# How does regulation affect beliefs ? Stock Market valuation of Orphan Drug Regulatory Approvals

Cyril Benoît, Philippe Gorry, Martin Zumpe

# How does regulation affect beliefs ?

# The case of Stock Market Valuation of Orphan Drugs Approvals

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# 1    Regulation and Industry Change: reversing cause and effect

The link between the evolution of regulatory institutions and the development of new schemes for value creation within an industry (i.e, its business model) has most often been studied from the angle of how sectorial change has affected the institutionalization of new policy instruments. More precisely, the line of questioning generally adopted has been whether or not political actors have sought to simply follow long term trends within an industrial sector - e.g., technological breaks or the evolving structure of innovation (Aghion and Howitt 1992), its exogenous conditions (Kane 1981) and more recently, economic crisis (Tirole 2012) - by creating an appropriate regulatory framework, consistent with the new environment in which private actors operate. If bureaucrats or politicians appear to have failed to ensure that new processes of value creation are translated into regulatory institutions that match the dynamics of the sector in question, other scholars regularly allege the capture of the political process by interest groups (Carpenter and Moss 2014). When alternatives make core activities that have generated profits for an industry obsolete or when its assets fail to generate value as they once did (McGahan 2004), firms and corporate actors reticent about, or unable to, change are indeed more likely to struggle to preserve existing institutions or, more frequently, to seek the protection from new ones – thereby orienting bureaucratic or political efforts towards taking safeguard measures rather than adapting or adjusting regulatory instruments to the evolutions of the market (Posner 1971, Stigler 1971).

Moving beyond these conceptualizations, however, Political Scientists have recently uncovered several examples where such common views prevent a full understanding of the status of regulation vis-à-vis industrial sectors and, by extension, markets. Indeed, studies led by scholars focusing on regulatory dynamics and regulatory operations have shown 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; Law and Libecap 2006). More fundamentally, this claim relies on the assumption that the market constitutes a set of prospects which, according to the mathematical theory of expectations (Billingsley 1999) "rely upon probability measures and in turn, upon countable and co-countable spaces" (Carpenter 2009). Put differently, regulation does not solely entail behaviors related to the new (dis)incentives it provides, but also affects beliefs leading to market operations, as well as promoting certain categories while delegitimizing others (Smith 2016). From this viewpoint, and because it creates the conditions for *confidence* (De Boef and Kellstedt 2004), regulation may be seen as an essential condition of possibility for marketplaces.

When associated with the issue of industrial change, this perspective offers an alternative way of conceptualizing the connection of this process to regulatory models or institutions. In some cases, regulation should be at least the *prior* condition for the emergence of a new business model, weakening some arguments at the core of capture and rent-seeking theories of regulation. This assumption relies on the capacity of the regulator to guarantee the safety and the quality of the new products or practices implied by an emerging change within a sector or, more broadly, because it may control several types of "lemons" problems occurring as a consequence of this process (Akerlof 1970). In addition, and because the development of a new business model has close links with the risk subjectively associated with the renewed form of commodities put on the market by consumers or any actor concerned (Heimann and Larry 1997), it may also be favored (and even caused) by the (regulatory) building of new principles, expectations, priorities or through the structuring of a particular demand (Carpenter 2010a). In this context, the *reputation* of the bureaucratic entity in charge of implementing those concepts appears to be a latent driving force, conditioning their effectiveness: actors within or outside the industry would be more able to recognize new forms of labels, products or rules of exchange if they are promoted through legitimate institutions, whose organizational image is associated with technical expertise, responsibility or competence (Carpenter 2010b).

If *information*, *confidence* and *reputation* (as three forms of *beliefs* structured through and by regulation) may be conceptualized as basic conditions for industrial change, there remains a residue of ambiguity concerning two critical questions. The first is that of causal mechanisms: how is the institutionalization of new regulatory schemes effectively perceived as a (positive or negative) signal, which in turn engenders specific conducts? One can expect that one impact of regulation would be to generate a dynamic of bureaucratic-industrial adaptation (by analogy with political-bureaucratic adaptation, see Wood and Waterman 1993) observable over time. A second question concerns the effect of regulation on the transition from a business model to another *per se* : what is, in the long run, the role played by regulation in the stabilization of new forms of value creation within an industry?

The aim of this article is to address this twofold challenge by drawing upon an empirical analysis of the stock market valuation of US Food and Drug Administration (FDA) "Orphan Drug" regulatory approvals. The US Orphan Drug Act was implemented in 1983 with the provision of several financial incentives designed to foster rare disease drug research and development (R&D), notably a seven-year marketing exclusivity for the treatments in question that we are considering in more detail in this paper. Operating within the FDA regulatory framework, this law defines an orphan drug as one "with

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efficacy against a disease affecting fewer than 200,000 people in the United States" (Haffner 2006). It is generally considered as a turning point: during the previous decade only 10 drugs were marketed for rare diseases and only 36 rare disease treatments had ever been authorized by the FDA. Since then, more than 400 orphan treatments have been approved (Seoane-Vasquez and al. 2008). Over the same period, scholars identified a change of business model within the pharmaceutical industry. Blockbuster oriented between the years 1960 to 1980, the sector experienced during the following decades a long-term decline of R&D productivity. A paradigm shift towards a new "nichebuster" model capable of filling the void created by this weakening of the previous one is said to have occurred (Montalban and Sakinç 2013). Whereas the pharmaceutical industry once produced mainly (relatively) cheap treatments for large populations during the major part of the century, the last thirty years it has tended to concentrate upon smaller groups of patients, more specialized products and very expensive ones (Messori et al. 2010) - three properties of orphan drugs, which represented between 1983 and 2006 more than 55% of the new molecular entities approved by the FDA (Haffner 2006). In this context, has the Orphan Drug Act acted as a positive signal, contributing to reorientating the conduct of the actors in the market? Did it participate in the shift from the blockbuster model to the nichebuster model in the pharmaceutical industry? And, in sum, how has this particular piece of regulation affected *beliefs* by providing actors with *information*, *confidence* and on the basis of the *reputation* of those in charge of its implementation?

To answer this question, we have modelled and tested the financial impact of FDA orphan drug approval decisions between 1983 and 2013. Our choice to focus on stock markets rather than the pharmaceutical industry itself is related to methodological and empirical concerns. On the one hand, the impact of a new legislation on the changing business model of an industry is difficult to measure through formal modelling. Shifting the reasoning to the reaction of stock markets allows us to observe the legitimacy of orphan drug from the view of a third actor and, by extension, the perception of this new category of product guaranteed by a regulator, the FDA. A second concern is more directly related to the structure of the pharmaceutical industry, and its recent transformations. During the last thirty years, and in the context of the evolution of its business model, the industry has experienced a growing financialization of its activities, which now constitutes a key aspect of the development of an increasing number of products, including mostly orphan drugs (Gagnon 2006). As a result, the viability of the rising engagement of pharmaceutical companies in new types of products stands and falls with its acceptance by investors. As the latter are mainly interested in value creation, an assessment of the

impact of orphan drug R&D on stock market valuations appears to be the most appropriate way to deal with this critical issue.

