# ORPHAN DRUG REPORT 2014

EvaluatePharma®

# Welcome to the EvaluatePharma® Orphan Drug Report 2014

The second 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 2020. Based on EvaluatePharma's coverage of over 4,800 of the world's leading pharmaceutical and biotech companies, the Orphan Drug Report 2014 highlights trends in prescription sales for orphan vs. non-orphan drugs, orphan designation analysis in the USA and Europe, product and company performance, phase III R&D spend and return on investment. Additional copies are available at: www.evaluategroup.com/orphandrug2014.

## 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.

EvaluatePharma's newest content set provides a fully integrated, single source for USA sales, volume and pricing information. In addition, annual cost per patient for the top selling drugs as well as number of patients treated is calculated for you. The analysis combines USA government data sources and is fully transparent as to the specific sources and the methodology of our calculations. Download our report Budget Busters: the shift to high-priced innovator drugs in the USA or visit www.evaluategroup.com/budgetbusters

To find out more about our these reports and Evaluate's full range of products and services contact us:


- **North America:**
  Debbie Paul
  Tel: +1 617 573 9453
  Email: debbie.paul@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


## Disclaimer

# 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. To date, 468 indication designations covering 373 drugs have been 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 506m)
- 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.

# EvaluatePharma®
# Foreword

EvaluatePharma's second Orphan Drug Report measures little slowdown in the growth of sales for agents that treat rare diseases. Sales of drugs designated as orphans by regulators in the US, Europe or Japan will grow at an annual rate of nearly 11% per year through 2020, compared to only about 4% for drugs treating larger populations.

The reason is clear. The industry has rushed to develop orphan drugs in recent years because they cost their developers less to put through clinical trials, and command higher prices when they do launch. Trial sizes are naturally smaller than for diseases with large populations, and the lack of alternative treatments give orphan agents an advantage when up for regulatory review. Tax incentives reduce development costs further. And when orphan drugs do reach the market, on average their cost per patient is six times that of non-orphan drugs, a clear indication of their pricing power.

This year's Orphan Drug report finds that orphan drug sales will constitute 19% of the total share of prescription drug sales by 2020, totalling $176bn. Thanks to soaring forecasts for its cancer immunotherapeutic Opdivo, Bristol-Myers Squibb is now forecast to leapfrog Novartis to become the biggest orphan company in six years. In the pipeline, Vertex Pharmaceuticals' cystic fibrosis combination VX-809 and Kalydeco has the most promise, with 2020 sales reckoned at $4bn. And orphan drug designations show no sign of slowing down, at least in the US, with a record 260 having been granted in 2013.

Looking ahead, there does not appear to be much to slow down the sector's rush into orphan indications. Revisions to the US Orphan Drug Act do tighten up some of the language in order to prevent manufacturers from creating subsets of patients that could inappropriately qualify as an orphan indication, but does not appear to have a major effect on development. With designations continuing to be on the rise, in all likelihood the number of orphan drugs that successfully complete the clinical and registration stages will be on the rise. However, the US has created the new breakthrough therapy category, so it is possible that certain orphan-type drugs could be diverted into that regulatory scheme.

Finally, the pricing environment remains favourable, but payers will be looking to manage escalating drugs bills as patent expiries slow in coming years. Although orphan populations are by definition the smallest, they represent big per-patient outlays, and insurers will be looking carefully at new tools to arrest cost growth as more and more orphan drugs launch. Expect more pressure on the drugs that represent the biggest budgetary drain, especially as increasing numbers of US patients will be receiving public subsidies with the implementation of the Affordable Care Act.

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

Foreword by:
Jonathan Gardner
Reporter, EP Vantage
jonathang@epvantage.com

# EvaluatePharma® Orphan Drug 2014 – Analysis Highlights

- Worldwide orphan drug sales forecast to total $176bn (CAGR 2014 to 2020:+10.5%); almost double overall prescription market growth (excluding generics)
- Orphan drugs set to be 19.1% of worldwide prescription sales by 2020 (excluding generics)
- Soliris (eculizumab) highest revenue per patient orphan drug in the USA
- Median cost per patient differential 19 times higher for orphan drugs compared to non-orphan
- Bristol-Myers Squibb set to climb to number one position in orphan drug sales to 2020
- Pharmacyclics, Vertex and Alexion set to march up the orphan sales ranking table
- Revlimid (lenalidomide) no.1 orphan drug in 2020
- Phase III orphan drug development cost half that of non-orphan; potentially a quarter with US tax breaks
- Phase III drug development time for orphan is no quicker than non-orphan
- Orphan drug FDA approval time 10 months vs. 13 months for non-orphan
- Expected return on investment of phase III/ filed orphan drugs 1.89 times greater than non-orphan drugs
- VX-809 + ivacaftor (Vertex) is most valuable R&D orphan drug
- Record year for FDA orphan designations in 2013 (260); European designations decline by 17%; Japan designations down 17%
- Imbruvica most promising new orphan drug approved by FDA in 2013
- 18.7% of EU orphan designations are for ultra-rare diseases
- Non-Hodgkin Lymphoma (NHL) is indication with most filed orphan drug designations in EU

# Table of Contents


7 Worldwide Orphan Drug Sales (2000-20)

8 Top 100 USA Drug Cost per Patient per Year 2010-14

9 2014: USA Revenue per Patient per Year for Top 20 Selling Orphan Drugs

10 Worldwide Orphan Drug Sales in 2020: Top 20 Companies

11 2020: Top 20 Selling Orphan Drugs in the World

12 Phase III Trial Size & Approval Time: Orphan vs. Non-Orphan

13 R&D Costs (PIII/ Filed) & Expected Investment Returns (NPV)

14 2020: Top 20 Orphan R&D Products based on NPV

15 USA, EU & Japan Orphan Designations per Year & Cumulative (1983-13)

16 FDA Approvals of Designations & New Drugs (NMEs/ BLAs): 2000 to 2013

17 FDA New Drug Approval Analysis (NMEs/ BLAs) 2013: Orphan vs. Non-Orphan

18 EU Orphan Designations: Historic Distribution by Prevalence

19 EU Orphan Designations: Top 20 Indications

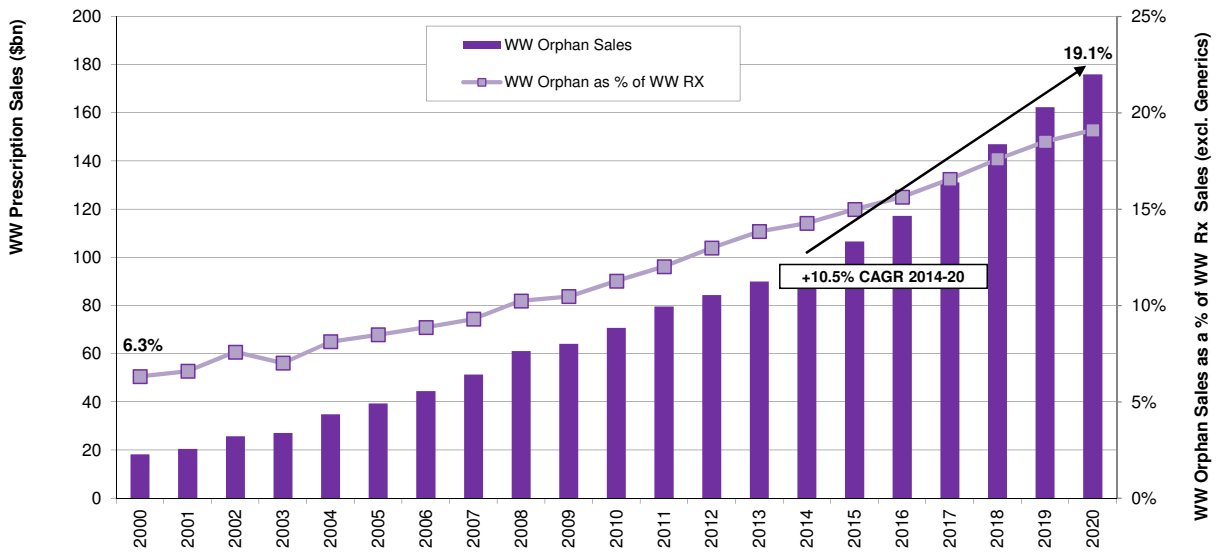
20 About EvaluatePharma®

# Worldwide Orphan Drug Sales (2000-20)

EvaluatePharma®

**Worldwide Orphan Drug Sales Forecast to Total $176bn (CAGR 2014 to 2020: +10.5%); Double Overall Rx Market Growth**
**Orphan Drugs Set to be 19.1% of Worldwide Prescription Sales by 2020 (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 10.5% per year (CAGR) between 2014 and 2020 to $176bn. The growth of the orphan drug market is almost double that of the overall prescription drug market, which is set to grow by 5.3% over the period 2014-2020.
Orphan drugs are set to account for 19.1% of global prescription sales in 2020, excluding generics, up from 6.3% in 2000.
In 2013 orphan drug sales increased 6.8% to $90bn vs. 2012, in contrast to non-orphan drug sales which decreased by 0.9% to $560bn.

**Worldwide Orphan Drug Sales & Share of Prescription Drug Market (2000-20)**
*Source: EvaluatePharma® (27 OCT 2014)*




**Worldwide Orphan & Prescription Drug Sales (2006-20)**

| WW Prescription Sales ($bn) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Year | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 |
| WW Orphan Drug Sales | 45 | 51 | 61 | 64 | 71 | 80 | 84 | 90 | 97 | 107 | 117 | 131 | 147 | 162 | 176 |
| *Growth per Year* | | *+15.4%* | *+19.0%* | *+4.8%* | *+10.4%* | *+12.5%* | *+6.0%* | *+6.8%* | *+7.3%* | *+10.5%* | *+9.9%* | *+11.9%* | *+12.1%* | *+10.4%* | *+8.4%* |
| *Orphan Sales as a % of Rx* | *8.9%* | *9.3%* | *10.3%* | *10.5%* | *11.3%* | *12.0%* | *13.0%* | *13.9%* | *14.3%* | *15.0%* | *15.6%* | *16.6%* | *17.6%* | *18.5%* | *19.1%* |
| WW Non-Orphan Drug Sales | 457 | 501 | 535 | 548 | 556 | 582 | 565 | 560 | 580 | 604 | 632 | 661 | 688 | 714 | 745 |
| *Growth per Year* | | *+9.6%* | *+6.9%* | *+2.3%* | *+1.5%* | *+4.6%* | *-2.9%* | *-0.9%* | *+3.5%* | *+4.3%* | *+4.6%* | *+4.5%* | *+4.2%* | *+3.8%* | *+4.3%* |
| WW Prescription (Rx) (less Generics) | 502 | 552 | 597 | 612 | 627 | 661 | 649 | 650 | 676 | 711 | 750 | 792 | 835 | 877 | 921 |
| *Growth per Year* | | *+10.1%* | *+8.0%* | *+2.6%* | *+2.5%* | *+5.5%* | *-1.8%* | *+0.1%* | *+4.0%* | *+5.2%* | *+5.4%* | *+5.6%* | *+5.5%* | *+5.0%* | *+5.0%* |

