Open Innovation in Pharmaceutical Industry: A case study of Eli Lilly

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Abstract

Open Innovation paradigm has been a phenomenon of increasing interest in the last two decades, especially since Henry Chesbrough coined this term in 2003, triggering the creation of a new whole body of knowledge. However, all this research work could not come up with a standardized, all-in-one theory. Instead, we find a heterogeneous series of models that cope with different aspects and fit into specific contexts and industries. Among these empirical experiences of Open Innovation, we find the pharmaceutical industry. The shift to Open Innovation in this industry presents several particularities, like the need to overcome the current productivity crisis as driver for change, or the R&D-intensive nature of the industry. In this scenario of urgency, the lack of a well-established theoretical model on Open Innovation makes difficult the task of implementing this paradigm.

In this research work, we explore in detail the process of adoption of Open Innovation in the pharmaceutical industry through a case study, and analyze the empirical findings by framing it inside the current theoretical framework. Through this analysis, we aim to highlight generalizable patterns, and specific elements from the current body of knowledge. These highlights might serve as input for the creation of a unified model of Open Innovation.

Keywords: Open Innovation, Pharmaceutical Industry, Drug Discovery, Big Pharma, Crowdsourcing, Open Source drug discovery.

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List of Abbreviation

CRO	Contract Research Organization
CSR	Corporate Social Responsibility
FIPCo	Fully Integrated Pharmaceutical Company
FIPNet	Fully Integrated Pharmaceutical Network
IMI	Innovative Medicines Initiative
IP	Intellectual Property
L2POC	Lean To Proof Of Concept
M&A	Merger and Acquisition
MDR	TB-Multidrug-resistant Tuberculosis
NME	New Molecular Entity
NCE	New Chemical Entity
NBE	New Biotech Entity
OI	Open Innovation
PD2	Phenotypic Drug Discovery
POC	Proof Of Concept
POS	Probability Of Success of drug development process
PPP	Public Private Partnership
p(TS)	Probability of Technical Success
R&D	Research & Development
SDK	Software Development Kit
SME	Small-Medium Enterprise
TBDA	Tuberculosis Drug Accelerator
TBDDI	Tuberculosis Drug Discovery Initiative
TD2	Target Drug Discovery
TSS	Technical and Scientific Services
WHO	World Health Organization
WIP	Work In Progress

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1. Introduction

Pharmaceutical industry is a highly innovation driven industry which throughout its history has contributed to the well-being of the humans by providing new medicines to address various diseases and have grown into one of the major sectors in the world. The global pharmaceutical industry is currently worth US$ 300 billion with few drug companies controlling almost one third of the market (World Health Organization, 2015). These few companies termed as the “Big pharma” have been thriving in the market by investing in R&D and commercialization of high value “blockbuster drugs”. A pharmaceutical company can be called as a Big Pharma based upon four criteria, namely the sales per year which should be above 2 billion USD, international presence which includes presence in USA, Europe and Japan, involvement in several therapeutic areas with R&D and marketing in at least five different therapeutic areas and an establishment of fully integrated pharmaceutical operations including internal R&D, manufacturing, clinical trials, regulatory, marketing and sales (Hedner, 2012).

However in the past decade the industry has faced and continuing to face several challenges in terms of patent expiration resulting in huge revenue loss, increasing R&D cost for new drug development, declining R&D productivity, growing competition from generic drug manufacturer, changes in the marketing climate with cost-constrained healthcare systems and rising customer expectation for new, cheaper and more effective therapeutic drugs. The model of innovation which was in practice in the past decade where the innovative activities were predominantly carried out in-house was claimed to be a broken model as the sustainability of the industry was under question (FierceBiotech, 2011). The Big pharmas have been working on several strategies to combat the challenges. Some of the major steps taken by them are by restructuring their innovation model. They are pursuing merger and acquisition, joint ventures, partnership, collaborative research with academia, Biotech companies, CROs and other smaller pharmaceutical companies. In the past decade the innovation model in the industry has evolved from an integrated one to collaborative to more open and networked model (Sadat et al, 2014).

In the open and networked model the boundaries between all the actors along the pharmaceutical innovation value chain becomes more porous where every contact is treated as a potential part of the innovation ecosystem. Studies reveal that there has been a growing trend in the industry towards Open Innovation (Khanna, 2012). Several Big Pharmas have also openly stated that they have or will move towards Open Innovation (OI, from now) but where along the innovation continuum it is being effectively adopted and by whom is a subject of ongoing research (Michelino et al, 2014) . However there have been a number of challenges with respect to the adoption of OI like IP management, Standardization of the process, Management difficulties with respect to virtually dispersed R&D, incentivization, lack of leadership, governance, technical do-ability, loss of architectural knowledge (Lowman et al, 2012). OI also poses a need for cultural change within the organization and alignment of the overall business strategy with the OI process. Firms should also rethink their business model and also have the ability to choose the right collaborations.

The concept of OI was established recently (2003) by Henry Chesbrough and lot of studies have been conducted to identify its various elements in different industries. Although certain elements of OI has been in practice in the Pharmaceutical industry in

various forms for a long time it has not been until recently that the concept is extensively studied specifically to this industry and there are a lot of ongoing research to establish a theoretical framework for OI in pharmaceutical industry. The pharmaceutical industry is a complex industry which involves several actors who practice OI at different levels. It would be interesting to understand the phenomenon from the perspective of the Big Pharmas since they are the main drivers of change in the innovation ecosystem of the industry, leading us to the goal of this paper.

1.1. Research Question

OI seems to be gaining a steady ground and recognition in most of the industries these days. In particular Big pharmas, owing to the crisis in the industry, are resorting to new strategies to keep up their growth and innovativeness with OI being one of them. Studying OI strategies of a particular Big Pharma in detail can provide valuable insights to other companies within the industry who wants to adopt the same approach with minimum risks. Further classifying them under the general OI paradigms or practices will add knowledge to the existing literature on OI. Hence our research question is as follows,

How do Big Pharmas implement OI?–A Critical analysis of the current OI practices through a case study.

1.2. Scope

The scope of the study is to examine some of the OI initiatives undertaken by a Big Pharma called Eli Lilly (referred also as Lilly, in this document) in the recent times. The research is constructed around the critical analysis and classification of the initiatives by Lilly under various new OI paradigms identified. We have limited our analysis to the drug discovery and development phase of the value chain in the Big Pharmas.

1.3. Outline

We first start with the literature review wherein we are trying to understand the concepts of OI. We provide the definition of OI and identify the various models of OI. We then try to understand the triggers and benefits of OI in general. We then continue our literature review to the pharmaceutical industry. We provide some insight on the Industry through some history, by explaining the current crisis in the industry and the ways adopted by Big Pharmas to combat the crisis. We then explain the importance of OI to Big Pharmas and the existing framework of OI in the pharmaceutical industry. The literature review is followed by the case study of a Big Pharma, Eli Lilly, and its OI practices followed by the analysis of the case study and conclusion.

2. Literature Review

In this chapter, we carry out a deep review of the existing knowledge related with the research question in order to provide the necessary background as a departing point for our discussion.

2.1. Open Innovation

The term “Open Innovation” was coined by Professor Henry Chesbrough, referring to the need for firms to adapt to a fast-changing environment, increasing competition and specialization of firms, among other factors. To face these challenges, OI is defined as “a paradigm that assumes that firms can and should use external ideas as well as internal ideas, and internal and external paths to market, as the firms look to advance their technology” (Chesbrough, 2003). Firms achieve this by commercializing “both its internal ideas and external ones from other companies, and search for ways to put their ideas on the market through the development of different routes that are not a part of its usual business” (Chesbrough, 2003). In other words, OI can be defined as “the use of purposive inflows and outflows of knowledge to accelerate internal innovation and expand the markets for external use of innovation, respectively.” (Chesbrough et al., 2006). It is important to note that OI is not a strategy of working with external parties; instead, it is about leveraging internal R&D. OI encourages companies to expand their pool of resources in order to achieve their growth objectives.

Triggers for OI: As briefly said before, there is a series of factors that may have pushed companies to shift their practices to OI. They are;

- The growing mobility of skilled professionals; meaning staffs are no more attached to a single company in a long term relationship and the labor market is becoming much more dynamic with employees changing location and roles more often (Chesbrough 2003; Gassman & Enkel 2004). This makes it difficult for a firm to maintain its core-competencies, as the staffs leaving will take the knowledge with them. As a result, large amount of knowledge now exists outside the boundaries of the firm. This fact encourages firms to open to the outside, tapping into the pool of external resources to maintain competencies and acquire new ones.
- The rise of venture capital funding: It is incentivizing the creation and development of new firms and startups. It also triggers consequences like restructuration of industries, increases in competition, shifts in the market share, etc. (Chesbrough, 2003). Specifically, these new entrants play an important role in what comes to innovation, as they often enter the market using highly innovative, disruptive products (Christensen, 2013).
- Faster cycles of product development, as products themselves become obsolete much more quickly than earlier (Harvey, 2010).
- Globalization of the markets, with the consequent hardening of the competition, as firms competes in a given industry at a global scale (Harvey, 2010).
- Increase of specialization is more and more necessary (Gassman et al., 2010). As the complexity of technologies grows, firms need to focus in a narrow area to master their competencies. This implies that other competencies should be dropped if the firm wants to keep focus and efficiency.
- The increasing capability of external suppliers (Gassman & Enkel, 2004) and the threat of competition from them.

Closed Innovation VS Open Innovation: Traditionally, firms sought for differentiation in the market by internally developing core competencies and protecting these against leakages to the outside, in order to keep their competitive advantage. This model was engineered by a science-driven type of innovation to feed the product development process, in an effort to continuously deliver new goods to the market to maintain its position in the industry (Chesbrough, 2003).

Considering the contextual changes referred above, it can be inferred that this traditional model–so-called Closed Innovation, is not performing anymore. In fact, a firm keeping this strategy has to possess a large range of technologies and domains of knowledge, which will result in the loss of specialization and increase of risks and effort, not to mention the resulting managerial and structural overheads. A good example of this model is the one carried out by Xerox in its PARC research facility (Chesbrough, 2003) in the decades of 1980 & 1990. This case shows how Xerox was very successful in developing new technologies, but then failed in later steps of the product development, because of an excessive tight corporate structure.

Therefore, a different strategy is required to keep the competitive advantage, by keeping the specialization of their core competencies, and, at the same time, tapping into existing non-core knowledge with minimized effort, and combining the whole to meet the ever-increasing quality standards. The figure below shows how the boundaries to incorporate external knowledge are different between closed (traditional) innovation, and OI.

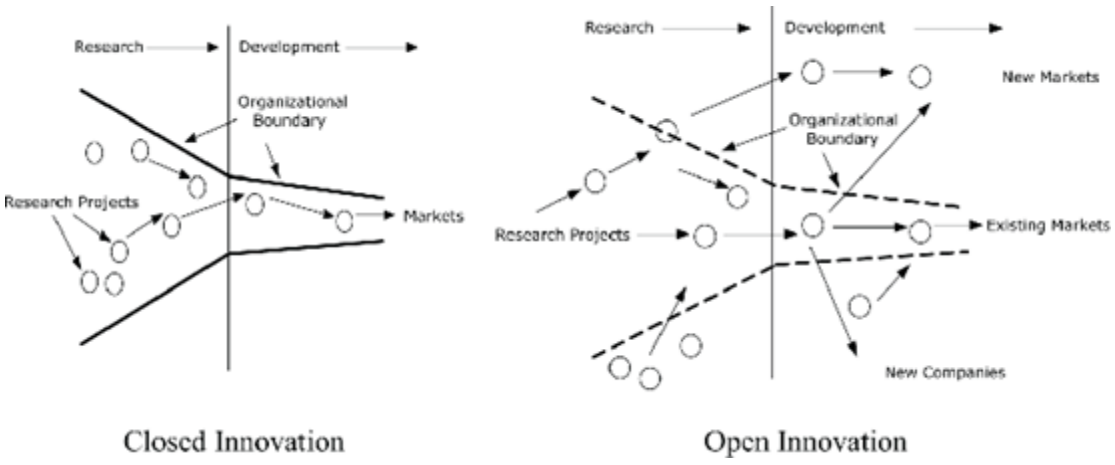

Figure 1-Close Innovation VS Open Innovation
(Chesbrough, 2003)

Hence, firms are being pushed to adopt OI in order to not become obsolete.

2.1.1 Practices in OI

Therefore, we can infer, in general lines, that OI paradigm is supported by the idea that knowledge is not anymore proprietary to the company, but it resides in employees, suppliers, customers, competitors, policy-makers and other stakeholders. So there is a need to make firm's boundaries more permeable (Chesbrough, 2006) and exploit this knowledge that leads into innovation by creating the proper mechanisms to interface with this external knowledge. When it comes to implement this paradigm, firms make

use of different mechanism to success in open the necessary linkages. These have been identified and analyzed by academia, resulting in the following classification of practices:

- *IP:* claimed to be the currency in OI (Hunter & Stephens, 2010), it implements the mechanisms and restrictions for firms to exploit existing knowledge under a regulatory frame.
  Trading of IP allows a firm to have additional revenues from its base of knowledge, without losing control of it, and preventing an eventual appropriability of the know-how by the competitors. But it can be also used as a strategy to create standards or technological paths (Teece, 2002).
  For the firm acquiring IP, it is a way to have quick access to non-core knowledge in order to focus on its competencies and speed-up the product development process. IP management implies a series of complexities, ranging from the pricing to usage restrictions (to encourage licensor to share knowledge minimizing the risk of appropriability from competitors.
- *Venturing:* broadly speaking, a venture is an alternative way of developing an innovation away from the established organizational structure of a consolidated firm. The reason for this is that established organization tends to filter out innovation out of the existing business model (Tidd et al., 2014). Venturing is a way to let these innovations to be developed in a more loose and dynamic environment, while allowing the parent firm to keep focus on their activities and avoid over complication of its structure.
  Venturing can take different forms: a split of a firm's division into a more-or-less independent contact, with the parent company benefiting from the knowledge of the child (spin off), or the firm's division being sold through M&A (spin out). Venture Capital is also used by firms themselves to ensure their access to certain knowledge from smaller, more innovative actors in the same industry (Tidd et al. 2014).
  This type of practices allows a company to spread the risk by diversifying the business model, reaching new markets, etc.
- *Collaboration & Networking:* even if every OI practice is based on an exchange between networked actors, we refer in this section to a series of more informal, dynamic practices that enables the creation of a "virtual company" (Tidd et al. 2014) in a network that facilitates the flow of knowledge.
  A variety of factors define the linkages: the actors or nodes in the, the points along the value chain at which they operate, the purpose of the relationship, the level of flexibility (from alliances more loose to formal joint-ventures) and the duration in time. All these factors create a whole range of typical linkages (Tidd et al., 2014).
  In these networks we find a balance of power, where the actions of one actor can affect other actors. Thus the place that a firm occupies in the network is of high strategic importance (Tidd et al., 2014). It would be also important to say that collaboration, as happen with other OI practices, is not without risks; collaborate in an OI environment can lead to leakage of information, or loose of ownership/leadership.

