Technical Change and the Incorporation of Biotechnology in the Pharmaceutical Industry

Área Temática: 5.8 Inovação, competências e Competitividade
JEL: O33, L22, L65

Autores: Murilo Montanari de Matos[1]; Sérgio Robles Reis de Queiroz[2]

Resumo:A indústria farmacêutica, ao longo de sua história, tem enfrentado inúmeras mudanças e desafios. Atualmente o setor passa por uma crise de produtividade em suas atividades de P&D. Este fato coloca uma série de questionamentos importantes, para o escopo deste estudo destacam-se dois: Como a indústria tem lidado com esta crise? As atitudes do setor trazem novas mudanças ou dinâmicas a este mesmo? A resposta que este artigo propõe é também o argumento que se procura defender, que é: a solução tentada pela indústria farmacêutica é tanto tecnológica quanto organizacional e esta solução reside fora das fronteiras da firma, sendo assim, as grandes empresas farmacêuticas estão usando estratégias, especialmente as aquisições de pequenas empresas de biotecnologia, para incorporar novas tecnologias que, em tese, vão aumentar a taxa inovativa das grandes empresas. Para se conseguir o objetivo proposto, este trabalho propõe combinar uma pesquisa bibliográfica focada na literatura econômica e na literatura especializada nas técnicas usadas para se desenvolver novas drogas para que se observe a evolução das atividades de P&D. Ademais, alguns dados importantes serão apresentados para sustentar algumas afirmações. Como conclusão, o artigo mostra que a evolução das atividades de P&D criou uma necessidade, nas grandes empresas farmacêuticas, que fez a incorporação de pequenas empresas de biotecnologia uma estratégia recorrente.

Palavras-chave: biotecnologia, indústria farmacêutica, mudança técnica, competências, aquisições
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Abstract: The pharmaceutical industry has undergone several changes and challenges, nowadays the industry is facing a R&D productivity crises. A series of questions arise from this fact, two of it can be highlighted as important for this study that are: how the industry is dealing with this crises? Does it bring new features to the sector? The answer that this article proposes it is also our argument, that is: the solution sought by the industry is both technological and organizational and it resides outside the large pharmaceutical enterprise's borders, therefore, those companies are using strategies, especially acquisitions of small biotech enterprises to incorporate new technologies that, arguably, will increase the large enterprise's innovative output. Therefore this article objective is to prove the argument. In order to achieve the objective proposed this work proposes to combine bibliographic research on the economic literature and the specialized literature on drug discovery techniques to describe this activity evolution, in addition, some important data will be present to sustain the assertions made. As a conclusion the article shows that the R&D activities evolution has created a biotechnology trajectory, in the pharmaceutical companies, that made the incorporation of small biotech enterprises a recurrent strategy.

Keywords: biotechnology, pharmaceutical industry, technical change, competences, acquisitions
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[1] Professor do Instituto de Economia da Universidade Federal de Uberlândia (UFU)
[2] Professor do Departamento de Política Cientifica e Tecnológica da Universidade Estadual de Campinas (Unicamp)

Introduction

The pharmaceutical industry is a recurrent theme among studies on the field of economics. Nowadays, what draws the attentions of scholars for this sector is the pharmaceutical R&D productivity crises, that consists on a non-proportional correlation between the New Molecular Entities (NME) - or New Chemical entities (NCE)- approved by the FDA and the R&D expenditures and patent applications. In other words, the industry is expending more on research activities and producing, relatively, much less innovations. For the purpose of this article it is interesting to question: how the industry deals with these recurrent and persistent crisis? The answer to that question can only be achieved by showing the pharmaceutical R&D evolution. As an outcome of that analyses, becomes clear that the industry, nowadays, is more dependent on small biotech enterprises for conducting their R&D, showing then a different form of organizing their R&D by relying on acquisitions –the use of external sources- for incorporating new techniques.

Departing from the R&D crises the literature is highly focused on cost perspective analyses that let important technological aspects aside(Comanor and Scherer 2013; DiMasi 2000; Grabowski and Vernon 2000; Grabowski and Vernon 1994). On the other hand the literature focused on technical change has put organizational aspects aside (Hopkins et al. 2007; Martin, Nightingale, 2000; Nightingale, and Kraft 2008, among others). The literature shows that the industry evolves towards a marked division of innovative labor and specialization of research activities (Gambardela, 1995; Hopkins, Nightingale, and Baden-Fuller 2012; Matos, 2016; Schweizer, 2005). As a result, there is a risk reduction and a greater ability to acquire new technological skills, that, in some cases, can completely replace parts of the innovative process (Cassiman and Veuglers, 2006; Hagedoorn

et al., 2012 and Hess and Roathermel, 2011). These positions carry with them a consensus: the large pharmaceutical companies have tried to incorporate biotechnology skills into their set of competences.

In this article it is argued that the answer sought by the industry is both technological and organizational and it resides outside the large pharmaceutical enterprise's borders, therefore, those companies are using strategies, especially acquisitions of small biotech enterprises to incorporate new technologies that, arguably, will increase the innovative output. Therefore this article objective is to prove the argument

Although the pharmaceutical industry is highly complex the solution of R&D problems are found in R&D itself, in the present case, the technological and organizational aspects of R&D. Therefore, this study is focused on the initial stages of R&D (drug discovery activities). In this stage, two major scientific fields, chemistry, and molecular biology, support the drug discovery activities. It is well known that the symbiosis between chemistry and pharmaceutical industry were highly successful. These two elements together could originate the most significant drugs in the twentieth century(Achilladelis and Antonakis, 2001). However, the chemical trajectory that underlines the pharmaceutical industry is facing a research productivity decline[3] (Drews, 2000; Nightingale *et al.*, 2007). According to Nightingale *et al.* (2007), the failure of a chemical trajectory can be attested only when one looks at the innovative process, especially, the drug discovery activities.

