

# THE ECONOMIC POWER OF ORPHAN DRUGS



THOMSON REUTERS™

DESPITE THE SMALLER PATIENT  
POOL FOR RARE DISEASE  
R&D, THE ECONOMICS OF  
ORPHAN DRUG DEVELOPMENT  
SHOWS GREAT POTENTIAL FOR  
COMMERCIALIZATION.

# OVERVIEW

Rare diseases, also known as orphan diseases, individually affect small groups of patients but collectively are estimated to affect 25 million people in the U.S. alone. Given the limited number of patient populations per disease, this has historically not been an area of R&D focus for mainstream pharmaceutical companies. However, that trend is changing, as pharmaceutical companies realize the revenue potential of orphan drugs that address unmet medical needs. Thomson Reuters undertook an analysis to determine whether or not orphan drugs are truly economically viable for pharmaceutical companies. In the first such analysis of this kind, it shows that the answer is, clearly: “they are.”

In the peer-reviewed article “[Orphan Drug Development: An Economically Viable Strategy for Biopharma R&D](#),” featured in *Drug Discovery Today*, researchers with Thomson Reuters Life Sciences Professional Services and Pfizer compared the economics of orphan versus non-orphan drugs for the first time. The report shows that the revenue potential of orphan drugs may offer greater profitability when considered across their lifetime.

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# BACKGROUND

The increased focus on rare diseases started in part because of the stimulus provided by the Orphan Drug Act (ODA) in the U.S. and similar Acts in other regions of the world. These Acts, coupled with high-profile philanthropic funding, shone a new light on orphan diseases and encouraged investment in R&D for a number of these debilitating conditions. As scientific understanding of rare diseases improves, the pharmaceutical industry is undergoing a transformative approach to drug therapy. The Thomson Reuters analysis shows that orphan drugs address a high unmet medical need and so benefit from a pricing structure that makes them commercially attractive to pharmaceutical companies. Case in point, the orphan oncology drug Rituxan (generic: Rituximab) is the world's second most profitable drug, just behind mainstream blockbuster Lipitor (generic as of November 2011), and is expected to garner more than \$150 billion in revenue over its lifetime, the majority of which is for orphan indications.

Current estimates from the National Institutes of Health and the European Organization for Rare Diseases indicate that there are approximately 7,000 rare diseases worldwide and that the recognized number of such diseases rises at the rate of approximately 250 per annum. Although each disease may only affect a small group, ranging from a handful up to 200,000 patients, collectively they affect tens of millions of people in North America alone.

A shared, global desire to address the unmet treatment needs of rare diseases led to the 1983 U.S. Orphan Drug Act, as well as similar Acts in 1991 in Singapore, 1993 in Japan, 1997 in Australia and in 2000 by the European Union. These Acts stimulated orphan drug research around the world, offering pharmaceutical companies potentially profitable incentives to focus on rare diseases.

The last decade has been the most productive period in orphan drug development, both in designations and approvals. This period of tremendous growth has also coincided with an increased focus on precision medicine. Orphan drugs are targeted at diseases of very high unmet medical need and therefore can receive rapid approval and high levels of reimbursement. As the data from Thomson Reuters suggests, this can make them commercially attractive for pharmaceutical companies.

Through careful analysis of the economics and investment case for orphan drug development and commercialization, this report shows that while orphan drugs target much smaller populations than traditional mainstream drugs, the high cost of therapy and attractive developmental drivers, such as government incentives, smaller and shorter clinical trials, extended exclusivity and high rates of regulatory success, have made top orphan drugs as equally viable as their non-orphan peers.

# METHODOLOGY

The data was aggregated by Thomson Reuters Life Sciences consultants who performed an economic analysis of orphan versus non-orphan drugs while collaborating closely with Cory Williams, MD, Ph.D., Pfizer.

Thomson Reuters compared the total value of orphan drugs from 1990 to 2030, using its vast information solutions including Thomson

Reuters Cortellis™, Integrity and Newport Premium™, while industry benchmarking data was provided by CMR International, a Thomson Reuters business and industry leader in global R&D pharmaceutical measurement. This comprehensive information spans multiple disciplines and supports the drug research and development lifecycle.

# FINDINGS AND OBSERVATIONS

Lipitor, used to prevent heart disease and lower high cholesterol, is the largest revenue-generating drug globally. It generated an estimated \$197 billion for Pfizer over its lifetime. The second largest revenue-generating drug is Rituxan, which has garnered significant sales

for the treatment of two rare (orphan) diseases: chronic lymphocytic leukemia and non-Hodgkin's lymphoma, as well as for the non-orphan indication rheumatoid arthritis.

Figure 1 lists the top 10 drugs globally, ranked by overall lifetime revenue potential.

