



**UNIVERSITY OF GOTHENBURG**  
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# **The Formal Structure of the U.S. Food and Drug Administration – Its Effects on Pharmaceutical Spending and Drug Innovation Character**

Department of Business Administration  
Management & Organization

Fall 2013

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# **Bachelor's Thesis**

## **ABSTRACT**

The pharmaceutical market is considered as one of the most regulated in the developed world. Still, we see an ongoing trend with increasing global pharmaceutical spending and lack of breakthroughs in life science discoveries. The reasons are different depending on which source you rely on. The payers, the originators and the drug agencies are arguably the key players in this market. This study examined the current status of the industry, how the market rules have changed and how the absence of isomorphism between the world's biggest drug agency, the U.S. Food and Drug Administration, and the pharmaceutical companies may be a source of the problems. The employees interviewed at the agency partly explained their views, which mostly were consistent with the current limited literature. In conclusion, the formal structure of an independent organization limits the isomorphism with the environment, and thereby the success for cost containment and drug innovation management.

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**Table 1.** Definition and description of abbreviations and terms.

<b>Abbreviation/Term</b>	<b>Description</b>
<b>Big Pharma</b>	The major pharmaceutical companies.
<b>Blockbuster</b>	A drug that generates more than one billion dollar/year in revenue for its owner.
<b>EMA</b>	European Medicines Agency. European Union's drug agency.
<b>EPB</b>	External Price Benchmarking: The price of a drug in a country is decided on the price of the same drug in a group of other countries.
<b>FDA</b>	The Food and Drug Administration. The national drug agency of USA.
<b>Generic Drug</b>	A drug product that is comparable to brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use.
<b>IRP</b>	Internal Reference Pricing: A drug's price in a country depends on the price of similar, potentially already off-patent drugs in the same country.
<b>Me-too Drug</b>	A drug that is structurally similar to already known drugs. Only minor differences in most aspects.
<b>NDA</b>	New Drug Application. A formal application where drug sponsors propose that the FDA approve a new pharmaceutical market entry.

<b>Abbreviation/Term</b>	<b>Description</b>
<b>NME</b>	New Molecular Entity. A product that contains active moieties that have not been approved by the drug agency previously.
<b>Orphan Drug</b>	Drugs for life-threatening or very serious diseases or disorders that are rare in prevalence and incidence.
<b>PMDA</b>	Pharmaceuticals and Medical Devices Agency. Japan's drug regulatory agency.
<b>Value-based pricing</b>	The price of a drug is based on an analysis where the cost of a drug is measured against its health benefits ("value for money").

# **Introduction**

## **Background**

The pharmaceutical market is one of the most regulated in the developed world (Garattini, Cornago and De Compadri, 2007). The governments have certain objectives such as maintaining and improving the health of their citizens through effective drugs in the domestic market and correct usage and information regarding the medications with marketing authorization. Although pharmaceuticals are essential for the healthcare system in any given society, the increasing expenditures have become a great issue (Mossialos, Mrazek and Walley, 2004), whether the payer is the government or a private insurer. As the world is facing an aging population (NIA, 2011) and the fact that people over age 65 are more likely to be regular prescription users than their younger counterpart (Lehrer, et al., 2000), a highly complex challenge has developed.

To manage the rising pharmaceutical expenditure, some health insurance systems apply the idea of pricing and reimbursement regulation. This approach is different depending on the country, but in general three forms exist: Internal Reference Pricing (IRP); External Price Benchmarking (EPB); and Value-based pricing (see table 1 for a summary of abbreviations and terms used in the text). They are common in Western Europe where 17% of the pharmaceutical industry's revenues were generated in 2011 (IFPMA, 2012). World's biggest pharmaceutical market, USA, had 34% of the industry's 2011 revenues. It is considered as a region with market-based pricing. However, managed care organizations (Slovick, 2011) as well as public social assistance programs (Friederiszick, et al., 2009) promote the use of cheaper options instead of the most expensive and novel drugs, as well as price negotiations, through different strategies. Thus the free pricing is to some degree regulated if the pharmaceutical company wants to be entitled reimbursement for its product.

This strategy has been quite successful which we will see in the next chapters, as expensive patented drugs in the same therapeutic cluster as generic substitutes are rarely the first choice to be prescribed due to they are not covered or

prioritized in most health insurance systems. But the problem has yet not been solved.

What can have caused this is highly debatable depending on the source you read, as the pharmaceutical industry, with astonishing annual revenues has several different key players that influence the market.

### **Research Problem**

The increasing expenditure issue the market is facing and the lack of breakthroughs in life science discoveries are signs of mismanagement from the stakeholders' part. It is impossible to blame one group or organization. At the same time, the need for pharmaceuticals shows no sign of decline – rather steady increase.

The changing business environment the companies have experienced as a reaction from the payers less willingness to reimburse and fewer novel drugs, have made them changing focus in their drug development programs, as the pharmaceutical industry, like any other industry, is profit driven. This has eventually created other challenges, such as drug shortage, less accessibility and extremely expensive drugs not covered by payers. This brings up the discussion on how a drug regulatory agency, which has the mission to oversee these problems, in such a traditional and innovative industry, have allowed this to evolve? Can this be the result of an environment where the companies have not been regulated enough? Is this a proof of lack of ability from the regulatory agencies to incorporate structural elements isomorphic with the environment?

### **Key Question This Work Can Address**

Has the formal structure of the U.S. Food and Drug Administration (FDA), the world's biggest drug agency, limited it from influencing the challenges in the pricing and reimbursement of pharmaceuticals and drug innovation character?



# **Theory Background**

## **The Institutionalization**

Organizations making up a specific field have a tendency to be the same in how they look and act (Miles, 2012). The theory behind this has the concept that in order to be accepted, organizational structures and processes search for meaning and stability in their own right. This is more prioritized than improving effectiveness and efficiency of the organization. Over time the structures and practices become more and more homogenous in the organization.

Institutions in general form are essential components in the environment. The regulative, but also normative and cognitive structures and activities they have, create some kind of stability and meaning for social behavior, as mentioned by Scott (1995, p. 33). The institutions laws, regulations, culture and ethics are some examples. To become legitimate by internal and external stakeholders, the organization's actions must be consistent with current norms, rules and beliefs (Miles, 2012, p. 146). The more they submit to the social norms, the more they earn the legitimacy to continue with their operations by increased resources and survival capabilities. Powell and DiMaggio (1991) emphasize how the institutionalized activities occur on interorganizational level when industry alliances and expectations from society define the social and expected organizational behavior, hence forcing organizations to look and act the same. Heugens and Lander (2009), discuss two disputes among institutional theorists, where the first one examines the supremacy the structure itself has over the agency. They ask the question whether it is the macro societal forces or the organization's actions that are behind the emergence of organizational structures and processes. The second dispute covers the influence of conformity on organizational structure.

