EvaluatePharma®

Orphan Drug
Report 2017

Evaluate®

Welcome to the EvaluatePharma®
Orphan Drug Report 2017

The fourth edition of EvaluatePharma's Orphan Drug Report brings together many of our analyses to provide top-level insight, from the world's financial markets, into the expected performance of the orphan drug market between now and 2022. Based on EvaluatePharma's coverage of over 5,000 of the world's leading pharmaceutical and biotech companies, the Orphan Drug Report 2017 highlights trends in prescription sales for orphan vs. non-orphan drugs, USA revenue per patient, orphan designation analysis in USA, Europe and Japan, product and company performance and the most valuable orphan drugs in development.

Additional copies are available at:
www.evaluategroup.com/orphandrug2017

Overview

An orphan drug is a pharmaceutical product aimed at rare diseases or disorders. 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 30 million Americans suffer from 7,000 rare diseases. Prior to the 1983 Act, 38 orphan drugs were approved. 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:

- **USA:** <200,000 patients (<6.37 in 10,000, based on US population of 314m)
- **EU:** <5 in 10,000 (<250,000 patients, based on EU population of 514m)
- **Japan:** <50,000 patients (<4 in 10,000 based on Japan population of 128m)

Financial Incentives by Law Include:

Market Exclusivity

- **USA:** 7 Years of marketing exclusivity from approval; Note: Majority of orphan drugs have a compound patent beyond 7 years. The market exclusivity blocks 'same drug' recombinant products. E.g. Fabrazyme (Genzyme, now Sanofi) vs. Replagal (Transkaryotic, now Shire).'Same drug' exclusion can be overturned if clinically superior (mix of efficacy/ side effects). E.g. Rebif overturned Avonex's orphan drug exclusivity (7 MAR 2002)
- **EU:** 10 Years of marketing exclusivity from approval

Reduced R&D Costs

- **USA:** 50% Tax Credit on R&D Cost
- **USA:** R&D Grants for Phase I to Phase III Clinical Trials ($30m for each of fiscal years 2008-12)
- **USA:** User fees waived (FFDCA Section 526: Company WW Revenues <$50m)

Methodology on Classifying an Orphan Drug

We have identified all products that have orphan drug designations filed in the US, EU or Japan. These are available as part of the core EvaluatePharma service. To further enhance analysis, we have defined a clean 'Orphan' sub-set of products following a number of criteria including:

- First indication approved is for an orphan condition
- Products expected to generate more than 25% of sales from their orphan indications. This has led to the exclusion of drugs such as Avastin, Enbrel, Herceptin, Humira and Remicade, all of which have orphan designations for indications contributing less than 25% of sales
- Trial sizes, with smaller Phase III trials suggesting orphan status
- Drug pricing, higher prices were taken as an indicator of orphan status

All sales analysis in the report is based on this clean 'Orphan' sub-set of products. Product sales represent total brand sales.

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.

Foreword

The steady and inexorable growth of the orphan drug market remains one of the prominent themes in the fourth edition of EvaluatePharma's Orphan Drug Report. What has changed in the last 12 months is the increased scrutiny of the price of these lifesaving products.

There is little doubt that insurers will continue to cover orphan drugs, due to the fact they are frequently the only option for patients and, for now, remain a relatively small part of overall budgets. But according to the findings in this year's report the market will carry on expanding rapidly, with sales growth forecast at 11% per year, more than twice the rate predicted for conventional drugs.

In fact, sales of orphan drug are expected to almost double between 2016 and 2022, to hit $209bn. This rapid growth and current willingness of payers to stump up for the huge price tags are two of the main reasons why the sector has become more and more attractive to some of the industry's biggest players.

> The image of the plucky small biotech striving to develop treatments for the rare diseases largely ignored by big pharma is long gone. Instead, this year we again find big pharma dominating the sector. Seven of the top 10 companies by orphan drug sales are global industry players, who have won approval for their biggest products in various niche indications.

However, some see big pharma's interest in this space as a potential problem, claiming that these groups are taking unfair advantage of the lower R&D cost, speedier approval times, favourable patent life and pricing incentives for developing orphan products.

And the pricing incentives are substantial. According to this year's report, of the top 100 drugs in the US the average cost per patient per year for an orphan drug was $140,443 in 2016, compared with $27,756 for a non-orphan.

Foreword

In what might spell trouble for the industry, payers and politicians are taking note.

Exondys 51 and Spinraza – both treat rare and fatal childhood illnesses - might have won broad approvals from the US regulator, but some payers are insisting on much narrower interpretations of their clinical effectiveness.

In February, Republican senator Chuck Grassley announced that he would be starting an investigation into potential abuses of the Orphan Drug Act. President Donald Trump has also expressed his concern over drug pricing; whether this will spill over into orphan drug pricing is unknown but not impossible.

As such, if the orphan drug industry is to continue to thrive it must continue to generate innovations that justify the huge cost of these life transforming treatments.

Report Author:
Andreas Hadjivasiliou
Analyst, EvaluatePharma
Andreas.Hadjivasiliou@evaluategroup.com

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

Analysis Highlights

- Worldwide orphan drug sales forecast to total $209bn (CAGR 2017 to 2022:+11.1%); approximately double overall prescription market growth

- Orphan drugs set to be 21.4% of worldwide prescription sales by 2022 (excluding generics)

- Median cost per patient differential 5.5 times higher for orphan drugs compared to non-orphan

- Celgene set to climb to number one position in orphan drug sales to 2022

- Shire to be largest company by sales in the orphan non-oncology space in 2022

- AstraZeneca, Abbvie and Johnson & Johnson set to march up the orphan drug sales ranking table

- Revlimid (lenalidomide) No.1 orphan drug in 2022

- Opdivo (nivolumab) No.1 orphan drug in Europe in 2022

- Orphan drugs forecast to account for 55% of the cumulative value of the European pipeline to 2022

- Axicabtagene Ciloleucel (Kite Pharma) is most valuable R&D orphan drug

- First decline since 2012 for FDA orphan designations in 2016 with 333; Record number of applications made to the FDA for orphan designation in 2016.

Table of Contents

Contents

Worldwide Orphan Drug Sales (2000-2022)

Worldwide Orphan Drug Sales Forecast to Total $209bn (CAGR 2017 to 2022: +11.1%); Double Overall Rx Market Growth. Orphan Drugs Set to be 21.4% of Worldwide Prescription Sales by 2022; (excluding generics).

EvaluatePharma® finds that the market for orphan drugs, based on the consensus forecast for the leading 500 pharmaceutical and biotechnology companies, will grow by 11.1% per year (CAGR)

between 2017 and 2022 to $209bn. The growth of the orphan drug market is more than double that of the overall prescription drug market, which is set to grow by 5.3% over the period 2017-2022.

Orphan drugs are set to account for 21.4% of global prescription sales in 2022, excluding generics, up from 6% in 2000.

In 2016 orphan drug sales increased 12.2% to $114bn vs. 2015, while non-orphan drug sales increased by 2.4% to $578bn.

Worldwide Orphan Drug Sales & Share of Prescription Drug Market (2000-2022)

Source: EvaluatePharma® February 2017
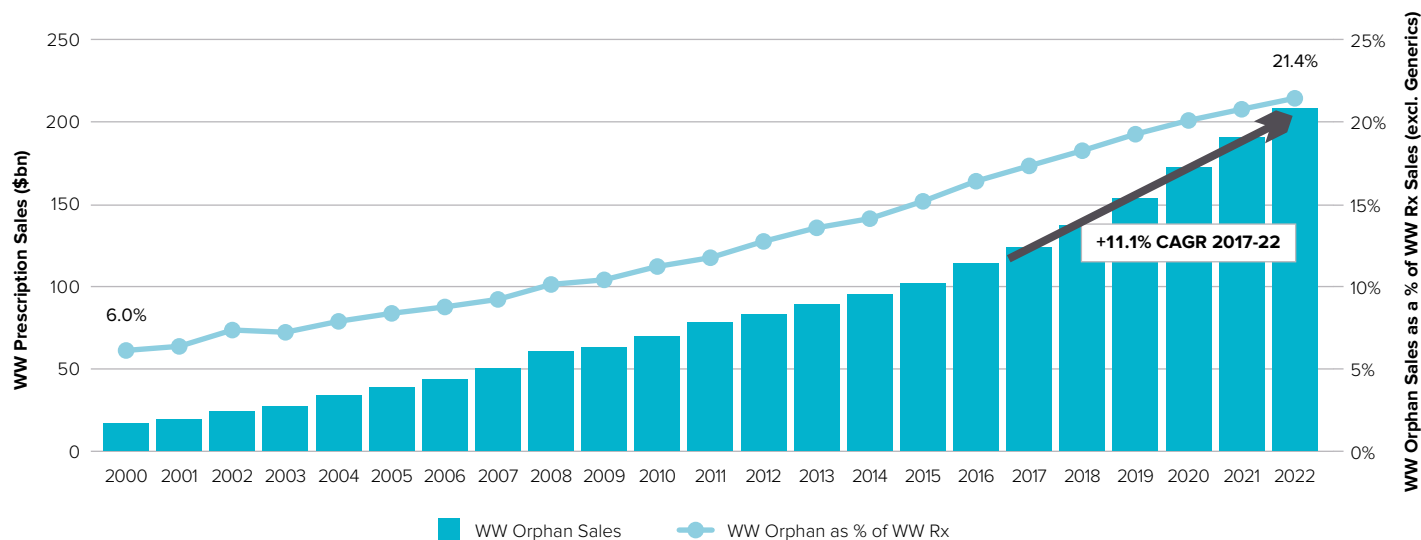
Worldwide Orphan & Prescription Drug Sales (2008-2022)

