

WORKING PAPER

NBER Conference on Economics Dimensions of Personalized and Precision Medicine 2017

**ORPHAN DRUG DESIGNATIONS AS VALUABLE INTANGIBLE ASSETS
FOR IPO INVESTORS IN PHARMA-BIOTECH COMPANIES**

This version: 06/11/17

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We thank colleagues of GREThA, especially Francesco Lissoni, and conferences participants at DRUID2016 and NBER PPMf2017 conferences for helpful comments. This work was supported by a grant from the French National Cancer Institute (INCa # 2015-178). The authors declare no conflict of interest.

JEL classification: G11 Portfolio choice·Investments decisions, G24 Investment Banking • Venture Capital • Brokerage • Ratings and Ratings Agencies, O32 Management of Technological Innovation and R&D, O34 Intellectual property and intellectual capital, G2 - Financial Institutions and Services, I1 – Health, L65 – Chemicals·Rubber·Drugs·Biotechnology

ABSTRACT

Orphan Drug (OD) legislation has been implemented with regulatory and financial incentives to encourage drug **innovation** in order to treat rare diseases. This study aims to test whether OD Designations (ODD) granted by the **Food and Drug Administration (FDA)** to pharmaceutical and **biotechnology** start-up companies may be considered as relevant signals in attracting entrepreneurial finance and increasing the amount invested at the time of the **Initial Public Offering (IPO)** in the US **stock markets**. Furthermore, before going public, ODDs may also influence access to other relevant resources for start-up companies, for instance **venture capital** investments, collaborative revenues and employees prior to the IPO. We found that the **signaling power** of ODD is positively and statistically significant for IPO investors in stock markets: an ODD prior to an IPO increases the IPO proceeds by about 37.5%. Regression results also suggest that ODDs are stronger than **patent** applications in attracting IPO investors and other valuable resources before that the company goes public. Scholarly and policy implications are discussed in the light of the signaling theory and drug development policies.

Keywords: Orphan Drug, Patents, Initial Public Offering (IPO), Venture Capital, Innovation, Biotechnology

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1. INTRODUCTION

Drug development is characterized by a long development cycle (between eight and 12 years on average) and a high attrition rate, especially between preclinical and clinical phases. Therefore, investment in pharmaceutical product development is highly risky because it involves substantial costs to develop a product candidate that may fail to obtain regulatory approval or to become commercially viable. Return on investment in the pharma-biotech sector depends heavily on patent protection for new drugs in order to provide a period of market exclusivity. Over the last few decades, the productivity of pharmaceutical companies measured by the number of new molecular entities has been steadily declining (Paul et al., 2010). A critical question to understand how the biotech sector operates has been called the “Pisano puzzle”: Why would money from investors flow into an industry in which profits are so hard to come by? (Pisano, 2006). According to Fernandez et al (2012), pharma-biotech venture capital investments underperform with an average internal rate of return of 1%. In the case of rare disease drug development, the question is even more relevant as sponsors are additionally confronted with a problem of low demand (Rzakhnov, 2006; Yin, 2008). Many biotech and rare disease drug sponsor companies have devoted impressive financial resources to Research and Development (R&D), including non-clinical development activities and clinical trials, while at the same time they are not generating revenues and cannot estimate with precision the extent of their future losses (Pisano, 2006; Rzakhnov, 2006; Yin, 2008; Lazonick, 2011).

For pharma-biotech start-ups the capacity to raise money through global pharmaceutical company partners, Venture Capitalists (VC) and IPO investors is a fundamental factor for drug innovation and orphan drug development. In contrast, 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 start-up companies are increasingly risk-averse and have become more cautious in selecting firms with a high growth potential, as they are usually young, unprofitable, insolvent, and with complex business models. These investors tend to measure investment potential by analyzing considerable data gathered on firms’ histories and their perceived market potential. Thus, companies intending to go public have to convince investors that they are worth investing in (Wilbon, 1999).

The literature has highlighted the value and the nature of different technology 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 inter-organizational networks (Stuart & al., 1999), 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 some technology characteristics which may be considered as technology signals helping to reduce uncertainty and skepticism regarding an IPO firm's performance. Among those signals patents have been at the center of the analysis (Long, 2002; Mann, 2005; Heeley, Matusik and Jain, 2007; Hsu & Ziedonis, 2008; Useche, 2014). Moreover, the number of products and their stage of development in the firm's drug portfolio have been shown to be relevant (Guo et al., 2005). The firm's technology posture and executive technological experience have been also explored (Wilbon, 1999), as well as the scientific status related to the presence of Nobel laureates (Higgins & al., 2011). We aim to test whether Orphan Drug Designations (ODD) applied prior to an IPO influence the way investors perceive biotech firms' potential through an increase in the amount invested at the time of the IPO in the US stock markets. We attempt to take into account the endogeneity of ODDs prior to IPOs by considering the simultaneous relationship between the firm's innovative outputs (jointly with patents) and IPO performance. Endogeneity occurs when the firm characteristics affecting the firm's decision to apply for an ODD before going public also determine the amount of cash collected at the IPO. Furthermore, before going public, ODDs may also influence access to other relevant resources for start-up companies, for instance venture capital investments, collaborative revenues and employees prior to the IPO.

We proceed as follows. First, we build an original database in which we consolidate a sample of Orphan Drug sponsor firms going public between 1995 and 2015. Second, through a simultaneous equations system approach, we explain how ODDs influence the firm's ability to raise money from IPO markets. Finally, we explore how ODDs may also be related to access to venture capitalist investors, collaborative revenues and employees prior to IPOs.

The outline of this paper is as follows. Section 2 briefly discusses the anatomy of the rare disease drug development market and the emergence of Orphan Drug Designations. Section 3 sets out the main characteristics which make ODDs valuable intangible assets and technology market signals for investors in biotech companies. Section 4 discusses the methodology and data.

Regression results, alternative models, and robustness checks are provided in Section 5. A discussion on the main results and the conclusions are presented in Section 6.

1.1. 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 10-20 years to yield a commercial product with highly uncertain prospects for success (Lazonick, 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% 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 in relation to a small number of consumers (Rzakhnov, 2006; Yin, 2008). According to Moors and Faber (2007), orphan drug development is particularly complex and risky because the disease lacks a knowledge base and patient groups for clinical trials are small. Therefore, OD development requires more collaboration with other stakeholders than 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. Orphan Drug sponsors mainly rely on four sources of funding to develop new drugs: (i) R&D government grants, (ii) venture capital investments, (iii) public equity markets and (iv) strategic alliances (Pisano, 2006). VC investments and, in most cases, R&D alliances involve a capital injection into the startup giving the venture capitalist or the established company an equity stake (Lazonick, 2001). Biotech startups 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 when the drug is approved (Lazonick, 2011).

Orphan drug sponsors, as well as other biopharmaceutical companies, still find it extremely difficult to predict how a particular new molecule will be safe and efficient 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 (Rzakhnov, 2006). Over the last few decades, advances in the

biotechnology industry have increased 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 effort, from patient groups frustrated at the lack of drugs approved to treat rare diseases, to pass orphan drug legislation (Yin, 2008). In order to stimulate innovation in rare disease drugs, the Orphan Drug Act (ODA) was adopted on January 4th 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 orphan drugs which are a particular kind of highly risky-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). After the ODA, orphan drug R&D became increasingly dynamic and more than 400 orphan treatments have been approved (Seoane-Vasquez et al., 2008; Garden et al., 2017¹). This spectacular turnaround proves 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 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 orphan drug sponsor firms to attract investors, and in reducing problems of asymmetric information and risk.