Being quite accepted in general, the institutional theory has also been criticized from some points. Kraatz and Zajac (1996) had limited success in finding evidence that supported the constraint of legitimacy. Also, high-status players seem to be able to deviate from the norm thanks to reputational capital, which is not the case for middle-status and low-status players (Phillips and Zuckerman,

2001). Further, some critics mention that the mechanisms underlying institutionalization have yet not been investigated. The effects are clearly examined, but with the absence of the processes that result in organizations becoming institutionalized, we may see organizations as “black boxes” without seeing the value inside of them (Phillips, Lawrence and Hardy, 2004).

### **Lack of Functioning Isomorphism**

Meyer and Rowan (1977, p. 342) explain that when markets expand, the complexity regarding relational networks increases. The size and technology creates a need for coordination, and organizations with rationalized formal structures. A bureaucratic structure, such as the FDA, is thought to be the most effective alternative to standardize and control subunits, which is true in the regulated pharmaceutical market. Further, to not lose their legitimacy, such organizations have to institutionalize certain elements as they are socially expected (Meyer & Rowan, 1977, p. 344), which was also mentioned in previous section. In the case of the FDA or any drug agency, it is to protect the public health by taking responsibility of the safety, efficacy and security of drugs in the market. While the safety and efficacy responsibility are highly institutionalized, the issue with cost containment has been neglected. One may argue that politicians or other organizations decide the financial part, but it cannot be denied that the FDA has high influence in the financial aspect of a drug e.g. review time before drug approval and exclusivity rights. A future area of significance could be cost-effectiveness. This area has grown in importance to contain a healthy pharmaceutical spending. Meyer and Rowan (p. 345) describe this phenomenon as a building block that an organization must incorporate to avoid illegitimacy. The authors continue to argue that the absence of this building block being incorporated in the organization makes it difficult to manage interdependencies. Consequently, the lack of exchange creates a difficult environment to operate successfully in. This could be one of the reasons behind the challenge of excessive pharmaceutical spending. Powell and DiMaggio (1991, p. 66) come with the same explanation: the organizational characteristics must adapt in the direction of environmental characteristics to survive and become successful. There are three mechanisms through which this isomorphic change

can occur: coercive, mimetic and normative (Powell and DiMaggio, 1991, p. 67-74).

### **Coercive Isomorphism**

The coercive isomorphism is the result of formal and informal pressures organizations experience by other organizations, which they are dependent on, and also the cultural expectations in the society they operate. We see this in our case where the FDA regulates organizations (i.e. pharmaceutical companies), and the changes they make (e.g. new guidelines in how to perform clinical trials) are a direct response to the drug agency's mandate. Meyer and Rowan (1977) have repeatedly stressed how organizations are increasingly homogenous in certain domains and organized around the rituals of conformity to wider institutions. This is not unique for the governmental arena. Sedlak (1981) describes how United Charities (an American charity trust), became homogenized the structures, methods and philosophies in order to adapt to the social service agencies that depended upon it. Also, the bigger size and scope of corporations make subsidiaries subject to standardized reporting mechanisms (Coser, Kadushin and Powell, 1982).

### **Mimetic Isomorphism**

Uncertainty is a force that encourages imitation. Operating in an environment that requires ambiguous goals in order to success, organizations tend to model themselves on other organizations (Powell and DiMaggio, 1991, p. 69). This mimetic response to uncertainty is a viable solution with little expense. The modeled organization is not always aware of the modeling and may sometimes not want to be copied. Westney (1987) gives an example of imitation when Japan in the late nineteenth century started its modernization by modeling new governmental initiatives on successful Western prototypes. This process, where the Japanese sent officers to study different institutions in different Western countries is today ironically used by American corporations in their efforts to implement Japanese models in order to improve productivity and personnel problems in their own firms. These developments also enhance their legitimacy as they try to adopt these "innovations". And the more reputable organization,

the more pressure felt to provide the programs other organizations offer. This shows how a skilled labor force or a broad customer base can lead to mimetic isomorphism.

### **Normative Isomorphism**

The last source of isomorphic organizational change is the normative. It stems mainly from professionalization. Professionals in general do have to compromise with nonprofessional regulators, clients, etc. Their complete futures are bound up with the fortunes of the organizations they are hired at (Hall, 1968). The professional power is assigned both by the state and the activities of the professions. Two mechanisms behind professionalization are of importance for the isomorphism. First one is the formal education and legitimation, a product by university specialists. Second one is the emergence and elaboration of professional networks, that cover organizations and across where new models can diffuse rapidly (Perrow, 1974). The filtering of personnel is an important source for normative isomorphism. This hiring process is highly selective and those who make it to the top are quite indistinguishable. An example is the findings of March and March (1977): All individuals that attained the position of school superintendent in Wisconsin, USA, had a background and orientation that made them inseparable regarding making further career advancement random and unpredictable. The same was the case for Fortune 500 board members studied by Hirsch and Whisler (1982). There seems to be an anticipation for individuals in any given organizational field to undergo a certain socialization that corresponds to common expectations regarding their personal behavior, appropriate style of dress, vocabularies used, etcetera (Cicourel 1970; Williamson 1975). The recruitment of similar type of people, tend to result in viewing problems from the same point of view, approaching decisions in similar way, and see the same policies (Kanter, 1977). Professionalization of management contributes to a commonly recognized hierarchy of status. With the designation of few large firms acting as key bargaining agents, and government recognition of these key organizations, give these actors legitimacy and visibility, which competing firms try to imitate with the hope of obtaining similar rewards (Useem, 1979). Thus, organizational fields with a large professionally trained

labor force are primarily driven by status competition. Lee (1971:51), for example noticed how hospital administrators were not concerned about efficient use of resources, but interested with status competition and parity in prestige.

Indeed the FDA has done major progress to become isomorphic, but in the rapid changing pharmaceutical environment, wrong elements which are legitimated externally may have been rationalized i.e. safety and efficacy area of drugs, rather than efficiency in general where cost-effectiveness of drugs is an example.

