Determinants of Vaccine R&D in the Pharmaceutical Sector

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The aim of this paper is to analyse the economic and financial assets that influence vaccine research investments by pharmaceutical companies. Starting from vaccine manufacturing process, the first part describes European Union (EU) and United States (US) regulatory systems and the relative Intellectual Property Rights (IPRs). Then, the main obstacles to vaccine research and the main strategies suitable to enhance it are discussed. The second part introduces an empirical analysis of 10 pharmaceutical companies' corporate Research and Development (R&D) from the 2008-2015 period by using STATA 12, through a Fixed Effect estimation of two models. The three hypotheses considered regard the main assets that influence vaccine research and why, the relevance of properties acquisition as a substitute for R&D as whether regulatory framework does obstruct investments choices or not. The results confirm that liquidity and size have a positive impact on vaccine research, whereas leverage influences it negatively. In addition, more acquisitions lead to fewer R&D investments since companies find less expensive to acquire knowledge rather than investing on it. Finally, a Chow Test that considers 2010 as a breaking point, led to no structural breaks for panel data, which implies that the new European Regulatory Directive on pharmacovigilance has no influence on the pharmaceutical companies' behaviour.

Introduction

A vaccine is a "complex, biological product made from living organisms with a natural tendency to change" (IFPMA 2016). A vaccine, however, is also a public good: everybody benefits from it, even those who do not vaccinate themselves. The "herd immunity" phenomenon, in fact, implies that people who are not immunized will eventually benefit from others' immunization: the more people are immunized, the less virus/bacteria/infections spread among other people. This means that there are fewer chances to be affected by the disease.

Vaccines have side effects, and they almost never offer full protection against the diseases, although they usually reach 90%-95% coverage (WHO 2017).

The paper is divided into two parts. In the first part, vaccine manufacturing process by pharmaceutical companies in the light of pharmaceutical regulatory frameworks will be explained, with a description of EU and US/Canadian frameworks. The main development process of a new product and its economic implications in terms of market exclusivity, patent laws, monopoly powers and pricing are described as well. Finally, all the literature regarding innovation will be reported: the main obstacles to vaccine research will be examined, and the main strategies suggested by literature for increasing research investments will be listed as well.

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The second part will include an in-depth analysis of the pharmaceutical companies' corporate R&D, with a focus on finding a way to assert the impact of pharmaceutical regulation on R&D. An empirical model will be used to assess factors affecting vaccine R&D expenditure for ten of the most important pharmaceutical companies worldwide. More specifically, the aim of the paper is to extrapolate some core hypotheses, if they are testable with respect to dataset, and fit with some considerations made in the descriptive part. Although particularly interesting, the analysis of the relationships between innovation and organizations, or governments interventions, would be beyond the scope of this section; therefore, a more specific approach has been considered, starting from companies' point of view. It has been chosen to focus on R&D expenditure items as a unique dependent variable, to get few, but significant results.

Theoretically, the paper's investigation will be based on two models inspired by Eger and Mahlich (2014) and Lee and Choi (2015), as in their research they have directly analysed pharmaceutical companies as well as research and development expenditures, both compared to the same theoretical frameworks. Thus, as there is a connection between the two studies, they yielded similar results and considered similar control variables as well. The main difference lies in the fact that one study relates research with sales, splitting them into different sectors to determine their impact individually, while the other is more focused on pharmaceutical companies' corporate assets.

The core of the research is to investigate and analyse how different economic and financial factors affect pharmaceutical companies' decisions to invest in vaccine research, by reviewing panel data of 10 big pharmaceutical companies from 2008 to 2015. Two models have been analysed through Fixed Effect estimation.

The overall interpretation of the results related to the paper's research is that the vaccine industry does not behave differently from other pharmaceutical sectors: the economic and financial assets, in fact, consider influence vaccine research as well as overall pharmaceutical research. Corporate finance heavily affects R&D investment choices: the company must be able to grow to obtain an overall profitability in sales. It is also required that it is very stable and has enough liquidity to cover its net debt. Plus, the company must be able to benefit from the coverage granted by the Data Protection and Market Exclusivity to cover (at least partially) the costs related to research projects; otherwise, once the coverage period has expired, the overall sales will no longer be sufficient to cover their R&D costs. Moreover, other pharmaceutical companies will start to produce generic drugs and sell them at lower prices so that competition will increase, and, as a result, individual profits from the "innovator" company will fall. Therefore, to fight information asymmetry, the company must be also able to hire and train specialized employees for obtaining additional know-how and technological innovation, which will be helpful to create new chemical entities and new products (Katz 2007). Therefore, the company may face any manufacturing difficulties linked to the core of the research and deal with the requests from regulatory authorities. Seemingly, the regulatory system does not directly affect R&D, even though this is an open issue deserving further investigations.

In addition, there is also the aim of determining whether pharmaceutical legislation has a direct impact on R&D expenditures or not. A Chow Test will be conducted on structural break of both models for the same period, to determine whether the coefficients and the regression are stable or not. Moreover, a new control variable – Acquisition Costs – has been included in the regressions, to check its importance with respect to R&D expenditures.

Literature Review

European Regulatory Framework

The European directive has been changed and improved several times. The first harmonization attempt dates to 1965, with the European Economic Community's (EEC) Directive of 26/01/1965. This document states that pharmaceutical products need to receive an official authorization before entering the market, thus matching exactly the European Economic Community's principles of market liberalization and protection of human rights, along with public health rights and drug marketing rules. Those criteria are still at the roots of the subsequent pharmaceutical directives and laws.

Ten years later, the authorization process has improved by a multistate procedure and a single, official European committee. In 1983, the committee selected some key points which a product needs to comply with to get the authorization. The 1987 and 1989 directives introduced a new committee with the aim of giving a pre-authorization for the product before the applicant's submission. Moreover, the "Guidelines on Good Manufacturing Practices" were attached to the marketing authorization's pipelines. One of the major innovations the 1993 Directive brought about was the creation of The European Medicine Agency (EMA) aimed at evaluating applicants' dossiers. Besides, it introduced a new centralized procedure for pre-marketing pharmaceutical authorizations. Three years later, this procedure was also supported by a centralized post-marketing authorization procedure. After the introduction of clinical tests guidelines in 2001 - which will be changed again in 2014[1], in parallel to Directive 2004/27. Those changes hit the "body" of the law, by covering the most important rules and adding new ones. More specifically, they introduced: new rules for the generic products approval; specific rules for "biosimilars"; the scope of the centralized procedure was extended; a thorough explanation of legal standards for marketing authorizations was provided; more information to patients and on marketing authorizations validity from a European member state were introduced. On business side, the changes solved, at least in part, some business flexibility issues, with faster approval processes and improved transparency, even though a stricter

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[1]Another major change occurred with the publication of four new sections of the Directive of 30/06/2004: the Regulation 726/2004, concerning the centralized procedure; the Directive 2004/27 that modifies the Code for Medicines for Human Use; the new regime for traditional herbal medicinal products embedded in the Directive 2001/83 and, finally, the changes aimed at Medicines for Veterinary Use – Directive 2001/82.

pharmacovigilance process was introduced. Greater support for Small and Medium Enterprises (SMEs) was secured as well. Some changes affected the "technical" side only, but others notably modified the pharmaceutical framework, such as the improved role of the centralized procedure: for the first time, in fact, the European Union could apply financial penalties for infringements. Currently, the latest dispositions include:

- The regulatory components, made of guidelines and directives.
- A detailed pipeline on manufacturing processes.
- A detailed pipeline for marketing authorization and input into the market of a drug; this also refers to the submission of the dossier that will be explained below.
- The guidelines for conducting quality, safety and efficacy tests.
- A detailed guideline on pharmacovigilance.

