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THE COMPLEXITY OF BIO-MOLECULES DEVELOPMENT AND BIOTECH FIRMS: CAN ALLIANCES HELP FILL THE VOIDS?

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ABSTRACT

Biotechnology is very complex, mainly due to the high investments required and the uncertainty of the long and critical R&D for the bio-molecular product development. In addition, firms must endure the risks and extreme long time from discovery to final product. The development of new pharmaceutical bio-molecules needs more than ten years of research and around 800 to 1.3 billion U.S. dollars. This critical convergence is so intricate that the success of biotechnology firms is extremely harsh, and many of them disappear in the first years of their lives. A conceptual framework is developed that incorporates potentials benefits or inconvenient associated to the use of strategic alliances. The paper proposes to identify if strategic alliances could be a significant player coveted in order to acquire the resources and skills gaps. Thus, the paper sets out the extent to which alliances could be an advantage for the acquisition of new dynamics capabilities and help to create value to these firms (or not). The goal is to discuss the complexity surrounding the creation and posterior development of biotechnology firms and evince the role that could play potential alliances on the development of these firms and of course elaboration of new bio-molecules. The success of biotechnology firms and bio-molecules will depend on several variables, not just one or two specifically. The creation of biotechnology firms does not seem to be very complicated in itself. However, that is complex, is how to make these organisations can be sustained over time. It seems that it is too complex to do so, starting with the very high costs associated with the development of bio-molecules, as well as the resources and skills necessary to achieve this. Finally, strategic alliances can come help fills this lack, without being a panacea, nor solve all the disadvantages and drawbacks associated.

KEYWORDS: ***Biotechnology, Alliances, Bio-molecules, R&D, Cost, Financing.***

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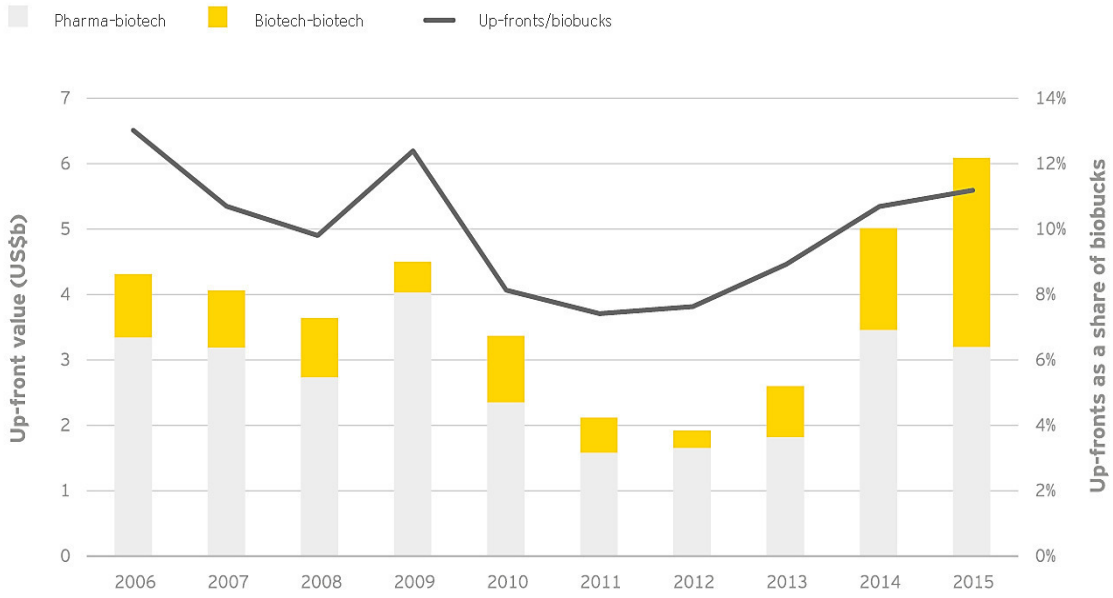
INTRODUCTION