1.2. Hypothesis: OD designations as valuable intangible assets and market signals

OD designations may be considered as valuable intangible assets which may attract investors in pharma-biotech start-up companies. Similarly to patent applications, OD designations may be considered as 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 & Ziedonis, 2008; Useche, 2014; Hoenig and Henkel, 2015). OD designations can represent a signal of the quality of a start-up’s technology according to the signaling theory of Spence (1973). In order to be effective, signals need to be observable and costly (Spence, 1973; Long, 2002; Hsu & Ziedonis, 2008; Useche, 2014). Observability describes the extent to which outsiders are able to notice the signal. Since the ODD is publicly disclosed by the FDA as a regulatory agency, the ODD signal is directly observable by outsiders. The comprehensive examination by the FDA Office of

¹ <https://www.innovationpolicyplatform.org/content/health-innovation-rare-diseases>.

Orphan Drug Products Development works as a certification mechanism, and might parallel the signaling power of patents (Heonig and Henkel, 2015). Investors will surely interpret Orphan Drug designations 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).

ODDs are also costly to obtain and they provide a selection mechanism which 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 the diseases lack a knowledge base and patient groups for clinical trials are small (Rzakhnov, 2006; Yin, 2008). In order to compensate and stimulate to some extent rare drug developers, Orphan Drug Designations offer several advantages which may suggest that the holder has a competitive advantage and offer a sign of their higher quality and technology compared to other companies. First, an OD Designation holder has an exclusive right, and may sell at an unregulated price over the 7-year period without competition. This monopoly starts at market approval date and is independent of intellectual property rights. Second, a subsequent innovator that develops a new drug prior to expiration of the 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 OD Designation provides a 50% tax credit on the clinic 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 can effectively be transferable to another company subject to the consent of the regulator. Fifth, an orphan designation and exclusive marketing right cannot be revoked later if the drug proves to have greater commercial potential, and is therefore considered as a real option. In addition, Orphan drugs have shorter development time than other drugs (Seoane-Vasquez et al., 2008).

In addition, ODD offers also powerful certification and reputational value. Moors and Faber (2007) suggest that ODDs may provide a powerful incentive for image improvement for finance seeking start-ups in orphan segments with a lack of profound knowledge base. The certification component of ODDs may also help orphan drug sponsors to find valuable external resources, such as competent R&D partners and valuable employees to hire. The ‘legal certification’ component of Orphan Drug Designations is assured by the FDA Office of Orphan Products Development

(OODP), which receives, reviews and eventually approves Orphan Drug 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 US or those drugs for which R&D investment would not be recovered by 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 previously for marketing. The ‘legal certification’ component of OD Designations 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, Rzakhanov (2008) suggests that OD designations may have similar characteristics to patent design and may be considered as a valuable intangible asset for their holder. However, Orphan Drug exclusivity offers the second broadest level of protection because the provision protects the Orphan designated indication against generic and full NDA approval (Seoane-Vasquez et al., 2008). It should be pointed out that market exclusivity is a post-approval incentive that begins 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 a New Drug Application (NDA) or a Biologics License Application (BLA). It is important to note that sponsors of ODs frequently qualify for fast-track status accelerated approval and 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, 2011).

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

However, there is little evidence on how Biotech IPO subscribers use OD Designations 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 higher amount of cash

invested at IPOs, other factors remaining fixed. We are also interested in allowing for differences in the value of OD designations compared to other intangibles assets, which are usually claimed as technology signals (for instance the patent portfolio) for IPO investors. 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).

2. DATA AND MEASURES

2.1. Data sources

We built an original database linking data from 5 different sources: i) the IPO prospectuses and S-1 registration statement database, ii) FDA Orphan Drug product designation database, iii) Orbit[®] patent database (owned by Questel), iv) the Pharmaproject[®] (owned by Citeline) for the drug pipeline and v) VentureSource[®] (owned by Dow Jones) for corporate and VC investment before IPO. IPO prospectus and forms S-1 were retrieved from different sources: the NASDAQ website, US Securities and Exchange Commission (SEC) archives and the EdgarOnline[®] database provider for historical data with financial, ownership and shareholder information. The FDA Office of Orphan Drug Products (OODP) maintains an OD designations and approvals database, where OD statuses are logged in, with product and designation information, as well sponsor information. The patent analysis was run in the worldwide collection of INPADOC (International Patent Documentation; EPO worldwide legal status database) family patents using the Orbit[®] patent research platform which provides an applicant search function based on company structure using FactSet[®] corporate tree data. (Useche, 2014).² Pharmaproject[®] is a proprietary data source including drugs developed in pharmaceutical markets worldwide from 1980 to date and has been used in pharmaceutical industry economics research (Hirai et al., 2012; and references therein). Finally, VentureSource[®] is a global database on companies backed by venture capital and private equity in every region, industry and stage of development and was used to retrieve details about rounds of financing.³

² Questel-Orbit is a patent database which 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.

³ <http://www.nasdaq.com>; <http://www.sec.gov/edgar/searchedgar/companysearch.html>; <http://pro.edgar-online.com>; <https://www.accessdata.fda.gov/scripts/opdlisting/oopd/>; <http://www.questel.com>; <http://www.dowjones.com/products/pevc/>

2.2. Sample description

Our approach to building the dataset was to identify IPO deals concerning Orphan Drug designation applicant firms from the United States, between January 1st 1995 and December 31st 2015. Our primary data source was the FDA Orphan Drug Product designation database. From 1983 to December 2015, more than 3000 OD were registered by some 1400 sponsors worldwide (including firms, universities, physicians, patient advocacy groups and other non-profit organizations). The OD designation trend accelerated from the year 2000 following several provisions implemented by the U.S. congress: Rare Diseases Act (2002), OOPD, Medicare Patient Access Drugs for Rare Diseases Act (2003) (Figure 1). All OD designation sponsor firms obtained 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 Orphan Drug designations which had been traded on 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 prospectuses and S-1 registration filings issued when those firms went public (n=253). Trends of IPOs with OD portfolios does not parallel the OD designation trends, and the acceleration of IPOs of OD firms is recent, except for a peak of IPOs around the dot-com bubble in 2000 (Figure 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 151 OD IPO firms between January 1st 1995 and December 31st 2015. These companies are mostly quoted on the NASDAQ (98%) and are US firms (92%). Most of these firms are drug companies operating in the pharmaceutical (73%), diagnostic or biotechnology (19%) sectors, and are considered Pharma-Biotech companies (93%) according to the SIC codes (Table 1). In that respect, our sample differs from the ones described by Higgins et al (2011) (they excluded SIC#2833) and is closer to the sample of Guo et al (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”, i.e., companies ranked in the top 50 by annual revenue.

2.3. Measures

2.3.1. Value-IPO proceeds as dependent variable

We are interested in how Orphan Drug sponsors use OD designations obtained prior to IPOs as a credible signal of high firm value and competitive advantage and to determine the future firm's performance on financial markets. We followed the literature and used traditional measures of performance which were mainly collected through the IPO prospectuses 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 et al., 2011), the pre-money valuation of the firm (Stuart et al., 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). This measure of IPO performance avoids potential problems of over allocation in the pre-money valuation (Ritter and Welch, 2002; Higgins et al., 2011). A log-transformed variable of *PROCEEDS* was used to address the valuation data skew and reduce its heterogeneity.

2.3.2. FDA Orphan Drug designation portfolio as independent variable

OD designations may have similar characteristics to patent designs. 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 claimed before, among other advantages, OD designation provides drug sponsors with a 50% tax credit for clinical trial costs, a fee waiver for regulatory activities, fast-track evaluation for market approval and some assistance from the Office of Orphan Products Development.

