanofi	Myozyme	5.3	7.8	+6.9%	4.0%	3.2%
8.	Vertex Pharmaceuticals	VX-659/VX-445 + Tezacaftor + Ivacaftor	3.0	7.8	+17.0%	2.3%	3.2%
9.	Alexion Pharmaceuticals	Soliris	4.1	7.2	+9.6%	3.2%	3.0%
10.	Pfizer	Vyndaqel	4.5	6.8	+7.2%	3.4%	2.8%

Worldwide Orphan Drug Sales in 2024: Top 20 Companies

Rank	Company	2024 Leading Orphan Product	WW Orphan Drug Sales ($bn)			WW Orphan Drug Market Share	
			2018	2024	% CAGR 18-24	2018	2024
11.	Amgen	Kyprolis	7.6	6.1	-3.7%	5.8%	2.5%
12.	Jiangsu Hengrui Medicine	Aitan	0.0	5.3	-	0.0%	2.2%
13.	AstraZeneca	Lynparza	0.8	4.1	+32.3%	0.6%	1.7%
14.	BioMarin Pharmaceutical	Valoctocogene Roxaparvovec	1.3	3.8	+19.9%	1.0%	1.6%
15.	Biogen	Spinraza	3.7	3.0	-3.6%	2.9%	1.2%
16.	Incyte	Jakafi	1.5	3.0	+12.4%	1.1%	1.2%
17.	Bristol-Myers Squibb	Yervoy	3.8	2.9	-4.3%	2.9%	1.2%
18.	Eisai	Lenvima	0.9	2.8	+20.9%	0.7%	1.2%
19.	CSL	Kcentra	1.9	2.7	+6.4%	1.4%	1.1%
20.	Syros Pharmaceuticals	Amnolake	3.1	2.7	-2.2%	2.4%	1.1%
	Total Top 20		90.4	139.5	+7.5%	69.2%	57.5%
	Other		40.2	103.0	+17.0%	30.8%	42.5%
	Total		130.6	242.5	+10.9%	100.0%	100.0%

Note: VX-669/VX-445 + Tezacaftor + Ivacaftor; Includes sales forecasts for Vertex triples, VX-445 + Tezacaftor + Ivacaftor or VX-669 + Tezacaftor + Ivacaftor.

All sales analysis based on EvaluatePharma®'s definition of orphan products, See 'Overview' section.

Sales represent company reported sales where available, otherwise based on an average of equity analyst estimates.

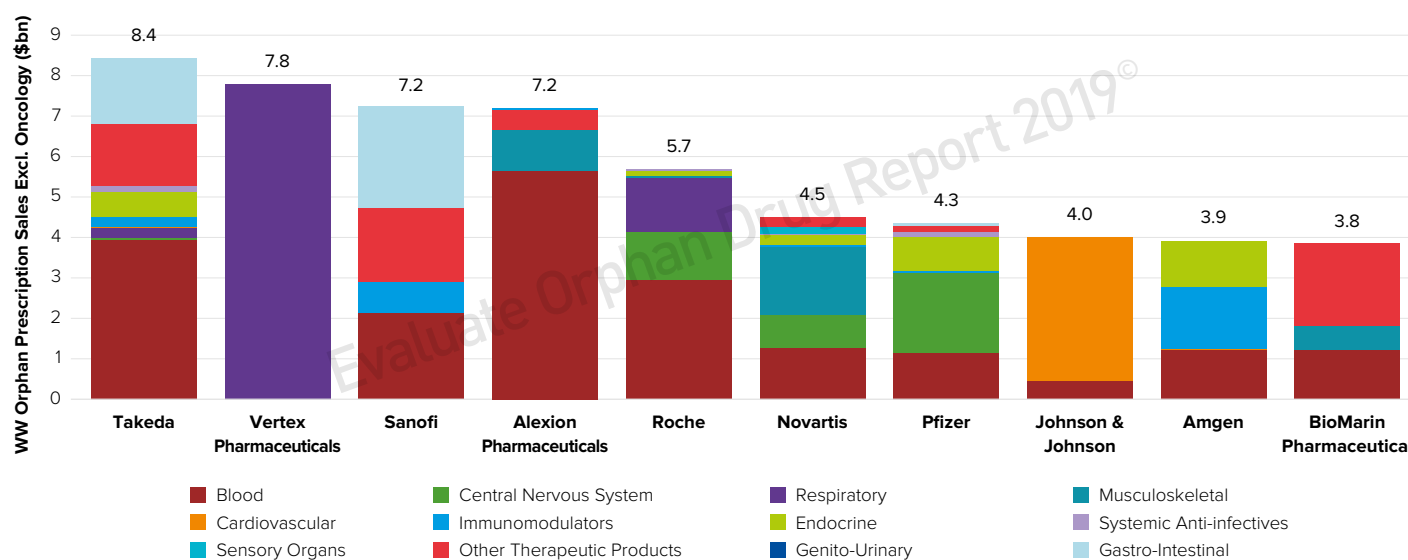# Worldwide Non-Oncology Orphan Drug Sales in 2024: Top 20 Companies

Takeda and Vertex Pharmaceuticals lead EvaluatePharma's non-oncology company ranking in 2024. Orphan drug sales from drugs targeting blood disorders continue to surpass those from other therapeutic categories.

EvaluatePharma® conducted a secondary analysis of the companies active in the non-oncology orphan drug therapy area. Takeda claim top place (see Figure 6) following the acquisition of Shire Pharmaceuticals, with orphan drug sales forecast to reach $8.4bn in 2024 (CAGR +29.8%). However, the difference between Takeda's total 2024 orphan drug forecast and that of fourth placed Alexion Pharmaceuticals is only $1.2bn. This is despite Takeda having an estimated 30 drugs in development, covering multiple therapy areas, while Alexion only have 5, mainly targeting blood and musculoskeletal disorders.

Key movers (Table 5), include argenx, GW Pharmaceuticals and bluebird bio who climb to 15th, 16th and 18th place, respectively. Lentiglobulin, being developed by bluebird bio, is expected to launch in 2019 for the treatment of sickle cell disease and in 2021 for thalassaemia. Argenx is a new entrant to the orphan drug space with Efgartigimod, currently the 4th highest ranking orphan R&D product with an NPV of $7.1bn (see Table 10), it is expected to launch in 2020 for the treatment of myasthenia gravis. A change in US federal law meant cannabis is no longer classed as a controlled substance, but products containing cannabis or cannabis derived products will continue to be regulated by the FDA. This led brokers to upgrade forecasts for GW Pharmaceutical's Epidiolex (cannabidiol) indicated for Lennox-Gastaut syndrome and Dravet syndrome; helping to contribute to a huge rise in their 2024 orphan drug forecast.