## TOP 10 REVENUE GENERATING DRUGS

FIGURE 1

Brand Name	Generic Name	Therapy Area	Marketer	Discount PV (B)	Present Day Peak Sales Value (B)
Lipitor	Atorvastatin	Metabolism	Pfizer	\$197	\$17
Rituxan	Rituximab	Oncology	Genentech	\$154	\$7
Humira	Adalimumab	MSP	Abbott Laboratories	\$146	\$8
Remicade	Infliximab	MSP	Janssen Biotech, Inc.	\$134	\$8
Enbrel	Etanercept	MSP	Amgen, Inc.	\$118	\$8
Advair / Seretide / Adair	Fluticasone Propionate + Salmeterol	Respiratory	GlaxoSmithKline	\$102	\$9
Plavix	Clopidogrel	Cardiovascular	Sanofi Aventis	\$101	\$11
Avastin	Bevacizumab	Oncology	Genentech	\$92	\$7
Norvasc / Istin	Amlodipine	Cardiovascular	Pfizer	\$91	\$7
Herceptin	Trastuzumab	Oncology	Genentech	\$86	\$6

**NOTE:** Discount PV is the discounted peak value of a drug's revenue over its lifetime. This number is an estimation based on the value of all historical revenues and future projected revenues. Rituxan is the only drug in the top 10 which has significant sales arising from orphan drug indications.

Source: Thomson Reuters Cortellis

# PROFITABILITY OF ORPHAN DRUGS

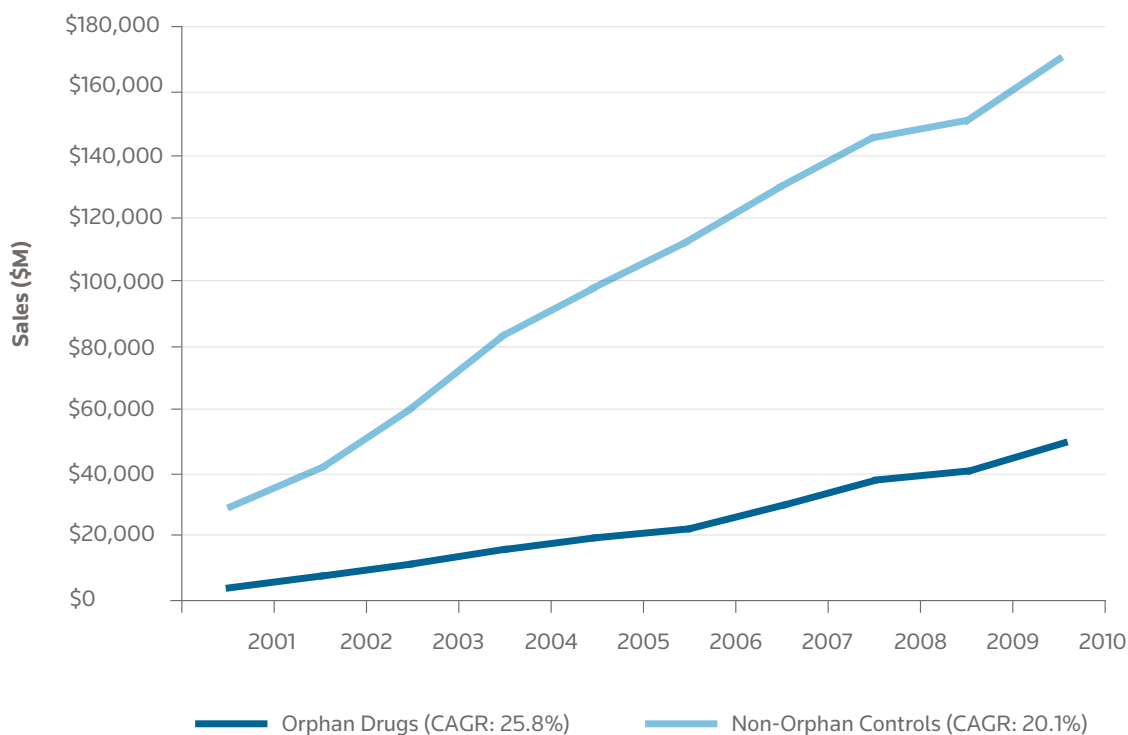
The orphan drug market was worth just over \$50 billion globally at the end of 2011, based on Thomson Reuters analysis. Spending on orphan drugs currently makes up approximately six percent of total pharmaceutical sales, assuming a total pharmaceutical market value of \$880 billion<sup>1</sup>. The compound annual growth rate (CAGR) of the orphan drug market between 2001 and 2010 was an impressive 25.8 percent, compared to only 20.1 percent for a matched control group of non-orphan drugs. This data, combined with the increasing number of orphan drug approvals, suggests that the CAGR of

launched orphan drugs will outshine that of the non-orphan control drugs over the next 30 years. This growth is partially due to the high number of biological orphan drugs, which are currently less susceptible to generic (biosimilar) erosion as compared to small molecules. Meaning, their high economic value continues beyond the end of patent expiration.