## **The Current Status in the Pharmaceutical Industry**

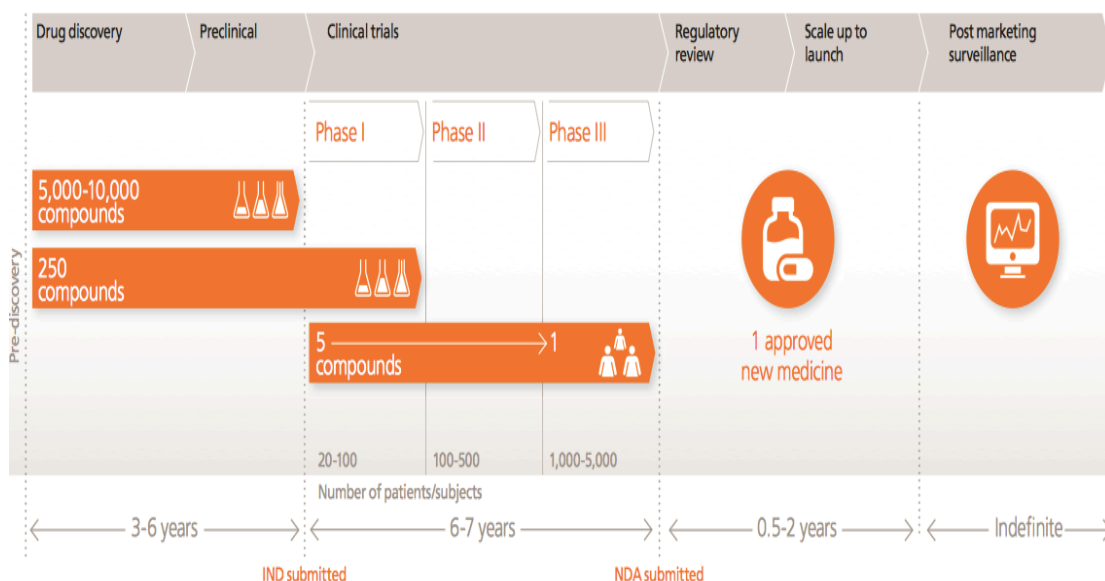
### **The Originators**

Looking specifically at the industry, we can divide the companies involved into two main subsectors: *originators* and *generic producers*. While originators products are developed through extensive research & development (R&D), clinical and sometimes post-marketing trials, and patented to protect the company's exclusive rights, the generic producers products are cheaper identical copies of originators drugs when they go off-patent (SelectUSA, 2013).

It is the originators that innovate new drugs for the market. Figures differ depending on source, but in general it takes 13-15 years (DiMasi, 1995) and costs an average of \$1 billion to develop a novel drug (DiMasi, Hansen and Grabowski, 2003). Figure 1 shows the timeline from the discovery of one potential drug candidate out of 5,000-10,000 tested compounds, to product launch. As a reward the company behind a novel drug can claim a much higher market price, so that they can compensate for the time and R&D-investments they have made.

However, the higher price is for a limited period of time. In the USA and EU the patent time is 20 years (subject to change) from the date of filing (FDA, 2012 and EGA, 2004) and as it expires any competitor is free to manufacture the same drug. This has, as we mentioned earlier, giving rise to pricing and reimbursement regulation to manage the staggering pharmaceutical costs for the payers.

**Figure 1.** Timeline from discovery to product launch for a successful drug (source: GlaxoSmithKline annual report 2012, p. 34).



### The Payers

Although the health insurance systems in the western European countries may differ, they are in general well developed and cover a great part of the citizens' pharmaceutical costs (Garattini, Cornago and De Compadri, 2007). The case is different in the USA where private health insurers cover differently (Berndt and Newhouse, 2010). As the pharmaceutical spending continues to grow worldwide (IFPMA, 2012), regulations are needed for the expenditure containment. As discussed earlier, reference pricing has been an effective way. At the same time, we do not see a decline in total expenditures. An aging world population and developing countries building well-functioning healthcare systems are two of the reasons. But the numbers of new drugs approved, which are an important factor in the increasing global spending, have declined. In fact, in 2012, the FDA approved 39 new drugs (including biologics), a 16 year high (C&EN, 2013). Also, we do need to include that the recent financial crisis has had a negative impact on the healthcare system and as a consequence on the pharmaceutical sector's revenue in the western world. Traditionally, the pharmaceutical sector has been less exposed during economic crisis, but is in this case not an exception (Behner, et al., 2009). This does however not change the fact that pharmaceuticals are not

just another typical product and dependent on the economic situation. The inelastic demand will continue to grow, as people need to take their medication continuously.

Because of the stricter pricing and reimbursement are set by national regulators where the expert panel views could be different, and the R&D activities are performed on a global level; the final outcome for a pharmaceutical product today is more unpredictable. The pricing and reimbursement model in each market of interest needs to be reviewed, as a novel drug could become a huge success in one country, but downgraded somewhere else. And this certainly affects the incentives of innovation.

### **The Drug Agencies**

To reach the market, a potential chemical or biological compound must be reviewed by drug agencies. Currently there are three national drug agencies of importance: The Food and Drug Administration (FDA), which is based in the USA; European Medicines Agency (EMA), the EU version of the FDA; Pharmaceuticals and Medical Agency (PAMD), the drug agency of Japan. The reason why these three authorities are the most influential ones is because of the fact that they together regulate the drug safety and efficacy aspect for markets that have a 63% share of the total pharmaceutical spending in the world (IFMPA, 2012). We will mainly be focusing on the FDA as the USA is the biggest pharmaceutical market, the FDA the oldest authority of the three mentioned, and the decisions made by them highly affect other markets. The agency has approximately 14,648 employees in 2013, where 10,534 are in the drug related field (FDA, 2013). The requested budget for 2013 was almost \$4.5 billion (FDA, 2013). The expertise area covers all aspects of a drug's safety and efficacy.

### **Changing Trend**

The major pharmaceutical companies, commonly known as Big Pharma, have the major share of the market. Their countries of origin vary, but are mostly localized to the western world. Some critics have compared the pharmaceutical market as an oligopoly and the reason for this can be referred to the huge costs,

the need for expertise in different fields, the time to develop new drugs, but also to mergers & acquisitions (M&A) the industry has experienced where multinational firms such as Wyeth and Schering-Plough have been acquired from different competitors and mergers have created AstraZeneca and Sanofi. This business condition makes it quite hard, if not impossible, for smaller companies to survive. The ten biggest pharmaceutical companies in the world are listed in table 2. Their accumulated revenues in 2012 were approximately \$414.7 billion. In this group we can see that the company that spent least percentage of annual revenues on R&D was Abbott Laboratories with 10.5%, while Johnson & Johnson spent most with 21.3% of its annual revenues.

