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Orphan Drug Designations as Valuable Intangible Assets for IPO Investors in Pharma-Biotech Companies

Philippe Gorry and Diego Useche

11.1 Introduction

Orphan drug (OD) legislation has been implemented with regulatory and financial incentives to encourage drug innovation in order to treat rare diseases. Similar to personalized and precision medicines, OD potential market populations, which are small, create low incentives for drug development compared with mass-market blockbuster drugs (Stern et al. 2017). Since the work of Spence (1973) and Podolny (1993), the role of signals in markets has been well documented in the literature. This chapter studies whether OD applied prior to an initial public offering (IPO) may be considered as a valuable intangible asset that influences the way investors perceive biotech firms' potential through an increase in the amount invested at the time of the IPO in the United States' (US) stock markets. For OD sponsors, the capacity to raise money through global pharmaceutical company partners, venture capitalists (VC) and IPO investors, is a fundamental factor for drug innovation and OD development. When confronted with a problem of low

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demand, OD development is characterized by a long development cycle (between eight and twelve years on average) and a high attrition rate, especially between preclinical and clinical phases. Therefore, because it involves substantial costs to develop a product candidate that may fail to obtain regulatory approval or to become commercially viable, investment in OD pharmaceutical product development is very risky.

Investors in high-tech firms have become more cautious over the last decade and have delayed their investments until firms demonstrate more tangible research outputs (Pisano 2006). Investors in biotech start-up companies are increasingly risk averse and have become more cautious in selecting firms with a high-growth potential while they are usually young, unprofitable, and niche-market oriented. These investors tend to measure investment potential by analyzing considerable data gathered on firms' histories and their perceived market potential. The literature has highlighted the value and the nature of different technological and organizational characteristics that may be considered as signals for IPO investors in high-tech companies. As organizational signals, the literature stresses, for example, the influence of venture capital (Lerner 1994; Gompers 1995), strategic alliances and interorganizational networks (Stuart, Hoang, and Hybels 1999; Danzon, Nicholson, and Pereira 2005), the firm's underwriter supporting the IPO firm (Loughran and Ritter 2004), and any other signals that may help reduce asymmetric information and improve IPO performance. The managerial and innovation literature has also analyzed several technological characteristics such as patents and drug portfolios that help to reduce uncertainty and skepticism regarding an IPO firm's performance (Mansfield, Schwartz, and Wagner 1981; Long 2002; Guo, Lev, and Zhou 2005; Mann 2005; Heeley, Matusik, and Jain 2007; Hsu and Ziedonis 2008; Useche 2014).

Thus, the companies intending to go public must convince evaluators that it is worth investing in them (Wilbon 1999; Useche 2014). The case of Aegerion Pharmaceuticals illustrates the difficulty to evaluate young OD developers. The company was founded in 2005 to develop novel therapeutics to treat rare genetic lipid disorders. Like many development-stage companies, Aegerion funded its operations through private placement of stocks, convertible debt, and venture debt while it was not generating revenue, and its accumulated deficit rose to $74.6 million in 2010. The company decided to go public after having started expensive Phase III clinical trials for its pivotal compound lomitapide in 2010. At that time, the company had only filed four patents, which is much less than the number of patent applications of rare diseases sponsors at the time of their IPO (on average, fifteen applications). In contrast, Aegerion was very active in searching for regulatory approval and support, and three orphan drug designations (ODDs) were already registered at the Food and Drug Administration (FDA) Office of Orphan Products Development (OOPD).

In this chapter, we document that ODD conveys a powerful certification

and reputational component that attracts IPO investors. ODD appears even to be more relevant than other technological characteristics, such as patent applications or later-stage drug compounds to attract IPO investors. These results are particularly important in a context of steadily declining numbers of new molecules and strong market imperfections to assure research and development (R&D) investments in rare diseases drugs. In the context of the biotech industry, the signaling literature has shown the dynamic value of signals across the industry life cycle. Based on the status signaling hypothesis (Podolny and Scott Morton 1999), Higgins, Stephan, and Thursby (2011) suggest that the importance of a signal diminishes when other measures of firm quality become available, reducing uncertainty. We report that the value of ODD for IPO investors is highly resilient to changes in the industry life cycle and stock market evolution.

The remainder of this chapter is as follows. Section 11.2 reviews the literature on the rare disease drug development market process, the emergence of ODDs (subsection 11.2.1) and sets out the main characteristics that make ODDs valuable intangible assets and technology market signals for investors in biotech companies (subsection 11.2.2). Section 11.3 discusses the methodology and data. Regression results, alternative models, and robustness checks are provided in section 11.4. A discussion on the main results and the conclusions are presented in section 11.5.

11.2 Background

11.2.1 Orphan Drug Legislation and the Rare Disease Drug Development Market: A Review

The biotechnology and pharmaceutical industries are characterized by highly uncertain technology development, intense competition, and a strong emphasis on intellectual property. The development of biotech drugs is a long and risky process in which it can take ten to twenty years to yield a commercial product with highly uncertain prospects for success (Lazonick and Tulum 2011). According to the literature (Pisano 2006; Hay et al. 2014), it is estimated that only one out of about 6,000 synthesized compounds has ever made it to market, and only 10 to 20 percent of drug candidates beginning clinical trials have ultimately been approved for commercial sale. Drug development for rare diseases is confronted with profound and persistent uncertainty and long-term risks that are remarkably costly relative to a small number of consumers (Rzakhanov 2006; Yin 2008). According to Moors and Faber (2007), OD development is particularly complex and risky because the rare disease lacks a knowledge base, and patient groups for clinical trials are small. Therefore, OD development requires more collaboration with other stakeholders than does conventional drug development (Moors and Faber 2007).

The anatomy of the orphan drug industry, which is mainly composed of biotech firms, is structured by strong intellectual property rights driving the feasibility and direction of technology development, the market for know-how, and finally, access to funding and R&D alliances. The OD sponsors mainly rely on four sources of funding to develop new drugs: (a) R&D government grants, (b) venture capital investments, (c) public equity markets, and (d) strategic alliances (Danzon, Nicholson, and Pereira 2005; Pisano 2006). The VC investments and, in most cases, R&D alliances involve a capital injection into the start-up, giving the venture capitalist or the established company an equity stake (Lazonick and Tulum 2001). Biotech start-ups depend heavily on R&D alliances, which usually include an R&D contract from the established company for the young firm to engage in drug development in exchange for intellectual property rights and marketing rights if the drug is approved (Lazonick and Tulum 2011).

The OD sponsors, as well as other biopharmaceutical companies, still find it extremely difficult to predict whether a particular new molecule will be safe and effective in humans. Sometimes, intellectual property rights may not provide sufficient incentive for drug R&D. Markets for new drugs may be too small for firms to operate (Rzakhanov 2006). Over the last few decades, advances in the biotechnology industry have increased the pathophysiological knowledge of diseases, the number of molecular targets to attack them, and novel approaches for cures (Pisano 2006). Until late in the 1970s, drugs with potential benefits to rare disease populations were "orphaned" (Rohde 2000). This evidence motivated lobbying efforts from patient groups frustrated at the lack of drugs approved to treat rare diseases to pass OD legislation (Yin 2008). In order to stimulate innovation in rare disease drugs, the US Orphan Drug Act (ODA) was adopted on January 4,1983. It was the first regulation adopted in the world to offer incentives for drug development for rare diseases on the basis of supply-side incentives. The ODA was enacted to stimulate the development and marketing of ODs that are a particular kind of high-risk development drugs used to treat rare diseases and conditions (Seoane-Vasquez et al. 2008). Indeed, before the ODA, only a small number of rare disease treatments were authorized by the FDA (Asbury 1991; Seoane-Vasquez et al. 2008; Garden, Gorry, and Paris 2016). After the ODA, OD R&D became increasingly dynamic, and since then more than 400 orphan treatments have been approved (Seoane-Vasquez et al. 2008; Garden, Gorry, and Paris 2016). This spectacular turnaround demonstrates that pharmaceutical companies no longer disregard rare diseases. In fact, OD research today appears to be one of the most dynamic business segments of the pharmaceutical industry (figure 11.1).

While the previous literature has shown that ODD had a significant impact on rare disease drug development, little is known about how ODDs may help OD sponsor firms to attract investors, and to mitigate problems of asymmetric information and risk.