2.4. Control variables

2.4.1. Drug pipeline and intellectual propriety portfolio.

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 patent filed by the firm over the four-year period before the IPO (*PATPPy4*). This window in the number of patent applications was to take 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% of identified molecules might make the transition to candidate and enter clinical trials (Hughes et al, 2010). So 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% success ratio (Hay et al., 2014).

In addition, we collected information on the number of years between the first Orphan Drug designation granted to the firm and the IPO date (*OD_EXPERIENCE*) which is used as an instrument in our empirical analysis. Drug development is highly regulated and firms have to file a new drug or biological license application (NDA or BLA) upon the completion of the clinical trial in order to get a Market Approval to launch their drug. Indeed, it has been demonstrated in the literature that the speed of FDA approval is linked to firms' characteristics (Oslon, 2004). Thanks to the Orphan Drug status, firms might benefit from technical assistance during the preparation of the file from the FDA Office of Orphan Products Development, and companies will be more likely to gain FDA OD regulatory experience before funding.

2.4.2. 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 prospectuses and the S-1 registration filings database, we collected data to control for the age of the company at IPO (*AGEATIPO*), 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 Research & Development expenses and the total collaborative revenues over the year before the IPO.

2.4.3. Venture capital and corporate venture capital support

We collected information related to venture capital support using the Venture Source database. Venture Capital support usually provides a sign 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* which is 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 greater IPO performance than ventures quoted without similar funding support.

2.4.4. Percentage of the firm sold and underwriter reputation

We followed the literature (Leland and Pyle, 1976; Brau and Fawcett, 2006; Higgins & al., 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 should consider 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. Then, like Higgins & al., (2011), we included a log of the percentage of total shares of

the firm that are sold (*PERCENT SOLD*). IPO performance is also related to underwriter reputation (Carter and Manaster, 1990). Underwriter reputation (UWREPUT) was measured with Loughran and Ritter's update (2004) 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.⁴

2.4.5. Market conditions

Finally, we used temporal, country and stock market differences in IPO deals. 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 1 if the companies were quoted on the NASDAQ (US). We included the variable *BIO_RATIO*, which is the ratio defined as the number of Biotech IPOs divided by the total number of IPOs in a given year (Higgins, M.J. et al., 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).

2.5. Summary Statistics

We present the description of variables and report descriptive statistics for the pharma-biotech companies sponsoring Orphan Drugs in Table 2. Some characteristics of OD sponsors prior to IPOs should be pointed out. First, it appears that about 48% of the companies applied for ODDs before the IPO while the remaining 52% applied for ODDs after the IPO. It also appears that, on average, OD sponsors applied for their first ODD 3 years before the IPO. In contrast, most of the companies going public applied for patents four years before the IPO (87%), and have a drug pipeline of 9 compounds on average at the time of the IPO, with only a minority of firms succeeding in pushing drug candidates into phase II clinical trial (38%). OD sponsor companies are R&D intensive firms spending on average of \$13 million while their revenue is on average \$7.34 million prior to their offering. OD firms have been supported by venture capitalists (73%) at least through 2 rounds of investment for 4-5 years prior to the IPO. The average amount raised by the IPO (based on proceeds) was \$43.57 million.

As a preliminary examination of the univariate relationships among the variables in the present study, Pearson correlation coefficients were estimated. Table 3 shows the results of these

⁴ Underwriter ranking data available from Shane Corwin's website <http://www3.nd.edu/~scorwin/>

estimations for each of the 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 found.

For example, proceeds from IPOs are correlated with the size of the firm (LOG EMPLOYEE+1) and R&D expenses. As one might expect, IPO proceeds are also correlated with venture capital funds as measured by (VCFUNDS+1). Moreover, the two VC measures (VCFUNDS+1 and VC_INTENSITY) are highly correlated. Finally, the more prestigious the lead underwriter (UWREPUT), the higher the amount of capital raised at IPO.

Our model may well contain several important additional inter-relationships between the relevant variables. To correctly measure the effect of the Orphan Drug Designation portfolio on IPO proceeds, we apply a switching simultaneous-equations model described in Maddala (1983) to control for this effect.

3. RESULTS

3.1. Econometric strategy

We present simultaneous equation estimates of a 6-equation model. We focus on our main Equation (Eq.1), which estimates the impact of Orphan Drug Designations (ODD) on IPO performance measured by the logarithm of the amount of cash collected by the firm i at the IPO date (*PROCEEDS*).

$$\log(IPOPROCEEDS) = \alpha_i + \gamma_i ODD_i + \lambda_i PAT_i + \beta_i X_i + \theta_i Y_i + w_i \quad (1)$$

We followed the literature (Leland and Pyle, 1976; Megginson and Weiss, 1991; Ritter and Welch, 2002; Brau and Fawcett, 2006; Higgins et al., 2011) and controlled for variables that have been associated with IPO valuation (Y_i). We then controlled for “underwriter reputation” taking into account the prestige of the IPO firm’s lead underwriter (UWREP). We used the underwriter reputation ranking proposed by Loughran and Ritter (2004).⁵ We followed the literature (Leland and Pyle, 1976; Brau and Fawcett, 2006; Higgins & al., 2011) and controlled for the percentage to be sold during the public offering (*PERCENT SOLD*) and two market condition controls

⁵ In robustness checks, we included a dummy variable (Prestigious underwriter) 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.

(*BIO_RATIO*) (Higgins & al., 2011) and Bubble (Chok and Qian, 2013). We also included the variables *VENTURE_BACKED* and *VC_INTENSITY* (Megginson and Weiss, 1991; Gompers, 1995, Brau and Fawcett, 2006). Finally, we also included a set of firm-related characteristics which may influence IPO performance (X_i). We included the age of the company (*AGE AT IPO*), the number of employees (*EMPLOYEES*), the total amount of collaborative revenues (*REVENUES*) and the R&D expenses (*R&D_EXPENSES*) over the year prior to the IPO. We also included a dummy variable coded one if the company's principal segment sector is pharmaceutical preparations (USSIC2834).

We followed the literature and attempted to account for the endogeneity of Orphan Drug Designations by considering the simultaneous relationship between the firm's innovative outputs (ODD and patent applications *PATAPPY4*) and IPO performance. Endogeneity occurs when the firm characteristics affecting the firm's decision to apply for ODD and *PATAPPY4* before going public also determine the amount of cash collected at IPO. Then we simultaneously estimated two equations for the number of patent applications (Eq.2) and the number of ODD applied for before IPO (Eq.3). We included a set of firm-related characteristics (X_i) which may influence access to innovative outputs prior to IPO. Note that Y_i IPO-related variables (*BIO_RATIO*, *UWREP*, *PERCENT SOLD*) absent from Eq.2 and Eq.3 form the exclusion restrictions that identify the model.⁶ There is no reason to consider that the percentage to be sold during the public offering, that the underwriter reputation, or that the market conditions at IPO, directly influence the number of innovative outputs developed in the long and risky process before IPO. In contrast, we included the amount of venture capital investments prior to IPO and the *VC_INTENSITY* which is considered here as a proxy for the length of VC involvement. In addition, we included the number of years between the first Orphan drug investment and the IPO date (*OD_EXPERIENCE*).

$$ODD_i = \alpha_i + \beta_i X_i + \varepsilon_i \quad (2)$$

$$PATAPPY4_i = \alpha_i + \beta_i X_i + w_i \quad (3)$$

Furthermore, ODD and *PATAPPY4* before going public may also influence access to other relevant signals for IPO investors, for instance venture capital investments and collaborative