**Table 2.** List of the top ten global pharmaceutical companies in 2012 (source: 2012 annual report of each company).

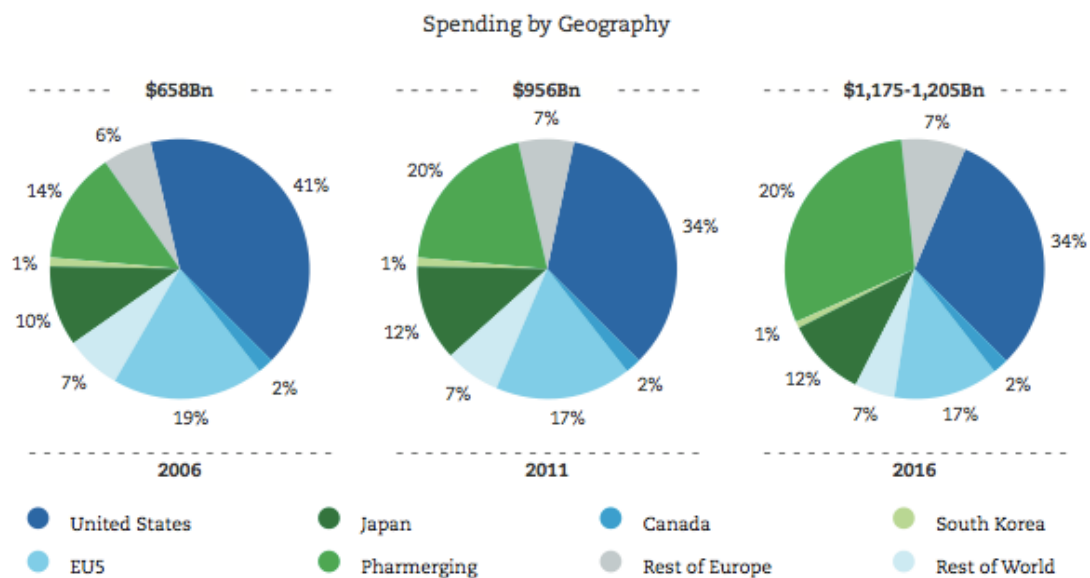
<b>Company Name and Origin</b>	<b>Revenues (billions of dollars)</b>	<b>Operating Profit (billions of dollars)</b>	<b>R&amp;D costs (billions of dollars)</b>	<b>R&amp;D costs (% of annual revenues)</b>
Johnson & Johnson (USA)	<b>67.2 (25.4)*</b>	<b>13.8</b>	<b>7.7 (5.4)*</b>	<b>11.5 (21.3)*</b>
Pfizer (USA)	<b>59.0</b>	<b>24.2</b>	<b>7.9</b>	<b>13.4</b>
Novartis (Switzerland)	<b>56.7</b>	<b>11.5</b>	<b>9.3</b>	<b>16.4</b>
Roche (Switzerland)	<b>47.8</b>	<b>14.8</b>	<b>8.9</b>	<b>18.6</b>
Merck (USA)	<b>47.3</b>	<b>8.74</b>	<b>7.9</b>	<b>16.7</b>
Sanofi (France)	<b>46.4</b>	<b>15.1</b>	<b>6.5</b>	<b>14.0</b>
GlaxoSmithKline (UK)	<b>39.9</b>	<b>12.5</b>	<b>5.3</b>	<b>13.2</b>
Abbot Laboratories (USA)	<b>39.9</b>	<b>8.8</b>	<b>4.2</b>	<b>10.5</b>
AstraZeneca (UK & Sweden)	<b>28.0</b>	<b>8.15</b>	<b>5.2</b>	<b>18.6</b>
Bayer HealthCare (Germany)	<b>24.3</b>	<b>4.2</b>	<b>4.0</b>	<b>16.5</b>



\*The numbers in brackets are for the pharmaceutical segment as Johnson & Johnson manufactures mainly non-pharmaceutical products but is still considered as the biggest pharmaceutical company in the world.

In 2011 the global pharmaceutical spending was \$956 billion, a 45% increase from 2006 (IFPMA, 2012). It is predicted to continue to grow and reach \$1,175-1,205 billion by 2016 due to an increased demand from the leading emerging countries (figure 2). The branded, patent protected products, which are the main income source for the research-based pharmaceutical companies, accounted for two-thirds of 2011's total market value.

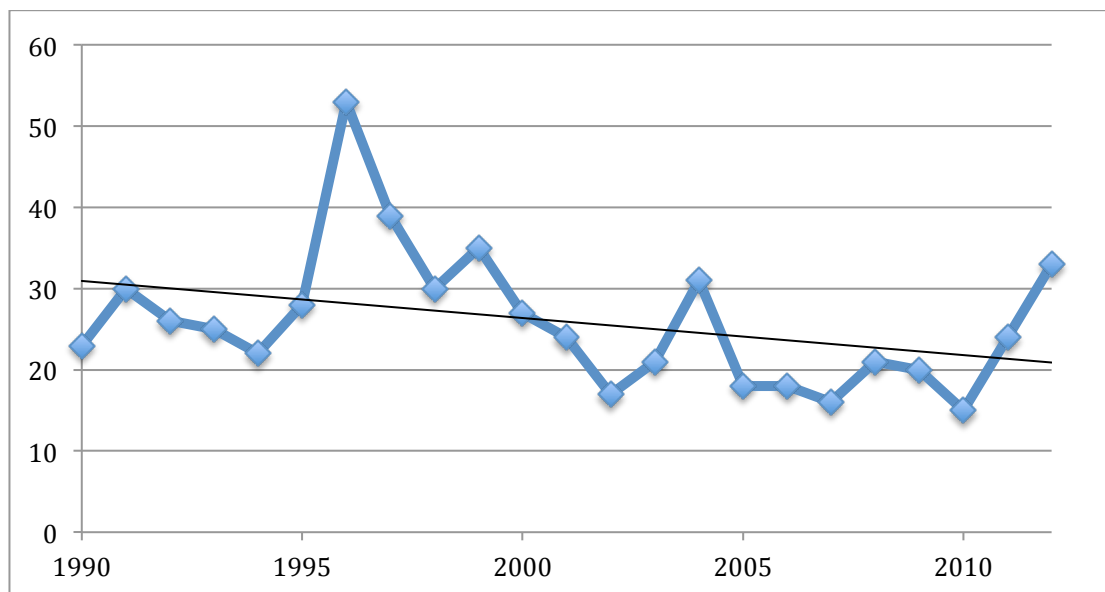
**Figure 2.** The global pharmaceutical spending in 2006, 2011 and 2016 outlook (source: IFPMA facts and figures 2012, p. 52).