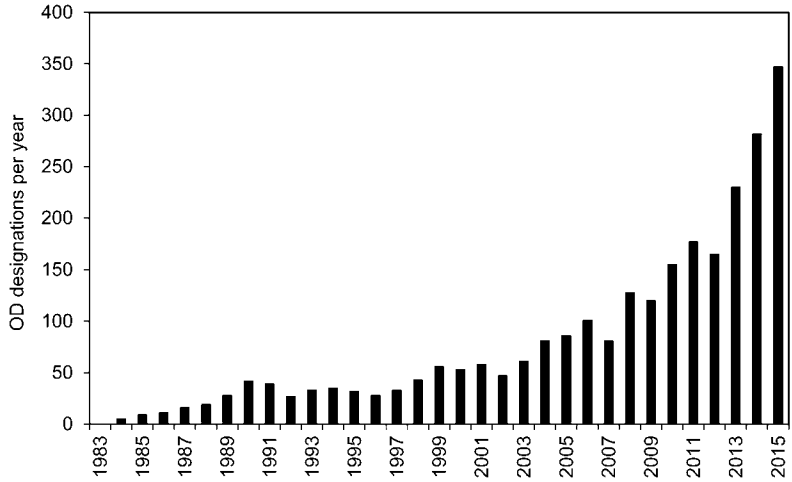

Fig. 11.1 FDA registration of OD designations from 1983 to 2015

11.2.2 Hypothesis: ODDs as Valuable Intangible Assets and Market Signals

ODDs may be considered as valuable intangible assets that may attract investors in pharma-biotech start-up companies. Similar to patent applications, ODDs may be considered signals because they are a readily observed attribute correlated with company performance and market strategy (Long 2002; Mann 2005; Heeley, Matusik, and Jain 2007; Hsu and Ziedonis 2008; Hoenen et al. 2014; Useche 2014; Hoenig and Henkel 2015). The ODDs can provide a signal of the quality of a start-up's technology, according to the signaling theory of Spence (1973) and Podolny (1993). In order to be effective, signals need to be observable and costly (Spence 1973; Long 2002; Hsu and Ziedonis 2008; Useche 2014). Observability describes the extent to which outsiders are able to take note of the signal. Since the ODD is publicly disclosed by the FDA—a highly visible regulatory agency, the ODD signal is directly observable by outsiders. The comprehensive examination by the FDA Office of Orphan Drug Products Development operates as a certification mechanism, and might parallel the signaling power of patents (Hoenig and Henkel 2015). Investors may interpret ODDs as a positive sign of the innovative capacity of the companies in question, in a market characterized by an astonishing pipeline of new innovative drugs developed by the major pharmaceutical companies in the past decades (Paul et al. 2010).

The ODDs are also costly to obtain and they provide a selection mechanism that allows observers to distinguish among different qualities and firm strategies. Even though sponsor firms granted ODDs by the FDA are exempted from the prescription drug-user fee, drug development for rare diseases is particularly costly, complex, and risky because rare diseases lack

a knowledge base and patient groups for clinical trials are small (Rzakhanov 2006; Yin 2008). In order to compensate and stimulate to some extent rare drug developers, ODDs offer several advantages, which may suggest that the holder has a competitive advantage and offers a sign of its higher quality and technology compared to other companies. First, an ODD holder has an exclusive right, and may sell at an unregulated price over the seven-year exclusivity period without competition. This monopoly begins at the market-approval date and is independent of intellectual property rights. Second, a subsequent innovator that develops a new drug prior to expiration of the pioneer's exclusivity right can replace the incumbent only if the new drug is "clinically superior" to the "old" drug on the market. This expiration of exclusivity does not call into question any intellectual property rights linked to the orphan drug. Third, for the drug sponsors, the ODD provides a 50 percent tax credit on the clinical trial cost, a fee waiver for regulatory activities, and some assistance from the Office of Orphan Products Development. Fourth, the FDA's exclusive marketing right is effectively transferable to another company subject to the consent of the regulator. Fifth, an ODD and exclusive marketing right cannot be revoked later if the drug subsequently proves to have greater commercial potential, and is therefore considered as a real option. In addition, ODs have shorter development time than other drugs (Seoane-Vasquez et al. 2008).

In addition, ODD offers powerful certification and reputational value. Moors and Faber (2007) suggest that ODDs may provide a powerful incentive for image improvement to finance-seeking start-ups in orphan segments with a lack of a profound knowledge base. The certification component of ODDs may also help OD sponsors find valuable external resources, such as competent R&D partners and valuable employees to hire. The "legal certification" component of ODD is assured by the FDA Office of Orphan Products Development (OOPD), which receives, reviews, and eventually approves OD requests. The main criterion to obtain an ODD is to develop drugs to treat rare diseases defined as those affecting less than 200,000 patients in the United States, or those drugs for which R&D investment would not be recovered by US product sales. In addition, the Orphan Drug Amendment of 1988 allows sponsors to request an ODD for any unapproved use of a drug without regard to whether other indications of the drug were approved for marketing previously. The legal certification component of ODDs may also facilitate access to contracts, grants, or subsidies, potentially increasing future firm performance. As such, it supports the appropriation of returns from innovation and facilitates cooperation with business partners.

For these reasons, among others, Rzakhanov (2008) suggests that ODDs may have similar characteristics to patents and may be considered as valuable intangible assets for their holder. However, OD exclusivity offers the second-broadest level of protection because the provision protects the orphan-designated indication against generic and full New Drug Applica-

tion (NDA) approval (Seoane-Vasquez et al. 2008). It is worth noting that market exclusivity is a postapproval incentive beginning on the date of the FDA market approval for the designated orphan indication. Policies on OD development operate within the FDA regulation framework: sponsors need first to file an Investigational New Drug (IND) before initiating clinical studies, and later on an NDA or a Biologics License Application (BLA).[1] It is important to note that sponsors of ODs frequently qualify for fast-track status, accelerated approval and/or priority review under the Prescription Drug User Fee Act of 1992 (Shulman and Manocchia 1997; Seoane-Vasquez et al. 2008). As a matter of practice, drug regulatory requirements might be more relaxed for rare diseases at the discretion of the FDA, and ODs are likely to qualify for lower approval standards (Kesselheim, Myers, and Avorn 2011).

The literature on OD designations has reported that ODs may be associated with higher firm performance. Rzakhanov (2008) reports that both OD designation and market-approved ODs are associated with higher market value for firms, but to a lesser extent than nonorphan drugs. His research was based on a pre-2000 heterogeneous sample of OD sponsor firms ($n = 60$) and biotech firms without OD under development, and covered the entire spectrum of firms from spinoffs to public companies.

However, there is little evidence on how biotech IPO subscribers use ODDs as a credible signal of high firm value, competitive advantage, and future firm performance on financial markets. We aim to study how ODDs may influence IPO investors through a larger amount of cash invested at IPOs, other factors remaining fixed. To address these issues, we perform econometric regressions on the relationship between various metrics of firm quality contained in patents prior to the IPO and the amount of cash collected at the IPO, while controlling for other factors that may influence IPO performance (Ritter and Welch 2002; Brau and Fawcett 2006).

11.3 Data and Measures

11.3.1 Data Sources

We built an original database linking data from five different sources: (a) the IPO prospectuses and S-1 registration statement database, (b) the FDA Orphan Drug product designation database, (c) the Orbit patent database (owned by Questel), (d) the Pharmaproject database (owned by Citeline) for the drug pipeline, and (e) VentureSource (owned by Dow Jones) for corporate and VC investment before IPO. IPO prospectuses and S-1 forms were retrieved from different sources: the NASDAQ website;[2] US Securi-

1. Pre-BLA and NDA meetings between the sponsor and the FDA typically occur late in the R&D cycle (usually in Phase 3).

2. http://www.nasdaq.com.

ties and Exchange Commission (SEC) archives;[3] and the EDGAR Online database[4] provider for historical data with financial, ownership, and shareholder information. The FDA Office of Orphan Drug Products (OOPD) maintains an OD designations and approvals database[5] where OD statuses are logged in with product and designation information, as well as sponsor information. Our patent data analysis was based on the worldwide collection of INPADOC (International Patent Documentation; EPO worldwide legal status database) family patents using the Orbit patent research platform,[6] which provides an applicant search function based on company structure using the FactSet corporate tree data (Useche 2014).[7] Drug information was mainly retrieved from Pharmaproject, a proprietary data source[8] including drugs developed in pharmaceutical markets worldwide from 1980 to date; this data set has been used in pharmaceutical industry economics research (Hirai et al. [2012] and references therein). To complement these data, we used FDA Center for Drug Evaluation and Research (CDER) archives, as well the Orphanet,[9] DrugBank,[10] PubChem,[11] and ChemSpider[12] databases to document the chemical or biological nature of the OD. Finally, we use VentureSource—a global database on companies backed by venture capital and private equity in across regions, industries, and stages of development to retrieve details about rounds of financing.[13]