Perspectives of OI (Gassman & Chesbrough, 2010): Alternatively, we find another interesting classification in OI practices suggested by Gassman & Chesbrough (2010) that attends not to the specific structure that the practice adopts, but to the firm's dimension where it operates (so-called, perspective). We thus find different perspectives into which a firm can develop new OI practices:

- *Spatial perspective:* related with geographical location of the firm's assets, markets, stakeholders, etc., it emphasizes the fact that firms operate in a global market.
- *Structural perspective:* refers to how an industry is structured, the value chain shared among different actors (suppliers, manufacturers, etc.) and how the firm is networked with these. This perspective deals with OI practices such as outsourcing, alliances, etc.
- *User perspective:* refers to any practice that aim to integrate the user within the innovation process, to obtain accurate feedback of their needs and requirements, and considering user himself as a source of innovation.
- *Supplier perspective:* seeks for OI practices where suppliers become a source of innovation.
- *Leveraging perspective:* aims to maximize the benefit from existing assets through marketing, business model innovation. IP plays an important role here.
- *Process perspective:* focus on how the OI paradigm is perceived and managed in a firm. For example, which kind of knowledge flows (inbound or outbound) is more significant.
- *Tool perspective:* emphasizes the need of tools to enable OI practices. Examples of these tools are SDKs in software industry or Tool Kits for users to enable mass Customization.
- *Institutional perspective:* this perspective deals with the balance between proprietary and public knowledge and how a firm uses a combination of both.
- *Cultural perspective:* deals with the organization culture and mindset, the style of management, the corporate structure, etc., and how these factors affect the adoption of OI.

2.1.2 Models of OI

Attending to the way a firm combines the different OI practices, and together with other factors (in special, the practices related with innovation management itself), academia has tried to establish models and classifications, yet with no success in creating a standardized set of OI models.

Marais & Schutte (2009); These authors provide a classification of 5 models from analyzing real-life examples. These models focus on maximizing the innovativeness of firms by creating linkages with users/customers in different ways:

- *Product platforms:* this approach involves developing and introducing a partially completed product/base product, for the purpose of providing a framework for prosumers (customer who helps a company to design and produce its products). This model implies that the organization has a complete control over the value chain and the scalability factor is high due to the involvement of the prosumers in the product development which creates a "network effect".
- *Idea competitions:* this model entails implementing a system that encourages competitiveness among contributors by rewarding successful submissions. The primary offering of idea competition thus focuses on gaining a large quantity of inexpensive ideas, while also gaining insight into the customer's needs and wants. Some of the criteria for this model to work are that the IP rights need to be formalized to protect the organization and the prosumer, a well-developed reward scheme, a relatable product/Service for the prosumers, organizational capability to assess and evaluate competition entries and a well marketed competition.

- *Customer immersion:* this technique involves extensive customer interaction through the employees of the host organization. Companies are thus able to accurately incorporate customer input, while also allowing them to be more closely involved in the design process and product management cycle. Customer immersion is more oriented towards the end of the product development cycle, but can be used earlier to identify the needs and wants for a new offering by the customers.
  The advancement in certain technologies like virtual product design, virtual reality environment etc., and also the new social-networking technologies have enabled the organizations to pull customers into the heart of the product development process (Marais, Schutte, 2009).
- *Collaborative product design and development:* the technique emphasizes the importance and responsibility of suppliers' and customers' role in the product design process and supply chain to result in increased productivity to the benefit of the organization, and eventually the customer. This model differs from platforming in the sense that the products eventually offered to the open-market is still finalized and controlled by the organization.
  The criteria for this model to work is a product/service that lends itself to collaborative design, well developed specification and contracts which is communicated well to the prosumers and an open communicative community environment.
- *Innovation networks:* this is similar to the idea competition model, the difference relates to the fact that the network of contributors is used to develop solutions to identified problems within the development process, as opposed to new products. The criteria for the model to work is organizational capability to assess competition entries, a well-defined problem, an active base of prosumers, well established communication channels and a clearly defined policies for remuneration and ownership of IP.

Pisano &Verganti (2008); Another interesting classification of OI models is proposed by Pisano &Verganti, who argue that there are two factors to consider when an organization decides to engage collaboration practices under the OI paradigm: the level of governance (from more hierarchical corporate structure, to more flat), and the level of participation (ranging from closed to open, where open implies a more significant engagement of the firm' culture for OI).

The figure below is a framework developed by Pisano and Verganti to assist an organization to decide on which OI model they should be choosing for the innovation processes of their organization. The innovation model would fit any one of the quadrants depending upon the governing role and level of openness of the organization:

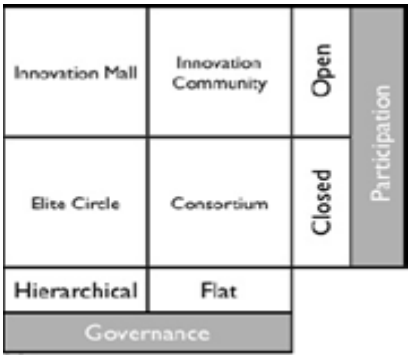

Figure 2-Decision-Making matrix (Pisano &Verganti, 2008)

The OI models inferred from the decision-making matrix can be defined as follows:

- *Innovation mall:* Organization post a problem, anyone can submit a solution, while the organization chooses the best solution.
- *Innovation community:* A flat network where all peers are equal and anyone can post a problem, or deliver a solution
- *Elite Circle:* Organization chooses participants, posts problems and selects the best solution.
- *Consortium:* Private network of peers that jointly chooses problems, and jointly reaches solutions.

Inbound/Outbound OI: A last classification of OI practices that we are considering defines 2 models based on the direction of the knowledge flow: inbound OI, or outbound OI (Chesbrough & Crowther 2006; Chesbrough and Bogers 2014):

- *Inbound open innovation:* is the practice of leveraging the discoveries of others: companies need not and indeed should not rely exclusively on their own R&D.
- *Outbound open innovation:* states that, rather than relying entirely on internal paths to market, companies can look for external organizations with business models that are better suited to commercialize a given technology.

A similar classification was proposed by Gassman & Enkel (2004), who referred to it as *outside-in innovation* (inbound) VS *inside-out innovation* (outbound). Furthermore, these authors signaled the existence of a 3rd classification, *coupled process*, which is a combination of both outside-in and inside-out flows by the same firm to complement both.

2.1.3 Benefits of OI

Roughly speaking, the advantage we can deduce from OI is that, the more external parties are involved in the innovation process, the better the overall quality of the resulting product or research (Busarovs, 2013). Going into detail, the positive outcomes of OI can be broken-down as follows:

- *Cost reduction:* Cutting down on the resources allocated to research and development, as an answer to the growing global competition that necessitates stringent cost management, might leave the company in a disadvantage. Through OI, firms can meet the increasingly complex demands of customers, while minimizing the costs of research and development as all parties involved will share the costs, hence achieving the desired innovation without the financial pitfall (Chesbrough, 2003).

- *Improvement of productivity in development & innovation:* Chesbrough (2003) described a complementary relationship between the organization's increased dependence on external knowledge sources in an open-innovation paradigm and the increased level of productivity in its R&D activities. Banri & Ayumu (2013) examined that relationship based on Japanese firm-level data, confirming Chesborough's (2003) hypothesis.
  Also, it was stated by Herzog (2008), that the involvement of outside, complementary knowledge will lead to achieve, sustain and advance paradigm-shifting innovations.
- *Accelerate time-to-market:* A key metric to determine the effectiveness of the implemented OI strategies was the time-to-market for their new products. The studies found that OI indeed shortened the time to market (Manceau et Al., 2011).
- *Increase differentiation:* The collective outcome of the aforementioned points is that an industrial organization that utilizes external (as well as internal) sources of knowledge and technical expertise is capable of producing technically superior products (as a result of its intellectually-diverse research and development teams) with reduced priced (since research and development costs will be split among different parties) that take less time to market. This means that adopting effective OI strategies can leverage the industrial organization's competitive status and distinguish the organization from its rivals (Manceau et Al., 2011).

2.2. Pharmaceutical Industry

By pharmaceutical industry we refer to any industrial activity whose goal is the development, production and marketing of drugs licensed for the use as medications. These drugs are classified into different categories based upon its origin (synthetic, plant-derived, antibiotics, etc.). As we will see along this chapter, the pharmaceutical industry has several unique characteristics: highly globalized and diversified, requiring big investments and bringing a tremendous benefit not only for the public health but also in terms of economic productivity (Scherer, 2000): the North American and European sales of new drugs (with a new active ingredient) accounts for almost 80% of the total sales in the world and together have a market share of 68.6% in the global pharmaceutical market which is worth approximately US $850 billion dollar. Pharmaceutical and Biotechnology industry in the world invest almost 15% of the total sales value in R&D making them the number one sector in R&D investment (Aamir et al.2014).

The pharmaceutical industry is knowledge intense, and is based on huge R&D investments: despite pharmaceuticals once emerged only in order to cure diseases, as time proceeded, it had become more and more an issue of business and a product of the investment. Today, there is no industry as complex as the pharmaceutical industry when it comes to doing business and making money.

The value chain of the pharmaceutical industry is complex, highly dependent on policies for drugs approval, and increasingly disaggregated, with Big Pharma collaborating in different ways with smaller actors (CROs, little biotech. firms, universities, etc.).

Some history: The history of pharmaceutical industry dates back to the mid-19th century where several chemical companies in the Europe like Sandoz, Bayer led the pharmaceutical industry with their strengths in organic chemistry, simultaneously in the US some of the pharmaceutical manufacturing big firm like Eli Lilly, Abbott, Smithkline were producing the over the counter drugs based on natural resources and were

dependant on the European companies for the chemically synthesized drugs. The largest growth in the pharmaceutical industry occurred after 2nd World War, with the discovery of Penicillin as the pivotal point, together with other products like vaccines, vitamins and sedatives. These led to the commercialization of the prescription drugs in these countries with funding from the government for further research and development with many chemical suppliers like Merck and Pfizer in the US, joining the prescription drug business. These pharmaceutical companies emerged as large integrated companies, representing a maturing pharmaceutical industry with their capabilities extending from Research and development, manufacturing, marketing and distribution of drug around the world (Sadat et al., 2014). Then, a Post-War boom happened in the sector, with the spin-off being a massive explosion of innovative new products that have saved millions of lives. However, the productivity of the industry has declined after the decade of the 70s (Hopkins et al., 2007; Garnier, 2008). The most evident proof of it is the rate of NME drug introductions in the market, as a measure of the outcome of this productivity and its associated cost: despite the cost of drug development has increased by 13.4% since the 1950s, the rate of success in the R&D activity is today low than ever (Hopkins et al., 2007; Garnier, 2008).

2.2.1. Value chain of the industry &definition

As preamble to the discussion that follows, we consider it necessary to provide details about how the industry is structured, its value chain, the involved stakeholders and some other key concepts and definitions.

Value Chain: The goal of the pharmaceutical industry is to discover and market new drugs. Thus, its main activity is the new drug R&D process. This process is structured into four sequential activities (research, development, manufacturing and marketing).The below figure explains the pharmaceutical innovation value chain.

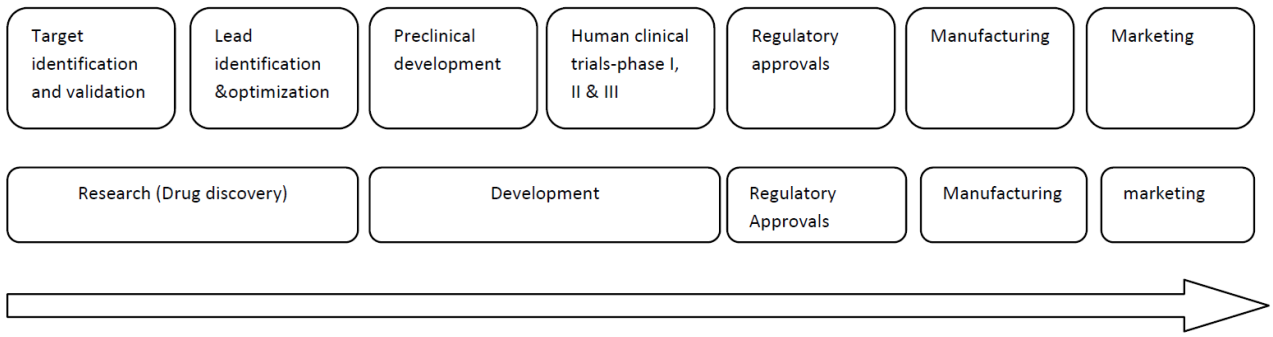

Figure 3-Pharmaceutical Innovation value chain (Sadat et al.,2014)

- *Research activities:* involves the identification and validation of new targets which is basically a naturally existing cellular or molecular structure that the drug in development is meant to act on, followed by further identification and optimization of a lead drug candidate which could be a new chemical entity (NCE) which are typically called the small molecules or a new biotech entity (NBE) that modulates that target which are called the biologics.
- *Development activities:* include preclinical experimentation of the new molecular entity, NME (new drug) in live cells, tissues or animal models to demonstrate its safety and effectiveness. The drug candidate is then clinically tested to demonstrate its safety and efficacy in humans (Pisano, 2006). Phase I clinical trials are done with

a small number of people, typically between ten and one hundred healthy volunteers to examine the drug's safety. Phase II trials are done with a larger number of patients between fifty and five hundred to further examine its safety, and determine effective drug doses. Finally, Phase III trials are undertaken using a very large number of patients up to thousands of patients in many different sites to explore its long-term safety and efficacy (Pisano, 2006).

- *Regulatory, manufacturing and marketing activities:* The NME which successfully passes through all these stages finally goes through approval stage, where it comes under the lens of regulatory boards of the place where it is to be manufactured and marketed.
  Such newly developed drugs are patented by the organizations to gain exclusive commercialization rights. Patent policies in the pharmaceutical industry grant 20 years for a firm to license-out the patented NME and maximize derived revenues, facilitating the reimbursement of the cost of associated R&D. After this period, a drug can be commercialized as generic with no revenue for the original developer.

R&D productivity (definition): In close relation with the value chain in the pharmaceutical industry, described above, we find the concept of R&D productivity, to measure the performance of the value chain. R&D productivity can be simply defined as the relationship between the value (medical and commercial) created by a new medicine (considered here to be an NME) and the investments required to generate that medicine (Paul et al. 2010). Thus, the R&D productivity is viewed as an aggregate representation of both the efficiency and effectiveness of the drug discovery and development process.