*Source: EvaluatePharma® (27 OCT 2014)*

*WW Orphan Drug Market CAGR 14-20 +10.5%*
*WW Non-Orphan Drug Market CAGR 14-20 +4.3%*
*WW Prescription (Rx) excluding Generics CAGR 14-20 +5.3%*

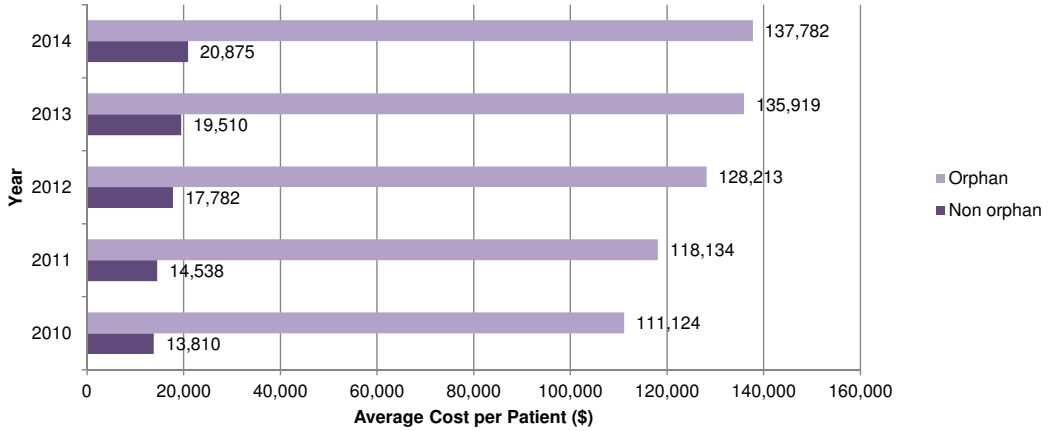
**Note:** Industry sales based on Top 500 pharmaceutical and biotech companies.
Sales to 2013 based on company reported sales data. Sales forecasts to 2020 based on a consensus of leading equity analysts' estimates for company product sales and segmental sales.
All sales analysis based on EvaluatePharma®'s clean 'Orphan' sub-set of products, as defined in the Overview section.

# Top 100 USA Drug Cost per Patient per Year 2010-14

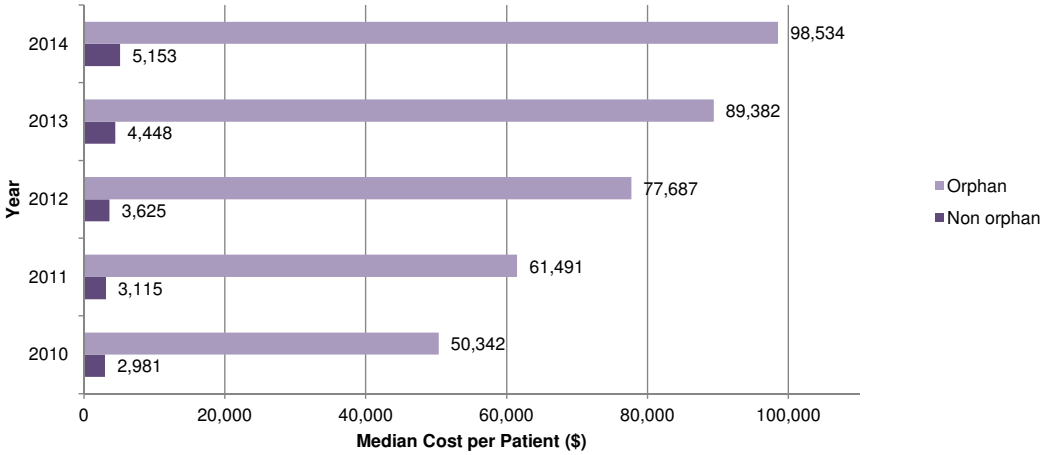
EvaluatePharma®

**Average Orphan Drug Cost to Patients $137,782 in 2014; Median Orphan Drug Cost $98,534**
EvaluatePharma® estimates that the average cost per patient per year in 2014 for an orphan drug was $137,782 versus $20,875 for a non orphan drug. The average and median drug price has increased year on year for both orphan and non orphan drugs since 2010.
The median price differential between an orphan and non orphan drug in 2014 was 19.1.
The median price of orphan drugs has almost doubled since 2010, while non orphans have increased by a factor of 1.7.

**Average Cost per Patient per Year 2010-14**
*Source: EvaluatePharma® (27 OCT 2014)*




**Median Cost per Patient per Year 2010-14**
*Source: EvaluatePharma® (27 OCT 2014)*




**Top 100 Orphan and non Orphan USA Drugs by Sales**
**Average and Median Cost per Patient per Year 2010-14**

| Average Cost per Patient ($) per year | 2010 | 2011 | 2012 | 2013 | 2014 | CAGR |
|---|---|---|---|---|---|---|
| Orphan | 111,124 | 118,134 | 128,213 | 135,919 | 137,782 | 5.5% |
| *Growth per Year* | | *6.3%* | *8.5%* | *6.0%* | *1.4%* | |
| Median price | 50,342 | 61,491 | 77,687 | 89,382 | 98,534 | |
| Non orphan | 13,810 | 14,538 | 17,782 | 19,510 | 20,875 | 10.9% |
| *Growth per Year* | | *5.3%* | *22.3%* | *9.7%* | *7.0%* | |
| Median price | 2,981 | 3,115 | 3,625 | 4,448 | 5,153 | |
| Median Price Differential (orphan/ non ophan) | 16.9 | 19.7 | 21.4 | 20.1 | 19.1 | |
| | | | Median price increase 2010-14: | | | |
| | | | | Orphan: | 1.96 | |
| | | | | Non orphan: | 1.73 | |

*Source: EvaluatePharma® (27 OCT 2014)*

**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 2014.

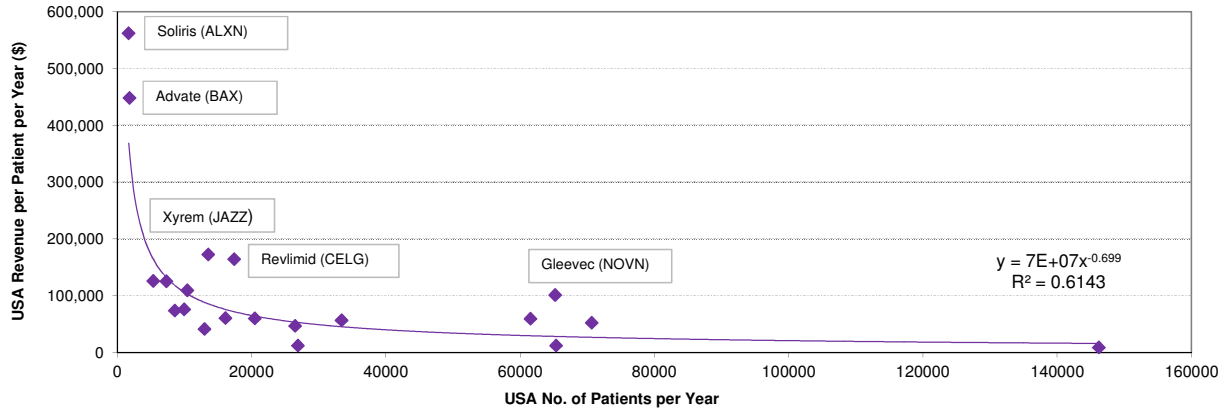
# 2014: USA Revenue per Patient per Year for Top 20 Selling Orphan Drugs

**Soliris Highest Revenue Orphan Drug in 2014; Revenue per Patient and Number of Patients Treated Moderately Correlated; Ultra Rare Drugs: Closer Correlation of Drug Price and Patient Numbers; Revlimid and Gleevec Priced at a Premium**

EvaluatePharma® finds that revenue per patient for the Top 20 USA selling orphan drugs is moderately correlated ($R^2 = 0.61$) to the number of patients treated in 2014. A similar analysis of the Top 10 selling Ultra Rare drugs confirms a closer correlation ($R^2 = 0.85$). 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, Advate and Cinryze confirm the pricing power resulting from ultra rare indications.

**Top 20 USA Orphan Drugs in 2014 by Sales; Revenue per Patient vs. No. of Patients Treated**

*Source: EvaluatePharma® (27 OCT 2014)*



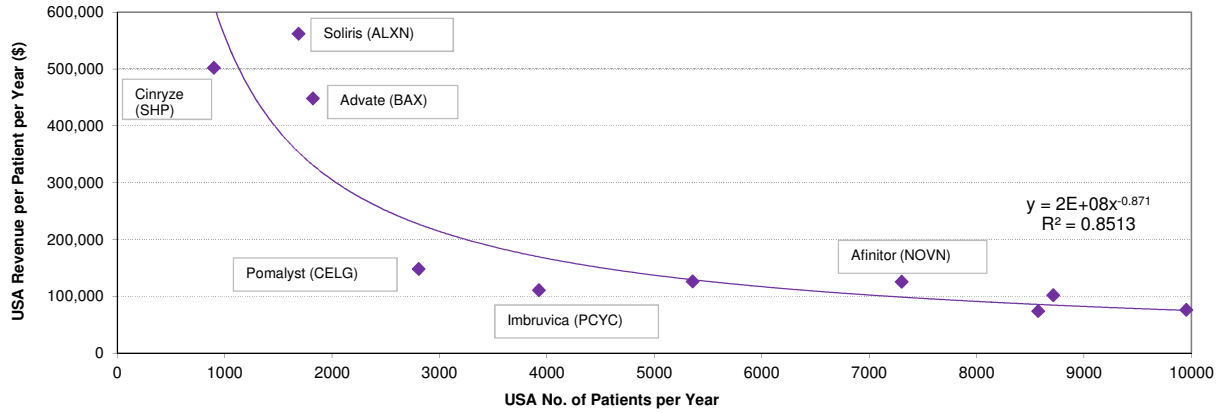

**USA Top 10 Selling Orphan Drugs in 2014 by Sales**

| Rank | Product | Generic Name | Company | USA Sales ($m) 2014 | Revenues per Patient 2014* | No. of Patients 2014 |
|---|---|---|---|---|---|---|
| 1 | **Rituxan** | rituximab | Roche | 3,707 | 52,454 | 70,679 |
| 2 | **Revlimid** | lenalidomide | Celgene | 2,865 | 164,859 | 17,380 |
| 3 | **Copaxone** | glatiramer acetate | Teva Pharmaceutical Industries | 2,700 | 59,862 | 61,533 |
| 4 | **Gleevec** | imatinib mesylate | Novartis | 2,023 | 101,442 | 65,240 |
| 5 | **Avonex** | interferon beta-1a | Biogen Idec | 1,908 | 57,124 | 33,406 |
| 6 | **Alimta** | pemetrexed disodium | Eli Lilly | 1,251 | 47,300 | 26,453 |
| 7 | **Rebif** | interferon beta-1a | Merck KGaA | 1,238 | 60,571 | 20,442 |
| 8 | **Velcade** | bortezomib | Takeda | 983 | 61,053 | 16,093 |
| 9 | **NovoSeven/ NovoSeven RT** | eptacog alfa | Novo Nordisk | 829 | 12,686 | 65,348 |
| 10 | **Advate** | factor VIII (procoagulant) | Baxter International | 816 | 448,653 | 1,820 |

*Source: EvaluatePharma® (27 OCT 2014)*

**Top 10 Ultra Rare USA Orphan Drugs in 2014 by Sales; Revenue per Patient vs. No. of Patients Treated**

*Source: EvaluatePharma® (27 OCT 2014)*




**Note:** Sales represent company reported sales where available, otherwise based on an average of equity analyst estimates.
USA sales represent sales for all indications.
EvaluatePharma® used Alexion Pharmaceutical's definition of an ultra rare orphan drug, disease affecting fewer than 20 individuals per million of population (0.2 per 10,000).
*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.