⁶ In other words, to consolidate the exclusion restrictions that identify our models, we considered that the determinants on the amount of cash collected at IPO are not necessarily the same as the determinants of PAT and ODD. In addition, the structural system approach has the advantage of allowing us to specify which variables are considered as endogenous in the system. Regression results in table 4 only consider the number of Orphan Drug Designations and the number of patents applied for four years before IPO as Endogenous.

revenues prior to IPO. We simultaneously estimated Eq.4 and Eq.5 in which ODD and PATAPPY4 before going public are determinants of the logarithm of the total amount of venture capital investments plus one prior to the IPO (eq.2) and the logarithm of the total amount of revenues plus one prior to the IPO (eq.3). We include a set of firm-related characteristics (X_i) and IPO-related characteristics (Y_i) that may influence access to VC investors and collaborative revenues prior to the IPO.

$$\log(VCFUNDS + 1) = \alpha_i + \gamma_i ODD_i + \lambda_i PATAPPY4_i + \beta_i X_i + \theta_i Y_i + z_i \quad (4)$$

$$\log(REVENUES + 1) = \alpha_i + \gamma_i ODD_i + \lambda_i PATAPPY4_i + \beta_i X_i + \theta_i Y_i + p_i \quad (5)$$

The simultaneous equations model also allows for exploration of other pathways through which technology signals (ODDs and patents) might affect venture capital investments and collaborative revenues prior to the IPO. In addition, we also explored how ODDs and patents might affect access to other relevant resources such as the number of employees at IPO. Then we simultaneously estimated equation Eq. 6 for the number of employees at IPO. We included a set of firm-related characteristics such as the age of the company at IPO and revenues, among others.

$$\log(EMPLOYEES + 1) = \alpha_i + \gamma_i ODD_i + \lambda_i PATAPPY4_i + \beta_i X_i + \theta_i Y_i + z_i \quad (6)$$

3.2. The value of OD designations and patents for IPO investors

Table 4 reports the results of our main simultaneous equation estimation (Eq.1). In model 1, we took into account the simultaneous relationship between the firm's innovative outputs and IPO performance and we performed simultaneous equations from Eq.1 to Eq.3.⁷ In model 2, we considered that ODD and PATAPPY4 before going public may also influence access to other relevant signals for IPO investors, for instance venture capital investments and collaborative revenues prior to the IPO (we performed simultaneous equations from Eq.1 to Eq.5). Finally, we performed our 6 equations system in which we took the simultaneous relationship between the firm's innovative outputs, access to venture capital investments, collaborative revenues, the number of employees before the IPO and IPO performance (see model 3).

⁷ Table 1 in Appendix 1 shows the estimation results for Equations 2 and 3 for our 3 simultaneous equations models.

We observe that the coefficients of *ODD* and *PATAPPY4* are significantly different from zero at the five and one percent level: this is strong evidence that firms going public with OD applications approved raise significantly more cash at IPO than other drug sponsors (From Model 1 to 3). Based on the coefficients *ODD* (0.347) for US biotech IPO deals and based on the fact that the median value of cash collected at IPO is \$56.9 million in the US stock markets, we can infer that an Orphan drug sponsor may raise an additional \$19.74 million, for an additional OD designation prior to an IPO, holding other factors fixed. Similarly, based on the coefficients *PATAPPY4* (0.099) for US biotech IPO deals and on the fact that the median value of cash collected at IPO is \$56.9 million in the US stock markets, we can infer that an Orphan drug sponsor may raise an additional \$5.63 million, for an additional patent application prior to an IPO, holding other factors fixed. We noticed that the coefficient of *ODD* is higher than *PATAPPY4* which suggests that Orphan Drug Designations as signals for IPO investors are stronger than patent applications prior to IPOs. Results also confirm the certification role of venture capitalists and underwriter reputation for IPO investors. Venture-backed IPOs have higher IPO valuations while the length of venture capital investment until IPO is negatively related to the amount of IPO collected at IPO. Market conditions also strongly influence the IPO proceeds. In contrast, the size and the age of the company at IPO are not taken into account by IPO investors.

3.3. Technology signals and access to other valuable resources

Table 5 reports the results for simultaneous equations Eq.4, Eq.5 and Eq.6 performed in model 2 and 3. In model 2, we show estimates for the simultaneous relationship between *ODD*, *PATAPPY4* and access to venture capital investments (Eq.4) and collaborative revenues prior to IPO (Eq.5). In model 3, we show estimates for an additional simultaneous equation for the logarithm of the number of employees at IPO. Estimation results show a positive and significant relationship between *ODD* and *PATAPPY4* and access to venture capital investments (Eq.4) and collaborative revenues before IPO (Eq.5). In contrast, increases in the amount of collaborative revenues and the presence of corporate venture capital investors reduce the amount of cash collected from venture capitalists (Eq.4 in models 2 and 3). Note that here again the coefficient of *ODD* is higher than *PATAPPY4* for Eq.4, Eq.5, Eq.6. This result suggests that Orphan Drug Designations are stronger than patent applications prior to IPO to attract valuable resources before the company goes public.

3.4. Alternative and Robustness check models

In the robustness checks presented in tables 6 and 7, we performed simultaneous equation models with alternative model specifications to test the stability of our coefficients with alternative configurations to solve the structural system. Then we introduced the variables *VENTURE_BACKED*, *BIO_RATIO*, *UWREP*, *PERCENT SOLD* in Eq.4 and Eq.5. Estimation results show that there is no significant impact of those variables on access to collaborative revenues and employees prior to IPO (See Table 6). We also introduced the variables *VENTURE_BACKED*, *BIO_RATIO*, *UWREP*, *PERCENT SOLD* in Eq.2 and Eq.3. Estimation results show that our initial assumption, which suggests that those variables do not influence the number of innovative outputs developed in the long and risky process before IPO, is validated. Considering our key explanatory variables, we observe that there is little variation in the coefficients and standard errors compared with model 3.

4. DISCUSSION AND CONCLUSION

We provide new insights into the literature on the role and nature of knowledge signals for uninformed observers (IPO investors) in US stock markets. We explore how Orphan Drug Designations are linked to a higher amount of cash collected at IPO while at the same time influencing access to other valuable organizational signals and resources for start-up development.

We performed simultaneous equations to take into account the endogeneity that may occur when the firm characteristics affecting the firm's decision to apply for knowledge signals before going public also determine the amount of cash collected at IPO. Furthermore, patents and ODDs before going public may also influence access to other relevant resources for start-up companies, for instance venture capital investments, collaborative revenues and employees prior to the IPO. Estimation results show a positive and significant relationship between ODD and PATAPPy4 and access to IPO investments at IPO, venture capital investments and collaborative revenues before the IPO. Regression results also suggest that Orphan Drug Designations are stronger than patent applications prior to the IPO to attract valuable resources before the company goes public.

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 et al., 2013). 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). This paper address for the first time the use of Orphan Drug Designations 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. Orphan Drug Designations share many properties with patents as intellectual assets: monopolistic market rights limited in time and space, quality signal, facilitating cooperative arrangements and transactional value. Indeed, we found that OD designations are more valuable than patents to attract IPO investors.

Since the OD Act, the FDA has granted more than 3000 OD Designations and approved more than 400 orphan drugs for marketing (Garden et al., 2017). 85% of the Orphan Drugs have been developed by small or medium sized pharma-biotech enterprises, and half of the market-approved orphan drugs belong to the biotechnology industry (Coté, 2012). The promise of a 7-year market exclusivity and the 50% tax credit for clinical drug testing are attractive enough for investors to balance the risk linked to targeting a niche market.