On this basis, we assume that in a context of uncertainty regarding the properties of orphan drugs during the years 1960 and 1970, the Orphan Drug Act may be considered as a political signal in favor of the development of commercial outlets for these products. This signal was then institutionalized through the FDA regulatory framework, a bureaucratic organization who played (and continued to play) a pivotal function in shaping and orienting the pharmaceutical market, condensing several forms of reputation and expertise (Carpenter 2010a, 2010b, Maor 2010, 2013, Maor et al. 2013). Regulatory approvals of orphan drugs by the FDA have thus acted as a mediation, iteratively reproducing this signal and combining it with several incentives. Investors have, positively or not, sanctioned this source of *information* (the approbation of a product labelled as "orphan drug") based on their *confidence* in this repeated signal. In return, their behaviors (and in fact, regulation) has had a causal effect on the reorientation of the business model of the pharmaceutical industry, contributing to stabilizing the shift in its R&D policy. In sum, the Orphan Drug Act as regulatory politics within the FDA would have rendered the outcomes in the market more countable and more integrable.

The remainder of this paper is organized as follows. Section 2 briefly reviews existing literature in the field and justifies choices regarding data selection and statistical methods. Our model is presented in section 3. Findings are reported in section 4 and discussed in section 5. Section 6 concludes.

# 2 Orphan Drugs and stock market reactions to regulatory announcements

The history of the Orphan Drug Act is generally told as a success story. Before the entering into force of this specific orphan drug legislation, R&D of treatments against rare diseases had came to a dead end: the rigorous drug safety requirements of the 1962 Kefauver-Harris Amendment dramatically increased the costs of drug development, inciting pharmaceutical companies to concentrate their efforts on common diseases and to disengage from rare disease treatments. Since 1983, Orphan drug R&D has clearly increased considerably. Indeed, the pace of applications for orphan drug status ("orphan drug designations" in the FDA terminology) is clearly still quickening. In the 1980s, the average number of yearly orphan drug designations was 54.67; in the present decade, this average number has risen to

211.25 (66.00 in the 1990s and 115.20 in the first decade of the 21th century). How far has regulation contributed to legitimizing this category of products amongst actors who have financially supported pharmaceutical companies?

Existing literature on stock market reaction to bureaucratic signals addresses several related questions: $a$) stock market reactions to news, $b$) the reaction of stock prices to decisions (concerning non-orphan treatments) of the FDA (or corresponding European agencies), and $c$) the impact of FDA orphan drug approvals on the effective duration of market exclusivity.

Fama et al. (1969) highlight a significant positive impact of stock splits on share prices, presumably due to the amelioration of investors' dividend expectations. Quarterly earnings announcements also induce significant effects on the stock returns of the concerned companies (MacKinley 1997). Cuellar Fernandez et al. (2010) have examined press releases concerning ICT firms (information and communication technology): they find that investors react positively to diversification, position-consolidating, and growth, but negatively to new product launches, apparently considered as risky. More closely related to the specific industrial background of our paper, Campart and Pfister highlight significant stock price fluctuations induced by legal disputes about intellectual property rights between pharmaceutical and biotechnological firms (Campart and Pfister 2002), as well as positive stock price responses to the formation of partnerships between firms belonging to this sector (Campart and Pfister 2003).

Evidence for positive stock price reactions to FDA announcements is given by Bosch and Lee (1994), Sharma and Lacey (2004) and Shortridge (2004). In this context, Campart and Pfister (2008) show that positive news concerning one firm induce significant stock price decreases among its direct competitors. Interestingly, markets seem to react negatively to first moves, i.e. to the fact that a firm is the first to enter a specific drug market segment (Sarkar and de Jong 2006). Indirect evidence for insider trading related to public FDA announcements of Phase III clinical trials is provided by Overgaard et al. (2000) and Rothenstein et al. (2011). Meanwhile, Himmelmann and Schierek (2012) have identified liquidity changes as possible sources of stock price increases induced by drug approval decisions of the European Medicine Agency. Finally, Seoane-Vazquez et al. (2008) have investigated whether the orphan drug market exclusivity device actually enables companies to extend the 20 years patent exploitation period[1]. They find a relatively small influence: FDA orphan drug approvals extend the effective marketing monopoly lifetime by less than one year.

However, we are aware of no literature dedicated to the evaluation of the specific financial impact

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[1]In fact, nearly every orphan treatment is also under patent cover.

of orphan drug R&D. In this respect, we chose movements in stock market prices as a measure of this financial impact. More specifically, we observed and analyzed percent changes in stock prices of companies occurring around the disclosure of FDA orphan drug approval decisions concerning orphan treatments developed by these companies. Stock prices are a particularly well suited variable, because they reflect the financial interests of the two major company players: stock price increases correspond to the creation of shareholder value; at the same time, stock price movements are critical for managers: they determine what leeway there is for generous manager remuneration, they condition the likelihood of takeovers, and have a decisive impact on managers' reputations.

We will therefore concentrate on the question of how FDA orphan drug approval decisions influence the stock prices of the involved pharmaceutical companies. Indeed, drug approvals are a critical step within the access path of a new drug to the market. By extension, this process is closely connected to the three components of investors' *beliefs*: are orphan drug regulatory approvals perceived as a credible source of *information*? Can they trust the regulator (*confidence*), on the basis of its expertise or its social authority (*reputation*, see also Moffit 2010) - knowing that, just a few years before, investing in orphan drugs R&D for manufacturers was not considered a legitimate option? This focus is also justified by the fact that they are directly linked to one of the major devices of the US orphan drug legislation: the seven-year market exclusivity period provided to FDA approved orphan treatments. Note in this context the chronological order of events: as a first step, firms request an orphan drug designation, which immediately triggers important orphan drug devices (tax credits, FDA fee waivers and eligibility for clinical research subsidies); FDA orphan drug approval decisions generates (in cases of acceptance) a second step and coincides with FDA marketing authorization for the treatment in question; importantly, the seven-year market exclusivity period starts right from the FDA orphan drug approval decision[2].

We counter-checked the results drawn from stock price movements by an event study approach, i.e. we analyzed the evolution of abnormal stock returns occurring around FDA orphan drug approval decision dates. Last but not least, we were confronted to the critical issue of disambiguation between the effects exerted by two types of FDA decisions: in fact, in the case of orphan treatments, FDA orphan drug approval decisions and FDA marketing approval decisions are simultaneously announced. In order to cope with this problem, we developed an innovative empirical approach: we built a paired-sample of

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[2]It is worth noting that *a priori*, stock prices not only react to FDA orphan drug approvals, but also to orphan drug designations, because the activation of important financial advantages (tax credits etc.) coincides with designation requests. However, the evaluation of the impact of orphan drug designations on stock prices is beyond the scope of the present paper.

orphan drugs and corresponding non-orphan drugs and we then compared aggregate price changes by means of the paired-sample Student's t-test.