11.3.2 Sample Description

Our approach to building the data set was to identify IPO deals concerning ODD applicant firms from the United States between January 1, 1995, and December 31, 2015. Our primary data source was the FDA Orphan Drug Product designation database. From 1983 to December 2015, more than 3,000 ODs were registered by some 1,400 sponsors worldwide (including firms, universities, physicians, patient advocacy groups, and other nonprofit organizations). The ODD trend accelerated from the year 2000 following several provisions implemented by the US Congress: Rare Diseases Act (2002), Office of Orphan Product Development, Medicare Patient Access Drugs for Rare Diseases Act (2003) (figure 11.1). All ODD sponsor firms

3. http://www.sec.gov/edgar/searchedgar/companysearch.html.
4. http://pro.edgar-online.com.
5. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/.
6. http://www.questel.com.
7. Questel-Orbit is a patent database that allows the users to build and organize patent portfolios and examine individual patents. The QPAT database has developed a family definition (FamPat family), which provides comprehensive family coverage of worldwide patent publications.
8. https://pharmaintelligence.informa.com.
9. http://www.orpha.net.
10. https://www.drugbank.ca.
11. https://pubchem.ncbi.nlm.nih.gov.
12. http://www.chemspider.com.
13. http://www.dowjones.com/products/pevc/.

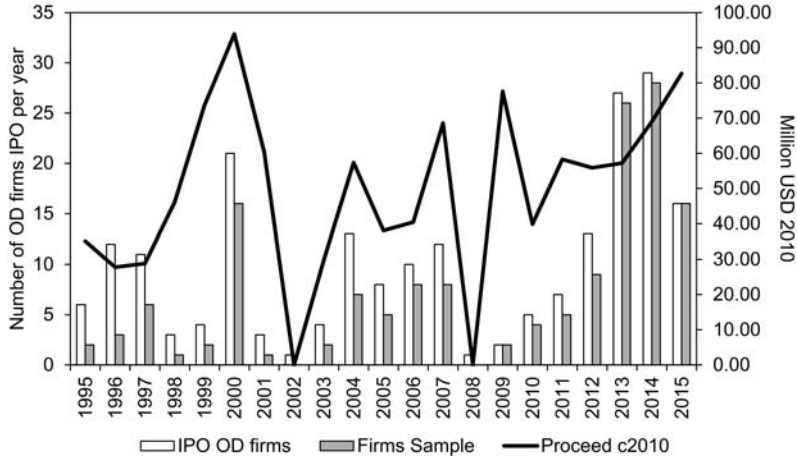

Fig. 11.2 Trends of OD firms IPO

were cross-referenced with firms that were listed, or had been listed, either on the New York Stock Exchange (NYSE) or on the National Association of Securities Dealers Automated Quotations (NASDAQ). We identified 277 firms applying for ODD that had been traded on the NYSE or NASDAQ. Next, we tracked all the OD applicants that had gone public since 1983 and collected IPO information primarily from the final IPO prospectus and S-1 registration filings issued when those firms went public ($n = 253$). Trends of IPOs with OD portfolios do not parallel the OD designation trends. The acceleration of IPOs of OD firms is more recent, except for a peak of IPOs around the dot-com bubble in 2000 (figure 11.2). The average amount of money raised by a firm going public is 49.55 million dollars (2010 constant dollars). It varies considerably over the twenty-year period (1995–2005) with a maximum of $93.91 million in 2000 at the time of the internet bubble (figure 11.2). Considering only those companies with available information about pre-IPO characteristics and the amount of cash collected at IPO, our final sample is composed of 146 OD IPO firms between January 1, 1995, and December 31, 2015. These companies are mostly quoted on the NASDAQ (98 percent) and are US firms (92 percent). Most of these firms are drug companies operating in the pharmaceutical (73 percent), diagnostic or biotechnology (19 percent) sectors, and are considered Pharma-Biotech companies (93 percent) according to their Standard Industrial Classification (SIC) codes (table 11.1). In that respect, our sample differs from the ones described by Higgins, Stephan, and Thursby (2011) (who excluded SIC no. 2833) and is closer to the sample of Guo, Lev, and Zhou (2005), except for one firm classified in the "surgical & medical instruments & apparatus" category. It is important to note that of the firms we included, none are classified as "big pharma," that is, companies ranked in the top fifty by annual revenue.

Table 11.1 SIC code distribution of OD firms IPO sample

SIC	Number of firms	Description
2833	1	Medicinal chemicals and botanical products
2834	108	Pharmaceuticals preparation
2836	26	Biological products, except diagnostic substances
3841	1	Surgical and medical instruments and apparatus
8731	10	Services—commercial, physical, and biological research
Total	146	

11.3.3 Measures

Value-IPO Proceeds as Dependent Variable

We are interested in whether OD sponsors use ODDs obtained prior to IPOs as a credible signal of high firm value, competitive advantage, and superior future firm performance on financial markets. Following the literature, we use traditional measures of performance, which were mainly collected through the IPO prospectus and S-1 registration filings database. Traditional measures of IPO performance are based on the amount of cash collected by the firm at the IPO (Chemmanur and Fulghieri 1994; Ritter and Welch 2002; Higgins, Stephan, and Thursby 2011), the premoney valuation of the firm (Stuart, Hoang, and Hybels 1999; Higgins and Gulati 2003), and the age of the venture at the IPO (Chang 2004). We chose as our key dependent variable PROCEEDS, the amount of cash collected by the firm i at the IPO date t. The dependent variable as well all the subsequent financial control variables are converted to millions of 2010 constant dollars using the consumer price index (2010 = 100) from the World Bank.[14] This measure of IPO performance avoids potential problems of overallocation in the premoney valuation (Ritter and Welch 2002; Higgins, Stephan, and Thursby 2011). A natural log-transformed variable of PROCEEDS was used to address the valuation data skew and reduce its heterogeneity.

FDA ODD Portfolio as Explanatory Variables

ODDs may have similar characteristics to patents. They are intangible assets of firms and a source of potential revenue streams, which are, however, not listed explicitly on a company's balance sheet. As objects of intellectual capital, they could be transferred to third parties under the law (licensing, merger and acquisition, bankruptcy). As discussed above, among other advantages, ODD provides drug sponsors with a 50 percent tax credit for clinical trial costs, a fee waiver for regulatory activities, fast-track evalua-

14. https://data.worldbank.org/indicator/FP.CPI.TOTLwith?locations=US.

tion for market approval, and some assistance from the Office of Orphan Products Development.

11.3.4 Control Variables

Intellectual Propriety Portfolio and Drug Pipeline

Patent protection of drugs in R&D is essential to the pharma-biotech industry business model in order to secure returns on large and risky investments. Therefore, we matched IPO information for each firm with the number of patents the firm filed (patents with priority date) from the Orbit database. We considered the total number of priority patents filed by the firm over the four-year period before the IPO (PATPPy4). This window length in the number of patent applications takes into account the fact that recent patents may provide the most current information about the firm's inventive capabilities at the time of the IPO (Useche 2014).

A classical indicator of research and development in the pharmaceutical industry is the number of drugs in development, otherwise known as the "drug pipeline." We identified in the Pharmaproject database the number of drugs under active R&D prior to the IPO (DRUGPIPEPRIORIPO). It has been estimated that only 10 percent of identified molecules might make the transition to a candidate drug and enter clinical trials (Hughes et al. 2011). For each firm, we computed the number of compounds under active development that successfully reached the stage of clinical trial Phase II (PHASE2PRIORIPO). We chose this stage indicator because it is pivotal in the drug development cycle: Phase II addresses therapeutic effectiveness, it has an average time-to-market of five years (Paul et al. 2010), and the Phase I stage is not discriminatory, with a 66 percent success ratio (Hay et al. 2014).