Figure 2 depicts the increased growth rate of orphan drugs compared with the lower growth rate of non-orphan control drugs.

## GROWTH RATE OF ORPHAN VERSUS NON-ORPHAN DRUGS (2001 - 2010)

FIGURE 2



Source: Thomson Reuters Cortellis

The analysis demonstrates that the impact of the smaller patient population is offset by the higher price demanded by orphan drugs. Drugs for rare diseases can secure higher prices due to the limited size of the patient population; there are fewer, if any, competitors; and, there is a high level of unmet need. In 2010, the industry's most expensive drug, Soliris, which costs more than \$409,000 per year for treatment of paroxysmal nocturnal hemoglobinuria (PNH), a rare life-threatening blood disease, brought in a total of \$541 million in total sales for Alexion Pharmaceuticals. This is a considerable achievement in terms of revenue, considering only four to six thousand people suffer from this disease in the United States.

Companies investing in rare diseases have been able to maximize the sales potential of existing drugs by repositioning them into additional rare diseases: 15 percent of the drugs analyzed by Thomson Reuters Life Sciences Professional Services had subsequent launches for additional rare diseases. Of the top 10 orphan drugs (shown in Figure 3), 6 had more than one rare disease indication, with a peak value (PV) averaging

at \$34.3 billion in overall revenue potential, compared to \$8.1 billion for drugs with only one orphan disease indication.

According to Manning & Napier, a financial services firm, the findings from Thomson Reuters align with the positive investor perception of the orphan drug market. This perception is highlighted by the higher valuation multiples of companies such as Biomarin and Alexion compared to traditional primary-care focused companies. These valuations reflect a broad interest of the financial markets in the orphan disease business model. The firm notes that the current sales and profit outlook related to orphan drug development is strong and positive. The increased stratified approach in the market could result in more scrutinized drug pricing, which could impact the business model materially. However, the expectation is that the model will maintain a competitive edge over traditional primary care. This competitive advantage will be essential in the face of the anticipated continued decline of the traditional primary-care business model.

## TOP REVENUE GENERATING ORPHAN DRUGS

FIGURE 3

Generic Name	Therapy Area	Discount PV (B)	Present Day Peak Sales Value (B)
Rituximab	Oncology	\$154	\$7
Ranibizumab	Ophthalmology	\$74	\$5
Somatropin (epr)	Metabolism	\$62	\$3
Lenalidomide	Oncology	\$60	\$5
Imatinib mesylate	Oncology	\$42	\$5
Filgrastim	Hematology	\$42	\$2
Glatiramer Acetate	MSP	\$40	\$4
Recombinant Factor VIII; Octocog alfa	Hematology	\$28	\$1
Bosentan (monohydrate)	Cardiovascular	\$27	\$2
Bortezomib	Oncology	\$24	\$2

Source: Thomson Reuters Cortellis

# ORPHAN DRUGS AND THE GENERIC PHARMACEUTICAL MARKET

The revenue generating power of an orphan drug, just as with non-orphan drugs, will lessen once it moves into the generics market. The benefit of orphan versus non-orphan drugs is that orphan drugs are protected by additional exclusivities. In the U.S., orphan drugs are awarded a seven-year Orphan Drug Exclusivity (ODE). Non-orphan new chemical entities are awarded five years of exclusivity upon approval, which means that orphan drugs receive two years of additional protection if the orphan indication is awarded upon approval. The seven-year orphan exclusivity can also start running later in the product's life cycle if the new indication is approved after the initial launch. However, in that case, ODE may not keep generics out of the market as generics may receive approval for those indications that are not protected by orphan drug exclusivity.

The extended period of exclusivity for these drugs means that they are insulated from generic competition for a potentially longer period than their non-orphan counterparts. Orphan drug exclusivity does not have any association with patents, and may or may not give exclusivity beyond the composition of the matter patent.

Information compiled by Thomson Reuters Newport Premium, an advanced product targeting and sourcing system focused on the global generics market, shows the approximate sales of drugs that saw their ODE expire in 2011 (Figure 4). Although the ODE has expired, many of these products continue to be protected from generic competition by patents and additional exclusivities in the U.S. market.