A static analyses of a particular time, in other words, a picture of the sector will not be sufficient to prove the argument and, as consequence, achieve the objective. The only possible way to explain the changes mentioned is through the evolution of the drug discovery activities. As a methodology, this work proposes to combine bibliographic research on the economic literature and the specialized literature on drug discovery techniques to describe this activity evolution, in addition, some important data will be present to sustain the assertions made.

[3]Pharmaceutical's research productivity can be summarized as the relation between the number of NCE and Money spent to produce those (Gassman*et al.*,2004).

This article is divided into three sections. The first section encompass, in the first place, why this article chose to focus on the drug discovery activities, finally it establishes biotechnology as a watershed in the drug discovery activities by discussing the technical evolution among the industry R&D, therefore, this section is an attempt to show the growing importance of biotechnology for the pharmaceutical industry. Sections two will show the growing importance of small biotech enterprises regarding their innovative output measured by NME. The third section is focused on how small biotechnology enterprises are organized and how the large pharmaceutical industry interact with these small companies, especially, through acquisitions. The article finishes with the conclusion

1 The evolution of drug Discovery activities.

This section will first present the stages and features that encompass the pharmaceutical R&D, along the other subsections it will be discussed the drug discovery activities evolution, through this evolution it will be possible to attest how these activity has changes and how new techniques were incorporated in an attempt to increase the R&D productivity.

In the pharmaceutical industry the process that leads to an innovation can be,mainly, divided in 4 main stages: (i) target identification, characterization and validation, followed by assay development; (ii) lead finding and optimization; (iii) ADMET[4], PK and PD[5] studies and (iv) clinical trials (Schwardt*et al*., 2003, pg. 2). Roughly in the pharmaceutical R&D the activities conducted before the clinical trials encompass the drug discovery process or activities-a set of activities that are highly focused in science where large enterprises employ their external sources of innovation (Gambardella, 1996; Nightingale, 2000; Drews, 2000 and Schweiser, 2005).

Even though the clinical trials are an important element in the R&D they compose a more routinized set of activities in which financial strength is essential (Comanor and Scherer, 2013; Gambardella, 1995 and Schwartzan, 1976). The R&D clinical trials include several routinized procedures that are highly regulated[6]. This process has its competitiveness rooted on the company's ability to perform tasks efficiently.

The more tests a company conducts, the more efficient it will be. Thus, the learning-by-doing component, majorly, determine the R&D competitiveness in this stage (Gambardella 1995 and Schwartzman, 1976). The impact of the new technologies has little effect on the clinical trials (Gambardella, 1995).

The opportunity for the companies to introduce innovations during the clinical trials are limited, but the ability to use the information is of extreme importance. (Gambardella, 1995; Schwartzman, 1976). The R&D clinical part generates relevant information that is utilized in the prior R&D stages, in order change compounds that are being tested, or to produce new medicines.

Regarding the technological efforts, it is during the drug discovery activities that the companies comprise the main part of their innovative efforts, then, encompassing a large part of the technological dynamics of this sector. Therefore, the activities upon which the drug discovery is based are better suited for understanding and analyzing process of technical change (Gambardella 1995 and Nightingale 2000). It is precisely in the drug discovery activities that companies employ new technologies from different sectors, in a way of seeking and producing more NCEs[7](new chemical entities), i.e. the productivity gains come from these set of activities.

1.1 Drug discovery before biotechnology.

[4]A set of test categories used together in drug discoveryto provide insight into how a pharmaceuticaldruginteracts with the body as a whole

[5]PK-PD is a technique that combines pharmacokineticsand pharmacodynamics. It integrates a pharmacokinetic and a pharmacodynamic model component into one set of mathematical expressionsthat allows the description of the time course of effect intensity in response to administration of a drugdose.

[6]For further knowledge about the steps and the typical clinical trial characteristics, please see: Gambardella, 1995, Schwartzman, 1976, FDA 1999 e FDA 1990 and the sites: www.clinicaltrials.gov and www.fda.gov

[7]NCE are the possible candidates for new drugs, that will be tested through clinical trials

The pharmaceutical industry origin is important, in order to attest what are the core competences held by this industry. As it is known the pioneered pharmaceutical companies span out from the dye industry (Landes, 1969). As point out by Landes(1969) and Murmann(2003) this sector was totally based on chemistry competences during the second industrial revolution. As Murmann(2003) discuss the German dye industry, the author makes clear that the advances and the knowledge in chemistry were the most important element for Germany to lead this industry, especially during the first half of the XX century. As the pharmaceutical industry span out from the dye industry it brought with it its knowledge base, in that sense, the core competences of the pharmaceutical industry are based on chemistry.

The capacity to innovate systematically is closely related to the institutionalization of a R&D department (Mowery, 2006; Campos, 2010). The pharmaceutical industry not only developed such a department but it also started to employ a systematic way to innovate, carried out by the use of random screening methodology (Schwartzman, 1976; Gambardella, 1995). This technique consists of testing all possible molecules endlessly in the search for the desired therapeutic effects (Grabowski and Vernon, 1982; Gambardella, 1995; Schwartzman, 1976). Random screening is a drug discovery method that combines empiricism to scientific advances, whose acme occurred between the 1940s and 1950sand produced excellent results, given the number of NME generated at the time (for better picturing this information, see graphic 1 on pg. 12)(Achilladelis and Antonakis, 2001).

The random screening success enabled the development of antibiotics and antihistamines, which were the set of innovations that defined the industry in the 1930s (Achilladelis and Antonakis, 2001).Even though, the random screening was a highly advanced technique at the time, it was, still, a highly empirical method. The discovery of an antibiotic through random screening required numerous attempts. For example, to achieve an efficient sulfonamide 5,000 molecules were tested (Vernon and Grabowsky, 1982). In addition, Schwatrzman (1976) shows the impressive example of Leerdele Laboratories, which tested 103,000 chemical compounds to get only a clue of an active compound against tuberculosis, following that clue, the company tested another 600 compounds to achieve an efficient product. Indeed, the empiricism allied with a continuous trial and error dynamics were the main characteristic of the R&D in early modern pharmaceutical industry.