Looking at the number of new molecular entities (NME) approved by FDA's Center for Drug Evaluation and Research (CDER) from 1990 to 2012, we can clearly see a downward trend in the last 22 years (figure 3), which has repeatedly been issued as one of the main challenges for the industry. Given the fact that a patent protected drug has the potential to become a blockbuster and generate billions of dollars in annual revenues for the pharmaceutical company shows how critical innovation is for the survival of the research-based companies. As fewer drugs are entering the market, several blockbusters have

lost their patents or are facing a near in the future patent loss. Pfizer, for example saw the patent expire for their cholesterol-reducing drug Lipitor®, the best-selling drug in the history of pharmaceuticals. In 2011, which was the final year with patent protection in the USA (it had lost its patent in a few other countries a year before), the drug accounted for approximately 14% of Pfizer’s total revenues (Pfizer, 2012). With \$125 billion in total sales before generic market entry, the exclusivity loss had a significant impact on the company. Due to generics cost at least 20-70% less in most markets (FTC, 2012), the branded product’s sales drop drastically.

**Figure 3.** NMEs approved between 1990-2012 (biologics excluded) by FDA (source: FDA’s summary of New Drug Application Approvals & Receipts).



Pfizer is not an exception in this case. From 2011 to 2020, 26 of the top 50 selling pharmaceutical products in the world (EvaluatePharma, 2012) have or are expected generic competition (Medco, 2011). Together they accounted for approximately \$121 billion in annual worldwide sales i.e. 12.6% of 2011’s total pharmaceutical spending. New products will enter the market and replace them, but to which degree is uncertain as the industry experience, as mentioned before, lower R&D productivity and more unwillingness from the payers to reimburse.

Germany, Europe's biggest pharmaceutical spender, had a generous free pricing market between 1996 to 2009, but joined other Western European countries in the stricter approach of pricing and reimbursement, with no thoughts of returning to the previous system (Henschke, Sundmacher and Busse, 2012). The objective of the generous pricing was to encourage R&D productivity so more promising drug candidates would enter the market without the risk of having their value downgraded during the development process. This idea of excluding patented pharmaceuticals from price regulation, led eventually to the launch of several me-too drugs that did not have any clear additional value in the safety or efficacy aspect, but a higher price label for a similar, already existing product (Henschke, Sundmacher and Busse, 2012). While in most cases similar, some of the me-too drugs have shown significant superior properties compared to competitors' products. Pfizer's Lipitor®, mentioned earlier, is one example. Not being the first drug approved market authorization in that particular therapeutic cluster; it suddenly became the drug of choice for its indication. Thus me-too drugs being rejected in an early stage may sometimes be a huge loss for the sector's stakeholders, but encouraged by the payers, which we will discuss in the next section.

### **Investigating The Pipelines**

To further understand how today's trend is among the aforementioned pharmaceutical companies; a review of their current drug pipelines was made. Abbott Laboratories was not included in the review due to lack of reliable source for their R&D product pipeline. The results are shown in table 3. As can be seen, the top five therapeutic areas of choice by the investigated firms are oncology, followed by central nervous system (CNS), immunology-inflammation, respiratory and vaccines. Rare diseases, which were previously neglected in the industry, considered costly, risky and mostly non-profitable, have currently 14 R&D-projects. Companies invested heavily in the cardiovascular area during the 90's, but the interest has decreased as other diseases and difficulties have changed the path for R&D-investments. The characteristics of the drugs have definitely changed, which do not come as a surprise when the industry tries to adapt to new conditions and demands. Specific targets are chosen and the

presence of me-too drugs is limited for example. These changes correctly provide the market a higher potential of new breakthrough medicines. However, the outcome of these new products, such as availability, shortage of other drugs and payers willingness to reimburse would show a better proof of correct management by the stakeholders or just a temporary solution.

**Table 3.** An estimate of current drug pipeline for nine of the biggest pharmaceutical companies (Abbott Laboratories excluded) in the world (source: drug pipeline of each company in December 2013 according to statements on their websites).

<b>Therapeutic Area</b>	<b>Number of Projects</b>
<b>Oncology</b>	184
<b>CNS</b>	58
<b>Immunology-inflammation</b>	53
<b>Respiratory</b>	49
<b>Vaccines</b>	42
<b>Cardiovascular/Hematology</b>	37
<b>Anti-infective</b>	35
<b>Diabetes</b>	18
<b>Rare Diseases</b>	14
<b>Ophthalmic</b>	9
<b>Hormone-control</b>	9
<b>Metabolism</b>	6
<b>Muscular-skeletal</b>	5
<b>Genitourinary</b>	4
<b>Renal</b>	3
<b>Obesity</b>	3
<b>Gastro-intestinal</b>	1

## Method

To understand how the FDA could influence the ongoing trend from their point of view, interviews were made with current FDA employees. Five persons in total were interviewed. Due to the FDA is based in Bethesda, MD, USA; it was impossible to do face-to-face interviews. Neither was it possible to do voice-over IP (e.g. Skype) interviews as too many of them had heavy schedules.

It is in our interest to see on which level the organization's awareness about pricing and reimbursement impact and the character of the new drug application (NDA) they receive and process is, from its own employees' perspective.

A primarily qualitative research approach (Silverman, 2001) was used to gain in-depth insights into the specific problem, but also a way of generating ideas for future research. In this way, we avoided and did not downplay statistical techniques (Silverman, 2001). A survey with mostly open-ended questions was sent thru e-mail to the employees, which they had approximately two weeks to answer (Dec 17 – Jan 2). If the answers were perceived as incomplete, i.e. misunderstanding of the question had occurred, s/he was contacted again for further explanations so the answer(s) would be correctly answered. By using a qualitative approach, the underlying factors would be identified (Silverman 2001). The number of interviewees was another reason the qualitative method was chosen over the quantitative. According to Silverman (2001), qualitative research's interview method consists of open-ended questions to small samples. Because of the nature of the questions, which potentially could produce answers in conflict with the employer's, all the respondents were guaranteed anonymity.

Due to the interview is web-based, the method does not allow one to understand the organization of talk and body movements (Silverman, 2001, p. 19). It makes it also difficult to add follow-up questions to some answers that may be spontaneous, which is hard to see in the absence of a face-to-face interview (Silverman, 2001, p. 19). However, a positive aspect is that it limits the interviewer to lead the interviewees in a desired direction that would bring a

subjective, rather than an objective view (Johnson, 2014). The subject could, as mentioned before, be viewed as sensitive for the respondents. By having a web-based survey the view of human behavior was avoided (Johnson, 2014), which could have caused inconvenience. The research ethic of guarantee of anonymity could give the employees a fair opportunity to answer as honest as possible (Decision Analyst, 2014). Furthermore, the answers written are each respondent's own opinion and should not be seen as official FDA statements by the reader.