In the case of (small) biotechnological companies, our approach also provides insight into the question of the funding impact of FDA orphan drug approval decisions: do these approvals enhance the companies' capacities to finance future orphan drug R&D? In fact, stock market prices may be considered as a good proxy for this funding impact, and this because they should be pushed up by FDA approval decisions, improving thus the fund-raising capacities during future secondary equity offerings[3].

Our main finding is that FDA orphan drug approval decisions have a significant influence on the evolution of the stock market prices and of returns of the concerned companies. Moreover, we are able to show that simultaneous FDA marketing approval/orphan drug approval decisions induce significantly higher stock price progressions than FDA "non-orphan" marketing approvals. These two results clearly suggest that investors appreciate the seven-year orphan drug marketing exclusivity, which in turn, has critical implications for our research question.

We invite the reader to keep in mind one important limitation of this study: the results presented in section 4 hold exclusively for companies quoted on the stock market. No lesson can thus be drawn concerning the entire population of orphan drug developing companies.

# 3    A statistical model of regulatory impact on financial valuation

According to the elements developed in section 1 and 2, we chose data and methods of data analysis likely to highlight the impact of FDA orphan drug approval decisions on stock market valuations. Before presenting theses features in the remainder of this section, we briefly recall the chronological order of events:

1. A firm requests an orphan drug designation for some treatment; immediately, the firm benefits from tax credits, FDA fee waivers and becomes eligible for clinical research subsidies ;

2. The FDA disseminates its orphan drug approval decision and its marketing authorization for the treatment in question; immediately, the firm obtains the seven-year market exclusivity for this orphan drug treatment.

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[3]This question is not really important for big pharmaceutical companies, that are generally able to self-finance R&D.

Following the approach of Overgaard et al. (2000), we have sought to illustrate the financial impact of FDA orphan drug approval decisions by means of graphical representations of the evolution of stock prices. More precisely, we decided to record stock price data going from 120 days *before* the FDA approval to 120 days *after* it; in fact, this time interval has proven to be well-dimensioned, because it allows to represent in a single graphic (*i*) periods where the FDA approval information has an impact on stock price movements and (*ii*) periods where this information has clearly no influence (i.e. periods far enough before and after this decision, e. g. Overgaard et al. (2000, figures 1 to 4) or Rothenstein et al. (2011, figures 1 and 2)). Just like Overgaard et al. (2000), we defined *"zero day"* as the last trading day before public disclosure of the FDA approval decision, *"day -120"* as the date occurring exactly 120 days before *zero day* and *"day +120"* as the date occurring exactly 120 days after it.

These methodological choices have practical implications to our data sample. Indeed, we could not retain orphan drugs (*i*) developed by unquoted companies, (*ii*) developed by companies that launched *too late* on stock markets (i.e. after the day *-120* associated to the orphan drug in question), and (*iii*) whose FDA approval dates are too recent to cover stock prices till day *+120* (in practical terms: FDA approval dates after 12-31-2012, because we established our sample in the month of July 2013)[4]. These method constraints explain why our sample contains only 137 among the roughly 400 FDA approved orphan treatments[5]. The 137 selected treatments had been developed by 60 different companies listed on the New York Stock Exchange, on the National Association of Securities Dealers Automated Quotations (NASDAQ) or involved in Over-The-Counter exchanges.

Since this paper aims at finding out general results about the financial impact of FDA orphan drug approvals, we had to go beyond isolated case studies of the 137 orphan treatments. So we had to find a way to aggregate sample data. In this context, we again adopted the approach of Overgaard et al. (2000). First, we calculated for each treatment $i$ the time series (from day *-120* to day *+120*) of the percentage changes $c_{i,t}$ of the associated stock prices between date day *-120* and date $t$:

$$c_{i,t} \equiv \frac{P_{i,t} - P_{i,-120}}{P_{i,-120}} \quad \forall i, \forall t \in \{-120, -119, ..., 0..., 120\}, \tag{1}$$

where $P_{i,t}$ is the stock market price at date $t$ of the company having developed treatment $i$. Then,

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[4]Some drugs had to be excluded from the sample because the associated stock prices series were atypical, namely they showed very few price movements (e. g. once a week).

[5]The term *orphan treatment* is more accurate than *orphan drug*, because one molecule may be counted several times in our data base; in fact, one and the same molecule may be used in different therapeutic fields, giving rise to several FDA orphan drug approval decisions.

we averaged these series over the entire sample in order to obtain the *mean percentage change*, noted $C_{i,t}$ :

$$C_{i,t} \equiv \frac{1}{137} \sum_{i=1}^{137} c_{i,t} \quad \forall t \in \{-120, ..., 120\}. \tag{2}$$

Time series graphs are likely to provide a first impression of the essential features of the evolution of mean percentage change $C_{i,t}$. One should namely expect an eye-catching upward displacement around *zero day* such as those highlighted by Overgaard et al. (2000, figures 1 to 4) and Rothenstein et al. (2011, figures 1 and 2): indeed, stock markets are supposed to welcome FDA orphan drug approvals, inducing increases of the associated stock prices.

The issue then arises whether this displacement is statistically significant. In order to answer this question, we make use of several significance testing methods. In this context, it should be noted that the standard event study approach results in an important loss of data (see below). Consequently, we start with a somewhat non-standard method which allows us to exploit the entire set of 137 orphan treatments. This method is based on an econometric time series model of $C_i, t$.

Time series modelling is especially useful when it comes to analyse the movements of some endogenous variable in a context of lack of convenient exogenous variables (see Brockwell and Davis (1996) for a comprehensive introduction to time series). We added to our $C_{i,t}$-time series model a dummy variable intended to capture the informational shock conveyed by the FDA orphan drug approval. This dummy variable is central to our first method of significance testing. In fact, we simply verified whether the parameter estimation associated to this dummy variable is significant at standard confidence levels.

In order to countercheck the result thus obtained, we implemented the breakpoint test of Chow (1960) which allows to decide upon the significance (or the absence of significance) of the structural break represented by the upward displacement in the $C_{i,t}$ series.

Event study methodology in the tradition of Fama et al. (1969) and Brown and Warner (1980, 1985) is another way of verifying the significance results achieved with time series modelling. The general idea of this approach is to break down firms' returns into normal and abnormal returns, and then to observe the evolution of aggregate abnormal returns over a time interval around the event-date (henceforth : *event-window*). Since event study methodology warns strongly against any overlap in the event-windows

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associated to the different orphan treatments (MacKinley 1997, p. 24), we chose a rather short time window going from *day -10* to *day +10*. In spite of this choice, we had to exclude no fewer than 60 observations from our data sample in order to avoid overlapping event-windows.