To illustrate this concept, we think of a project for drug development as characterized by its high complexity, high risk and uncertainty, where a promising project can lead to a commercialized drug much less effective than expected, or even, to unexpected failure (with the consequent loss of resources). At this regard, we can see the drug R&D process as a funnel (often referred as pipeline), where the projects at the beginning of the process will be progressively dropped among the different phases. As a result only few of the inputs will reach the end of the pipeline. The following image illustrates this point:

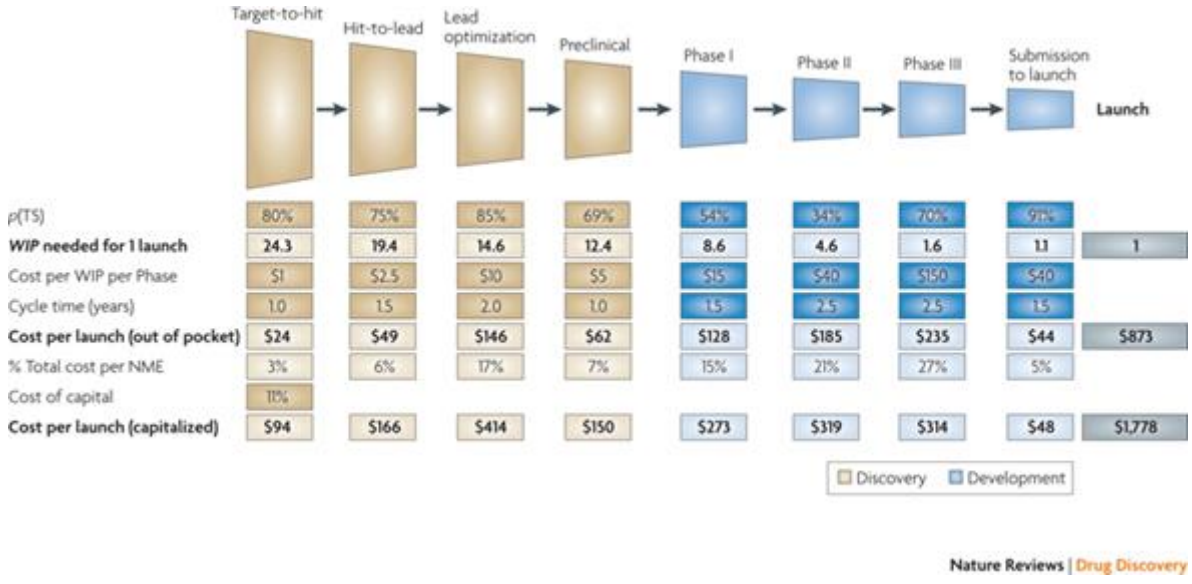

Figure 4-R&D model yielding costs to successfully discover and develop a single NME (Paul et al., 2010)

The figure above represents a model of R&D productivity (Paul et al. 2010), where each phase has an attrition rate (*p(TS)*, probability of technical success). Then, in order to obtain a single successful NME at the end of the process, it is statistically required to have 24.3 ongoing projects (*WIP*, Work In Progress).

This model identifies other factors that influence the productivity:

- Amount of scientific and clinical research being carried out by an organization. This is the WIP, or the number of project in the pipeline.
- p(TS), details regarding the nature of the compound under research, of the targeted disease, can make this rate vary.
- Value delivered by the drug users, once commercialized.
- Development cycle time, or time required to complete the project.
- Cost required for the whole development process.

2.2.2. Current situation of Crisis

When having a look to the contemporary picture of the pharmaceutical industry, we have first to look at the triggers that have set such a picture. This trigger is the decline in R&D productivity in the industry during the first decade of the 21st century, which has been widely discussed and documented (Dimasi, 2003; Munos, 2009). Although investment in pharmaceutical research and development has increased substantially in this time, there is a lack of corresponding increases in the output in terms of NMEs: the cost of drug R&D has increased by 13.4% since the 1950s, although the estimate seems to vary by studies: DiMasi et al. (2003) report the average cost is US $800 million to upward US $1.3 billion, but other authors claim the current average total cost to bring a new NME into the market to be up to 1.8 billion dollars (Khanna, 2012). Same way, the risk associated with the drug development process is increasing (with the consequent increase in the firm's overall cost): in average, only a 4% of the drugs in development pipeline will reach the market (Paul et al., 2010). All these figures indicate that therapeutic innovation has become more challenging. The reasons for this drop in the productivity are claimed to be the following:

- *Risky therapeutic areas:* It has been proven more and more difficult to discover new chemical entities with the potential to be developed into new "first in class" drugs (Pammolli et al., 2011).
  In the one hand, therapeutic areas where the risk of drug development (possibility of success of the drug development process, POS) are already exploited, and incremental innovation in these areas is discouraged by the policies.
  As a consequence, R&D investments tend to focus on new therapeutic targets, which are characterized by high uncertainty and difficulty, but lower expected post-launch competition. These new therapeutic areas correspond to rare diseases, unmet therapeutic needs and unexploited biological mechanisms.
  On the other hand, we find some other areas, less risky, but commercially non-viable (Judd, 2013). These include tropical diseases, antimicrobials and neuroscience projects and, in general, areas lacking of large markets, appropriate reimbursement, or the period of 'patent life' to gain a return on investment is too short.
- *Restrictive regulation for drug approvals*: Over the past decade, there have been serious concerns about the industry's integrity and transparency (Paul et al. 2010); in special, around drug safety (Khanna, 2012) and efficacy, compromising the

industry's image. As result, policy makers had increased regulatory scrutiny (Angell 2005).

On the top of the increasing complexity of the drug discovery process, there are some other factors that put the industry under a scarcity of economic resources to finance its increasingly-expensive R&D activities, therefore maximizing the risk in such an investment. These factors are (Paul et al. 2010):

- *Patent expiration:* Given the patent policies in the pharmaceutical industries, a firm keeps exclusive commercialization rights on a patented drug for only 20 years. In relation with this, it is stated that upcoming patent expirations between 2010 and 2014 have been estimated to put more than US$209 billion in annual drug sales at risk, resulting in $113 billion of sales being lost to generic substitution (Paul et al. 2010). Other authors give an estimation of US $290 billion or losses between 2012 and 2018 (Aamir et al., 2014).
- *Strained health public budgets:* in the current socio-economical context, governments worldwide are reducing public healthcare budgets. Additionally, the population in many western countries is quickly ageing (Khanna 2012), with the consequent increase in the expense per patient.

The consequence is the trend for prescription of generic, cheaper drugs, in a try to implement a cost-efficiency approach. Other trends include the usage of alternative therapeutic options.

Additionally, we can consider the last group of reasons contributing to this stagnation of the productivity in the pharmaceutical industry. These refer to corporate practices and strategies inside the Big Pharmas that are not adapting properly to the new context, shaped by the factors developed above. For example, Khanna (2012) refers to corporate culture that doesn't promote innovation, or conservative strategies in R&D. More concrete examples include:

- *"Blockbuster model" & pipeline gap*: we use this term (Chesbrough 2011) to refer to the traditional strategy of focus on the discovery and development of a blockbuster drug to maximize the profit. This strategy might not be fit with the current context, as the low productivity (often, blockbuster drugs are in therapeutical areas that are already exploited) make it highly risky. Having concentrated big stakes in a single R&D project, the numbers of drugs in the R&D pipeline are lesser. Thus, the failures of the blockbuster drug lead to a gap in the pipeline.
- *Managerial culture*: As science-driven industry, innovation in pharmaceutical industry should come from scientific knowledge. However, in many cases, we find that innovation is stifled by managers with little or no scientific knowledge over-managing or even micro-managing the R&D process (Cuatrecasas, 2006; Paul et al., 2010)

2.2.3. Consequences of the crisis

The most immediate consequence of the situation outlined above is, of course, the stagnation of the industry in term of finance and growth. To overcome this reduction in revenues, the industry uses non-NME filings as another source for revenues and profits (Munos 2009, Cohen 2005).

But the effects go far beyond if we consider the pharmaceutical industry serves the public health. It has been stated (Lichtenberg 2005) that 40% of the 2-year increase in

life expectancy measured from 1986–2000 can be attributed to the outcome from the pharmaceutical industry. Not to mention other discoveries such as antibiotics, or controls for the impact of obesity. A collapse of the pharmaceutical industry could, therefore, lead to a decrease of the life expectancy, especially if we consider the rise in diseases such as diabetes and childhood obesity (Paul et al. 2010).

Industry structure & stakeholders: Another big category of consequences of the productivity crisis refers to the change in the structure of the industry that aims to overcome the budget restrictions and minimize the increasing risk: the value chain of the R&D process is now more disaggregated, with different actors involved at different stages. Thus, the Big Pharmas don't own the whole R&D process anymore, and are adapting their strategies to be more networked, partnered and leveraged from a fully integrated model (Paul et al. 2010). The following picture illustrates the different stakeholders we find today, and how they relate to each other:

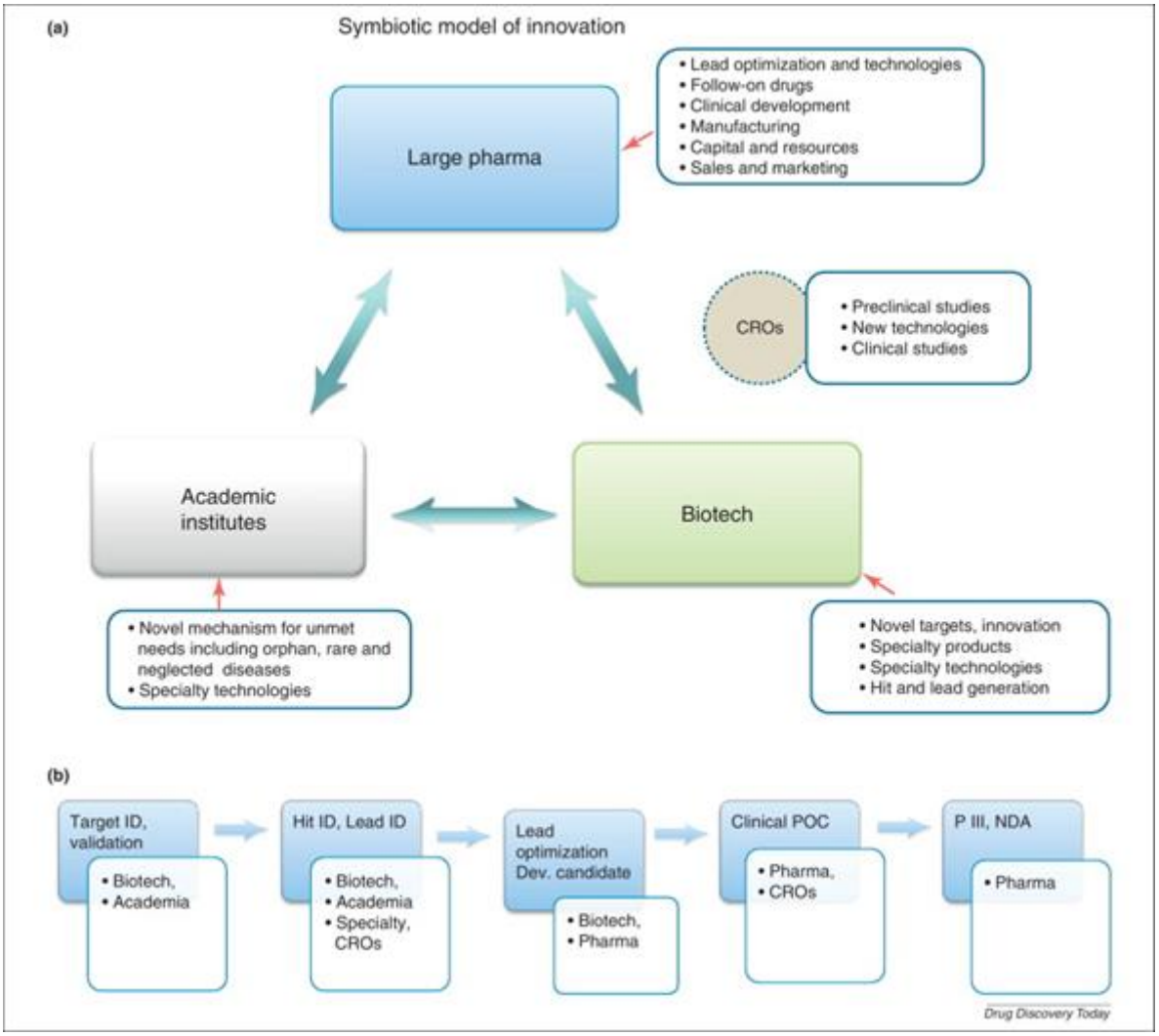

Figure 5-Drug discovery and critical partners (Khanna, 2012)

In the figure above, in section *a)* we find the different actors with their main activities, while in section *b),* each actor is matched with the phase of the R&D process in which they are mainly involved.

Regarding the relationship between the different actors, Big Pharmas, despite not owning or controlling the whole R&D process anymore, they keep the initiative in what comes to big projects, by managing the links with the rest of the actors through outsourcing, externalization, M&A, or more subtle ways of collaboration such as licensing, alliances, Crowdsourcing, etc.

- *Externalization & Outsourcing to CROs:* Through externalization, these big firms can reduce the expense in technology, while tapping in external knowledge to tackle innovation challenges. While this practice was traditionally carried out with CROs for the drug development phase (a relatively mature stage of the R&D process), the current trend indicated that the drug discovery phase is also externalized to Biotech firms, or carried out in collaboration with Universities. Complementing this externalization strategy, Big Pharmas are closing their in-house R&D activities: Global players like GSK, Astra Zeneca and Pfizer externalized 40-50% of the in-house R&D activities in 2012. This led to the closure of many large R&D facilities globally.
  The reason for this externalization strategy to CROs is mainly economic: drug discovery is highly dependent on state-of-the-art technology to allow innovation, whose cost is growing. As technology becomes more advanced, with higher specificity and larger throughput, it is unclear if any of these technologies will still pay off in the long run. By contracting out the research to a CRO, Big Pharmas pays only a fraction of the expected total. In the other hand, CROs can invest in these technologies. If specialized, CROs become the provider of choice for specific technologies; they can advance more quickly than the singular pharmaceutical company. They will run more experiments with more partners, and gain more learning as a result. Separate contracts by different pharmaceutical companies can lead to cost savings for all parties, and quicker development times (Gassmann and Reepmeyer 2005; Hu et al., 2007).
- *Alliances with Biotech companies:* In this relationship, the biotechnology company provides the innovation, whereas the pharmaceutical partner contributes its capacities to discover and develop jointly an early drug candidate with the purpose of having access to the drug project later. These Biotech companies are often the result of a spin-out from academia, or from the redundant activities of Big Pharmas. They often adopt an extroverted R&D strategy focusing on best opportunities for drug candidates, offering non-differentiating capabilities, ideas, know-how and technologies. Thus, Big Pharmas can use these early alliances to familiarize with a new technology or therapeutic area without investing too many resources (Schuhmacher, 2013).
  The reason for these alliances is more functional than economical: It is worth it to say that relationship between Big Pharma and Biotech companies are not limited to alliances, but also take place under outsourcing contracts, M&A, or even licensing contracts. In the last two cases, the goal of Big Pharmas is to have access to knowledge and IPs existing in the Biotech firm.
- *Collaboration with Academia:* Universities are another partner with whom Big Pharmas collaborate while opening the R&D process at earlier stages. At the same time, Universities find Big Pharmas as a new source of financing, in a moment where their traditional streams of funding from governments are decreasing (Gassman et al. 2010).
  The importance of academic alliances has resulted in a geographic re-centralization of the remaining in-house R&D hands-on activities close to the centers of academic excellence (Boston, Cambridge, Oxford). Lab-based R&D facilities have been

replaced by virtual research and project management units in order to collect and preserve the scientific expertise in the therapeutic areas of interest (AstraZeneca, Neuroscience iMed, Cambridge, MA, USA).

Cost VS Innovativeness: We can thus appreciate how the restructuration of the industry to face the productivity crisis pursues two main goals: to adopt a cost-efficient approach (and improve the time-to-market), and to increase innovation by adopting OI-like practices. The first has been achieved more or less successfully (Schuhmacher, 2013; Chesbrough, 1911). However, the second is still a serious concern for the industry. Deeper insights on these setbacks are discussed later on.