Pharmacovigilance and increased transparency towards the public domain are crucial topics as well. Moreover, under this new Directive, the marketing authorization seems to be more related to a public health issue than to an inter-firm asset of the pharmaceutical company: as it regards everyone, in fact, it is more likely that it would be managed by a regulator who is external to the company.

Pharmacovigilance Framework

Certainly, a harmonized regulatory system involved less efforts for obtaining know-how information related to the development process, more safety for new products marketing and more transparency among Countries. The latter effect is also enhanced by several IT systems, which also improve knowledge exchange.

Today the regulatory system involves 31 Member States of the European Economic Agreement (EEA), the European Medicines Agency (EMA) and the European Commission, connected through a network based on the exchange of information – mostly, reporting newest side effects of some drug introduced in their market, clinical trials, or manufacturing insights. However, it is also true that other states, which are not official members of European regulatory system, follow European directions in setting their own authorization process and even though some details are very different, the results are quite almost the same. The European regulatory framework is structured with clear and equally fundamental steps.

Dossier Presentation and Marketing Authorization

The first phase involves a procedure that might affect only some European countries or all of them; it can be therefore "decentralized", "by mutual recognition" or "centralized". It regards the application for the authorization, which implies a dossier filling-in, to be performed using the Common Technical Document format (CTD). The dossier can be submitted in one single set, which is called "Stand Alone Procedure", or in a "Consolidated" fashion. CTD has a pyramid-like structure[2].

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[2]Art. 10c of the Directive 2000/83.

On the top we find the first module, which is not in CTD format and contains regional information apt to manage the application for a new product authorization. This section includes: Manufacturing Licenses (ML) and manufacturers' Good Manufacturing Practice certificates (GMPc), attesting that the manufacturing facilities are in compliance with the international standards on the medicinal product's quality; Quality Expert reports (modules 1.4.1, 1.4.2, 1.4.3) providing a signed declaration by quality, pre-clinical and clinical experts on the product's quality, safety and efficacy; Risk Management Plan, Pharmacovigilance System (modules 1.8.2 and 1.8.1) and Environmental Risk Assessment (1.6), which details all rules and processes followed by the company with reference to Pharmacovigilance and the risks associated with the environment; Summary of Product Characteristics (SmPC), Labelling and Package leaflet (PIL) and the relative mock-ups, aimed at distribution and counselling aimed at patients (PIL) or physicians (SmPC).

The second section contains pre-clinical, clinical and quality overviews and summaries in tabular format. Module 3 is the chemical-pharmaceutical section, and it includes all the technical/quality details of the drug along with its manufacturing process (manufacturers, manufacturing process flow diagram and description, validation, quality control, specifications, stability data etc…). This information is strictly confidential and usually legally safeguarded.

The Drug Master File (DMF) is a document containing all detailed information about the drug manufacturing process, i.e. an "extended" and detailed version of the module 3. To consult the DMF, the authority, requests the applicant a "letter of access", which is usually attached to the dossier: by doing so, the authority has free access to this file and can compare this extended version to the short one provided by the applicant (module 3) in order to verify the exact correspondence of the manufacturing process (European Commission, 2001 directive).

In addition to this, the applicants often ask for a "Certificate of Suitability" (CeP or CoS) from the European Directorate for the Quality of Medicines & Health Care (EDQM), the successor of European Pharmacopoeia and European Department for the Quality of Medicines (European Commission 2001). This institution has the task of monitoring the public health by checking both drug and the quality standards application. This document is therefore an extra quality standards certification, which obviates the need to submit the letter of access to the DMF attached to the module 3 of the dossier.

The fourth and fifth sections regard all pre-clinical and clinical tests conducted on the product, which differ from those carried out in United States or in other regulatory systems. In Europe, these tests are in fact based on the European Pharmacopoeia, while the US has its own pharmacopeia (US PI). Pharmacopeia are huge textbooks containing complete sets of technical, administrative and chemical directions concerning many topics, including drug development and quality & safety checks.

Once the application is submitted, the dossier is evaluated by the authority. The aim is to analyse quality, safety and efficacy standards as well as to assess risk-benefit ratio for that product, which must be positive. They also verify whether the pre-clinical and clinical tests comply with Good Laboratory Practices and Good Clinical Practices standards. In cases of vaccines' marketing authorization

applications, the authority also evaluates the percentage of paediatric population that needs to be immunized in order to send this report – previously approved by the applicant - to the European Medicine Agency in form of clinical development plan. Finally, if all these processes have a positive outcome, the applicant receives the Marketing Authorization (MA) for the product, which legally allows its marketing. However, for biological products (like vaccines) some additional steps need to be implemented before.

Registration
- Centralized procedure: the applicant submits a single dossier to EMA. Following this procedure, the Marketing Authorization allows the company to market the product in all 31 European Member States. For some categories of products (including vaccines), duly listed in the Annex of the Regulation 726/2004, the Centralized procedure is mandatory (European Commission, 1984).
- Mutual recognition procedure: this procedure is based on the mutual recognition, by Member State(s) concerned, of a national marketing authorization granted by the Member State of reference.
- Decentralized procedure: for medicinal products not falling within the centralized procedure's mandatory scope, the applicant may request one or more concerned Member State(s) to approve a draft assessment report, a summary of product characteristics, labelling and package leaflet as proposed by the chosen reference Member State.
- National procedure: the applicant requests the marketing authorization for one Member State only.

Quality Assessment
As mentioned above, in case of vaccines, after marketing authorization an additional quality check is required. With chemical-pharmaceutical products, this check is made by the applicant him/herself only but in case of biological drugs, the control is performed also by a European control laboratory always according to the directives contained in the European Pharmacopeia and in the EDQM.

In order to market the registered drug, for every batch produced the applicant must send to the Authorities a Marketing Information Form (MIF)[3] along with a Batch Release.

Marketing Information Form is a document that the applicant needs to fill and send to the Member State where the product is going to be marketed, along with the Batch Release On the other hand, the Batch Release is a certificate issued by a certificated European laboratory following a double-check on the product quality standards. The quality tests conducted on the product are the same as those reported in the dossier (module 3) and performed by the company itself before the Batch Release: for this reason, the European laboratory's results must confirm those reported in the Certificate of Analysis provided by the applicant along with the commercial lots. Quality controls can be implemented as follows:

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[3](MIF template is provided in Annex IV of the Guideline on Control Authority Batch Release).

- In-house methods: not following the European Pharmacopeia. These methods are developed by the applicant in its own facility, and in this case the company must provide the European laboratory with the internal Standard Operating Procedures, including methods' description and results;
- European Pharmacopeia following the methods described in the European pharmacopeia monographs[4].

Pharmacovigilance

This part of marketing authorization is probably the most important in terms of practice and health care. On a regular basis, authorities perform Pharmacovigilance inspections at pharmaceutical companies[5]. This step is crucial: in fact, although many clinical studies have been conducted, it is also true that they refer only to a limited number of subjects, whereas after its marketing the drug will be administered to thousand and billions of people of different ages, sexes, races and so on. Statistically speaking, several new variables can trigger the data.