The chemical industry, considered as the first to have had a scientific base, constitutes a very heterogeneous sector. Molecular biology is complemented by the chemical industry in its steps, and the integration of these two fields of knowledge has brought out the young biotechnology sector, which is indivisible for developing bio-molecules. In addition, the development of biopharmaceuticals firms from 1920s to now results in the emergence of medium and large multinational companies intensives in R&D that work today in biotechnology[1]. The biotechnology firms were restructured while being interested in the always-promising sectors of pharmacy and agrochemicals. These two sectors form oligopoly structures in an environment of very high competition. In these industries, the R&D department is the primary component of importance, and the costs to complete an innovating product are often very high. For example, it will be necessary to "invest" from ten to fifteen years and, between 800 million U.S. and more than 1.3 billion dollars U.S. on average for a new bio-molecule to be available on the market, included in these figures are the opportunity costs of development[2]. The knowledge conditions are the primary sticky in the biotechnology sector; high uncertainty, asymmetries and high transactions costs produce a critical effect and, the strategic alliances could be one answer at this dilemma[3]. This article aims to shed light on the ambiguities of a complex causal structural strategic alliance, notably (asymmetric differences and opportunism)[4-5]. In fact, a relative big number of studies have been made on the relationship between alliances, advantages, disadvantage or performance (taken in the broad sense: profitability, but also growth, and stability, among others). However, there is less work to explain the influence of partnership on specific growth or failure of biotech firms. Bas and Niosi (2007)[6] have shown that in the biotechnology sector, the small firms have systematically lowed rates of survival and intellectual property; and, in this ecosystem, the alliances structure may assist these small biotechnology firms (SBF) in attaining a better performance. Notwithstanding the research of Ernst & Young (2016)[7] shows that the up-front value (in billions dollars U.S.) of alliances between biotech-biotech firms and biotech-pharma firms is down and up systematically, in the United States and Europe. (Figure1).

Figure 1
US and European Alliances Based on up-front Payment, 2006-2015



Source: Ernst & Young, 2016[7]

Yet, as shown in Table 1, transactions (expressed in millions dollars U.S.) inside of partnerships between biotech-biotech firms and/or biotech-pharma firms are increasingly important.

Table 1
Alliances with Big up-front Payments, 2015

Firm	Country	Partner	Country	Up-front payments (US$m)
Celgene	US	Juno Therapeutics	US	1,000
Gilead Sciences	US	Galapagos	Belgium	725
Sanofi	France	Regeneron Pharmaceuticals	US	640
Celgene	US	Astra Zeneca	UK	450
Sanofi	France	Lexicon Pharmaceuticals	US	300
Astra Zeneca	UK	Innate Pharma	France	250
Novartis	Switzerland	Aduro Biotech	US	225
Janssen Pharmaceuticals	Belgium	Achillion Pharmaceuticals	US	225
Bristol-Myers Squibb	US	Promedior	US	150
Biogen	US	Applied Genetic Technologies	US	124
Merck Serono	Switzerland	Intrexon	US	115
Vertex Pharmaceuticals	US	CRISPR Therapeutics	Switzerland	105
Merck & Co.	US	ModerRNA Therapeutics	US	100
Mistsubishi Tanabe Pharma	Japan	Akebia Therapeutics	US	100
Intrexon	US	University of Texas M.D. Anderson Cancer Center	US	100

Ernst & Young, 2016[7]

Many factors influence the behaviour of the firms and they show very different performances in an environment of similar characteristics. The literature shows that companies do not have the same components nor the same competences or routines. Companies generate a variety of different dynamics capabilities, as if each one of them were equipped with limited rationality or influenced by the social and collective nature of learning[8-11]. Firms do not have identical resources and they do not react in the same way either to same internal or external stimuli, which results in certain companies growing much more quickly than others[12-13]. In this complex scenario, the question that we will try to answer is: Can alliances help fill the voids stemming from the complexity of the bio-molecules development processes performed by biotechnology firms? We will analyse, if the biotechnology firms with alliances develop an advantage in the acquisition of new capabilities, and if they are more efficient in developing new products. Is the number of alliances between biotech-biotech and/or biotech-pharma increasing or decreasing in the last years? Strategic alliances are a widely used means of gaining access to know-how and are positively related to new product development[14]. In despite, technological and commercial alliances between specialized biotechnology firms (SBF) and large companies (generally multinationals pharma) are not sufficient to support the cost and the fast growth of the technology. The extensive work done from 1980 in the management of biotechnology firms, particularly on the alliances, has tried to present these like the central axis of the growth of biotechnology firms. Although, the cooperation agreements are extremely important in the search of missing competencies and resources (access to capital, distribution chains, asymmetrical reduction, greater and better protection of the intellectual property, etc.), we could also say that the alliances by itself do not explain and nor justify the growth of many biotechnology firms. Alliances are very important for the acquisition of market, capabilities, knowledge and resources, but this fact is only one variable in a portrait that we could describe as "typical" in biotechnology, which is observable in the "virtuous circle" growth of the firms. The companies that make experimental research in human health and genomic, usually protect their inventions by patents, can attract venture capital or any other form of financing and will growth more quickly and better than others will. This strategy may open the doors to potential alliances.