Figure 6: Worldwide Non-Oncology Orphan Drug Sales in 2024 by Therapy Category for the Top 10 Companies

Table 5: Worldwide Non-Oncology Orphan Drug Sales, Lead Therapy Category & Total Market Share for the Top 20 Companies (2018-2024)

Rank	Company	WW Orphan Sales ($bn)			WW Market Share			Lead Therapy Category	Number of Products Contributing to Total Orphan Drug Sales	
		2018	2024	% CAGR 18-24	2018	2024	Rank Chg. (+/-)		2018	2024
1.	Takeda	1.8	8.4	29.8%	2.4%	6.4%	+15	Blood	25	30
2.	Vertex Pharmaceuticals	3.0	7.8	17.0%	4.1%	5.9%	+5	Respiratory	3	4
3.	Sanofi	4.9	7.2	6.7%	6.6%	5.5%	-	Gastro-Intestinal	11	19
4.	Alexion Pharmaceuticals	4.1	7.2	9.6%	5.5%	5.4%	-	Blood	3	5
5.	Roche	2.4	5.7	15.8%	3.2%	4.3%	+6	Blood	5	9
6.	Novartis	2.6	4.5	9.5%	3.5%	3.4%	+4	Musculoskeletal	5	12

Worldwide Non-Oncology Orphan Drug Sales in 2024: Top 20 Companies

Rank	Company	WW Orphan Sales ($bn)			WW Market Share			Lead Therapy Category	Number of Products Contributing to Total Orphan Drug Sales	
		2018	2024	% CAGR 18-24	2018	2024	Rank Chg. (+/-)		2018	2024
7.	Pfizer	2.3	4.3	11.4%	3.0%	3.3%	+6	Central Nervous System	11	14
8.	Johnson & Johnson	3.5	4.0	2.3%	4.7%	3.0%	-2	Cardiovascular	5	5
9.	Amgen	6.6	3.9	-8.4%	8.8%	2.9%	-7	Immunomodulators	5	5
10.	BioMarin Pharmaceutical	1.3	3.8	19.9%	1.7%	2.9%	+11	Other Therapeutic Products	5	8
11.	Biogen	3.7	3.0	-3.6%	5.0%	2.3%	-6	Musculoskeletal	3	6
12.	CSL	1.9	2.7	6.4%	2.5%	2.1%	+3	Blood	5	5
13.	Novo Nordisk	2.6	2.3	-1.9%	3.5%	1.8%	-4	Blood	5	7
14.	Merck KGaA	2.3	2.1	-1.3%	3.1%	1.6%	-2	Central Nervous System	6	6
15.	argenx	0.0	1.9	-	0.0%	1.5%	-	Immunomodulators	0	1
16.	GW Pharmaceuticals	0.0	1.7	-	0.0%	1.3%	+90	Central Nervous System	1	1
17.	Jazz Pharmaceuticals	1.6	1.7	1.6%	2.1%	1.3%	-	Central Nervous System	3	3
18.	bluebird bio	0.0	1.7	-	0.0%	1.3%	-	Blood	0	2
19.	Kyowa Hakko Kirin	0.3	1.6	-	0.4%	1.2%	+14	Other Therapeutic Products	5	6
20.	Teva Pharmaceutical Industries	2.6	1.6	-8.0%	3.6%	1.2%	-12	Central Nervous System	4	4
	Total Top 20	48	77	8.5%	63.8%	58.4%				
	Other	27.0	55.1	12.6%	36.2%	41.6%				
	Total	**74.5**	**132.5**	**10.1%**	**100.0%**	**100.0%**				

Note: All sales analysis based on EvaluatePharma®'s definition of orphan products, See 'Overview' section. Analysis excluded products categorized in the oncology therapeutic category to produce a non-oncology company list.

Sales represent company reported sales where available, otherwise based on an average of equity analyst estimates.

Share of Worldwide Orphan Drug Sales by Therapy Category (Excluding Oncology) and Lead Companies

Blood, Central Nervous System and Respiratory are the leading therapeutic categories in both 2018 and 2024, accounting for more than 50% of orphan drug sales (when excluding oncology).

EvaluatePharma® finds that blood therapies command the largest market share in both 2018 and 2024, while musculoskeletal and sensory organ therapies see the biggest growth in share of sales between 2018 and 2024 (see Figure 7). Biogen continue to be the lead company within the musculoskeletal segment, however the company's market share is considerably eroded as newer players Novartis, Alexion Pharmaceuticals and Sarepta Therapeutics all increase their market share. The forecasts for other therapeutic

categories generally remains the same (see Table 6).

Vertex continues to be the leading company for respiratory with an increase in market share of 46% mainly arising from expected sales of its triple combinations for cystic fibrosis while Pfizer replace Teva as the market leader in CNS due to generic erosion of Copaxone (glatiramer acetate; patent expiry) sales.

Both in 2018 and 2024, the dermatology therapy category is expected to capture the smallest orphan drug market share. This is in line with dermatology only having few indications classified as rare diseases and also indicates low R&D activity in this category.

Figure 7: Share of Worldwide Non-Oncology Orphan Drug Sales by Therapeutic Category (2018 & 2024)
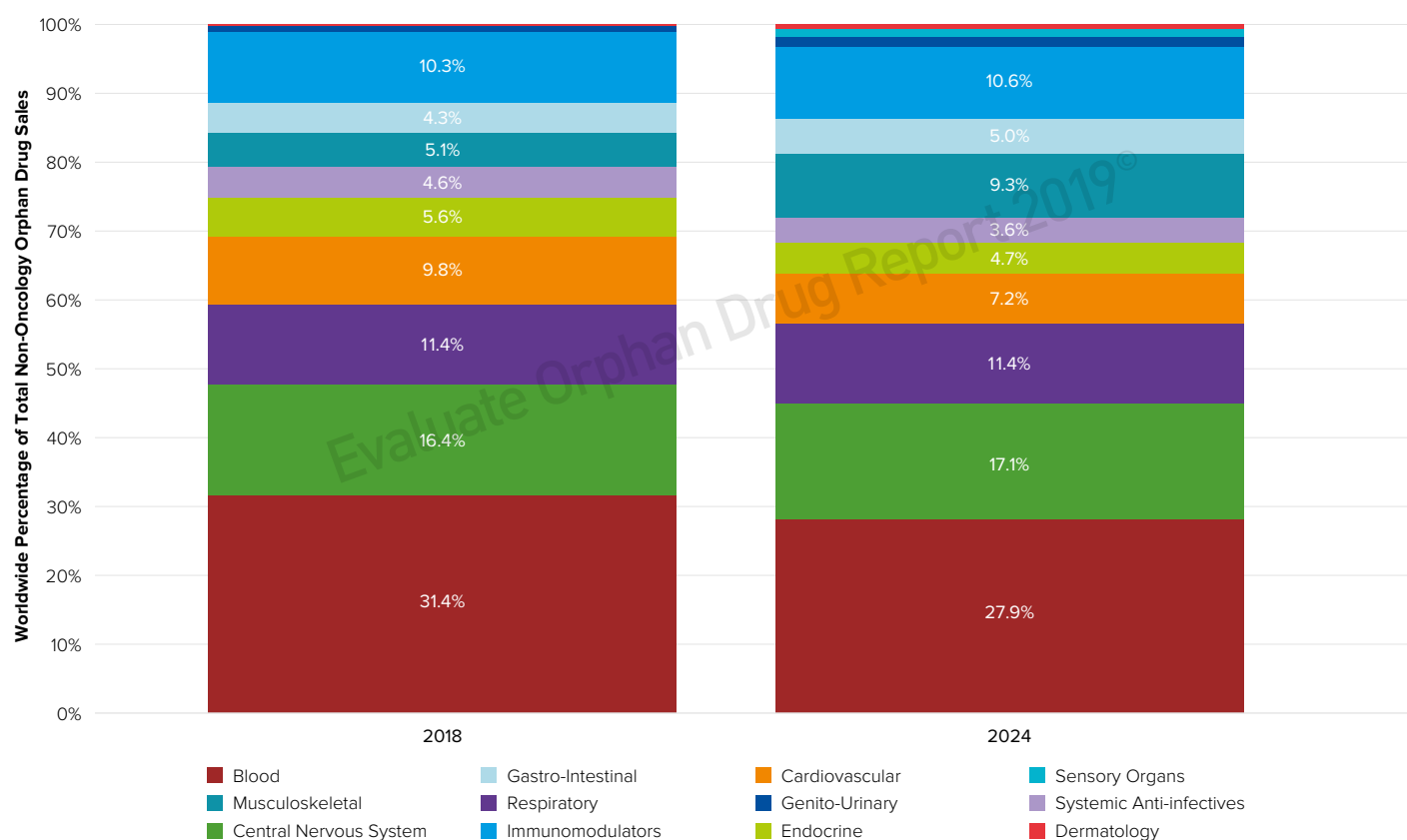
Share of Worldwide Orphan Drug Sales by Therapy Category (Excluding Oncology) and Lead Companies