This easiest way of computing abnormal returns is given by the *constant mean return model*:

$$r_{i,t} = \mu_i + a_{i,t}, \tag{3}$$

where $r_{i,t}$ is the period $t$ return of the firm having developed orphan treatment $i$, $\mu_i \equiv \frac{1}{110} \sum_{t=-120}^{-11} r_{i,t}$ the firm's mean return over the estimation-window [*day -120, day -11*] and $a_{i,t}$ its abnormal return (with a standard deviation which should be time-invariant). Following Brown and Warner (1985, p. 28), we obtain the associated t-statistics by dividing $ar_{i,t}$ by its estimated standard deviation:

$$\theta_{i,t} = \frac{a_{i,t}}{\sqrt{\frac{\sum_{t=-120}^{-11}(a_i,t-\mu_i)^2}{109}}} \quad t = \{-10, -9, -8, ..., 10\} \tag{4}$$

as well as the aggregate t-statistics for day $t$:

$$\Theta_t = \frac{\sum_{i=1}^{77} \theta_i, t}{\sqrt{77}} \quad t = \{-10, ..., 10\} \tag{5}$$

Aggregate abnormal returns are given by:

$$A_t = \frac{1}{77} \sum_{i=1}^{77} a_{i,t} \quad t = \{-10, ...10\} \tag{6}$$

i.e. by the mean value of $a_i, t$ over the 77 remaining orphan treatments of our sample (MacKinley 1997, p. 24). Finally, we had to account for the fact that FDA orphan drug approval decisions systematically coincide with FDA marketing approval decisions. *A priori*, it is thus not clear whether significant displacements in the evolution of $C_{i,t}$ are due to marketing approval or to orphan drug approval. In order to distinguish between the effects exerted by these two types of events, we built a paired-sample. We namely matched 33 orphan and "non-orphan" treatments: we associated to each orphan treatment a non-orphan treatment which shares its key characteristics: same therapeutic field; same kind of company (i.e. we matched start-ups with start-ups and great companies with great companies); and contemporaneity (we allowed for a maximum time distance of 15 month between the FDA orphan drug approval and the marketing approval decision in favour of the associated non-orphan treatment).

In the case of a significant influence of the orphan drug status, stock market prices should grow faster in the orphan sample than in the non-orphan sample. In order to test this assumption, we retained a statistical approach largely inspired by Overgaard et al. (2000): we first calculated the percent progression of stock market prices from *day -120* to *day + 10*, $c_{i,10} \equiv \frac{P_{i,10} - P_{i,-120}}{P_{i,-120}}$ ; then we used the paired-sample Student's t-test with the aim of comparing the $c_{i,10}$-means of the orphan sample (henceforth: $\bar{c}_{orphan}$) and of the non-orphan sample (henceforth: $\bar{c}_{other}$).

# 4  Stock market valuation of Orphan Drugs regulatory approvals

Figure 1 draws the time series graph of mean percentage changes in stock prices $C_{i,t}$.

**Figure 1:** Mean percentage changes of stock prices
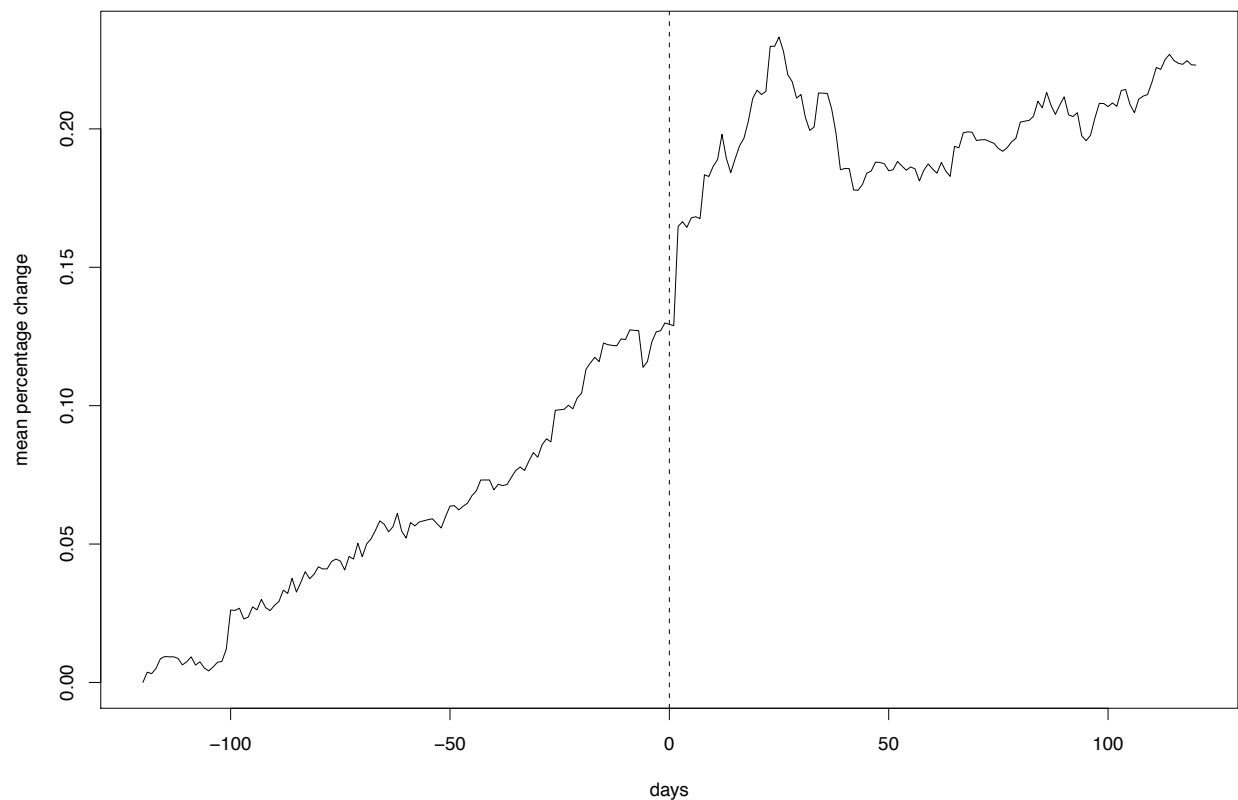
As expected, we can easily identify an upward shift immediately after zero day: stock markets seem to react positively to the disclosure of FDA orphan drug approvals. It clearly suggests that the $C_{i,t}$ series is non-stationary. The augmented Dickey-Fuller test confirms this impression (DF = -1.3329, Lag order = 6, p-value = 0.8565). Consequently, we chose the first difference $\triangle C_{i,t} \equiv C_{i,t} - C_{i,t-1}$ as the endogenous variable of our model. We then explored a large range of model specifications. The best outcome in terms of information criteria (Akaike and Bayesian information criteria, henceforth: AIC and BIC) was obtained by the specification:

$$\triangle C_{i,t} \equiv \alpha_0 t + a_1 D_s, \tag{7}$$

where the "shock" dummy variable $D_s$ takes value 1 at date $t = 2$ and 0 at all other dates. This specification corresponds to a trend affected by a shock dummy variable. Main features of the model are reported in Table 1. Figure 2 plots observed versus fitted values of the percentage changes $C_{i,t}$.