Among medicines, we distinguish between drugs and biologicals. Drugs are manufactured through chemical synthesis while biologicals are manufactured in living systems using recombinant DNA technology. Independently of the OD status, the FDA regulates differently chemical-based drugs and biological-based drugs through NDA or BLA, respectively.[15] Since 1993, the number of BLAs registered at the FDA (mean = 4.65; maximum = 12; minimum = 1) was less than the number of new molecular entities (mean = 24.47; maximum = 47; minimum = 11), and varied over time with the maximum of registered molecules occurring in 1996, a minimum in 2005, and a maximum of BLA applications in 2015 (Mullard 2016). Therefore, we identified in our data set the number of chemical-based OD (ODD_CHEM) and biological-based OD (ODD_BIO) products developed by the firm prior to its IPO in order to take into account the different trends and regulatory regime.

15. https://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/default.htm.

In the last decades, oncology has been the main therapeutic area of interest of the pharmaceutical industry R&D (Mullard 2016). Therefore, it is important to control for the therapeutic area of ODD pipeline prior to its IPO. Based on the ODD registered by the FDA, we encoded our data set according to the therapeutic area using the Anatomical Therapeutic Classification (ATC)[16] at Level 1. The ODDs were dispersed among the fourteen different ATC classes with a strong concentration of ODD on ATC Class L, that is, antineoplastic and immunomodulators drugs. Thus, we computed the number of ODD Class L prior to the IPO (ODDkcpriorIPO). Because the ODA has been implemented for rare diseases, which in most cases are genetic diseases, we built in addition another control variable that cannot be captured appropriately through the ATC classification. This control variable, ODDRDpriorIPO, measures the number of ODs filed by the firm prior to its IPO with any genetic disease designations, according to the Online Mendelian Inheritance in Man (OMIM)[17] dictionary.

Age, Collaborative Revenues, and R&D Investments at IPO

Previous research has shown that experienced entrepreneurs are more likely to be able to secure financial resources and go public (Gompers 1995). From IPO prospectus and the S-1 registration filings database, we collected data to control for the age of the company at its IPO (AGE AT IPO), which is calculated as the difference between the effective date of the IPO and the date of incorporation. In addition, we also controlled for the amount of R&D expenses and the total collaborative revenues over the year before the IPO.

Venture Capital and Corporate Venture Capital Support

We collected information related to venture capital support using the Venture Source database. Venture Capital support can provide a signal of confidence about the firm's management, technology, and capabilities (Megginson and Weiss 1991; Gompers 1995; Brau and Fawcett 2006). For these reasons, we included the dummy variable VENTUREBACKED, which indicates whether the IPO was backed by one or more venture capital firms, and the dummy CORPVCAP, which is equal to one if the IPO was backed by one or more corporate venture capitalists (CVC) and zero otherwise. We also introduced the number of venture capital rounds before the IPO (VCROUND), the variable VCINTENSITY defined as the number of years between the first VC investment and the IPO date, and the variable VCFUND defined as the amount of money collected from venture capitalists prior to the IPO. It is expected that venture-backed companies produce a superior IPO performance relative to ventures quoted without similar funding support.

16. https://en.wikipedia.org/wiki/Anatomical_Therapeutic_Chemical_Classification_System.
17. http://www.omim.org.

Percentage of the Firm Being Sold and Underwriter Reputation

We followed the literature (Leland and Pyle 1977; Brau and Fawcett 2006; Higgins, Stephan, and Thursby 2011; Carter and Manaster 1990) and controlled for the percentage of the firm to be sold during the public offering and for underwriter reputation. The literature has shown that the market considers the sale of a large portion of the company as a negative sign. Indeed, a large share of the company being sold may signal that the current owners have negative inside information on the company. Thus, like Higgins, Stephan, and Thursby (2011), we included the natural log of the percentage of total shares of the firm that are sold (PERCENT SOLD) as an explanatory variable. The IPO performance is also related to underwriter reputation (Carter and Manaster 1990). Underwriters' reputation (UWREPUT) was measured with Loughran and Ritter's (2004) update of the underwriter reputation rankings developed by Carter and Manaster (1990). The lead underwriter was matched by name with the ranking score in Jay Ritter's database.[18]

Market Conditions

Finally, we used temporal, country, and stock market differences in IPO deals as explanatory variables. It has been documented that IPOs tend to come in waves, characterized by periods of hot and cold markets. First, we introduced a dummy variable coded one if the companies were quoted on the NASDAQ (US), else it was zero. We included the variable BIO_RATIO, which is the ratio of the number of biotech IPOs divided by the total number of IPOs in a given year (Higgins, Stephan, and Thursby 2011). Finally, we controlled for the dot-com bubble in 1999 and 2000, years known to have impacted the life science industry. It has been demonstrated in the literature that firms raised more cash from the NASDAQ stock market during this hot issue period (Chok and Qian 2013).

11.3.5 Summary Statistics

We present the description of variables and report descriptive statistics for the pharma-biotech companies sponsoring ODs in table 11.2. Several characteristics of OD sponsors prior to IPOs merit discussion here. First, about 49.31 percent of the companies have applied for ODDs before the IPO. Also, on average, OD sponsors applied for their first ODD 2.8 years before the IPO. In contrast, most of the companies going public applied for patents four years before the IPO (89.72 percent), and had a drug pipeline of 9.2 compounds on average at the time of the IPO. Prior to the IPO, ODD firms had more chemical compound (63.7 percent) than a biological drug (45 percent) in their R&D portfolio. Around 38.8 percent of the ODD port-

18. Underwriter ranking data available from Shane Corwin's website http://www3.nd.edu/~scorwin/.

Table 11.2 Variable description and summary statistics

Variable code	OD firms Mean	Min.	Max.	Definition	Source
Dependent variables					
LOG (PROCEEDS)	17.623	10.812	19.445	Logarithm of amount collected at IPO	IPO prospectus
ODD	0.863	0	6	Number of orphan drug designations applied by the firm at date of IPO	OD database
PATAPPy4	15.137	0	328	Number of patents applied for by the firm in last four years prior to IPO	Q-Qpad
PHASE2PRIORIPO	1.116	0	7	Number of drugs in at least Phase II in the pipeline prior to IPO	Pharma project
LOG (R&D_EXPENSES)	2.0942	–2.078	4.368	Logarithm of research and development expenses in year prior to IPO	IPO prospectus
AGE AT IPO	8.349	2	23	Age of company at IPO	IPO prospectus
EMPLOYEES	59.007	0	470	Number of employees at date of IPO	IPO prospectus
LOG (REVENUES + 1)	1.018	0	4.989	Logarithm of the total revenues in year prior to IPO	IPO prospectus
SICSEC2834	0.726	0	1	DV* recorded a value of 1 if company's principal segment is SIC 2834, 0 otherwise	IPO prospectus
LOG (PERCENT SOLD)	–1.388	–4.529	0	Logarithm of percentage of firm to be sold during a public equity offering	IPO prospectus
UWREPUT	0.041	0	1	The prestige of the IPO firm's lead underwriter	Ritter ranking
VENTURE BACKED	0.733	0	1	*DV recorded a value of 1 if company is a venture-capital-backed IPO, 0 otherwise	Venture source
CORPVCAP	0.178	0	1	*DV recorded a value of 1 if company is a corporate venture-backed IPO, 0 otherwise	Venture source
NASDAQ	0.973	0	1	*DV recorded a value of 1 if company was quoted on NASDAQ (US)	IPO prospectus
BIO_RATIO	0.208	0.023	0.357	Ratio of biotech IPOs divided by total number of IPOs in a given year	Capital IQ
BUBBLE	0.123	0	1	*DV recorded a value of 1 if company was quoted on 1999 or 2000	IPO prospectus
ODLAGGEDT4	0.438	0	6	Four years lagged number of orphan drug designations applied by the firm	OD database
ODEXPERIENCE	2.840	0	22.838	Number of years from the first orphan drug designation to IPO	OD database
DRUGPIPEPRIORIPO	0.425	0	18	Number of drugs launched in the pipeline prior to IPO	Pharma project
LICENSINGPRIORIPO	1.683	0	14	Number of drugs under license in the pipeline prior to IPO	Pharma project
ODDKcpriorIPO	0.26	0	9	Number of orphan drug designations in ATC class L applied by the firm at date of IPO	OD database
ODDRDpriorIPO	0.24	0	5	Number of orphan drug designations for genetic diseases applied by the firm at date of IPO	OD database
ODDkc	0.171	0	1	*DV recorded a value of 1 if company applied for at least one cancer ODD, 0 otherwise	OD database
CHEM	0.637	0	1	*DV recorded a value of 1 if company has a chemical ODD prior to IPO, 0 otherwise	OD database
BIO	0.45	0	1	*DV recorded a value of 1 if company has a biological ODD prior to IPO, 0 otherwise	OD database