Therefore, the company needs to constantly monitor and upgrade all the information about side effects and databases. For instance, they need to report those side effects that are particularly dangerous and can affect anyone: both company's people and citizens. These side effects are listed in the drug information sheet that also contains a section where citizens can report any kind of side effects directly to the manufacturing company.

Furthermore, the company must send to EMA a Periodic Safety Update Report, including a summary of data relevant to medicinal product's benefits and risks, a scientific evaluation of the risk-benefit balance and all data relating to the sales volume of the product, with the following frequency: every six months before the product's placement on the market, every six months during the first two years following market entry and once a year for the subsequent two years; finally, at three-yearly intervals thereafter.

A single assessment of Periodic Safety Update Reports (PSUSA) will be performed for medicinal products authorized in more than one Member State and for all medicinal products containing the same active substance or the same combination of active substances and for which a Union reference date and periodic safety update reports' frequency has been scheduled.

Additional Requirements

Additional requirements regard anything that needs to be done or has occurred after the product's registration and licensing.

This process involves many assets, such as follow-up measures, Post-Authorization Measures (PAM), Post-Authorization Safety Study (PASS), Post-Authorization Efficacy Study (PAES), ongoing stability studies, new trials on the

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[4]The aim here is to build a "bridge" between manufacturer and patients, so that other companies and applicants can rely on this process once they decide to invest in a new vaccine or other kinds of product. Finally, after the Marketing Authorization approval, the national regulatory agencies or EMA monitor the product development by regular inspections (European Commission 2001, art.111).

[5]European Commission 2001.

population as well as any kind of variation to the previous marketing authorization[6].

USA and Canada

Canada and USA share some similarities and some differences as well. First, it is important to remind that both their regulatory systems are deeply rooted in the English law: the first regulation – in the form of a bill approved by the English parliament – regarding the Bureau of Chemistry, the 1862 predecessor of Food and Drug, was created after a pharmacist of a small village poisoned more than 400 people, adding by mistake arsenic to a drug (Kurian 1998).

Canada enforced a similar law a few years later, in 1875, mostly due to alcohol's excessive use; it became a bill on its own in 1884, with the "Adulteration Act", which stated some standards related to pharmaceutical products' strength, quality and purity. Some other members of the Commonwealth followed the same principles, just like US: in the 1906 the first "Pure Food and Drug Act" was amended, which provided a products' regulation at national level. The Directive contained some black holes though thus it was later amended. The 1917 Sherley Amendment brought about a major change, which was nullified after some time due to certain sections that were considered fraudulent. In the 1937, also in US a tragedy like Thalidomide's in Germany occurred. Some companies produced liquid sulphanilamide that was marketed without any previous clinical trials, causing the death of more than 100 people. Following that accident, in 1938 the Congress approved "The Federal Food, Drug, and Cosmetic Act", which also introduced a big institution for the pharmaceutical regulatory system: The Food and Drug Administration (FDA). Replacing the previous New Drug Administration, the agency was established with the aim of ensuring that the marketing authorization would be issued only after checking the product's safety. Very similar to the European regulatory system, the US regulation required that several criteria should be respected, such as clinical and drug efficacy tests. However, the format was a bit complicated to understand and apply, so it was subject to many simplifications and adjustments.

Most of the time, American companies implemented their products' tests or manufacturing process in Canada, because this Country had less strict rules and regulation was not as rigorous as it was in the United States. In 1951, however, according to the latest changes in the Food and Drug Act, the Canadian government required that, in order to obtain marketing authorization, any new product should be submitted to the Food and Drugs Divisions of the Department of Health and Public Welfare, with the aim of "promoting and preserving the health, safety and well-being of all Canadians" (McMahon 1994), called also "Health Protection Board" (HPB). This department not only is comparable to the US FDA but has also some duties - including diseases and risk-benefit ratio monitoring, identification and control - - that belong to the US Environmental Protection Agency and Centre for

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[6]European Commission 2008.

Disease Control. Both FDA and HPB issue pipelines and information tools, GMP and report on clinical trials addressed to applicants and manufacturers.

After the Thalidomide tragedy, which also involved US and Canada citizens, the US government increased the FDA monitoring power and control (Kefauver-Harris Amendments 1962), along with the Good Manufacturing Practices definition. Usually, the GMP's rules are so strict and cost-demanding, that they constitute a true barrier for small companies that intend to develop a new product. This counterbalances the strict safety's requirement that USA pursue with the FDA. With this law, US government also created the New Drug Applications and Investigational New Drugs institutions, which are still operational today. Canada followed the US example, by re-arranging its own regulatory system in a very similar way.

The differences between Canada and US are based on different legal framework. The authorities involved in the pharmaceutical regulatory systems are different in relation to the different systems. It is also essential to bear in mind that those countries are guided by the Common Law, which implies both written and non-written rules. This system is quite different from the European Civil Law system. Although it may appear that the chief difference between the two law systems lies in the kind of product they monitor, this is not entirely true. Legally speaking, the Canadian Food and Drugs Act is a federal criminal law, and it regards every product sold on Canadian territory. This includes also foreign companies that have their products marketed in Canada. The US Food and Drug Administration is a federal law: it implies that if a product is entirely produced and sold in one country, that product falls within the local jurisdiction. However, this almost never happens, since the clause contained in the law states that if any items, such as ingredients or label, are distributed in different countries, that product is under FDA jurisdiction.

Pre-Clinical Phase

The sponsor, which usually is the manufacturer, sends the Notice of Claimed Investigational Exemption for a New Drug (IND) – in US – and the Investigational New Drug Submission – in Canada –, although US foreign clinical trials are not included in the document, which raised disputes among experts because other countries might not be aware of the side effects and other relevant information. Basically, with this document the applicant and the sponsor, i.e., the manufacturer, underline the safety and the efficacy of their product, by showing the results of their pre-clinical trials, the manufacturing process in detail, and how they want to proceed with the remaining tests. Especially for vaccines, this part may determine the rise and fall of the product, thus it is very important that the applicant submits the approval request when he/she has as many data as possible, in order to persuade the authorities to move to the clinical phase.

Clinical Phase

The applicant needs also to attach all the clinical trials conducted on the product and any information that FDA and HPB may judge relevant. In case of vaccines, the authorities are highly focused on ensuring the safety of the vaccines

they approve. More specifically, before the approval, FDA entrusts a community of scientists and experts with the task of personally analysing the vaccines effectiveness and quality. All this despite that the NDA documentation shows any details and trials conducted on it. They also inspect the applicant's laboratories, checking their manufacturing system and whether the GMP principles are complied with. In case of vaccines, lab tests always involve animal first: only when animal tests are 100% effective and safe and the test safety on humans has been proven, clinical trials are conducted on individuals, and volunteers are recruited. Even if the vaccine is aimed at children, tests are carried out on adults only.

Phase Agency Review

Once that the NDA and NDS are approved, the FDA and the HPB officially issue the marketing authorization for the drug. Then a period of strict effects' monitoring follows, where the companies are required to periodically send reports concerning side effects, additional requirements, additional tests or relevant discoveries, just as it happens with the European regulatory system.

