Biopharmaceuticals and firm organization in Argentina. Opportunities and challenges

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Abstract

In Argentina, some biotechnology firms operating in the human health sector managed to enter into the biosimilars segment of global biopharmaceutical markets at an early stage. These firms' forms of organization and their articulation with local science and technology infrastructure have played a key role in the development of business strategies in an institutional context that does not facilitates the resolution of the particular risks and uncertainties – be they technological, regulatory, or commercial – associated with these products. This paper examines the strategies of selected firms, using case studies. It postulates that firm organization in economic groups, and the articulation in public/private networks enables local firms to successfully surmount the obstacles faced by innovative biotechnology firms in peripheral countries, which leads in turn to the achievement of technological and financial advantages.

Key words: biotechnology – pharmaceutics industry – firm strategies – value chain – developing countries

I. Introduction

The aim of this paper is to analyze the different organizational forms of biopharmaceutical firms in Argentina following the emergence of molecular biology.

Several authors who have analyzed the way modern biotechnology (MB) has evolved in the human health sector have pointed out that its development was accompanied by significant institutional changes. These transformations led to the shift from an open science model to one of proprietary science, in which scientific knowledge can be patented and turned into intangible assets to which a financial value can be assigned (Coriat and Orsi, 2002; Coriat, Orsi, and Weinstein, 2003).[1] These institutional changes enabled solutions to the financing and risk management problems associated with research and development (R&D), thus facilitating the entry of numerous specialized biotechnology firms into the market. However, the resulting institutional configuration has brought other problems related to the coordination of the learning processes and the competences needed to develop a new molecule, thus limiting the possibilities of achieving noticeable increases in R&D productivity (Hopkins, et al., 2007; Pisano, 2006).

Additionally, firms have had to master a growing spectrum of heterogeneous competences which have increased the complexity of the knowledge base (Pisano, 2006; Lavarello and Jelinski, 2010).The coexistence of different problem-solving patterns has posed great challenges for R&D organization. Thirty years into the molecular biology revolution, the health biotech industry has not been yet consolidated.

[1] The most widely accepted definition of biotechnology is the application of science and technology to living organisms, plants, products, and their models, modifying both living and non-living materials for the production of knowledge, goods, and services. In its modern sense, biotechnology is defined as the use of cells, molecules, and genetic processes in the production of goods and services. (Zika et al. 2007; Van Beuzecom et al. 2006; OECD 2005).

Different types of technological strategies coexist in these sectors, ranging from the development of new commercial blockbusters to process innovations oriented towards reducing costs during the clinical phases of biosimilar development. Each of these strategies shows different firm configurations in the R&D value chain.

Firms from emerging countries enjoy a certain degree of freedom to enter the market, particularly the biosimilars market and niches for specific treatments. These opportunities are becoming more relevant due to developed countries' need to reduce their health budgets. Various firms from emerging countries – including India, China, Korea, and Costa Rica – have accessed the biosimilars market in recent years.

In this context, Argentina has witnessed the emergence of a small number of pharmaceutical firms or economic groups which have undertaken developments in the biosimilars sector and developed other MB-based products and services. However, Argentina's institutional configuration is very different to that of central countries, especially the USA. In particular, the absence of market mechanisms enabling risk distribution and access to financing constitutes a major challenge for firms looking to diversify into these areas.

This paper is structured around the following question: What forms of organization do biotechnology firms in Argentina adopt and how are influenced by the scientific, economic, and institutional opportunities available? For this purpose, we have chosen to use case studies as our methodological approach. We started with a selection of "ideal types" of firms, which are based on a typology of the strategies followed by biotechnology firms which takes into account their form of organization and degree of specialization. Case studies that were representative of local industry were then selected from within each type.

The paper is organized as follows: Section 2 presents the discussion in the literature on the difficulties hampering the consolidation of a new technological paradigm in the health sector in light of the different waves of biotechnology and the emergence of a new competitive context in which business strategies are oriented both towards the market for brand-name products and towards that for biosimilars. Section 3 analyzes the structure of the biopharmaceutical industry in Argentina, emphasizing its differences and similarities to those of central countries. Section 4 presents the differences in the strategies and forms of organization of Argentina-based biotechnology firms, through case studies of three of the main firms in the sector. Finally, section 5 revisits these case studies through a comparative analysis, emphasizing the variety of ways in which firms respond to the opportunities opened up by scientific and regulatory changes, and asks about the potential of these firms and the limits and possibilities to extending these experiences to other biopharmaceutical firms in the country.