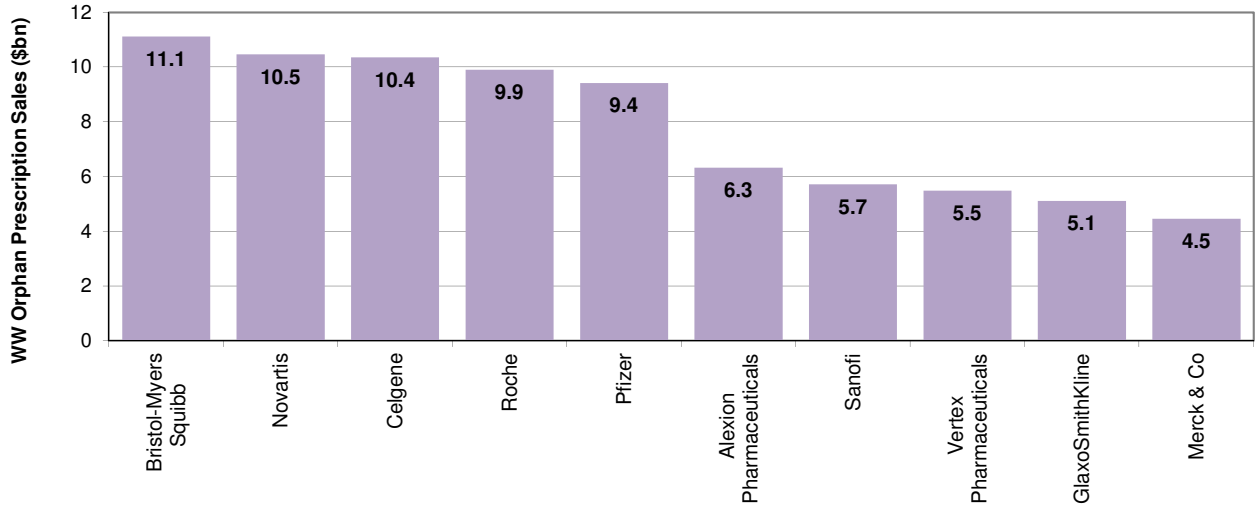
# Worldwide Orphan Drug Sales in 2020: Top 20 Companies

EvaluatePharma®

**Bristol-Myers Squibb to Overtake Novartis as Number One in Orphan Drug Sales in 2020**
**Alexion and Vertex Set to March up the Orphan Sales Ranking Table**

EvaluatePharma® finds that Bristol-Myers Squibb will overtake Novartis as the world's number one orphan drug company in 2020, climbing up 12 places, and pushing Novartis down to number two.
Bristol-Myers Squibb's total sales from orphan drugs is set to reach $11.1bn in 2020, with $6bn coming from Opdivo alone.
Celgene maintains its place in third position with $10.4bn in sales in 2020 due mainly to Revlimid.
Pharmacyclics enters the top 20 due entirely to its single product, Imbruvica.
Within Global Majors, Roche is down two places to 4th, Pfizer down one place to 5th, GlaxoSmithKline up six to 9th.

**WW Orphan Prescription Drug Sales in 2020: Top 10 Companies**
*Source: EvaluatePharma® (27 OCT 2014)*




**Worldwide Orphan Drug Sales (2013/2020): Top 20 Companies & Total Market**

| | Company | WW Orphan Sales ($bn) 2013 | 2020 | % CAGR 13-20 | WW Market Share 2013 | 2020 | Chg. (+/-) | Rank Chg. (+/-) |
|---|---|---|---|---|---|---|---|---|
| 1 | **Bristol-Myers Squibb** | **2.3** | **11.1** | 26% | 2.3% | 6.3% | +4.0% | +12 |
| 2 | **Novartis** | **11.3** | **10.5** | -1% | +12% | 5.9% | -5.7% | -1 |
| 3 | **Celgene** | **5.7** | **10.4** | 9% | 5.9% | 5.9% | -0.0% | - |
| 4 | **Roche** | **9.5** | **9.9** | 1% | +10% | 5.6% | -4.3% | -2 |
| 5 | **Pfizer** | **5.3** | **9.4** | 9% | 5.4% | 5.4% | -0.1% | -1 |
| 6 | **Alexion Pharmaceuticals** | **1.6** | **6.3** | 22% | +2% | 3.6% | +2.0% | +13 |
| 7 | **Sanofi** | **3.3** | **5.7** | 8% | 3.4% | 3.2% | -0.2% | - |
| 8 | **Vertex Pharmaceuticals** | **0.4** | **5.5** | 47% | +0% | 3.1% | 2.7% | +24 |
| 9 | **GlaxoSmithKline** | **1.9** | **5.1** | 15% | 2.0% | 2.9% | +0.9% | +6 |
| 10 | **Merck & Co** | **1.3** | **4.5** | 19% | +1% | 2.5% | +1.2% | +10 |
| 11 | **Johnson & Johnson** | **2.1** | **4.2** | 11% | 2.1% | 2.4% | +0.2% | +3 |
| 12 | **Baxter International** | **3.3** | **4.0** | 3% | +3% | 2.3% | -1.1% | -4 |
| 13 | **Novo Nordisk** | **2.7** | **3.9** | 5% | 2.8% | 2.2% | -0.6% | -1 |
| 14 | **Bayer** | **4.2** | **3.8** | -1% | +4% | 2.2% | -2.2% | -8 |
| 15 | **Eli Lilly** | **3.0** | **3.7** | 3% | 3.1% | 2.1% | -1.0% | -4 |
| 16 | **Pharmacyclics** | **0.0** | **3.6** | 122% | +0% | 2.0% | +2.0% | +65 |
| 17 | **Shire** | **1.8** | **3.5** | 10% | 1.8% | 2.0% | +0.2% | - |
| 18 | **Actelion** | **1.9** | **3.3** | 9% | +2% | 1.9% | -0.1% | -2 |
| 19 | **Amgen** | **1.6** | **3.3** | 11% | 1.6% | 1.9% | +0.2% | -1 |
| 20 | **Biogen Idec** | **3.0** | **2.8** | -1% | +3% | 1.6% | -1.5% | -10 |
| | **Total Top 20** | **66.0** | **114.5** | +8.2% | 68.3% | 65.1% | -3.2% | |
| | **Other** | **30.7** | **61.5** | +10.4% | 31.7% | 34.9% | | |
| | **Total** | **96.6** | **176.0** | +8.9% | 100.0% | 100.0% | | |

*Source: EvaluatePharma® (27 OCT 2014)*

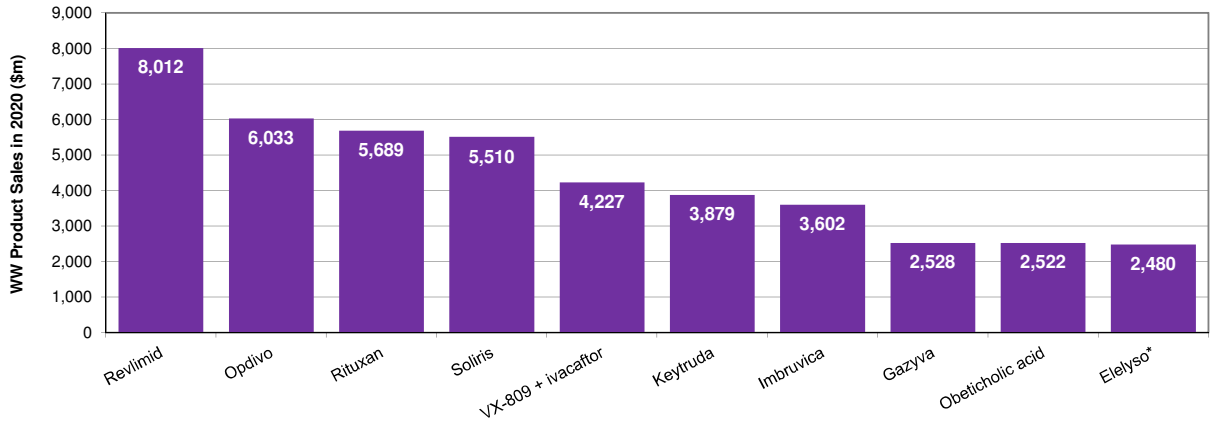
**Note:** All sales analysis based on EvaluatePharma®'s clean 'Orphan' sub-set of products, as defined in the Overview section.

# 2020: Top 20 Selling Orphan Drugs in the World

EvaluatePharma®

**Revlimid (lenalidomide) No.1 Orphan Drug in 2020**
EvaluatePharma® finds that Revlimid is the world's largest orphan drug in 2020, with sales of $8bn 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 diseases Non-Hodgkin's lymphoma and multiple myeloma and remains in development for a number of other orphan conditions.
Bristol-Myers Squibb's Opdivo for multiple myeloma & Hodgkin's lymphoma is set to be a distant second with $6bn in worldwide sales.