*DV = Dummy variable.

folio prior to the IPO was dedicated against cancer and 50.7 percent against genetic diseases. Only a minority of firms succeeded in pushing drug candidates into Phase II clinical trial (38 percent). The OD sponsor companies were R&D-intensive firms spending on average $13.40 million, while their revenue is on average $7.46 million prior to their IPO. The OD firms were supported by venture capitalists (73.2 percent) at least through two rounds of investment for four to five years prior to the IPO. The average amount raised by the IPO (based on proceeds) was $62.76 million.[19]

As a preliminary examination of the bivariate relationships among the variables in the present study, Pearson correlation coefficients were estimated. Table 11.3 presents the results of these estimations for each pair of variables. The analysis indicates that several of the variables are positively correlated to one another, and many of the findings reported in earlier research are evident in the values reported there. For example, proceeds from IPOs are strongly correlated with R&D expenses. As one might expect, IPO proceeds are also correlated with the presence of venture capitalist backing. Moreover, the number of patents applied for four year before the IPO is correlated with R&D expenses and the former is also correlated with VC investments.

11.4 Econometric Strategy

11.4.1 The Main Model

We use the following model to test our hypotheses.

$$\log(\text{IPOPROCEEDS})_i = \alpha_0 + \Upsilon_i \text{ODD}_i + \beta_i X_i + w_i. \quad (1)$$

We aim to test the impact of orphan drug designations (ODD) on IPO performance measured by the natural logarithm of the amount of cash collected by the firm *i* at the IPO date (PROCEEDS). We follow the literature (Leland and Pyle 1977; Megginson and Weiss 1991; Ritter and Welch 2002; Brau and Fawcett 2006; Higgins, Stephan, and Thursby 2011) and control for variables that have been associated with IPO valuation (X_i). We included a dummy variable (UWREP) taking the value one if the underwriter reputation ranking proposed by Loughran and Ritter (2004) is equal to or greater than 8.00, and zero otherwise. We followed the literature (Leland and Pyle 1977; Brau and Fawcett 2006; Higgins, Stephan, and Thursby 2011) and controlled for the percentage to be sold during public offering (PERCENT SOLD) and two market conditions controls (BIO_RATIO) (Higgins, Stephan, and Thursby 2011) and BUBBLE (Chok and Qian 2013). We also included the variable VENTURE_BACKED taking the value one if the company has been supported by at least one venture capitalist, zero other-

19. The amount of cash collected at IPO, the R&D expenses, and the revenues were transformed in millions of 2010 constant dollars.

Table 11.3 Pearson Correlation matrix

		1	2	3	4	5	6	7	8	9	10	11	12
1	LOG (PROCEEDS)	1.0000											
2	ODD	0.0900	1.0000										
3	PATAPPy4	0.1074	0.1479	1.0000									
4	PHASE2PRIORIPO	0.0534	0.1301	0.1001	1.0000								
5	LOG (R&D_EXPENSES)	0.4059*	–0.0391	0.2323	0.1263	1.0000							
6	AGE AT IPO	–0.1915	0.3506*	0.3066	0.1867	0.0527	1.0000						
7	EMPLOYEES	0.2347	0.1197	0.3916*	0.2497	0.4440*	0.1881	1.0000					
8	LOG (REVENUES + 1)	0.1578	0.0870	0.3217	0.1821	0.3798*	0.2548	0.6350*	1.0000				
9	SICSEC2834	0.1838	–0.1182	0.1223	0.0178	0.1687	–0.0913	0.0809	0.1291	1.0000			
10	LOG (PERCENT SOLD)	0.0990	–0.0049	–0.0483	0.0350	–0.0691	0.0020	–0.1152	–0.0714	0.0725	1.0000		
11	UWREPUT	0.1346	–0.0814	0.1083	0.0095	0.1052	0.0151	0.2449	0.1671	–0.0267	–0.0140	1.0000	
12	VENTURE BACKED	0.3084	–0.0109	0.0124	–0.1610	0.3547*	–0.0227	–0.0264	0.0652	0.1824	0.0335	0.1260	1.0000
13	CORPVCAP	0.1094	0.1223	0.0967	0.0166	0.1784	0.1316	0.0797	0.1677	0.0069	0.0284	0.0834	0.2835
14	NASDAQ	0.1564	–0.0194	0.0802	–0.2251	0.1609	–0.0811	–0.1688	–0.0369	0.1787	0.1710	0.0350	0.0878
15	BIO_RATIO	0.0274	0.1201	0.0523	0.1342	–0.1102	0.2377	–0.1697	–0.0331	–0.0103	0.0418	0.0854	0.0739
16	BUBBLE	0.1783	–0.0838	–0.0002	0.0173	0.0830	–0.1779	0.1083	0.0274	–0.0484	–0.1066	0.0268	–0.0546
17	ODLAGGEDT4	0.0322	0.8251*	0.1776	0.0511	–0.1260	0.3391*	0.1126	0.1349	0.0059	0.0388	–0.0907	0.0148
18	ODEXPERIENCE	0.0835	0.6531*	0.0723	0.1121	0.0010	0.2752	0.1051	0.0340	0.0257	0.0701	–0.1042	0.0107
19	DRUGPIPEPRIORIPO	0.0469	0.3973*	–0.0264	–0.0827	0.0008	–0.0331	0.1492	0.1840	0.0719	–0.0009	–0.0314	0.0130
20	LICENSINGPRIORIPO	0.1254	0.2736	0.0027	0.3559*	0.1350	0.0185	0.2990	0.3018	–0.0959	–0.0652	0.0117	–0.0603
21	ODDKcpriorIPO	0.0478	0.2028	0.0125	0.0231	0.0289	0.1606	0.0209	–0.0454	0.0748	0.0348	–0.0589	0.0542
22	ODDRDpriorIPO	0.0875	0.5212*	0.0683	0.0656	0.0406	0.0982	0.0109	0.0096	–0.1625	–0.0233	–0.0223	0.0315
23	ODDcancer	0.0063	0.2748	–0.0275	0.1673	–0.0471	0.1060	–0.0133	–0.0956	0.0775	0.0305	–0.0948	0.0298
24	CHEM	0.0403	0.0450	–0.1111	–0.0617	0.0310	–0.0440	–0.0824	–0.0888	0.2463	0.0720	–0.0612	–0.0320
25	BIO	–0.0512	0.0829	0.0777	0.1563	0.0735	0.1299	0.2646	0.1538	–0.2504	–0.0877	0.0216	–0.0474

		13	14	15	16	17	18	19	20	21	22	23	24
13	CORPVCAP	1.0000											
14	NASDAQ	0.0787	1.0000										
15	BIO_RATIO	–0.0219	0.0049	1.0000									
16	BUBBLE	0.0421	0.0634	–0.2530	1.0000								
17	ODLAGGEDT4	0.0669	0.0312	0.0894	–0.1013	1.0000							
18	ODEXPERIENCE	0.0011	–0.0067	0.0603	–0.1188	0.6828*	1.0000						
19	DRUGPIPEPRIORIPO	–0.0742	0.0171	–0.0894	–0.0445	0.5464*	0.4106*	1.0000					
20	LICENSINGPRIORIPO	0.0353	–0.1757	–0.0337	0.1219	0.2928	0.2747	0.3896*	1.0000				
21	ODDKcpriorIPO	–0.0158	0.0477	–0.0811	–0.0614	0.0786	0.1339	0.1288	0.1025	1.0000			
22	ODDRDpriorIPO	0.2506	–0.0021	0.0740	0.0496	0.4450*	0.2546	0.1017	0.0665	–0.0660	1.0000		
23	ODDcancer	–0.1182	0.0769	–0.0064	–0.1165	0.1860	0.3049	0.1791	0.1557	0.6208*	–0.1056	1.0000	
24	CHEM	–0.1003	–0.0381	–0.1004	0.0199	0.0230	0.0676	0.1016	–0.0605	0.0875	–0.0299	–0.0013	1.0000
25	BIO	0.0848	–0.0175	–0.0611	0.0812	0.0663	0.0355	0.0467	0.1377	0.0894	0.1453	0.1025	–0.8006*

*Significant at the 10 percent level.

wise (Megginson and Weiss 1991; Gompers 1995; Brau and Fawcett 2006). We also included the natural logarithm of the total amount of collaborative revenues (REVENUES) and the R&D expenses (R&D_EXPENSES) in the year prior to the IPO. In addition, we also include the age of the company (AGE AT IPO) and the number of employees (EMPLOYEES) at the time of the IPO. Finally, we included a dummy variable coded one if the company's principal segment sector is pharmaceutical preparations (USSIC2834), else zero.