2.3. Existing framework of OI in the Big Pharmas

Here we review some theories on OI developed specifically to explain the requirements and trends observed in the pharmaceutical industry.

2.3.1. Degree of Externalization

Several models of OI have been identified in the Big Pharmas. A framework has been established based upon the level of openness of a company considering two factors, firstly, the externally acquired innovation which is defined by all the R&D projects along the clinical development phase of the Pharmaceutical innovation value chain acquired from outside the company. Here however we should note that the preclinical stages have not been taken into consideration for establishing the framework. The second factor considered for the framework is the choices of innovation management. Here the choice of innovation management basically reflects the strategic decision made by the company in managing their innovation which could be either predominantly internal or predominantly external. By analyzing some of the Big Pharmas under the factors mentioned above, four different types of OI models were identified, the knowledge creators, the knowledge integrators, the knowledge translators and the knowledge leveragers which is illustrated in the Figure below (Schuhmacher et al., 2013):

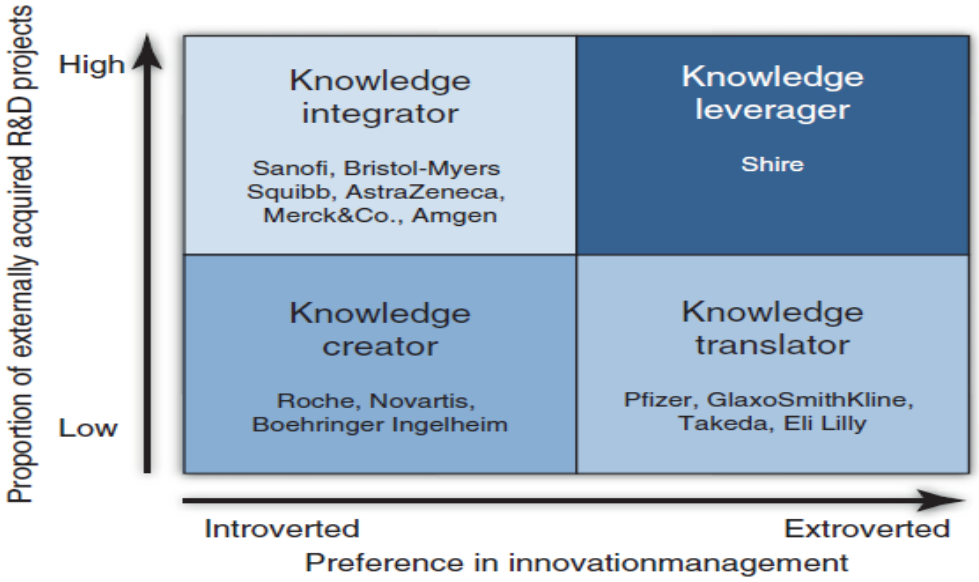

Figure 6-Four new types of innovation model in Pharmaceutical Industry (Judd, 2013)

In the knowledge creator model, the R&D projects acquired are mainly through university partnership or collaborations which are used as a supplement for the

internally carried out mainstream R&D projects, which are further developed using in-house talents and resources. Whereas in the knowledge integrator model most of the R&D projects are acquired or in-licensed through external sources and developed & managed further using the expertise of the company's internal resources. The third model, the knowledge translator model is very similar to the knowledge creator model but except for the fact that it uses outsourcing and partnership/collaboration as a tool to manage their R&D project efficiently in order to reduce cost or use the specialization or technical capabilities of the external sources to take the R&D projects to the next level. The fourth model which is the knowledge leverager model is rarely found in practice with very few companies in the Pharma industry implementing them. In this model majority of the innovation is generated from outside that is drug candidates, technological know-hows, technical skills are acquired from external sources to gain maximum benefit out of the internally available resources, further the innovation is managed through almost "virtual network" by extensive collaborations.

2.3.2. Structural Perspective of Open Innovation

The various OI strategies that has been in practice in the pharmaceutical industry are in-licensing, minority equity investments, acquisitions, joint ventures, purchase of technical and scientific services, non-equity alliances, licensing out, spinning out of new ventures, supply of technical and scientific services, corporate venturing investments (Bianchi at al., 2011). Let us further see how the Big Pharmas have been implementing the various OI strategies for a long time and how the stakeholders are involved in the various strategies along the innovation value chain of the Big Pharmas.

Non-equity strategic Alliances; "is an alliance in which two or more firms develop a contractual-relationship to share some of their unique resources and capabilities to create a competitive advantage" (Uddin & Akhter, 2011).

Such strategic alliances are also taking place at the early stages of the innovation value chain, at the target identification and validation stage. It is purely contractual collaboration without any equity involvement. It typically occurs with technology bearing biotech firms, universities, CROs and competitors (Bianchi et al, 2011). It helps to enrich the drug pipelines of Big Pharmas which are currently deficit as stated earlier. It is less formal than the joint venture. Outsourcing is a typical example of non-equity strategic alliance (Uddin & Akhter, 2011).

A very good example of such a strategic alliance from recent times would be between the Big Pharma Sanofi and the biotech company called Evotec in Germany. The aim of the alliance is to improve innovation in drug discovery and preclinical development and building drug pipeline focused on oncology. The alliance will serve to pioneer OI by both Sanofi and Evotec planning to combine their drug screening compound libraries which together will comprise of 1.7 million small molecules which would be made available for Evotec as well as for other pharma and biotech companies. They will also enter into a strategic outsourcing agreement wherein Evotec will provide drug discovery services to Sanofi for a contract period of 5 years (Globenewswire, 2015).

The current trend in the industry also shows that many Big Pharmas are outsourcing drug discovery particularly discovery of small molecule drugs along with clinical trials to CROs and Biotech firms in emerging countries like china and India(Zhang, 2014). Big Pharmas also form alliances with other Big Pharmas to access production capacity and distribution channels in order to commercialize the new drug discovered (Bianchi et al, 2011).

Joint venture: "When two or more firms form a legally independent firm to share their collaborative capabilities and resources to achieve competitive advantages in the market, it is termed as joint venture. Joint ventures are effective in establishing long-term relationship and in transferring tacit knowledge" (Uddin & Akhter, 2011).

Big Pharmas typically establish joint ventures with biotech companies and other Big Pharmas mainly for the purpose of research collaboration which leads to the generation of IPs which further yields commercial value. Joint ventures are also established to share skills, expertise, cost and risks (Austin, 2008). In recent times we can see a surge in Big Pharmas forming joint ventures with local pharmaceutical companies in emerging markets like china and India (Sadat et al., 2014). Such ventures are primarily for the purpose of R&D, Technology, and Investment and Cross border marketing opportunities (Ramesh & Kumar, 2012).

More recently we can see Big Pharmas joint venturing with academic institutes. In 2013 the Karolinska Institute and AstraZeneca have established a joint venture called the Karolinska Institutet-AstraZeneca Integrated Cardio metabolic Centre.

Mergers and acquisition (M&A): Big Pharmas are making M&A with other smaller pharmas and biotechnology companies to strengthen their drug pipelines and tap the potentials offered by the projects carried out by them for specialty drugs against diseases like malaria, HIV, Hepatitis C, tuberculosis etc. The acquisition of Swiss Biotech Company called Okairos by GSK is a very good example of one such M&A by Big Pharmas (Sadat et al., 2014). M&A is also adopted as a strategy for cost cutting and downsizing. M&A are claimed to help in cutting down the marketing expenses and thereby increasing the profit margin. Pfizer is one of the Big Pharmas which is well known for its downsizing activities. It has acquired several smaller biotech and pharma companies in the past decade and further closed down its numerous R&D sites in the US. However, the recent studies indicate M&A to have a negative impact on the R&D productivity. This claim was supported by inspecting the drug pipelines of certain Big pharmas which were heavily involved in M&A activities. It was found that M&A had caused almost 40% of drug compounds to be in the phase II clinical for more than 3 years in Pfizer which is way below the industry standard. (LaMattina, J. L. 2011).

Research funding:

Some of the Big Pharmas are also funding basic research carried out by universities which will be incubated and scouted by the biotech companies joining hands with the Big Pharmas. Recent example is Sanofi funding the projects from academia in France which would be supported and carried forward by German biotech company Evotec (Globenewswire, 2015).

Outsourcing & Purchase of technical and scientific services: In the pharmaceutical Industry, Biotech companies and certain CROs which are part of the SME play a major role in technology bridging by forming a separate cluster of industries which are known as Technical and Scientific services (TSS). They have the ability to transfer knowledge and diffuse technology into the innovation systems of larger pharmaceuticals. They act as a connecting bridge between universities and the Big Pharmas for the transfer of science and technology from universities to large pharmaceutical. They provide value added services along the line of technology transfer from universities to the Big Pharmas. A typical example of TSS is the purchase of potential compounds or monoclonal antibodies by Big Pharmas from dedicated biotech firms (DBF) for further development and commercialization. Another example would be the purchase of high

throughput drug screening systems by Big Pharmas from platform biotech firms. (Chiaroni et al. 2007).

In-licensing: Occurs during the pre-clinical tests. Big pharma secure the right to use a specific drug candidate which is patented by a biotech firm or pharmaceutical company. The Big pharma develop the drug further which goes through the testing and then marketed. The companies will then share the profits of the venture through the terms laid out in the in-licensing agreement. If a product is never developed and put on the market, then they share the losses (Bianchi et al., 2011).

Minority equity investment: Big Pharmas also buy stakes in biotech firms and smaller pharmaceuticals which will provide reduced royalty rates for drug discovered to the Big Pharmas in order to further develop and market them.

R&D Spin-out: A spin-out venture is a new venture formed out of bigger organization and is established as an independent business by taking the resources like IP, technology and other assets from the parent company. However the parents company gets an equal share in the new venture in order to compensate for the loss of equity in the original shares. Such spin-out are particularly helpful in taking forward R&D projects in pharmaceuticals which are of lower strategic importance, under-exploited and those that does not fall under the core competency of the company. Such spin-out activities are carried out by large pharmaceutical as an alternative to closing down of projects in order to reduce cost. It also helps in cutting down the capital investments and risks associated with an R&D project. It can also be termed as a strategic move to develop increased R&D efficiency and effectiveness. Such spin-out ventures of Big Pharmas can also act as an outsourcing destination for them for both drug discovery and development stages. Such spin-off is helpful in the inward flow of innovation for the Big Pharmas and the integration of internal and external knowledge helps to improve the technological know-hows and absorptive capacity of Big Pharmas. However there are certain disadvantages associated with spin-off ventures like increased coordination cost, IP spillovers and potential threat of the new venture turning into a competitor. (Festel& De Cleyn, 2011)*.*

Out-licensing: Out-licensing is about using external resources for the further development of internally developed drug candidates. Out-licensing is relatively new outbound strategy of Big Pharmas. It is considered to be a very difficult strategy as drugs which is being out-licensed by a large pharmaceutical industry might gain a negative image in the market and will not be in-licensed by any other companies to commercialize it. Also this strategy will kill certain projects within Big Pharma which might not be acceptable to many working in those projects. However Big Pharmas like Eli Lilly, Roche, Novartis, Merck and recently Bayer have adopted this strategy owing to benefits that out-licensing provides under certain circumstances. During the project portfolio management certain project which is of less strategic importance to the company might be terminated but out-licensing helps to keep those projects alive even though outside the boundary of the firm and also provides some additional revenues to the company.

Out-licensing is adopted as an option by a Big Pharma for other reasons(market size for the drug- if the market seems to be smaller for the drug developed, then Big Pharmas prefer to out-license the compounds in the drugs to companies who cater to smaller markets).The drug's compliance, meaning if there is a similar drug which is going to be marketed by a competitor, then Big Pharma terminate the manufacturing of that particular drug and license out the compound in them) the drug's administration,

meaning if the competitors develops a better way to administer a drug, larger pharma prefer to license out to companies which has the technology to develop such administration) Price projection and reimbursement by medical insurance companies- if the pricing yields lesser profit or if the drug is not covered under the insurance then Big Pharmas license out those drugs to companies who are still interested in them for other reasons (Reepmeyer, 2006)

Corporate venturing investments: Is investment of company's funds directly into external start-up companies. It is defined by the Business dictionary as the "practice where a large firm takes an equity stake in a small but innovative or specialist firm, to which it may also provide management and marketing expertise; the objective is to gain a specific competitive advantage". Large pharmaceuticals typically invest in biotech startups as a new strategy to combat the productivity crisis and to increase the inflow of innovation.

Thus after reviewing the existing frameworks of OI in the Big Pharmas and the various general OI models, we can say that all the aspects of OI has not been taken into consideration while studying the phenomenon in the pharmaceutical industry. Only the structural aspects like how big Pharmas are collaborating in the industry, with whom and to what extent is touched upon. Hence there is a need to take a closer look into the implementation of OI in the industry in particular the Big Pharmas in order to get a better understanding.

3. Methodology

In this chapter, we present the methodology that we have used to frame the critical analysis of the phenomena presented above. Thus, we describe the combination of tools and approaches (research paradigm, data collection methods, etc.) that have been used to come up with an answer to the research question in a systematic and methodical way. The research was designed keeping in mind the nature of the phenomena under study, but also resources constraints –mainly, time. Also, the design of the methodology was mainly based on the models proposed by Collis et al. (2013) and Yin (2013).

More specifically, the objective of this research is to investigate an existing situation (OI practices in the pharmaceutical industry), by describing it through a case study methodology, and further analysis of it. From this, it can be inferred that the nature of the research is thus analytical.

3.1. Research Paradigm

The research paradigm used to conduct the current research relies mainly on interpretivism, though we also support in positivist elements. In one hand, we appreciate positivist elements in certain elements of the theoretical framework, such as R&D productivity, which is approached in existing literature with statistical and quantitative methods. In the other hand, however, most of the elements we go through are of an interpretative, subjective nature: OI theories –including classifications, benefits, etc., insights in the industry crisis, etc. We can therefore affirm that the research topic fits better under interpretivism. This is also in line with the process selected to carry out the research –a case study, as a qualitative method of data collection, based on the observation of various dimensions of the phenomena, rather than its measurement.

3.2. Research Design

As presented before, the research purpose is going to be descriptive and analytical in nature, to come up with trends and patterns on how Big Pharmas implement OI-like models to overcome the current scenario of crisis in their industry. The logic of the research is, thus, inductive, as we depart from an empirical sample of the studied phenomena to propose a generalized, standardized view that fits into the existing theoretical frameworks of OI, and can be extended to other cases.

Regarding the combination of different techniques to set up the whole methodology, it would be worth it to say that we make use of data triangulation method to build our case study. Also, regarding the theoretical framework, we make use of several, "parallel" theories in OI; despite they partially overlaps, we use them in the analysis of the case study in order to provide a richer outcome that include several points of view.

The different steps that were carried out to design and plan the methodology could be summarized as follow: we first set the research paradigm based on the nature of the field of study, to select the case study as the most appropriate methodology. Then, we reviewed the existing knowledge to gain knowledge on the researched fields, and better define the remaining aspects of the methodology. Then, we defined the sample (the company to base our case study), and the unit of analysis (observed OI practices in the studies company). Finally, we set the type of the case study, together with the dimensions of the analysis (based on the established theoretical framework) into which

we map the case to come up with the opportunities and challenges posed by OI practices under each dimension.