**Top 10 Selling Orphan Drugs in 2020 by Worlwide Sales**
*Source: EvaluatePharma® (27 OCT 2014)*




**Worldwide Top 20 Selling Orphan Drugs in 2020**

| | | | | | | WW Product Sales ($m) | | |
|---|---|---|---|---|---|---|---|---|
| Rank | Product | Generic Name | Company | Phase (Current) | Pharmacological Class | 2013 | 2020 | CAGR |
| 1 | **Revlimid** | lenalidomide | Celgene | Marketed | Immunomodulator | 4,280 | **8,012** | +9% |
| 2 | **Opdivo** | nivolumab | Bristol-Myers Squibb | Marketed | Anti-programmed death-1 (PD-1) MAb | - | **6,033** | n/a |
| 3 | **Rituxan** | rituximab | Roche | Marketed | Anti-CD20 MAb | 7,503 | **5,689** | -4% |
| 4 | **Soliris** | eculizumab | Alexion Pharmaceuticals | Marketed | Anti-complement factor C5 MAb | 1,551 | **5,510** | +20% |
| 5 | **VX-809 + ivacaftor** | ivacaftor; lumacaftor | Vertex Pharmaceuticals | Phase III | Cystic fibrosis transmembrane conductance regulator (CFTR) corrector | - | **4,227** | n/a |
| 6 | **Keytruda** | pembrolizumab | Merck & Co | Approved | Anti-programmed death-1 (PD-1) MAb | - | **3,879** | n/a |
| 7 | **Imbruvica** | ibrutinib | Pharmacyclics | Marketed | Bruton's tyrosine kinase (BTK) inhibitor | 14 | **3,602** | +122% |
| 8 | **Gazyva** | obinutuzumab | Roche | Marketed | Anti-CD20 MAb | 3 | **2,528** | +159% |
| 9 | **Obeticholic acid** | obeticholic acid | Intercept Pharmaceuticals | Phase III | Farnesoid X receptor (FXR) agonist | - | **2,522** | n/a |
| 10 | **Elelyso*** | taliglucerase alfa | Pfizer | Marketed | Glucocerebrosidase | 49 | **2,480** | +75% |
| 11 | **Tasigna** | nilotinib hydrochloride monohydrate | Novartis | Marketed | BCR-ABL tyrosine kinase inhibitor | 1,266 | **2,468** | +10% |
| 12 | **Yervoy** | ipilimumab | Bristol-Myers Squibb | Marketed | Anti-CTLA4 Mab | 960 | **2,377** | +14% |
| 13 | **Pomalyst** | pomalidomide | Celgene | Marketed | Immunomodulator | 305 | **2,097** | +32% |
| 14 | **Alimta** | pemetrexed disodium | Eli Lilly | Marketed | Thymidylate synthase inhibitor | 2,703 | **2,057** | -4% |
| 15 | **DCVax-L*** | - | Northwest Biotherapeutics | Phase III | Cancer vaccine | - | **2,046** | n/a |
| 16 | **Kyprolis** | carfilzomib | Amgen | Marketed | Proteasome inhibitor | 73 | **1,943** | +60% |
| 17 | **Avonex** | interferon beta-1a | Biogen Idec | Marketed | Interferon beta | 3,005 | **1,885** | -6% |
| 18 | **Sprycel** | dasatinib | Bristol-Myers Squibb | Marketed | Tyrosine kinase inhibitor | 1,280 | **1,815** | +5% |
| 19 | **NovoSeven/ NovoSeven RT** | eptacog alfa | Novo Nordisk | Marketed | Factor VII | 1,649 | **1,810** | +1% |
| 20 | **Imbruvica** | ibrutinib | Johnson & Johnson | Marketed | Bruton's tyrosine kinase (BTK) inhibitor | - | **1,741** | n/a |
| | **Other** | | | | | **65,437** | **111,256** | +7% |
| | **Total** | | | | | **90,079** | **175,977** | +11% |

*Source: EvaluatePharma® (27 OCT 2014)*

**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.

# Phase III Trial Size & Approval Time: Orphan vs. Non-Orphan

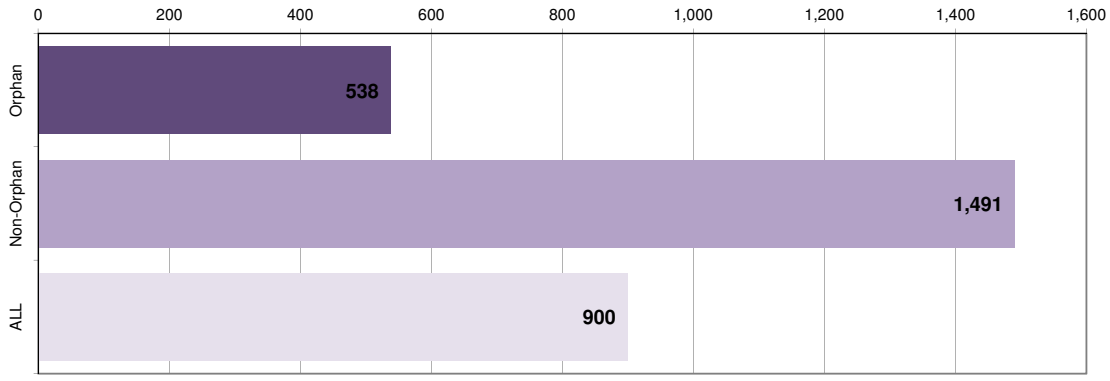
EvaluatePharma®

**Phase III Orphan Drug Development Cost Half that of Non-Orphan; Potentially a Quarter with US Tax Breaks**
**Phase III Drug Development Time for Orphan is No Quicker than Non-Orphan**
**Orphan Drug FDA Approval Time 10.2 months vs. 13.0 months for Non-Orphan**

EvaluatePharma® estimates that the average phase III clinical trial cost for an orphan drug is roughly half that of non-orphan drugs at $99m, vs. $188m for a non-orphan. In addition, with 50% US tax credit, available via the Orphan Drug Act, the potential cost could be a quarter of non-orphan at $49m vs. $188m for non-orphans.

Orphan drugs required a median 538 patients for phase III trials, versus a median 1,491 patients for non-orphan drugs. The average phase III trial sizes came in at 731 patients for orphan drugs versus 3,540 for non-orphans. EvaluatePharma® found that there was no statistically significant difference in phase III trial length, at a median of 2.89 years. Median FDA approval times were 10 months for orphan vs. 13 months for non-orphans, due to orphans tending to receive Priority Review.

**Phase III Trials Sizes: Orphan vs. Non-Orphan**
*Source: EvaluatePharma® (27 OCT 2014)*

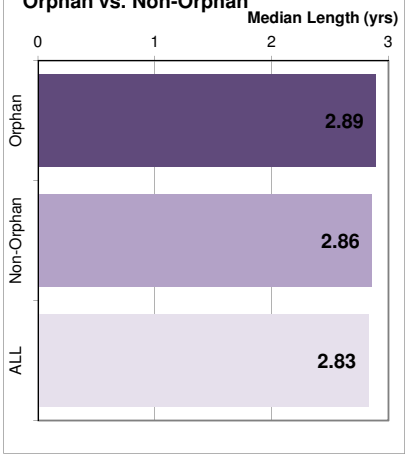



**Average Phase III Trials Sizes (All New Drug Products Entering Phase III from 1 JAN 2000)**

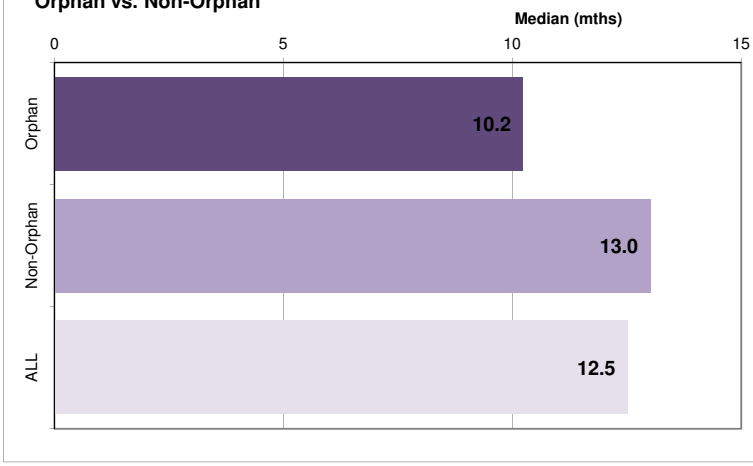
| | Phase III Trial Size | | | | | Phase III Cost ($m) Estimated | | | Potential 50% US Tax Credit | |
|---|---|---|---|---|---|---|---|---|---|---|
| Product Type | Median | Average | No. of Products (n=) | Total Patients | % of | Median | Average | Total | Median | Average |
| **Orphan** | 538 | 731 | 421 | 307,620 | 9% | 97 | 99 | 41,487 | 48 | 49 |
| **Non-Orphan** | 1,491 | 3,540 | 890 | 3,150,830 | 91% | 143 | 188 | 167,717 | 143 | 188 |
| **ALL** | 900 | 2,638 | 1,311 | 3,458,450 | **100%** | 122 | 160 | 209,204 | | |
| *Orphan / Non-Orphan =* | *36.1%* | *20.6%* | *47.3%* | | | *67.6%* | *52.3%* | *24.7%* | *33.8%* | *26.1%* |

Source: EvaluatePharma® Success Rates (27 OCT 2014)

**Phase III Trials Length (yrs): Orphan vs. Non-Orphan**




**FDA Approval Time: Orphan vs. Non-Orphan**




**Average Phase III & FDA Approval Times**

| | Phase III Length (yrs) | | | FDA Filed to Approved (mths) | | |
|---|---|---|---|---|---|---|
| Product Type | Median | Average | No. of Products (n=) | Median | Average | No. of Products (n=) |
| **Orphan** | 2.89 | 3.55 | 173 | 10.24 | 10.65 | 210 |
| **Non-Orphan** | 2.86 | 3.22 | 415 | 13.02 | 12.75 | 497 |
| **ALL** | 2.83 | 3.32 | 588 | 12.53 | 12.13 | 707 |
| *Orphan / Non-Orphan* | *+1.1%* | *+10.0%* | | *-21.3%* | *-16.5%* | |

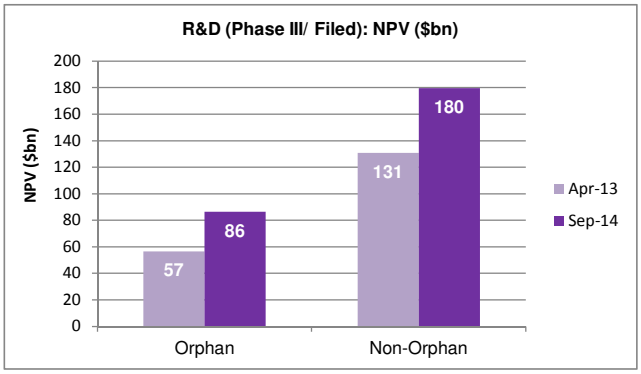
*Source: Provisional Data from EvaluatePharma®'s Forthcoming Success Rates & Clinical Trial Timelines (27 OCT 2014)*

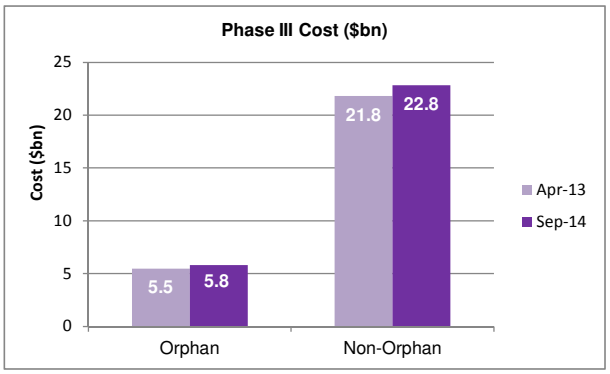
**Note:** Analysis based on Lead indication. An analysis using supplementary indications yielded comparable trends.