A few background questions (see appendix) were given to the interviewees, such as gender, age, education background, role and years in the FDA. This made it possible to distinguish or link the employees' opinions if certain trends were shown in the results. Later in the analysis and discussion sections, the current literature and the nine pharmaceutical companies' drug pipelines are compared with the respondents' opinions and ideas.

After all five interviewees had responded to the questions, patterns in the produced answers, but also any differences and similarities between the respondents were observed.

## **Empirical Data**

All five interviewees are employed at the CDER division of the FDA. Their main role is to review and evaluate data for drug approval, submitted by pharmaceutical companies. Their strong educational background, with Ph.Ds. in relevant field also shows how competent the agency's employees are. Their experience within the FDA spans from 1 year to 5 years, together a total of 12 years. They have also had previous interaction in their careers with the pharmaceutical industry and regulatory agencies, prior to the FDA.

Unfortunately, one of the respondents did not provide full answers to most of the questions. The main reason was his official position in FDA, but also lack of knowledge. Although the survey was designed to minimize suspiciousness and

create comfort, the nature of the questions could be perceived as sensitive, thus this did not come as a surprise.

When asked what they think can be underlying factors behind the changes in the industry, two of the respondents mentioned the evolving science. Three of them, explained the profit driven phenomena the companies have to follow which appear in different shapes; biologic drugs that are hard to make generic of; outsourcing to developing countries such as China and India; development costs and limited R&D breakthroughs. The explanation to why the drugs today differ from the ones that were introduced 10-20 years ago is that the industry focuses on different therapeutic areas from time to time; therapies for harder targets are being developed (i.e. more biologic, individualized and pediatric drugs). None of them saw differences with previous and current drugs with respect to the safety and efficacy issues.

Three of the employees were able to respond to the question about the financial model (i.e. the agency is financed partly by user fees) and how it may affect the organization. Overall they did not see any conflict of interest. In the follow-up question, which asked for their opinion regarding the relationship between the agency and the industry, the responses could be summarized with the words cooperative, coexistence and co-development.

The recent switch from blockbuster drugs to drugs targeting small populations that cost multifold more and the consequences this may have for the stakeholders, was apparent among three of the respondents, but also understandable. According to them, the drug price per capita for the orphan products is still comparable with blockbuster drugs, and the public must understand that the industry is not a charity organization. This may lead to limited access to such extremely expensive drugs, but in fact a better scenario than if they would never had been developed. Additionally, although the FDA cannot regulate the price directly, they actively work to reduce the costs for these drugs in their own way, e.g. by speeding up the review time and waive the user fee.

On the question if the agency should, except the drug and safety, also consider the cost of the product when reviewing new drug applications, none of the respondents agreed with that. FDA manage the scientific part of the drug development, but can affect the financial part, as mentioned previously, by extending exclusivity rights, user fee etc. One of the respondents underlined the fact that any drug can be approved as long as it is safe and effective, not taking into account the price tag of the product.

Further, when the interviewees were asked about their thoughts on the lack of innovation and increased global pharmaceutical spending being unsustainable for the market, and FDA's role in this issue, some interesting answers were given. Three of the respondents said that the FDA has taken initiatives that may eventually evade this problem, which also is the agency's main mission. One respondent claimed that the presumption was false, due to that generic drugs occupy 80% of the market, and the financial part is determined by politics, not by the agency. Another respondent explained how FDA is at the end of the drug development pipeline; how government should not regulate the economic part, but let the market take care of it. The need for science progress was also, and obviously, of importance.

When asked if they saw any link between the increasing global pricing and reimbursement regulations affecting the drug innovation, the opinions varied. One answered that it was a question for the payers. Two other answers were given, where the first one claimed that the companies' revenues had not declined and the pipeline problems could be referred to changing science. The second answer brought up the fact that the whole business is highly risky, with long cycles but also high return. With less return, the industry would face less investment.

In one question, the current product pipeline (table 3) was exemplified and the interviewees were asked what could be behind this trend, looking at the key stakeholders. Interestingly, one respondent's simple answer was the business



model the pharmaceutical industry is based on i.e. unmet medical need that need to be filled by sufficiently evolved science and an existing market. Another respondent also came across the unmet medical need and market part, but also explained the scientific part in terms of difficulties in current available treatments and success rate. Two other respondents also mentioned the important role of the market. One of them pointed at the fact that the agency has beneficial regulation roles for tropical diseases such as malaria, but as the market is almost non-existent in the U.S. and western world in general, they do not receive any submissions for this certain disease, and confirms that the FDA has limited impact on the companies' preferences.

Only two of the respondents answered on the question regarding the increasing issue of drug shortages, especially of older generic drugs. One answered instantly on profit and the low interest on manufacturing drugs where the profit is low and the competition high. The second respondent mentioned that the FDA is taking steps to regulate this problem. The industry is for example obligated to inform the agency if they have plans to change their product line or decrease the production of a specific product. Thereby the FDA can proactively prevent drug shortages.

In the final question, where the interviewees were asked about their ideas and suggestions on how the FDA could improve the innovation climate in the industry, two respondents underlined that the FDA promotes and welcomes a climate of innovation for the whole industry. One respondent specifically issued the safety challenge as the most costly and low-efficient part in the drug development process. He suggests that if the agency lowered the safety bar upon approval and moved the main part to post-market, the result could eventually accelerate drug innovation and development.

## **Analysis**

Throughout the answers, the scientific focus is clearly obvious. The FDA is highly specialized in this field. Hirsch and Whisler (1982) and March and March (1977) studies showed how the hiring process in some organizations ended with the

recruitment of people that were indistinguishable. The more top-level the less separable were the candidates, which was typical for normative isomorphism. The adaptation to the changing market rules have been challenging as could be read in the literature overview. Changing science and harder targets are two reasons why, which the respondents and the literature both referred to. Looking at the increasing global pharmaceutical spending, the majority of the respondents gave a clear answer that the agency is working towards a more sustainable structure, i.e. more isomorphism. The statement from one respondent that generic drugs have 80% stands in conflict with the literature that states that branded products accounted for nearly two-thirds of the global market in 2011 (IFPMA, 2012). He may have referred to the local U.S., and not the global market.