**Table 1:** Estimates of the time series model (7)

|  | Estimate | SD | t-value | $\Pr(> \lvert t \rvert)$ |
|---|---|---|---|---|
| $\alpha_0$ | 0.0012 | 0.0003 | 4 | 8.4493e-05 |
| $\alpha_1$ | 0.0175 | 0.0030 | 5.8333 | 1.7560e-08 |
| | AIC = -1928.78 | AICc = -1928.68 | BIC = -1918.34 | $\sigma^2$ = 1847e-05 |

Since these curves tend to overlap, model (7) seems to be well specified. It is worth noting, however, that this specification does not convey an ideal distribution of estimated errors. The statistics of the Shapiro-Wilk test clearly indicates that errors cannot be supposed to be normally distributed (W = 0.9264, p-value = 1.387e-09); this shortcoming is not too problematical since our sample is sufficiently large to make use of the central limit theorem. What is more problematic is that according to the White test, dispersions are affected by heteroskedasticity ($nR^2$ = 51.146, p-value = 4.5540e-11, see also Figure 6 in appendix); it should be noted that this is somehow unavoidable in time series that include major shift movements. Finally, error terms seem not to be autocorrelated (see figures 5/6 in appendix).

The most important result conveyed by table 1 is that the shock dummy coefficient $\alpha_1$ is significant at standard confidence levels. Since the t-value of $\alpha_1$ is very far from the critical values associated to these levels, this result should remain valid despite the presence of heteroskedasticity. We would like to stress out that this significant shock takes place on *day +2*, and thus one day after the disclosure of FDA orphan drug approval decisions.

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**Figure 2:** Observed against fitted series of mean percentage stock price changes
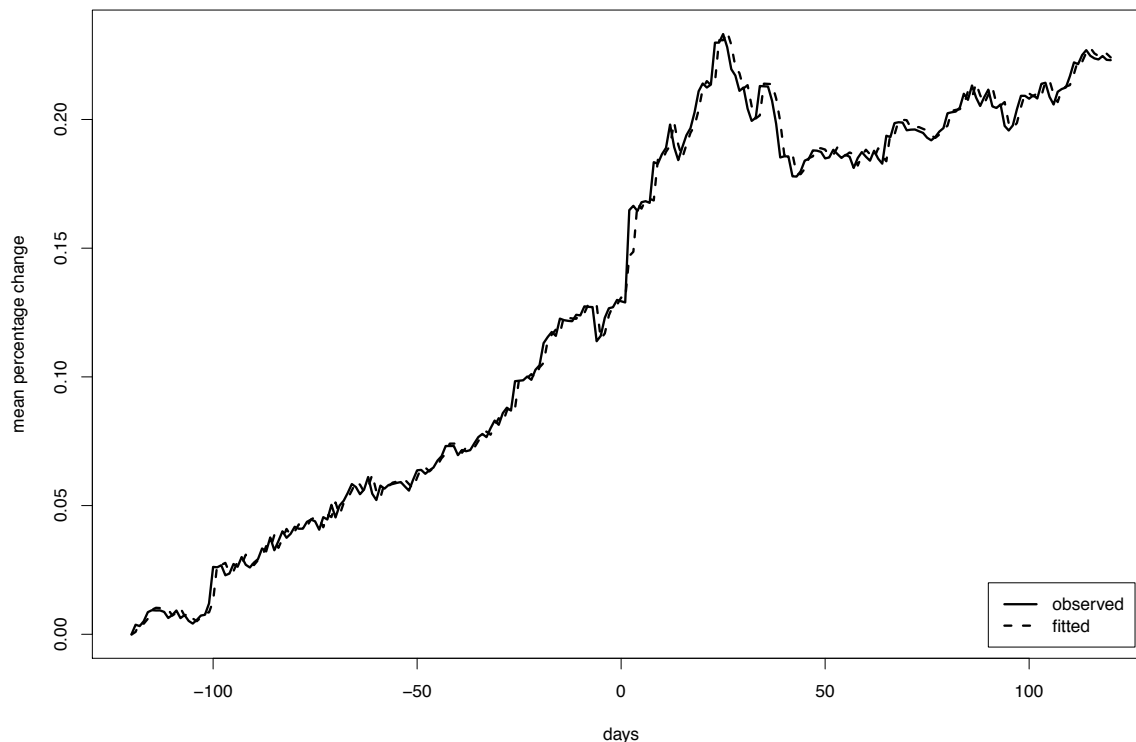


In order to counter-check the significance result presented in the latter subsection, we apply the Chow breakpoint test to a version of model (7) from which we removed the shock dummy variable. The F-statistics shows that at a 1% confidence level, the $\alpha_0$ coefficient is significantly different before and after disclosure of FDA approval decisions (F = 6.9979, p-value = 0.0087). The structural break highlighted by the Chow test clearly suggests that FDA decisions have a significant impact on the evolution of the $C_{i,t}$ series. In this context, we should account for the heteroskedasticity problems mentioned above. As shown by MacKinnon (1989), the standard Chow breakpoint test is remarkably robust to heteroskedasticity when the sample is split-off right in the middle. Since this is nearly exactly the case in our study (we have in fact 121 observations before and 120 after FDA decision disclosure), the significance result obtained in this subsection can reasonably be considered as being trustworthy.

The previous results are clearly confirmed by the event study approach. Perhaps most interestingly, we get confirmation of the rather surprising result that stock markets react with a delay of one day

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**Figure 3:** Average abnormal returns from *day -10* to *day + 10*.
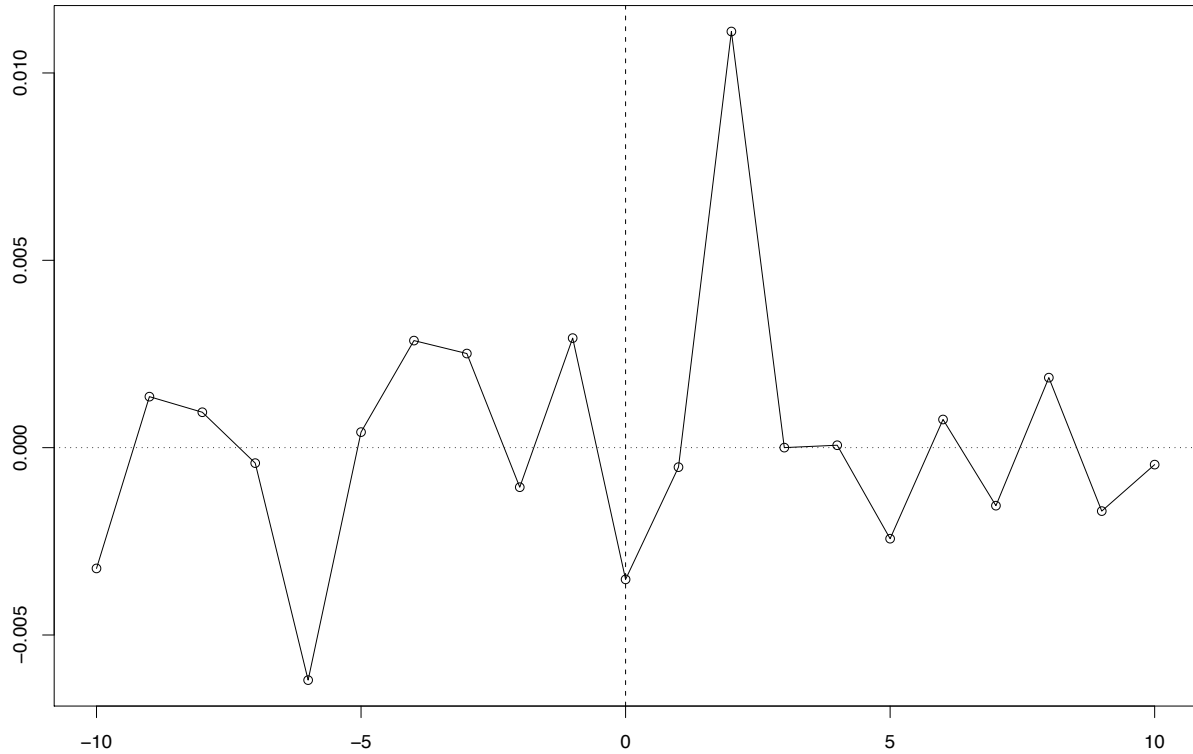