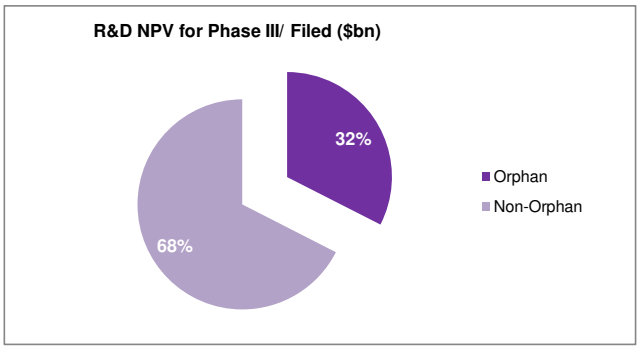
# R&D Costs (PIII/Filed) & Expected Investment Returns (NPV)

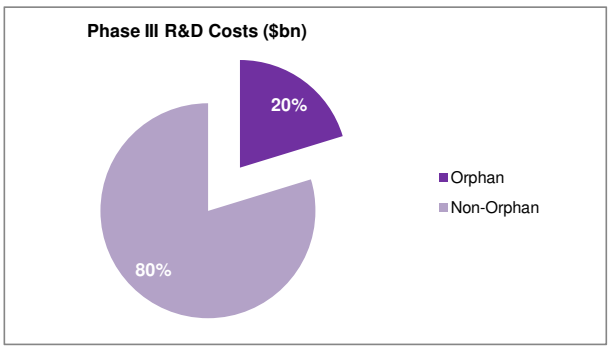
EvaluatePharma®

**Expected Return on Investment of Phase III/ Filed Orphan Drugs 1.89 Times Greater than Non-Orphan Drugs**
**Phase III/ Filed Orphan Drugs are 20% of Industry Phase III R&D Spend, but 32% of the Value Creation in the Industry**
EvaluatePharma® finds that the current value, based on NPV, of pipeline phase III/ filed orphan drugs is $86bn versus $180bn for non orphans. When looking at the industry's expected phase III costs to bring all products to market, orphan drugs cost $5.8bn versus $22.8bn for non orphans. We have not assumed any US tax credits in the calculation. The main difference in cost is driven by the differing phase III trial sizes, with all current phase III/ filed orphans set to require a total of 35,367 patients for phase III trials, versus 497,013 patients for non-orphans.
The current expected return on investment can be calculated taking the NPV divided by the phase III cost. The industry's expected return on orphan drugs is almost double (14.9 times) the investment (phase III), versus 7.9 times the investment on non-orphans. The cost of running a Phase III trial has remained relatively constant across both drug categories year on year but the NPV attached to these assets has increased.




| Value Creation (NPV) for NMEs<br>Phase III/ Filed with NPV | | | | | | Phase III Clinical Trial Cost (estimated)<br>Available Current Phase III Costs | | | | Expected Return<br>NPV minus Phase III Cost | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Type | NPV ($bn) 2013 | NPV ($bn) 2014 | As a % | Avg. Product NPV ($m) | No. of Products (n=) | No. of Patients | Phase III Cost ($bn) | As a % | No. of Products (n=) | Net Return NPV - Phase III Cost | NPV/ Phase III Cost |
| Orphan | 57 | 86 | 32% | 1,005 | 86 | 35,367 | 5.8 | 20% | 61 | +80.6 | 14.9 |
| Non-Orphan | 131 | 180 | 68% | 1,044 | 172 | 497,013 | 22.8 | 80% | 104 | +156.7 | 7.9 |
| **Total** | **187** | **266** | **100%** | **1,031** | 258 | **532,380** | **28.7** | **100%** | 165 | **+237.4** | **9.3** |
| *Orphan/ Non-Orphan* | *+43.3%* | *+48.1%* | | *+96.3%* | *+50.0%* | *+7.1%* | *+25.4%* | | *+58.7%* | *+51.5%* | |
| *Orphan/ Total* | *+30.2%* | *+32.5%* | | *+97.5%* | *+33.3%* | *+6.6%* | *+20.3%* | | *+37.0%* | *+34.0%* | |

*Investment Return Relative to Non-Orphan* **1.89**

*Source: Provisional Data from EvaluatePharma®'s Forthcoming Success Rates & Clinical Trial Timelines (OCT 2014)*

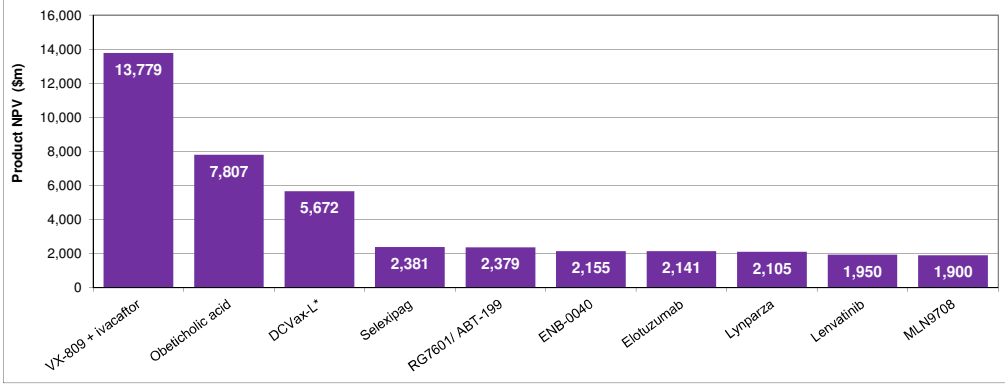
**Note:** The sample size for product NPVs (n=258) is greater than the estimates of phase III trial sizes (n=165). This is due to NPVs being split by licensing deals. Not all products have an estimate of Phase III trial costs, mainly due to the fact certain products entered Phase III prior to 1 JAN 2000 (the current starting date of EvaluatePharma®'s Success Rate Model).
Phase III trial costs have been estimated based on an algorithm using cost per patient per year.

# 2020: Top 20 Orphan R&D Products based on NPV

EvaluatePharma®

**Vertex's VX-809 + Ivacaftor World's Most Valuable R&D Orphan Drug**
EvaluatePharma® finds that Vertex's cystic fibrosis transmembrane conductance regulator (CFTR) corrector in development for cystic fibrosis, is the world's most promising R&D orphan drug, with an NPV of $13.8bn. 32% of the total orphan NPV is attributed to the top 3 ranked products. Novartis, AstraZeneca and Vertex each have two products ranked in the top 20 (Vertex products include VX-809 and combination with ivacaftor).

**Top 10 Orphan Drugs in 2020 (Phase III/ Filed) by NPV**
*Source: EvaluatePharma® (27 OCT 2014)*




**Worldwide Top 20 Orphan R&D Products based on NPV (Sales, NPV, PIII Cost & Expected Return)**

| Rank | Product | Company | Phase (Current) | Pharma Class | Sales ($m) 2020 | WW NPV | R&D PIII Cost $m) | Phase III Trial Size | Return NPV/ PIII Cost | Strategy |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **VX-809 + ivacaftor** | Vertex Pharmaceuticals | Phase III | Cystic fibrosis transmembrane conductance regulator (CFTR) corrector | 4,227 | **13,779** | 101 | 1,002 | 136 | Organic |
| 2 | **Obeticholic acid** | Intercept Pharmaceuticals | Phase III | Farnesoid X receptor (FXR) agonist | 2,522 | **7,807** | 78 | 180 | 100 | Organic |
| 3 | **DCVax-L*** | Northwest Biotherapeutics | Phase III | Cancer vaccine | 2,046 | **5,672** | 87 | 300 | 65 | Organic |
| 4 | **Selexipag** | Actelion | Phase III | Prostacyclin I2 (PGI-2) receptor agonist | 1,272 | **2,381** | 184 | 1,820 | 13 | In-licensed |
| 5 | **RG7601/ ABT-199** | AbbVie | Phase III | B-cell lymphoma 2 (Bcl-2) inhibitor | 790 | **2,379** | 107 | 370 | 22 | Organic |
| 6 | **ENB-0040** | Alexion Pharmaceuticals | Filed | Alkaline phosphatase enzyme therapy | 816 | **2,155** | 13 | 30 | 166 | Company acquisition |
| 7 | **Elotuzumab** | Bristol-Myers Squibb | Phase III | Anti-signalling lymphocyte activation molecule (SLAMF7) MAb | 711 | **2,141** | 141 | 1,390 | 15 | In-licensed |
| 8 | **Lynparza** | AstraZeneca | Filed | Poly (ADP-ribose) polymerase (PARP) inhibitor | 666 | **2,105** | 298 | 2,940 | 7 | Company acquisition |
| 9 | **Lenvatinib** | Eisai | Filed | Vascular endothelial growth factor receptor (VEGFr) tyrosine kinase inhibitor | 737 | **1,950** | 104 | 360 | 19 | Organic |
| 10 | **MLN9708** | Takeda | Phase III | Proteasome inhibitor | 663 | **1,900** | 112 | 703 | 17 | Company acquisition |
| 11 | **VX-809** | Vertex Pharmaceuticals | Phase III | Cystic fibrosis transmembrane conductance regulator (CFTR) corrector | 736 | **1,827** | 101 | 1,002 | 18 | Company acquisition |
| 12 | **Sebelipase alfa** | Synageva BioPharma | Phase III | Lysosomal acid lipase | 813 | **1,697** | 22 | 50 | 78 | Organic |
| 13 | **CDX-110** | Celldex Therapeutics | Phase III | EGFr cancer vaccine | 502 | **1,695** | 127 | 440 | 13 | Company acquisition |
| 14 | **Algenpantucel-L** | NewLink Genetics | Phase III | Cancer vaccine | 540 | **1,544** | 101 | 1,002 | 15 | Organic |
| 15 | **Farydak** | Novartis | Filed | Pan-deacetylase inhibitor | 448 | **1,543** | 122 | 768 | 13 | Organic |
| 16 | **Patisiran** | Alnylam Pharmaceuticals | Phase III | Transthyretin RNAi therapeutic | 537 | **1,488** | 87 | 200 | 17 | Organic |
| 17 | **TKI258** | Novartis | Phase III | VEGFr 1-3, FGFr 1-3, platelet-derived growth factor receptor (PDGFr) & angiogenesis RTK inhibitor | 329 | **1,438** | 88 | 550 | 16 | Company acquisition |
| 18 | **Daratumumab** | Johnson & Johnson | Phase III | Anti-CD38 MAb | 436 | **1,431** | 80 | 500 | 18 | In-licensed |
| 19 | **Tremelimumab** | AstraZeneca | Phase III | Anti-CTLA4 Mab | 400 | **1,427** | 104 | 655 | 14 | In-licensed |
| 20 | **Gevokizumab** | XOMA | Phase III | Anti-interleukin-1 beta (IL-1b) MAb | 536 | **1,378** | 87 | 300 | 16 | Organic |
| | **Other** | | | | **7,280** | **28,721** | | | | |
| | **Total** | | | | **27,008** | **86,457** | **5,813** | **35,367** | **14.9** | |
| | | | | **vs. Non-Orphan:** | **57,632** | **179,581** | **22,842** | **497,013** | **7.9** | |

