



feature

Orphan drug development: an economically viable strategy for biopharma R&D

Kiran N. Meekings¹, kiran.meekings@thomsonreuters.com, Cory S.M. Williams² and John E. Arrowsmith¹

Orphan drug incentives have stimulated research into diseases with significant unmet medical need. Although the targeting of orphan diseases is seen by industry as an attractive strategy, there are limited economic data available to support its use. In this paper we show that the revenue-generating potential of orphan drugs is as great as for non-orphan drugs, even though patient populations for rare diseases are significantly smaller. Moreover, we suggest that orphan drugs have greater profitability when considered in the full context of developmental drivers including government financial incentives, smaller clinical trial sizes, shorter clinical trial times and higher rates of regulatory success. The data support the targeting of rare diseases as an important component of a successful biopharma R&D strategy.

Introduction

The 1983 US Orphan Drug Act (ODA) provides incentives to the pharmaceutical industry for developing drugs to treat rare diseases and has stimulated clinical research, helping to address the significant unmet medical need for these diseases. Similar acts introduced in 2000 in the EU, 1991 in Singapore, 1993 in Japan and 1997 in Australia have further stimulated research globally. Current estimates indicate that there are ~7000 rare diseases in the USA affecting ~25 million people, many of whom are children [1]. Additionally, ~250 new rare diseases are described annually [1]. The past decade has been the most productive period in the history of orphan drug development, in terms of average annual orphan drug designations and orphan drug approvals [2]. The 2001–2010 compound annual growth rate (CAGR) in orphan drug designations is ~10%, compared with a negative

CAGR for new molecular entities (NMEs) overall for the same period [3] (<http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm>). Orphan drugs represent an increasing proportion of NME approvals by the FDA (~30% in 2010) [2]. This period of growth for orphan drug approvals has coincided with tremendous industry focus and activity on developing targeted therapies and supporting the evolution to stratified and personalized medicine, a trend that has been central to the development of many orphan drugs [4–6].

The ODA encourages the development of drug therapies for diseases that affect fewer than 200 000 people in the USA, or diseases for which sales in the USA are unlikely to recoup R&D costs. If a sponsor's drug meets either criterion the company receives orphan drug designation with related incentives and benefits, including seven-year FDA-administered market exclusivity,

tax credits of up to 50% of R&D costs, R&D grants, waived FDA fees and protocol assistance [7]. Before the introduction of the act, pharmaceutical companies developing drugs for rare diseases risked doing so at a loss. The act now provides some financial security and enables companies to invest in improving the health of patients with rare diseases. Similar incentives are available in the other regions that encourage R&D investment in orphan diseases.

Increased pipeline attrition coupled with increased R&D spending means that R&D productivity within large pharmaceutical companies is becoming increasingly challenging. As a result, some pharmaceutical companies are diversifying and exploring new disease areas and pathways to enhance pipeline value, including the targeting of orphan and/or rare diseases. Orphan diseases are often regarded as being commercially attractive because of the high unmet medical need and

BOX 1

Methodologies and calculations used in analysis of orphan drug value**Methodologies and calculations****Orphan drug dataset generation**

Drugs with orphan drug designation from Thomson Reuters' Integrity were supplemented with publically available sources of orphan drug approvals published by the FDA and EMA. Drugs were included if they had FDA or EMA (or both) regional approvals for the indication. Out of the 86 drugs, 75 received designation in the USA, 49 in the EU and 44 in both. Drugs launching for additional significant non-orphan designations were excluded from the analysis.

Control non-orphan drug dataset generation

Drugs containing sales from orphan designations were excluded from the total sample of Thomson Reuters' Forecast drug forecasts. Drugs where peak sales were not captured and combination therapies were also excluded. Remaining drugs launching between 1987 and 2011 were treated as the control non-orphan dataset.