Table 6: Worldwide Non-Oncology Orphan Drug Sales and Lead Company by Therapy Category (2018-2024)

Therapeutic category	WW Annual Sales ($bn)		2018		2024	
	2018	2024	Lead Company	Share of Market	Lead Company	Share of Market
Blood	21.3	33.1	**Shire**	21.6%	**Alexion Pharmaceuticals**	17.0%
Central Nervous System (CNS)	11.1	20.3	**Teva Pharmaceutical Industries**	23.8%	**Pfizer**	9.8%
Respiratory	7.8	13.6	**Vertex Pharmaceuticals**	39.2%	**Vertex Pharmaceuticals**	57.4%
Musculoskeletal	3.5	11.0	**Biogen**	49.9%	**Biogen**	15.0%
Cardiovascular	6.7	8.5	**Johnson & Johnson**	37.8%	**Johnson & Johnson**	41.9%
Immunomodulators	7.0	12.5	**Amgen**	64.1%	**argenx**	15.4%
Gastro-Intestinal	2.9	6.0	**Sanofi**	65.2%	**Sanofi**	41.8%
Endocrine	3.8	5.6	**Novo Nordisk**	28.5%	**Amgen**	20.2%
Systemic Anti-infectives	3.1	4.2	**Merck & Co**	29.3%	**Insmed**	15.8%
Sensory Organs	0.1	1.5	**Bausch Health Companies**	44.1%	**Spark Therapeutics**	32.3%
Genito-Urinary	0.6	1.5	**AMAG Pharmaceuticals**	51.2%	**Retrophin**	29.0%
Dermatology	0.0	0.7	**MediWound**	100.0%	**Krystal Biotech**	34.6%

Note: All sales analysis based on EvaluatePharma®'s definition of orphan products, See 'Overview' section. Analysis excluded products categorized in the oncology therapeutic category to produce a non-oncology company list.

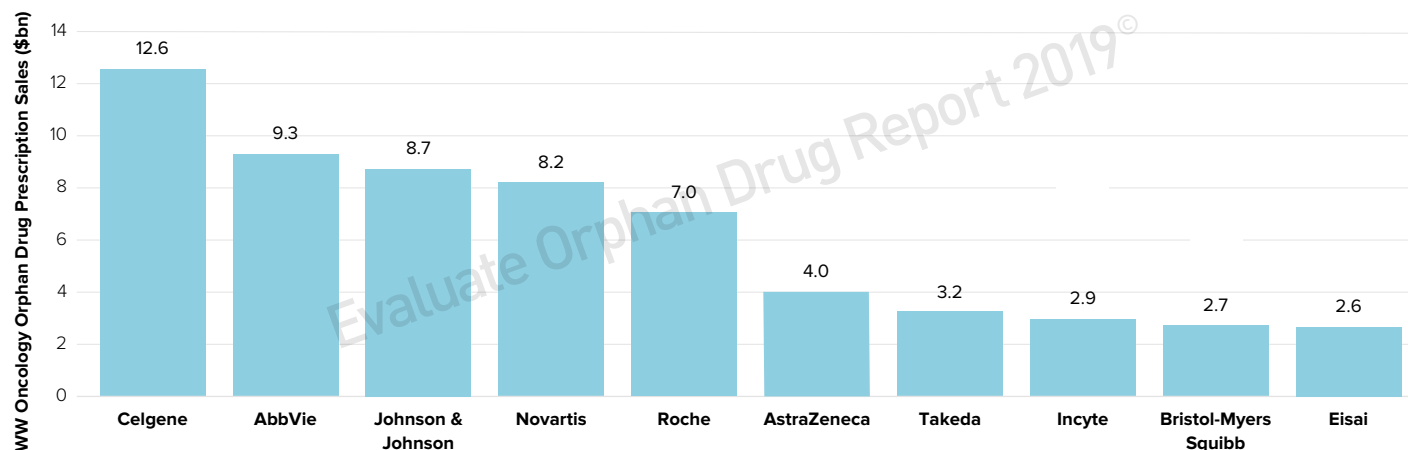# Worldwide Oncology Orphan Drug Sales in 2024: Top 20 Companies

Celgene, the overall orphan drug market leader, is also expected to be the top oncology orphan drug company in 2024 with sales of $12.6bn. This is despite the company's sales remaining flat from 2018 to 2024 and its worldwide market share decreasing by 50%.

EvaluatePharma® finds that generic erosion of sales of Celgene's lead therapy, Revlimid (lenalidomide) will lead to a decrease in the company's market share in 2024 despite the anticipated launch of other oncology-orphan products, such as the CAR-T therapies Liso-Cel and bb2121 (see Figure 8 and Table 10). All top 4 companies will garner the majority of their 2024 orphan drug sales from products

used to treat haematological malignancies, underscoring that the oncology-orphan drug market is more lucrative than the non-oncology market. According to sales forecasts, the companies that will see the greatest change in ranking are GlaxoSmithKline, Rexahn Pharmaceuticals and Blueprint Medicines. All three companies had no oncology orphan drugs in 2018 but are expected to penetrate this market by 2024, owing to the launch of new treatments. Overall, 2024 sales generated in this segment by the leading three companies – Celgene, AbbVie, Johnson & Johnson – are expected to account for only about 30% of the overall worldwide sales in this market suggesting that this market is becoming more fragmented.

Figure 8: Worldwide Oncology Orphan Drug Sales in 2024 for the Top 10 Companies

Table 7: Worldwide Oncology Orphan Drug Sales & Total Market Share for the Top 20 Companies (2018-2024)

Rank	Company	WW Orphan Sales ($bn)			WW Market Share			Number of Products Contributing to Total Orphan Drug Sales	
		2018	2024	% CAGR 18-24	2018	2024	Rank Chg. (+/-)	2018	2024
1.	Celgene	12.6	12.6	0.0%	22.4%	11.4%	-	6	12
2.	AbbVie	3.3	9.3	18.7%	5.9%	8.4%	+4	2	4
3.	Johnson & Johnson	4.9	8.7	10.1%	8.7%	7.9%	+1	6	5
4.	Novartis	7.6	8.2	1.2%	13.5%	7.4%	-1	12	13
5.	Roche	7.9	7.0	-1.9%	14.1%	6.4%	-3	5	9
6.	AstraZeneca	0.7	4.0	33.6%	1.3%	3.7%	+8	2	5
7.	Takeda	2.1	3.2	7.7%	3.7%	2.9%	+1	4	5
8.	Incyte	1.5	2.9	12.3%	2.6%	2.7%	+1	2	2
9.	Bristol-Myers Squibb	3.6	2.7	-4.4%	6.4%	2.5%	-4	3	3
10.	Eisai	0.7	2.6	25.6%	1.2%	2.4%	+5	4	6
11.	Pfizer	2.2	2.5	1.8%	4.0%	2.2%	-4	10	11
12.	Amgen	1.0	2.2	13.5%	1.8%	2.0%	-	2	3
13.	Gilead Sciences	0.4	2.1	32.3%	0.7%	1.9%	+5	2	4

Top 14-20 continued over...