As to vaccines, any kind of side effect not already included in the drug information sheet should be reported through the Vaccine Adverse Event Reporting System. The reports are monitored both by FDA and the Centres for Disease Control and Prevention: however, many side effects embedded in the VAERS might not be related to the vaccine, as they could have occurred after a vaccination period and reported by mistake for this reason. Scientists consider a new vaccines' side effect only after examining its causes, whether it could biologically be correlated to the vaccine or not and whether it would have occurred anyway, independently of the vaccination.

Also, the Advisory Committee on Immunization Practices has a major role in US, which includes medical and public health sectors' experts who have the task of providing vaccine-related technical comments and considerations, based on trials and side effects data evaluations.

Marketing Authorization Phase

In recent years, products' renewal timing has been considerably shortened in US. For cases FDA deems special, i.e., they need to be particularly monitored, the average renewal timing is nine months, whereas, for traditional cases, the average timing is nineteen months. In case of manufacturers with a reputation for appropriate manufacturing process and transparency, the average time can be reduced to fifteen months only. After that period, the drugs are still monitored but without involving further bureaucratic mechanisms.

On the other hand, before the latest law update, Canada had the slowest regulatory system for renewals: on average, it took thirty-four months for a drug to be renewed. Thankfully, this time span has been reduced due to the last changes in the Therapeutics Product Directorate. It is also important to remind that Canada allows "special" conditions for emergency cases as well as for drugs that can significantly improve the health status of many patients. This results in fast procedures and more flexibility.

Vaccines are almost never registered as equivalent drug. This is because an equivalent drug does not require to supply data for modules 4 and 5, since the original drug is well-established. Therefore, the authorization of an equivalent drug is obtained by providing only literature sources and then adding equivalency tests. However, vaccines are biological, not chemical-pharmaceutics products: thus, they do require clinical data. The earlier vaccines – from 60's – did not have this documentation, but over time the ministers of health and national regulations have become increasingly strict and demanding.

Barriers to Vaccine Research

Although nowadays the market seems to value around $24 billion, with an increase in the next years until reaching $61 billion in 2020 (Oxfam 2021), the overall vaccine research is decreasing so far. From 1967 to 1980 in US, the companies involved in vaccine research sector reduced from 26 to 17. This is almost 50% less in only 13 years (Douglas and Samant 2018). Thanks to external organizations like GAVI or Bill and Melissa Gates foundations, vaccine research gained a little more relevance in the business sector of pharmaceutical companies, although this also led to an increase in terms of pricing.

There are two main factors which need to be taken into considerations for a proper R&D analysis of vaccine sector. The first is that nowadays vaccine sectors are becoming more and more a *niche* sector: there are many big and wealthy pharmaceutical companies, but very few of them rather invest in vaccines. Novartis, for instance, has sold all his vaccines to GSK in the previous year; they only kept the "flu vaccine" sector with all the related products. This decision has been taken considering the R&D expectations on vaccine research, by estimating the perspectives from the percentage of vaccine sales with respect to overall sales. Since most of the time they do not exceed 10% of overall sales, vaccine sector is often cropped out, or it might get less attention than the others. COVID-19 even worsened the situation, making very difficult to find sponsorships for clinical trials and with modified clinical trials protocols (Sawad and Turkistani, 2021). COVID-19 exposed the fragility of the industry which had to rush towards a development of a vaccine for a totally new disease. The lack of funds in research led governments to pay big amount of fundings to find a formula for an efficient COVID-19 vaccine (Torreele 2020).

Secondly, despite the huge net value of the pharmaceutical companies, vaccine research represents only a small percentage of the overall R&D expenditures. Moreover, even though those companies who are still active in the market are keeping their expenses almost stable, or even higher than the previous years, the number of NCEs has been drastically decreasing. Forty percent of worldwide drug produced between 2009 and 2017 did not repay the sales forecasts in the first two years (Mlika et al. 2020).

One of the reasons could have logistic sources: the process for registering a drug is very long and complicated. Most of the times, people who suffer from those kinds of diseases do not have time to wait for the usual procedure of marketing authorization. Differently from what happened with COVID-19 vaccines, the WHO

pre-qualification, which is necessary for checking the quality and safety properties of the vaccines, usually requires around 200 days to be completed. It has been assumed that almost the half amount of the costs which needs for developing a drug, are those related to all the tests required from regulatory authorities.

Another obstacle is created by the companies indeed: most of the times, big companies rather focus on other sectors and they do not enhance the marketing authorization of drugs for vaccines; the duty to follow the long and complicated registration procedure is taken by companies which create equivalent drugs, after waiting for the timing of market exclusivity and patent protection derived from the originator ones.

Despite all these considerations, it is not clear whether regulatory systems have been influenced private research in positive or negative way, because it is very controversial to empirically verify the influence of regulatory systems on companies' R&D. The evolution of regulatory system has led to stricter and heavier controls on new drug approvals; while this might be positive from consumer side, since it grants more safety and effectiveness for patients, from supply side this means that the process of developing a new drug is even longer and more complicated than before. The prevalent opinion according to literature is that regulatory framework negatively affects the incentives to corporate research; while this could be true, it is also important to consider that this influence should not be overrated. Pharmaceutical regulation might be one of the causes for the fall of R&D research, but it seems hard to believe that innovation and corporate decisions are just guided by this constraint. This topic will be one of the core researches of the empirical analysis of this paper.

R&D Enhancing Strategies

In the latest years pharmaceutical companies, especially the largest ones, have shown a new trend. According to Access to Medicine Index (2016), which drafts the most detailed and complete report on pharmaceutical companies, in 2016 the 67% of R&D projects concerning high-priority, low-incentive products have been implemented in partnerships. Most partnerships are built between companies and external sources, such as public institutions or no-profit organizations, but 14% of partnerships occur between pharmaceutical companies. Most corporations involve those products for which there would not be a market, or with low-incentives perspectives.

Partnerships allow pharmaceutical companies not only to haste the research process, by merging knowledge of both companies' portfolio but also to share the costs of research involved in the process-making. Moreover, it has been shown that they increase the number of projects under their R&D pipeline, along with sales revenues for both companies.

Another new trend consists in knowledge and R&D pipelines acquisition through product diversifications. The most important, latest case is Novartis-GSK acquisition. Novartis has recently sold a large portion of its portfolio (influenza vaccine excluded) to GSK, for USD 7.01 billion. On the other hand, GSK has enhanced its products portfolio, and its expected profits will be higher over the

next years. More specifically, GKS now has *Menveo* and *Bexsero* vaccines, both treating meningitis disease, which have been sold in 62 and 38 countries so far, respectively. The acquisition allowed both companies to increase their geographic area of relevance, especially in US, where Novartis had a strong relevance in relation to regulatory approvals.

Other kind of acquisitions usually occurs between large and small companies, in order to obtain cutting-edge technologies or new drugs products. Not only this is the main reason why pharmaceutical sector is becoming increasingly small, in terms of number of firms currently operating in the market, but it is also a consequence of the high barriers and products-making related costs. Only large companies can afford to invest so much in new R&D processes, and this is also why they are willing to obtain knowledge by acquisitions rather than relying on external incentives.

Empirical Analysis

Hypotheses and Methodology

Considering the research's purpose, three key hypotheses will be considered and analysed.