However, it remains unclear which of the market exclusivity or the tax refund is the more effective incentive 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, the lowering of drug R&D costs, and the short-term balance sheet?

Seoane-Vazquez et al. (2008) found a small influence of OD market exclusivity, extending the patent exploitation monopoly lifetime by less than one year. Therefore, we may argue that IPO investors are more interested in the competitive advantage related to the tax credit, and not that related to market exclusivity. But a clear separation between the effects of these two incentives is not possible.

Finally, it also appears that ODD is more correlated with higher VC and global pharmaceutical partner investments prior to IPO than patent applications are. However, the dynamics of such signaling effects have not been investigated: it remains to be seen if the signaling function of ODD varies over the sequential rounds of financing for small biotechnology firms, and diminishes over time as has been demonstrated in the literature (Hoenen et al., 2014).

Future studies should also examine more explicitly the trade-offs associated with alternative quality signals at different stages of drug development and the relative importance of those signals (Guo et al., 2005).

These findings also have important implications for policymakers. The OD Act with its regulation and financial incentives succeeded in attracting private investments, and represents an opportunity for biotech companies, which depend heavily on venture capital.

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. Recently the FDA implemented a new support for stimulating the development of new antibiotics, the “Generating Antibiotics Incentives Now” or GAIN.⁸ The new law provides an additional five years of exclusivity. It remains to be seen whether this legislation will succeed in attracting biotech companies and private investors.

Despite these successes in developing orphan drugs, academic researchers and rare disease advocacy patient organizations, especially in Europe, have raised questions about the financing of drug R&D for rare diseases. The European Commission introduced an orphan drug legislation in 2000 providing incentives for companies, such as a 10-year market exclusivity and fee waivers. Future work should explore whether ODD are also signals for the European stock markets and whether they are also more valuable than patent protection to attract investors. It could also be interesting to compare the European Union and the US in terms of the signaling value of Orphan Drug Designation for investors.

⁸ <https://www.congress.gov/bill/112th-congress/house-bill/2182>

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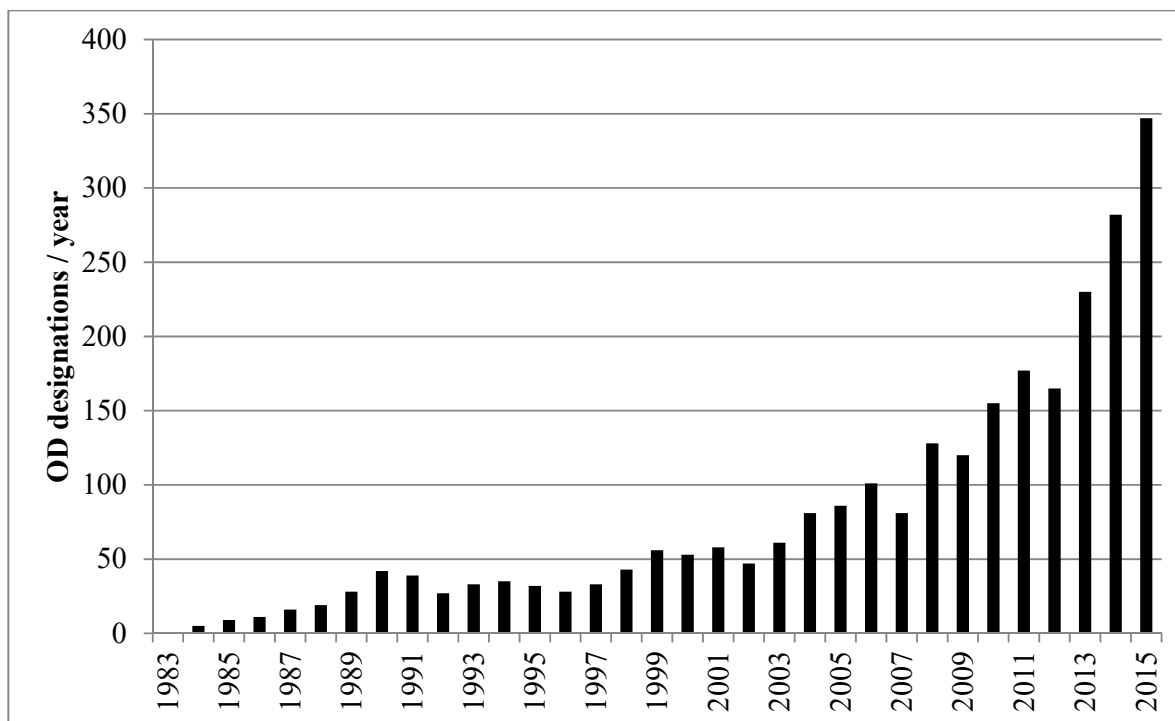
Figure 1. FDA registration of OD designations from 1983 to 2015.

Figure 2. Trends of OD firms' IPOs.

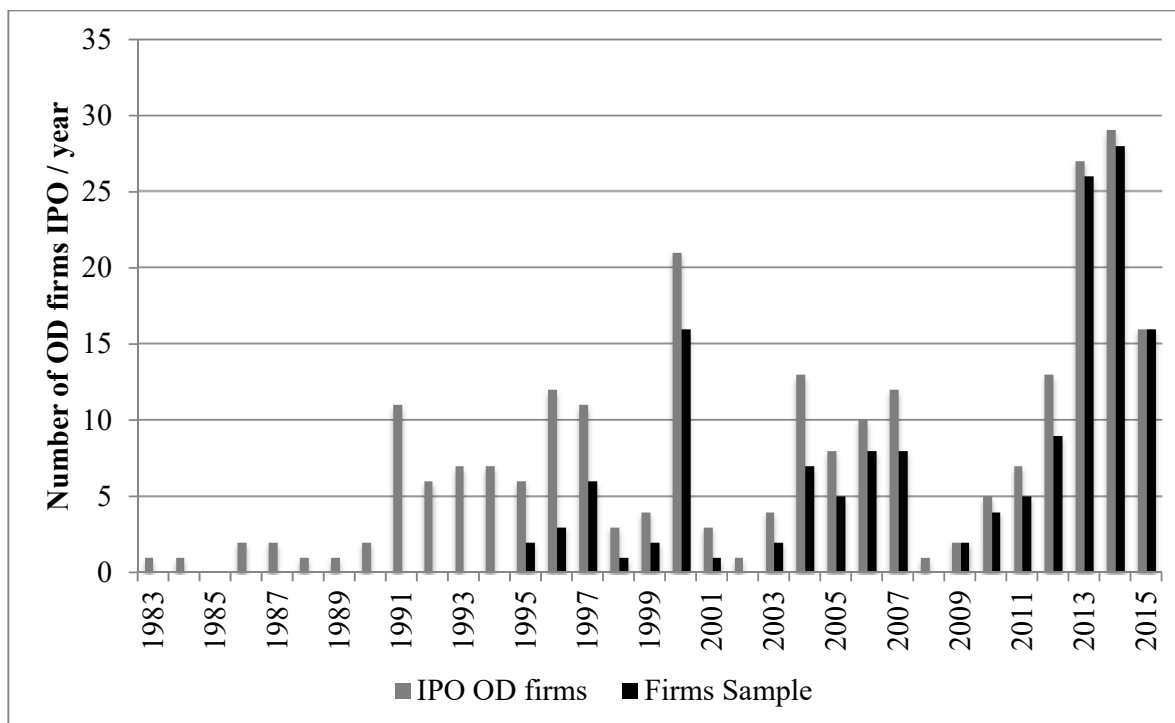


Table 1. SIC code distribution of OD firms' IPO sample

SIC	Number of firms	Description
2833	1	Medicinal chemicals and botanical products
2834	110	Pharmaceuticals preparation
2836	29	Biological products, except diagnostic substances
3841	1	Surgical & medical instruments & apparatus
8731	10	Services-commercial physical & biological research
Total	151	