3.3. Data Collection

The research is predominantly based on secondary data, referencing books, articles, scientific journals, reports published by consultancy firms, government website and the case study subject's website.

3.3.1. Sample case study

Regarding the empirical side of the research, the method used relies on a qualitative approach (given the nature of the topic in research), implemented through a retrospective case study, which provides the basis for the application of ideas and extension of methods.

The subject of study is Eli Lilly as an example of the central agent of the studied phenomena –the so-called Big Pharmas. The size is reduced to a single company –i.e. a single-case study (Yin, 2013). The reasons for this are, in one hand, time constraints; in the other, this reduced sample size gives us the opportunity to provide deep insight on the topic. The main reasons of having chosen Eli Lilly as sample are: their engagement with OI model, the amount of information available to base our research, and the innovativeness of the firm' OI practices.

The unit of analysis used in the case study is what we define as OI practice –an independent business process in the firm that pursuit the goals of OI paradigm. However, the OI practices that we consider operates at different levels of the firm's business model –i.e., strategy VS open sources practices; we must, therefore, consider it as an embedded case study (Yin, 2013).

The type of the case study, always following the classification provided by Yin (2013), is descriptive and exploratory: we provide first a description of the OI practices of the company based on the information retrieved from external sources, and adopt an explanatory style to match the described practices into existing theories.

Lastly, data triangulation practices have been used to create the case study, as data sources are of different nature: from academic literature to firm's corporate information and advertising, passing through reports from consultancy firms. With this, we aim to enrich the case study and strengthen the outcomes of the research.

3.4. Limitation

The main limitation of the conducted research turns around the case study. The case study relies on secondary data rather than primary data. This is due to the uncertainty associated with establishing contacts and securing appointment for interviews with the relevant personnel in the pharmaceutical companies in the limited time frame when this research was carried out.

3.5. Delimitation

To feed our analysis of OI in the pharmaceutical industry, we limit the data collection to a single company. While this allows to feed the analysis with insightful data, it limits the generalizability of the research conclusions. Even though the studied company implements OI in line with their corporate culture and management style, with an innovative approach, the representativeness of the studied sample can be criticized.

However, we argue that the selection of the sample was actually based on the success of the firm in implementing OI: despite the eccentricity of Lilly's OI practices, we state they are representative and generalizable as they might be adopted by other firms, given its success.

Additionally, during our analysis, we have neither considered dimensions nor variables that require to be measured in order to be analyzed, we rather stick to the ones which can be observed and analyzed qualitatively.

Lastly, in the case study we have only chosen the OI initiatives which can be associated with the drug discovery and development phase of the industry value chain as described, in the scope of the research.

4. Case Study

In this chapter we present empirical data through a retrospective case study that focuses on how Big Pharma like Eli Lilly is adopting OI. For this, we present the company and relate it to industry context described in the literature review chapter. Then, we focus on their OI aspects, studying each OI practice independently, but placing attention on how these relate with each other through Lilly's global strategy. We then propose a discussion around the empirical data, by analyzing the findings against the theoretical framework and suggesting challenges and opportunities based on the reviewed knowledge.

4.1. History

Eli Lilly and Company was founded in 1876 in Indianapolis, USA, by Colonel Eli Lilly, a pharmaceutical chemist and veteran of the American Civil War, after whom the company was named.

The company, initially a medical wholesale company, quickly became successful, hitting US $1 million of sales in 1905 (Lilly, 2015a). This success allowed Lilly to expand its business and rapidly evolve from drug manufacturer and wholesale, into an innovative drug developer; by 1913, Lilly had begun to build a large R&D plant (Taylor, 1989), and came up with several product innovations; for example, gelatin coating for pills and capsules (Indiana Historical Society, 2015a) and process innovation to improve the productivity (Taylor, 1989). By 1932, with the designation of Eli Lilly as new president, the company modernized itself with the introduction of scientific management principles and expanding collaborations with university researchers (Madison, 1989); and in 1934, the company's first overseas subsidiary was established in England (Lilly, 2015a; Madison, 1989). The 2nd World War brought a new wave of growth, with new blockbuster products (Madison, 1989), and the expansion of its activities abroad in the USA (Madison, 1989). From 1950, with the company having become public, Lilly continued delivering successful products (indianahistory.org, 2013b), expanding its facilities (Bodenhamer, 1994) and expanding globally (Indiana Historical Society, 2015a). From the decade of the 70s, Lilly looked for new markets to face the increasing presence of generic drugs in the market, diversifying into other areas such as cosmetics, medical instruments and agricultural chemicals indianahistory.org, 2013a). In the 90s, however, bad financial results (Associated Press 1993) made the management to "narrow the vision" of the company (Associated Press 1993), selling companies in its "Medical Device and Diagnostics" division, and incorporating others in the area of biotechnology (James, 2007).

Some of Lilly's accomplishments are, being the first company to produce insulin in 1923 (Madison, 1989) –including one of the first pharmaceutical companies to produce human insulin using recombinant DNA, or being the first to mass-produce the Salk polio vaccine in 1955 (Indiana Historical Society, 2015b), and penicillin in the decade of the 40s (Madison, 1989). Lilly is also the world's largest manufacturer and distributor of psychiatric medications, including Prozac. In the other hand, Lilly also accounts for having paid the largest criminal fine in U.S. history ($1.415 billion) for illegal marketing of some products (Medheadlines, 2009).

Some statistics: Today, Lilly has more than 37,000 employees, where 7,400 work with R&D. Its products are marketed in 125 countries. In 2011, Lily spent more than $5 billion on R&D in its facilities in eight countries around the world, where these costs represented the 21 per cent of the company's net sales that year (Dahlem, 2012). Lilly

is considered the 9th world's biggest pharmaceutical company and thus one of the Big Pharmas (Forbes, 2012), and is considered the world's largest manufacturer and distributor of medications used in psychiatric and mental health.

4.2. Crisis

As previously discussed, the pharmaceutical industry suffers of a productivity crisis since the first decade of the 21st century. Lilly, despite its advantageous position, was not an exception and was affected also by this context (Bloomberg, 2001).

In this regard, a remarkable fact was the patent expiration for Prozac. This drug, introduced in the 1980s and the company's best-selling product for treatment of depression, accounted among the most recent successful developments of the company and the most financially successful drug in the history of the industry: Prozac sales in the US accounted for around 20 per cent of the company's overall revenue, according to Lilly's 2001 financial report (pmlive.com, 2011). Lilly lost its U.S. patent protection for this product in 2001, which triggered a drop in sales of 23% from 2000 to 2001, including a 66 per cent decline in the fourth quarter of 2001 (pmlive.com, 2011), with financial consequences of $36.8 billion dollar of losses in equity (Bloomberg, 2001).

Another important shortcoming was the fine imposed on Lilly by the US government, for illegal marketing of its best-selling product, the atypical antipsychotic medication, Zyprexa (medlines.com, 2009). Apart from the direct, financial impact, this event triggered a wave of distrust that turned out in more restrictive regulations for drug approvals (Paul et al., 2010; Khanna, 2012).

Another big factor that negatively affected Lilly is the denominated "Risky therapeutic areas" discussed in the literature review chapter. Indeed, psychopharmacology, one of the historical core areas, is widely recognized to be stagnated, with no single novel drug reaching the market in more than 30 years (Fibiger, 2012).

4.3. Strategy

The immediate answer from Lilly's management to the setbacks described above included the increase in R&D budget about 30%, to more than $2.2 billion, hiring of 700 scientists in 2000 and in a search for the next blockbuster drug, focused only on the most promising projects with potential to reach US $500 million in annual sales (the already mentioned, "blockbuster strategy"). Another immediate response was to diversify the core therapeutic areas in which the company focused its R&D, so that the situation they had in the mid-1990s, of having 35% of their sales dependent on Prozac, won't repeat itself (Bloomberg, 2001). Thus, the firm extended their areas from psychopharmacology to a large portfolio including Neuroscience, Oncology, Endocrinology, Cardiovascular, Musculoskeletal, Autoimmune and Urology (Dahlem, 2012).

These were only the first steps in a progressive change of strategy towards a more open, sustainable model in the given context. When specifically looking at how Lilly is integrating OI practices in its strategy, it has to be remarked that the firm had a long tradition of collaborating with external actors (to quote an example, to achieve the mass-production of penicillin together with the University of Toronto, in 1940s).

Office of Alliance Management: To consolidate this approach and develop it from a partnership-based into a network-based, Lilly created, in 1999, the Office of Alliance Management, whose mission was to source innovation based on a 3-step process (“find

it/get it/create value" –Stach, 2006). This initiative, pioneer in the industry, perceived each partnership as a complementary part of the global strategy, and controlled the alignment and balance in each relation (Eli Lilly, 2015).

FIPCo & FIPNet: Further development of the above strategy led to the creation of FIPCo and, ultimately, FIPNet. FIPNet iterates the fact that not all activities took place within the company and this term was a better fit. Therefore, FIPNet, aims to transform "from a Fully Integrated Pharmaceutical Company to a Fully Integrated Pharmaceutical Network" (Ernst & Young, 2010), allowing Lilly to share the technology and make it easier collaborations, where Lilly is not necessarily the central actor, but can lead to benefits for Lilly in the long run, due to its position as creator of the network (Schwartz & Huff, 2010). FIPNet enables the creation of such network through 3 lines of action: Outsourcing (level 1), OIed R&D (level 2), and corporate venturing (level 3); the image below illustrates the transition from the former FIPCo strategy to FIPNet, achieved through these 3 levels of action.

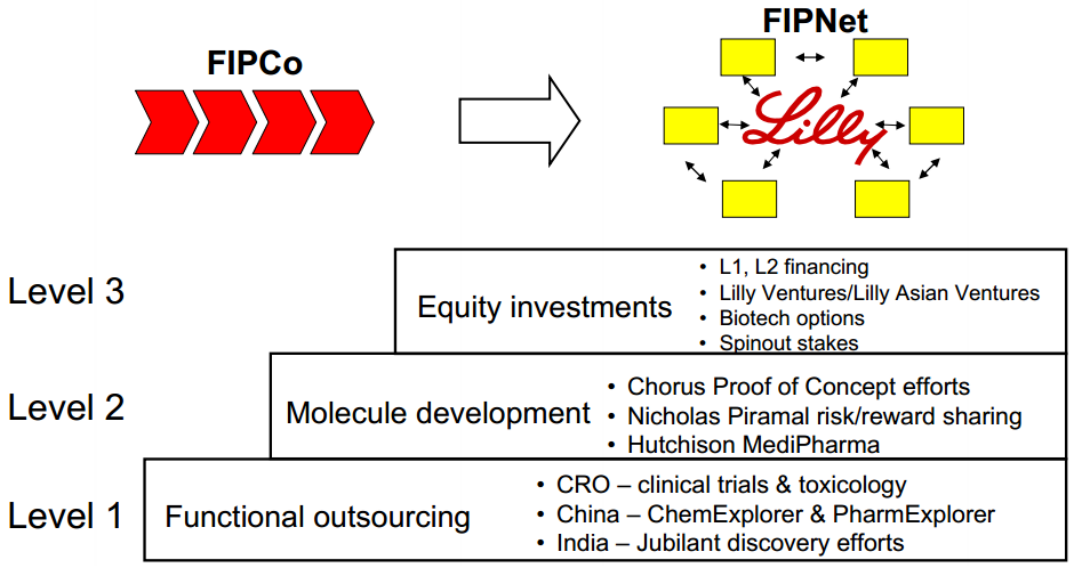

Figure 7-FIPNet, transforming Eli Lilly's Business Model (Dahlem, 2012)

Role of China & India: An important part of this network is the collaboration with India (Jubilant, Suven Life Sciences) and China (ChemExplorer&PharmExplorer, Hutchinson MEdiPHarma) (Dahlem, 2012; Mroczkowski, 2011). This approach represents a third way between continuing the development under high financial risk and abandoning it when a promising discovery is made. By sharing the risk with these firms, they are offered payments and royalties while Lilly receives the IP rights. Lilly opted for this flavor of partnerships because of several reasons. In one hand, these entrant firms had skilled scientists who having been working in the Western world and took back knowledge to Asia. In the other hand, they want to gain further knowledge from western companies (Rezaie et al. 2012). Not to mention the low-cost option that these partners represents by being located in emerging markets.

4.4. OI initiatives by Eli Lilly

In this chapter we will have a look on various initiatives taken by Lilly as a part of their strategy to evolve their business model and improve R&D productivity.

4.4.1. Chorus

As a part of the strategic evolution of the R&D capabilities of Lilly, the model of chorus was born within Lilly in the year 2002. Chorus was developed as a part of an initiative aimed to explore alternative R&D approaches within the organization. Lilly claims chorus to be a unique model among the pharmaceutical companies. The model uses external venture capital and a virtual network which consists of both Lilly's scientists and hundreds of experts & companies from around the world. Chorus helps to determine the probability of technical p(TS) of a compound in the shortest time and at the lowest cost termed as "lean to proof of concept", L2POC. (Owens et al., 2015).The term "proof-of-concept, POC" means that a drug must be effective and show no signs of serious side effects (Bonabeau et al., 2008)

Chorus began as an operationally independent drug development organization which takes care of the de-prioritized projects within Lilly for example project which do not fall under the core competency of Lilly, projects with extremely uncertain clinical results, projects with history of marginal results, but eventually transformed itself into a radical model in early phase clinical development. Chorus conducts independent research to determine whether a compound will continue or be discarded before it proceeds to the phase II and phase III in human clinical trials which are the most expensive and time consuming phase of the drug development process. Only the reduced number of molecules or compounds with higher p(TS) from chorus will be taken forward by Lilly to the clinical phase.

Chorus model is based upon the "Quick win fast fail" model (Paul et al., 2010) where the focus is to establish POC well ahead of the phase II clinical trial. The cost to establishing a POC for an NME through chorus was just US $6 million as compared to the traditional approach which cost almost US $22 million (Paul et al., 2010). In this model the R&D investment is redistributed from the later stages of drug development to the "R&D sweet spot" illustrated in the figure below, thereby reducing the late stage attritions which tends to be more expensive.

Chorus utilizes external experts to take advice on experimental design and drug delivery, it also uses external vendors to provide manufacturing, toxicology and clinical work that the unit requires. Chorus manages all the vendors and experts through a software tool developed by chorus enterprise themselves known as "Voice". Through Voice, Chorus maintains the network of vendors and experts and thus reduces the in-house workload and the fixed cost required to carry out the process internally (Bonabeau et al., 2008).