Source: EvaluatePharma® February 2017

	WW Prescription Sales ($bn)														
Year	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
WW Orphan Drug Sales	60	63	70	78	83	89	96	101	114	124	137	154	172	191	209
Growth per Year		+4.6%	+10.6%	+12.1%	+6.5%	+7.4%	+6.9%	+6.1%	+12.2%	+8.6%	+11.1%	+12.1%	+11.9%	+11.0%	+9.5%
Orphan Sales as a % of Rx	10.1%	10.3%	11.1%	11.8%	12.8%	13.7%	14.2%	15.2%	16.4%	17.3%	18.2%	19.2%	20.1%	20.8%	21.4%
WW Non-Orphan Drug Sales	535	547	557	585	568	565	578	565	578	592	616	647	686	727	766
Growth per Year		+2.1%	+1.9%	+5.1%	-2.9%	-0.5%	+2.3%	-2.3%	+2.4%	+2.3%	+4.0%	+5.1%	+6.0%	+6.0%	+5.4%
WW Prescription (Rx) (less Generics)	596	610	627	663	651	655	674	666	692	715	753	801	858	918	975
Growth per Year		+2.3%	+2.8%	+5.9%	-1.8%	+0.5%	+2.9%	-1.1%	+3.9%	+3.3%	+5.2%	+6.4%	+7.1%	+7.0%	+6.2%

WW Orphan Drug Market CAGR 17-22 +11.1%

WW Non-Orphan Drug Market CAGR 17-22 +5.3%

WW Prescription (Rx) excluding Generics CAGR 17-22 +6.4%

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

Sales to 2015 based on company reported sales data. Sales for 2016 based on available company reported sales data. Sales forecasts to 2022 based on a consensus of leading equity analysts' estimates for company product sales and segmental sales.

All sales analysis based on EvaluatePharma®'s clean 'Orphan' sub-set of products, as defined in the Overview section.

Top 100 USA Drug Cost per Patient per Year 2012-2016

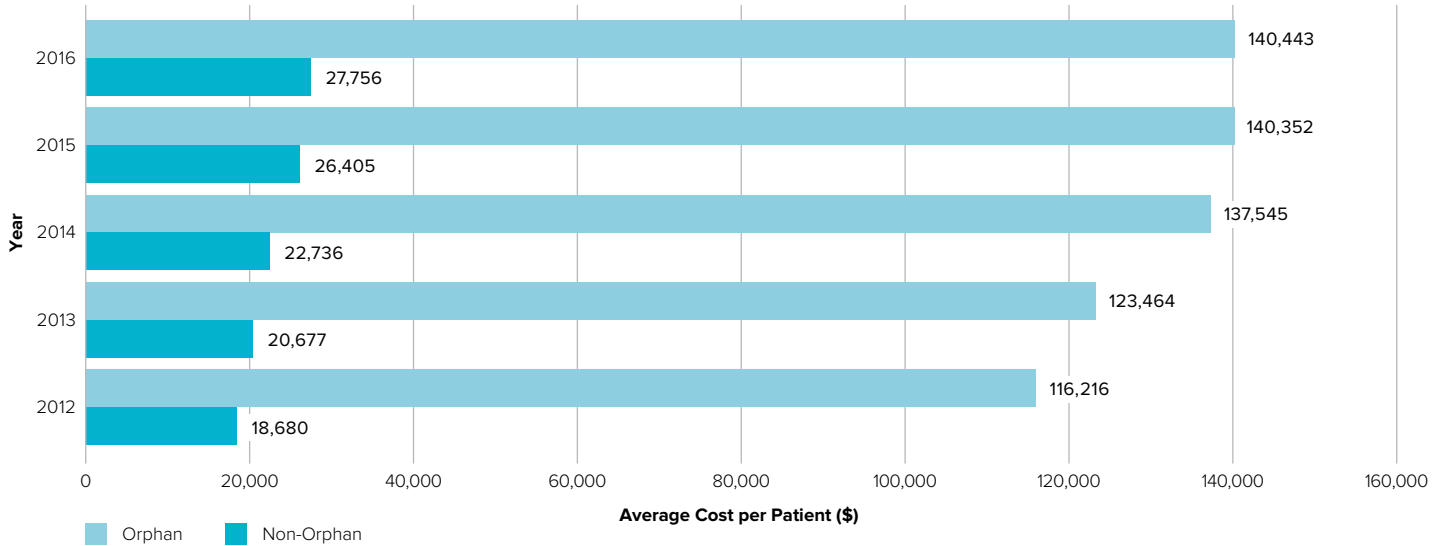**Average Orphan Drug Cost to Patients $140,443 in 2016; Median Orphan Drug Cost $83,883.**

EvaluatePharma® estimates that the average cost per patient per year in 2016 for an orphan drug was $140,443 versus $27,756 for a non-orphan drug. The average drug price has increased year on year for both orphan and non-orphan drugs since 2012. The median price differential between an orphan and non-orphan drug in 2016 was 5.5 compared to 9.8 in 2012.

The median price of orphan drugs and non-orphan drugs has increased by a factor of 1.3 and 2.3 since 2012 respectively.
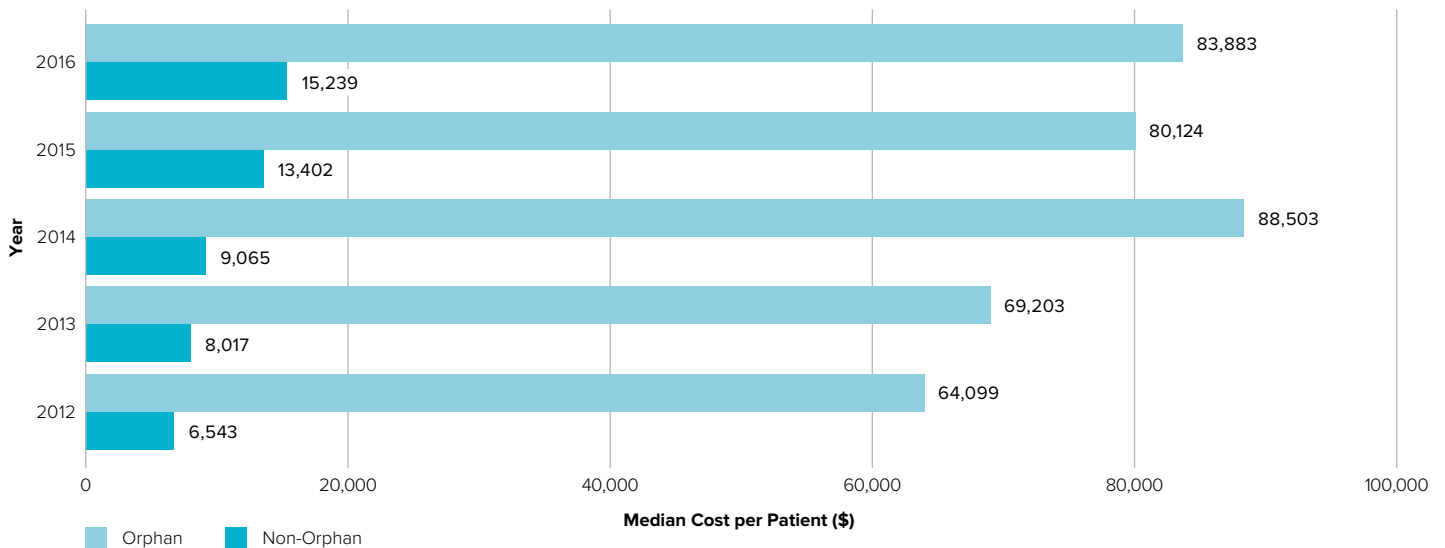
Average Cost per Patient per Year 2012-2016