Forecasting

Global sales forecasts for the orphan drugs were obtained from Thomson Reuters' Forecast. Sales comprised consensus sales forecasts and/or proprietary sales forecasts licensed through BioMedTracker (<http://www.biomedtracker.com/>). Drug forecasts for 1987–2030 were completed by filling in missing years using standard forecasting uptake and generic erosion curves.

Discounting cash flows

The orphan and control forecast data were discounted to present-day (2011) value using the average US 1-yr nominal interest rate between 1987 and 2030. This equated to an interest rate of 4.46% and a discount rate of 4.27%.

Present value (PV)

The total present value of all yearly revenues generated by sales of a drug for the forecasted period was calculated by combining the yearly discounted cash flows for the forecasted period.

Statistical analysis

The Mann–Whitney nonparametric statistical test was used to compare the launch year pattern between datasets.

A step-wise regression model was constructed to investigate independently the impact of orphan drug classification on PV.

Compound annual growth rate (CAGR)

The year-over-year growth rate over a specified period of time. Calculated by:

$$\text{CAGR} = \left(\frac{\text{Value}^{\text{end}}}{\text{Value}^{\text{start}}} \right)^{(1/t)} - 1$$

attractive prices the related drugs can procure. However, as yet, this assumption has not been substantiated by data. Here, we provide a thorough analysis of the economics and investment case for orphan drug development and commercialization. In addition, we examine the potential implications of increased orphan drug development for the further evolution of targeted therapies within industry.

Profiling our orphan drug sample set

Orphan drug ($n = 86$) and control-matched non-orphan drug ($n = 291$) forecasts were generated using Thomson Reuters' databases for the period

1990–2030. See Box 1 for details on overall methodology and statistical analyses.

The orphan and control non-orphan drug sample sets had remarkably different compositions for therapeutic area mix. Most notably, the orphan drug sample set had a much higher share devoted to oncology drugs compared with the non-orphan drug sample set, at 47% vs 10%, respectively. This is consistent with the overall universe of orphan drugs in the FDA database, for which oncology has the highest number of orphan designations [2]. In addition, the orphan drug sample set has a much higher share of large- vs small-molecule drugs, compared with

the non-orphan drug sample set. Again, this is consistent with previous analysis [8].

Orphan drugs represent an increasingly important component of the pharmaceutical market and have equal revenue-generating potential to non-orphan drugs

According to our analysis of strategically important drugs within industry, orphan drugs currently make up 22% of total drug sales, and the CAGR of the orphan drug market between 2001 and 2010 was an impressive 25.8%, compared with only 20.1% for the matched controls (Fig. 1a). This, combined with the increasing number of orphan drug approvals, has resulted in orphan drugs becoming an increasingly large and important part of the global pharmaceutical market. Our data additionally suggest that the CAGR of launched orphan drugs will continue to outstrip that of non-orphan drugs for the period 2010–2030. We therefore believe that sales from orphan drugs will continue to be an increasingly important contributor to total pharmaceutical market sales.

A present value (PV) of revenue analysis was carried out to compare the total (1990–2030) value of orphan drugs compared with non-orphan drugs. The PV of the overall orphan drug sample set was US\$1041 billion compared with US\$3344 billion for the non-orphan matched controls. This translated to a mean PV per drug of US\$12.1 billion and US\$11.5 billion for orphan and non-orphan drugs, respectively. The total PV of orphan and non-orphan drugs corresponds to a mean per-year economic value of US\$406 million for an orphan drug, compared with US\$399 million for a non-orphan drug (Fig. 1b). The mean per-year economic value, in 2010 terms, is US\$637 million for an orphan drug and US\$638 million for a non-orphan drug (Fig. 1b). This finding of parity in mean per-year economic value between orphan and non-orphan drugs is remarkable and indicates significant revenue opportunity for orphan drugs. Additionally, whereas the mean PV for non-orphan drugs remained approximately constant at just over US\$600 million between 2000 and 2010, the mean PV of orphan drugs nearly doubled from US\$351 million in 2000 to US\$637 million in 2010 (Fig. 1b).