*Source: EvaluatePharma® (27 OCT 2014)*

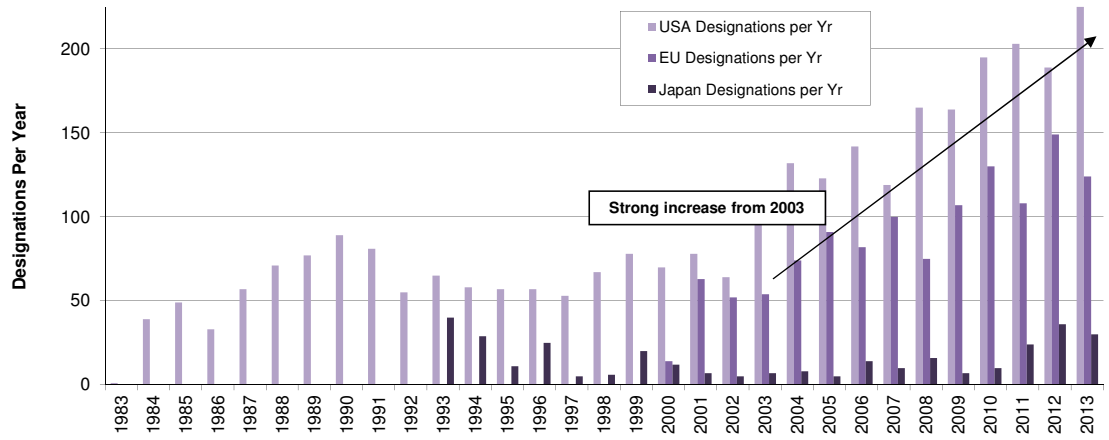
**Note:** * Forecast based on a single broker model.
Sales represent company reported sales where available, otherwise based on an average of equity analyst estimates.
Phase III trial costs represent an assumption on current phase III trial size for lead indication(s), derived from the enrolment size listed on clinicaltrials.gov via Evaluate Clinical Trials.
Factor VIII products for haemophilia A & B classified as orphan drugs.

# USA, EU & Japan Orphan Designations per Year & Cumulative (1983-13)

EvaluatePharma®

**FDA Orphan Designations Increase 38% in 2013; European Designations down 17%; Japan Designations down 17%.** EvaluatePharma® found that the number of US orphan drug designations increased 38% in 2013 to 260, the highest number of designations seen so far, reversing the decline seen in 2011. European orphan designations declined 17% to 124. After a record year in 2012, orphan designations in Japan also declined 17% to 30 designations.

**USA, EU & Japan Designation per Year (1983-2013)**
*Source: EvaluatePharma® (27 OCT 2014)*

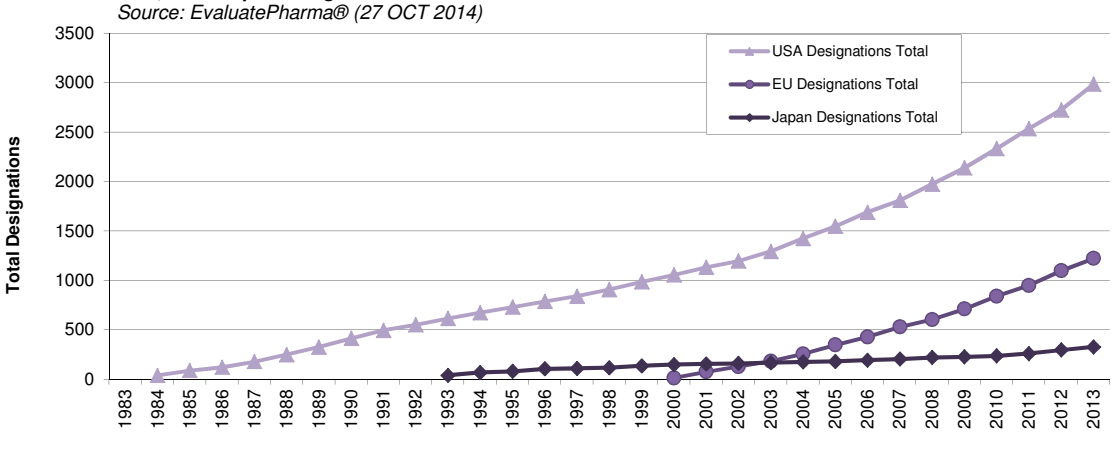



**US, EU & Japan Orphan Designations per Year (2000-13)**

| Orphan Designations | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Year | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 |
| USA OD Applications | 88 | 129 | 115 | 167 | 174 | 174 | 191 | 181 | 185 | 250 | 323 | 306 | 264 | 346 |
| *Growth per Year* | | *+47%* | *-11%* | *+45%* | *+4%* | *+0%* | *+10%* | *-5%* | *+2%* | *+35%* | *+29%* | *-5%* | *-14%* | *+31%* |
| USA Designations Accepted | 70 | 78 | 64 | 96 | 132 | 123 | 142 | 119 | 165 | 164 | 195 | 203 | 189 | 260 |
| *Growth per Year* | | *+11%* | *-18%* | *+50%* | *+38%* | *-7%* | *+15%* | *-16%* | *+39%* | *-1%* | *+19%* | *+4%* | *-7%* | *+38%* |
| *% Accepted* | | *89%* | *50%* | *83%* | *79%* | *71%* | *82%* | *62%* | *91%* | *89%* | *78%* | *63%* | *62%* | *98%* |
| EU Designations per Yr | 14 | 63 | 52 | 54 | 74 | 91 | 82 | 100 | 75 | 107 | 130 | 108 | 149 | 124 |
| *Growth per Year* | | | *-17%* | *+4%* | *+37%* | *+23%* | *-10%* | *+22%* | *-25%* | *+43%* | *+21%* | *-17%* | *+38%* | *-17%* |
| Japan Designations per Yr | 12 | 7 | 5 | 7 | 8 | 5 | 14 | 10 | 16 | 7 | 10 | 24 | 36 | 30 |
| *Growth per Year* | | *-42%* | *-29%* | *+40%* | *+14%* | *-38%* | *+180%* | *-29%* | *+60%* | *-56%* | *+43%* | *+140%* | *+50%* | *-17%* |

*Source: EvaluatePharma® (27 OCT 2014); USA OD applications per year from PAREXEL Consulting*

**USA, EU & Japan Designations Cumulative Total**
*Source: EvaluatePharma® (27 OCT 2014)*




**Cumulative US, EU & Japan Orphan Designations & US Approvals per Year (2000-13)**

| Orphan Designations Cumulative Total | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Year | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 |
| USA Designations Total | 1,057 | 1,135 | 1,199 | 1,295 | 1,427 | 1,550 | 1,692 | 1,811 | 1,976 | 2,140 | 2,335 | 2,538 | 2,727 | 2,987 |
| *Growth per Year* | | *+7%* | *+6%* | *+8%* | *+10%* | *+9%* | *+9%* | *+7%* | *+9%* | *+8%* | *+9%* | *+9%* | *+7%* | *+10%* |
| EU Designations Total | 14 | 77 | 129 | 183 | 257 | 348 | 430 | 530 | 605 | 712 | 842 | 950 | 1,099 | 1,223 |
| *Growth per Year* | | | *+68%* | *+42%* | *+40%* | *+35%* | *+24%* | *+23%* | *+14%* | *+18%* | *+18%* | *+13%* | *+16%* | *+11%* |
| Japan Designations Total | 148 | 155 | 160 | 167 | 175 | 180 | 194 | 204 | 220 | 227 | 237 | 261 | 297 | 327 |
| *Growth per Year* | | *+5%* | *+3%* | *+4%* | *+5%* | *+3%* | *+8%* | *+5%* | *+8%* | *+3%* | *+4%* | *+10%* | *+14%* | *+10%* |

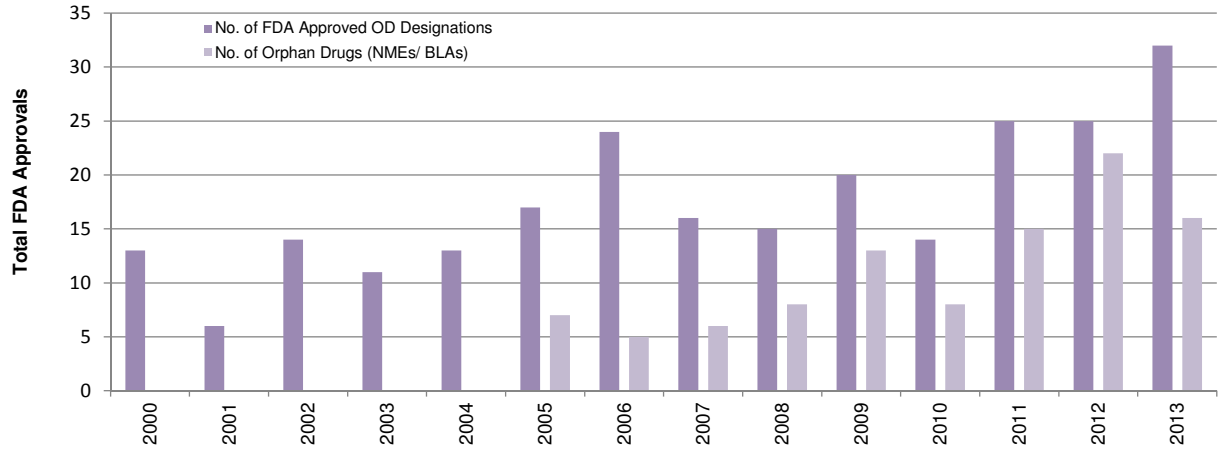
*Source: EvaluatePharma® (27 OCT 2014)*

# FDA Approvals of Designations & New Drugs (NMEs/BLAs): 2000 to 2013

EvaluatePharma®

**FDA Approves 16 New Orphan Drugs in 2013 vs. 22 in 2012; Orphans 46% of Total FDA New Drug Approvals in 2013**
**FDA Approves 32 Designations in 2013 vs. 25 in 2012.**
EvaluatePharma® finds that 16 new orphan drugs (NMEs/ BLAs and biologicals) were approved in 2013 out of 35 new drugs.
Orphan drugs represented 46% of the industry's new drug output in 2013.
Overall the FDA approved 32 designations in 2013 vs. 2012. This includes new indication approvals of already marketed products.