Although highly laborious, the results obtained through random screening outweighed any economic cost within this technique (Gambardella, 1995 Schwartzman, 1976; Vernon and Grabowsky, 1982). The whole process had the principle of a "roulette" with a high success rate (Nightingale *et al.* 2007). But, in the 1960s, this procedure started to show some exhaustion, and therefore productivity declined (Schwartzman, 1976; Grabowsky and Vernon, 2000; Nightingale, 2000; Nightingale *et al.* 2007; Gambardella, 1995; Vernon and Grabowsky, 1982). To solve the drop in random screening's productivity, companies sought to increase the efficiency of drug discovery methods (Nightingale, 2000), but still based on chemistry related competences, following a well succeeded trajectory that had already enabled the random screening to be successful.

One possible way to increase the efficiency of drug discovery activities, by further developing the industry' core competencies, was narrow the potential candidates through the construction of better hypothesis on how the new compounds would attack the disease (Gambardella, 1995, Amzel 1996, Bohacek*et al., 1996*).

Before the advent of biotechnology the pharmaceutical R&D was following a trajectory based on chemistry related capabilities. The industry was focused on overcoming the random screening problems by reducing the empirical factor and as consequence increasing the rationality of the innovative process. This new technique could be addressed in several ways as: discovery by design (Gambardella, 1995) or rational drug design.In sum, they are a rational approach for drug design. This new approach in the drug discovery activity is exemplified by the structured base design (SBD)technique (Amzel, 1996, Bohaeck et al. 1996, Gane and Dean, 2000;Schwardt*et al.*, 2003).

In this context, the answer sought by pharmaceutical companies was to develop ways to design a "perfect" molecule for the desired purposes, instead of randomly test numerous candidates. The structured

based design encompasses several techniques in order to build a component considering the needed purposes to be achieved, i.e. a molecule was designed to bind perfectly to a protein. Therefore, in a rational design approach, the ability to build better drugs relates, closely, to the understanding of how chemical receptors bind and the structure of target, as put by Amzel (1998) "design strategies rely on initially identifying a compound or compounds (the leads) that bind to the target" (Amzel, 1998, pg 367). Therefore, SBD has a simple logic, first the target[8] needs to be identify, through the target structure a new molecule is designed, that, in theory, is capable of binding to the target.

In order to design and discover the target structure some techniques are needed, being X-ray crystallography and NRM the most successful ones into discovering the target structure (Amzel, 1998; Gane and Dean, 2000 and Schwardt et al. 2003). In addition, Gane and Dean (2000) also gave the example of docking techniques that are computer algorithms that allow to test if the molecule can bind to the target, being it a *in silico* technique. For these authors the SBD is a viable possibility that depends on computer models (docking) for testing and designing molecule structures, but these models are not capable of dealing with several complexities that emerge from biding problems, therefore many computer tested molecule could not work in reality or could work in reality but not at the computer models (Gane and Dean, 2000).

All those techniques show an interesting fact, they are all derived from competences held by the pharmaceutical companies being them derived from chemistry and physics principles, none of these techniques are derived from molecular biology knowledge base, in that sense, they are not biotechnologies. Therefore, the SBD is a solution within the scope of the pharmaceutical industry knowledge base.

1.2 Drug discovery afterbiotechnology

So far, this study has discussed how drug discovery activities have attempted to reduced its empirical character and became more complex through a rational method. More recently, biotechnology has brought a new impetus to R&D through various ways of searching for new drugs and further expanding the research scope of pharmaceutical companies.

Biotechnologies dedicated to the pharmaceutical industry are a series of techniques that span out from the molecular biology scientific base. The discovery of the double helix by Watson and Crick in 1953 was "the triumph of molecular biology and the signal that it had arrived as a discipline". (Kenney, 1987, pg. 19).The first step into the establishment of a biotechnology-based industry was given in 1973 by the possibility of transferring organism's genetic material through plasmids[9], rather than using special types of virus. This technique was considered "(…) the simple pivotal event in the transformation of the 'basic' science of molecular biology into an industry" (Kenney, 1987, pg. 23). Thus, techniques based on molecular biology enable the genetic alteration, introduction of genes into organisms and ability to divide and to construct DNA sequences in vitro (Martin, 1999).

One of the promising advances in the field of research with extraordinary outcomes to biotechnology was the Human Genome Project (HGP), a significant research effort, undertaken from 1991 to 2003. The HGP aimed to decode the human genetic sequence. This research effort was a milestone in how biotechnology could be useful for the pharmaceutical industry (Macarron, 2011; McKelvy and Orsenigo, 2001 and Quéré, 2004). As an outcome, the HGP enable the opportunity of exploiting, economically, compounds that directly affect the interactions between genes expressions and the manifestation of diseases and, therefore, change the way diseases were diagnosed and treated (McKelvy and Orsenigo, 2001 and Quéré, 2004).

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[8]A **biological target** is anything within a living organism to which some other entity (like an endogenous ligand or a drug) is directed and/or binds, resulting in a change in its behavior or function

[9]Plasmids are DNA molecules capable of reproducing chromosomal DNA independently.

The HGP is a revolution in biotechnology (Macarron, 2011; Quéré, 2004) whose development took place outside the pharmaceutical companies. Nowadays, pharmaceutical enterprises come to depend more and more on biotech companies, which have been increasing their competencies for drug discovery. Therefore, the development and application of this new set of tools were done through partnerships between businesses.As a research effort that allows the creation of a new set of technologies, the HGP has established the infrastructure in which molecular biology dedicated to genetic was linked into solving important aspects of pharmaceutical industry problems (Martin *et al.*, 2011). This process enhanced the interaction between large pharmaceutical companies and small biotechnology companies (Quéré, 2004 and Martin *et al.*, 2011).