Theoretical Aspects

For several years, alliances between independent companies have not ceased to multiply, in order to start R&D programs, production scheduling or for the development and marketing of technological products[13-15]. The explanations, which we find in the literature, that justify the existence of such alliances, are numerous and sometimes ambiguous. Several authors claim that the technological environment is in constant transformation and the speed of change is very fast[16]. Thus, alliances with large established companies can be to pursue the development of their technologies, as well as to guarantee their subsequent commercialization[3]. The facts look that the alliances between biotech-pharma continue to move about thousand million dollars U.S. around the world, as it is shown in the table 2.

Table 2
Big Biobucks Alliances, 2015

Firm	Country	Partner	Country	Total potential value (US$m)	Up-front payments (US$m)
Vertex Pharmaceuticals	US	CRISPR Therapeutics	Switzerland	2,625	105
Bristol-Myers Squibb	Germany	UniCure	Netherlands	2,307	82
Sanofi	France	Regeneron Pharmaceuticals	US	2,165	640
Gilead Sciences	US	Galapagos	Belgium	2,075	725
Amgen	US	Xencor	US	1,745	45
Sanofi	France	Lexion Pharmaceuticals	US	1,700	300
Ultragenyx Pharmaceutical	US	Arcturus Therapeutics	US	1,570	10
Sanofi	France	BioN Tech	Germany	1,560	60
AstraZeneca	UK	Innate Pharma	France	1,275	250
Bristol-Myers Squibb	US	Promedior	US	1,250	150
AbbVie	US	Halozyme Therapeutics	US	1,193	23
Vertex Pharmaceuticals	US	Parion Scinces	US	1,170	80
Biogen	US	Applied Genetic Technologies	US	1,124	124
Amgen	US	Kite Pharma	US	1,110	60
Janssen Pharmaceuticals	Belgium	Achillion Pharmaceuticals	US	1,100	225

Ernst & Young, 2016[7]

The term “alliance” or “cooperation”, as Yoshino and Rangan (1995)[17] and Ingham and Mothe (2000)[18] explain, generate very heterogeneous realities. This concept is sometimes unclear, because it is employed to express all the contractual forms, such as joint ventures, consortia, licenses, distribution and R&D agreements, etc. To define alliance is a complex task. This is due to the ambiguity of the terms and the generic use made of these concepts that cover innumerable possibilities (“coalition”, “partnership”, “agreement”, “cooperation between firms”, etc). The concepts of cooperation or alliance are often ambivalent[19]. The expression “cooperation” relates to the relations established in a durable way to divide limited resources, without putting the autonomy of the partners in jeopardy. In addition, the duration of alliance, according to several authors, is more often of a strategic nature[16]. Alliances are contractual, formal cooperation agreements, as opposed to the multiple informal forms of cooperation. The definitions show the diversity of concepts. Combe (1995)[20] defines alliance as an association of a formal or informal character, between two or several concurrent companies (or potential competitors) or complementary, with or without financial participation. The allied companies try to rather develop, produce or market goods by sharing their competences than resorting to the commercial contract whose range is limited to the short term or total integration, marked by the disappearance of an entity. This concept coincides with that proposed by Jolly (1995)[21]. The author adds that the acquisitions of unilateral grant of licenses, research under contract or total fusions are operations that escape to the alliance. For Gulati (1999)[22] strategic alliances are voluntary cooperation agreements that imply exchanges, division or co-development and which can include contributions such as financing, technology or specific goods. The growth of high technology companies, based on knowledge, plays a very important role in the development of the agreement. However, this role can be played in various ways. For example, the major genomics firms employ an extensive network strategy across multiple firms. The value accrued to all increases substantially with the diversity of minds addressing the application of the new knowledge[23]. Either, the companies choose internal development independently, or they prefer external growth hierarchically or cooperatively. It is well illustrated, that the majority of alliances in the biotechnology sector are vertical in collaboration between two organizations, under an alliance contract, engaged in many activities like R&D or financing in the value chain[24]. Evidence suggests that complementary business level strategic alliance, especially vertical ones, have the greatest probability of creating a sustainable competitive advantage[25]. In addition, alliance can help the partners to rise in the market hierarchy[26] or development and or access to foreign market[13-27]. However, Audretsch and Feldman (2003)[3] consider that strategic research alliances provide the implements for knowledge spillovers, but, at the same time, it is difficult to measure the benefits in terms of knowledge generation and refinement. In such situations, each partner contributes with a part of his resources and competencies including technology, equipment, skills or resources, financing, know-how, knowledge to create a novel technological approach, among others[28]. In response to their contribution, the partners will seek to benefit from the outcomes, which can be shared, or not, in the intellectual property or any other forms of advantage considered in the agreement. The knowledge is created through the partners in the alliance[18-28] as a result of the collective learning generated by the partners during the cooperation agreement. More the agreement is longer, dynamic and interactive, much more the possibilities of learning and accumulation of knowledge will increase for the partners. The experience of partner is critical for the success or failure of the alliance[29-30].