Year

Year	Orphan	Non-Orphan
2016	140,443	27,756
2015	140,352	26,405
2014	137,545	22,736
2013	123,464	20,677
2012	116,216	18,680

Average Cost per Patient ($)

■ Orphan ■ Non-Orphan

Median Cost per Patient per Year 2012-2016

Year

Year	Orphan	Non-Orphan
2016	83,883	15,239
2015	80,124	13,402
2014	88,503	9,065
2013	69,203	8,017
2012	64,099	6,543

Median Cost per Patient ($)

■ Orphan ■ Non-Orphan

Top 100 Orphan and Top 100 Non-Orphan USA Drugs by Sales
Average and Median Cost per Patient per Year 2012-2016

Source: EvaluatePharma® February 2017

Average Cost per Patient ($) per year	2012	2013	2014	2015	2016	CAGR
Orphan	116,216	123,464	137,545	140,352	140,443	4.8%
Growth per Year		6.2%	11.4%	2.0%	0.1%	
Median price	64,099	69,203	88,503	80,124	83,883	
Non-orphan	18,680	20,677	22,736	26,405	27,756	10.4%
Growth per Year		10.7%	10.0%	16.1%	5.1%	
Median price	6,543	8,017	9,065	13,402	15,239	
Median Price Differential (orphan/non-orphan)	9.8	8.6	9.8	6.0	5.5	
				Median price increase 2012-2016:		
				Orphan:	1.31	
				Non-orphan:	2.33	

Note: All sales analysis based on EvaluatePharma®'s clean 'Orphan' sub-set of products, as defined in the 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 USA sales for 2016.

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.

2016: USA Revenue per Patient per Year for Top 20 Selling Orphan Drugs

Soliris Highest Revenue Orphan Drug in 2016; Revenue per Patient and Number of Patients Treated Correlated.
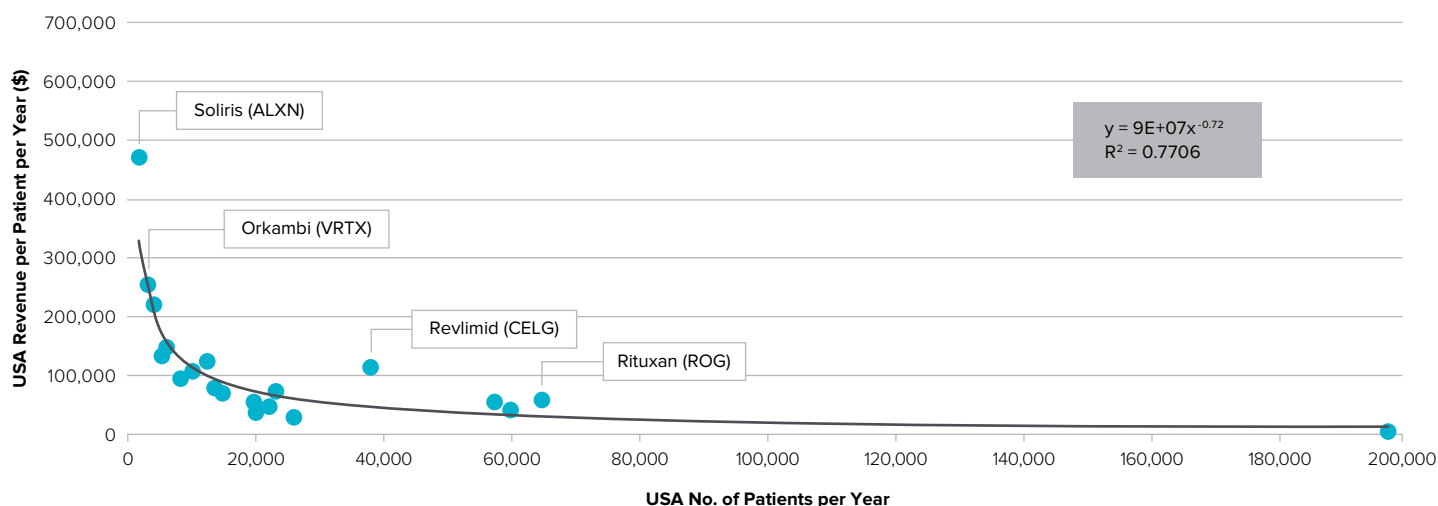
Orphan Drugs That Treated Fewer Than 10,000 Patients: Stronger Correlation of Drug Price and Patient Numbers.

EvaluatePharma® finds that revenue per patient for the Top 20 USA selling orphan drugs is correlated ($R^2 = 0.77$) to the number of patients treated in 2016. A similar analysis of the Top 10 selling orphan drugs that treated fewer than 10,000 patients confirms a closer correlation ($R^2 = 0.94$). This analysis confirms industry perceptions that smaller patient groups allow a pricing premium to be achieved versus non-orphans. Products such as Gleevec support the notion of an innovation premium for drugs that create a step change in treatment options and therapy outcomes. Soliris confirms the pricing power resulting from indications witht the fewest number of patients.

Top 20 USA Orphan Drugs in 2016 by Sales; Revenue per Patient vs. No. of Patients Treated

Source: EvaluatePharma® February 2017

Chart labels: Soliris (ALXN); Orkambi (VRTX); Revlimid (CELG); Rituxan (ROG)

$$y = 9E+07x^{-0.72}$$
$$R^2 = 0.7706$$

X-axis: USA No. of Patients per Year
Y-axis: USA Revenue per Patient per Year ($)

## USA Top 10 Selling Orphan Drugs in 2016 by Sales

Source: EvaluatePharma® February 2017

Rank	Product	Generic Name	Company	USA Sales ($m) 2016	Revenues per Patient 2016*	No. of Patients 2016
1.	**Revlimid**	lenalidomide	Celgene	4,417	113,887	38,301
2.	**Rituxan**	rituximab	Roche	3,970	61,009	65,286
3.	**Copaxone**	glatiramer acetate	Teva Pharmaceutical Industries	3,257	56,427	57,728
4.	**Opdivo**	nivolumab	Bristol-Myers Squibb	2,664	43,083	60,579
5.	**Avonex**	interferon beta-1a	Biogen	1,675	71,752	23,425
6.	**Imbruvica**	ibrutinib	AbbVie	1,580	126,040	12,775
7.	**Sensipar**	cinacalcet hydrochloride	Amgen	1,240	6,196	198,130
8.	**Gleevec**	imatinib mesylate	Novartis	1,214	110,202	10,486
9.	**Velcade**	bortezomib	Takeda	1,133	55,691	20,353
10.	**Xyrem**	sodium oxybate	Jazz Pharmaceuticals	1,114	73,899	15,074

Top 10 USA Orphan Drugs in 2016 by Sales (fewer than 10,000 patients treated); Revenue per Patient vs. No. of Patients Treated
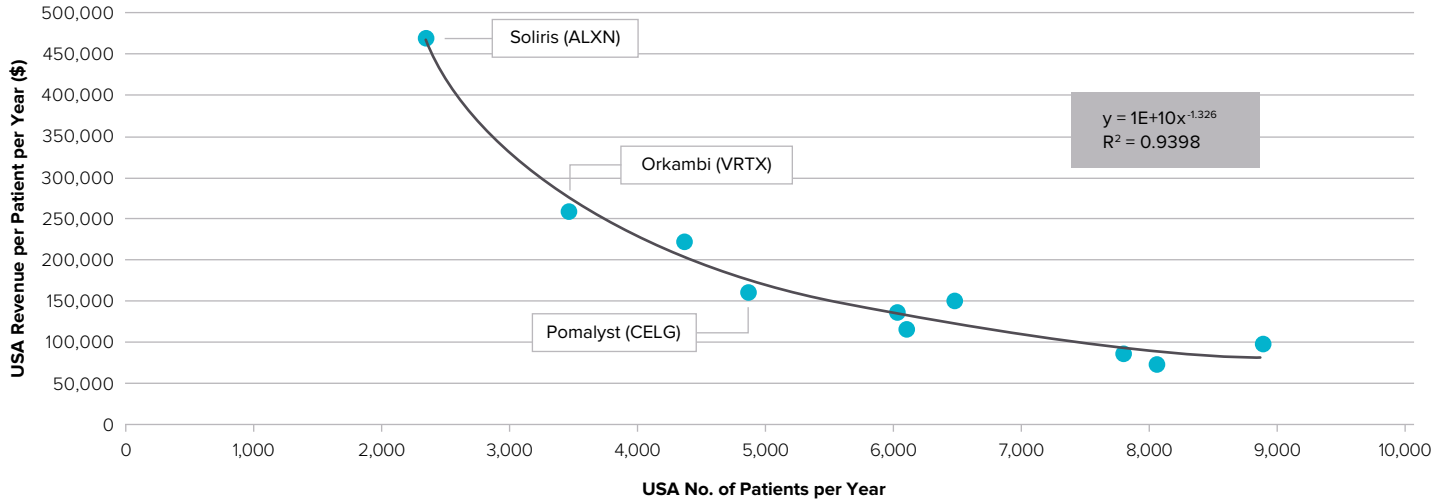
Source: EvaluatePharma® February 2017

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

USA sales represent sales for all indications.