The genomic advance reinforces the path of increasing complexity that encompasses the drug discovery activities. In this cycle technological progress is technologically appropriated by the pharmaceutical companies, therefore, it may increase the search activities productivity, as a result broadening the treatment mechanisms and, at the same time, increasing the drug search activities complexity (Nightingale and Madhi, 2006). In this context, there is a need for specialized companies to participate in the innovative process of the large companies, due to the impossibility of any enterprise to handle such complex and diverse activity (Gassman*et al.*, 2004; Martin *et al.*, 2011; Quéré 2004). This process lead to a

> "growth in externally supported R&D, a new networked industrial structure has evolved, dominated by large firms this facilitates the rapid growth in the number of small biotech and genomics forms seeking to discover new drugs since the 1980s"(Martin *et al.*, 2011, pg 153)

The techniques encompassing biotechnologies has brought new impetus to the pharmaceutical industry. But those changes are, also, associated with the evolution of the pharmaceutical industry organization, this point will be later discussed.

Biotechnology is nowadays a tool – or methodology – for new molecules discovery with a, possible, high rate chance of creating active components (Gambardella, 1995; Gisling and Noteboon, 2006; Henderson *et al.* 1999; Nightingale, 2000; Powell *et al.*; Santos, 2003; among others). Biotechnology enables the use of new research technologies, in addition to those already existing in the pharmaceutical industry. Thus, biotechnology as a new methodology can increase the pharmaceutical industry ability to generate possible candidates for new components (Gisling and Noteboon, 2006; Nightingale, 2000; Nightingale and Madhi, 2006; Powell *et al.*, 1996; Santos, 2003).

Biotechnology has established itself as an "industry" dedicated to drug discovery and its success is evident when one observes its use for these kind of activity (Drews, 2000, Hopkins *et al.* 2007; Pereira and Williams, 2007). The adaptation of biotechnology to this type of activity was successful, especially, regarding the technology and knowledge appropriation conducted by large pharmaceutical companies.

The incorporation of biotechnology means that the drug discovery activities are relying even more on biotechnology competences as this search activity evolves.

> "[The] discovery process begins on the scale of the gene often demanding molecular biology to connect [the gene] human disease and determine the function of these same genes ... So the drug discovery underwent a change towards molecular biology computing and genomic science in recent years." (Schimid*et al.*, 2001, pg 42)

This statement makes clear that pharmaceutical companies have been growing a greater dependence on the knowledge and skills derived from molecular biology, especially, for its drug discovery activities. Nowadays, Big-Pharma that do not hold expertise in biotechnology are unable to develop new medicines.

Mostly interesting, through biotechnology a new trajectory was put in practice among the pharmaceutical R&D. The biotechnologies gave the discovery activities much larger scale into screening molecules. The High Throughput Screening (HTS) is one of the most prominent biotechnology and it has increased, significantly, the capacity of enterprises to screen new compounds through patronization and automatization (Nigtingale, 2000; Pereira and Williams, 2007).

The HTS is, basically, the automation of random screening through biotechnologies enabling companies to test more components in a very short time (Nightingale, 2000; Hopkins *et al* 2007, Pereira and Williams, 2007). According to Houston and Banks (1997) before HTS an enterprise could possibly check 75000 components of the same class for 20 targets. The HTS allowed testing a million components, within a

class, for 100 targets. The HTS was a breakthrough among techniques to test components. It is a technology that increased the scale in the drug discovery process, as it enhances the number of candidates for new medicines. Yet, many say that this technology was unable to improve the quality of components[10] (Nightingale 2000 Nightingale and Madhi 2006; Gassman*et al*., 2004).

The extensive use of HTS, generating good results (see table 1, pg. 10) and with dedicated teams specialized on running this technology (Macarron, 2011; Pereira and Williams, 2007) a new R&D path based on these competences was built and developed outside the pharmaceutical industry. Those technologies follow a different logic from the rational drug design approach (Amzel, 1996; Macarron et all. 2011; Willians and Pereira, 2007).Whereas the structure base design looks to construct a specific molecule for a desired target; the HTS enables the pharmaceutical industry to screen several known compounds in order to find some therapeutic effect. One technique follows a rationalization path while the other follows a path in which the pharmaceutical industry can test more molecules in less time (Gane and Dean, 2000).

Although being recent the HTS has already proved to be effective on generating leads, not only that but this technique is well diffused over the large pharmaceutical companies, showing that these companies were quick into incorporating these technique. The next table shows some important drugs, whose hits were found through HTS, and the companies responsible for the discovery.

Table 1: Examples of recently approved drugs with origins in HTS hits

Drug (US trade name; company)	Indication	Year HTS was run	Year of FDA approval
Gefitinib (Iressa; AstraZeneca)	Cancer	1993	2003
Erlotinib (Tarceva; Roche)	Cancer	1993	2004
Sorafenib (Nexavar; Bayer/Onyx Pharmaceuticals	Cancer	1994	2005
Tipranavir (Aptivus; BoehringerIngelheim)	HIV	1993	2005
Sitagliptin (Januvia; Merck & Co)	Diabeter	2000	2006
Dasatinib (Sprycel; Bristol-Myers Squibb	Cancer	1997	2006
Maraviroc (Selzentry; Pfizer)	HIV	1997	2007
Lapatinib (Tykerb; GlaxoSmithKline)	Cancer	1993	2007
Ambrisentan (Letairis; Gilead)	Pulonary Hypertension	1995	2007
Etravirine (Intelence; Tibotec Pharmaceuticals)	HIV	1992	2008
Tolvaptan (Samsca; Otsuka Pharmaceutical)	Hyponatraemia	1990	2009
Eltrombopag (Promacta; GlaxoSmithKline	Thrombocytopaenia	1997	2008

Source: Macarron*et al*.,2011, pg. 190

Many could think that different logic approaches are mutually exclusive, but in the pharmaceutical industry these two approaches are used together(Amzel, 1998; Schwardt, 2003; Macarron et all. 2011; Pereira and Williams, 2007). In today's pharmaceutical industry HTS is one of the main generators of leads, according to Macarron*et al.* (2011) from the 58 drugs approved from 1991 to 2008, 19 had their origin through the use of HTS, as partially shown in the previous table (see table 1, pg10).