II. Background: The successive waves of biotechnologies and their effects on the coordination of the value chain

According to the literature, MB has revolutionized forms of R&D organization in the global pharmaceutical industry. However, there is not enough available evidence to conclude that there has been a consolidation of a new sector of specialized biotech firms which have replaced existing large multinational firms (MNFs) in the pharmaceutical industry.

2.1. A technology that is yet to move beyond a pre-paradigmatic state

Numerous authors argue that despite the fact that MB has existed for thirty years, the health sector still lacks a consolidated (bio) technology paradigm (Pisano, 2006; Hopkins et al., 2007; Cockburn and Stein, 2010). A technological paradigm is a shared pattern for solving common techno-economic problems based on selected scientific principles (Dosi, 1988). No such pattern has been established for biotechnology in the health sector. The development of MB in that sector has been characterized by the emergence of successive waves of biotechnology (recombinant proteins, monoclonal antibodies, genomics, proteomics, stem cells, tissue engineering, gene therapy), but these have not yet been articulated into a well-defined set of common problems and solutions. Each wave has given rise to the entry of new specialized biotechnology firms and to new models of industrial organization, which have had an impact on the management of large pharmaceutical firms.

Four phases can be identified in this development (Pisano, 2006; Hopkins et al., 2007; Cockburn et al., 2010):

a) 1976–1985: This first stage focused on recombinant protein and monoclonal antibodies platforms. These are large-molecule technologies which replaced the hormones that were being produced through extractive methods – such as insulin or growth hormones – with new molecules produced with noticeably higher productivity levels (erythropoietin [EPO], interferon, interleukins, the unsuccessful first stage of monoclonal antibody development). In a context of major changes in intellectual property rights and financial institutions, these new technologies gave rise to the emergence of the first specialized biotechnology firms, such as Genentech (1976), Biogen (1978), and Amgen (1980), using an organization model that was based on the integration of all phases of the innovation chain, including the production stage and the commercialization of their own products

b) 1986-1992: When the expected financial returns and reductions in risk during clinical phases did not materialize, a new wave of biotechnological innovations emerged which aimed to diversify into new therapy types (gene therapy, tissue engineering, cell therapy), specific diseases (cancer and others), the search for methodologies for understanding the basic mechanisms of illness, and the identification of chemically synthesized molecules through rational drug development methods. The difficulties encountered during the development of new recombinant molecules led firms to exploit the complementarities between molecular biology and chemical synthesis capabilities. Molecular biology techniques were applied in order to expand the existing heuristics of chemical synthesis and to implement rational drug design methods. In this context, a major vertical division arose within the industry: biotechnology firms focused on R&D up to preclinical stages, and large MNFs focused on development and marketing. Suppliers specializing in biomedical tools and equipment emerged during this time (Hopkins et al., 2007).

c) 1992–late 1990s: Driven by the large-scale human genome programs, a new organization model was developed based on the *industrialization of R&D*, starting with genomics, high throughput screening (HTS) technologies, bioinformatics (*in silico* analysis of large quantities of data), and recombinant

chemistry (allowing economies of scale and scope).[2] Several specialized firms focused on mastering a certain technological platform, providing services to other firms, rather than moving towards therapeutic applications or specific products. Others made progress in the discovery of new drug targets, offering supplies for product development. However, as in the previous phase, there was a clear division of labour between biotechnology firms and large pharmaceutical firms.

d) 2000 onwards: There is a tendency towards diversification with varying degrees of coherence. The strategies developed in the 1990s were not as successful as had been hoped: R&D productivity did not increase and new "targets" were not validated fast enough. Many pioneering firms of the previous biotech waves ended up being absorbed by large pharmaceutical companies, while others deepened their pre-competitive articulations through networks and alliances (Hopkins et al., 2007; Nightingale and Martin, 2004; Cockburn and Stern, 2010). This gave rise to some mega corporations which adopted integrated schemes with varying degrees of complementarities between product lines.