EvaluatePharma® analysed the Top 10 selling USA drugs which treated fewer than 10,000 patients in 2016.

*Revenues per patient: An estimate of the dollar ($) revenues per year received, by a company, per patient for a drug in the USA 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.

All sales analysis based on EvaluatePharma®'s clean 'Orphan' sub-set of products, as defined in the Overview section.

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 2022: Top 20 Companies

Celgene Number One in Orphan Drug Sales in 2022 with BMS and Novartis in Second and Third Place. AZ, Abbvie and J&J Set to March up the Orphan Sales Ranking Table.

EvaluatePharma® finds that Celgene will overtake Novartis as the world's number one orphan drug company in 2022, climbing two places, and pushing Novartis down to number three.

One product contributes the majority of orphan sales for two of the top four; Celgene (Revlimid, 80% of sales) and BMS (Opdivo, 68% of sales).

Seven of the Top 10 companies by orphan drug sales in 2022 are forecast to be Global Majors.

The Top 5 companies in 2022 are forecast to account for almost one third (30.6%) of the orphan drug market.

WW Orphan Prescription Drug Sales in 2022: Top 10 Companies

Source: EvaluatePharma® February 2017
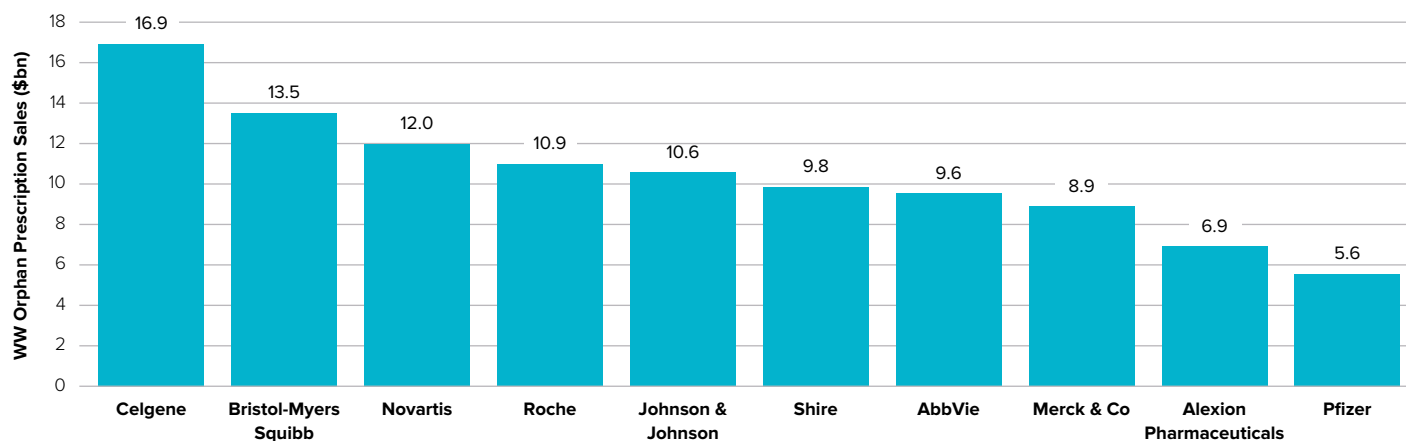
Worldwide Orphan Drug Sales (2016-2022): Top 20 Companies & Total Market

Source: EvaluatePharma® February 2017

Rank	Company	WW Orphan Sales ($bn)			WW Orphan Market Share			Rank
		2016	2022	% CAGR 16-22	2016	2022	Chg. (+/-)	Chg. (+/-)
1.	Celgene	9.1	16.9	11%	8.0%	8.1%	+0.1%	+2
2.	Bristol-Myers Squibb	6.6	13.5	13%	5.8%	6.5%	+0.6%	+2
3.	Novartis	12.9	12.0	-1%	11.3%	5.7%	-5.6%	-2
4.	Roche	10.0	10.9	1%	8.8%	5.2%	-3.6%	-2
5.	Johnson & Johnson	2.8	10.6	25%	2.4%	5.1%	+2.6%	+10
6.	Shire	5.4	9.8	10%	4.7%	4.7%	-0.1%	-1
7.	AbbVie	1.9	9.6	31%	1.7%	4.6%	+2.9%	+12
8.	Merck & Co	2.6	8.9	23%	2.3%	4.3%	+1.9%	+8
9.	Alexion Pharmaceuticals	3.1	6.9	14%	2.7%	3.3%	+0.6%	+1
10.	Pfizer	5.2	5.6	1%	4.6%	2.7%	-1.9%	-4
11.	Sanofi	3.6	5.5	7%	3.2%	2.6%	-0.6%	-3
12.	Vertex Pharmaceuticals	1.7	4.8	19%	1.5%	2.3%	+0.8%	+8
13.	Biogen	3.1	4.1	5%	2.7%	1.9%	-0.8%	-2
14.	Actelion	2.3	3.8	9%	2.0%	1.8%	-0.2%	+4
15.	AstraZeneca	0.2	3.7	57%	0.2%	1.8%	+1.5%	+29

Rank	Company	WW Orphan Sales ($bn)			WW Orphan Market Share			Rank
		2016	2022	% CAGR 16-22	2016	2022	Chg. (+/-)	Chg. (+/-)
16.	Amgen	3.0	3.5	3%	2.7%	1.7%	-1.0%	-3
17.	Eli Lilly	3.1	3.1	0%	2.7%	1.5%	-1.2%	-5
18.	Bayer	3.5	2.9	-3%	3.1%	1.4%	-1.7%	-9
19.	BioMarin Pharmaceutical	1.0	2.8	19%	0.9%	1.4%	+0.5%	+7
20.	Jazz Pharmaceuticals	1.4	2.7	11%	1.3%	1.3%	+0.0%	+4
	Total Top 20	82.7	141.7	+9.4%	72.6%	67.7%	-4.9%	
	Other	31.1	67.5	+13.8%	27.4%	32.3%		
	Total	113.9	209.2	+10.7%	100.0%	100.0%		

Note: All sales analysis based on EvaluatePharma®'s clean 'Orphan' sub-set of products, as defined in the Overview section.

Worldwide Orphan Drug Sales in 2022 Excluding Oncology: Top 20 Companies

**Shire and Alexion lead EvaluatePharma®'s non-oncology company orphan ranking in 2022.**

EvaluatePharma® conducted a secondary analysis of the companies active in the Orphan drug space excluding orphan products in the oncology therapy area. Shire is forecasted to remain the top selling company in this space in 2022 with $7.9bn in sales.

This space is growing at a CAGR of 7.7% with sales forecasted at $94.6bn in 2022. The top 20 companies will represent 66% of the non-oncology orphan space by 2022.

The non-oncology space represents 53% of the orphan market in 2016 and is forecasted to decrease to 45% by 2022.

WW Orphan Drug Sales in 2022 Excluding Oncology: Top 10 Companies

Source: EvaluatePharma® February 2017
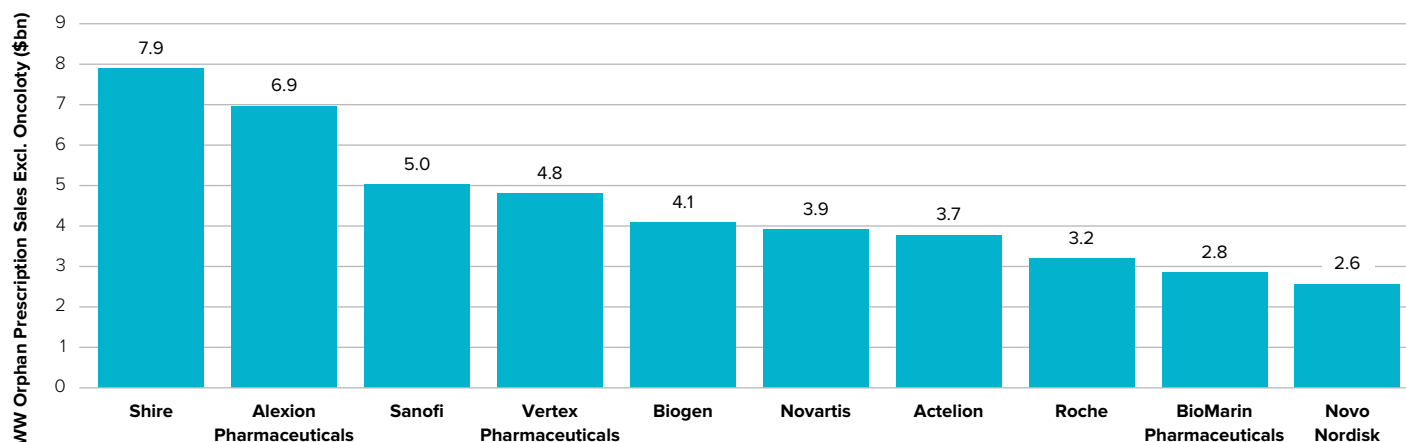
Worldwide Orphan Drug Sales Excluding Oncology: Top 20 Companies & Total Market

