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EMPIRICAL ECONOMIC ANALYSIS OF ORPHAN DRUG INNOVATION

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ABSTRACT

In many countries, governments are trying to stimulate the development of new drugs for unmet health needs with public policy measures. A common policy between the United States (US) and European Union (EU) is the legislation on Orphan Drugs (OD). This term is dedicated to treatments for rare diseases benefiting in EU and the US of a special status with economic incentives to encourage R&D in the pharmaceutical industry. While OD legislation has more than 15 years in EU, and more than 30 years in US, one may wonder about the effectiveness of this legislation on the development of new OD, on the profitability of these OD for the pharmaceutical industry, and the rationality of the pricing and reimbursement of these drugs.

So, we wish to address the impact of this legislation on pharmaceutical innovation for rare diseases with a EU-US comparison.

To explore this question, we have gathered a multidisciplinary research team involving 4 laboratories with economists from different fields, political scientists, pharmacist and physician, belonging to the University of Bordeaux, Sciences Po Bordeaux, the “Ecole des Mines” and the Paris School of Economics in association with public research organizations (CNRS) or health institution (Assistance Publique - Paris Hospitals, AP-HP), and close collaboration with researchers at the Business School of Imperial College in London. The added value of the consortium is to bring together diverse expertise and share preliminary data accumulated by each member.

The research project focuses on 6 objectives: analyzing the effectiveness of technology transfer and identifying market friction mechanisms, studying the attractiveness of private investment in OD R&D and the survival of biotechnology companies, measuring the R&D failure rate and the risks associated with OD R&D, and finally comparing the different mechanisms of price regulation, and their impact on OD. Methodologically, the project is based on: an original OD database built in the laboratory GREThA by the project coordinator, and quantitative approaches (descriptive statistics, econometrics and modeling) and qualitative (semi-structured interviews). Its originality is to use financial economics methods to meet the innovation economy of assumptions that can inform public policy in health economics.

1. BACKGROUND

The pharmaceutical market is highly regulated with regulations as important factors that impact therapeutic research and innovation on several levels. Innovators must prove safety, clinical efficacy and cost-effectiveness of their products before and after obtaining marketing authorisation. Pharmaceutical firms are among the top investors in research and development (R&D) and their innovative success has greatly expanded the treatment arsenal over the last century. However, despite the biotech revolution and advances in genomics, the sector continues to have attrition rates and lengthy product development, translating into higher R&D costs and drug prices. Indeed, pharmaceutical spending tends to increase at a faster pace than total health spending or GDP in OECD countries while numerous unmet medical needs still exist. A number of important policy measures seek to promote drug innovation. These include those intended to encourage university technology transfer (the **Bayh-Dole Act** in the United States in 1980 and **Allegre's law** in France in 1999), to reward innovation using market incentives (the 1984 Hatch-Waxman Act in the US), and to reduce regulatory costs (the foundation of the European Medicine Agency (EMA) in 1995). One policy common to both the US and the European Union is **Orphan Drug legislation** (Kesselheim AS, (2011)).

Rare disorders is the name of diseases, with varied aetiology and low-prevalence for the majority of which there is no treatment available. They are frequently life-threatening or chronically debilitating with significant impact on quality of life. About 5000 identified diseases are classed as orphan because of the lack of diagnosis, prevention & treatment. While each rare disorder affects few people, their aggregate consequence for public health is large; it affects 30 million people in Europe, or 9% of the EU population. It is estimated that 350 million people worldwide suffer from rare diseases. Drug development for these diseases has been limited by a lack of understanding of the pathophysiology mechanisms and the relative unavailability of subjects for clinical trials, as well the prohibitive cost of investing in a novel drug with poor market potential. Because of the small potential market size, rare disorders frequently have few treatments and are considered "orphan."