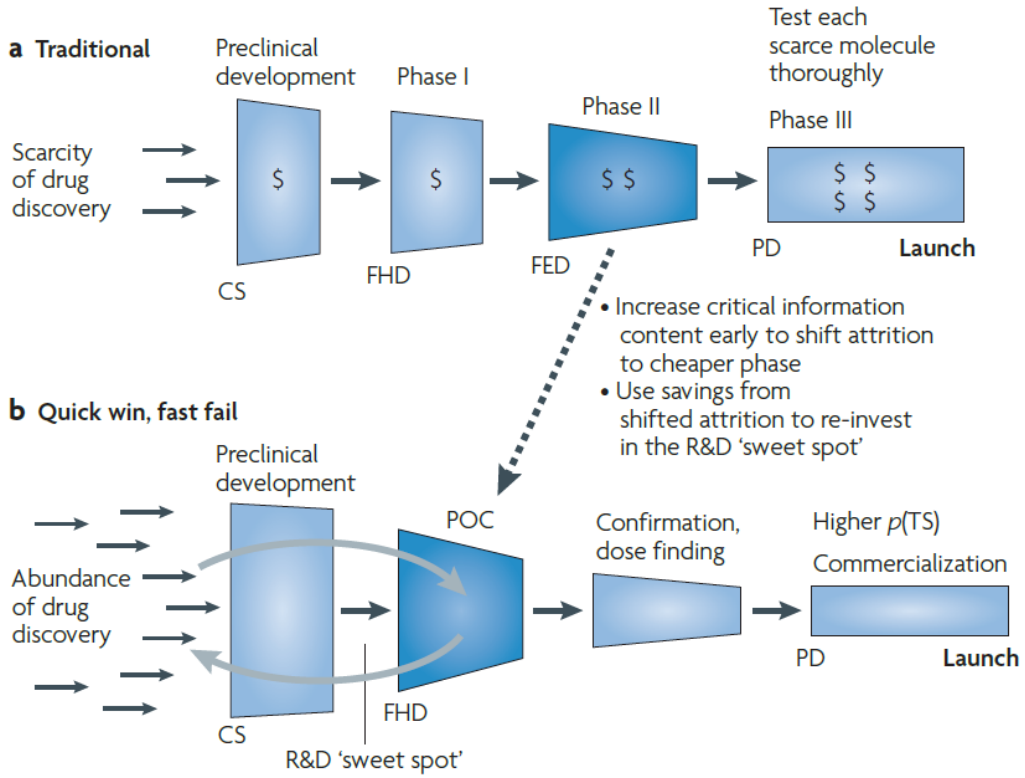

Figure 8-The quick win, fast fail drug development paradigm (Hunter & Stephens, 2010)

4.4.2. Innocentive

In an effort to explore the application of internet in Business, the idea of Innocentive was born in the year 1998 at Lilly and the minds behind them were Alpheus Bingham and Aaron Schacht. In 2001 Innocentive was launched with majority of the seed funding from Lilly. Darren Carroll led the launch effort and became the first CEO of Innocentive (Brand, 2011, p.58).

Innocentive was the first internet-based platform designed to help connect Seekers, those who had difficult research problems, with Solvers, those who came up with creative solutions to these problems (Bloomberg Business, 2009). Innocentive's clients at the start were mostly R&D intensive companies whose innovations were based upon chemistry, Biochemistry, biology and material science which were typically industries like Pharmaceutical, Chemical, consumer goods and petrochemicals (Allio, 2001). The employees of Innocentive worked with the scientists from these firms and provided them with separate "pavilions" on its website which was divided based upon the topic area. The scientist could post their problems anonymously in these pavilions and seek solutions from a global community of independent scientists and scientific organizations that were associated with Innocentive. The best possible solution which satisfies the criteria jointly set by the Innocentive employees and the client scientists or the seekers will be awarded. Innocentive provides the seekers with tools and methodologies specific to their industry to define their problems more precisely.

In 2005, Innocentive was spun out of Lilly through external venture capitalists investments; however, Lilly retains 20% of ownership in the firm and seats on the boards of directors. (Eli lilly& Company, 2015). The model of Innocentive has since then been adopted by a wide array of industries and in recent times it has been extended to

disciplines like Business and Entrepreneurship, Information Technology, Food and Agriculture and Social Innovations (Innocentive, 2015). The clients or seekers are not only private organizations but also government organizations and non-for profits organizations and public sector organizations (Salah & McCulloch , 2011). Innocentive has for a long time been in partnership with organizations like NASA, AstraZeneca, Cleveland Clinic, Lilly &Company, Procter& Gamble, Scientific American, Syngenta, The Economist, Thomson Reuters, etc. but in recent times have partnered with the Department of Defense, and several government agencies in the U.S. and Europe to rapidly generate innovative new ideas and solve problems faster, more cost effectively, and with less risk than ever before. Innocentive currently has more than 355,000 registered solvers from 200 different countries. More than 13 million solvers through strategic partnership, more than 2000 challenges posted till today with more than 40,000 solutions submitted to those problems. The success is estimated to be around 85% and the award amount ranges from US $5000 to 1 million based upon the complexity of the problem posted. (Innocentive, 2015).

Here we present an example of how Innocentive helped Lilly in speeding up its R&D process and develop intermediate compounds in the drug development process at a reduced cost. Dr.Chris Schmid was the R&D operations manager in the chemical process group at Lilly. He and his group were working on the synthesis of a new chemical compound for which they had determined the raw material but to start from the scratch was a tedious and time consuming process. Hence, they wanted somebody else to synthesize the intermediate compound so that they can take it from there to the final compound. Schmid later posted their problem on Innocentive and in just 3 months they got it solved through a solver scientist involved with Innocentive for award money of 25,000 USD. The solver scientist was a retired chemist from the R&D operation in Lilly. The process was iterative meaning with Innocentive as the mediator the process went through several feedback loops before it was finally accepted and rewarded by Lilly. Schmid also quoted that “they could have not solved the problem in-house for just 25000 USD”. The retired chemist had mentioned that he did it for not only monetary benefits but also for the intellectuals' aspects of it which brought him satisfaction. So it was basically a win-win situation for everybody involved in the process. (Innocentive, 2004).

Even though Innocentive is spun out of Lilly, they still have partnership with them and use a platform called innocentive@Lilly which is different from the external Innocentive network but still as efficient as it is. The platform is used to connect seekers and solvers within Lilly (Schwartz & Huff, 2010).

4.4.3. TBDDI

TBDDI is Lilly’s Tuberculosis drug discovery initiative launched in the year 2007. TBDDI is a not for profit initiative by Lilly established with both public and private partnerships with organizations and research institutes like Merck, IDRI, national institute of allergy and infectious diseases in the USA and the Bill and Melinda Gates Foundation (Eli Lilly & Company, 2015). The purpose of the initiative was to accelerate early stage drug discovery for TB and enrich the pipeline with new clinical candidates. Through this program, Lilly has made its compound library (about 800, 000 compounds) and research tools available to all the investigators and institutions who want to be a part of this program. A research module was developed by Lilly with the help of IDRI to select the right investigators or institutions to take part in this initiative by scientific evaluations of their submissions. US $20 million has been invested into this initiative which is a part

of the Lilly's MDR-TB partnership investment for CSR (Lilly, 2015). In 2009, Academia Sinica, The national academy of sciences of Taiwan which constitutes 24 institutes and 7 research centers joined as a member in TBDDI. The public-private partnership has resulted in a formation of unique consortium which involves private pharmaceuticals, government agencies, universities, philanthropic organizations and research institutes (PR newswire, 2009)

TBDDI is integrated with the TB Drug Accelerator (TBDA), an innovative collaboration between seven leading pharmaceutical companies and four research institutions to expedite the development of new TB drugs. The seven companies include Abbott, AstraZeneca, Bayer, Lilly, GlaxoSmithKline, Merck and Sanofi (GBChealth, 2014). Companies share targeted sections of their compound libraries and best anti-TB compound prospects in this unique initiative, which breaks away from traditional R&D practices. (GBChealth, 2014).

4.4.4. Open innovation drug discovery program

When it came up to improve the productivity of the R&D process, apart from the increase in R&D budget mentioned above, and in line with the FIPNet strategy, Lilly opened up the R&D process in more subtle ways other than the use of outsourcing (Mroczkowski, 2011). These approaches that rely on the idea of opening up company's resources and expertise to trigger an exchange of knowledge, were implemented by PD2 (launched in 2009) and TD2 (launched in 2011).

The common traits of these two initiatives reside in the fact that Lilly opens up the R&D process to external collaboration by sharing (without charge) its internal resources (basically, molecules in company's portfolio to be used as starting points on drug discovery and development) with external scientist (mainly, academia, and small biotechnology companies –Hunter 2014). In exchange, Lilly will profit from external skills and expertise applied on the shared resources by having access to the results that external collaborators came up with after carrying out R&D efforts based upon the molecules initially provided by Lilly's PD2 and TD2. Specifically, Lilly's goal here is to receive quality inputs from the outside rather than a high quantity of proposal submissions.

The specific way in which Lilly profit from these results is the following: the external investigator, who needs to sign up and accept a Material Transfer Agreement to become a member of the platform, will submit back to Lilly his R&D results for evaluation. Based on this evaluation, Lilly and the investigator will negotiate how to leverage the discovery, i.e. through licensing or collaboration. In this negotiation, Lilly holds the priority to first reach an agreement with the scientists (Eli Lilly, 2012b) while, in the other hand, the investigator keeps, by default, the IP rights on the molecule solution and is free to leave with the patent as an option.

Digging into detail in these two initiatives, we can appreciate the following differences:

DISCOVERY APPROACH	ENDOCRINE/CARDIOVASCULAR	ONCOLOGY	NEUROSCIENCE	TUBERCULOSIS
Phenotypic drug discovery	Insulin secretion Wnt pathway activator GLP-1 secretion	Anti-angiogenesis		TB screening module (IDRI)
Target drug discovery	GPR119 agonist APJ agonist NTP inhibitor	HK2 inhibitor	mGluR2 allosteric agonist CGRP antagonist	

Figure 9-Open Innovation assays at Lilly (Hunter, 2014)

PD2. The set of molecules offered through PD2 focuses on endocrinology and oncology diseases such as diabetes and cancer (Eli Lilly, 2012a). The key value of PD2 is that it allows scientists to have their compounds screened against phenotypic, disease-relevant assays that were already established within Lilly, so that they focus on phenotypic drug discovery (the earliest step in the R&D process). Since its creation, Lilly has created a network of 70 small biotechnology companies and 174 academic institutions, and it has helped the company to diversify its portfolio of compounds (Lee, 2011).

TD2. It offers resources to focus within the same therapeutic areas as PD2, but also extends to cardiovascular and neuroscience areas. Also, the resources it proposes to external collaborators are not limited to molecules, but also relevant computational methods to let investigators carry out structure-based research on the initial results (Hunter, 2014). The key difference between PD2 and TD2 is, however, that TD2 emphasizes the collaboration effort on the drug optimization step of the R&D process (this is, the later stage than PD2 focus on). This, by sharing molecules that are target-based, already-validated (i.e., the molecule has been proved to be active against another disease-related biological agent.

4.5. Discussion

In order to provide some insights on the efficiency and efficacy of Lilly's approach on OI, let's now analyze the empirical findings from this case study by comparing the different OI initiatives that Lilly is carrying out with the different theories on OI that we have reviewed previously.

4.5.1. Strategy – FIPNet& Chorus

One of the things that first call the attention to Lilly's implementation of OI is its holistic approach, as a way to overcome the setbacks of OI. Indeed, there exists a debate around implementation of OI in the pharmaceutical industry, where it is argued that adoption of OI practices has remarkable setbacks (Festel et al., 2011; Grabowski et al. 2008). These risks vary depending on the type of OI practice:

- *Outsourcing,* either as an alliance with a BioTech firm or as an externalization of a part of the R&D process to a CRO, often seeks for the reduction of costs (Lowman et al., 2012), with other positive effects (faster product development time, faster approvals by regulators –Lowman et al., 2012). But this partial approach is claimed to reduce the innovativeness of the R&D process, as outsourcing might also lead to loss of the "whole-process knowledge" (Festel et al., 2011), not to mention the increased complexity of managing relationships with external partners.

- *M&*A, are also under debate, with some academics challenging the efficiency of these actions (Grabowski et al. 2008), arguing that the outcome of this type of alliance is "1+1 = 1", or somewhat of 30% of capacity reduction.
- *Joint ventures*, and other peer-to-peer collaborations, imply the risk of dis-alignment between the implied parties, with each actor looking for its own self-interest, limiting the outcome of the collaboration. Main causes of this dis-alignment are claimed to be divergence in goals, cultural mismatch, insufficient trust or geographical issues (Tidd et al. 2014).

These setbacks are caused, to some extent, because OI are adopted by companies with a specific, short-term goal, as highlighted previously. However, Lilly has integrated every OI initiative under the FIPNet, considering the long-run goals of the company and balancing the different practices to obtain synergistic total result. As an example of this, we can appreciate, in the following picture, how two of the described OI practices, together with Lilly's venturing strategy as one of the core layers of the FIPNet strategy, fit into different stages of the end-to-end R&D process in a coordinated way.

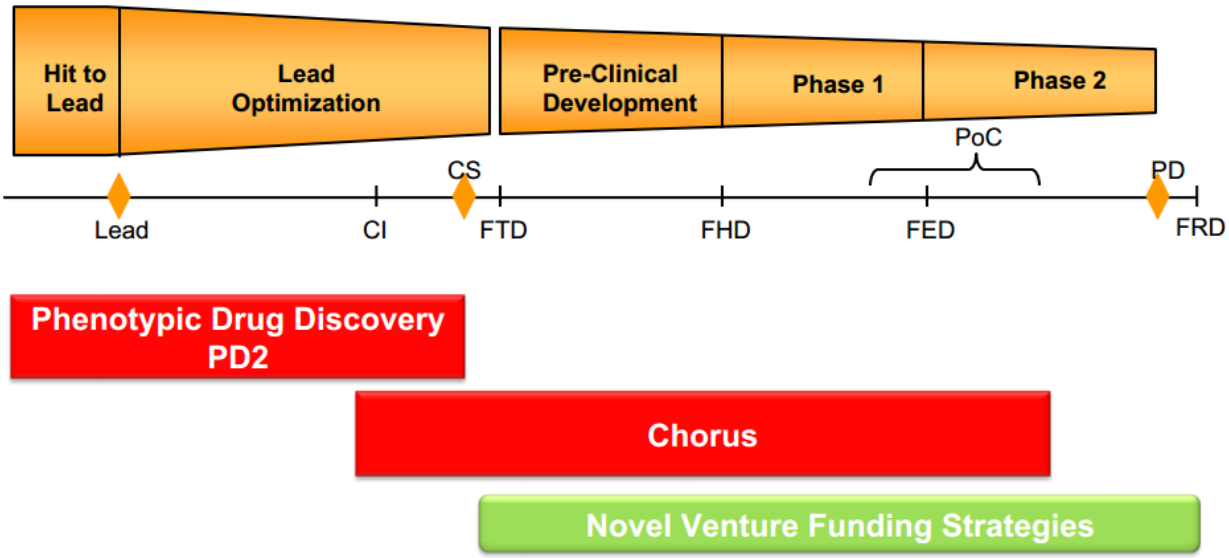

Figure 10-Lily external R&D initiatives (Dahlem, 2012)

As FIPNet strategy relies on the concept of networked company, it is important to emphasize that Lilly has achieved a mature network where it holds an optimal position. A low-evolved network can be perceived as an aggregation of bilateral relationships or dyads, making the alignment of each actor more difficult as relations are bilateral (Tidd et al. 2014). An example of this could be the early approach of Lilly in FIPCo (figure below). But Lilly evolved the network into a decentralized model, as it is shown in the picture below.

