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feature

Financing drug discovery for orphan diseases☆

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Recently proposed 'megafund' financing methods for funding translational medicine and drug development require billions of dollars in capital per megafund to de-risk the drug discovery process enough to issue long-term bonds. Here, we demonstrate that the same financing methods can be applied to orphan drug development but, because of the unique nature of orphan diseases and therapeutics (lower development costs, faster FDA approval times, lower failure rates and lower correlation of failures among disease targets) the amount of capital needed to de-risk such portfolios is much lower in this field. Numerical simulations suggest that an orphan disease megafund of only US$575 million can yield double-digit expected rates of return with only 10–20 projects in the portfolio.

Introduction

The drug development process has become expensive, lengthy and risky. In response to these characteristics, and to the lackluster performance of investments in the biotech and pharma sectors over the past decade, traditional sources of financing for such endeavors – private and public equity – are waning as capital shifts to less risky investments. Fernandez *et al.* [1] argued that this problem can be addressed by increasing the scale of investment and pooling a large number of drug development efforts into a single financial entity or 'megafund'. The benefits of diversification—lower aggregate risk with more 'shots on' goal—yield a more attractive risk-adjusted return and a higher likelihood of success. This, in turn, allows the megafund to raise the required amount of capital to achieve sufficient diversification by issuing 'research-backed obligations' (RBOs): bonds that are collateralized by the portfolio of potential drugs and their associated intellectual property. Because RBOs are structured as bonds, they can be designed to appeal to fixed-income investors, who collectively represent a much larger pool of capital than do venture capitalists, and who have traditionally not been able to participate in investments in early-stage drug development. For example, the total size of the US venture capital industry in 2012 was US$199 billion, whereas the comparable figure for the US bond market was US$38 trillion.

To illustrate the mechanics of megafund financing using RBO securities, Fernandez *et al.* [1] provided an analytic framework, simulation software and empirical examples involving cancer-drug-development programs. Their simulation results suggest that RBO structures can, in principle, generate reasonable returns for debt and equity investors, while at the same time providing a bridge for translational research in the drug approval process. In a follow-on study, Fagnan *et al.* [2] proposed an analytic framework for evaluating the impact of third-party guarantees on RBO transactions, and found that such guarantees can improve the economics of RBO transactions at very low expected cost to the guarantor. However, the examples in Fernandez *et al.* [1] and Fagnan *et al.* [2] rely on very large portfolios of hundreds of candidate compounds, which raises several operational challenges in the practical implementation of such a megafund.

In this Feature, we explore the applicability of the RBO approach by extending the framework to accommodate drug discovery for orphan diseases. Because of the unique pathological

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characteristics of many orphan diseases, as well as the considerable support provided by the Orphan Drug Act of 1983 (ODA), orphan drug development projects frequently have higher success rates and shorter times to approval but still generate potential lifetime revenues that are comparable to non-orphan drugs despite their much smaller target patient population. To capture a realistic representation of the RBOs, we use numerical simulation techniques to compute the investment returns of a hypothetical portfolio of orphan drug development projects. Given empirically plausible assumptions for revenues, costs and probabilities of success for orphan diseases, we find that much smaller portfolios than those of Fernandez *et al.* [1] – containing only 10–20 compounds and requiring less than US$575 million in capital – are sufficiently diversified to yield reasonable investment returns for RBO investors. Although the investment returns of RBOs are positively related to portfolio size owing to the impact of financial leverage, for certain types of projects the required threshold of assets can be modest and it might be worthwhile to target these projects for an initial proof-of-concept of the megafund financing structure.

Orphan diseases and the ODA

In the 30 years since the ODA was passed, the orphan disease landscape has changed drastically. Orphan diseases, formally defined as those that affect fewer than 200,000 individuals in the USA [3], were once anathema to the pharmaceutical industry. Today, this once-ignored category of diseases commands a market worth nearly US$90 billion annually [4] and is believed to serve more than twice the number of all US cancer patients – at least 25 million Americans are afflicted with one of almost 7000 recognized rare diseases [5]. Clearly as a collective, rare diseases are not rare at all.

Before 1983 and the ODA, orphan diseases posed too many challenges for industry to confront seriously. Approximately 80% of rare diseases are caused by underlying genetic defects, which can be hard to identify [6]. Others are caused by exposures to rare and unusual toxins. Some orphan diseases are so uncommon that afflicted individuals might not be correctly diagnosed for many years, and there are instances of afflicted individuals never receiving a correct diagnosis [7]. Additionally, the rigorous standards of the FDA for clinical trials often meant that assembling patient populations of sufficient size for testing was exceedingly difficult. The ODA has been broadly acclaimed for its effectiveness in diminishing these barriers to development.