Worldwide Oncology Orphan Drug Sales in 2024:
Top 20 Companies

Rank	Company	WW Orphan Sales ($bn)			WW Market Share			Number of Products Contributing to Total Orphan Drug Sales	
		2018	2024	% CAGR 18-24	2018	2024	Rank Chg. (+/-)	2018	2024
14.	Seattle Genetics	0.5	2.1	28.0%	0.9%	1.9%	+3	1	2
15.	Ipsen	1.1	1.7	7.2%	2.0%	1.6%	-4	3	3
16.	BeiGene	0.1	1.5	49.4%	0.2%	1.3%	+12	1	3
17.	Rexahn Pharmaceuticals	0.0	1.4	-	0.0%	1.3%	+42	0	1
18.	GlaxoSmithKline	0.0	1.3	-	0.0%	1.2%	+41	0	3
19.	Blueprint Medicines	0.0	1.3	-	0.0%	1.2%	+40	0	2
20.	Eli Lilly	1.2	1.3	1.6%	2.1%	1.2%	-10	4	4
	Total Top 20	51.3	78.7	7.4%	91.5%	71.6%	-19.9%		
	Other	4.8	31.3	36.8%	8.5%	28.4%			
	Total	56.1	110.0	11.9%	100.0%	100.0%			

Note: All sales analysis based on EvaluatePharma®'s definition of orphan products, See 'Overview' section. Analysis excluded products categorized in the oncology therapeutic category to produce a non-oncology company list.

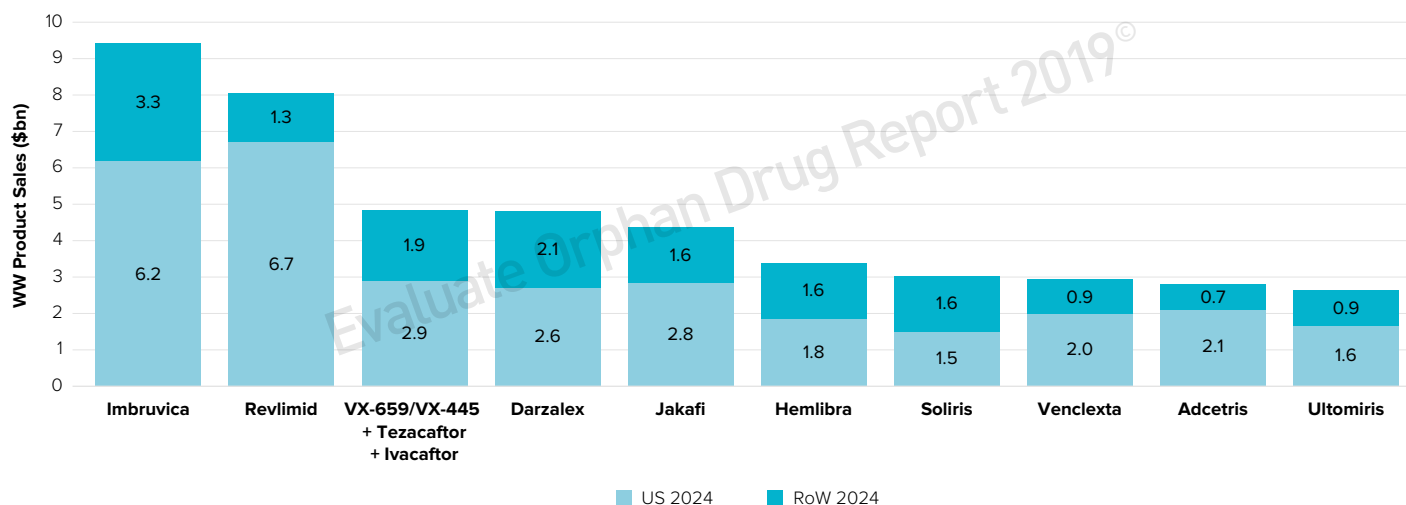# Worldwide Orphan Drug Sales in 2024: Top 20 Products

Revenue from the top 10 orphan drugs accounts for almost 20% of the total orphan market in both 2018 and 2024.

EvaluatePharma® finds that revenue from the top two drugs, Imbruvica (ibrutinib) and Revlimid, accounted for approximately 60% of the total revenue attributable to the top 10 orphan drugs in 2018. This is expected to decrease to almost 38% by 2024. However, the 2024 difference in forecast sales between second place Revlimid and Vertex's triple combination, in third place, seems insurmountable at $3.3bn, compared to those ranking lower in the table. Overall, the top 5 drugs account for almost 13% of the total orphan drug market in 2024 – and with the exception of the Vertex triple combinations – have orphan drug designations within the three key markets: the US, Europe and Japan (regional product designation data not shown). While 95% of the top 20 drugs have an orphan drug designation in the US and either Europe or Japan, all bar Soliris and Tafinlar are expected to generate more than 50% of their 2024 sales revenue within the US. Oncology drugs continue to dominate the sector with more than 60% of the top 20 orphan products indicated within this therapeutic category.

Key movers (see Table 8), include Vyndaqel (tafamidis meglumine; +111.7% CAGR) and Hemlibra (emicizumab; +56.5% CAGR). Vyndaqel has been available within Europe since 2012 and is currently under FDA review for the treatment of transthyretin amyloid cardiomyopathy (ATTR-CM) while Hemlibra launched in 2017 as a prophylactic treatment for Haemophilia A. Sales of Rituxan (rituximab) are forecast to decrease at the highest CAGR (-15.3%) from $6.9bn in 2018 to $2.6bn in 2024 following sales erosion from biosimilars.

Figure 9: Top 10 Selling Orphan Drugs in 2024 by Worldwide Sales (All Indications)

Table 8: Worldwide Top 20 Selling Orphan Drugs in 2024

Rank	Product	Generic Name	Company	Phase (Current)	Mechanism of Action	WW Product Sales ($bn)		
						2018	2024	CAGR
1.	Imbruvica	ibrutinib	Abbvie/Johnson & Johnson	Marketed	Bruton's tyrosine kinase (BTK) inhibitor	4.45	**9.4**	13.3%
2.	Revlimid	lenalidomide	Celgene/BeiGene	Marketed	Interleukin-6 (IL-6) antagonist; Natural killer (NK) cell stimulant; Natural killer T-cell (NKT) stimulant; Tumour necrosis factor alpha (TNFa) inhibitor; Vascular endothelial growth factor (VEGF) inhibitor	9.82	**8.1**	-3.2%
3.	VX-669/ VX-445 + Tezacaftor + Ivacaftor	-	Vertex Pharmaceuticals	Phase III	Cystic fibrosis transmembrane regulator (CFTR) corrector; Cystic fibrosis transmembrane regulator (CFTR) potentiator	0.00	**4.8**	n/a
4.	Darzalex	daratumumab	Johnson & Johnson	Marketed	Lymphocyte differentiation antigen CD38 antibody	2.03	**4.8**	15.4%
5.	Jakafi	ruxolitinib phosphate	Incyte/Novartis	Marketed	Janus kinase 1 (JAK1) inhibitor; Janus kinase 2 (JAK2) inhibitor	2.36	**4.4**	10.7%