Alliance Management

Before approaching the modes of alliance management, it is interesting to note that biotechnology firms are involved in alliances in all stages of the value chain, that aim at exploitation of existing technology, by partnering with organizations that are closer to the market (big or

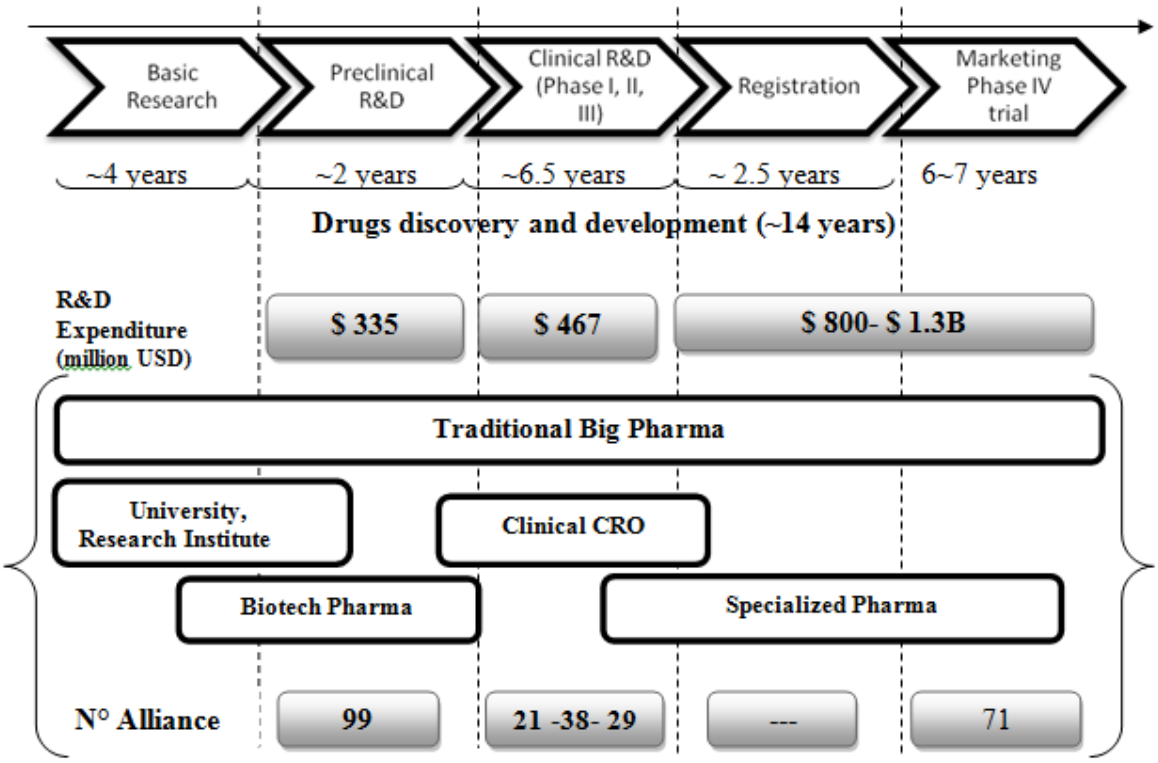
medium pharmaceutical companies, clinical research organizations, or large-scale manufacturers). These alliances often focus pass through complex clinical trials, gaining FDA approval for example, and marketing it to customers[31-32]. This critical situation, can be used as the base for better negotiating the "contract agreement", that should include program objectives; agreement duration; the implement choice; clarification of mutual interest; instruments of direction, execution and control of the agreement; rules or principles of exploitation and how to protect results; and finally, the liquidation of the cooperation agreement. Taking into account these elements and stipulating the measurements and objectives most simply and clearly, the alliance agreement should obviously be facilitated. Thus, the strategies of a manager will depend on the partner objectives, the time of the alliance, the type of technology to be exploited and the market to be used. It would also be necessary to consider the characteristics of each manager, because there are not two managers who will react in an identical way when facing the same constraint[33-34]. In addition, it is important to consider environmental uncertainty in management. This contingency can be caused by a request of technology, by the preferences of the customer, the actions of the competitors, the governmental policies, and the suppliers' capabilities, but also by the potential partners. The experience and how the partners are organized to work with each other, is one of the keys for successful alliance[3-25-29]. A skilful alliance manager is able to face the problems and overcome the difficulties more easily. The difficulties, we refer to are the social environment including language and culture, the other partners, and legal framework[17]. However, it is necessary that the objectives of the allies are as complementary and explicit as possible. It is essential also to establish a joint data carrier and that the process is as interactive as possible. Thus, the alliance success will depend on the experience, quality, and the manager's talent[3-25-29]. The alliance management is not an easy task, due to the multiplicity of constraints. Managers must compose, within the existing legislation, the structures of the market in which the alliance evolves or with the existing capacities of communication[16]. The size of the partners (asymmetric influence) is another characteristic that should be considered, because the input met by the multinational corporation in alliances should not be necessarily the same that of an SBF. In addition, the modes of alliance management will change according to whether they are national or international, high-tech or mature technology, formal or informal, as much as their goals, sometimes, which present divergent characteristics[6]. In fact, the modes of alliance management should normally be specific to the culture of the companies that begin in the cooperation. Moreover, in any agreement, it will be necessary also to consider the management of the intellectual property that will result from this cooperation agreement[3-16]. The alliance, is a learning organization and represents a source of know-how advantage that depends on the basic intangible knowledge of its members[35-36]. Thus, learning is the only