Table 2. Variable description and summary statistics

Variable code	OD firms			Definition	Source
	Mean	Min	Max		
Dependent variables					
<i>LOG (PROCEEDS)</i>	17,60	10,88	19,39	Logarithm of amount collected at IPO.	IPO prospectus
Independent variables					
ODD	0,91	0,00	7,00	Number of Orphan Drug designations granted by FDA to firm prior to IPO	FDA database
Controls					
<i>PATAPPy4</i>	13,07	0,00	94,00	Number of patents filed for by the firm in last four years prior to IPO	Orbit
<i>LOG (REVENUES+1)</i>	7,54	0,00	18,69	Logarithm of the total revenues in year prior to IPO	IPO prospectus
<i>LOG (R&D_EXPENSES)</i>	15,87	11,82	18,27	Logarithm of Research and Development expenses in year prior to IPO	IPO prospectus
<i>DRUGPIPEPRIORIPO</i>	9,24	0,00	68,00	Number of drug candidates under development prior to IPO	Pharmaproject
<i>PHASE2PRIORIPO</i>	1,13	0,00	7,00	Number of drug candidates engaged at least in clinical trial phase II prior to IPO	Pharmaproject
<i>ODEXPERIENCE</i>	3,03	0,00	23,00	Number of years since the first Orphan Drug designation granted prior to IPO	FDA database
<i>LOG (AGE AT IPO+1)</i>	2,12	0,00	4,17	Logarithm of age of company at IPO	IPO prospectus
<i>LOG (EMPLOYEES+1)</i>	3,62	0,00	6,15	Logarithm of the number of employees at date of IPO	IPO prospectus
<i>VENTURE BACKED</i>	0,74	0,00	1,00	DV recorded a value of 1 if company is a venture capital-backed IPO, 0 otherwise	VentureSource
<i>VC_ROUND</i>	2,78	0,00	11,00	Number of Venture Capital rounds at date IPO	VentureSource
<i>VC_INTENSITY</i>	4,70	0,00	21,00	Number of years from the first Venture Capital investment to IPO	VentureSource
<i>LOG (VCFUNDS+1)</i>	13,37	0,00	19,57	Logarithm of amount collected from Venture Capitalist prior to IPO.	VentureSource
<i>CORPVCAP</i>	0,18	0,00	1,00	DV recorded a value of 1 if company is a corporate venture-backed IPO, 0 otherwise	VentureSource
<i>UWREPUT</i>	7,02	0,00	9,10	Prestige of the IPO firm's lead underwriter	Ritter ranking
<i>LOG (PERCENT SOLD)</i>	-1,37	-4,53	0,80	Logarithm of percentage of firm to be sold during a public equity offering	IPO prospectus
<i>NASDAQ</i>	0,97	0,00	1,00	DV recorded a value of 1 if company was quoted on NASDAQ (US)	IPO prospectus
<i>BIO_RATIO</i>	0,21	0,02	0,36	Ratio of Pharma-Biotech IPOs divided by total number of IPOs in a given year	Capital IQ
<i>BUBBLE</i>	0,12	0,00	1,00	DV recorded a value of 1 if IPO occurred during the bubble internet (1999 or 2000)	IPO prospectus
<i>SICSEC2834</i>	0,72	0,00	1,00	DV recorded a value of 1 if company's principal segment is SIC 2834, 0 otherwise	IPO prospectus

*DV=Dummy variable

Table 3. Pearson Correlation matrix

	1	2	3	4	5	6	7	8	9	10
1 LOG (PROCEEDS)	1.0000									
2 ODD	0.0541	1.0000								
3 PATAPPy4	0.1587	-0.0826	1.0000							
4 LOG (REVENUES+1)	0.0335	0.0820	0.2127	1.0000						
5 LOG (R&D_EXPENSES)	0.4231*	-0.0174	0.3729*	0.2656	1.0000					
6 DRUGPIPEPRIORIPO	0.0540	0.2726	0.0738	0.0960	0.1498	1.0000				
7 PHASE2PRIORIPO	0.0996	0.1250	0.0833	0.0302	0.1728	0.4140*	1.0000			
8 LOG(AGE AT IPO)	0.0155	0.2947	0.1468	0.1647	0.1940	0.1807	0.2117	1.0000		
9 LOG(EMPLOYEES+1)	0.4031*	0.0842	0.2970	0.4661*	0.6230*	0.1224	0.1191	0.0837	1.0000	
10 CORPVCAP	0.0969	0.0806	0.2320	0.1470	0.1665	0.0449	0.0224	0.1436	0.1896	1.0000
11 LOG (PERCENT SOLD)	-0.0071	-0.0370	0.0523	-0.0911	-0.0549	-0.0210	0.0042	-0.0256	-0.0528	0.0508
12 UWREPUT	0.3470*	0.0875	0.0991	0.0957	0.3906*	0.1364	0.0411	0.0384	0.4111*	0.1292
13 VENTURE BACKED	0.3141	-0.0151	0.1938	0.0327	0.3550*	-0.0092	-0.1481	0.0931	0.1849	0.2754
14 LOG (VCFUNDS+1)	0.3354*	-0.0015	0.2197	0.0407	0.3912*	0.0082	-0.1375	0.1188	0.2009	0.2793
15 VC_INTENSITY	0.0546	0.0354	0.2690	0.1183	0.3400*	0.0912	-0.0245	0.4230*	0.0924	0.3021
16 BIO_RATIO	0.1456	0.1085	-0.0614	-0.1846	0.0042	-0.0115	0.1587	0.2565	-0.2480	-0.0138
17 BUBBLE	0.1077	-0.0972	0.0503	0.1054	0.0166	0.0571	0.0122	-0.1629	0.2106	0.0417
18 NASDAQ	0.1594	-0.0105	0.0977	-0.0067	0.1629	-0.0864	-0.2168	-0.0700	0.1012	0.0770
19 SICSEC2834	0.1798	-0.1266	0.1883	0.0201	0.1722	0.0244	0.0167	-0.0779	0.0615	0.0264
20 ODEXPERIENCE	0.0524	0.6870*	-0.0826	-0.0011	-0.0633	0.2221	0.0849	0.2592	0.0271	-0.0339
	10	11	12	13	14	15	16	17	18	20
11 LOG (PERCENT SOLD)	1.0000									
12 UWREPUT	-0.0754	1.0000								
13 VENTURE BACKED	0.0526	0.2047	1.0000							
14 LOG (VCFUNDS+1)	0.0459	0.2248	0.9961*	1.0000						
15 VC_INTENSITY	0.1233	0.0559	0.6271*	0.6437*	1.0000					
16 BIO_RATIO	0.0342	-0.0368	0.0914	0.1098	0.1353	1.0000				
17 BUBBLE	-0.1118	0.1994	-0.0631	-0.0721	-0.1504	-0.2559	1.0000			
18 NASDAQ	0.1640	0.1748	0.0911	0.1007	-0.0020	0.0106	0.0607	1.0000		
19 SICSEC2834	0.0419	0.0748	0.1641	0.1691	0.0462	-0.0061	-0.0396	0.1700	1.0000	
20 ODEXPERIENCE	0.0559	0.0310	-0.0337	-0.0191	0.0822	0.0720	-0.1302	0.0008	0.0015	1.0000