We followed the literature and attempted to account for the endogeneity of ODDs at the time of the IPO. Endogeneity arises if unobserved firm characteristics affecting the decision to apply for ODDs may also influence IPO pricing. Some of these variables are unobserved, such as specific firm characteristics and management quality, and are incorporated in the error terms in w_i in equation (1). The correlation between the error term and our ODD variable of interest will result in biased parameter estimates reflecting endogeneity. We tried to deal with endogeneity by way of a generalized method of moment (GMM) estimator. In our choice of instruments, we choose the number of years between the first OD application and the IPO date (ODEXPERIENCE). Greater experience with the FDA Office of Orphan Drug Products Development may facilitate future applications (Olson 2004). In contrast, there is no reason to think that IPO investors have the capacity to determine the number of years from the first OD application to IPO. In addition, we introduced the variable ODLAGGEDT4, which is the number of ODDs applied before the date of the IPO lagged four years. Here, we followed Anderson and Hsiao (1981) who used lagged variables as instruments for themselves (see also Baltagi and Khanti-Akom 1990; Windmeijer 2005).

11.4.2 Results

Table 11.4 reports the results of our two estimation procedures for the main model (equation [1]): ordinary least squares (OLS) regression (Model 1) and second stage of GMM estimator (Model 2). We observe that there is little variation across OLS and GMM regressions. Estimations results suggest that an additional ODD before IPO is related with an increase of about 20 percent and 18.9 percent in proceeds collected by companies at IPO, from OLS and GMM estimates, respectively. Several tests presented at the bottom of the table (Model 2) validate our instrumental variable approach and fail to reject the exogeneity of ODD.[20] Based on the coefficient ODD (0.183)

20. Tests of overidentifying restrictions, presented at the bottom of the table, fail to reject the exogeneity of the instruments with Sargan statistics (0.501, *p*-value 0.479) that confirms the validity of the instruments. In addition, the instruments' relevance condition is satisfied because the instruments are statistically related with the number of ODDs before IPO at the 5 percent and 1 percent level, respectively. First-stage regressions are available upon request. In checking for the weakness of the instruments, we find that *F*-statistics of 130.22 that largely exceeds the critical value of 19.93 for GMM with 1 percent level of relative bias. Then, we firmly reject the null hypothesis of weak instruments.

Table 11.4 The value of OD designations for IPO investors

	1 OLS LOG (PROCEEDS)	2 GMM LOG (PROCEEDS)
ODD	0.183**	0.173**
	(0.0747)	(0.0809)
PATAPPy4	0.000900	0.000913
	(0.00149)	(0.00301)
PHASE2PRIORIPO	0.0266	0.0275
	(0.0678)	(0.0729)
LOG (R&D_EXPENSES)	0.297***	0.295***
	(0.0718)	(0.0877)
AGE AT IPO	–0.0693**	–0.0685***
	(0.0337)	(0.0190)
EMPLOYEES	0.00281**	0.00285
	(0.00127)	(0.00179)
LOG (REVENUES + 1)	–0.00501	–0.00509
	(0.0125)	(0.0120)
SICSEC2834	0.223	0.219
	(0.272)	(0.191)
LOG (PERCENT SOLD)	0.309	0.308**
	(0.223)	(0.157)
UWREPUT	0.311**	0.302
	(0.138)	(0.430)
VENTURE BACKED	0.467*	0.469**
	(0.242)	(0.214)
CORPVCAP	–0.0175	–0.0147
	(0.186)	(0.223)
NASDAQ	0.421	0.428
	(0.311)	(0.556)
BIO_RATIO	2.160**	2.168***
	(0.945)	(0.815)
BUBBLE	0.482***	0.481*
	(0.173)	(0.257)
Constant	12.13***	12.14***
	(0.946)	(1.285)
Observations	146	146
Adjusted_*R*-squared	0.289	0.289
Sargan-Hansen test		0.501 ($p = 0.479$)
First stage *F*-statistic		130.7***
Anderson canon. corr. LM statistic		97.76***
Wu-Hausman test		0.049 ($p = 0.8259$)

Note: Robust standard errors in parentheses.

***Significant at the 1 percent level.

**Significant at the 5 percent level.

*Significant at the 10 percent level.

for US biotech IPOs deals and based on the fact that the median value of cash collected at IPO is around $49.55 million in the US stock markets, we can infer that an orphan drug sponsor may raise around $9.06 million, for an additional OD designation prior to an IPO, holding other factors fixed.

Results from the OLS model also confirm the positive certification role of venture capitalists and underwriter reputation for IPO investors. Results also suggest that larger companies in terms of number of employees and R&D expenses have greater IPO valuations. In contrast, the age of the company at IPO is negatively related with larger amounts of cash at the time of the IPO. As expected, market conditions also strongly influence the IPO proceeds. Notice that the coefficients of the number of patents applied before IPO with a four-year window (PATAPPy4) and the number of drugs in at least Phase II in the pipeline prior to IPO (PHASE2PRIORIPO) are positive, but not statistically significant.

An important issue in the signaling literature involves the dynamic value of signals across the industry life cycle. In the context of the biotech industry, Higgins, Stephan, and Thursby (2011) suggest that the importance of a signal diminishes when other measures of firm quality become available, reducing uncertainty. We follow the Higgins, Stephan, and Thursby (2011) methodology to disentangle the value of ODD before and after 2000 and 2003. We choose those two different dates because (a) the year 2000 was the year of the completion of the first draft of the human genome sequence (International Human Genome Sequencing Consortium 2011) and the implementation of the OD legislation in Europe;[21] and (b) between 2000 and 2003, the US Congress passed the Rare Diseases Act[22] in 2002 to establish the statutory authorization for the Office of Rare Diseases, the Medicare coverage and reimbursement for ODs was reinforced under the Medicare Modernization Act (MMA)[23] of 2003, and finally the Human Genome Project was declared complete in April 2003. Those scientific and regulatory events should improve the medical research and the medical care of rare diseases for the benefit of the firms engaged in OD R&D.

Therefore, we interact our different variables with dummies coded equal to one if the company went public before and after 2000 (Model 3) and 2003 (Model 4). In table 11.5, we observe that the difference in the value of ODD is not statistically significant in each of the two-time windows that suggest that the value of ODDs for IPO investors was highly resilient to changes in the industry life cycle and stock market evolutions.

Finally, in table 11.6 we also explore whether the value of ODD varies across the type of drugs (chemical or biological) and disease indications.

21. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:en:PDF.

22. https://www.govtrack.us/congress/bills/107/hr4013.

23. https://www.govtrack.us/congress/bills/108/hr1.