**FDA Orphan Drug Marketing Approvals & Orphan Drugs New Drugs (NMEs/ BLAs)**
*Source: EvaluatePharma® (27 OCT 2014)*




**FDA Approved Orphan Designations & Drugs**

| Year | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of FDA Approved OD Designations | 13 | 6 | 14 | 11 | 13 | 17 | 24 | 16 | 15 | 20 | 14 | 25 | 25 | 32 |
| *% Chg.* | | *-54%* | *+133%* | *-21%* | *+18%* | *+31%* | *+41%* | *-33%* | *-6%* | *+33%* | *-30%* | *+79%* | *+0%* | *+28%* |
| No. of Orphan Drugs (NMEs/ BLAs) | | | | | | 7 | 5 | 6 | 8 | 13 | 8 | 15 | 22 | 16 |
| *% Chg.* | | | | | | | *-29%* | *+20%* | *+33%* | *+63%* | *-38%* | *+88%* | *+47%* | *-27%* |
| *NME - Orphans* | | | | | | 6 | 3 | 5 | 6 | 9 | 5 | 11 | 20 | 15 |
| *BLA - Orphans* | | | | | | 1 | 2 | 1 | 2 | 4 | 3 | 4 | 2 | 1 |
| *Biologicals - Orphans* | | | | | | 1 | 2 | 2 | 2 | 6 | 1 | 3 | 1 | 3 |

**Total FDA Approval Count (Orphan & Non-Orphan)**

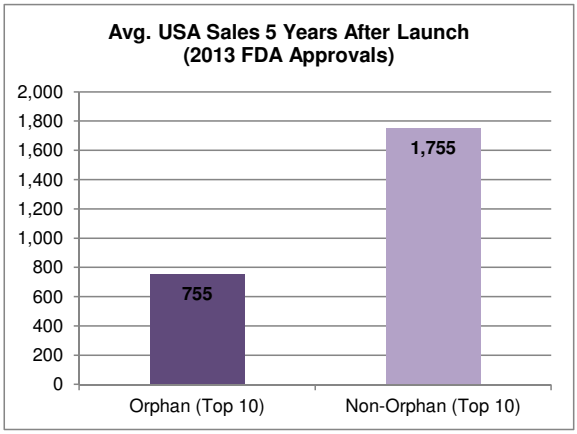
| Year | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of NMEs Approved | 27 | 24 | 17 | 21 | 31 | 18 | 18 | 16 | 21 | 19 | 15 | 24 | 33 | 25 |
| No. of Biologicals Approved | 6 | 8 | 9 | 14 | 7 | 10 | 11 | 10 | 10 | 15 | 11 | 11 | 10 | 10 |
| **Total NMEs + Biologicals** | **33** | **32** | **26** | **35** | **38** | **28** | **29** | **26** | **31** | **34** | **26** | **35** | **43** | **35** |
| *% Chg.* | | *-3%* | *-19%* | *+35%* | *+9%* | *-26%* | *+4%* | *-10%* | *+19%* | *+10%* | *-24%* | *+35%* | *+23%* | *-19%* |
| No. of Orphan Drugs (NMEs/ BLAs) | | | | | | 7 | 5 | 6 | 8 | 13 | 8 | 15 | 22 | 16 |
| *as a % of Total* | | | | | | *25%* | *17%* | *23%* | *26%* | *38%* | *31%* | *43%* | *51%* | *46%* |

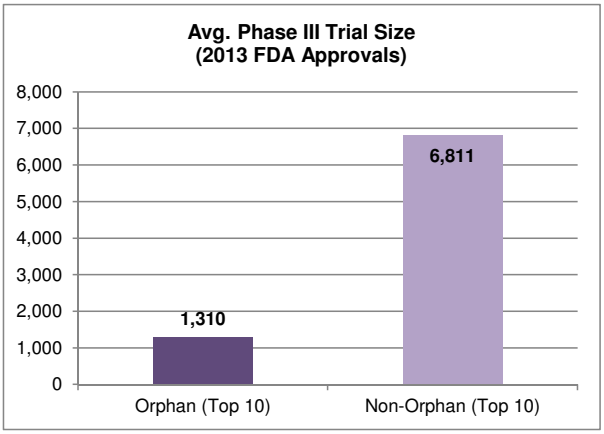
**Note:** Audited orphan drug NME count currently available from 2005+.

# FDA New Drug Approval Analysis (NMEs/ BLAs) 2013: Orphan vs. Non-Orphan

EvaluatePharma®

**Imbruvica Most Promising New Orphan Drug Approved by FDA in 2013**
**Top 10 Orphan Drugs have 43% the Sales Potential of Non-Orphan but Delivered at 50% of the Phase III Trial Cost**
EvaluatePharma® finds that Imbruvica, from Pharmacyclics, for chronic lymphocytic leukaemia is the most promising new orphan drug approved in 2013, with expected US sales in 2018 of $2,365m.
The top 10 orphan drugs approved in 2013 are expected to sell on average $755m in the USA market, five years post launch. This compares with $1,755m for non-orphans approved in 2013.
The average Phase III trial size for the top 10 orphans was 1,310 patients vs 6,811 for top 10 non-orphans approved in 2013.




**Top 10 Orphan New Molecular Entities approved in 2013: Ranked on USA Consensus Sales in 2018**

| | Product | OD Indication | Company | Approved | US Sales ($m) 2013 | US Sales ($m) 2018 | Phase III Trial Size | R&D PIII Cost ($m) |
|---|---|---|---|---|---|---|---|---|
| 1 | **Imbruvica** | Leukaemia, chronic lymphocytic (CLL) | Pharmacyclics | Nov 2013 | 14 | 2,365 | 2,430 | 241 |
| 2 | **Pomalyst** | Leukaemia, chronic lymphocytic (CLL) | Celgene | Feb 2013 | 246 | 1,082 | 792 | 123 |
| 3 | **Gazyva** | Multiple myeloma | Roche | Nov 2013 | 3 | 1,049 | 2,631 | 260 |
| 4 | **Mekinist** | Melanoma | GlaxoSmithKline | May 2013 | 16 | 755 | 1,439 | 142 |
| 5 | **Opsumit** | Pulmonary fibrosis, idiopathic | Actelion | Oct 2013 | 4 | 742 | 1,292 | 128 |
| 6 | **Adempas** | Melanoma | Bayer | Oct 2013 | 4 | 382 | 1,367 | 135 |
| 7 | **Tafinlar** | Pulmonary hypertension | GlaxoSmithKline | May 2013 | 25 | 365 | 1,367 | 135 |
| 8 | **Rixubis** | Haemophilia B | Baxter International | Jun 2013 | 5 | 31 | 250 | 71 |
| 9 | **BAT** | Botulism treatment | Emergent BioSolutions | Mar 2013 | - | 23 | 224 | 95 |
| 10 | - | - | - | - | - | - | - | - |
| **Top 10** | | | | | 316 | 6,794 | 11,792 | 1,330 |
| Other | | | | | 35 | 0 | | |
| **Total** | | | | | **351** | **6,794** | | |
| | | | | *Average for Top 10:* | | *755* | *1,310* | |
| | | | | *As a % of non-orphans:* | | *43%* | *19%* | *50%* |

**Top 10 Non-Orphan New Molecular Entities approved in 2013: Ranked on USA Consensus Sales in 2018**

| | Product | Company | Approved | US Sales ($m) 2013 | US Sales ($m) 2018 | Phase III Trial Size | R&D PIII Cost ($m) |
|---|---|---|---|---|---|---|---|
| 1 | **Sovaldi** | Gilead Sciences | Dec 2013 | 136 | 5,383 | 3658 | 181 |
| 2 | **Tecfidera** | Biogen Idec | Mar 2013 | 864 | 3,769 | 4351 | 215 |
| 3 | **Tivicay** | GlaxoSmithKline | Aug 2013 | 30 | 1,640 | 3269 | 162 |
| 4 | **Kadcyla** | Roche | Feb 2013 | 240 | 1,575 | 2688 | 266 |
| 5 | **Invokana** | Johnson & Johnson | Mar 2013 | 128 | 1,178 | 10979 | 311 |
| 6 | **Xofigo** | Bayer | May 2013 | 54 | 1,078 | 921 | 143 |
| 7 | **Anoro Ellipta** | GlaxoSmithKline | Dec 2013 | - | 1,071 | 5968 | 211 |
| 8 | **Breo Ellipta** | GlaxoSmithKline | May 2013 | 8 | 964 | 27118 | 767 |
| 9 | **Brintellix** | Takeda | Sep 2013 | 9 | 717 | 7707 | 273 |
| 10 | **Aptiom** | Dainippon Sumitomo Pharma | Nov 2013 | - | 171 | 1450 | 144 |
| **Top 10** | | | | 1,470 | 17,545 | 68,109 | 2,673 |
| Other | | | | 44 | 588 | | |
| **Total** | | | | **1,513** | **18,133** | | |
| *Source: EvaluatePharma® (27 OCT 2014)* | | | *Average for Top 10:* | | *1,755* | *6,811* | |

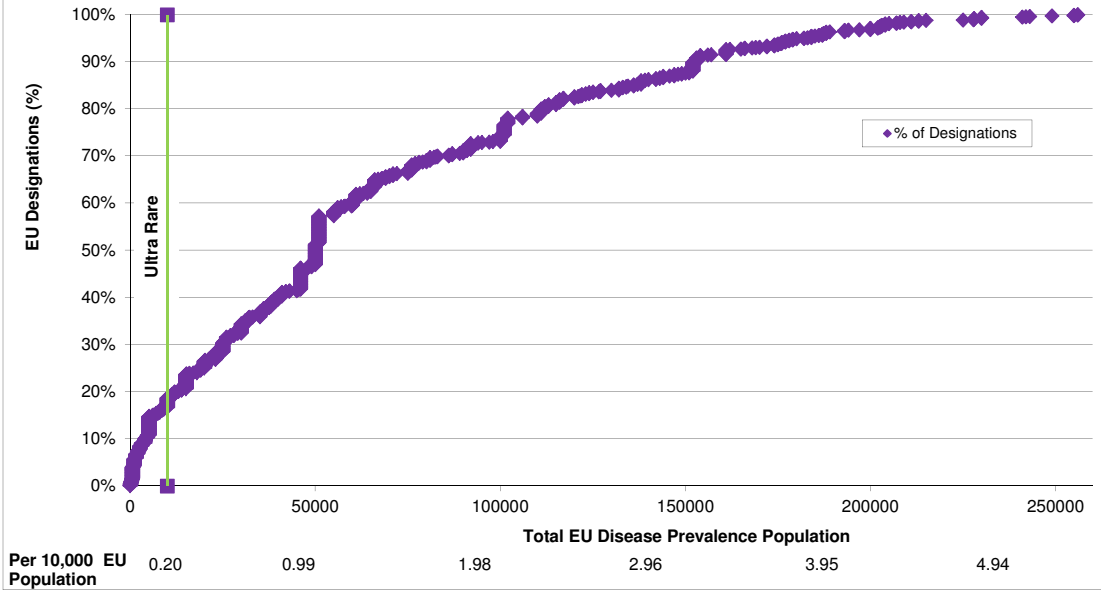
**Note:** USA forecast sales 5 years after launch (2018) were used to rank new molecular entities.