* p<0.1

** p<0.05

*** p<0.01

Table 4. The value of OD designations for IPO investors

	1	2	3
	Eq.1	Eq.1	Eq.1
	<i>LOG(PROCEEDS)</i>	<i>LOG(PROCEEDS)</i>	<i>LOG(PROCEEDS)</i>
<i>ODD</i>	0.281** (0.125)	0.286** (0.124)	0.361*** (0.123)
<i>PATAPPy4</i>	0.100*** (0.0261)	0.0987*** (0.0261)	0.0995*** (0.0261)
<i>UWREPUT</i>	0.0706* (0.0407)	0.0696* (0.0407)	0.0686* (0.0407)
<i>VENTURE BACKED</i>	0.903*** (0.304)	0.780** (0.303)	0.845*** (0.303)
<i>BIO_RATIO</i>	2.656*** (0.788)	2.638*** (0.788)	2.592*** (0.788)
<i>LOG (PERCENT SOLD)</i>	-0.0162 (0.147)	-0.0132 (0.147)	-0.00465 (0.147)
<i>SICSEC2834</i>	-0.156 (0.245)	-0.128 (0.245)	-0.168 (0.245)
<i>LOG (R&D_EXPENSES)</i>	-0.0444 (0.140)	-0.0624 (0.140)	0.212 (0.136)
<i>DRUGPIPEPRIORIPO</i>	-0.00719 (0.00962)	-0.00691 (0.00961)	-0.00776 (0.00959)
<i>LOG (AGE AT IPO+1)</i>	-0.238 (0.201)	-0.190 (0.201)	-0.244 (0.200)
<i>LOG (EMPLOYEES +1)</i>	0.170 (0.146)	0.347** (0.144)	-0.152 (0.132)
<i>CORPVCAP</i>	-0.552* (0.297)	-0.501* (0.297)	-0.382 (0.297)
<i>LOG (REVENUES+1)</i>	-0.0309** (0.0145)	-0.0771*** (0.0132)	-0.0647*** (0.0132)
<i>VCINTENSITY</i>	-0.106*** (0.0351)	-0.0940*** (0.0350)	-0.115*** (0.0349)
<i>BUBBLE</i>	0.235 (0.267)	0.240 (0.267)	0.251 (0.267)
<i>NASDAQ</i>	0.0244 (0.519)	0.0250 (0.519)	0.00979 (0.519)
Simultaneous Equations			
<i>Technology signals (ODD and PATAPPy4)</i>	Yes	Yes	Yes
<i>Other relevant signals (VCFUNDS and REVENUES)</i>	No	Yes	Yes
<i>Other valuable ressources (Employees)</i>	No	No	Yes
<i>Constant</i>	15.83*** (1.926)	15.75*** (1.926)	13.26*** (1.904)

Robust standard errors in parentheses.

* p<0.1

** p<0.05

*** p<0.01

Table 5. The value of OD designations and access to other valuable resources

	2		3		
	Eq.4	Eq.5	Eq.4	Eq.5	Eq.6
	<i>LOG</i>	<i>LOG</i>	<i>LOG</i>	<i>LOG</i>	<i>LOG</i>
	<i>(VCFUNDS+1)</i>	<i>(REVENUES+1)</i>	<i>(VCFUNDS+1)</i>	<i>(REVENUES+1)</i>	<i>(EMPLOYEES)</i>
<i>ODD</i>	0.723*** (0.244)	1.439 (0.977)	0.990*** (0.234)	1.946** (0.956)	0.299*** (0.108)
<i>PATAPPy4</i>	0.366*** (0.0178)	0.766*** (0.151)	0.369*** (0.0178)	0.718*** (0.151)	0.0839*** (0.0153)
<i>UWREPUT</i>	0.121*** (0.0267)		0.118*** (0.0267)		
<i>VENTURE BACKED</i>	17.51*** (0.630)		17.74*** (0.630)		
<i>BIO_RATIO</i>	1.858*** (0.534)		1.692*** (0.531)		
<i>LOG (PERCENT SOLD)</i>	-0.306*** (0.0992)		-0.276*** (0.0987)		
<i>SICSEC2834</i>	-1.392*** (0.467)	-2.821 (1.887)	-1.534*** (0.467)	-2.877 (1.886)	-0.413* (0.216)
<i>LOG (R&D_EXPENSES)</i>	-0.756*** (0.254)	-2.212** (1.011)	0.222 (0.226)	0.0814 (0.975)	0.341*** (0.102)
<i>DRUGPIPEPRIORIP O</i>	-0.0133 (0.0199)	-0.0306 (0.0773)	-0.0163 (0.0198)	-0.0334 (0.0771)	-0.00531 (0.00900)
<i>LOG (AGE AT IPO)</i>	-0.434 (0.399)	-0.327 (1.595)	-0.627 (0.396)	-0.593 (1.589)	-0.212 (0.184)
<i>LOG (EMPLOYEES +1)</i>	0.0129 (0.273)	2.145** (1.050)	-1.766*** (0.177)	-1.411 (0.964)	
<i>CORPVCAP</i>	-1.787*** (0.566)	-3.179 (2.307)	-1.362** (0.563)	-1.804 (2.301)	-0.152 (0.265)
<i>LOG (REVENUES+1)</i>	-0.218*** (0.0206)		-0.174*** (0.0200)		-0.0250** (0.0116)
<i>VCINTENSITY</i>	-0.0896 (0.0697)	-0.131 (0.275)	-0.165** (0.0691)	-0.251 (0.274)	-0.0710** (0.0312)
<i>BUBBLE</i>	-0.468*** (0.176)		-0.429** (0.175)		
<i>NASDAQ</i>	-0.273 (0.333)		-0.327 (0.333)		
<i>ODEXPERIENCE</i>					
<i>LOG (VCFUNDS+1)</i>		-0.0848 (0.138)		-0.0761 (0.138)	0.00648 (0.0162)
<i>Constant</i>	9.977*** (3.327)	28.87** (13.85)	1.075 (3.160)	6.346 (13.59)	-1.902 (1.512)

Robust standard errors in parentheses.

* p<0.1

** p<0.05

*** p<0.01

Table 6. Alternative specifications with the entire simultaneous equations system

	Eq.1	Eq.4	Eq.5	Eq.6	Eq.2	Eq.3
	<i>LOG(PROCEEDS)</i>	<i>LOG (VCFUNDS+1)</i>	<i>LOG (REVENUES+1)</i>	<i>LOG (EMPLOYEES+1)</i>	<i>ODD</i>	<i>PATAPPy4</i>
<i>ODD</i>	0.361*** (0.123)	0.990*** (0.234)	1.946** (0.956)	0.299*** (0.108)		
<i>PATAPPy4</i>	0.0995*** (0.0261)	0.369*** (0.0178)	0.718*** (0.151)	0.0839*** (0.0153)		
<i>UWREPUT</i>	0.0686* (0.0407)	0.118*** (0.0267)				
<i>VENTURE BACKED</i>	0.845*** (0.303)	17.74*** (0.630)				
<i>BIO_RATIO2</i>	2.592*** (0.788)	1.692*** (0.531)				
<i>LOG (PERCENT SOLD)</i>	-0.00465 (0.147)	-0.276*** (0.0987)				
<i>SICSEC2834</i>	-0.168 (0.245)	-1.534*** (0.467)	-2.877 (1.886)	-0.413* (0.216)	-0.378** (0.172)	5.797** (2.449)
<i>LOG (R&D_EXPENSES)</i>	0.212 (0.136)	0.222 (0.226)	0.0814 (0.975)	0.341*** (0.102)	-0.0838 (0.0927)	-2.447** (1.175)
<i>DRUGPIPEPRIORIPO</i>	-0.00776 (0.00959)	-0.0163 (0.0198)	-0.0334 (0.0771)	-0.00531 (0.00900)	0.0140** (0.00715)	0.0102 (0.102)
<i>LOG (AGE AT IPO)</i>	-0.244 (0.200)	-0.627 (0.396)	-0.593 (1.589)	-0.212 (0.184)	0.313** (0.145)	0.758 (2.055)
<i>LOG (EMPLOYEES+1)</i>	-0.152 (0.132)	-1.766*** (0.177)	-1.411 (0.964)		0.124 (0.105)	7.636*** (0.916)
<i>CORPVCAP</i>	-0.382 (0.297)	-1.362** (0.563)	-1.804 (2.301)	-0.152 (0.265)	0.308 (0.211)	0.836 (2.982)
<i>LOG (REVENUES+1)</i>	-0.0647*** (0.0132)	-0.174*** (0.0200)		-0.0250** (0.0116)	0.00925 (0.0112)	0.802*** (0.105)
<i>VCINTENSITY</i>	-0.115*** (0.0349)	-0.165** (0.0691)	-0.251 (0.274)	-0.0710** (0.0312)	-0.0504* (0.0258)	0.809** (0.362)
<i>BUBBLE</i>	0.251 (0.267)	-0.429** (0.175)				
<i>NASDAQ</i>	0.00979 (0.519)	-0.327 (0.333)				
<i>ODEXPERIENCE</i>			-0.0761 (0.138)	0.00648 (0.0162)	0.0175 (0.0135)	-0.0492 (0.191)