Orphan drugs (OD) is the term used for drugs intended to treat rare diseases and which qualifies as viable from a scientific aspect but that would not be economically viable in the absence of policy intervention. To encourage development of such drugs, the US introduced OD legislation in 1983, and Europe followed with similar measures in 2000. The legislation both lowers the R&D costs associated

with OD development, through tax credits, reduced regulatory fees, and fast-track approval, as well as increasing the potential revenue by extending the period of market exclusivity. More than 600 drugs have been designated “orphan” since the introduction of these policies (Zaur Rzakhstanov, (2008).

The policies created incentives for pharma firms to redirect their efforts towards niche markets and away from the so-called blockbuster model of targeting chronic diseases with high prevalence, such as heart disease and ulcers (Montalban M. et al., 2013). However, since these niche markets often attract only 1-2 firms, the resulting lack of competition often leads to high prices for orphan drugs. As many are used for chronic diseases, they represent growing expenditures and have raised concerns among payers and patients.

Today half of OD present on the market are actually anti-neoplastic therapies, and 7 of the 10 top-selling cancer drugs in U.S. sales in 2011 were OD (IMS Health numbers), with true blockbuster exceeding one billion \$ annual revenue for some drugs (Rituxan, Avastin, Herceptin, Gleevec). OD status gave the opportunities for pharma firms to move from blockbuster business model to nichebuster to find new markets & sources of profits at a time where Big Pharma have troubles with generic competition and drying drug pipeline. The possibilities offered by personalized medicine today are immense with pharmacogenomic profiling of tumors in patients. But rising prices and growing expenditures on oncology drugs have caused significant concern among payers and patients. Therefore, OD have become a major issue for health economy and the sustainability of health insurance systems as a potential source of future social inequality (Sullivan R. *et al.*, 2011).

Indeed, there is an important policy debate about accessibility, cost-effectiveness, and reimbursement by health protection systems. Often, these issues are addressed using pharmacoeconomic analysis, or establishing cost/effectiveness through health technology assessment and value-based pricing as a means to estimate a drug price linked to the benefits it offers to patients and society. While estimating the medical benefits associated with a drug is challenging, it is even more difficult to determine the true cost of the R&D behind a drug. Multiple parties, including both the public and private sectors, may contribute. Both sectors face an opportunity cost: for the government, funding of medical research means reducing spending elsewhere. For the private sector, funding R&D means forgoing investment opportunities elsewhere, usually referred to as a cost of capital (DiMasi J *et al.*, 2003). Empirical evidence suggests that small biotechnology firms may pursue different drug R&D strategies than large firms, which may be relevant for OD. The breakdowns of costs, and their trends, have important implications for public health,

innovation, and industrial policy. Many different stakeholders are affected: patients, firms, and health agencies. Thus far, a lack of data as well as transparency in economic studies have been lacking.

2. OBJECTIVES

How to conceal the cost of innovation and the sustainability of public health system? At the present time, political agenda are focusing on reinforcing innovation policies to sustain the economy. Therefore public stakeholders invest in high risk activity while the benefits are captured by the firms. This is a dilemma for public health future unless advance in post-genomic medicine cut down the risk and the cost of R&D & clinical trials.

We are interested in how these policies promote pharmaceutical innovation and affect the development of drugs for rare diseases. There are many related questions: does the OD act foster the development of drugs that would be unprofitable otherwise? What is the cost of OD R&D? Is the OD market a new strategic opportunity for big pharma?

Previous studies have documented that such incentives can lead to positive outcomes (Wästfel, 2006; Heemstra, 2009) but may also have unintended consequences. An empirical & theoretical economic analysis on effect of policies on OD for rare diseases in EU compared to the US is needed.

We have been successfully granted in 2015 by the French national institute of cancer (INCa) for a 3-years research program on drug innovation and inequality in rare cancers (Grant # INCA_9530; <http://www.e-cancer.fr/Institut-national-du-cancer/Appels-a-projets/Appels-a-projets-resultats/SHS-ESP-2015>).