Worldwide Orphan Drug Sales in 2024: Top 20 Products

Rank	Product	Generic Name	Company	Phase (Current)	Mechanism of Action	WW Product Sales ($bn)		
						2018	2024	CAGR
6.	Hemlibra	emicizumab	Roche/Chugai Pharmaceutical	Marketed	Coagulation factor IXa antibody; Coagulation factor X antibody	0.23	3.4	56.5%
7.	Soliris	eculizumab	Alexion Pharmaceuticals	Marketed	Complement factor C5 antibody	3.56	3.1	-2.5%
8.	Venclexta	venetoclax	AbbVie	Marketed	B-cell lymphoma 2 (BCL-2) inhibitor	0.34	2.9	42.7%
9.	Adcetris	brentuximab vedotin	Takeda/Seattle Genetics	Marketed	Tumour necrosis factor receptor superfamily member 8 (TNFRSF8) antibody	0.87	2.8	21.3%
10.	Ultomiris	ravulizumab	Alexion Pharmaceuticals	Approved	Complement factor C5 antibody	0.00	2.6	n/a
11.	Rituxan	rituximab	Roche/Pharmstandard	Marketed	B-lymphocyte antigen CD20 antibody	6.93	2.6	-15.3%
12.	Lenvima	lenvatinib mesylate	Eisai/Merck & Co	Marketed	Vascular endothelial growth factor receptor (VEGFR) antagonist	0.54	2.5	29.0%
13.	Lynparza	olaparib	AstraZeneca	Marketed	Poly (ADP-ribose) polymerase 1 (PARP1) inhibitor; Poly (ADP-ribose) polymerase 3 (PARP3) inhibitor; Poly (ADP-ribose) polymerase (PARP) inhibitor	0.65	2.5	25.1%
14.	Pomalyst	pomalidomide	Celgene	Marketed	Tumour necrosis factor alpha (TNFa) inhibitor	2.04	2.0	0.0%
15.	Vyndaqel	tafamidis meglumine	Pfizer	Marketed	Transthyretin (TRR) dissociation inhibitor	0.02	2.0	111.7%
16.	Ninlaro	ixazomib citrate	Takeda	Marketed	Proteasome subunit beta type-5 inhibitor	0.59	2.0	22.1%
17.	Yescarta	axicabtagene ciloleucel	Gilead Sciences	Marketed	B-lymphocyte antigen CD19 CAR-T cell therapy	0.26	2.0	39.5%
18.	Yervoy	ipilimumab	Ono Pharmaceutical/Bristol-Myers Squibb	Marketed	Cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) antibody	1.33	1.9	6.3%
19.	Efgartigimod	efgartigimod	Bristol-Myers Squibb/Ono Pharmaceutical	Marketed	Neonatal Fc receptor (FcRn) antagonist	0.00	1.9	n/a
20.	Tafinlar	dabrafenib mesylate	Novartis	Marketed	Serine/threonine-protein kinase B-Raf inhibitor	1.16	1.9	8.6%
	Other					93	175	11.0%
	Total					131	242	10.9%

Note: VX-669/VX-445 + Tezacaftor + Ivacaftor; Includes sales forecasts for Vertex triples, VX-445 + Tezacaftor + Ivacaftor or VX-669 + Tezacaftor + Ivacaftor.

Sales represent company reported sales where available, otherwise based on an average of equity analyst estimates.

Worldwide sales represent sales for all indications.

All sales analysis based on EvaluatePharma®'s definition of orphan products, See 'Overview' section.

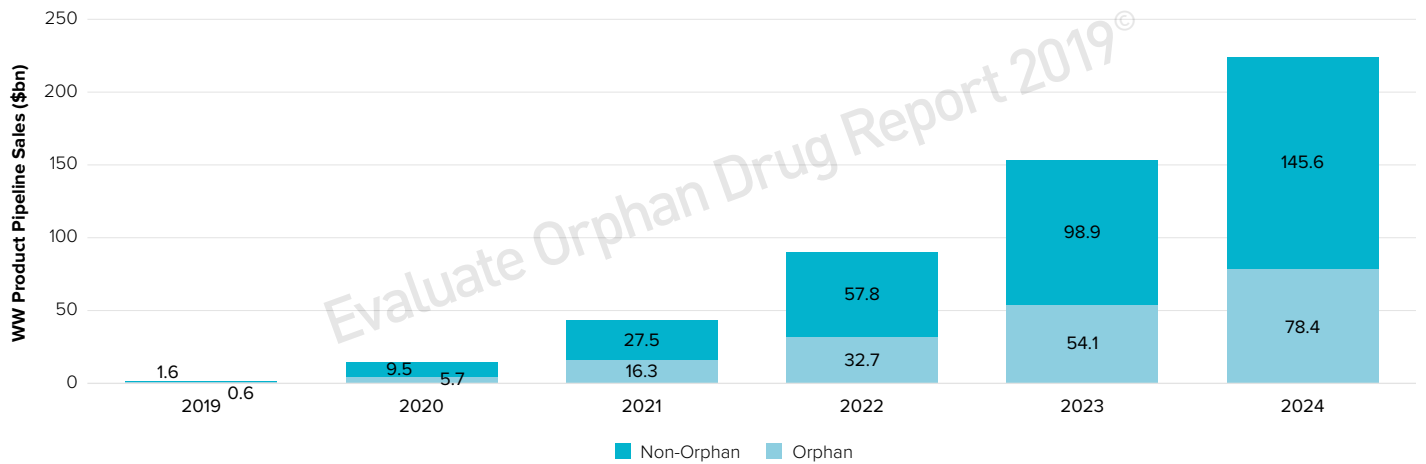# Worldwide Sales of Pipeline Orphan and Non-Orphan Products (2019-2024)

**Pipeline orphan drug sales to account for over a third of total R&D pipeline sales through to 2024.**

EvaluatePharma® finds that pipeline orphan drugs are expected to generate almost $190bn in sales between 2019 and 2024 and to account for an increasing proportion of worldwide sales (from 27% in 2019 to 35% in 2024; see Figure 10). The majority (approximately 70%) of these sales are forecast to come from the US market (see Figures 11a and 11b).

The value creation from orphan R&D drugs based on consensus forecasts is more than 15% higher for orphan R&D drugs (+163.4% CAGR) compared to non-orphan R&D drugs (+145.6% CAGR) (see Table 9). Oncology dominates the development landscape with more than half of the orphan pipeline targeting oncology indications (see Table 10). By 2024, orphan drugs currently in R&D are expected to garner sales of over $78bn while non-orphan drugs in R&D are expected to generate sales of about $146bn.
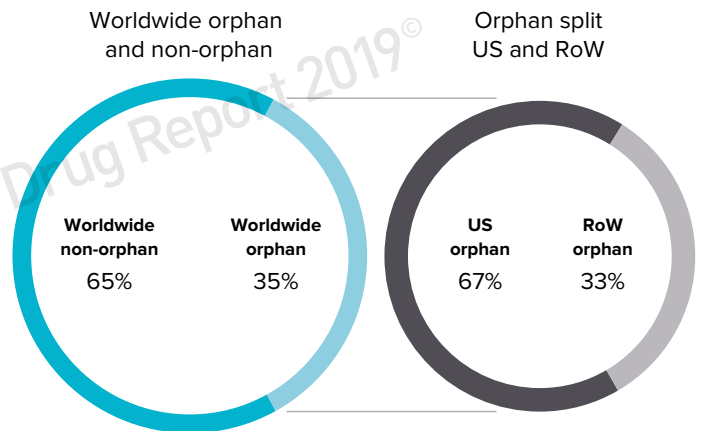
Figure 10: Worldwide Sales of Pipeline Orphan and Non-Orphan Products (2019-2024)

Figure 11a: Worldwide Pipeline in 2019: Orphan vs. Non-Orphan
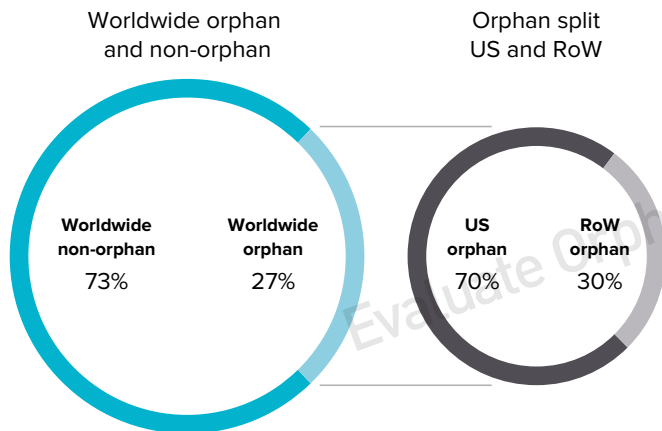
Figure 11b: Worldwide Pipeline in 2024: Orphan vs. Non-Orphan