This analysis suggests that the impact of a smaller treatable patient pool is offset by the higher pricing of many orphan drugs, the increased market share, the longer exclusivity period and faster uptake rate that orphan drugs often garner as a result of the high unmet medical need in many of these diseases [4]. Orphan drugs can secure incredibly high pricing.

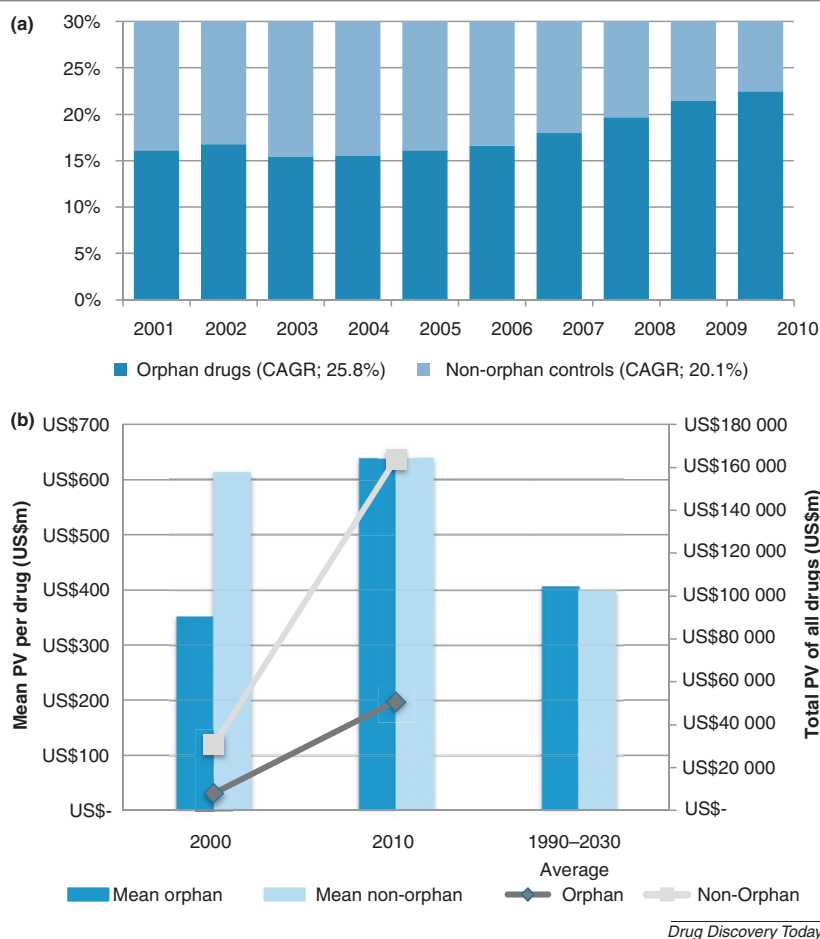


FIGURE 1

Present value (PV) analysis of orphan and non-orphan drugs suggests increasing value of orphan drugs. Forecasted revenues for 86 orphan drugs and 291 non-orphan drugs were discounted back to present-day values. Orphan drugs constitute a growing proportion of strategic drug sales, with 22% of sales coming from orphan drugs in 2010 (a). Orphan drug sales expanded with a CAGR of 25.8% compared with 20.1% for matched non-orphan controls (a). In addition, the mean value of an orphan drug increased from US\$351m in 2000 to US\$637m in 2010 (b). By contrast, the mean value of a non-orphan drug remained approximately constant at just over US\$600m (b). Over the entire 1990–2030 forecast period, the mean per-year economic value for an orphan drug was US\$406m, compared with US\$399m for a non-orphan drug (b).

For instance, the most expensive drug in the world in 2010, Soliris® (Alexion Pharmaceuticals), costs US\$409 500 per year for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), which enabled it to capture US\$541 million sales in 2010, an incredible feat bearing in mind there are only an estimated 4000–6000 patients in the USA with PNH. An ongoing debate is whether these prices are sustainable within the context of the current health system [9]. Several creative reimbursement approaches (e.g. cross-subsidies, risk-sharing schemes) have been implemented, which spreads the risk, bringing the cost down toward the payer's cost-effectiveness threshold [10].