Lack of innovation being a main challenge comes repeatedly in mind for the interviewees. One employee opposed the fact of the falling trend in revenues for the companies, which they compensate with e.g. M&A and cutting staff. The R&D-investments as percentage of annual sales are currently unchanged but could as another respondent underlined, that a decline in revenues would eventually lead to less investment, hence less innovation. The answers on the question of drug shortage were consistent with Jensen and Rappaport (2010) article about the low priority of older generic drugs and the increasing profit driven thinking. Further, regarding the formal structure, none of the employees agreed on FDA taking a bigger responsibility in influencing a healthy price level of the drugs, thus become more isomorphic to its environment.

The respondents explained the current product pipeline as a result of the market. The high success rate, unmet medical need and difficulties in current available treatments were all reasons for the companies focused therapeutic areas. Friederiszick, et al. (2009) also came up with this conclusion. The profit driven phenomena leading to R&D investments in diseases that affect small populations compared to 10-20 years ago when the industry's R&D investments were in the psychiatric and cardiovascular diseases, show how the cycle changes from time to time, where regulations for example orphan drugs (Reaves, 2003)

may have been involved to influence. Still the drug price per capita is quite the same between the cheaper blockbuster drugs and the expensive specialized drugs, which one of the interviewees was concerned about that it could lead to limited access.

Cost-effectiveness studies have been suggested to improve the management of drug innovation and spending issues that the sector is suffering from. There were no suggestions of this by the respondents. However, one employee had an idea of decreasing the safety bar, which eventually would decrease the cost of the development cost significantly.

## **Discussion**

Meyer and Rowan (1977) repeatedly mention how important it is with isomorphism for organizations success and survival. They also mention that powerful organizations force their relational networks to adapt to their structures and relations. The pharmaceutical industry, as well as the FDA are both well known for having huge influence on their environment. The respondents described the relationship in positive terms although the never-ending debate on who influence whom the most continues. Some critics say that the industry has the edge; given the fact that 42% of CDER was financed by industry fees in 2007 (Stone, 2012), with no signs of decreasing. Phillips and Zuckerman (2001) argued about high-status players being able to deviate from the norm thanks to reputational capital. But at the same time, the FDA is considered as much more transparent organization than the pharmaceutical companies. Powell and DiMaggio (1991, p. 74) argue that organizations can greatly resist the demands of organizations that they are not dependent on. This can be one of the reasons to why a clear isomorphic change has not been noticed in an independent organization as the FDA, although the market rules have changed drastically. The two authors continue with the hypothesis that when the relationship between means and ends is uncertain, the more an organization will model itself after organizations that it considers as successful. This can be an explanation to why pharmaceutical companies put their R&D budgets on certain therapeutic areas from time to time. This mimetic trend also limits the number of

targets for the benefit of the patient, but as a profit driven industry, it is almost impossible to influence the preferences. More regulations can be a solution to manage this problem, but it would eventually lead to less return and an ineffective incentive for continuous innovation.

Powell and DiMaggio (1991, p. 76) also write about how more interactions between organization and agencies of the state could result in increased isomorphism in the field as a whole. Here we see again the need for better communication between the main actors in the sector. As for now, it is quite hard to say which part, the agency, or the industry, is submitting and becoming isomorphic to the other part.

Previous research covering the specific link discussed is limited, in spite of the fact that it may have a critical role in spending and the number and characteristics of drugs launched in the future market, partial explanations behind the trend can be found in current literature. Kanavos and Reinhardt (2003) discuss how policymakers, by subjecting similar products (the so called me-too drugs) to pricing pressure from reference pricing, they can shift the R&D-investments made by the pharmaceutical companies to more useful innovative drugs. Thereby safety and efficacy are not the only aspects concerned when reviewing a new product for the stakeholders, but also clinical and cost effectiveness are included in the social rate of return.

To innovate pharmaceuticals, not just of financial importance for its owner, but also for public interest, can by viewers be seen as a win-win situation. In the past, the industry had a strong focus on developing drugs in the same therapeutic cluster, as they had a high potential to become blockbusters and well received by the payers (E.CA Compact, 2012). As the rules have changed, drug manufacturers have for example been encouraged to innovate orphan drugs used to treat rare diseases (Reaves, 2003). But at the same time, more and more reports regarding drug shortage of off-patent substances give a hint of the consequences of price regulations. Jensen and Rappaport (2010) discuss the sudden shortage of the drug propofol, a fast-onset, shortacting, sedative-

hypnotic agent that healthcare professionals have come to rely on as standard of care. Propofol is an off-patent drug that has been on the market for years. There are a limited number of manufacturers of this product due to complexity in the production process. However, the low profit margin could be a more causing factor than the two previously mentioned as pharmaceutical companies may favor newer, more profitable products in their production lines. This dilemma, where well-proven and relatively cheap, traditional drugs sometimes have a lower priority among the manufacturers, and which drug regulatory agencies arguably cannot affect strongly, shows how harmful drug shortage can be for the healthcare system. As discussed earlier, new drugs enjoy patent protection for a certain time. During this time the company behind the drug must be compensated for all the R&D costs made. Price regulations may therefore be an effective way for the payers to keep the expenditure within a healthy range and still promote innovation. There are however different views regarding this subject. In a study of the German market, Henschke, Sundmacher and Busse (2012), described how the 2011 Act for Restructuring the Pharmaceutical Market in Statutory Health Insurance (AMNOG) created pharmaceutical cost containment and an expected €2 billion in health insurance cost savings. Prior to that, the manufacturer set the patented drug's price. The purpose of the act was to negotiate (i.e. regulate) the price that reflects the additional benefit of the pharmaceutical compared to the appropriate competitor. Although applied in several European countries as Germany is used as a reference for pharmaceutical price setting, Abbott (1994) questions this type of price regulation for being effective. The main conflict it may cause is the introductory price, which Henschke, Sundmacher and Busse (2012) also mentioned briefly. Here, Abbott clearly showed how pharmaceutical companies in a regulated market launch prices 50% higher than in an unregulated market. After seven years the unregulated price exceeds the regulated. The overall result depends on the social and corporate discount rates, thus making the question of pricing even more complex. Abbott also wrote how price and reimbursement regulation in general provides the incentive to produce efficiently, which in this case would result in more useful innovative drugs. However, he underlines that this is more realistic in stable markets where both the cost and the demand are constant over

time, which is contrary to the pharmaceutical market with high and volatile demand (e.g. pandemics) and short product life cycles.