Table 9: Worldwide Pipeline Sales of Orphan and Non-Orphan Products by Year (2019-2024)

R&D pipeline	WW sales ($bn)						CAGR
	2019	2020	2021	2022	2023	2024	
Orphan	0.6	5.7	16.3	32.7	54.1	78.4	163.4%
Non-orphan	1.6	9.5	27.5	57.8	98.9	145.6	145.6%
% Orphan sales	27%	38%	37%	36%	35%	35%	
Total	**2.2**	**15.2**	**43.8**	**90.5**	**153.1**	**224.0**	**151.0%**
Cumulative orphan	0.6	6.4	22.7	55.3	109.5	187.8	
Cumulative non-orphan	1.6	11.1	38.6	96.4	195.3	341.0	
Total						**528.8**	

Note: Sales based on EvaluatePharma®'s proprietary European Drug Forecasts module. Sales represent sales for all indications.

All sales analysis based on EvaluatePharma®'s definition of orphan products, See 'Overview' section.

Top 20 Orphan R&D Products in 2024, Based on NPV

Top 5 orphan drugs amass 25% of forecast orphan pipeline sales in 2024; 40% of the top 20 drugs could also be blockbusters.

EvaluatePharma® finds that the top 5 orphan drugs amass 25% of forecast orphan pipeline sales in 2024 and have a combined NPV of $53bn; 34% of the forecast NPV of all pipeline orphan drugs. Vertex Pharmaceuticals, who are expected to have 4 products contributing to 2024 orphan drug sales, solely focus on developing drugs within the respiratory therapeutic category (as shown in Table 5). Their lead R&D products – the VX-669/VX-445 + Tezacaftor + Ivacaftor triples – are in development for the treatment of cystic

fibrosis and are forecast to generate $4.8bn sales in 2024; 11% of the combined forecast for pipeline orphan R&D drugs (see Table 10). Similarly, argenx, who focus on haematological disorders and bluebird bio, who focus on immunomodulators take 4th and 5th place, respectively. Overall, drugs being developed for oncology indications dominate the orphan pipeline landscape as do those therapies utilising cell and gene technologies. Additionally, while almost half of the top 20 pipeline products have been developed in-house, the remainder are mostly being developed by larger companies and have been either in-licensed or acquired.

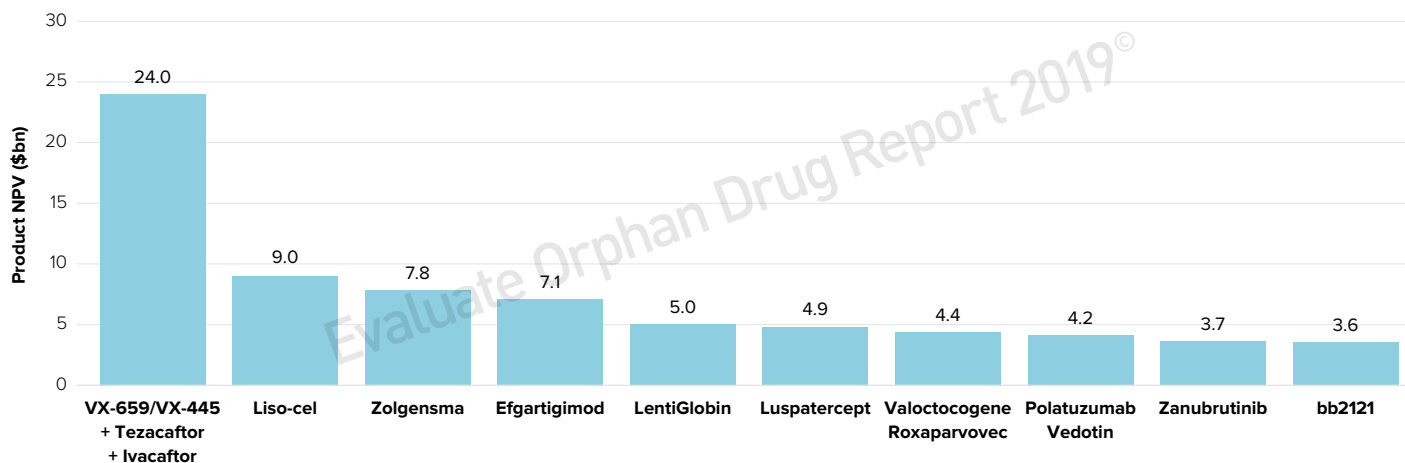## Figure 12: Top 10 R&D Orphan Drugs (Phase III-Filed), in 2024, Based on NPV

Table 10: Worldwide 2024 Sales and NPVs of the Top 20 Orphan R&D Drugs (Phase III-Filed), Based on NPV

Rank	Product	Company	Phase (Current)	Mechanism of Action	Sales ($bn) 2024	WW NPV ($bn)	Strategy
1.	VX-659/VX-445 triplet therapy	Vertex Pharmaceuticals	Phase III	Cystic fibrosis transmembrane regulator (CFTR) corrector; Cystic fibrosis transmembrane regulator (CFTR) potentiator	4.8	24.0	Organic
2.	Liso-cel	Celgene	Phase III	B-lymphocyte antigen CD19 CAR-T cell therapy	1.4	9.0	Company acquisition
3.	Zolgensma	Novartis	Filed	Survival of motor neuron 1 (SMN1) gene therapy	1.6	7.8	Company acquisition
4.	Efgartigimod	argenx	Phase III	Neonatal Fc receptor (FcRn) antagonist	1.9	7.1	Organic
5.	LentiGlobin	bluebird bio	Filed	Haemoglobin beta (HBB) gene therapy	1.5	5.0	Organic
6.	Luspatercept	Celgene	Phase III	Activin receptor 2b antagonist	1.1	4.9	In-licensed
7.	Valoctocogene Roxaparvovec	BioMarin Pharmaceutical	Phase III	Coagulation factor VIII gene therapy	1.2	4.4	In-licensed
8.	Polatuzumab Vedotin	Roche	Filed	IgM membrane glycoprotein antibody	0.9	4.2	Organic
9.	Zanubrutinib	BeiGene	Filed	Bruton's tyrosine kinase (BTK) inhibitor	1.1	3.7	Organic

Top 20 Orphan R&D Products in 2024, Based on NPV

Rank	Product	Company	Phase (Current)	Mechanism of Action	Sales ($bn) 2024	WW NPV ($bn)	Strategy
10.	**bb2121**	Celgene	Phase III	Anti-B-cell maturation antigen (BCMA) CAR-T cell therapy	0.2	**3.6**	In-licensed
11.	**Risdiplam**	Roche	Phase III	Survival motor neuron 2 (SMN2) protein regulator	0.8	**3.4**	In-licensed
12.	**Avapritinib**	Blueprint Medicines	Phase III	Proto-oncogene c-Kit (CD117) inhibitor; Platelet-derived growth factor receptor (PDGFR) D816V antagonist	0.9	**3.2**	Organic
13.	**Isatuximab**	Sanofi	Phase III	Lymphocyte differentiation antigen CD38 antibody	0.5	**2.4**	In-licensed
14.	**IMAB362**	Astellas Pharma	Phase III	Claudin 18.2 (CLDN18.2) protein inhibitor	0.4	**2.3**	Company acquisition
15.	**Ipatasertib**	Roche	Phase III	Serine/threonine-protein kinase AKT inhibitor	0.5	**2.3**	In-licensed
16.	**DCC-2618**	Deciphera Pharmaceuticals	Phase III	Proto-oncogene c-Kit (CD117) inhibitor; Platelet-derived growth factor receptor (PDGFR) antagonist	0.7	**2.0**	Organic
17.	**Vosoritide**	BioMarin Pharmaceutical	Phase III	Atrial natriuretic peptide receptor A (ANPRA) agonist; Fibroblast growth factor receptor 3 (FGFR3) antagonist	0.6	**2.0**	Organic
18.	**GLPG1690**	Galapagos	Phase III	Autotaxin inhibitor	0.6	**2.0**	Organic
19.	**AMT-061**	uniQure	Phase III	Coagulation factor IX gene therapy	0.7	**1.9**	Organic
20.	**bb2121**	bluebird bio	Phase III	Anti-B-cell maturation antigen (BCMA) CAR-T cell therapy	0.4	**1.9**	Organic
	Other				**22.8**	**59.2**	
	Total				**44.8**	**156.4**	
				vs. Non-Orphan:	**68.1**	**240.4**	