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## APPROXIMATE SALES OF ORPHAN DRUGS WITH ODE EXPIRATIONS IN 2011

FIGURE 4

2011 U.S. Sales (in M)	Drugs with Orphan Exclusivity in the U.S. Expiring in 2011	Active Ingredient	Orphan Indication
>\$500	SENSIPAR	Cinacalcet hydrochloride	Hyperparathyroidism
\$300	VIDAZA	Azacitidine	Myelodysplastic syndrome
\$50-100	ACETADOTE	Acetylcysteine	Acetaminophen overdose
	CLOLAR	Clofarabine	Acute lymphoblastic leukemia
\$5-15	TINDAMAX	Tinidazole	Bacterial vaginosis and trichomoniasis
	VENTAVIS	Iloprost	Class III Primary Pulmonary arterial hypertension
	NUTRESTORE	Glutamine	Used with growth hormone and indicated for congenital short bowel
\$1 or less	APOKYN	Apomorphine hydrochloride	Parkinson's disease and associations with the disease
	LUVERIS	lutropin alfa	Fertility medication for infertile hypogonadotropic hypogonadal (LH deficiency)
	MEMBRANEBLUE	Trypan blue	Dye used for staining membranes during eye surgery
	PENTATE CALCIUM TRISODIUM	Pentetate calcium trisodium	Treatment of internal contamination of plutonium, americium or curium
	PENTETATE ZINC TRISODIUM	Pentetate zinc trisodium	Treatment of internal contamination of plutonium, americium or curium

Source: Thomson Reuters Newport Premium, IMS Health

The orphan drug with the highest annual sales, Sensipar, generated over \$500 million in revenue in 2011. Orphan drugs with mid-level sales,

such as Vidaza, are also economic powerhouses generating between \$100 and \$500 million in revenue by the end of 2011.

# CHALLENGES AND OPPORTUNITIES WITH ORPHAN DRUG DEVELOPMENT

There are several challenges associated with orphan drug development. Two noteworthy obstacles include the difficulty in locating and recruiting patients and the logistical problems related to trial organization. These factors are thought to increase the costs incurred by orphan drug R&D. However, using data from

*CMR International*, a Thomson Reuters business, research shows that trials focused on orphan drugs are significantly shorter and have a quicker review time than trials involving non-orphan drugs. According to researchers, these positive factors, plus others shown in Figure 5, are likely to outweigh the aforementioned challenges.

## INCENTIVES FOR ORPHAN DRUG DEVELOPMENT

FIGURE 5

R&D Drivers	Commercial Drivers
Tax credits	Favorable reimbursement
R&D grants	Fewer hurdles to approval
Waived FDA fees	Longer exclusivity
Shorter development timelines	Lower marketing costs
Greater regulatory success	Faster uptake
	Premium pricing

A substantial number of orphan drugs in the sample set were oncology-related: 40 percent of the orphan drugs in the sample set dealt with oncology, compared to only 10 percent in the non-orphan drug sample set. This is consistent with orphan drugs across the FDA database. The orphan drug samples also had a larger share of biological versus small molecule drugs. One possible reason for the intense focus on this particular therapeutic area is that the underlying genetic aberration of oncology often provides the signature for disease identification. In the pharmaceutical industry, oncology has also taken the lead in the recent evolution to customized, or precision, medicine. The approach of utilizing biomarkers in targeting treatments and therapies further explains this therapeutic area's majority share of orphan drug approvals, in addition to

the field's susceptibility to smaller, individualized subsets of larger patient populations.

It has long been speculated that the heyday of the blockbuster drug model has declined or died. But, researchers found that of the 86 orphan drugs included in the study, 25 were blockbusters; meaning, 29 percent of orphan drugs have annual sales greater than \$1 billion. This is comparable to 83 out of the 291 non-orphan drugs that were considered to be blockbusters (which is also 29 percent). The number of blockbusters approved each year remained constant between 2000 and 2010, suggesting that the blockbuster model is not dead, but remains an important part of pharmaceutical R&D, supplemented by emerging areas such as rare disease research.

## CONCLUSION

Despite the smaller patient pool for rare disease R&D, the economics of orphan drug development and potential for commercialization are attractive when compared to their non-orphan counterparts. Economic drivers such as tax credits, grants, waived FDA fees, reduced timelines for clinical development and higher probability of regulatory approval, coupled with commercial drivers such as premium pricing, faster uptake, lower marketing costs and longer market exclusivity, further fuel the economic power of orphan drug development.

Thomson Reuters research also highlights the need to characterize and identify specific rare disease patient populations and enable the evolution to precision medicine. This approach allows for increased focus on sub-diseases within more common, non-orphan conditions.

Ultimately, the analysis validates the significance of targeting rare diseases in the global pharmaceutical market. This attention will not only potentially affect the lives of millions worldwide who suffer from rare diseases, it will also propel the evolution of precision medicine.



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