Robust standard errors in parentheses.

* p<0.1

** p<0.05

*** p<0.01

Table 7. Alternative specifications with the entire simultaneous equations system

	Eq.1	Eq.4	Eq.5	Eq.6	Eq.2	Eq.3
	<i>LOG(PROCEEDS)</i>	<i>LOG (VCFUNDS+1)</i>	<i>LOG (REVENUES+1)</i>	<i>LOG (EMPLOYEES+1)</i>	<i>ODD</i>	<i>PATAPPy4</i>
<i>ODD</i>	0.334*** (0.121)	0.993*** (0.242)	1.970** (1.005)	0.304*** (0.117)		
<i>PATAPPy4</i>	0.0965*** (0.0263)	0.374*** (0.0153)	0.741*** (0.163)	0.0925*** (0.0164)		
<i>DRUGPIPEPRIORIPO</i>	-0.00641 (0.00939)	-0.0154 (0.0200)	-0.0278 (0.0798)	-0.00495 (0.00951)	0.0139* (0.00714)	0.00289 (0.101)
<i>UWREPUT</i>	0.0676 (0.0420)	0.0860 (0.0579)	-0.143 (0.345)		0.0215 (0.0367)	0.0530 (0.305)
<i>VENTURE BACKED</i>	0.923*** (0.274)	18.04*** (0.426)		0.237 (0.261)	0.239 (0.240)	-2.261 (2.217)
<i>BIO_RATIO</i>	2.408*** (0.811)	1.924** (0.867)			0.867 (0.733)	-2.236 (4.486)
<i>LOG (PERCENT SOLD)</i>	-0.00261 (0.149)	-0.274* (0.159)			-0.125 (0.135)	0.284 (0.824)
<i>SICSEC2834</i>	-0.174 (0.242)	-1.583*** (0.465)	-3.133 (1.947)	-0.462** (0.229)	-0.367** (0.171)	5.876** (2.423)
<i>LOG (R&D_EXPENSES)</i>	0.196 (0.133)	0.215 (0.221)	0.229 (1.018)	0.319*** (0.107)	-0.106 (0.0940)	-2.270** (1.146)
<i>LOG (AGE AT IPO)</i>	-0.227 (0.198)	-0.560 (0.404)	-0.464 (1.605)	-0.191 (0.193)	0.255* (0.150)	0.629 (2.044)
<i>LOG (EMPLOYEES+1)</i>	-0.113 (0.131)	-1.788*** (0.174)	-1.774* (1.011)		0.140 (0.111)	7.423*** (0.907)
<i>CORPVCAP</i>	-0.366 (0.296)	-1.426** (0.562)	-1.861 (2.385)	-0.196 (0.280)	0.314 (0.210)	0.997 (2.956)
<i>LOG (REVENUES+1)</i>	-0.0630*** (0.0131)	-0.178*** (0.0197)		-0.0338*** (0.0119)	0.0106 (0.0113)	0.801*** (0.102)
<i>VCINTENSITY</i>	-0.121*** (0.0333)	-0.184*** (0.0615)	-0.367 (0.227)	-0.0822*** (0.0315)	-0.0421 (0.0260)	0.886*** (0.321)
<i>ODEXPERIENCE</i>					0.174*** (0.0163)	-0.548** (0.228)
<i>Constant</i>	13.43***	0.796	5.397	-1.639	0.537	10.09

Robust standard errors in parentheses.

* p<0.1

** p<0.05

*** p<0.01

Appendix

Appendix Table 1. Estimations of OD designations and patents for 3 simultaneous equations models

	1		2		3	
	Eq.2	Eq.3	Eq.2	Eq.3	Eq.2	Eq.3
	ODD	PATAPPy4	ODD	PATAPPy4	ODD	PATAPPy4
<i>SICSEC2834</i>	-0.393** (0.172)	4.910** (2.454)	-0.395** (0.172)	4.521* (2.453)	-0.378** (0.172)	5.797** (2.449)
<i>LOG (R&D_EXPENSES)</i>	-0.0181 (0.0931)	2.414* (1.328)	-0.0160 (0.0931)	2.820** (1.326)	-0.0838 (0.0927)	-2.447** (1.175)
<i>DRUGPIPEPRIORIPO</i>	0.0141** (0.00715)	0.0222 (0.102)	0.0141** (0.00715)	0.0151 (0.102)	0.0140** (0.00715)	0.0102 (0.102)
<i>LOG (AGE AT IPO+1)</i>	0.307** (0.145)	1.057 (2.066)	0.303** (0.145)	0.0922 (2.061)	0.313** (0.145)	0.758 (2.055)
<i>LOG (EMPLOYEES +1)</i>	0.0140 (0.106)	1.586 (1.512)	-0.00368 (0.106)	-1.938 (1.445)	0.124 (0.105)	7.636*** (0.916)
<i>CORPVCAP</i>	0.349* (0.211)	4.685 (3.004)	0.344 (0.211)	3.736 (3.002)	0.308 (0.211)	0.836 (2.982)
<i>LOG (REVENUES+1)</i>	0.00932 (0.0112)	0.124 (0.160)	0.0140 (0.0112)	1.054*** (0.109)	0.00925 (0.0112)	0.802*** (0.105)
<i>VCINTENSITY</i>	-0.0557** (0.0258)	0.556 (0.368)	-0.0568** (0.0258)	0.332 (0.367)	-0.0504* (0.0258)	0.809** (0.362)
<i>ODEXPERIENCE</i>	0.177*** (0.0164)	-0.299 (0.233)	0.177*** (0.0164)	-0.326 (0.230)	0.174*** (0.0163)	-0.575*** (0.220)
<i>LOG (VCFUNDS+1)</i>	0.0182 (0.0135)	-0.0954 (0.192)	0.0189 (0.0135)	0.0418 (0.191)	0.0175 (0.0135)	-0.0492 (0.191)
<i>Constant</i>	-0.000730 (1.229)	-39.16** (17.53)	0.00512 (1.229)	-37.99** (17.52)	0.625 (1.226)	10.79 (16.57)

Robust standard errors in parentheses.

* p<0.1

** p<0.05

*** p<0.01