Biotechnological and rational design approaches are, indeed, complementary as put by Amzel (1998)

> "the process of structure base design requires identification of a suitable protein, determination of the structure of the target protein, implementation of an easy and reliable high-throughput screening assay, identification of a lead compound development of computer assisted methods for estimating the affinity of new compounds and access to a synthetic route to produce the design compounds"(Amzel , 1998 , pg. 366)

Clearly it was shown that the discovery of new molecules is a highly multidisciplinary step (Drews, 2000; OTA 1991; Schwartzman, 1976; Gambardella, 1995; Gassman*et al.*, 2004) whose evolution is carried out by the incorporation and construction of different competences and technologies. Therefore, the technical evolution has created a demand for biotechnologies in the drug discovery activities.

[10]Gane and Dean (2000) attest that HTS is capable of producing workable molecules in the same rate as SBD

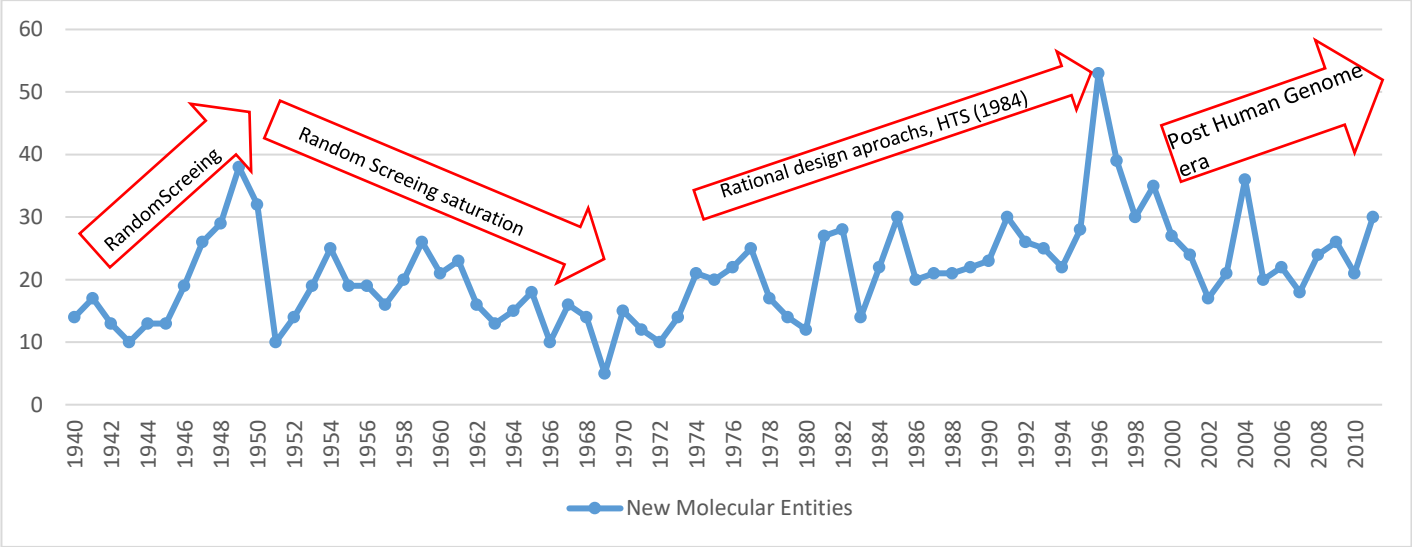
This section and the previous one were focused on the technological history of the pharmaceutical industry, encompassing the evolution of drug discovery activities. Through this sections was possible to show the incorporation of biotechnology into the drug discovery activities. Nevertheless, the incorporation of biotechnology in the pharmaceutical industry is not a purely technological phenomenon. This process is linked to changes in the way the global industry is organized. The Big-Pharma in a movement of decentralizing its research activities resort to external sources of innovation, mainly, biotech start-ups in an attempt to enhance its drug discovery activities. However, technological and organizational changes in the pharmaceutical industry occurred at the same time, so, it is impossible to attest that one lead to another. Therefore, in this study these two changes occupy separate sections.

2 The growing importance of small biotech companies

On the previous section it was explained the several techniques used in the pharmaceutical industry for drug discovery and how they come from different knowledge bases. The argument of this article implies that the small enterprises are important agents in the pharmaceutical industry set of innovations. Therefore it is necessary to show the growing importance of these small enterprises in the industry' innovative output

As happens in all high-technology sectors the main driver of competition is innovation. For the pharmaceutical industry the NCE or NME are the candidates for new medicines, they were already tested and have a great chance of becoming new products. In that sense, enterprises that are producing more NME are the ones with the most dynamic R&D. The first important step is to look atthe NME approval over the years, as shown in graphic 1 (pg. 19). In addition in this graphic it is shown the main technologies used for drug discovery in each period as it was described in the previous sections

Graphic 1: New molecular entities approved by the FDA over the years and the main technologies used for drug discovery

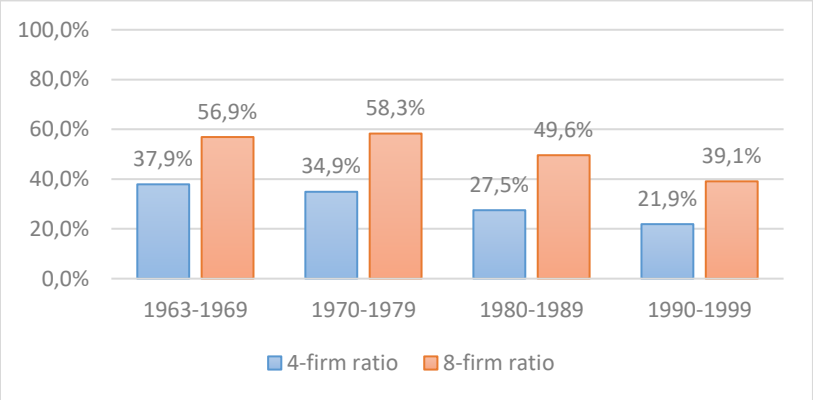


Source: Matos, 2016

By looking, only, at the NME approved over the years (se graphic above) it is possible to attest a cyclical behavior, there are periods, which the approvals are high, and periods in which approvals are below average. When one combines the approvals with the main technologies a correlation starts to appear. It is possible to glimpse technology as generator of these cyclical behavior. Therefore, as the NCE approvals starts to decrease a new technology can increase the NME again, in addition to new technologies these movements of increase are associated with learning curves and technology improvement.