Source: EvaluatePharma® February 2017

| Rank | Company | WW Orphan Sales ($bn) | | | WW Market Share | | | Rank |
		2016	2022	% CAGR 16-22	2016	2022	Chg. (+/-)	Chg. (+/-)
1.	Shire	5.3	7.9	7%	8.7%	8.3%	-0.4%	-
2.	Alexion Pharmaceuticals	3.1	6.9	14%	5.1%	7.3%	2.2%	+4
3.	Sanofi	3.3	5.0	7%	5.5%	5.3%	-0.1%	+1
4.	Vertex Pharmaceuticals	1.7	4.8	19%	2.8%	5.0%	2.3%	+10
5.	Biogen	3.2	4.1	4%	5.2%	4.3%	-0.9%	-
6.	Novartis	3.9	3.9	0%	6.5%	4.1%	-2.4%	-3
7.	Actelion	2.3	3.7	9%	3.8%	4.0%	+0.2%	+4
8.	Roche	2.0	3.2	8%	3.3%	3.4%	0.0%	+5
9.	BioMarin Pharmaceutical	1.0	2.8	19%	1.7%	3.0%	+1.3%	+9
10.	Novo Nordisk	2.9	2.6	-2%	4.8%	2.7%	-2.1%	-3
11.	Pfizer	2.6	2.5	-1%	4.4%	2.6%	-1.7%	-3
12.	Teva Pharmaceutical Industries	4.1	2.3	-9%	6.8%	2.4%	-4.3%	-10
13.	Jazz Pharmaceuticals	1.2	2.2	10%	2.0%	2.3%	+0.3%	+4
14.	Bayer	2.4	2.0	-3%	4.0%	2.1%	-1.9%	-5
15.	Intercept Pharmaceuticals	0.0	1.8	129%	0.0%	1.9%	+1.9%	+61

Worldwide Orphan Drug Sales in 2022 Excluding Oncology: Top 20 Companies

Rank	Company	WW Orphan Sales ($bn)			WW Market Share			Rank
		2016	2022	% CAGR 16-22	2016	2022	Chg. (+/-)	Chg. (+/-)
16.	Boehringer Ingelheim	0.8	1.8	16%	1.3%	1.9%	+0.7%	+7
17.	Merck KGaA	2.4	1.4	-8%	3.9%	1.5%	-2.4%	7
18.	Amgen	2.2	1.3	-8%	3.6%	1.4%	-2.2%	-6
19.	Otsuka Holdings	0.4	1.2	19%	0.7%	1.3%	+0.6%	+9
20.	bluebird bio	-	1.1	-	-	1.1%	-	-
	Total Top 20	44.8	62.5	+5.7%	74.1%	66.1%	-8.0%	
	Other	15.7	32.1	+12.7%	25.9%	33.9%		
	Total	60.5	94.6	+7.7%	100.0%	100.0%		

Note: All sales analysis based on EvaluatePharma®'s clean 'Orphan' sub-set of products, as defined in the Overview section. Analysis excluded products categorized in the oncology therapeutic category to produce a non-oncology company list.

2022: Top 20 Selling Orphan Drugs in the World
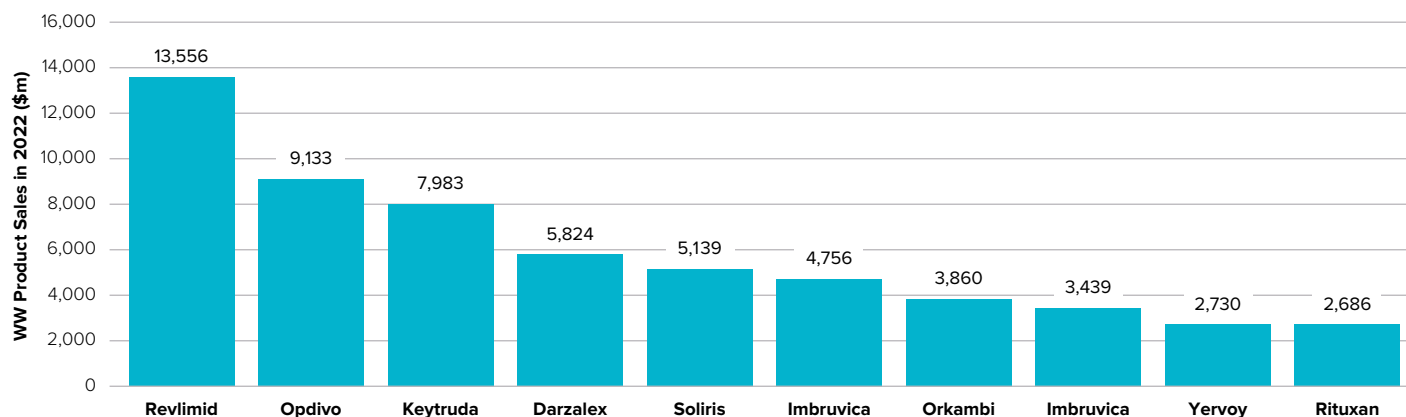
Revlimid (lenalidomide) No.1 Orphan Drug in 2022.

EvaluatePharma® finds that Revlimid is the world's largest orphan drug in 2022, with sales of $13.6bn for all indications. Revlimid from Celgene was first approved in December 2005 for the orphan treatment of myelodysplastic syndrome. Revlimid is also approved for the orphan indications Non-Hodgkin's lymphoma and multiple myeloma and remains in development for a number of other orphan conditions.

Bristol-Myers Squibb's Opdivo approved for multiple myeloma & Hodgkin's lymphoma, and designated for hepatoma, glioblastoma, small cell lung cancer and oesophageal cancer is set to be a distant second with $9.1bn in worldwide sales.

Top 10 Selling Orphan Drugs in 2022 by Worldwide Sales

Source: EvaluatePharma® February 2017

Bar chart — WW Product Sales in 2022 ($m):
- Revlimid: 13,556
- Opdivo: 9,133
- Keytruda: 7,983
- Darzalex: 5,824
- Soliris: 5,139
- Imbruvica: 4,756
- Orkambi: 3,860
- Imbruvica: 3,439
- Yervoy: 2,730
- Rituxan: 2,686

Worldwide Top 20 Selling Orphan Drugs in 2022

Source: EvaluatePharma® February 2017

Rank	Product	Generic Name	Company	Phase (Current)	Pharmacological Class	WW Product Sales ($m)		
						2016	2022	CAGR
1.	Revlimid	lenalidomide	Celgene	Marketed	Immunomodulator	6,974	**13,556**	+12%
2.	Opdivo	nivolumab	Bristol-Myers Squibb	Marketed	Anti-programmed death-1 (PD-1) MAb	3,774	**9,133**	+16%
3.	Keytruda	pembrolizumab	Merck & Co	Marketed	Anti-programmed death-1 (PD-1) MAb	1,402	**7,983**	+33%
4.	Darzalex	daratumumab	Johnson & Johnson	Marketed	Anti-CD38 MAb	572	**5,824**	+47%
5.	Soliris	eculizumab	Alexion Pharmaceuticals	Marketed	Anti-complement factor C5 MAb	2,843	**5,139**	+10%
6.	Imbruvica	ibrutinib	AbbVie	Marketed	Bruton's tyrosine kinase (BTK) inhibitor	1,580	**4,756**	+20%
7.	Orkambi	ivacaftor; lumacaftor	Vertex Pharmaceuticals	Marketed	Cystic fibrosis transmembrane conductance regulator (CFTR) corrector	980	**3,860**	+26%
8.	Imbruvica	ibrutinib	Johnson & Johnson	Marketed	Bruton's tyrosine kinase (BTK) inhibitor	638	**3,439**	+32%
9.	Yervoy	ipilimumab	Bristol-Myers Squibb	Marketed	Anti-cytotoxic T lymphocyte associated protein 4 (CTLA4) MAb	1,053	**2,730**	+17%
10.	Rituxan	rituximab	Roche	Marketed	Anti-CD20 MAb	7,410	**2,686**	-16%