The robust revenue-generating potential of orphan drugs is further enhanced in cases where drugs have multiple orphan disease approvals. From the orphan drugs we analyzed, 15% had subsequent launches for additional orphan

diseases. There was a clear correlation between being launched for multiple orphan disease indications and overall value. Indeed, six of the top ten orphan drugs (by PV) had more than one orphan disease indication launch, and the PV of drugs launching for more than one orphan disease indication averaged at US\$34.3 billion, compared with US\$8.1 billion for drugs launching for only one orphan disease indication.

To investigate the sequencing of orphan drug designations further, a sample of 192 drugs with orphan approval milestones in Thomson Reuters' Integrity was analyzed. From the 192 drugs launched for orphan diseases, 145 launched for the orphan disease as the primary approval. The remaining 47 launched for a non-orphan disease prior to approval for an orphan disease. Although this suggests some drugs do move from non-orphan into orphan disease indications, it is significantly more probable

(χ^2 ; $P = 1.5 \times 10^{-12}$) that a drug will target an orphan disease indication first. This preferred sequence ensures that the drug secures premium pricing in a smaller target population before moving to a larger population. Out of the 192 approved drugs, 8.3% went on to gain approval for larger non-orphan disease indications and 12.5% gained subsequent approvals for additional orphan diseases.

Are orphan drugs more profit than non-orphan drugs?

A comparative analysis of the net present value of profits for orphan vs non-orphan drugs was not possible owing to unavailability of detailed cost data and benchmarks (e.g. costs of orphan vs non-orphan drug development and SG&A costs). However, we provide evidence here that clinical trials are shorter and regulatory filings are more successful for orphan drugs vs non-orphan

drugs. In addition, companies can lower R&D costs as a result of the various ODA benefits (e.g. fee waivers, R&D grants, tax incentives).

Clinical trials involving orphan drugs are challenging for a number of reasons including a lack of validated endpoints, difficulties with locating patients and logistical problems in clinical trial organization [11]. The latter two reasons can contribute significantly to the costs of clinical trials [12]. However, clinical trials involving orphan diseases require fewer patients than those involving non-orphan diseases [12,13]. In addition, using CMR International data, we found that trials involving orphan drugs are significantly shorter than those involving non-orphan drugs. Our analysis showed that the average time from Phase II to launch (there were insufficient numbers of Phase I orphan drugs to analyze) was 3.9 years for orphan drugs, compared with 5.42 years for non-orphan drugs. We hypothesize that, on balance, the smaller and shorter clinical trials and the various cost:benefit incentives from the ODA translate to lower costs of orphan drug development compared with non-orphan drug development (Fig. 2).

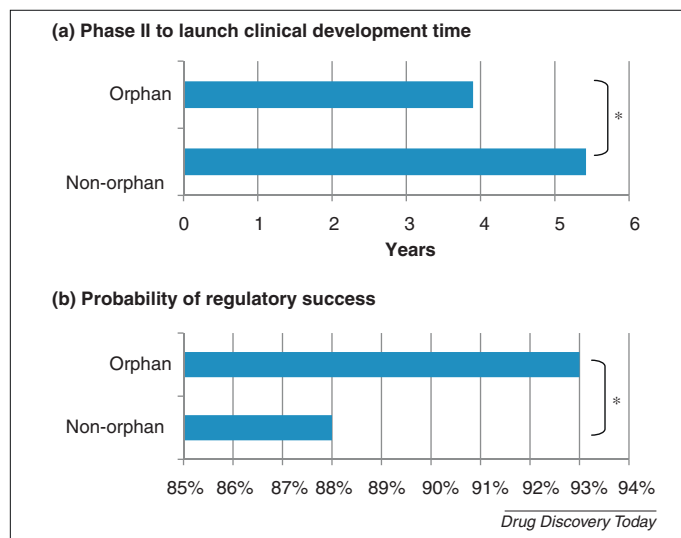


FIGURE 2

Attractive clinical trial metrics of orphan drug development. Orphan drugs show decreased Phase II to launch clinical trial development times **(a)** and greater probability of regulatory success upon filing **(b)** compared with non-orphan drugs. *denotes statistical significance ($p < 0.05$).