Table 11.5 The value of ODD before and after 2000 and 2003

	3		4	
Variables	2000	Rob std. err.	2003	Rob std. err.
BEFORE_ODD	0.184**	(0.0882)	0.287***	(0.0882)
BEFORE_PATAPPy4	0.000703	(0.00560)	0.00376	(0.00500)
BEFORE_PHASE2PRIORIPO	–0.131	(0.0852)	–0.0502	(0.0953)
BEFORE_LOG (R&D_EXPENSES)	0.333**	(0.153)	0.205	(0.143)
BEFORE_AGE AT IPO	–0.0283	(0.0240)	–0.0205	(0.0253)
BEFORE_EMPLOYEES	0.00462	(0.00304)	0.00560*	(0.00292)
BEFORE_LOG (REVENUES + 1)	–0.144	(0.115)	–0.161	(0.103)
BEFORE_SICSEC2834	0.171	(0.224)	–0.0192	(0.205)
BEFORE_LOG (PERCENT SOLD)	–0.290	(0.488)	0.343*	(0.197)
BEFORE_UWREPUT	0.206	(0.272)	0.162	(0.311)
BEFORE_VENTURE BACKED	–0.0952	(0.253)	0.0981	(0.230)
BEFORE_CORPVCAP	–0.133	(0.311)	–0.457	(0.316)
BEFORE_NASDAQ	–0.304	(0.591)	0.606	(0.503)
BEFORE_BIO_RATIO	7.266***	(2.241)	6.922***	(2.352)
AFTER_ODD	0.194**	(0.0952)	0.203**	(0.0967)
AFTER_PATAPPy4	0.00175	(0.00195)	0.00184	(0.00195)
AFTER_PHASE2PRIORIPO	0.0570	(0.0896)	0.0525	(0.0929)
AFTER_LOG (R&D_EXPENSES)	0.242***	(0.0916)	0.259***	(0.0924)
AFTER_AGE AT IPO	–0.0828**	(0.0406)	–0.0822**	(0.0406)
AFTER_EMPLOYEES	0.00276	(0.00184)	0.00261	(0.00194)
AFTER_LOG (REVENUES + 1)	–0.00202	(0.0950)	–0.00117	(0.0965)
AFTER_SICSEC2834	0.353	(0.360)	0.374	(0.379)
AFTER_LOG (PERCENT SOLD)	0.333	(0.235)	0.403	(0.268)
AFTER_UWREPUT	0.212	(0.136)	0.232*	(0.138)
AFTER_VENTURE BACKED	0.685**	(0.330)	0.678*	(0.354)
AFTER_CORPVCAP	0.183	(0.231)	0.198	(0.240)
AFTER_NASDAQ	0.366	(0.520)	0.180	(0.535)
AFTER_BIO_RATIO	1.838	(1.119)	2.013*	(1.133)
Constant	16.23***	(0.599)	16.39***	(0.584)
Observations	146		146	
R-squared	0.393		0.396	
ODD (Wald test)	0.01 (0.93)		0.48 (0.4915)	

***Significant at the 1 percent level.

**Significant at the 5 percent level.

*Significant at the 10 percent level.

In Model 5, we interact our key independent variable (ODD) with dummy variables coded one for firms with at least one chemical-based drug (CHEM) and for firms without chemical-based drug (NOCHEM). In Model 6, we disentangle across firms with at least one biologic-based drug (BIO) and firms without any biologic-based drugs (NOBIO). Then, we perform Wald tests to check if the coefficients are statistically larger. In Model 5, the Wald test of ODD_CHEM—ODD_NOCHEM > 0 suggest that ODDs are not statistically different for firms with chemical and nonchemical compounds.

Table 11.6 Alternative models for heterogeneous ODDs

	5 OLS LOG (PROCEEDS)	6 OLS LOG (PROCEEDS)	7 OLS LOG (PROCEEDS)
ODD_CHEM	0.171**		
	(0.0797)		
ODD_NOCHEM	0.200**		
	(0.0826)		
ODD_BIO		0.183***	
		(0.0654)	
ODD_NOBIO		0.174*	
		(0.102)	
ODDkc			0.195***
			(0.0690)
Other_ODD			0.166*
			(0.0941)
Controls as in table 11.4	Yes	Yes	Yes
Observations	146	146	146
Adjusted *R*-squared	0.359	0.359	0.359
Wald test	0.22 (0.6384)	0.01 (0.9042)	0.17(0.6831)

***Significant at the 1 percent level.
**Significant at the 5 percent level.
*Significant at the 10 percent level.

In the same line in table 11.6, in Model 6 the Wald test of ODD_BIO-ODD_NOBIO > 0 suggests that the coefficient of ODD for biologic-based drugs is not statistically different for other no biologic-based drugs. Moreover, we disentangle the value of ODDs between cancer indications and others in Model 7. Again, the Wald test suggests that coefficients are not statistically different. However, notice that the coefficient of ODD_NOBIO and other_ODD is statistically significant at 10 percent, but not at the 5 percent level. This reduction in the *p*-value may be linked to the heterogeneity of the value of ODD for chemical and biological drugs[24] and noncancer diseases (other_ODD).[25]

11.4.3 Alternative and Robustness Check Models

In robustness checks presented in table 11.7, we performed alternative model specifications to test the stability of our coefficients. In Model 8, we used the total number of drugs in the companies' pipeline prior to the IPO instead of the number of drugs in at least Phase II in the pipeline prior to the IPO. In Model 9, we also introduced the natural logarithm

24. The firm OD portfolio could be a mix of chemical and biological drugs in development or only one of two classes.
25. Other_ODD control variable aggregates all ATC therapeutic class except class L.

Table 11.7 Alternative specifications

Variables	8	9	10	11	12	13	14	15	16	17
ODD	0.188**	0.186**	0.186**	0.181**	0.181**				0.171**	0.181**
	(0.0805)	(0.0798)	(0.0798)	(0.0764)	(0.0759)				(0.0768)	(0.0886)
PATAPPy4	0.000755	0.000760	0.000726		0.000919	0.00118	0.00114		0.00104	0.000950
	(0.00160)	(0.00160)	(0.00159)		(0.00145)	(0.00156)	(0.00152)		(0.00153)	(0.00149)
LOG (R&D_EXPENSES)	0.290***	0.280***	0.271***	0.288***	0.287***	0.250***	0.258***	0.251***	0.281***	0.282***
	(0.0761)	(0.0769)	(0.0797)	(0.0701)	(0.0703)	(0.0806)	(0.0748)	(0.0800)	(0.0769)	(0.0756)
AGE AT IPO	–0.0693**	–0.0695**	–0.0699**	–0.0689**	–0.0701**	–0.0572*	–0.0562*	–0.0556*	–0.0726**	–0.0706**
	(0.0343)	(0.0341)	(0.0343)	(0.0327)	(0.0342)	(0.0322)	(0.0318)	(0.0304)	(0.0361)	(0.0351)
EMPLOYEES	0.00314**	0.00319**	0.00311**	0.00323**	0.00309**	0.00383**	0.00394**	0.00401**	0.00299**	0.00303**
	(0.00150)	(0.00150)	(0.00153)	(0.00142)	(0.00140)	(0.00165)	(0.00154)	(0.00172)	(0.00151)	(0.00149)
UWREPUT	0.280*	0.267*	0.266*	0.291**	0.289**	0.120	0.114	0.122	0.297**	0.291**
	(0.146)	(0.146)	(0.145)	(0.135)	(0.132)	(0.112)	(0.109)	(0.116)	(0.137)	(0.134)
VENTURE BACKED	0.482*			0.482*	0.484*	0.542**	0.516*	0.539**	0.490**	0.500**
	(0.254)			(0.258)	(0.259)	(0.249)	(0.269)	(0.248)	(0.246)	(0.240)
LOG(VCFUNDS + 1)		0.0283**	0.0299**							
		(0.0137)	(0.0133)							
DRUGPIPEPRIORIPO	–0.00321	–0.00335								
	(0.0111)	(0.0111)								
PHASE2PRIORIPO			0.0391			0.0408		0.0401	0.0231	0.0244
			(0.0523)			(0.0654)		(0.0649)	(0.0637)	(0.0646)
OTHER_DRUG_PIPELINE			–0.00506							
			(0.0107)							
ODDKcpriorIPO									0.0635	
									(0.0875)	
ODDRDpriorIPO										–0.00760
										(0.0753)
Constant	16.41***	16.43***	16.34***	16.34***	16.38***	16.22***	16.31***	16.17***	16.35***	16.33***
	(0.431)	(0.436)	(0.452)	(0.414)	(0.420)	(0.508)	(0.480)	(0.514)	(0.448)	(0.449)
Controls as in table 11.4	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*
Observations	146	146	146	146	146	146	146	146	146	146
Adjusted *R*-squared	0.359	0.361	0.362	0.358	0.358	0.327	0.325	0.326	0.361	0.359

Note: Robust standard errors in parentheses.