More than thirty years on, the new biotechnology paradigm has not yet brought about the revolution initially predicted nor the consolidation of the paradigm. New technologies have not displaced the old ones: the two complement each other in some cases, and coexist in others. The major innovation associated to biotechnology is the emergence of a new industry configuration and new forms of organization of the industry. Considering the recent developments in pharma-biotechnology in the USA, several authors have pointed out some central features of this configuration: the co-evolution of greater scientific and technological opportunities; new types of financial risk capital; and the accelerated process of privatization of scientific and technological knowledge (Pisano, 2006; Hopkins et al., 2007).

With regard to industry configuration, there are complementarities between market arrangements and more direct governance forms. Though large pharmaceutical firms still lead the market, biotechnology starts ups explain the dynamics of the industry. High rates of entry and exit are central traits of this configuration. But only a small proportion of these start ups survive, mostly assuming different kinds of alliances or integrated forms of organization with big pharma.

This configuration has not totally resolved three great challenges of the biotechnology business (Pisano, 2006): risk management and financing; the integration of the different waves of biotechnology into a coherent knowledge base; and the capacity to accumulate learning processes within organizations. In the context of the predominant institutional configuration in the USA, the problem of risk management and financing was "resolved" through a set of changes: development of risk capital, reforms to capital market regulations, the opening up of the frontier of what is patentable, growth of private-sector funding within academia.

In contrast, the different organizational models have not managed to integrate the vast amount of highly complex and heterogeneous knowledge into a coherent knowledge base, nor have they generated flexible routines that allow firms to accumulate the learning achieved through experimentation within each successive technology platform. As a result, certain authors (Hopkins et al., 2007), while recognizing the substantial

[2] High-throughput screening (HTS) is a method for experimentation which allows millions of biochemical, genetic, or pharmacological tests to be carried out very quickly. *In silico* analysis refers to studies carried out by computer or computer simulation.

impact biotechnology has had on drug discovery, the expansion of available targets, and new clinical practices, point out that the promises made by biotechnology regarding increases in the productivity of biotechnology R&D downstream are yet to be fulfilled. Other authors have expressed their doubts about the finance-led dynamic of this industry and the effects of the increasing privatization on advances in biotechnology. Dasgupta and David, 1994; Coriat et al., 2003 among others, argue that the proliferation of intellectual property rights (IPR) over partial and fragmentary aspects of scientific knowledge has turned into a paradoxical example of the "tragedy of the commons". Furthermore, the bias in R&D activities that comes with the growing "privatization" of strategic science and technology (S&T) decisions could become an obstacle to the promotion of S&T developments aimed at finding answers to national economic and social priorities.

2.2. A new competitive scenario: biosimilars

Since the late 1990s, whilst the difficulties discussed above were unfolding, the first wave of biotechnological products entered a new stage of imitative growth. The expiry of patents for products that emerged from early developments in biotechnology posed new competitive challenges. These processes, together with the existence of a double standard in IPR, gave rise to a new segment in the biopharmaceutical product market: **biosimilars**, also known as follow-on biologics (FOB). These are subsequent versions of biotechnological drugs (or active ingredients for the pharmaceutical industry) which are produced and marketed – once approved by the appropriate regulatory body – after the patent protecting the original innovative product has expired; or sometimes before it has expired, in markets with flexible IPR systems and regulations. When the molecules to be reproduced are not complex and the productive and regulatory processes can be carried out at a low relative cost, a sort of "commoditization" of biotechnological products takes place, since these become cheaper than branded products.

The current size of the global biosimilars market is estimated to be approximately 10 percent of sales of biopharmaceutical medicines (USD 7–8 billion), which in turn represent, on average, between 10 and 15 percent of the pharmaceutical products market. The dynamics of these markets are well above those of conventional drugs: in 2006, the annual growth of biomedicines was 20 percent, compared to 7 percent for traditional drugs. Sales of biosimilars for 2010 are estimated to be between three and four times greater than those of 2007, as a result of the expiry of patents for various biotechnological blockbusters[3] (Zica et al., 2007). The biosimilars market is increasingly attracting the attention not only of start-ups entering the industry by imitating or copying technologies developed in central countries, but also that of large pharmaceutical firms. Major players' growing interest in this segment and in the development of these products is due to the fact that the public sectors of industrialized and developing countries (especially those in the European Union) are seeking to cut health system costs and expand their cover to include these new drugs.