to FDA decisions: indeed, figure 3 shows an impressive peak of positive aggregate abnormal returns on day + 2, which is significant at all standard confidence levels (see the p-value column of table 3 in appendix). The aggregate abnormal returns associated to the other days of the event-window [*day -10, day +10*] are not statistically significant, with the exception of day -6 at a 10% confidence level.

Table 2 presents the results of the test. At a 10% confidence level, the mean of the orphan sample $\bar{c}_{orphan}$, is significantly greater than that of the non-orphan sample $\bar{c}_{other}$. The paired-sample Student's t-test is well suited to check this visual impression. In fact, the key assumptions underlying this test are verified[6].

Figure 4 shows boxplots of the (paired) orphan and non-orphan samples of stock price percent

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[6]The set of differences between orphan treatments and the associated non-orphan treatments can be considered as normally distributed (Shapiro-Wilk normality test: W = 0.9843, p-value = 0.9037); and the variances of the two sub-samples appear to be equal (F = 1.1168, p-value = 0.7565).

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**Table 2:** Paired-samples Student's t-test (comparison of distribution means $\bar{c}_{orphan}$ and $\bar{c}_{other}$)

| alternative hypothesis | t-statistics | p-value | confidence interval |
|---|---|---|---|
| $\bar{c}_{orphan} > \bar{c}_{other}$ | 1.3469 | 0.09373 | [-0.0148,+∞] |
| $\bar{c}_{orphan}$ - $\bar{c}_{other} = 0.0574$ | $\bar{c}_{orphan}$ | $= 0.1660$ | $\bar{c}_{other} = 0.1086$ |
| $SD_{orphan} = 0.2238$ | $SD_{other}$ | $= 0.2118$ | $n = 33$ |
| confidence level $= 95\%$ | | | df=32 |

progression $c_{i,10}$. The distribution of the orphan sample seems clearly to be located at a higher level than that of the non-orphan sample.

**Figure 4:** Distributions of percent progression in stock prices $c_i, 10$ (orphan drugs vs. other drugs)
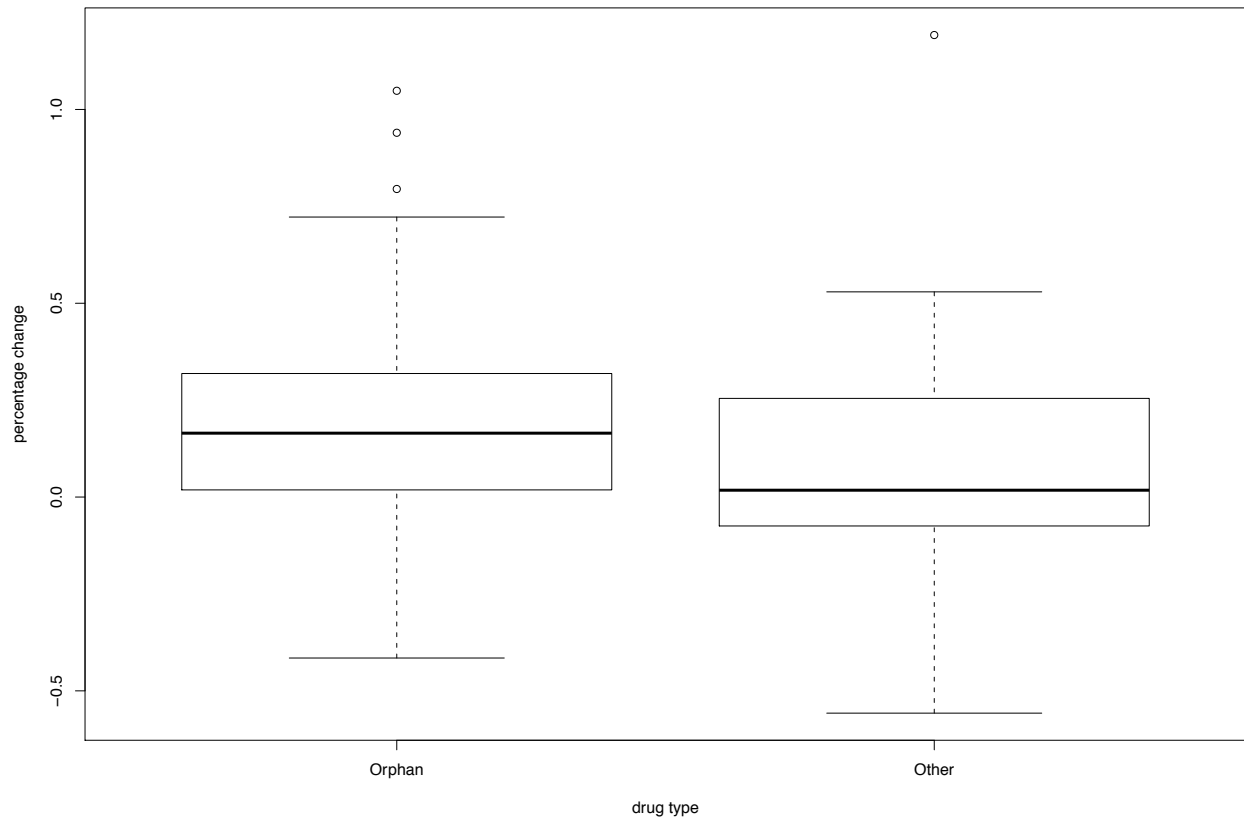
# 5 Bureaucratic signals as instituting beliefs

The results presented in the previous section are somehow unexpected. It is in fact rather surprising that the very modest marketing exclusivity extensions provided by FDA orphan drug approvals (Seoane-Vazquez et al., 2008) have proved sufficient to induce significant upward shifts in the evolution of stock market prices. Similarly, it was not necessarily foreseeable that the small difference in marketing exclusivity lifetime between orphan and non-orphan treatments could lead to a significant gap in mean stock price progressions. Note in this context that these results cannot be attributed to other devices of the orphan drug legislation (such as tax credits etc.), because these advantages are activated at the moment of orphan drug designation, and thus well before zero day (indeed several years before in the vast majority of cases). Our explanation for these results is that the influence of FDA orphan drug approvals goes beyond the simple quantitative effect of extended marketing monopoly lifetime. Accordingly, it may have influenced *beliefs* of investors, through its design and the properties of the institutions structuring the implementation of the Orphan Drug Act.