Note: VX-669/VX-445 + Tezacaftor + Ivacaftor; Includes sales forecasts for Vertex triples, VX-445 + Tezacaftor + Ivacaftor or VX-669 + Tezacaftor + Ivacaftor.

Sales represent company reported sales where available, otherwise based on an average of equity analyst estimates.

Factor VIII products for haemophilia A & B classified as orphan drugs.

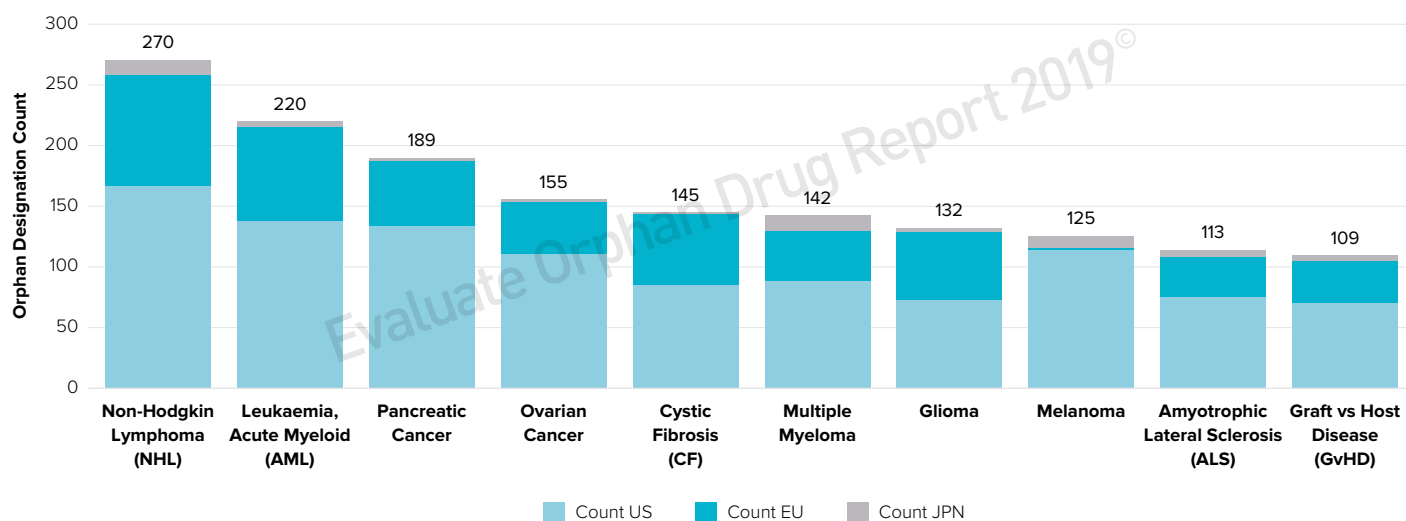# Top 10 Orphan-Designated Indications by Region (1983-2018)

Non-Hodgkin lymphoma (NHL) was granted more orphan drug designations in the last 35 years than any other indication.

EvaluatePharma® finds that during 1983-2018 (See Figure 13), approximately 70% of indications with the most orphan designations, were oncology indications. In first place was NHL with 270 designations. One of the reasons why this indication has the highest number of orphan designations is because NHL is not one disease but a group of haematological cancers which include all types of lymphoma except Hodgkin's lymphomas. In-line with this, haematological indications generated the highest revenue for orphan drugs in 2018, with the forecast for 2024 being on par (see

Figures 8 and 9). At a regional level, while NHL was the most designated indication in the US and Europe, the number of Japanese designations this indication was awarded is comparable to multiple myeloma (see Table 11). There is little change when looking at the most highly designated indications over the shorter timeframe of the last 15 years (data not shown) with 9 of the top 10 indications remaining the same. When considering designations made in 2018 alone, NHL, acute myeloid leukaemia (AML) and pancreatic cancer also claim the top three spots, highlighting that the large unmet need in these indications has not yet been fully addressed and the need for innovative therapies remains.

Figure 13: Top 10 Orphan-Designated Indications by Designation Counts per Region (1983-2018)

Table 11: Top 10 Orphan-Designated Indications (1983-2018) by Region Compared with 2018 Overall Rank

Rank	Indication	Orphan Designations 1983 - 2018			Orphan Designations 2018
		Count US	Count EU	Count JPN	Overall Rank
1.	Non-Hodgkin lymphoma (NHL)	167	91	12	1
2.	Leukaemia, acute myeloid (AML)	138	77	5	3
3.	Pancreatic cancer	134	53	2	2
4.	Ovarian cancer	110	44	1	27
5.	Cystic fibrosis (CF)	84	60	1	6
6.	Multiple myeloma	88	41	13	11
7.	Glioma	72	57	3	8
8.	Melanoma	114	2	9	78
9.	Amyotrophic lateral sclerosis (ALS)	75	33	5	4
10.	Graft vs host disease (GvHD)	71	33	5	9

Orphan Drug Designation Counts by Region and Year (2004-2018)

Worldwide, the number of products granted an orphan drug designation in 2018 compared to 2017 decreased by 27% in the US, 16% in the EU and 27% in Japan. The US continues to lead the EU and Japan in granting orphan designations.

EvaluatePharma® finds that the number of orphan designations granted by the FDA in 2018, fell by almost 30% to 335 (see Table 12). This may be due to the FDA having streamlined operations in 2017 to reduce the lag time in reviewing applications resulting in a smaller backlog. The designations granted by the EMA and MHLW also fell for the second year running, by 16% and 27% respectively. The number of orphan designations granted by the MHLW in 2018 was its lowest since 2010. Furthermore, the cumulative number of orphan drug designations granted by the FDA continues to be more than double the number granted by the EMA and nearly 10 times higher than those granted by the MHLW (see Figure 15 and Table 12), supporting our finding that the US is the most lucrative orphan drug market (see Figures 11a and 11b).