H1: Which are the vaccine development's determinants, and what are the relationships between those assets and vaccine research

The core of this hypothesis is to find out the main drug development's determinants and what is the relationship between the drug development intensity and variables that directly impact on the process. The new models will take into consideration some of the control variables used by the background models, by focusing on the ones that were considered as research investments' determinant. The purpose is to check the coefficients' sign and significance in relation to vaccine research, to see whether a difference between pharmaceutical research as a whole and its sub-sample vaccine research exists.

H2: Acquisitions have a negative impact on vaccine R&D

Following the tendency to broaden the framework, as literature and recent researchers have done, it was decided to include the "Acquisitions" variable with the purpose to detect whether it would impact on R&D investment decisions for pharmaceutical companies.

New empirical findings in literature suggest that there is an obvious connection between acquisitions and R&D expenditures. The innovation process might be more related to technological acquisitions rather than to formal R&D productivity, in terms of new machineries, researchers and knowledge acquisition. Recently, this has been partially confirmed by other authors, who showed that innovation process is pushed by new equipment's' supply (Mukoyama 2006). In the vaccine industry, for pharmaceutical companies Technological Acquisition might work as

a "substitute" of Research and Development, since pharmaceutical companies find less expensive to purchase the license or the whole in-process products from an external - usually smaller - company, rather than investing in research on their own. Therefore, a negative relation between acquisitions costs and Research and Development costs is expected: when companies decide to invest on acquisitions, they will rather spend less for their own R&D.

The cost-related "Acquisitions" is the variable included, as a comparison to research and development's costs. Acquisitions are associated with partial or total acquisitions of external companies or products, plants and equipment as well as other intangible assets.

> H3: Testing for coefficients' stability suggests that regulation has no direct effects on vaccine R&D

Some part of the literature attributes a significant relationship between pharmaceutical regulation and research investments. What is crucial is that there is no way to directly analysing this relationship. The only way to do so is to rely on proxy variables, although there is a huge difficulty in determining that econometric variable which uniquely points to pharmaceutical regulation.

Thus, it has been decided to analyse the impact of pharmaceutical regulation by testing whether a difference in R&D investments in relation to some specific changes in European regulatory system does exist. This paper will test whether there is a difference in the regression compared to 2010. In 2010 some huge changes in Pharmacovigilance sector occurred, which strengthened the process to achieve greater safety and security for new drugs. The test will be made by using a Chow Test for structural breaks (Chow 1960). Since Chow Test only analyses whether a structural break occurs or not, the only plausible assumption is that Chow Test will check the stability or instability presence in regressions.

Data and Indexes

The analysis covers 2008-2015 period. This period is largely determined by the availability of data regarding vaccine R&D expenditures. The analysis will be conducted on 10 pharmaceutical companies: Pfizer (2008-2015), Johnson & Johnson (2008-2015), Novartis (2008-2015), CSL Limited (2008-2015), Roche (2008-2015), Abbott (2008-2015), Astra Zeneca (2008-2015), Merck (2008-2015), Sanofi Aventis (2008-2010) which became Sanofi (2011-2015), Glaxo-Smith-Kline (2008-2015).

Data were collected from the companies' financial and annual reports. Some data concerning the number of employees per year were also collected by a website tool for data collection. All the indexes were converted in USD and expressed in millions of dollars.

Table 1 shows descriptive statistics for Model 1, whereas Table 2 shows descriptive statistics for Model 1.

Table 1. *Descriptive Statistics – Model 1*

Variable	Obs	Mean	Std. Dev.	Min	Max
RDcostsvac~s	78	1265.768	1595.687	132	6820
OPERATINGP~1	80	41392.33	166573.1	941	985100
CASHFLOW	80	21885.8	101770.3	-7800	812000
SG	70	1.15226	11.09338	-47.15909	30.08585
logMSCost	80	8.893555	1.02319	6.2106	9.996522
COSTOFSALE~1	80	10236.55	6360.287	290	22740
Nemployees	80	87853.9	45259.81	11400	177870.1
Debt	80	12532.8	11009.71	0	48600
Acquisitio~s	80	4405.332	12126.07	0	101600

Table 2. *Descriptive Statistics – Model 1*

Variable	Obs	Mean	Std. Dev.	Min	Max
RDcostsvac~s	78	1265.768	1595.687	132	6820
EUsalesove~1	80	13217.34	10381.63	806	39590
EUsq	80	2.81e+08	3.79e+08	649636	1.57e+09
USAsalesov~1	80	13806.78	8971.908	1100	35680
SalesTotal~U	80	10523.44	8532.86	0	28850
SG	70	-1.15226	11.09338	-30.08585	47.15909
Nemployees	80	87853.9	45259.81	11400	177870.1
Debt	80	12532.8	11009.71	0	48600
Acquisitio~s	80	4405.332	12126.07	0	101600

Overall, the maximum and minimum values suggest that there are consistent differences between firms. Research expenditure is quite linear and increasing over the years for every firm except for Novartis, which had a considerable decrease in vaccine research. This is also consistent with the fact that in 2015 Novartis sold up all its vaccine products to GSK (Novartis Financial Report 2015), keeping Influenza Vaccine only. Net Debt is very volatile, which means that firms often work to reduce large amounts of debts, only for increasing it again later. The number of employees does not vary much over the time, even though, due to financial crisis, some companies have reduced their workforce.

"Business Scale", "Age of the company" and "Tobin's q" were not included in the first and second model respectively since they proved to be not statistically significant in the background models.

"Cost of Sales" has been not included in Model 1 due to the high correlation with Marketing, Selling, and General expenses, while it was kept in Model 2 since, in the background model, Cost of Sales turned out to be not statistically significant.

"Sales in the Rest of the World" variable was removed from Model 2 since in the background model it turned out to be not statistically significant. "Sales in US" was included as data collected from financial reports, instead of computing the index by adding the residuals up. Moreover, it is low correlated with EU sales and its squared term

Models and Equations

Two models will be used to analyse factors affecting vaccine research in relation to research and development expenditures.
Model 1:

$$RD_{it} = \alpha + \beta_1 PROF + \beta_2 CF_{it} + \beta_3 ACQ_{it} + \beta_4 LEV_{it} + control\ variables + \mu_{it}$$

The first model will use Profitability, Acquisitions, liquidity and Leverage as main determinants for vaccine research, and the control variables will be Size, Sales Growth and Marketing-Selling-General expenses.

The model will use logarithmic indexes' forms assuming a Cobb-Douglas production function; in addition, the probability of finding outliers is reduced.

Model 2:

$$RD_{it} = \alpha + \beta_1 EUs_{it} + (\beta_2 EUs_{it})^2 + \beta_3 USs_{it} + control\ variables + c_i + \gamma_{it} + \mu_{it}$$

The second model includes sales as determinant factor for R&D, and it considers Growth, Acquisitions, Liquidity and Leverage as control variables. For the second model, logarithms of variables related to overall sales were used.