The research project is organized around 3 main objectives and 6 tasks, with the aims of:

- to analyze the politics of OD approval regulation within the EU and US and understand the past & undergoing political work of the stakeholders (firms, patients advocacy group, State).
- to characterize the drug market (both EU and US) for rare diseases with approved Orphan Medicinal Product status in order to get insight on determinants of OD markers' development
- to look for the role of university research spillovers in driving private sector productivity, and the role of competition that could affect R&D in orphan drug development.

- to investigate whether OD status can be signals to financial markets and impacts on the way investors perceive drug R&D for rare diseases.
- to explore the survivability of biotech IPOs developing drugs with or without OD designation.
- to analyze the factors associated with failure of OD projects during the different stages of R&D,
- to study FDA orphan drug market approval announcements influence on stock prices of the sponsor pharmaceutical companies
- to compare the prices obtained in different countries and link them with price setting regulations.

3. PRELIMINARY RESULTS

3.1. *“Characterization of drugs for rare diseases with approved Orphan Medicinal Product status*

While FDA and EMA are providing annual statistics on OD designations trends and the data are publicly available, there are only few publications with deep analysis of the OD R&D, and event less academic work addressing the efficiency of OD status as incentives for innovative drug R&D. Seoane-Vazquez and colleagues (15) published a landmark paper in the field, depicting the OD market. They, however, looked only at the FDA OD trends, while there are no studies that try to cross analyze US and EU OD market. In 2007 the FDA listed 1793 orphan designations and 322 approvals since the implementation of the US OD act (1983). Their main contribution at that time was the demonstration that the 7-year orphan drug market exclusivity provision had a positive yet relatively modest overall effect, and cancer was the main group of diseases targeted for orphan approvals. The 1983 Orphan Drug Act obviously marked a turning point: during the decade before only 10 drugs were marketed for rare disease and only 36 rare disease treatments had ever been authorized by the FDA since 1983, more than 400 orphan treatments had been approved by the FDA.

In 2013, we estimate that FDA listed 2995 orphan designations and 436 approvals sponsored by 1313 different companies. Biotech companies represent 86% of the OD designation demands while big pharma share disposes of 33% of the shares of the OD market approval.

This spectacular turnaround proves that pharmaceutical companies no longer disregard rare disease treatments. In fact it is just the exact opposite: orphan drug research appears nowadays as one of the most dynamic business segments of the pharmaceutical industry.

This research will thus will characterize extensively the drug market (both EU and US) for rare diseases

with approved Orphan Medicinal Product status in order to get insight on determinants of OD markers' development.

3.2. : *Orphan drug market for rare diseases as a social construction*”

Recent studies led by scholars focusing on regulatory dynamics and regulatory operations suggest that the outcomes of regulatory institutions should be interpreted through their capacities to shape a conceptual order of credible and/or relevant information that otherwise might not exist (Carpenter 2004, Carpenter & Ting 2007, Law & Libecap 2006). More formally, this statement relies on the assumption that the market constitutes a set of prospects where, according to the mathematical theory of expectations [Billingsley 1999] “rely upon probability measures and in turn, upon countable and co-countable spaces” [Carpenter 2010]. Put differently, regulation does not solely entail behaviours related to the new [dis]incentives it provides, but also affects beliefs leading to market operations, as well as promoting categories while delegitimizing others. Under this view, regulation may be seen as an essential condition of possibility for marketplaces (Balleisen & Moss 2010). Compared to other topics in the field, and albeit of critical importance, the way norms promoted by regulatory institutions are diffused and are appropriated or not by their audiences received little attention, and still lacks of a model grasping some of its essential features.

The goal of our work is to provide a contribution to this emerging literature on the basis of an empirical analysis of the stock market valuation of US Food and Drug Administration (FDA) “Orphan Drugs” approval. The US Orphan Drug Act (ODA) was implemented in 1983 with the provision of several financial incentives to foster rare diseases drug research & development, and operates within the FDA regulation framework. The 1983 OD Act is generally considered as a turning point: during the previous decade only 10 drugs were marketed for rare disease and only 36 rare disease treatments had ever been authorized by the FDA. Since then, the orphan drug R&D reveals an increasing dynamics and more than 400 orphan treatments have been approved (Seoane-Vasquez et al. 2008). We assume that the reason for this growing interest needs to be search in the way that regulatory politics within the FDA rendered the outcomes in the Orphan Drugs market more countable and more integrable.