Rank	Product	Generic Name	Company	Phase (Current)	Pharmacological Class	WW Product Sales ($m)		
						2016	2022	CAGR
11.	**Pomalyst**	pomalidomide	Celgene	Marketed	Tumour necrosis factor alpha (TNFa) inhibitor	1,311	**2,604**	+12%
12.	**Gazyva**	obinutuzumab	Roche	Marketed	Anti-CD20 MAb	199	**2,369**	+50%
13.	**Opdivo**	nivolumab	Ono Pharmaceutical	Marketed	Anti-programmed death-1 (PD-1) MAb	1,020	**2,083**	+13%
14.	**Jakafi**	ruxolitinib phosphate	Incyte	Marketed	Janus kinase (JAK)-1/2 inhibitor	853	**2,080**	+16%
15.	**Tasigna**	nilotinib hydrochloride	Novartis	Marketed	BCR-ABL tyrosine kinase inhibitor	1,739	**2,058**	+3%
16.	**Uptravi**	selexipag	Actelion	Marketed	Prostacyclin (PGI2) receptor agonist	249	**1,936**	+41%
17.	**Ocaliva**	obeticholic acid	Intercept Pharmaceuticals	Marketed	Farnesoid X receptor (FXR) agonist	13	**1,832**	+129%
18.	**Ofev***	nintedanib esylate	Boehringer Ingelheim	Marketed	Tyrosine kinase inhibitor	763	**1,827**	+16%
19.	**Venclexta**	venetoclax	AbbVie	Marketed	B-cell lymphoma 2 (Bcl-2) inhibitor	37	**1,825**	+91%
20.	**Niraparib**	niraparib	TESARO	Filed	Poly (ADP-ribose) polymerase (PARP) inhibitor	-	**1,794**	n/a
	Other					80,445	129,652	+8%
	Total					113,854	209,166	+10.7%

Note: * Forecast based on a single broker model.

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 clean 'Orphan' sub-set of products, as defined in the Overview section.

# 2022: Top 10 Selling Orphan Drugs and Pipeline in Europe

Opdivo (nivolumab) No.1 Orphan Drug in Europe in 2022.

EvaluatePharma® finds that Opdivo is Europe's largest orphan drug in 2022, with sales of $2.4bn for all indications. All of the orphan drugs in the top 10 are already marketed, with all but one forecast to continue to grow through to 2022. Orphan drugs are set to account for 55% of the cumulative value of the European pipeline through to 2022. Orphan products forecasted to launch in the coming years are expected to grow at a CAGR of 116% vs. non-orphan pipeline drugs which are forecasted to grow at 95% CAGR.

Top 10 Selling Orphan Drugs in 2022 by Europe Sales

Source: EvaluatePharma® February 2017
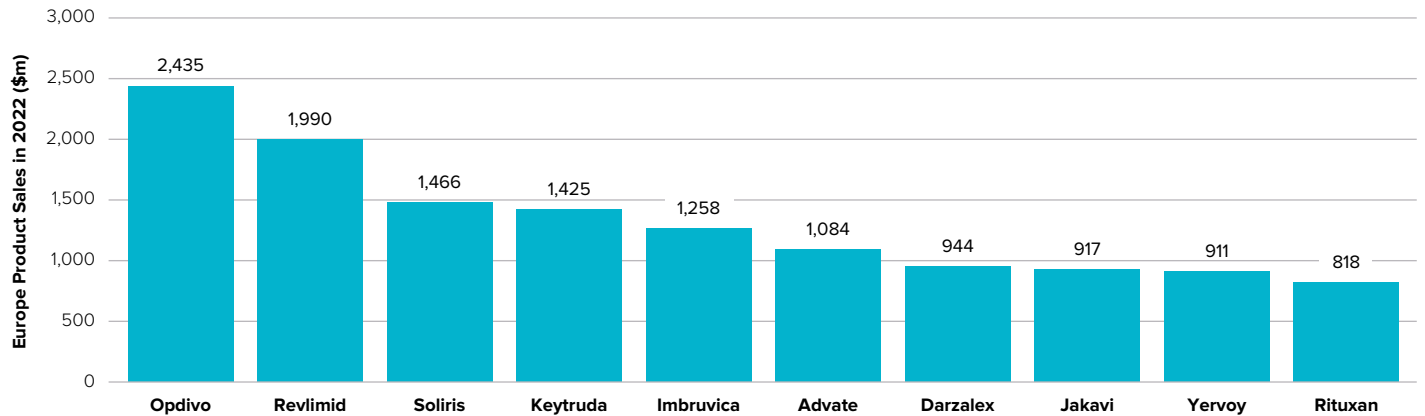
Europe: Top 10 Selling Orphan Drugs in 2022

Source: EvaluatePharma® February 2017

Rank	Product	Generic Name	Company	Phase (Current)	Pharmacological Class	Europe Product Sales ($m)		
						2016	2022	CAGR
1.	**Opdivo**	nivolumab	Bristol-Myers Squibb	Marketed	Anti-programmed death-1 (PD-1) MAb	523	**2,435**	+29%
2.	**Revlimid**	lenalidomide	Celgene	Marketed	Immunomodulator	1,254	**1,990**	+8%
3.	**Soliris**	eculizumab	Alexion Pharmaceuticals	Marketed	Anti-complement factor C5 MAb	898	**1,466**	+9%
4.	**Keytruda**	pembrolizumab	Merck & Co	Marketed	Anti-programmed death-1 (PD-1) MAb	161	**1,425**	+44%
5.	**Imbruvica**	ibrutinib	Johnson & Johnson	Marketed	Bruton's tyrosine kinase (BTK) inhibitor	348	**1,258**	+24%
6.	**Advate**	factor VIII (procoagulant)	Shire	Marketed	Factor VIII	789	**1,084**	+5%
7.	**Darzalex**	daratumumab	Johnson & Johnson	Marketed	Anti-CD38 MAb	6	**944**	+133%
8.	**Jakavi**	ruxolitinib phosphate	Novartis	Marketed	Janus kinase (JAK)-1/2 inhibitor	504	**917**	+10%
9.	**Yervoy**	ipilimumab	Bristol-Myers Squibb	Marketed	Anti-cytotoxic T lymphocyte associated protein 4 (CTLA4) MAb	206	**911**	+28%
10.	**Rituxan**	rituximab	Roche	Marketed	Anti-CD20 MAb	2,113	**818**	-15%
	Other					**17,510**	**27,250**	+8%
	Total					**24,312**	**40,496**	+8.9%

European Pipeline to 2022: Orphan vs. Non-orphan

Source: EvaluatePharma® February 2017
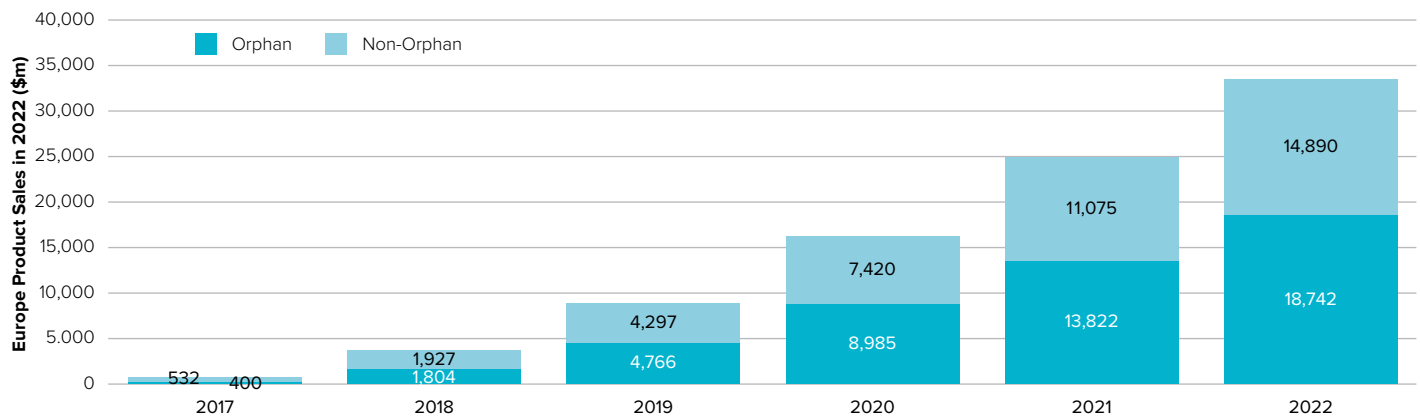
Europe: Pipeline of Orphan vs. Non-orphan Drugs to 2022

Source: EvaluatePharma® February 2017

R&D Pipeline	2017	2018	2019	2020	2021	2022	CAGR
			Europe Sales ($m)				
Orphan	400	1,804	4,766	8,985	13,822	18,742	+116%
Non-orphan	532	1,927	4,297	7,420	11,075	14,890	+95%
% Orphan Sales	43%	48%	53%	55%	56%	56%	
Total	932	3,732	9,064	16,405	24,898	33,633	+105%
Cumulative Orphan	400	2,204	6,971	15,956	29,778	48,521	
Cumulative Non-orphan	532	2,459	6,757	14,176	25,252	40,142	
Total						88,663	

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

All sales analysis based on EvaluatePharma®'s clean 'Orphan' sub-set of products, as defined in the Overview section.