STATA 12 has been used as a statistical tool for panel regressions and analysis. The time effect estimator was included in the equation. The underlying assumption is that there might be some time-specific effect δ t affecting all firms in the same manner. One example could be the Ebola epidemic in 2014, or the Financial Crisis in 2008. Therefore, the model was estimated by considering a dummy variable for each period, which Stata 12 computes on its own, without the necessity of doing it manually. Fixed Effect estimation was used to compute the analysis of the two models

Results

Tables 3 and 4. *Model 1 and 2: Results*

```
Model 1 - Results
---------------------------------
                             (1)
                     R&D vaccines
---------------------------------
Profitability               0.108
                          (0.121)

Cash Flow                 0.121**
                         (0.0372)

Growth                    0.00461
                        (0.00342)

Market./Admin Expe~s       -0.443
                          (0.249)

Size                      0.162**
                         (0.0573)

Leverage                -0.0942**
                         (0.0303)

Acquisitions             -0.0843*
                         (0.0394)
Fixed Effect                  YES
Time Effect                   YES
---------------------------------
Observations                   57
R-squared                   0.437
---------------------------------
Standard errors in parentheses
* p<0.10, ** p<0.05, # p<0.01
Robust Estimation
```

```
Model 2 - Results
---------------------------------
                             (1)
                     R&D Vaccines
---------------------------------
Sales EU                    2.259#
                          (0.599)

(Sales EU)^2               -1.080#
                          (0.312)

Sales US                  0.00435
                          (0.337)

Growth                    0.00530
                        (0.00354)

Cash Flow                  0.169#
                         (0.0411)

Size                      0.105**
                         (0.0404)

Leverage                 -0.110**
                         (0.0367)

Acquisitions            -0.0837**
                         (0.0326)
Fixed Effect                  YES
Time Effect                   YES
---------------------------------
Observations                   57
R-squared                   0.488
---------------------------------
Standard errors in parentheses
* p<0.10, ** p<0.05, # p<0.01
Robust Estimation
```

As expected, Stata has dropped many observations. Moreover, the interclass correlation rho and the standard deviation of residuals within group indicate the presence of strong individual effects. R-squared, which is around 43% for the first model and 49% for the second, suggest that a Fixed Effect estimation for this model quite fit data.

Although a large part of literature confirms the relationship between profitability and research, unexpectedly, profitability was not statistically significant in our model. Sales Growth and Marketing-Administration-General expenses were not significative. This could also be due to the small number of observations included in the dataset. On the other hand, Cash Flow, Size and Leverage turned out to be statistically significative with 5% significance and the sign confirms the background literature. A 1% increase in liquidity is associated with a 12% increase in vaccine research; a 1% increase in employment is related to a 16% increase in vaccine research whereas a 1% increase in debt is related to a 9% decrease in vaccine research.

Vaccine research investments seem to act in a similar way as overall drug research and development investments. Even in this case, liquidity, size and leverage influence investments decisions, even though Growth, in terms of sales, and general expenses seem not to be so relevant for vaccine research.

For the second model, the economic and financial assets considered in the research influence vaccine research just as they influence general pharmaceutical research investments. The Sales in Europe, along with the squared term, show 1% significance level. The dichotomist sign of the two variables also confirms the background literature: while research is positively correlated with sales, it is negatively correlated with the sales in squared terms. This might suggest that sales follow a skewed distribution, as it will be explained later. US sales and Growth turned out to be not statistically significant. Cash Flow and Leverage were statistically significant at 1% and 5% respectively. A 1% increase in liquidity is correlated with a 17% increase in vaccine research, whereas a 1% increase in debt is correlated with a 11% decrease in vaccine research.

Cash Flow and Acquisitions were more statistically significant in this model compared to the first: this could be due to the absence of Profitability as an independent variable and the presence of Sales as covariates explaining the dependent variable.

Employment was significant at 5% level, with a positive correlation with the dependent variable. This confirms the finding of the first model and the background literature, although it is important to consider the idea that this variable might be connected to acquisitions. Increasing employment by 1% is related to increasing R&D intensity by 10%. Even though the Correlation Matrix indicates a low correlation between the two variables (see Appendix), the introduction of a new control variable might have influenced the significance of the others.

One important thing to consider is that Sales Growth did not appear statistically significant in neither of the two models. Although this may be due to small observations, it might also suggest that an increase in overall sales does not directly influence vaccine research. On the other hand, sales distributed per geographical area seem to have a notable impact on investment decisions.

As expected, Acquisitions turned out to be statistically significant with a negative correlation as compared with R&D, even though the significance is 10% only: this might be even larger when including additional observations in the dataset. Increasing acquisition costs by 1% leads to an 8% decrease in vaccine research.

In Model 2, Acquisitions turned out to be negatively correlated with R&D, just like in the first model, even though here the phenomenon was more significant (5% as opposed to 10% of the previous model). Increasing acquisition costs by 1% leads to an 8% decrease in vaccine research. This result is like those obtained in the first estimation.

Chow Test Estimation

Chow Test for structural breaks was computed on the unrestricted model and two sub-samples, referring to pre-2010 and post-2010 period. The F-test and the relative p-value gave such results that it was not possible to reject the null hypothesis of no structural breaks in the panel data. This also means that there is no structural difference in the parameters of the two restricted sub-samples, and the coefficients remain stable with respect to what-supposed-to-be the breaking year (2010).

Discussion

More Liquidity Means More Research

Liquidity's positive relevance in vaccine research is the key that better explains how economic growth and Innovation are extremely connected. As Veira et al. (2008) stated: "If the investments in technology are large, the economic growth and productivity convergence will be higher". Some authors (Dimitri 2013) also suggest that "financial performance may depend not only on the ability to bring new drugs to the market, but also on doing it faster than competitors".

This also means that companies can cover their short-medium debts, even though this might not be the case for long-term Debts. The complex procedure involved in vaccine production requires huge financial resources, and the decision-making process on new investments is related to the burden of information asymmetry and moral hazard issues. This is also why an adequate capital reserve is crucial for research investment decisions.

COVID-19 epidemic is an example of how much countries and pharmaceutical companies are economically intertwined in vaccine research. In the paper of Çakmakli et al. (2021) it is showed that the global GDP loss of counterfactual of global vaccination can be higher than the cost of manufacturing and distribution of the vaccine itself. They also argue that "increasing the production and supply of vaccines produces significant economic benefits for the world economy at minimal cost".

Stability Influences Investment Decisions

As expected, leverage is negatively correlated with R&D. Research is not an urgent investment: therefore, riskier investments might be affected also by the company's high debt-equity ratios and this causes disinvestments in research. On the other hand, if the firm is more stable, it can face medium-long term projects more easily, which are often related to new research investments. Governments should exploit this barrier to the market by providing incentives and lump-sum taxes to develop new vaccines (Xue 2020).

Employment Can Enhance Research

In general, it has been stated that large companies are more willing to invest in R&D due to the lower burden on liquidity constraints as well as to higher diversification between products and scale/scope economies. This evidence is also consistent with previous literature (Coad and Rao 2008), which confirmed the positive relationship between R&D and firm growth in the short-term. Capasso et al. (2014) confirmed the evidence for medium term as well.

Both models analysed in this paper, showed a positive correlation between vaccine research investments and employment. Figure 1 shows the average number of employees per year in the 10 firms involved in the research: it is possible to see that the overall employment level has been slightly increasing from 2011 onwards, with a little decrease between 2012 and 2013. In this case, the overall employment increase could mean that pharmaceutical companies have decided to hire people necessary for the company's economic growth, which implies that more people are involved in vaccine research projects. Examining the scope of employment for pharmaceutical companies goes beyond the aim of this paper, and further analysis should be made to better understand whether more employment is related to research investments and specialized labour or not.