First we empirically illustrate this claim on the basis a rich data set mixing the launching of OD and the stock prices and stock market indexes. We used time-series analysis to examine the financial impact of the

FDA OD market approval announcement. We find that OD marketing approval decisions have a significant influence on stock price movements and abnormal returns of the pharmaceutical companies. Moreover, OD approval decisions induce higher stock price progressions than standard market approval. These results indicate that the OD financial incentives, seven-years marketing exclusivity and tax-credit, constitutes an important financial stimulus; they also suggest that this device favors future OD research by improving fund-raising capacities of the biotechnology firms.

Second, we try to formalize these findings consistently with our results and with additional historical data. We conceptualize the progressive legitimation of the OD category by the FDA among financial investors as a process of Bayesian repeated games (Forges & Salomon 2014) introducing new expectations (in the sense of Billingsley). We find that regulation changed progressively investors' beliefs through a similar pattern as the adaptive signal processing described by Oppenheim and Schafer (1989, see also Carpenter 1996). Some indications for further investigations on the basis of this formal model are then provided.

Benoit C. & Gorry P., How does regulation affect beliefs? The case of Market Valuation of Orphan Drug. *American Political Science Association*, Working paper, 2016.

3.3. “Attractiveness of capital investment in OD development by biotech industry”

Drug development for rare diseases has been limited by the prohibitive cost of investing in a novel drug with niche market. To stimulate the industry, Orphan Drug (OD) legislation was put in place in the United States with incentives including tax-credit and market exclusivity. This study aims to test whether OD Designations (ODD) granted by the Food and Drug Administration (FDA) to start-up companies may be considered as relevant signals in attracting investors at the time of the Initial Public Offering (IPO) in the US stock markets. We build an original database in which we consolidate a sample of OD sponsor firms going public between 1995 and 2015. We attempt to take into account for endogeneity of ODD behavior prior to IPO by considering the simultaneous relationship between the firm innovativeness (the patent portfolio), and IPO performance. Furthermore, ODD before going public may also influence the access to other resources as venture capital investments, collaborative revenues and employees prior to 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 increase the IPO proceeds by about 37,5%. Regression results also suggest that ODD are stronger than patents applications to attract IPO investors and other valuable resources before that the company goes public.

Our results clearly indicate that the OD legislation constitute an important financial stimulus. They also suggest that this device favors future OD research via improved fund-raising capacities of the biotechnology firms. This type of supply side incentive seems to be stronger in attracting external investor than patent protection. It remains to know if the signaling function of ODD varies over the sequential rounds of financing, and diminish overtime as it has been demonstrated in the literature for patent.

Gorry P. & Useche D., Orphan Drug Designations as valuable intangible assets for IPO investors in PHARMA-biotech Companies, DRUID conference working paper, 2016.

3.4. : *Stock valuation of orphan drug approval*

The US Orphan Drug (OD) Act was implemented in 1983 with the provision of several financial incentives to foster rare diseases drug research & development. As most of the incentives are not contingent to an ultimate research success, one may wonder about the effects of such public health policy. Very little empirical research have been performed on the subject. In order to answer this question, we use the event-study methodology developed in finance, based on the efficient market hypothesis to investigate the financial impact of the FDA OD market approval announcement. We find that OD marketing approval decisions have a significant influence on stock price movements and abnormal returns of the pharmaceutical companies. Moreover, OD approval decisions induce higher stock price progressions than standard market approval.

These results clearly indicate that the OD financial incentives, seven-years marketing exclusivity and tax-credit, constitutes an important financial stimulus; they also suggest that this device favours future OD research via improved fund-raising capacities of the biotechnology firms.

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