Yet another interesting fact is unveiled as a one takes a closer look into some specific aspects of the NCE. First the share of NCE approved that was originated on large pharmaceutical enterprise's R&D is decreasing even though new technologies are been incorporated, this movement is shown in graphic 2 and figure 3 on pg. 13 and 14.

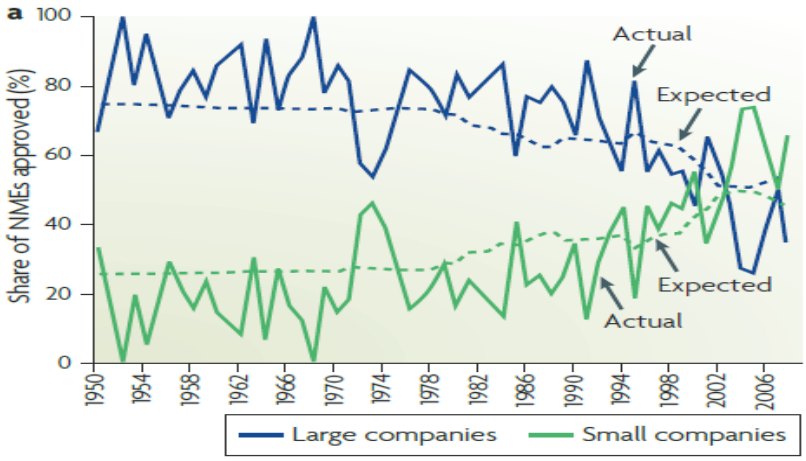
Graphic 2: Concentration of output in the pharmaceutical industry. Share of total United States new molecular entity (NME) approvals by the leading four and eight firms in number of approvals for the period.



Source: (DiMasi, 2000, pg 1183)

The larger enterprises are losing space on the total of NCE approved. But not to other large companies, this place has been taken by small pharmaceutical companies. According to Munos (2009), in 2004 large and small companies had each registered 50% of the NME; in 2008, small businesses' share grew,reaching70%. Amore detailed analysis of the NME shows a change in their nature and origin. The new NME are still focused on therapeutic areas already supplied by a wide range of products. Whereas, science and research have expanded and diversified the technology frontier into new or unexplored therapeutic areas (Paul *et al.*, 2010; Pammolli, 2011; Munos, 2009). According to Paul *et al.* (2010), in 2009, only 29% of the NME could be actually considered as an improvement when compared to drugs already in use. The evolution of NME indicates, at the same time, a change in the innovative dynamics of the pharmaceutical industry as well as an inability of large companies to diversify their innovations.

Figure 1: Share of NME approved by large and small companies



Source: Munos, 2009, pg. 965

The graphic above makes almost undeniable the fact that small pharmaceutical enterprises are becoming more innovative than the large ones. The Big-Pharma advocates that the rising cost of developing new molecules limits and restricts the success of their innovative activities. Many studies have tried to calculate the cost of a new molecule, more recently DiMasi and Grawbowski (2007) and Scherer (2010), however, these studies are marked by difficulties and discrepancies in estimating the actual cost of molecules (Morgan *et al.*, 2011). Despite this problem, the study conducted by DiMasi and Grawbowski (2007) is notable for one interesting conclusion: the costs for developing new molecules have steadily increased over the years, but they are relatively equal for pharmaceutical and biotechnology companies. In 2005 biotech companies would spend US $ 1,241 billion for each new molecule, while the costs of new molecules for pharmaceutical companies is about of US$ 1,318DiMasi and Grawbowski (2007).

Biotechnology is as expensive as pharmaceutical industry in producing new drugs. Therefore, the increasing NCE registered by small companies (Munos, 2009) is not an outcome of cost reduction. Therefore, the production costs of new drugs are not able to explain or show how the industry is dealing with its R&D problem. Second, the technological evolution of this industry raise some important elements over this discussion. But the incorporation of new technologies goes beyond a technical choice or a simple deterministic technological trajectory. The way the industry is dealing with its R&D must take into account how the industry has organized itself as new actors- the biotechnology- appeared as a drug discovery industry

3 Corporate strategies for incorporating biotech competences in the innovative process.

In this section it will be discussed how the demand of new technologies is being satisfied. This process is linked to changes in the way the global industry is organized. The Big-Pharma is decentralizing its research activities resort to external sources of innovation, mainly, biotech start-ups in an attempt to incorporate new competences to its drug discovery activities.

The creation of a biotechnology industry, composed by small biotech enterprises, focused on solving pharmaceutical problems can be seen as a typical American movement. Although many nations tried to emulate a similar system for biotech industry, based on regional clustering, venture capital and incentive policies, the cases of success outside the US are rare, being Cambridge the one that stands out (Malerba and Orsenigo, 2015).

At the end of the 1970s and beginning of the 1980s, the biotechnology and pharmaceutical industry were organized as follow. Biotechnology was scattered through universities within several research projects conducted by professors and in small enterprises that spanned off from the academic environment (Audretesch, 2003 and Kenney, 1986, Zucker and Darby, 2002). Through several government incentives biotechnology was fostered and it left the academic realm of research to become a sector based on academic start-ups (Audretesch, 2003; Kenney, 1986; Malerba and Orsenigo, 2015; Powell *et al.l.*, 1996). Although biotechnology and pharmaceutical technology were highly complementary especially in the drug discovery activities, the pharmaceutical enterprises had little competencies in this field. In the end

> "[i]n the emerging field of biotechnology, the lack of corporate expertise led to an all unique new arrangements between industry and corporations at institutional levels that are affecting a number of universities traditional values and norms" (Kenney, 1986, pg 28)

According to Sharp (1999), the large pharmaceutical enterprises in a first moment did not engage in creating biotechnology competencies, but they kept some research inside to develop some absorptive capabilities (Cohen and Levinthal, 1989) and to keep up with the technical advance. In a second moment, in the mid of the 1980s, the Big-Pharma started to interact with small biotech enterprises, in particular, through collaborations and acquisitions. Those interactions were attempts to internalize some critical biotechnology competencies (Ahuja and Katila, 2001; Cassiman and Veuglers, 2006; Cullen and Dibner, 1993; Malerba and Orsenigo, 2015; Powell *et al.l.* 1996; Makri*et al.*,2010; Gambardela, 1995; Hagedoorn*et al.*,2002; Cloodt and Hagedoorn, 2006; Sharp, 1999). Almost all Big-Pharma have some scouting team that looks for promising new technologies developed by small biotech companies. Those scouting teams are institutionalized actions towards increasing the interaction with small biotech corporations (Matos, 2016).