**Figure 1.** *Employment Level (Average), 2008-2015*
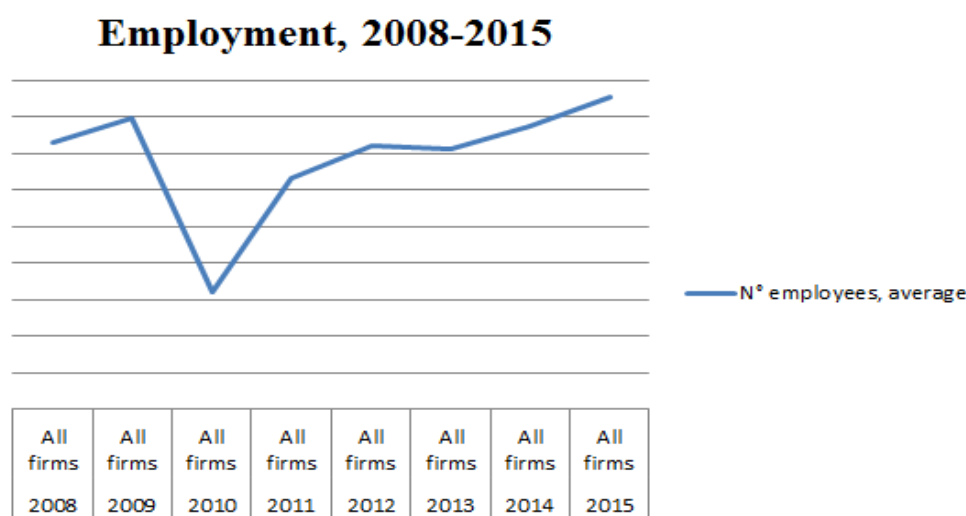
Source: Own elaboration.

Sales Follow a Skewed Distribution

One of the most interesting findings is that the non-linear variable (*Sales*q) is negatively correlated with R&D expenditures. This is consistent with the existing literature; in particular, Scherer (1999) showed that activities based on IPO – High Technology Companies – follow a skewed outcome distribution. The author also showed that joint ventures start-ups sales are highly skewed thanks to a dataset of 383 start-ups investments provided by Venture Economics and another consisting of 670 start-up investments (Scherer et al. 2000).

Grabowski and Vernon (2000) analysed the sales distributions of 64 New Chemical Entities -NCEs- in US market from 1980 to 1984, in pharmaceutical industry. They also analysed the sales distributions of Orphan NCEs with respect to Non-Orphan ones from 1988 to 1982, and then compared them to the first estimation. Any analysis conducted showed that the sales revenues in US followed a highly skewed distribution.

Figure 2. *US Sales Distributions of New Chemical Entities, 1980-1984 and 1988-1992, with Orphan Drugs Included in the Period 1988-1992*
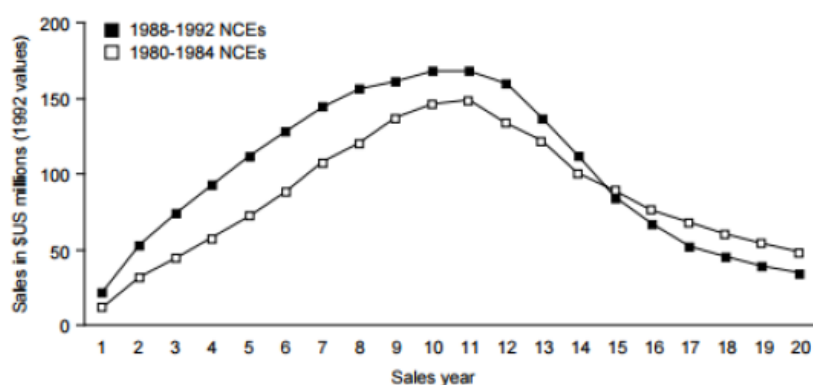
Source: Grabowski and Vernon 2000.

Figure 2 outlines that R&D investments behave like joint-venture private investments of start-ups or public market investments in high-technology companies. The common denominator is the high level of risk all these activities involve. In the case of pharmaceutical companies, the risk is even higher due to lengthy processes, competitors with rival products and regulatory problems. Figure 1 also shows that many products are licensed even though they feature very small peaks in terms of sales revenues. As firms are aware that they will not be able to fully recover their R&D costs related to the new product, it is sufficient that the marketed product covers the incremental or variable costs. These results show that there is very high variability in sales performance for large pharmaceutical companies: they found out that firms with an average of $US300 and $US500 million R&D spending in 1980s, had aggregate sales between US$100 million and $US3 billion during 1988-1992 period. Similar results have been obtained by Romano et al. (2020) by considering COVID-19 outbreak on medicines' sales.

This might also be linked to the market exclusivity expiration and the upcoming equivalent drugs introduced in the market. In EU, data protection lasts around 8 years while market exclusivity for both vaccines and drugs lasts 10 years. In US, the protection for Biological products (including vaccines) lasts around 10 years. This perfectly matches with the situations described in the figures above: after 10 years, sales start to significantly decrease. The loss of monopoly power and the raise of perfect substitutes lead to a sales and profits' decrease.

Pharmaceutical Companies Find More Profitable "Acquiring" Knowledge rather than Investing in Research on Their Own

Malik et al. (2008) claim that almost 40% of activities regarding applied research are undertaken externally. The authors also report that the chief reason why companies rather leave research projects to others is the lack of in-hours R&D and technical expertise. The second and third relevant reasons are cost, and time amount correlated with the research and development process. Beside uncertainty, the capability of reducing risk is also a very important asset for outsourcing R&D activities. The "ease of managing projects externally" was considered the least important assets in comparison with others previously mentioned.

Most of the outsourcing research projects concern applied activities that are considered less "strategic" from the company's point of view. This is coherent with the vaccine sector and with the results obtained in this paper. Technology Acquisitions enhance process innovation for pharmaceutical industries, since companies would rather "acquire" knowledge instead of "producing" on their own for all the reasons stated so far.

Regulation does not Obstruct Research Investments

It is important to remind that Chow Test did not test for "pharmaceutical regulation" and its impact on R&D, but it simply checked whether there are structural breaks in the panel data regarding a specific breaking point. In this case, the breaking point taken into consideration was 2010, due to the new, huge Directive regarding Pharmacovigilance. In this regard, Chow Test estimated that companies did not change their behaviour with respect to that period. On the other hand, it is also important to stress that the new Pharmacovigilange rules, even though crucial for changing the previous frameworks, are not directly related to the research and the production of New Chemical Entities. Pharmacovigilance affects post-marketing phase as well as new products' re-examination. This might also mean that Chow Test would lead to different results if a different breaking point were considered: for example, it might be useful to analyse the 2012 Directive regarding New Clinical Trial regulation, which enabled international collaborations and simplified manufacturing processes. Further examinations are needed, perhaps including the newest European rules on pharmaceutical regulation.

Moreover, their whole research assumes that US market is less regulated than the European one. Recently, the divergence between the two systems has been considerably smoothed out. In asserting that price control has a negative impact on

R&D and then commenting that it should be abolished, the other side of the coin should be also taken into consideration: less regulation means less protection of consumers' purchasing power, and more monopoly power for pharmaceutical companies.