In 1983, orphan drugs were not considered legitimate products, neither by manufacturers nor investors. During the political process, the basic incentives of the US pharmaceutical market were recognized as the main reason for that situation. Albeit based on this diagnosis, the Orphan Drug Act did not offer a perfect "compensation" for the manufacturers: however, it led to a publicization of rare diseases (Huyard 2011) and integrated this issue within the regulatory framework of an agency seen as the gatekeeper of the pharmaceutical market (see Carpenter 2010b). The institutionalization of orphan drugs within this regulatory scheme constituted a source of *information*, by providing investors with a durable definition of these products, and by delegating the operationalization of this policy to an agency whose procedures are known and stabilized. Simultaneously, this process created the conditions for *confidence*, observable through the signaling effect provided by the FDA regulatory approvals. In fact, the orphan drug marketing exclusivity offers a better quality of protection than standard patent laws: competing companies requesting FDA marketing authorization have to prove therapeutic superiority with respect to any FDA-approved orphan treatment applying to the same therapeutic indications. Additional experimentations required by the regulator can thus be considered as a guarantee for uninformed or poorly informed investors on the quality of (relatively) unknown products (Carpenter and Ting 2007). In any case, this situation is closely linked to the *reputation* of the FDA, since it is when an orphan drug is approved by the agency that it is value by investors, meaning that the single designation is not enough

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to give the products all the legitimacy related to its qualification as such. This interpretation thus suggests that investors equate the FDA orphan drug approvals to the innovative capacity of the companies in question. Rather than reorienting the actors' behaviors on the market (practically no outlets for orphan drugs existed prior 1983), this bureaucratic signal shaped its ruling structures, iteratively reproducing the first political signal made through the 1983 Orphan Drug Act. Consequently, one of the key institutional features of the orphan drug market intertwined with the decisions of a bureaucratic organization[7].

Regulation has also certainly contributed to the shift from a business model to another within the pharmaceutical industry. During the time period tested, the sector has been involved in a profound transformation: the decline of R&D productivity has made it increasingly hard for companies to develop new blockbuster drugs. As a response, they have progressively been moving towards the rare diseases markets. In this respect, our results suggest that investors evaluate R&D successes very positively in the orphan drug market. This may be interpreted as a sign of the underlying acceptance by investors of the strategic reorientation towards a new nichebuster-oriented business model. But due to their critical impact for some of the most strategic steps of the development of new pharmaceutical products, they have also played a significant role in this change : if investors seem to validate the increasing importance attached by pharmaceuticals and biotechnological companies to the orphan drug market segment, this state of affairs also implies a positive funding impact of orphan drug regulatory approvals. As a consequence, the increase of stock prices should favor the fund raising capacities of small biotechnological firms (namely via future secondary equity offers) and hence their ability to continue the quest for new treatments. Correlatively, a positive appreciation of this bureaucratic signal acts as a powerful incentive for firms to accentuate their positioning regarding this new type of products. According to our results, it is indeed clear that the implementation of the Orphan Drug Act matters on this point: by improving the stock price of the companies in question, investors have in turn reinforced the shift within the sector. If the cause and effect links are difficult to estimate through our results, it is nonetheless clear that these two dynamics have been mutually reinforcing.

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[7]One may wonder about the surprising lack of responsiveness of stock markets highlighted in our results: prices react in fact with a lag of one day after the disclosure of FDA orphan drug approval decisions. This state of affairs may be due to the fact that important market participants (such as mutual et pension funds) are engaged in teamwork decision procedures (with a division of labour particularly between security analysts and portfolio managers).

# 6 Conclusion

In this paper we have found a significant influence of FDA orphan drug approvals on the evolution of the stock market prices and of the abnormal returns of the companies whose treatments had been approved. In a time series modeling framework, the dummy variable which captured the informational shock of FDA orphan drug approvals has proved significant as regards all standard confidence levels. Event study methodology highlights that an abnormal return is positive and highly significant one day after disclosure of the FDA decisions. These results are confirmed by the Chow breakpoint test which indicates a significant structural break at the moment of FDA orphan drug approvals. Finally, the paired-sample Student's t-test shows that the stock price progressions induced by simultaneous FDA marketing approval/orphan drug approval decisions are significantly higher than those caused by FDA marketing approvals of comparable "non-orphan" treatments.

While orphan drug appeared to be poorly considered by the manufacturers during the years 1960 and 1970 (and was relatively unknown by investors), the Orphan Drug Act and the delegation of its implementation to a bureaucratic organization structured some of the essential conditions of possibility of the market for these products. Since then, FDA regulatory approvals for rare disease treatments have become a clear signal for investors who, by their valuation work, have legitimated in return orphan drugs amongst manufacturers - and by this means, contributed to the shift from a business model to another within the industry. In that case, political actors and regulation (through providing actors with *information* and on the basis of their *confidence* in bureaucratic institutions) operated before the creation of the market for orphan druges – a market which was virtually inexistent prior to this intervention. Beyond the simple quantitative effect of the seven-years marketing exclusivity associated with the decision of the FDA, the significant impact of the regulatory framework depends upon the *reputation* of the regulator - regulatory *approval*, after the experimentation phases, being more highly valued than the single *designation* of a product as an orphan treatment.

This result would not appear surprising to those familiar with the social organization of the pharmaceutical market. In some respects, the development of the market for orphan drugs shares similarities with that of the pharmaceutical market as a whole where "*regulation did not intrude upon a pre-existing marketplace; it constituted a new marketplace*" (Carpenter 2010b, see also Marks 1997). In this context, it is important to develop additional empirical research focused on how regulation affects confidence and beliefs. Here, we have simultaneously examined the concepts of *information*, *confidence* and *reputation*

through the reactions of the stock market to bureaucratic announcements. However, more work needs to be done to identify the boundaries between the respective effects of these three dominant features common to numerous regulatory institutions, including for markets (apparently) less regulated than the pharmaceutical one (see also Carpenter et al. 2010). In this context, linkages could usefully be developed between quantitative studies and sociologically informed research on the politics of industries and industrial policy (Jullien and Smith 2008).

# References

Aghion, P. and Howitt, P. (1992) A Model of Growth Through Creative Destruction, *Econometrica*, 60(2): 323-351.

Akerlof, G. (1970) The market for "lemons" : quality uncertainty and the market mechanism, *Quarterly Journal of Economics*, 84(3): 488-500.

Billingsley, P. (1999) *Convergence of Probability Measures*, Second Edition, New York: Wiley.

Bosch, J-C and Lee, I (1994) Wealth effects of food and drug administration (FDA) decisions, *Managerial and Decision Economics*, 15(6): 589-599.