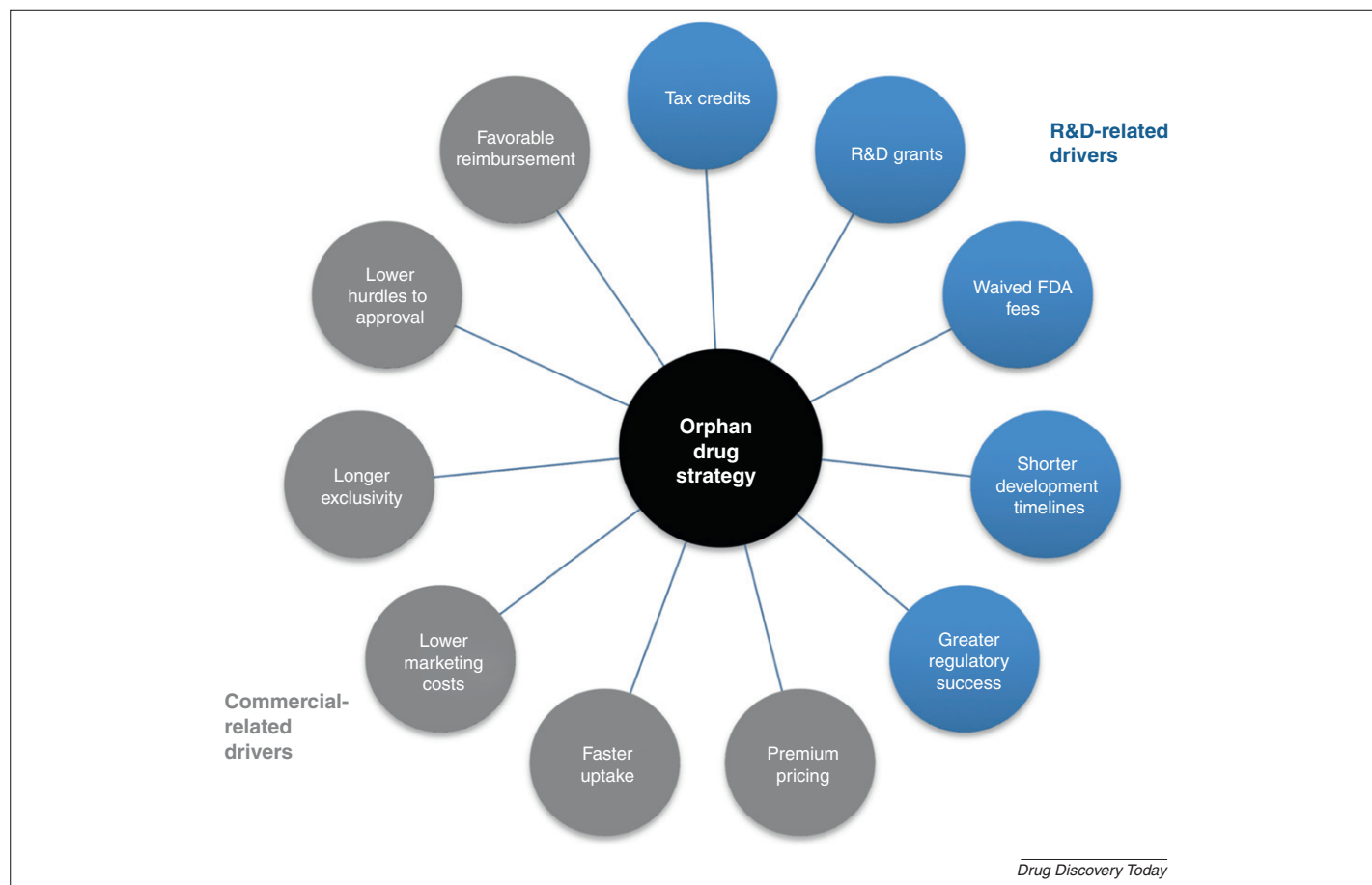


FIGURE 3

Summary of incentives for orphan drug development. There are a number of key drivers that could explain the favorable economics for orphan drugs; we have classified these drivers as R&D-related or commercial-related.