2022: Top 20 Orphan R&D Products based on NPV

Axicabtagene Ciloleucel World's Most Valuable R&D Orphan Drug.
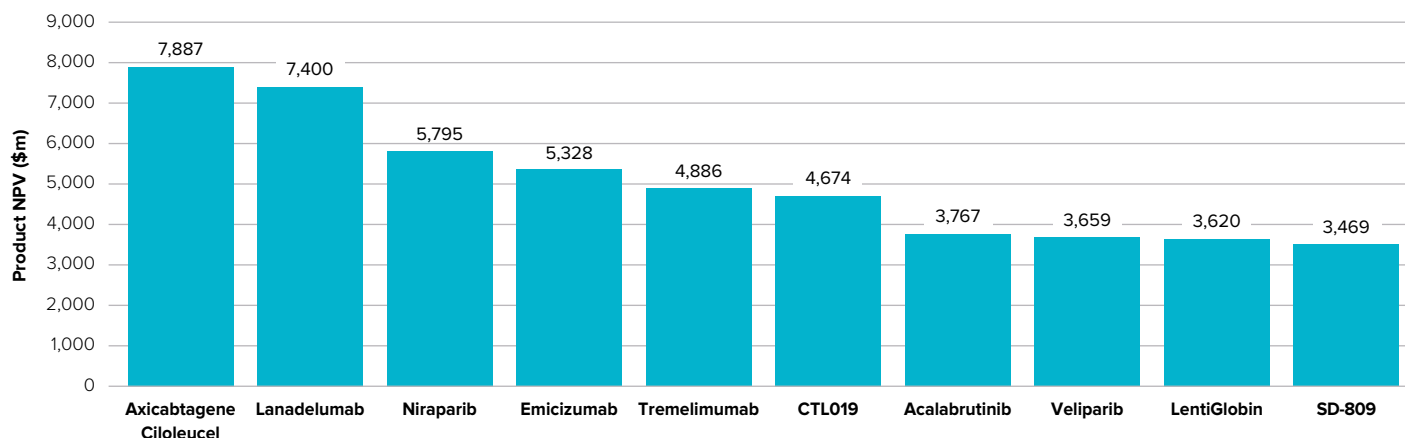
EvaluatePharma® finds that Kite Pharma's Anti-CD19 chimeric antigen receptor (CAR) T cell therapy in development for Non-Hodgkin's lymphoma, is the world's most promising R&D orphan drug, with an NPV of $7.9bn. The top 3 ranked products account for 19% of the total orphan NPV.

Of the products in R&D eight are classed as being developed in-house or having been in-licensed. The remaining four products were acquired through a company acquisition.

Top 10 Orphan Drugs in 2022 (Phase III/Filed) by NPV

Source: EvaluatePharma® February 2017

Worldwide Top 20 Orphan R&D Products based on NPV (Sales, NPV)

Source: EvaluatePharma® February 2017

Rank	Product	Company	Phase (Current)	Pharma Class	Sales ($m) 2022	WW NPV	Strategy
1.	**Axicabtagene Ciloleucel**	Kite Pharma	Filed	Anti-CD19 chimeric antigen receptor (CAR) T cell therapy	1,699	**7,887**	In-licensed
2.	**Lanadelumab**	Shire	Phase III	Anti-plasma kallikrein MAb	1,094	**7,400**	Company acquisition
3.	**Niraparib**	TESARO	Filed	Poly (ADP-ribose) polymerase (PARP) inhibitor	1,794	**5,795**	In-licensed
4.	**Emicizumab**	Roche	Phase III	Anti-factor IXa/X bispecific MAb	1,456	**5,328**	In-licensed
5.	**Tremelimumab**	AstraZeneca	Phase III	Anti-cytotoxic T lymphocyte associated protein 4 (CTLA4) MAb	1,289	**4,886**	In-licensed
6.	**CTL019**	Novartis	Phase III	Anti-CD19 chimeric antigen receptor (CAR) T cell therapy	917	**4,674**	In-licensed
7.	**Acalabrutinib**	AstraZeneca	Phase III	Bruton's tyrosine kinase (BTK) inhibitor	968	**3,767**	In-licensed
8.	**Veliparib**	AbbVie	Phase III	Poly (ADP-ribose) polymerase (PARP) inhibitor	854	**3,659**	Organic
9.	**LentiGlobin**	bluebird bio	Phase III	Haemoglobin gene therapy	969	**3,620**	Organic
10.	**SD-809**	Teva Pharmaceutical Industries	Filed	Vesicular monoamine transporter 2 (VMAT2) inhibitor	1,019	**3,469**	Company acquisition

Rank	Product	Company	Phase (Current)	Pharma Class	Sales ($m) 2022	WW NPV	Strategy
11.	**Masican***	AB Science	Filed	c-kit tyrosine kinase, platelet-derived growth factor receptor (PDGFr) & fibroblast growth factor receptor 3 (FGFR3) inhibitor	928	**2,935**	Organic
12.	**Luspatercept**	Celgene	Phase III	Activin type IIB antagonist	462	**2,715**	In-licensed
13.	**Avelumab**	Pfizer	Filed	Anti-programmed death-1 ligand-1 (PD-L1) MAb	674	**2,447**	In-licensed
14.	**Emicizumab**	Chugai Pharmaceutical	Phase III	Anti-factor IXa/X bispecific MAb	349	**2,427**	Organic
15.	**Selinexor**	Karyopharm Therapeutics	Phase III	Exportin 1/chromosome region maintenance protein 1 (XPO1/CRM1) inhibitor	766	**2,205**	Company acquisition
16.	**NEOD001**	Prothena	Phase III	Anti-beta-amyloid (Abeta) MAb	584	**2,106**	Organic
17.	**Isatuximab**	Sanofi	Phase III	Anti-CD38 MAb	387	**1,956**	Company acquisition
18.	**Midostaurin**	Novartis	Filed	FMS-like tyrosine kinase 3 (FLT3) inhibitor	436	**1,862**	Organic
19.	**KRN23**	Kyowa Hakko Kirin	Filed	Anti-fibroblast growth factor (FGF23) MAb	673	**1,554**	Organic
20.	**Copanlisib**	Bayer	Phase III	Phosphatidylinositol 3-kinase (PI3K) inhibitor	343	**1,535**	Organic
	Other				**11,943**	**40,355**	
	Total				**29,604**	**112,581**	
				vs. Non-Orphan:	**73,433**	**286,420**	

Note: 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.

* Forecast based on a single broker model.

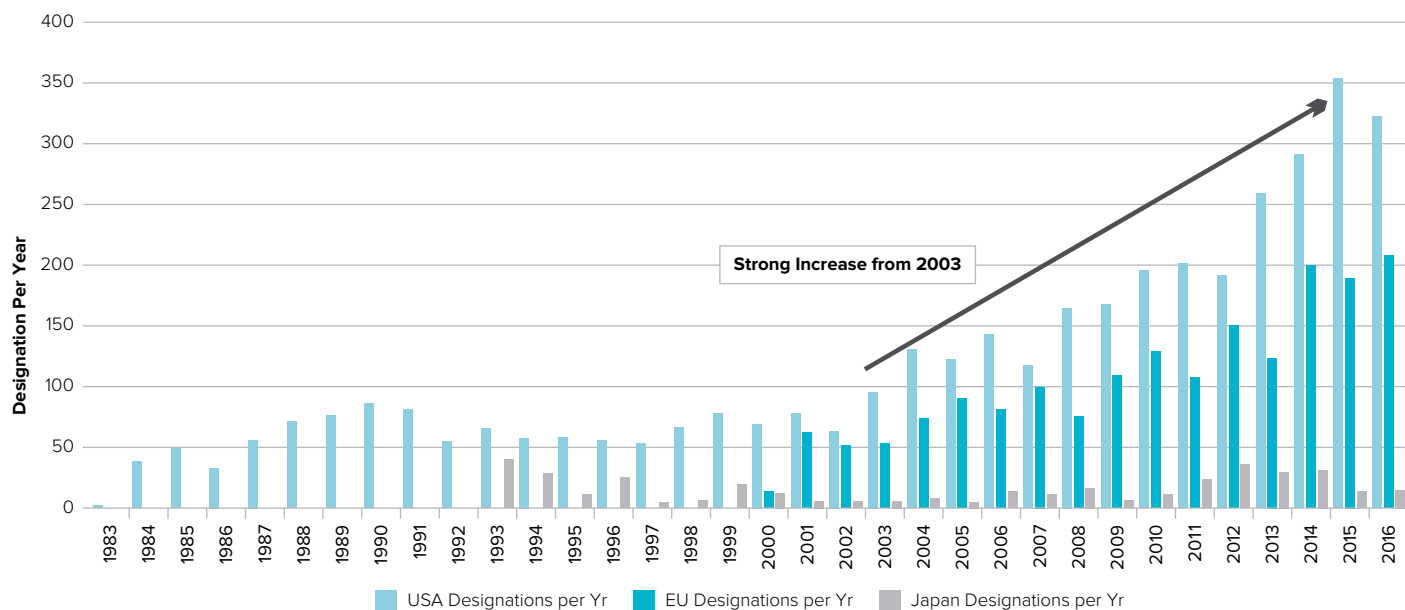# USA, EU & Japan Orphan Designations per Year & Cumulative (1983-2016)

FDA Orphan Designations Decrease by 6% in 2016; European Designations up 9%; Japan Designations up 15%.