Brockwell, P. J. and Davis, R. A. (1996) *Introduction to Time Series and Forecasting*, New York: Springer.

Brown, S.J., Warner, J.B. (1980) Measuring security price performance, *Journal of Financial Economics*, 8: 205–258.

Brown, S.J., Warner, J.B. (1985) Using daily stock returns - the case of event studies, *Journal of Financial Economics* 14: 3-31.

Campart, S., Pfister, E., (2002) Les conflits juridiques liés à la propriété industrielle : le cas de l'industrie pharmaceutique et biotechnologique, *Revue d'Economie Industrielle* 99: 87-105.

Campart, S., Pfister, E., (2003) The value of interfirm coopertaion: an event study of new partnership announcements in the pharmaceutical industry, Working Paper.

Carpenter, D. (2009) Confidence Games: How does regulation constitute markets? in Balleisen, Edward J., and Moss, David A. (ed.) *Government and markets: Toward a new theory of regulation*, Cambridge: Cambridge University Press, Chap. 5.

Carpenter, D. (2010a) Reputation, Information and Confidence: the Political Economy of Pharma-

ceutical Regulation, in Farber, Daniel et O'Connell, Anne Joseph. (ed.) *Public Choice and Public Law*, Northampton: Edward Elgar Publishing.

Carpenter, D. (2010b) *Reputation and power: organizational image and pharmaceutical regulation at the FDA*, Princeton: Princeton University Press.

Carpenter, D. and Ting, M. (2007) Regulatory Errors with Endogenous Agendas, *American Journal of Political Science*, 51(4): 835–53.

Carpenter, D. and Moss, D. (2014) *Preventing Regulatory Capture: Special Interest Influence and how to limit*, New York: Cambridge University Press.

Carpenter, D., Grimmer, J., Lomazoff, E. (2010) Approval regulation and endogenous consumer confidence: Theory and analogies to licensing, safety, and financial regulation, *Regulation & Governance*, 4(4): 383-407.

Chow, G.C (1960) Tests of equality between sets of coefficients in two linear regressions, *Econometrica*, 28(3): 591-605.

Cuellar Fernandez, B., Fuertes Callen, Y. and Lainez Gadea, J.A. (2010) Stock price reaction to non-financial news in European technology companies, *European Accounting Review*, 20(1): 81-111.

De Boef, S. and Kellstedt, P. (2004) The Political (and Economic) Origins of Consumer Confidence, *American Journal of Political Science*, 48(4): 633-649.

Fama, E.F., Fisher, L., Jensen, M.C. and Roll, R., (1969) The adjustment of stock prices to new information, *International Economic Review* 10(1): 1-21.

Gagnon, M-A (2006) Finance and Differential Accumulation in the global pharmaceutical industry, CAFCA Conference, Concordia University, May.

Haffner, M. (2006) Adopting Orphan Drugs - Two Dozen Years of Treating Rare Diseases, *New England Journal of Medicine*, 354(5): 445-447.

Heimann, C. and Larry, F. (1997), *Acceptable Risks: Politics, Policy and Risky Technologies*, Ann Arbor: University of Michigan Press.

Himmelmann, A., Schierek, D. (2012) Drug approval decisions: a note on stock liquidity effect, *Journal of Empirical Finance*, 19: 640-652.

Huyard, C. (2011) When public authorities foster and equip a protest movement. The invention of "rare diseases" in the United States and Europe, *Revue Française de Science Politique* [English], 61(2): 183-200.

Jullien, B. and Smith, A. ed. (2008) *Industries and globalization : the political causality of difference*, Basingstoke: Palgrave.

Kane, E. (1981) Accelerating Inflation, Technological Innovation, and the Decreasing Effectiveness of Banking Regulation, *Journal of Finance*, 36: 355- 367.

Law, M. and Libecap, G. (2006) The Determinants of Progressive Era Reform: The Pure Food and Drugs Act of 1906, in *Corruption and Reform: Lessons from America's Economic History*, Glaeser, E and Goldin, C. eds. Chicago: University of Chicago Press, 319–42.

MacKinley, A.C., (1997) Event studies in economics and finance, *Journal of Economic Literature* 35: 13-39.

Mackinnon, J.G (1989) Heteroskedasticity-robust tests for structural change, *Empirical Economics*, 14(2): 77-92.

Maor, M. (2010) Organizational Reputation and Jurisdictional Claims: The Case of the U.S. Food and Drug Administration, *Governance*, 23(1): 133-159.

Maor, M. and Raanan, S. (2013) The Effect of Salient Reputational Threats on the Pace of FDA Enforcement, *Governance*, 26(1): 31-61.

Maor, M., Gilad, S. and Ben-Nun Bloom, P. (2013) Organizational reputation, regulatory talk, and strategic silence, *Journal of public administration research and theory*, 23(3), 581-608.

Marks, H. (1997) *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900-1990*, Cambridge: Cambridge University Press.

Mcgahan, A. (2004) How industries change, *Harvard Business Review*, 82(10): 86-94.

Messori, A., Cicchetti, A. and Patregani, L. (2010) Orphan drugs: Relating price determination to disease prevalence, *British Medical Journal*, 341(7770): Online.

Moffitt, S. (2010) Promoting Agency Reputation through Public Advice: Advisory Committee Use in the FDA, *Journal of Politics*, 72(3): 880-893.

Montalban, M. and Sakinç, M. (2013) Financialization and productive models in the pharmaceutical industry, *Industrial and Corporate Change*, 22(4): 981-1030.

Overgaard, C., van den Broeck, R., Kim, J.H and Detsky, A.S (2000) Biotechnology stock prices before public announcements: evidence of insider trading, *Journal of Investigative Medicine*, 48(2): 118-124.

Posner R., (1971) Theories of Economic Regulation, *The Bell Journal of Economics and Management Science*, 5(2): 335-358.

Rothenstein, J. M., Tomlinson, G., Tannock, I. F. and Detsky, A. S. (2011) Company stock prices before and after public announcements related to oncology drugs, *Journal of the National Cancer Institue*, 103(20): 1507-1515.

Sarkar, S.K., de Jong, P.J., (2006) Market response to FDA announcements, *The Quarterly Review of Economics and Finance*, 42: 586-597.

Sharma, A., Lacey, N., (2004) Linking product development outcomes to market valuation: the case of the U.S. pharmaceutical industry, *Journal of Product Innovation Management*, 21(5): 297-308.

Shortridge, R.T., (2004) Market valuation of successful versus non-successful R&D efforts in the pharmaceutical industry, *Journal of Business Finance & Accounting* 31: 1301-1325.

Smith, A. (2016) *The Politics of Economic activity*, Oxford: Oxford University Press.

Stigler, G. (1971) The theory of Economic Regulation, *The Bell Journal of Economics and Management Science*, 2: 3-21.

Tirole, J. (2012) Overcoming adverse selection: How public intervention can restore market functioning, *American Economic Review*, 102: 29-59.

Wood, D. and Waterman, R. (1993) The Dynamic of Political-Bureaucratic Adaptation, *American Journal of Political Science*, 37(2): 497-528.