The ODA and its subsequent revisions provided several important economic incentives to sponsors of orphan drugs. To jumpstart therapeutic development in the rare disease category, the ODA created research grants specifically for orphan drug research, implemented tax credits of up to 50% for clinical testing costs, authorized expedited regulatory review for orphan drugs and, most importantly, established a 7-year period of marketing exclusivity that precludes FDA approval of the same or generic drugs for the same orphan indication [8]. The exclusivity provision is distinct from a patent and, in many cases, provides additional protection from competition by generics and other potential market entrants.

The combination of the ODA incentive program and several significant scientific breakthroughs in molecular biology and genome sequencing has resulted in three decades of innovative and fruitful orphan drug discovery. Before the ODA, the FDA had approved fewer than ten drugs for orphan diseases; today, that figure stands at more than 350 unique drugs (http://www.accessdata.fda.gov/scripts/opdlisting/oopd/). Currently, orphan drugs are at the forefront of global pharmaceutical R&D trends. Although the compound annual growth rate (CAGR) between 2001 and 2010 for new molecular entities as a whole was negative, the CAGR for orphan designations over the same period was robust at approximately 10% [9]. The overall drug market also reflects this trend. Orphan drugs currently comprise 22% of total drug sales with a CAGR of 25.8% during 2001–2010, compared with 20.1% for the non-orphan market [8]. Some industry developments suggest that these strong figures could continue to rise as the evolution toward more-targeted therapies and stratified medicine progresses.

The suitability of orphan drugs for RBO financing

Orphan drugs are particularly well suited to portfolio financing. A primary reason is the significantly higher rates of success that orphan drug development projects enjoy when compared with those of other disease groups such as oncology or neurodegenerative disorders. Orphan diseases are largely caused by a mutation in an individual's genetic code, most commonly manifested as a malfunction or absence of one or more key proteins. If the underlying genetic defect can be identified and characterized, it is often possible to create highly targeted and effective therapies to address the malfunction and its symptoms [9]. Similar targeting methodologies have been used to combat rare cancers, notably for drugs such as Rituxan® and Gleevec®. Consequently, the odds of a new orphan drug receiving FDA approval are significantly higher than those of a non-orphan counterpart. For orphan drugs that entered clinical testing between 1993 and 2004 we estimate the overall regulatory success rate to be approximately 22%, whereas the comparable figure for non-orphan drugs was approximately 11% [10] and the rate for anticancer compounds was even lower at only 6–7% [10].

The success or failure of orphan drug development projects is also less likely to be correlated across diseases as a result of the large proportion of orphan diseases that display monogenic pathology or act through largely unrelated mechanisms [11]. This observation is particularly significant given the central role that correlation has in determining the risk of a portfolio of candidate drug compounds. Although we are not aware of any longitudinal estimates of historical correlations among drug development projects, the scientific basis of orphan drugs suggests that correlations are likely to be small, especially when contrasted with other disease groups such as oncology. Many types of cancers have similar pathologies, such as the deregulation of specific signaling pathways and mutations in crucial oncogenes. As an example, consider the Janus kinase/signal transducers and activators of transcription (JAK/STAT) and transforming growth factor (TGF)-β pathways, each of which has been linked to dozens of oncologic diseases [12,13]. Of course, there are several orphan drugs in oncology but, in contrast to larger classes of oncology drugs that share a common mechanism such as tyrosine kinase inhibition or antiangiogenesis, orphan drugs (as a distinct category) act against a wider variety of targets.

Furthermore, orphan drugs have been shown to have almost equivalent lifetime revenue potential to non-orphan therapies. According to Thomson Reuters, an average orphan drug can be expected to attain sales of US$100–500 million per year [14]. Small patient population sizes are often compensated for by high per-patient revenues. For example, Soliris®, a drug to treat paroxysymal nocturnal hemoglobinuria (a rare blood disease affecting fewer than 6000 individuals in the USA), is priced at more than US$400,000 per patient per year [9]. Consequently, the blockbuster drug model that is characteristic of many top-selling non-orphan drugs is equally applicable to the orphan market: compounds in the top 29% of orphan drugs are

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