In addition, the global market coverage of pharmaceutical companies and their relevant products implies that EU regulatory systems affect non-European countries as well. Thus, it is not possible to define for sure whether the up-to-date European regulatory systems negatively influence corporate research and development: the only way to make this kind of considerations is to analyse the regulatory systems' effect. Even though the changes occurred in EU systems only, it is not possible to make a sharp distinction between EU and US regulatory systems consequences, since companies operate in both markets and their revenues do not come merely from made-in-Europe products sold throughout Europe.

Conclusions

The main purpose of this paper is to empirically investigate and analyse how different economic and financial factors affect pharmaceutical companies' decisions to invest in vaccine research, by reviewing panel data of 10 big pharmaceutical companies from 2008 to 2015. Two models have been analysed through Fixed Effect estimation. The descriptive part is crucial to better understand the results of the econometric regressions and the relevant interpretations and discussions.

The overall interpretation of the results related to the paper research is that the vaccine industry does not behave differently from other pharmaceutical sectors: the economic and financial assets, in fact, consider influence vaccine research as well as overall pharmaceutical research. Corporate finance heavily affects R&D investment choices: the company must be able to grow to obtain an overall profitability in sales. It is also required that it is very stable and has enough Liquidity to cover its Net Debt. Plus, the company must be able to benefit from the coverage granted by the Data Protection and Market Exclusivity in order to cover (at least partially) the costs related to research projects. In fact, once the coverage period has expired, the overall sales will no longer be sufficient to cover their R&D costs. Moreover, other pharmaceutical companies will start to produce generic drugs and sell them at lower prices so that competition will increase, and, as a result, individual profits from the "innovator" company will fall.

Therefore, to fight information asymmetry, the company must be also able to hire and train specialized employees for obtaining additional Know-How and Technological Innovation, which will be helpful to create New Chemical Entities and new products. Besides, the company will face any manufacturing difficulties linked to the core of the research and deal with the requests from regulatory authorities. Seemingly, the regulatory system does not directly affect R&D, even though this is an open issue deserving further investigations.

What differs most is the need to develop new vaccines, which is way less compared to the requests for Innovator drugs. Also, in the case of vaccines the decision-making process could be longer and more complicated compared to other drugs since vaccine research is more complex and requires plenty of time and

money to be successfully completed. Pharmaceutical companies alone cannot fully sustain health standards' needs or epidemic diseases which occur worldwide. Public sector does not seem to help them either, or many discussions about how to properly sustain vaccine research are still in progress. For this reason, an increasing number of companies are disinvesting in vaccine research, leaving this industry in the hands of few large pharmaceutical companies.

All the strategies commonly used in this sector are crucial for finding new ways to incentivize R&D. Push Programs provide a "basic" research funding for increasing know-how and improving technological techniques. Pull Programs aim to incentivize the final output to "pull" companies towards a specific product's development. Vaccine Purchase Commitments lie between a Pull and a Push program, where sponsors and manufacturers submit a contract by setting the price at which sponsors buy the final product. Even so, they are actually very difficult to rearrange. Although it has been shown that those mechanisms are still valid today, it is also true that Financial Crisis might lead to reconsider the Push, Pull or Advanced Commitments programs' applicability. In 2012 more than $130 billion dollars were invested in pharmaceutical research: only $527 million dollars came from companies, whereas the major funders were public institutions and organizations. Another issue related to external funding is the Time Inconsistency involved in long-term decision-making, which, due to the usual time-consuming vaccine research, might change over time.

Public debts are growing faster than ten years ago, and private industries have been squeezed by the decrease of demand from customer-side. Governments had to disinvest in health care programs, although people's life expectation has grown. Like any other industry, pharmaceutical companies have suffered from the crisis as well. It might be necessary to further investigate the Innovation and manufacturing technologies-related issues inside pharmaceutical companies, perhaps by identifying those companies mainly focusing on generics, innovator drugs, vaccines or other kind of products. This is also related to the consideration that increasingly few pharmaceutical companies are investing in vaccine research.

It would be interesting to assert the organizations' relevance in terms of R&D incentives, perhaps analysing the pharmaceutical firms' market structure and the monetary collaborations with GAVI, MSF, WHO and other organizations. What is clear is that vaccine research industry is very complex and requires huge efforts in terms of time, costs and technological progress. This means that vaccine industry is increasingly becoming a niche sector, due to externalities and high barriers to entry, and that it is crucial to find triggers suitable to promote Innovation. Most important, those triggers must be able to counter all the negative financial, institutional, legal and pharmaceutical issues that could hinder R&D projects and investments.

Finally, to improve access to new products and make them available to everyone, a further attempt to support this industry should be made. Health standards will improve along with the quality of life, which will eventually influence the economic growth of the country.

Despite political considerations, which are beyond the aim of this paper, the only relevant fact is that, whether public opinion likes it or not, vaccines are useful

for increasing life expectations and effectively treating dangerous and costly epidemic diseases. This would also lead to fewer inequalities and more sources for economic growth in underdeveloped countries.

Acknowledgments

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Appendix: Correlation Matrices

It is important to underline that Debt and Acquisitions are not correlated. Moreover, there are no multicollinearity issues between EU sales and its squared term, since Stata did not drop either of the two covariates, and since the squared term is not a linear combination of EU sales.

Table 5. *Model 1 – Correlation Matrix*

	RDcost~s	OPERAT~1	CASHFLOW	SG	Market~o	COSTOF~1	Nemplo~s	Debt	Acquis~s
RDcostsvac~s	1.0000								
OPERATINGP~1	-0.1060	1.0000							
CASHFLOW	0.6944	-0.1193	1.0000						
SG	-0.0699	0.1319	0.0291	1.0000					
Marketings~o	0.5485	-0.1992	0.5256	-0.0657	1.0000				
COSTOFSALE~1	0.4103	-0.1823	0.5710	-0.0352	0.8483	1.0000			
Nemployees	0.1407	-0.1701	0.3180	-0.1409	0.7104	0.6760	1.0000		
Debt	-0.0731	-0.1586	-0.1590	-0.0420	0.5652	0.3681	0.4741	1.0000	
Acquisitio~s	-0.1481	0.0504	-0.0942	0.1887	-0.1449	-0.1261	-0.0951	-0.0113	1.0000

Table 6. *Model 2 – Correlation Matrix*

	RDcost~s	EUsale~1	EUsq	USAsa1~1	SalesT~U	SG	CASHFLOW	Nemplo~s	Debt	Acquis~s
RDcostsvac~s	1.0000									
EUsalesove~1	0.8352	1.0000								
EUsq	0.9127	0.9497	1.0000							
USAsalesov~1	0.6841	0.7896	0.7408	1.0000						
SalesTotal~U	-0.5129	-0.3105	-0.4429	0.1278	1.0000					
SG	0.0699	0.1026	0.0213	0.0707	-0.0526	1.0000				
CASHFLOW	0.6944	0.7713	0.7765	0.5305	-0.2600	-0.0291	1.0000			
Nemployees	0.1407	0.4181	0.2805	0.5242	0.4580	0.1409	0.3180	1.0000		
Debt	-0.0731	0.0638	-0.0271	0.5286	0.6325	0.0420	-0.1590	0.4741	1.0000	
Acquisitio~s	-0.1481	-0.1104	-0.0824	-0.1893	-0.0985	-0.1887	-0.0942	-0.0951	-0.0113	1.0000