Friederiszick, et al. (2009), get close on pricing and reimbursement regulation versus innovation. They see a trend where the health authorities are moving to cost-effectiveness considerations rather than the cost-cutting policies they previously had. With this regulatory system the R&D direction of the pharmaceutical firms would likely be to first-in-class drugs as they have the potential of becoming highly recognized. As a consequence, firms would cancel projects where they see the risk of ending up as a later-in-class drug. Because of this, the diversity within certain future classes could be limited until generic competition is allowed. This is probably the case for markets that apply IRP. Looking at EBP, they see the risk of not launching new products in countries with low willingness to pay and focusing R&D investments on countries with high willingness to pay as the return would most likely be significantly higher. Regarding value-based pricing, pharmacoeconomic assessment may be viewed as the most fair method of pricing and reimbursement, but difficulties arise on how to measure the benefits generated to the society at large, and not only to individual users. Furthermore, the shifting innovation model to more tailored drugs (i.e. drugs that treat rare diseases or only a part of the population suffering from a disease) has indeed been a result of decreasing returns and to some degree difficulty to discover new drugs that target large and heterogeneous primary care patients. But these so called personalized drugs can cost several hundreds of thousand dollars per treated patient and year compared to perhaps a couple of thousand of dollars for the ones that are for primary care patients. The R&D spending is still high for drugs aimed for small patient populations and therefore the price will be considerably higher for the product.

The cost-effectiveness importance has made firms conducting pharmacoeconomic studies on their products. To eliminate the risk of bias and ensure substantial evidence for claims, the FDA has drafted guidelines for such practices, but in reality there are no standards for valuing health benefits. Usually, the perspective of the user decides whether or not a drug is cost-effective.

Historically being an organization overseeing drugs' safety and efficacy, Neumann, Zinner and Paltiel (1996) criticize the agency's lack of competence in the area of cost-effectiveness and consequently how they manage it. The authors mention an example of a drug that was over 700% more expensive than its competitor's, but reduced the risk of mortality with only 1%. Still it had 70% of the market share. There is another example of a drug with an initial price tag 4900% higher than an alternative that has been compounded by pharmacies for years (Gleason, 2013). Although the company lowered the price and eventually filed for bankruptcy, it raises question marks on how it was allowed market entry and potentially create uncertainty among physicians on which drug they should prescribe.

Additionally, a recently published article (Sullivan, et al., 2011) discusses how cancer care costs grow and why affordability, but also accessibility and value should be confronted. This report brings back the issue of old, well-proven, but not so profitable drugs being phased out for the benefit of newer, multifold expensive drugs.

The suspiciousness that exists especially between the drug regulatory agency and the companies does not facilitate the problems with innovation and spending. The struggle between the formal structure of the FDA, with an intrinsic unwillingness to adapt too much to the environment, thus increase the cooperation, overseeing an industry with profit driven companies that not always have the patient's health as main interest, continues. One can wonder how the reaction would be if the FDA one day took into consideration the price of a new drug that would be 90% as good as the safest and most effective one in the current market (i.e. first line treatment), but only 10% of the cost?

## **Conclusion and Future Research**

This thesis has tried to investigate how the need of better management of pharmaceutical spending and drug innovation, probably is being partly limited by the formal structure of a highly respected and influential drug regulatory. In an extremely complex and internationalized business, challenges arise

continuously. Once seen as an industry with a prosperous future, the results of the mismanagement have gradually become inevitable. There is a high awareness of this issue, but as there is no certain source causing this problem, no concrete solutions can be found. It can clearly be observed that the agency has rigidity, mostly created from institutionalization of their traditional responsibilities in the drug and safety area. The key question asked if a link can be seen between the formal structure of the organization and pharmaceutical spending and drug innovation character. While it has been underlined that there are several factors behind the challenges in this specific sector, it cannot be boldly to partly put some of the criticism on the FDA. A flexible, isomorphic and more rapid approach to the changing environment could definitely create a better business environment for Big Pharma and the rest of the companies in the pharmaceutical industry.

Future researches need to be done. Although the field that has been investigated in this work has limited literature, it is definitely of interest for the stakeholders and more data within this area would certainly improve the management of a sustainable pharmaceutical market.



## **Acknowledgements**

The author is truly indebted to all five employees at the Food and Drug Administration's Center for Drug Evaluation and Research, Bethesda, MD, USA, for their invaluable contributions. Without them, and especially one of them, this work would never have been accomplished. Thank you also to the supervisor Richard Nakamura, Ph.D., at School of Business, Economics and Law, University of Gothenburg, for guidance.

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# Appendix

## *Interview questions*

### **1. Age**

If you do not want to specify age, please type in an age interval e.g. 30-39, 40-49 etc.

### **2. Gender**

### **3. What is your education background?**

Please specify, e.g. PhD in pharmacology, MSc in Chemistry etc.

### **4. What is your role/title in the agency?**

### **5. How many years have you worked in the FDA?**

### **6. The pharmaceutical industry has seen several changes in the last couple of years. What underlying factors do you think are behind these changes?**

### **7. How do you think the current financial model (PDUFA) for parts of the agency is perceived by the public?**

### **8. In your opinion, what is the nature of the relationship between the Agency and the regulated industry?**

### **9. In your opinion, are there any differences in the types of drugs that are being approved now, 10, and 20 years ago?**

### **10. Currently companies have switched from developing “blockbuster” products to niche products targeting small populations. The cost for such products are often multifold higher compared to products aimed toward**

**larger patient populations. In your opinion, what are the major issues with increased cost for such products for patients, doctors, and insurance institutions (government or private)?**

**11. Do you feel that the agency should consider the cost of the product when reviewing new drug applications?**

**12. The pharmaceutical market experience increased spending because of aging population and developing countries investing in their healthcare systems. But at the same time fewer drugs are granted market entry. There have been discussions how this trend is not sustainable. What changes do you think are needed for a more effective sector regarding innovation and cost containment? Do you think FDA could contribute to a more sustainable development?**

**13. How would you say the increasing global pricing & reimbursement regulations affect the drug innovation for the research-based pharmaceutical companies? Could they be linked in your opinion?**

**14. Looking at the current drug pipeline in nine of the biggest pharmaceutical companies, we can see that the therapeutic areas targeted are 1. Oncology 2. CNS 3. Immunology-inflammation 4. Respiratory 5. Vaccines. Which factors do you think could be behind this trend looking at the key stakeholders e.g. the innovating pharmaceutical companies and the regulatory agencies?**

**15. Drug-shortages have repeatedly been reported, especially on older generic drugs. Why has this problem become recurring in this highly regulated area covered by the FDA?**

**16. Finally, having answered the previous questions, do you have any ideas/suggestions on how the FDA could improve the innovation climate in the pharmaceutical industry?**