EvaluatePharma® found that the number of US orphan drug designations granted decreased 6% in 2016 to 333. Despite this,

the number of applications to the FDA reached a new high of 582, a 23% growth on 2015. At a 57% acceptance rate this resulted in the lowest acceptance level since 2002. European orphan designations grew by 9% in 2016 reversing a 5% fall in 2015.

USA, EU & Japan Designations per Year (1983-2016)

Source: EvaluatePharma® February 2017

US, EU & Japan Orphan Designations per Year (2002-2016)

Source: EvaluatePharma® February 2017; USA OD applications per year from PAREXEL Consulting

Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
USA OD Applications	115	167	174	174	191	181	185	250	323	306	264	346	467	472	582
Growth per Year		+45%	+4%	+0%	+10%	-5%	+2%	+35%	+29%	-5%	-14%	+31%	+35%	+1%	+23%
USA Designations Accepted	64	96	132	123	143	119	165	169	197	203	197	261	292	354	333
Growth per Year		+50%	+38%	-7%	+16%	-17%	+39%	+2%	+17%	+3%	-3%	+32%	+12%	+21%	-6%
% Accepted		83%	79%	71%	82%	62%	91%	91%	79%	63%	64%	99%	84%	76%	57%
EU Designations per Yr	52	54	74	91	82	100	75	109	130	108	149	124	201	190	208
Growth per Year			+37%	+23%	-10%	+22%	-25%	+45%	+19%	-17%	+38%	-17%	+62%	-5%	+9%
Japan Designations per Yr	5	7	8	5	14	10	16	7	10	24	36	30	32	13	15
Growth per Year		+40%	+14%	-38%	+180%	-29%	+60%	-56%	+43%	+140%	+50%	-17%	+7%	-59%	+15%

（）

USA, EU & Japan Designations Cumulative Total

- USA Designations Total
- EU Designations Total
- Japan Designations Total
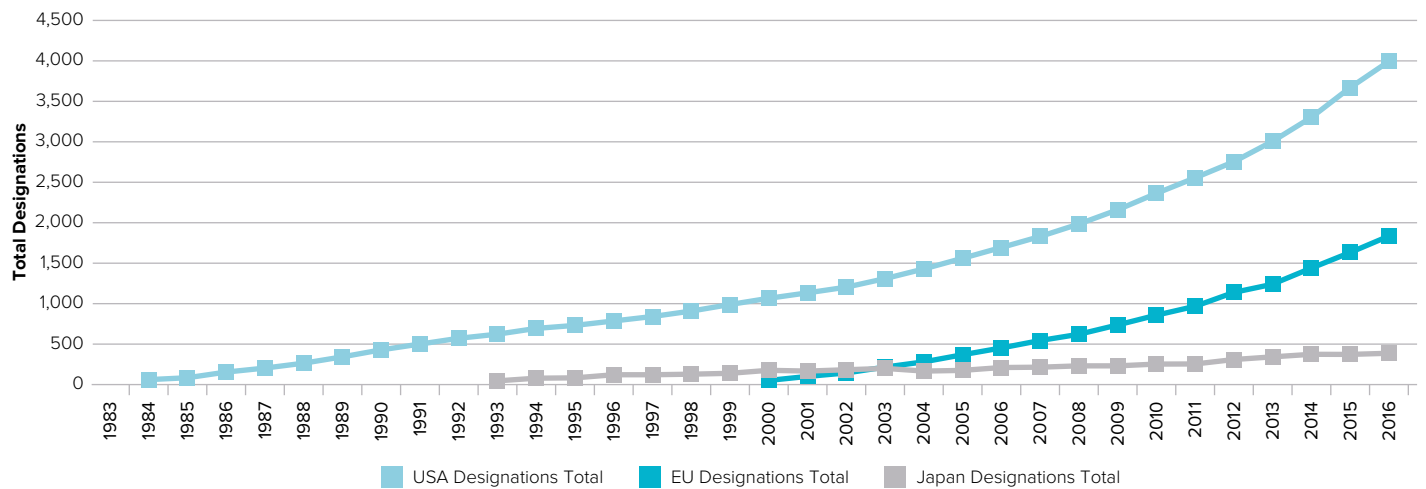
Cumulative US, EU & Japan Orphan Designations & US Approvals per Year (2002-2016)

Year						Orphan Designations Cumulative Total									
	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
USA Designations Total	1,197	1,293	1,425	1,548	1,691	1,810	1,975	2,144	2,341	2,544	2,741	2,997	3,288	3,642	3,976
Growth per Year		+8%	+10%	+9%	+9%	+7%	+9%	+9%	+9%	+9%	+8%	+9%	+10%	+11%	+9%
EU Designations Total	129	183	257	348	430	530	605	714	844	952	1,101	1,225	1,426	1,616	1,824
Growth per Year			+40%	+35%	+24%	+23%	+14%	+18%	+18%	+13%	+16%	+11%	+16%	+13%	+13%
Japan Designations Total	160	167	175	180	194	204	220	227	237	261	297	327	359	372	387
Growth per Year		+4%	+5%	+3%	+8%	+5%	+8%	+3%	+4%	+10%	+14%	+10%	+10%	+4%	+4%

About EvaluatePharma®

Since 1996 EvaluatePharma has been providing senior decision makers within the pharmaceutical industry with an essential service that models the sector from the viewpoint of the world's financial markets.

EvaluatePharma's forward looking view of the market is hugely influential as it displays the consensus of expectations, which influence company stock market valuations. The forecasts of equity analysts reveal their perspectives on individual company performance, industry trends and the macro economic environment.

EvaluatePharma has captured the consensus forecasts of equity analysts and seamlessly integrated them with the historic results, as reported by companies. From this comprehensive view of the industry, its past and expected future performance emerges and can be analysed using EvaluatePharma. Analyses range from total market trends and therapeutic overviews to individual company performance and product progress.

Whatever your view on the future of the industry, EvaluatePharma is the essential guide to value in the pharma and biotech sector.

To find out more about this report and Evaluate's range of services please contact us:

North America: Tom Moore
Tel: +1 617 573 9454 / Email: thomas.moore@evaluategroup.com

Rest of the World: Will Hau
Tel: +44 (0)20 7377 0800 / Email: will.hau@evaluategroup.com

Japan: Hiroshi Yamazaki
Tel: + 81 (0)80 1164 4754 / Email: hiroshi.yamazaki@evaluategroup.com

For general questions: Christine Lindgren
Tel: +1 617 866 3906 / Email: christine.lindgren@evaluategroup.com

Evaluate is the trusted provider of commercial intelligence including product sales and consensus forecasts to 2022 for commercial teams and their advisors within the global life science industry. We help our clients make high value decisions through superior quality, timely, must-have data and insights, combined with personalised, expert client support.

EvaluatePharma® delivers exclusive consensus sales forecasts and trusted commercial insight into biotech and pharmaceutical performance.
@EvaluatePharma

EvaluateMedTech® sets a new standard in commercial analysis and consensus forecasts of the global medical device and diagnostic industry.
@EvaluateMedTech

EvaluateClinical Trials® delivers unique clinical trial intelligence expertly curated to efficiently analyse the global clinical trial landscape.
@EPClinicalTrial

EP Vantage an award winning editorial team, provides daily commentary and analysis with fresh perspectives and insight into current and future industry trends.
@EPVantage

Evaluate Custom Services provides customised solutions to help you access, analyse and manage the information you need to support effective decision-making.

The Evaluate services enable the life science community to make sound business decisions about value and opportunity.

www.evaluate.com