It is suggested that, because orphan diseases are often the result of single genetic aberrations, pharmaceutical intervention targets are more easily identified and, by targeting these aberrations, there is a higher likelihood of R&D success [14]. Because orphan drugs are designated late in the development process, most commonly in Phase III, it is not possible to determine the overall R&D success of orphan vs non-orphan drugs [7,15,16]. We can therefore only accurately determine the success of the regulatory process for those compounds that are filed. We note, however, that a proportion of orphan-designated drugs are never filed and are not available for this analysis. For example, it has been suggested that sponsors developing orphan drugs seek regulatory agency advice more frequently, which could lead to drugs being discontinued before filing. This hypothesis cannot be tested using available data. Although the hypothesis on the difference in regulatory success between orphan and non-orphan drugs cannot be fully tested using available data, we could compare the probability of regulatory success of orphan drugs to all drugs approved between the years 1997 and 2009, using data collated by CMR International. Data collected from 23 to 48 predominantly mid-size and large pharma companies (the number of companies varied by year) demonstrated a 5% increased probability of regulatory success for filed orphan drugs compared with the whole population (93% vs 88%).

We suggest that, taken together, lower costs, higher rates of regulatory success and parity of revenue-generating potential translate into higher profitability of orphan vs non-orphan drugs.

Conclusions

The economics and investment case for orphan drug development and commercialization are favorable and, as suggested by the results presented here, more favorable compared with non-orphan drugs. This is remarkable given the smaller target patient populations for orphan diseases. There are a number of key drivers that could explain the favorable economics for

orphan drugs. We have classified these drivers as being R&D-related or commercial-related (Fig. 3). R&D-related economic drivers are underscored in the fundamentals of the ODA (e.g. tax credits, R&D grants, waived FDA fees), as well as shorter timelines for clinical development and a higher probability of regulatory approval. Commercial-related economic drivers include premium pricing, faster uptake, relatively lower marketing costs and longer market exclusivity.

The need to characterize and identify specific orphan and/or rare disease patient populations puts orphan drug development in an important position in the development of targeted therapies. Drug development for orphan diseases can further enable the evolution to stratified medicine, with a deliberate philosophy to consider 'sub-diseases within diseases' [17]. This 'sub-disease' philosophy requires all stakeholders involved in orphan drug R&D to focus not only on translating molecular target and pathway insights from orphan diseases to non-orphan diseases but also to explore and characterize 'sub-diseases' proactively within more-common, non-orphan conditions. There is precedence for the recognition of such characterization under the ODA. Late-stage melanoma, which has more than 50 orphan drug designations [3], is a 'sub-disease' with a definition based on clinical features that are medically distinct within melanoma. The 'sub-disease' philosophy requires moving beyond clinical features to ensure a rigorous approach is applied to define 'sub-diseases', and to identify the related patient subpopulations, based on molecular information (e.g. etiology, pathophysiology, treatment, outcomes and even genotype-to-phenotype correlations). The favorable economics for orphan drug development and commercialization would be supportive of this philosophy.

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Kiran N. Meekings¹

Cory S.M. Williams²

John E. Arrowsmith¹

¹Thomson Reuters Life Sciences Consulting, The Johnson Building, 77 Hatton Garden, London EC1N 8JS, UK

²Pfizer, Strategy & Portfolio Solutions, Pfizer, 235 East 42nd Street, New York, NY 10017, USA