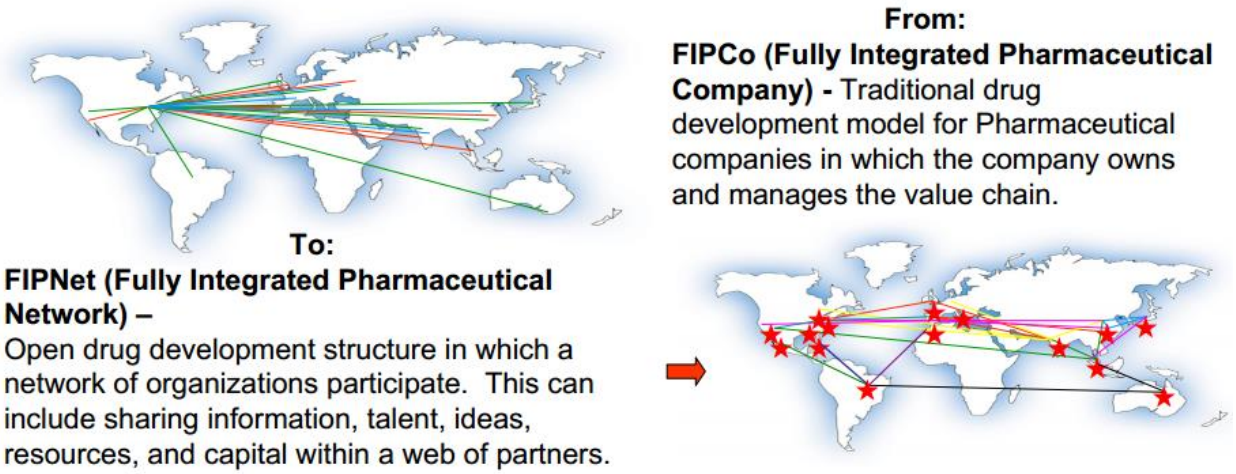

Figure 11-FIPCo to FIPNet transition (Dahlem, 2012)

As discussed previously, this approach allows interactions between peers where Lilly does not take any stake, but these side relationships may bring new knowledge to the network where Lilly is in an advantageous position to create value from it (Schwartz & Huff, 2010). This advantageous position from the fact of being the orchestrator of such a network, and the consequent influence in the network (Tidd et al. 2014).

Then, considering in one hand the focus that Lilly puts on the creation and management of this network as a way to stimulate the flow of knowledge, and in the other hand, the framework proposed by Schuhmacher et al. (2013), we can clearly classify Lilly as a Knowledge Translator. This idea is supported by the fact that most of the analyzed OI initiatives (Chorus, PD2 & TD2) get its starting point from company's internal knowledge.

Chorus: One example of how Lilly maximize the outcomes from their network to add value to its R&D process is Chorus. This complex initiative is unique (only parts of this model have been embraced by some competitors –Owens et al. 2015) and hard to categorize into any classification from OI theories, due to its ad-hoc design for the value chain of the pharmaceutical industry. The key point is that Chorus boost the productivity of the R&D process by relying in a virtual team, whose creation is only possible by tapping into the existing Lilly's network of external vendors, manufacturers, scientist and consultants (Owens et al. 2015), establishing, to some extent, a collaborative product development (Marais &Schutte, 2009). Despite of the managerial complexity that such a virtual organization can imply, Lilly has managed to run this alternative R&D model with low costs (Owens et al. 2015).

In the other hand, we appreciate that the relations on whom the Chorus virtual organization relies adopt the shape of externalization and outsourcing. These, as stated earlier in this section, presents certain risks compared to other more loose forms of collaboration, such as the stagnation of the innovativeness of the R&D process. At this regard, the success of this initiative seems to come from the way this alternative value chain is implemented as an efficient business process.

4.5.2. Crowdsourcing

Innocentive can be classified as Crowdsourcing initiative by Lilly. The term "Crowdsourcing" is the combination of two words “crowd” and “outsourcing” coined by

Jeff Howe (Howe, 2006b). Oxford English dictionary defined it as "Practice of obtaining information or sources by soliciting input from a large number of people" .However for pharmaceutical industry, Crowdsourcing is an outside-in or inbound process of OI which uses internet as a platform or tool to enrich the knowledge base of the firm's R&D. Crowdsourcing in pharmaceutical industry can be classified under the innovation mall framework of OI which was discussed earlier in the literature review. It uses Products Platforms and idea competition models discussed earlier to implement OI. Crowdsourcing is about using online communication to broadcast a problem which was not possible to be solved in-house. Studies have indicated that Crowdsourcing has a tremendous impact on solving scientific problems (Lakhani et.al, 2007). The case study indicates that the Crowdsourcing phenomenon has been adopted by R&D intensive industries like pharmaceutical in the early phase of drug discovery. The case study also indicates that Crowdsourcing involves heterogeneous group of individuals or organizations which are both private and public with no geographic limitations. According to the website crowdsourcing.org which provides information and insights on the subject of Crowdsourcing and application of Crowdsourcing models in various industries, there are five categories of Crowdsourcing which are ideation-based, expertise-based, freelance services, software services and micro-tasks. Crowdsourcing for pharmaceutical industry can be categorized as an expertise based task which involves the crowd wisdom of only highly qualified researchers and scientists. Thus Crowdsourcing for pharmaceutical industry has resulted in an open community of highly qualified researchers and scientists working towards a particular goal. Following Innocentive, there are other Crowdsourcing initiatives in the areas of early-stage drug discovery like Bayer's Grant4target initiative which is slightly different from Innocentive approach since it also seeks novel ideas for collaborative research in the discovery of new therapeutic options (Lessl et al., 2011). Although there are advantages of reduced overheads and enormous availability of human resources at any time through Crowdsourcing, there are certain difficulties like managing a large scale of solvers, facilitating to provide an environment where the solvers can compete and communicate with each other and establishing proper reward and recognition systems. IP management also plays a major role in Crowdsourcing initiatives.

4.5.3. Public-Private partnerships (PPP)

TBDDI initiatives by Lilly shows the emergence of Public-private consortium for drug development particularly for tropical and neglected diseases. PPP is an efficient model which bridges the gap between basic research and clinical development by bringing together the expertise from academics, pharmaceutical industry, public sector and government for a common goal of improving public health. Such initiatives can be classified under the institutional perspective of OI and is synonymous with the innovation network model discussed in the literature review. Increasing R&D cost meant that the pharmaceutical company's unwillingness to develop drugs for diseases which afflict population with no purchasing power or diseases which affect only few population. PPPs are effective models in OI since sharing of resources occurs at an increased scale. With the involvement of the government, more and more potential partners would be interested to share risk and get involved. PPPs are also useful in establishing networks, research databases and biobanks for future research in neglected diseases (WHO, 2013). With government in many developing countries investing more and more to improve public health and provide better insurance coverage (McKinsey&Company, 2012), PPPs can bring in new forms of economic activities to a region or a country which can benefit all the stakeholders involved. Thus PPPs cannot only be seen as a

CSR initiative. There are different kinds of PPPs identified by WHO, they are 1) Research partnerships, 2) Product development partnership, PDP and 3) PPP for concept development and overall systems strategy.

Research partnerships aim at developing innovative technology platforms in high priority disease areas. Innovative Medicines Initiative (IMI), which was launched in 2008 with total funding of €2 billion, is a good example of a research partnership where focus is on joint development of tools and methods. PDP on the other hand focuses on specific drug development for specific neglected diseases like TB, malaria etc. TBDDI initiative can be classified under PDP. The third kind of PPP aims to bring over all system reforms and focuses on issues like pricing, market authorization and sustainable models for innovation. However, some of the challenges in PPP are sustainability of funding, involvement of SMEs as much as large companies, consortium leadership and project management, IP management and performance measurement. (WHO, 2013).

4.5.4. Open Source – PD2 & TD2

When analyzing PD2 and TD2 Lilly's initiatives, they are to be considered together. Despite the different scientific nature in its outcome (drug target discovery in PD2, versus drug optimization in TD2), both share the same structural approach: Lilly's intellectual resources are disclosed for free (which is very innovative in pharmaceutical industry, highly protective with IP), to trigger new external discoveries that can be accessed by Lilly in the future.

The fact that this opening up of the R&D process happens at its earliest stages of the process is not by coincidence: it is at the early phases of the product development process that innovation is more critical (Tidd et al. 2014). By tapping in a wide pool of external knowledge, previously built under Lilly' FIPNet global strategy, and together with an intelligent IP management (collaborators are stimulated to collaborate as they can keep the rights on their discoveries), Lilly workaround limiting factors for innovation that the normal R&D activity presents as a standardized process (Tidd et al. 2014).

This approach shares some traits with OI theoretical models such as Collaborative Product Development and Innovation Network (Marais &Schutte, 2009) –yet, obviating some specificities from the complexity of the pharmaceutical industry, not considered in that framework. This initiative is also worth to be analyzed from the tool perspective (Gassman & Chesbrough, 2010): PD2 & TD2 can be seen as a tool kit for researchers, making more convenient access to the knowledge disclosed by Lilly. However, what make unique these two initiatives are its similarities to the so-called Open Source practices, widely adopted in IT industry, but unknown in other industries. The underlying idea of the Open Source model establishes that a product (in this case, software) should be freely available to benefit a larger community and, ultimately, be improved by that community. The reason why this model is mostly specific to IT industry is that software is easy to share, especially with the arrival of Internet (Rosen, 2005). Lilly has succeed in adapting this model to the pharmaceutical industry despite the barriers (IP as a key asset for firms, difficulty in sharing the product, absence of a open community and difficult access for the community to required technology for further development). Indeed, the outcomes that PD2 and TD2 are bringing to Lilly are equivalent to the ones observed in the IT industry: less R&D expenditure, faster time-to-market, etc. (Rosen, 2005).

4.5.6 Summary of discussion

To wrap up of our case study analysis, we propose a comparison of the different OI practices analyzed. The comparison criteria are mainly based on aspects from the reviewed OI theories that we have considered of special usefulness to classify the described practices from the case study.

	Strategy (FIPCo & FIPNet)	Chorus	Innocentive	TBDDI	PD2 & TD2
Type of practice	Networking	Outsourcing	Collaboration	Collaboration	IP, Collaboration
Perspective	Spatial, Structural, Process	Structural, Supplier,	Process, Tools,	Institutional, Cultural	Leveraging, Tools
OI Model	N/A	Collaborative product development	Products Platforms, Idea competition	N/A	Innovation Network
Type of collaboration	Innovation Community	Elite Circle	Innovation Mall	Consortium	Innovation Mall
Outbound/Inbound	Coupled	Inbound	Inbound	Coupled	Coupled
Other Considerations	Core Strategy	Internal OI	Crowdsourcing	PPP	Open Source
Stage in value chain	Whole	Drug Development	Drug Development	Drug Development & Discovery	Drug Discovery
Benefits	High engagement in OI. Holistic approach.	Improve time, cost & innovativeness of products.	Improve innovativeness in value chain	CSR practice. Reduce cost & risk	Leverage value of assets

Figure 12 – Comparison of Lilly's OI practices (developed by the authors)

5. Conclusion and recommendation for future research

A critical study was conducted on the concepts of OI. At first, we tried to understand the definition, the models, the triggers and benefits of OI in general with respect to all industries and then in order to understand how Big Pharmas implement OI, we had to first understand the industry as a whole. So we conducted some research on the history of the pharmaceutical industry, the various stakeholders involved in the industry, the innovation value chain of Big Pharmas, the crisis in the industry and how it has affected the Big Pharmas. We also tried to understand the existing framework of OI in Big pharmas based upon the degree of externalization and structural perspectives. We realized that OI has been in practice in the Big Pharmas in various forms for long time but they have been typically implemented in a bilateral fashion owing to the limitation of technology and IP management. Through the case study we tried to gather information on the latest OI initiatives in a Big Pharma. We realized that there are new upcoming tools like Crowdsourcing and open source drug discovery being implemented by Big Pharmas which uses the advancement in information technology to make the OI initiatives multilateral in nature which involves multiple actors from all over the world making the innovation network boundary more porous. We also realize that the Big pharma's innovation value chain has become more and more disintegrated and companies are developing strategies like FIPNet as a part of their core innovation strategy to make the network more integrated yet decentralized, so that they don't lose control in the growing innovation eco-system. We also realize that certain companies have unique methods to implement OI. In our case study chorus can also be classified as an internal OI where a part of the R&D process is disintegrated internally although it uses certain elements of externalization. We also see the formation of consortiums with multiple partnerships emerging between Big Pharmas and other stakeholders to explore new therapeutic areas which would otherwise be unexplored.

Thus we can say that new OI practices initiated by Big Pharmas are bringing in systemic changes in the pharmaceutical industry which is hard to resist considering the benefits that it might provide for all the actors involved. OI practices in the industry are evolving and mitigating the challenges with respect to OI is a collective responsibility in the industry.

Our analysis can provide inputs for developing a framework for OI in pharmaceutical industry or a comparative analysis for OI practices in other Big Pharmas. The analysis can also be extended to others stakeholders in the industry and the OI practices can be studied from their perspective. That is for example the benefits and challenges faced by SMEs as a result of the systemic changes brought by the Big Pharmas through its OI initiatives can a be an interesting topic to study.

References

Aamir, M., Ahmad, S. T., Mehmood, Q. S., Ali, U., Jamil, R. A., & Zaman, K. (2014). *The Challenge of Patent Expiry: A Case Study of Pharmaceutical Industry.* Mediterranean Journal of Social Sciences, 5(27P3), 1728. Chicago.

Allio, R. J. (2004). *CEO interview: the InnoCentive model of open innovation*.Strategy& Leadership, 32(4), 4-9

Angell, M. (2005). *The truth about the drug companies: how they deceive us and what to do about it.* New York: Random House Trade Paperbacks. Chicago.

Associated Press (1993). *New Lilly Chief Doesn't Have Own 'Agenda'.* Kokomo Tribune (Kokomo, IN).

Austin, M.(2008).*Business Development for the Biotechnology and Pharmaceutical Industry.* Retrieved from https://books.google.se

Banri, I., Ayumu, T. (2013*). Open Innovation, Productivity, and Export: Evidence from Japanese firms.*RIETI Discussion Paper Series 13-E-006.

Bianchi, M., Cavaliere, A., Chiaroni, D., Frattini, F., &Chiesa, V. (2011). *Organisational modes for Open Innovation in the bio-pharmaceutical industry: An exploratory analysis*. Technovation, 31(1), 22-33.

Bloomberg.com (2001). *Eli Lilly: Life after Prozac.*Retrieved from http://www.bloomberg.com/bw/stories/2001-07-22/eli-lilly-life-after-prozac

Bloomberg Businessweek (2008). *How P&G Pampers New Thinking.*

Retrieved from http://www.businessweek.com/stories/2008-04-02/how-p-and-g-pampers-new-thinking

Bodenhamer, D. J., & Barrows, R. G. (Eds.). (1994). *The encyclopedia of Indianapolis.* Indiana University Press. Chicago.

Bonabeau, E., Bodick, N., & Armstrong, R. W. (2008). *A More Rational Approach to New-Product Development.*Harvard Business Review,86(3): 96-102

Brand, J., (2011).*The Crowdsourcing Handbook – Everything you need to know about Crowdsourcing .* Retrieved from https://books.google.se

Busarovs, A. (2013).*Open Innovation: Current Trends and Future Perspectives.* Humanities and Social Sciences: Latvia, Vol. 21. No. 2, pp. 103–119.