way to survive within cooperation, but also to obtain a differential growth. The organizational learning takes place in a process of social interaction through which an accumulation of knowledge occurs (organizational or not), which can contain knowledge or know-how[18]. Knowledge, is an abstract concept, built consciously or unconsciously by the interpretation of a group of information acquired through experience and meditation in the practice, which could give to its owner a mental and/or physical skill in its art[37]. Authors generally argue that, from a structural point of view, knowledge is build by the information produced by the persons within the organizations. In their turn, the organizations are used as a support or, they offer the context so that the process of knowledge founding takes place thanks to the interaction of the community. The creation of knowledge must thus be a construction in constant interaction[36]. Inkpen (1996) [38], indeed, argues that the generation of new knowledge is based on the capabilities of transformation deployed by the managers. They are responsible for setting up the conditions of change necessary for the absorption or the assimilation of all new knowledge. This assimilation represents a process of learning accumulation of their individual skills, as well as the routines belonging to each organization are made profitable by the cooperative project[37].

Alliances between Biotech-Biotech; Biotech-Pharma; Biotech Firms or Biotech-University

Biotechnology is a technological process founded on knowledge and can be defined as the application of science and engineering to the methods, processes and techniques referred to as recombination of the DNA, and/or within biological systems[39]. This definition includes recombination of the DNA, cellular fusion, genomic components and its related techniques, as well as the advanced techniques like the bioprocess engineering. All these techniques applied directly or indirectly to microorganisms, humans, animal or vegetable cells or parts of these, can facilitate the development and production of new bio-molecules and cells, new organisms and procedures to improve in an innovative way, which already exist. In this context, university researchers including molecular biologists, medical doctors, as well as genetic and chemical engineers dominate the general concepts surrounding molecular biology[40]. However, these same scientists have neither the skills of management to organize companies, nor financing skill to market their products and this is why they are often constrained to search the partners for a cooperation agreement[16]. Stuart et al. (2007)[24] estimate that half of all biotechnology firms have been founded by university scientists, most of whom maintained academic appointments post-founding and is a channel that may increase this type of alliances between universities and SBF. The approach between SBF and large pharmaceuticals companies begin usually with a research contract or information exchange. Then, if the circumstances are favourable, the firms will be able to think of constituting partnerships that are much more formal. These alliances are often cemented partly through the support of governments. Being given the importance attached to biotechnology, the governments of the industrialized countries encourage universities and their researchers to patent and market the know-how of their products[16]. Alliances in biotechnology (including genomics firms) are different from alliances in other technologies. For example, biotechnology is unable to produce prototypes; it must, contrary to the other sectors, faces the uncertainty of