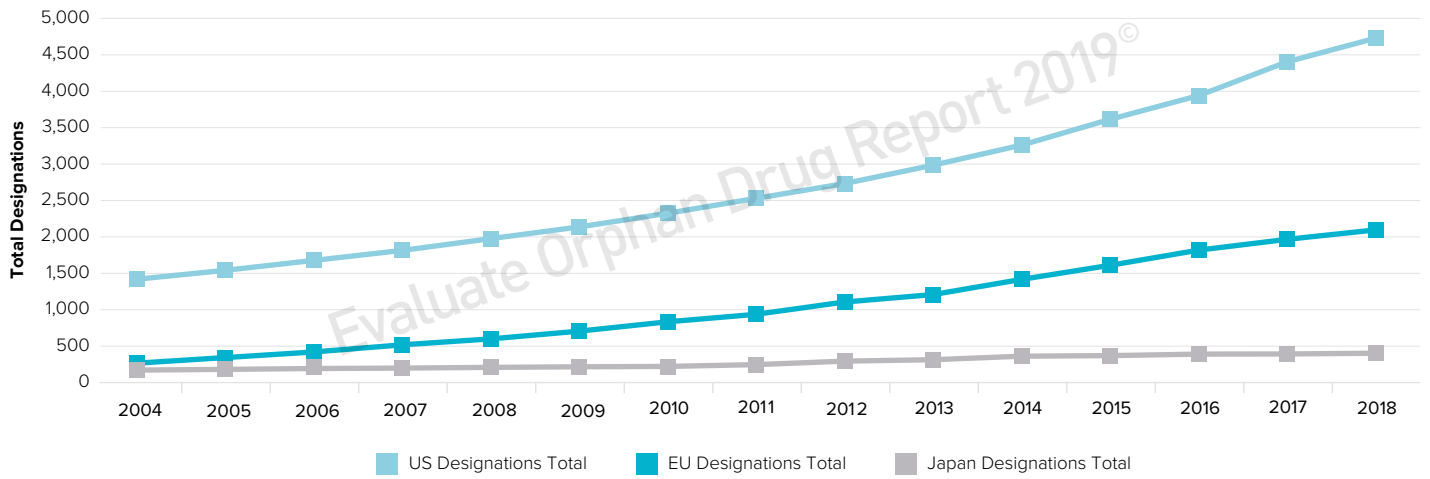## Figure 14: Counts and Growth in Orphan Designation by Region, per Year (2004-2018)
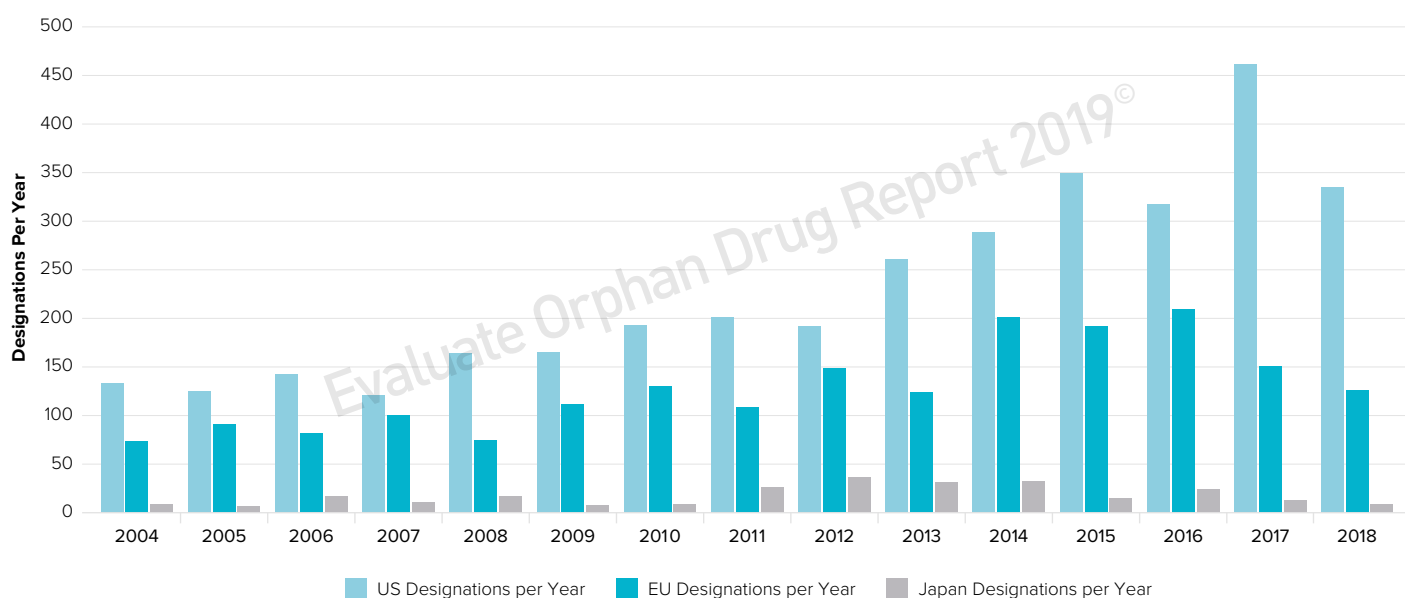
Table 12: Counts and Growth in Orphan Designations by Region, per Year (2004-2018)

Year	Orphan Designations														
	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
US Designations per Year	132	124	142	120	164	166	193	200	192	261	288	349	317	461	335
Growth per Year		-6%	+15%	-15%	+37%	+1%	+16%	+4%	-4%	+36%	+10%	+21%	-9%	+45%	-27%
EU Designations per Year	73	91	82	100	74	110	129	107	148	124	201	191	210	150	126
Growth per Year			-10%	+22%	-26%	+49%	+17%	-17%	+38%	-16%	+62%	-5%	+10%	-29%	-16%
Japan Designations per Year	8	5	15	10	15	7	9	25	36	30	32	14	23	11	8
Growth per Year		-38%	+200%	-33%	+50%	-53%	+29%	+178%	+44%	-17%	+7%	-56%	+64%	-52%	-27%

Figure 15: Cumulative Count of Orphan Drug Designations by Region, per Year (2004-2018)

Table 13: Cumulative Count and Growth in Orphan Designations by Region, per Year (2004-2018)

Year							Orphan Designations Cumulative Total								
	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
US Designations Total	1,423	1,547	1,689	1,809	1,973	2,139	2,332	2,532	2,724	2,985	3,273	3,622	3,939	4,400	4,735
Growth per Year		+9%	+9%	+7%	+9%	+8%	+9%	+9%	+8%	+10%	+10%	+11%	+9%	+12%	+8%
EU Designations Total	255	346	428	528	602	712	841	948	1,096	1,220	1,421	1,612	1,822	1,972	2,098
Growth per Year		+24%	+23%	+14%	+18%	+18%	+13%	+16%	+11%	+16%	+13%	+13%	+8%	+6%
Japan Designations Total	167	175	180	195	205	220	227	236	261	297	327	359	373	396	407
Growth per Year		+5%	+3%	+8%	+5%	+7%	+3%	+4%	+11%	+14%	+10%	+10%	+4%	+6%	+3%

Evaluate

Evaluate provides trusted commercial intelligence for the pharmaceutical industry. We help our clients to refine and transform their understanding of the past, present and future of the global pharmaceutical market to drive better decisions. When you partner with Evaluate, our constantly expanding solutions and our transparent methodologies and datasets are instantly at your disposal, along with personalised, expert support.

Evaluate gives you the time and confidence to turn understanding into insight, and insight into action.

EvaluatePharma offers a global view of the pharmaceutical market's past, present and future performance with consensus forecasts to 2024, company financials, pipelines and deals.

🐦 @EvaluatePharma

EvaluatePharma Vision provides the first single view of the risk and reward of the R&D landscape with consensus forecasts, R&D costs at drug and trial level, success rates, predictive timelines and trial outcomes.

EvaluateMedTech tracks, benchmarks, and forecasts global performance for the medical device and diagnostic industry with consensus forecasts to 2024, company financials and more.

Evaluate Custom Solutions improves your strategic decision-making with customised solutions and deep insights that draw on our industry expertise and trusted commercial intelligence.

Vantage provides award-winning, thought-provoking news and insights into current and future developments in the industry, and is the only pharmaceutical news service underpinned by Evaluate's commercial intelligence.

🐦 @Vantageanalysis

www.evaluate.com