Carroll,J.(2011, May 24*). Big Pharma embraces "open innovation" trend to fix a broken R&D model.*Retrieved from http://www.fiercebiotech.com/story/big-pharma-embraces-open-innovation-trend-fix-broken-rd-model/2011-05-24

Chesbrough, H. (1911). *Pharmaceutical innovation hits the wall: how open innovation can help.* Pharmaceutical Innovation, 2, 02. Chicago.

Chesbrough, H. W. (2003). *Open innovation: The new imperative for creating and profiting from technology.* Harvard Business Press. Chicago

Chesbrough, H. (2006). *Open innovation: a new paradigm for understanding industrial innovation.* Open innovation: Researching a new paradigm, 1-12.

Chesbrough, H., &Crowther, A. K. (2006). *Beyond high tech: early adopters of open innovation in other industries.*R&d Management, 36(3), 229-236. Chicago.

Chesbrough, H., &Bogers, M. (2014). *Explicating open innovation: clarifying an emerging paradigm for understanding innovation.New Frontiers in Open Innovation*. Oxford: Oxford University Press, Forthcoming, 3-28. Chicago.

Chiaroni, D., Chiesa, V., De Massis, A., Frattini, F., 2007. *The knowledge bridging role of technical and scientific services in* knowledge-intensive *industries*. International Journal of Technology Management 41 (3/4), 249–272

Cohen, F. J. (2005). *Macro trends in pharmaceutical innovation*. Nature Reviews Drug Discovery, 4(1), 78-84. Chicago.

Collis, J., & Hussey, R. (2013). *Business research.*Pan Macmillan. Chicago.

Cuatrecasas, P. (2006). *Drug discovery in jeopardy*. Journal of Clinical Investigation, 116(11), 2837. Chicago.

Dahlem, Andrew M. (2012). *Open Innovation, Networks, and. Strategic Partnerships in Drug.* Discovery and Development. Retrieved from http://fnih.org/sites/all/files/documents/Andrew_Dahlem.pdf

DiMasi, J. A., Hansen, R. W., & Grabowski, H. G. (2003). *The price of innovation: new estimates of drug development costs.* Journal of Health Economics, 22/2: 151–85.

Eli Lilly (2012a). *Open Innovation Drug Discovery. The Lilly PD2 and TargetD2 Initiatives: A New Paradigm for Open Innovation.* Retrieved from https://openinnovation.lilly.com/dd/docs/oidd_executive_summary.pdf

Eli Lilly (2012b). *The Science of Open Innovation.* Retrieved from https://openinnovation.lilly.com/dd/science-ofopen-innovation/index.html

Eli Lilly (2015). *Alliance Management, sourcing Innovation.* Retrieved from http://www.lilly.com/research-development/Pages/alliance-management.aspx

Eli Lilly & Company (2015). *Innovative drug development.* Retrieved from http://www.lilly.com/Responsibility/medicine-development/Pages/innovative-drug-development.aspx

Ernst & Young (2010). *Beyond the borders –Global Biotechnology Report 2010*, 22.

Festel, G., De Cleyn, S. H., Boutellier, R., &Braet, J. (2011). *Optimizing the R&d Process Using Spin-Outs: Case Studies from the Pharmaceutical Industry*. Research-Technology Management.

Festel, G., & De Cleyn, S. H. (2011). *R&D Spin-outs in the Pharmaceutical Industry.* Journal of Business Chemistry, 8(3), 101-113.

Fibiger, H. C. (2012). *Psychiatry, the pharmaceutical industry, and the road to better therapeutics.* Schizophrenia bulletin, 38(4), 649-650.

Forbes (2012). *The World's Biggest Public Companies.* Retrieved from http://www.forbes.com/global2000/

Garnier. (2008). *Rebuilding the R&D Engine in Big Pharma Reply.*Harvard business review, 86(12), 115-115. Chicago.

Gassmann, O., &Enkel, E. (2004, July). *Towards a theory of open innovation: three core process archetypes.*R&D management conference (Vol. 6). Chicago.

Gassmann, O., &Reepmeyer, G. (2005). *Organizing Pharmaceutical Innovation: From Science-based Knowledge Creators to Drug-oriented Knowledge Brokers*. Creativity and Innovation Management, 14/3: 233–45.

Gassmann, O., Enkel, E., &Chesbrough, H. (2010). *The future of open innovation*. R&D Management, 40(3), 213-221. Chicago.

GBCHealth (2014, August*). Eli Lilly: Searching for New Tuberculosis Drugs.* Retrieved from http://www.gbchealth.org/eli-lilly-searching-for-new-tuberculosis-drugs/

Globe Newswire (2015).*Evotec and Sanofi Sign Definitive Agreement for Major Multi-Component Strategic Alliance.* Retrieved from http://globenewswire.com/newsrelease/2015/03/20/717004/10125700/en/Evotec-and-Sanofi-Sign-Definitive-Agreement-for-Major-Multi-Component-Strategic-Alliance.html

Grabowski, H., & Kyle, M. (2008). *Mergers and alliances in pharmaceuticals: effects on innovation and R&D productivity.* The Economics of Corporate Governance and Mergers, 262.

Hagel, J., Brown, J.S., (2009, April 8) *The Next Wave of Open Innovation.* Retrieved from http://www.bloomberg.com/bw/stories/2009-04-08/the-next-wave-of-open-innovationbusinessweek-business-news-stock-market-and-financial-advice

Hedner, T. (2012). *Change in the pharmaceutical industry: aspects on innovation, entrepreneurship, openness, and decision making*

Herzog, P. (2008).*Open and Closed Innovation: different cultures for different strategies. Dissertation.*UniversitatMünster. University of Münster, Germany.

Hippel, E. v., & Krogh, G. v. (2003). *Open Source Software and the "Private-Collective" Innovation Model: Issues for Organization Science.* Organization Science.

Hopkins, M. M., Martin, P. A., Nightingale, P., Kraft, A., & Mahdi, S. (2007). *The myth of the biotech revolution: An assessment of technological, clinical and organisational change.* Research policy, 36(4), 566-589. Chicago.

Howe, J. (2006). *The rise of crowdsourcing*. Wired magazine, 14(6), 1-4

Hu, M., Schultz, K., Sheu, J., &Tschopp, D. (2007). *The innovation gap in pharmaceutical drug discovery & new models for R&D success*. Kellogg School of Management.

Hunter, J., & Stephens, S. (2010). *Is open innovation the way forward for big pharma?.* Nature Reviews Drug Discovery, 9(2), 87-88. Chicago.

Hunter, J. (2014). *Collaboration for innovation is the new mantra for the pharmaceutical industry.* Drug Discovery, 9. Chicago.

indianahistory.org (2013a). *Eli Lilly & Company*. Retrieved from http://www.indianahistory.org/ourservices/bookspublications/hbr/elililly.pdf

indianahistory.org (2013b). *Polio and Eli Lilly and Company*. Retrieved from http://www.indianahistory.org/teachers-students/plan-a-field-trip/Polio%20and%20Lilly%20background%20essay.pdf

Innocentive (2015). *what we do.*Retrieved from http://www.innocentive.com/about-innocentive

Innocentive (2004).*Compound interest found outside company walls- InnoCentive helps Eli Lilly and Company speed R&D.* Retrieved from http://www.pws-osri.org/business/0609advboard/6.8%20InnoCentive_Case_Study.pdf

James, A. (2007). *Icos Voters Approve Buyout by Eli Lilly.* Retrieved from http://www.seattlepi.com/business/301248_icos26.html

Judd, D. B. (2013). *Open Innovation in Drug Discovery research comes of age.* Drug discovery today, 18(7-8), 315. Chicago.

Khanna, Ish. (2012). *Drug discovery in pharmaceutical industry: productivity challenges and trends.* Drug discovery today, 17(19), 1088-1102.

Krishnaswami, S., &Subramaniam, V. (1999). *Information asymmetry, valuation, and the corporate spin-off decision.*

Lakhani, K. R., Jeppesen, L. B., Lohse, P. A., & Panetta, J. A. (2007). *The value of openess in scientific problem solving*. Division of Research, Harvard Business School

LaMattina, J. L. (2011). *The impact of mergers on pharmaceutical R&D.* Nature Reviews Drug Discovery, 10(8), 559-560.

Lee, J.A. et al (2011). *Open Innovation for Phenotypic Drug Discovery: The PD2 Assay Panel*. J. Biomol Screening, Volume 16 (6) 588-602.

Lessl, M., Bryans, J. S., Richards, D., &Asadullah, K. (2011). *Crowd sourcing in drug discovery.* Nature Reviews Drug Discovery, 10(4), 241-242

Lichtenberg, F. R. (2005). *The impact of new drug launches on longevity: evidence from longitudinal, disease-level data from 52 countries, 1982–2001*. International journal of health care finance and economics, 5(1), 47-73. Chicago.

Lilly (2015). *Lilly global health programs report- Finding New Solutions Through Partnership.* Retrieved from http://www.lillyglobalhealth.com/en/media/pdfs/lilly-global-health-programs-report-2015.pdf

Lowman, M., Trott, P., Hoecht, A., & Sellam, Z. (2012). *Innovation risks of outsourcing in pharmaceutical new product development.*Technovation, 32(2), 99-109.

Madison, J. H. (1989). *Eli Lilly, a Life, 1885-1977*. Indiana Historical Society. Chicago.

Manceau, D., Moatti, V., Fabbri, J., Kaltenbach, P. F., Bagger-Hansen L. (2011) *Open Innovation: Analysing what Open Innovation Changes in the Way Companies Innovate in terms of Partner Relationships, Internal Organization and Innovation Performance.*ESCP Europe & Accenture, France.

Marais, S.J., Schutte, C.S.L., (2009). *The development of Open Innovation Models to assist the innovation process*. 23rd Annual SAIIE Conference.

Maylor, Harvey (2010) Project Management, 4th edition. Harlow: Pearson Education Ltd.

McKinsey&Company(2012). *Unlocking pharma growth- Navigating the intricacies of emerging markets*. Retrieved

fromhttp://www.mckinsey.com/~/media/mckinsey/dotcom/client_service/pharma%20and%20medical%20products/pmp%20new/pdfs/emerging_markets_compendium_2012.ashx

Medheadlines.com (2009*). Eli Lilly Gets $1.4B Fine for Zyprexa Off-Label Marketing.* Retrieved from http://medheadlines.com/2009/02/eli-lilly-gets-14b-fine-for-zyprexa-off-label-marketing/

Michelino, F., Lamberti, E., Cammarano, A., & Caputo, M. (2014). *Measuring Open Innovation in the BioPharmaceutical Industry*. Creativity and Innovation Management.

Michelino, F., Caputo, M., Cammarano, A., &Lamberti, E. (2014*). Inbound and Outbound Open Innovation: Organization and Performances*. Journal of technology management & innovation, 9(3), 65-82.

Mroczkowski, T. (2011). *The New Players in Life Science Innovation: Best Practices in R&D from Around the World*. Pearson Education (pp. 248-253). Chicago.

Munos, B. (2009). *Lessons from 60 years of pharmaceutical innovation*. Nature Reviews Drug Discovery, 8/12: 959–68.

Owens, P. K., Raddad, E., Miller, J. W., Stille, J. R., Olovich, K. G., Smith, N. V., & Scherer, J. C. (2015). *A decade of innovation in pharmaceutical R&D: the Chorus model.* Nature Reviews Drug Discovery, 14(1), 17-28. Chicago.

Pammolli, F., Magazzini, L., &Riccaboni, M. (2011). *The productivity crisis in pharmaceutical R&D.* Nature Reviews Drug Discovery, 10/6: 428–38.

Paul, S. M., Mytelka, D. S., Dunwiddie, C. T., Persinger, C. C., Munos, B. H., Lindborg, S. R., & Schacht, A. L. (2010). *How to improve R&D productivity: the pharmaceutical industry's grand challenge.* Nature reviews Drug discovery, 9(3), 203-214.

Pisano, G.,Verganti, R. (2008), *Which kind of collaboration are you?.* Harvard Business Review, 86 (12), pp. 78-96.

pmlive.com (2011). *This month in pharma: Prozac's patent expires*.

Retrieved from http://www.pmlive.com/pharma_news/this_month_in_pharma_prozacs_patent_expires_321487

PR Newswire (2009, September 29). *The Lilly TB Drug Discovery Initiative Announces New Collaborator.* Retrieved from http://www.prnewswire.com/news-releases/the-lilly-tb-drug-discovery-initiative-announces-new-collaborator-62568267.html

Ramesh, H.N.,Ajay Kumar, T.R.,(2012). *Setting up a Joint Venture between Pharma and Biotech companies – A Study.*Retreieved from https://www.theinternationaljournal.org/ojs/full/vol01no12_rjebs.pdf

Reepmeyer, G., (2006). Risk-sharing in the Pharmaceutical Industry-The Case of Out-licensing. Retrieved from https://books.google.se

Rezaie, R., McGahan, A. M., Daar, A. S., & Singer, P. A. (2012). Innovative drugs and vaccines in China, India and Brazil. Nature biotechnology, 30(10), 923-926.

Rosen, L. (2005). *Open source licensing: software freedom intellectual property law.* Prentice Hall Professional , 69-71.

Sadat, T., Russell, R., & Stewart, M. (2014). *Shifting paths of pharmaceutical innovation: Implications for the global pharmaceutical industry*. International Journal of Knowledge, Innovation and Entrepreneurship ,Volume 2 No. 1, 2014, pp. 6—31

Salah, H., McCulloch, J., (2011*) New Models of Innovation in Life Sciences* Retrieved from

http://www.marsdd.com/wp-content/uploads/2012/12/MaRSReport-Models-of-Innovation.pdf

Scherer, F. M. (2000). *The pharmaceutical industry.* Handbook of health economics, 1, 1297-1336. Chicago.

Schuhmacher, A., Germann, P. G., Trill, H., &Gassmann, O. (2013). *Models for open innovation in the pharmaceutical industry.* Drug discovery today, 18(23), 1133-1137. Chicago.

Schwartz, K., & Huff, B. (2010*). The story of Eli Lilly's open innovation journey—How one company developed a mature model*. PDMA Visions, 19-22. Chicago.

Stach, G. (2006). *Business alliances at Eli Lilly: A successful innovation strategy*. Strategy & Leadership, 34(5), 28-33.

Taylor, R. M. (1989). *Indiana: A new historical guide*. Indiana Historical Society. Chicago.

Teece, D. J. (2002). *Managing Intellectual Capital: Organizational, Strategic, and Policy Dimensions*. Oxford: Oxford University Press.

Tidd, J., Pavitt, K., & Bessant, J. (2001). *Managing innovation* (Vol. 3). Chichester: Wiley.Chicago.

Uddin, M. B., & Akhter, B. (2011). *Strategic alliances and competitiveness: Theoretical framework*. Journal of Arts, Science and Commerce, *2*, 43-54.

World Health Organization (2015). *Pharmaceutical Industry*. Retrieved from http://www.who.int/trade/glossary/story073/en/

World Health Organization (2013) *New approaches to promoting innovation.* Retrieved from http://www.who.int/medicines/areas/priority_medicines/Ch8_1PPPs.pdf

Yin, R. K. (2013). *Case study research: Design and methods*. Sage publications. Chicago.

Zhang,J. (2014, July 1).*Global Drug Discovery Outsourcing Market Gaining Momentum.*Retrieved from http://www.lifescienceleader.com/doc/global-drug-discovery-outsourcing-market-gaining-momentum-0001