The biotechnology industry is, mainly, composed by small companies[11], according to the OECD[12], in 2013, 67% of the biotech companies in the world had less than 50 employees and 72% of the US biotech companies had less than 50 employees. These small enterprises have a reduced financial capacity but are potentially innovative. On the other hand, the Big-Pharma are financially robust, however, they are facing a crisis in their innovation productivity. It is easy to comprehend that one of the ways for overcoming the weak points on both sides is through interaction (Matos, 2016). According to Malerba and Orsenigo 2015, pg 15:

> "…[L]arge corporations realized that they could not rely solely on their internal knowledge to discover and developed new drugs. The prospect of the expiration of most key patents in the coming decade coupled with strengthening competition from a generic segment, put pressure on attempts to discover and develop new blockbusters. Big companies reacted to this challenge first through a wave of mergers and acquisitions. Second as already mentioned they increasingly started to rely on small biotech companies and academics for new molecules and research technics, though licenses and collaboration agreements".

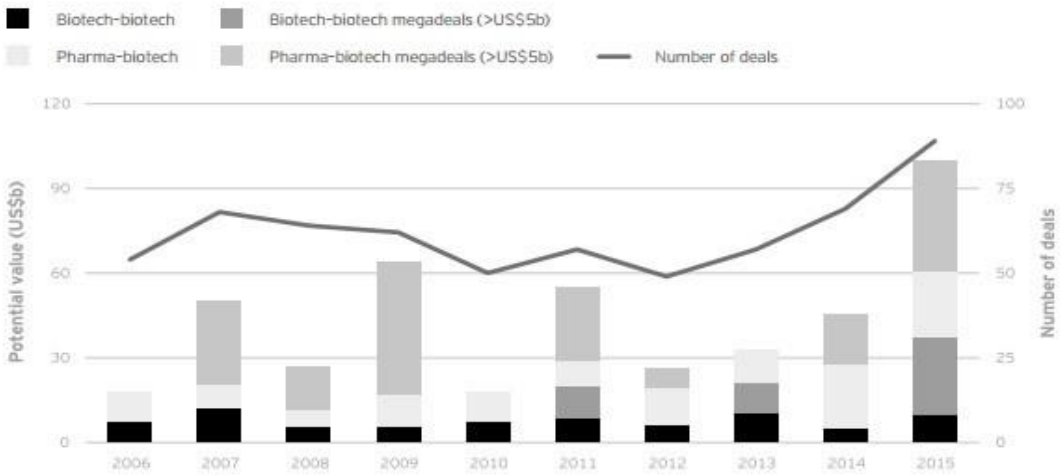
[11]Some of them being already large enterprises, like Amgen.

[12]OECD Science, Technology and Industry Scoreboard 2013 indicators on biotechnology updated on july 2015

Alliances dedicated to research reduce the innovation activity risk and give the financial help needed for the small enterprises to develop its products and enhance the Big-Pharma's capabilities regarding biotechnology (Audretsch, 2003). Not only that, alliances are a way for large companies to obtain information about the portfolios and pipelines of small businesses, therefore, to reduce uncertainty and facilitate the acquisition. In this matter, alliances can have a pre-acquisition role allowing large pharmaceutical enterprises to gather better information enabling acquisitions to have a better chances of success (Higgins and Rodriguez, 2006). Actually, when the collaborations happen before the acquisitions, it becomes an important step for a successful negotiation and incorporation (Matos, 2016).

Along with collaborations, M&A (mergers and acquisitions) are seen as an important strategy for firms, allowing them to obtain and enhance its technological competencies (see next figure 3, pg.17). There are several types of acquisitions driven by several factors, which may change according to sectors and enterprises size (Chakrabarti*et al*, 1994). Nevertheless, this study deals with acquisitions driven by technological aspects. Therefore, when enterprises engage in technological acquisitions, which are increasing over the years (see next figure) they are intending to increase their technological outputs (Anderssen and Xiao, 2015; Ahuja e Katila, 2001; Hagedoorn*et al.*, 2002; Cloodt and Hagedoorn, 2006; Makri*et al.*, 2010).

Figure 2: M&A in the pharmaceutical industry, in the USA and Europe, between 2006 and 2015



Fonte: Beyond Borders, 2016, pg 65

The graphic above shows exactly that M&A between pharmaceutical and biotech enterprises cannot be ignored in terms of deals and value. The incorporation of small biotech companies into large pharmaceutical firms follow a model, in which research teams are maintained, and the small biotech firm productive capacity is dismantled. Each purchased company acts as a new R&D team, specialized in biotechnology, which was added to the set of innovation activities held by the large corporations.(Schweizer, 2005). This integration model highlights the goal of pharmaceutical companies as the incorporation of biotechnology capabilities into their R&D through this type of acquisitions. Although this M&A model is not unanimous among large pharmaceutical companies, it indicates changes in the innovation process and the nature of M&A.