# EU Orphan Designations: Historic Distribution by Prevalence

EvaluatePharma®

**18.7% of EU Orphan Designations for Ultra Rare Diseases**
EvaluatePharma® found that 18.7% (243 out of 1,302) of EU Orphan drug designations are for an ultra rare orphan disease. An ultra rare designation is classed as having an EU prevalence of 10,000 or less individuals (0.20 per 10,000). In the ultra rare segment 21.4% (51) orphan drug designations were granted for designations with a prevalence of less than 501 individuals. At the other end of the prevalence scale just 0.6% (8) of designations were granted for diseases with a prevalence of 240,000 or more individuals.

**Historic Distribution of Orphan Drug Designations in the EU**
*Source: EvaluatePharma® (27 OCT 2014)*




**Distribution and Count of EU Orphan Designations Based on Prevalence**

| EU Prevalence | % of Total | Cumulative % of Total | Designation Count | Designation Count 2013* | Increase in Designations | % Increase in Designations |
|---|---|---|---|---|---|---|
| 0 - 10,000 | 18.7% | - | 243 | 198 | 45 | 23% |
| 10,000 - 20,000 | 7.8% | 26.5% | 102 | 85 | 17 | 20% |
| 20,000 - 30,000 | 7.9% | 34.4% | 103 | 91 | 12 | 13% |
| 30,000 - 40,000 | 5.7% | 40.1% | 74 | 60 | 14 | 23% |
| 40,000 - 50,000 | 11.1% | 51.2% | 145 | 133 | 12 | 9% |
| 50,000 - 100,000 | 23.1% | 74.3% | 301 | 254 | 47 | 19% |
| 100,000 - 150,000 | 13.2% | 87.6% | 172 | 135 | 37 | 27% |
| 150,000 - 200,000 | 9.5% | 97.1% | 124 | 91 | 33 | 36% |
| 200,000 - 260,000 | 2.9% | 100.0% | 38 | 25 | 13 | 52% |
| **Total** | **100.0%** | | **1302** | **1072** | **230** | |

*Source: EvaluatePharma® (27 OCT 2014)*

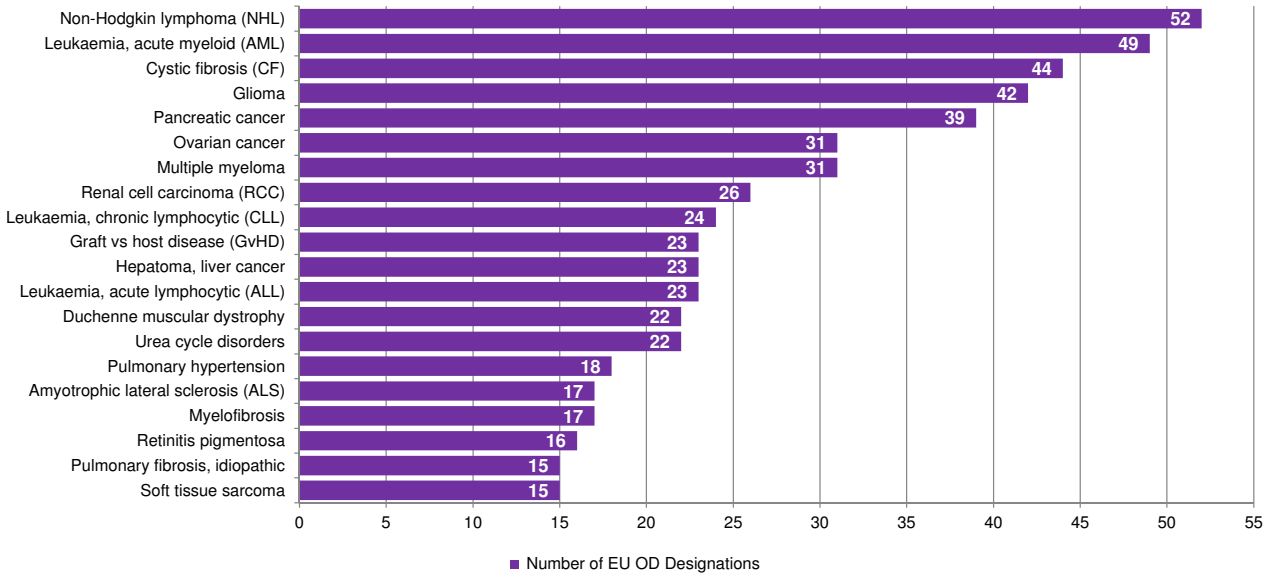
**Note:** Based on available EU prevalence data for a specific designation. EU total population taken to be 506,300,000. EvaluatePharma® used Alexion Pharmaceuticals' definition of an ultra rare orphan drug, disease affecting fewer than 20 individuals per million of population (0.2 per 10,000).
* Count based on designation counts from EvaluatePharma® Orphan Drug report 2013.

# EU Orphan Designations: Top 20 Indications

EvaluatePharma®

**Non-Hodgkin's lymphoma (NHL) is the Indication with Most Filed Orphan Drug Designations in EU**
EvaluatePharma® finds that non-Hodgkin's lymphoma (NHL) is the indication with the most orphan designations in the EU. Just over half (11) of the top 20 indications fall within EvaluatePharma's® Cancer categorization with 5 in the Blood and Blood Forming Malignacies subcategory. Other notable indications include historically well defined populations and indications such as cystic fibrosis and Duchenne muscular dystrophy.The Top 20 indications account for 42% of indications sought in the EU. Duchenne muscular dystrophy was the only indication in the top 20 to have an EU prevalence of less than 1.0.

**Top 20 EU Orphan Designations**
*Source: EvaluatePharma® (27 OCT 2014)*




**Top 20 Orphan Drug Designation Indications in the EU**

| Rank | Indication | Total EU Designations | As a % | EU Prevalence (per 10,000) |
|---|---|---|---|---|
| 1 | Non-Hodgkin lymphoma (NHL) | 52 | 4% | 3.6 |
| 2 | Leukaemia, acute myeloid (AML) | 49 | 4% | 2.7 |
| 3 | Cystic fibrosis (CF) | 44 | 3% | 1.3 |
| 4 | Glioma | 42 | 3% | 2.2 |
| 5 | Pancreatic cancer | 39 | 3% | 2.0 |
| 6 | Ovarian cancer | 31 | 2% | 3.5 |
| 7 | Multiple myeloma | 31 | 2% | 3.2 |
| 8 | Renal cell carcinoma (RCC) | 26 | 2% | 4.2 |
| 9 | Leukaemia, chronic lymphocytic (CLL) | 24 | 2% | 4.0 |
| 10 | Graft vs host disease (GvHD) | 23 | 2% | 1.0 |
| 11 | Hepatoma, liver cancer | 23 | 2% | 2.7 |
| 12 | Leukaemia, acute lymphocytic (ALL) | 23 | 2% | 1.2 |
| 13 | Duchenne muscular dystrophy | 22 | 2% | 0.5 |
| 14 | Urea cycle disorders | 22 | 2% | 1.2 |
| 15 | Pulmonary hypertension | 18 | 1% | 2.2 |
| 16 | Amyotrophic lateral sclerosis (ALS) | 17 | 1% | 1.0 |
| 17 | Myelofibrosis | 17 | 1% | 1.0 |
| 18 | Retinitis pigmentosa | 16 | 1% | 3.7 |
| 19 | Pulmonary fibrosis, idiopathic | 15 | 1% | 3.0 |
| 20 | Soft tissue sarcoma | 15 | 1% | 3.0 |
| **Sub Total** | | **549** | **42%** | |
| Other | | 772 | 58% | |
| **Total** | | **1321** | **100%** | |

*Source: EvaluatePharma® (27 OCT 2014)*

**Note:** Designations assigned based on closest possible match to existing indications within EvaluatePharma®. For example: EU Designation: Adult acute myeloid leukaemia with 11q23 (MLL) abnormalities is mapped to Leukaemia, acute myeloid (AML).

# Evaluate's Solutions for the Life Science Industry

**At Evaluate, our focus is on the business success of our clients.**
Our services are delivered via online subscriptions and through custom solutions. Contact us today to find out more.

## EvaluatePharma®

**Leader in consensus forecasts and analysis of pharma and biotech**

- Consensus sales forecasts of leading Wall Street analysts, currently to 2020
- Must-have insights in an integrated, standardized platform
- Interactive NPV discount cash flow model for asset valuation and Calendar of Events tool

## EvaluateMedTech™

**A new standard in medtech industry analysis via a consensus view**

- Consensus forecasts of leading Wall Street analysts, currently to 2020
- Simplified medtech classification system correlated to FDA and company specified segments
- Six integrated FDA databases and EU CE Mark approvals

## EvaluateClinical Trials™

**High quality global clinical trial intelligence linked to essential commercial insights**

- Full records of ClinicalTrials.gov, EudraCT and a Japanese Clinical Trials data source
- Integrated with in-depth EvaluatePharma product and indication information
- Unique search fields for custom analysis and reporting

## EP vantage
Powered by Evaluate

**Award-winning commentary and analysis by industry experts**

- Daily round up of share price movements
- Future market events that will impact product value
- Searchable news and commentary powered by high quality Evaluate data

**For more information please visit www.evaluategroup.com.**
**On Twitter: @evaluatepharma, @evaluatemedtech, @epclinicaltrial, @epvantage.**

## Download this complimentary report at:
## www.evaluategroup.com/orphandrug2014
## Please share this link with a colleague.

**To find out more about the findings in this report and EvaluatePharma®'s orphan drug market intelligence, please contact:**


- **North America:**
  Debbie Paul
  Tel: +1 617 573 9453
  Email: debbie.paul@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


Established in 1996, Evaluate is the leader in high quality life science sector analysis. EvaluatePharma delivers exclusive consensus forecasts and trusted commercial insight into biotech and pharmaceutical performance. EvaluateMedTech sets a new standard in integrated analysis and consensus forecasts of the global medical device and diagnostic industry. EvaluateClinical Trials delivers unique intelligence to efficiently and accurately analyze the global clinical trial landscape. A team of over 85 dedicated healthcare analysts employ rigorous methodologies to collate, organize and deliver the most-up-to-date commercial performance data available. An award-winning editorial team of journalists writing under the EP Vantage name support EvaluatePharma's analysis. The Evaluate services enable the life science community to make sound business decisions about value and opportunity.

Evaluate™


**Evaluate – Headquarters –** Evaluate Ltd., 11-29 Fashion Street, London E1 6PX United Kingdom
Tel: +44 (0)20 7377 0800 – Fax: +44 (0)20 7539 1801

**Evaluate – North America –** EvaluatePharma USA, Inc., 15 Broad Street, Suite 401, Boston, MA 02109 USA
Tel: 1-617 573-9450 – Fax: 1-617 573-9542

**Evaluate – Japan –** EvaluatePharma Japan KK, Tokyo, Japan
Tel: +81 (0) 80 1164 4754

**www.evaluate.com**