living organisms, and the ethics and the danger of environmental contamination. The final product development in biotechnology is generally longer (between 10 to 15 years), very complex, and with higher uncertainty, and in the case of products regarding human health, pre-clinical and clinical phases need to be considered between 800 to 1.3 billion dollars US for the final product, as showed in figure 2. Contrary to others high-tech products like software, whose funds returns are quasi-immediate, in biotechnology, the return on the investments requires several years [3-25-28].

Figure 2
Expenditure and Complexity from Basic Research to Final Product in Biotech Pharma Firms



The legal aspect of biotechnology processes is expensive, complex and slow, contrary to technology information for example[16]. Thus, uncertainty related to the market is omnipresent. The objective of strategic alliances between the large companies (generally pharmaceuticals companies) and the specialized biotechnology firms (SBF), is to obtain an advantage for the acquisition of new capabilities, which are very expensive or impossible to obtain inside, or which would take too much time to reproduce inside the company. There is a kind of information exchange, which is possible only if each company agrees to lose a certain degree of autonomy. Thus, the SBF will lose a few advantages, especially at the decisional level, in order to gain other advantages. These advantages can be represented in the SBF by the access to financing, laboratory equipments, large international markets, or by the admission to certain markets whose cultural barriers are difficult to cross, as can be the case of Japan or China[3-16-41]. For Audretsch and Feldman (2003)[3], knowledge has a crucial role in alliances and more particular in alliances between universities and SBF since universities are a very good source of basic knowledge. SBF are characteristically the commercial application of university knowledge and are very specialized in the types of products and applications they pursue. However, the progress of biotechnology firms drive to maintain close links with universities[24] or another firms, small or medium firms, in life science.

Why the Biotechnology Firms seek to Cooperate?

The high costs of biotechnology R&D, the long duration of clinical trials, as well as the expenditure of marketing and product commercialization, exceed the financial possibilities of the small-specialized biotechnology companies. To fill this gap, these companies must sign agreements of cooperation with large companies or with peers (biotech-biotech and or biotech-pharma). These alliances, not only provide new sources of financing for the R&D, but they also make possible the participation of various team members to diversify and reduce uncertainties inherent to the development of new products. In general, alliances between small/large, small/small or large/large companies materialize to combine complementary competences and resources. In this direction, the gaps of the small companies are related to industrial R&D, manufacturing, marketing, obtaining patents and accelerate the governmental approval of products[6-42]. In turn, the pharmaceutical companies research new innovating products to fill their pipeline. The sectors where the large companies take part in agreements with smaller companies are often the pharmaceutical, agro/bio, and chemical sector[23].

Generally, the SBF will establish alliances with:

- *Multinationals Pharmaceuticals Companies*: By the experience, the potential to increase the probability to patent and exportation, the financial capacity, the distribution networks, and the skill in R&D.
- *Universities*: By the intellectual capital and the equipment of laboratories.
- *Governmental laboratories*: By the high capabilities in R&D and financials contacts.

Audretsch and Feldman (2003)[3]; Burt, 2004[28]; Gottinger *et al.* (2010)[16]; Das and Kumar (2011)[43]; Subramanian et al. (2013)[44] analyze also the principal reasons that lead the companies to establish cooperation agreements in biotechnology. According to these authors, the allies seek mainly:

- The possibility of fast technology exploitation;
- The medium-term incomes generation;
- The risk and uncertainties partition in the new products development;
- The access to the financing, otherwise very difficult;
- Credibility;
- Expertise in R&D, which the partner has.