The small enterprises ability to innovate is maintained through its incorporation as an R&D unit (Schweizer, 2005). By combining acquisitions driven by technological elements and the model of integration showed by Schweizer (2005), it is possible to attest that acquisitions of small biotech enterprises are driven by the potentiality that small biotech enterprises can bring to the Big-Pharma's R&D. Several studies have pointed a positive relation between acquisitions of small enterprises and an increase in the acquiring technological output (Anderssen and Xiao, 2015; Ahuja and Katila, 2001; Hussinger, 2010; Szücs, 2014).

The form the industry has organized its R&D shows how biotechnologies is being incorporate by large pharmaceutical enterprises. Those enterprises do not hold strong competencies on biotechnologies, but they have financial power. On the other hand, small biotech enterprises have contingencies regarding their pipeline especially on running the clinical trials. In addition, the biotechnology sector is organized among several small enterprises that sometimes have just one candidate for a drug. These two actors show an evident organizational complementarities because the small enterprises are like R&D facilities ready to be bought, because of their size and also because biotechnology became specialized on drug discovery techniques (Schweizer, 2005).

On the organization side, authors such as Comanor and Scherer (2013); Gleadle *et al.* (2013); Light and Lexchin (2012); Hopkins *et al.* (2012); Higgins and Rodriguez (2006); Munos (2009); Paul *et al.* (2009), among others, attest that large pharmaceutical enterprises have chosen the acquisitions as an option for the acquisition of new technologies. These two different size enterprises, also, build a clear division in their R&D activities, whereas, the small enterprise deals with new technologies and the discovery of new drugs; the large pharmaceutical enterprises are responsible for conducting the clinical trials. Therefore, the activities closer to research is where the small enterprise competence is employed (Matos, 2016).

The incorporations of new technologies, through acquisition of small enterprises, became a well-established behavior, up to 50% of the large pharmaceutical enterprises' new technologies were projects that started at small biotech enterprises (Matos, 2016). In addition, as shown in table 2 (pg. 21), the majority of enterprises, at the time they were acquired, had their main products at the early stages of R&D. Although, this fact indicates that enterprises are giving up the early stages of research, the Big-Pharma still can profit from small enterprises innovation.

Table 2: Overview of the acquired biotech enterprises form 2005 to 2012

Companies		Development stage of main product	
Country	**Percentage of the total acquired**	**Stage**	**Percentage of the total acquired**
Austria	1%	No product	8%
Canada	1%	Stage 0	17%
Switzerland	3%	Stage 1	13%
France	2%	Stage 2	21%
Germany	2%	Stage 3	13%
Holland	1%	Stage 4	2%
UK	11%	Product at the market	26%
USA	78%		

Source: Matos, 2016, pg. 69

The success of enterprises' innovation is linked to the company control over complementary competences. Sometimes, it is not enough to dominate the core competences, because due to the sectors characteristics an imitator could better appropriate the spill-over effects and dislocate the enterprise that had first introduced the innovation. In that context, the complementary competences can work as a mean to protect the innovation and reduce the spill-over effects (Teece, 1986).

In the pharmaceutical industry the small biotech companies do not control the whole R&D process, they have strong capacities on the first stages of R&D, but, these enterprises do not have expertise and financial strength to conduct the clinical trials or late stages of innovation. Whereas, the Big-pharma have a complete knowledge over the whole R&D, not only that, they also have financial capabilities, and control over complementary competences, especially marketing, sales channels and access to physicians. Therefore, by controlling these complementary competences and the core competences, the Big-pharma can incorporate and appropriate the technology developed by small enterprises.

Looking at the way the pharmaceutical sector is organized today, the large pharmaceutical and small biotechnology companies are organized, networked, through collaborations, in order to innovate. This behavior indicates that biotechnology "follows a well-established, historical pattern of slow and incremental of technological diffusion"(Nightingale and Martin, 2004, pg. 564) in which new technology is being

incorporated gradually to large pharmaceutical companies (Zucker and Darby, 1997). Thus, the coexistence of these two types of enterprises and an increasing number of M&A and collaborations between them shows that this is how small companies research effort are further incorporated into large pharmaceutical companies pool of competencies.

CONCLUSION

The pharmaceutical productivity crises has created a need for large pharmaceutical enterprises, in order to satisfy this need those enterprises are seeking for technological solutions that are incorporated through corporate strategies, mainly, alliances and acquisitions.

This article linked technical evolution to organizational strategies and showed how the latter is used to incorporate the first. This was done through the observations that today's pharmaceutical industry has changed its R&D into a highly complex and multidisciplinary activity, where small biotech enterprises are becoming increasingly important in bringing new capabilities to the old and well-succeeded Big-Pharma.

The investment in the new technologies occurs differently from the way they were conducted research in past decades. The pharmaceutical industry innovative process between the 1930s and the 1970s was carried out by the companies in a "lonely" way; the company was able to build competencies for technologies efficiently, especially when drug discovery was mainly based on chemistry. Currently, the establishment of biotechnology as a drug discovery industry has added new actors into the innovative process.

On technological side, this article has shown the technological evolution of drug discovery activities focusing, mainly, on two technologies, the structure base design and the HTS. The SBD follows a rational drug design logic and it could be classified as a technology that encompass the core competences of large pharmaceutical enterprises, this technique is, somehow, the technical evolution of a chemistry based trajectory, especially because it uses X-ray crystallography and NRM. On the other hand, HTS comes from a different knowledge base, this technique has unfolded from molecular biology advances, therefore, HTS was developed outside the pharmaceutical industry and it is not based on the core competences of a large pharmaceutical industry.

The new capabilities are incorporated by the Big-Pharma through interactions that enable the small biotech enterprise to contribute to the large pharmaceutical enterprise. As biotechnology becomes a complementary technique and, in some cases, a substitute technology in the pharmaceutical industry's R&D, the small enterprises can contribute to large pharmaceutical enterprises by building technologies and capabilities that will be used to enhance the Big-Pharma's research productivity and efficiency. As this process evolves R&D becomes even more multidisciplinary.

Technology complementarity, between pharmaceutical industry and biotechnology, is a condition for the competences being of large pharmaceutical company's interest. However, the process of incorporating new competences are set both on technology and on the way the pharmaceutical industry is organized. These two elements can mold the enterprises behavior.

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