***Significant at the 1 percent level.

**Significant at the 5 percent level.

*Significant at the 10 percent level.

of the amount of cash collected from venture capitalists prior to the IPO (LOG(VCFUNDS + 1)) instead of a dummy variable VENTURE_BACKED. Here, we examined possible differences in the intensity of venture capital support prior to IPO. In Model 10 we added simultaneously the number of drugs in at least Phase II and all the other drugs under development by the firm at the time of the IPO. Regression results suggest that increases in the intensity of VC support also influence the amount of cash collected at IPO. In contrast, different measures of the drug pipeline developed are not statistically significant for IPO investors.[26] In addition, regressions results suggest that removing patents and/or pipeline variables do not change the value of the ODD as a credible signal (Models 11 and 12). In the same line, we remove ODD (Model 13) and the value of patents and/or pipeline is still not statistically significant. We also remove the patent variable in Model 14 and the pipeline variable in Model 15 in order to check if the remaining variables capture part of the effect of the removed variables. Results suggest that this is not the case. Finally, in Models 16 and 17, we introduce the variables ODDKcpriorIPO (the number of ODD for antineoplastic and immunomodulators drugs) and ODDRDpriorIPO (the number of ODs filed by the firm prior to its IPO with any genetic disease designations), respectively. Regression results suggest that additional ODDKc and ODDRD are not related to higher IPO valuations, other factors remaining fixed.

11.5 Discussion and Conclusion

This chapter examines whether ODDs operates as credible signals for IPO investors in US stock markets. To this end, we have built an original database linking data from five different sources: the IPO prospectus and S-1 registration statement database, the FDA Orphan Drug product designation database, the Orbit patent database, the Pharmaproject database for the drug pipeline, and VentureSource for corporate and VC investment before the IPO.

We demonstrate that ODDs reflect a valuable intangible asset with a powerful certification and reputational component that attracts IPO investors. The above-mentioned impact of ODDs on IPO financing might be explained by two main functions of an ODD for pharma-biotech start-ups: its signaling value, and its productive effects (exclusionary and/or markets for technology effects).

Since the OD Act, the FDA has granted more than 3,000 ODDs and approved more than 400 ODs for marketing (Garden, Gorry, and Paris

26. In robustness checks not presented here, we also introduce the total number of patent applications prior to IPO instead of the patents applied four years before IPO. Results reflect that the patent portfolio is not taken into account by biotech IPO investors. For the sake of brevity the regressions are not included, but results are available upon request. Send all correspondence to: philippe.gorry@u-bordeaux.fr.

2016). Eighty-five percent of the ODs have been developed by small or medium-sized pharma-biotech enterprises, and half of the market-approved ODs belong to the biotechnology industry (Côté 2012). The promise of a seven-year market exclusivity and the 50 percent tax credit for clinical drug testing are attractive enough for investors to balance the risk linked to targeting a niche market.

Our study has both scholarly and policy implications. Our analysis contributes to the theoretical and empirical literature on entrepreneurial finance, which has examined a number of issues related to start-up financing and patents (Conti, Thursby, and Thursby 2013). This chapter addresses for the first time the use of ODDs as a signal in the context of IPO financing. This signal is particularly important for the biotech industry as the drug development process, which is expensive, lengthy, and risky, depends heavily on external investment funds. The ODDs share many properties with patents as intellectual assets: monopolistic market rights limited in time and space and quality signals, both facilitating cooperative arrangements and transactional value. Moreover, we have reported evidence implying that ODDs are more valuable than patents to attract IPO investors.

In addition, the importance of the ODD status signal for IPO investors does not seem to diminish over time. We tested two periods of IPO, before and after, 2000 and 2003, and we found no statistical difference. These results are contrary to those of Higgins, Stephan, and Thursby (2011). This is surprising to the extent that this time period has experienced many scientific breakthroughs and regulatory developments supporting OD R&D and markets (human genome sequencing, Rare Disease Act, MMA, OD legislation in Europe). Our results suggest that the value of ODD for IPO investors is highly resilient to changes in the industry life cycle, which indicates an insufficient maturity of the OD firms' industry subsector.

However, it remains unclear which of the regulatory incentive or the financial incentive linked to the OD status is the more effective measure; is market exclusivity, limiting the competition and approval of another version of the same orphan drug the most powerful signal for investors as it secures long-term monopoly profits, or are investors more sensitive to the tax credit and the lowering of drug R&D costs. We may expect that the reduction in orphan drug tax credits in the Tax Cuts and Jobs Act of 2017 (December 2017),[27] from 50 percent of research and development costs to 25 percent may not only discourage OD sponsors but also external finance (Lindsley 2017). Future research on the value of ODs for investors after the recently passed tax legislation may lighten up on the importance of tax credit for OD sponsors and investors.

As innovative drugs, we can make the assumption that every orphan drug has a patent protection. Seoane-Vazquez et al. (2008) find that OD mar-

27. https://www.gpo.gov/fdsys/pkg/BILLS-115hr1enr/html/BILLS-115hr1enr.htm.

ket exclusivity increased the average maximum effective patent and market exclusivity life of ODs by 0.8 years. Moreover, neither the firm nor the investor could assess the OD market exclusivity advantage in comparison to the patent monopoly at the time of the IPO. An alternative or complementary explanation would be that the two years of additional data exclusivity linked to the OD market exclusivity delays a generic drug entry under the Hatch-Waxman Paragraph IV provision.[28] Paragraph IV challenges are only relevant for chemical-based drugs. In our model, the amount of money raised at the time of IPO is different between chemical or biological OD portfolio, but note this difference is not statistically significant.

An OD is defined as one drug for one therapeutic indication (named "designation" by the FDA). This suggests that ODD may hinder follow-on entry into those same therapeutic indications. However, the evidence suggests this is not true. It still remains possible for any sponsor (the first mover or any other firm) to apply with the same drug for another therapeutic indication (e.g., the nitric oxide drug is registered by six different sponsors for nine different ODDs), or to apply for the same therapeutic indication (e.g., two different ODs, phenanthroline and cytarabine, are sponsored by two different firms, Aptose Bioscience and Celator Pharmaceutical, for one therapeutic indication—acute myeloid leukemia). Therefore, the impact of ODD on follow-entry into specific disease markets might be limited. In our sample data, only fourteen firms succeeded in obtaining a market approval for a total of thirty-one different ODDs, with a success rate of ODD prior to the IPO to obtain a market approval equal to 23 percent and an average time of 9.52 years. In the face of such a low probability and distant horizon, investors may not be sensitive to this advantage.

By process of elimination, one might conclude that the remaining OD tax credit advantage may be the driver of OD value at the time of the IPO. Therefore, if ODDs are valuable intangible assets, we might expect that they are monetized on the stock market by investors once the firms are public. Hughes and Poletti-Hughes (2016) show that ODD holders have a greater return on assets (ROA) than non-OD firms, and ROA increases for each additional OD in the portfolio. However, these results are based on measures of OD market authorization and not based on the earlier ODD. Miller (2017) reports that the firm's stock price increases after the announcement of the ODD, especially for oncology drugs and small firms, but on the other hand Rothman (2017) reports a price crash following the broad reaction of the market, arguing for psychological impacts on investors. Theses contradictory findings can be interpreted in the light of the working paper of Dong, Hirshleifer, and Teoh (2017), who provide evidences that stock mar-

28. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm047676.htm.

ket overvaluations positively affect corporate innovation activities. Thus, one could argue that IPO investors are more interested in the competitive advantage related to the tax credit, and not that related to market exclusivity. Otherwise, the patent portfolio would be more important for IPO investors that ODDs. Notably, the OD tax credit might be of importance for start-up companies even though they may not be profitable until the OD is launched on the market, because this tax credit has a carry-back/carry-forward provision, which could be of value for investors at the time of IPO.

These findings also have important implications for policymakers. The OD Act with its regulation and financial incentives succeeded in attracting private investments, creating an opportunity for biotech companies who depend on external finance. If one could draw a parallel between rare and neglected diseases, orphan-type legislation might provide a solution to attract investments to support drug development for tropical diseases, for example (Anderson 2009). This type of supply-side incentive seems to be stronger in attracting external investors than patent protection.

Despite these successes in developing orphan drugs, academic researchers and rare disease advocacy patient organizations have raised questions about the financing of drug R&D for rare diseases (Côté 2012). The European Commission introduced OD legislation in 2000 providing incentives for companies, such as a ten-year market exclusivity and fee waivers. Future research might explore whether ODDs are also signals for the European (not just United States) stock markets and whether they are also more valuable than patent protection in attracting investors. It might also be interesting to compare the European Union and the United States in terms of the signaling value of ODDs for investors. Future research might also examine more explicitly the trade-offs associated with alternative quality signals at different stages of the drug development and the relative importance of those signals (Guo, Lev, and Zhou 2005).

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