The large companies often look for agreement with SBF, when certain competences are difficult to obtain in the large corporations, and the goal is to increase the number of products in their pipeline[16]. In addition, many competences of the large companies, in particular in biology, genetics, genomics and proteomic do not exist in the small ones. The large companies thus prefer to join the small ones, rather than with other great multinationals in order to preserve their options on new technology. Actually, the statistics show that the number of agreements contracts is undercut after many years, but the amounts of the transactions are in constant augmentation. The money invested in this type of transactions is increasingly higher and higher. On average, 2007 alliances garnered US$173.4 million; in 2013, average deal size grew to US$180.7 million[7].

RESULTS AND DISCUSSION

For a few years (just to the crash of high technologies in 2001), biotechnology has been one of the high-tech sectors having a most fast growths in the world. According to a study published in 2000 by Industry Canada[45], this expansion was four times more quickly than the average of the economy in general. The fast growth of the biotechnology companies has been very high, but on the other hand, it is limited to a very restricted number of companies[6-46]. Small companies accounting for 80% of total compose the biotechnology sector and they are usually very young (less of ten years)[45]. Moreover, the firms of this size are innovative, albeit with intellectual property gaps, but are generally well equipped with intellectual resources, though not so much in financial resources[6]. The theory of the resources of the company and the theory of the competences postulate that the internal capabilities have a direct effect on the growth of the companies[48]. Originality/value – This article proposes to identify if alliances between biotech/biotech; biotech/pharma and even biotech/universities could be an advantage for the acquisition of new dynamics capabilities and help to create value to these firms (or not). Practical implications – The proposed conceptual framework supports the complexity for development biotechnology firms and bio-molecules and how the alliances can help fill that void (or not). Research limitations/implications – The paper provides a conceptual point derived from the literature analysis. The limiting of this study is that does not can conclude so absolute true influence of alliances in maintaining biotechnology firms over time, as neither can be affirmed or denied, if the alliances are a key element in the creation of bio-molecules. For both, their success will depend of several variables, not just one specifically. The creation of biotechnology firms seems not to be very difficult, against, maintain and grow, seems to be much too complex, starting from the basis of costs, resources and skills needed in a period of time long enough. Several of these firms know the difficulty to capture and or maintain their competences over time. Alliances can come help fill this lack of competences and resources, without being a panacea, nor solve all the disadvantages and drawbacks associated. In a next step, an empirical analysis based on the proposed concept would complete the theoretical findings.

CONCLUSION

Specialised Biotechnology Firms (SBF) aspiring to develop bio-molecules, must face to enormous difficulties and risks that are traditional of high-tech firms. Nevertheless, in this particular technology, also we are in the presence of firms demanding multifaceted research with the addition relative to the highly financial requirement (800-1300 million US $). A variety of knowledge and competences extremely specialized, several risks related to the very long time to develop just one bio-molecule and to its approval (up to 10 years), as well as problems of ethical order, etc. These risks lead to biotech firms to build strategic alliances, both between analogous SBF-SBF or SBF-Pharmaceuticals firms or SBF-Universities trying to hunt missing capabilities and resources. Alliances can provide additional financial resources and complementary capabilities to the SBF. Nevertheless, alliances are just one of the many tools necessary to increase the chances of being successful in a world as competitive and complex like to the development of bio molecules. Some of the resources provided by the alliances can be crystallized in activities like access to laboratories, marketing, manufacture, distribution. However, the SBF needs more than a simple alliance for growth and endure. They need a “virtuous circle” with the interaction of many factors such as venture capital (financing), intellectual property (protection and defence), human capital (knowledge), among others. The power of all these factors under the umbrella of the “virtuous circle” plus the alliance will be positioning favourably the SBF to a growth and survival. The recurring financial crisis has strongly influenced the ability of fledgling SBF to fund innovation, but the number of alliances is highly cyclical and in this moment and after many years of depression they are increasing. However, there is nothing to suggest or guarantee that having a strategic alliance of any kind can allow an SBF to reduce complexity gaps and obtain the missing capabilities and resources, and succeed in the development of one bio-molecule. The variables involved in the strategic alliances of SBF are several and only a combination of

these can help the SBF to survive and create value, not just one alliance. The constantly changes that are manifested in the development, patenting and commercialisation of new bio-molecules, without forgetting the long time that this process entails, make necessary to follow the evolution year after year of this high-tech sector, that is very complex, but at the same time it is fascinating.

CONFLICT OF INTEREST

Conflict of interest declared none.

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