Competition is growing within markets for biotechnology products. New producer countries are emerging in the biosimilars markets, such as South Korea, India, and China, which – with differences in their productive and marketing strategies resulting from the quality of their products and the size of their domestic markets – direct their exports towards countries with flexible regulations while attracting investment from

[3] Blockbusters are medicines with huge sales volumes and which are one of the strategic R&D objectives of pharmaceutical firms.

MNFs that are becoming interested in FOBs. At the same time, the entry barriers to biosimilars markets in central countries are increasing.

In contrast to what has been taking place in markets for chemical synthesis generics, there are high barriers to entry into biosimilar markets. The most noteworthy of these are barriers associated with the R&D and production stages (which require large investments and specific competences); regulatory frameworks (the properties of biosimilars must be demonstrated vis-à-vis the original products); the intensification of competition due to innovative firms' diversification into biosimilars; and the cost of the marketing needed to ensure their acceptance by doctors and hospital systems (de Desai, 2009; Pisano, 2006; Zica et al., 2009).

In short, although the move towards the production of biosimilar drugs (which is currently underway in Argentina and other developing countries) may open up commercial opportunities and obtain the support of public health programs, headway must first be made on a set of institutional and organizational learning processes in which public-private articulation plays a key role.

Firms from peripheral countries are responding in a variety of ways to the challenges posed by the different waves of biotechnologies, the growth of the biosimilars market, and the reconfiguration of the value chain. It is worth asking if the forms of organization of local biotechnological firms are sustainable. In Argentina there are experiences – most of which are still in their early years – which seek to take advantage of the opportunities opened up by new biotechnologies through idiosyncratic forms of organization.

III. Modern biotechnology in the human health sector in Argentina

The diffusion of MB into the human health sector took place early in Argentina, at the beginning of the 1980s, only a few years after the first global wave of these technologies. As a result, Argentina became for several years one of the first producers – along with Cuba – of recombinant proteins in Latin America.

3.1. Specific features of the pharmaceutical biotechnology industry in Argentina

Local production has been based on strategies of copying or imitating molecules developed and patented abroad. Until now, MB has been used in the human health sector for the production of first-generation recombinant protein biosimilars, including drugs, active pharmaceutical ingredients (APIs), and diagnostic reagents. Efforts have been directed towards innovations in production processes, some of which have led to patents being granted.

Biomedicine production has been developed by specialized local start-ups closely linked to (or associated with) local laboratories that have diversified into biomedicines production. The pharmaceutics industry is characterized by the coexistence of domestic laboratories and few MNFs subsidiaries importing brand-name medicines.

The diversification towards biosimilars on the part of local pharmaceutical laboratories was driven by international market opportunities. The specific factors that initially pushed the development of these productions were the capabilities accumulated by certain laboratories in the production of extractive biologics, and the expiry of patents on some biotechnological products. These strategies would not have been possible, however, if Argentina had not had relevant public scientific and technological (S&T)

infrastructure, a major school of biomedicine, and highly qualified human resources in the scientific disciplines associated with the MB development. Argentina has a long tradition in R&D activities and graduate education in biotechnology or associated fields. It has the highest number of researchers per active person in Latin America: 3.06/1000 (Gutman and Lavarello, 2012). Developments in the scientific fields of cell and molecular biology, and in complementary activities such as bioprocesses, chemicals and agronomics, have supported the adoption and diffusion of MB in different sectors and disciplines. Research on biotechnology started decades ago in university laboratories and several institutions -such as Malbrán, Fundación Campomar, CONICET- made possible the development of medicines, vaccines, and other health-related products.

However, there was little articulation between public and private agents of the national innovation system. The S&T public institutions, created during the import substitution economic period, played a central role in the adoption and diffusion of technology. A linear model of technological transfer was followed, with limited participation of private agents in R&D activities, and scant absorption capabilities (Niosi, 2006; Bisang, Gutman, Lavarello, Sztulwark, and Diaz, 2006). The creation of horizontal support instruments for R&D activities since the second half of the 1990s only partially solved this weakness of the National Innovation System (Diaz et al., 2006). A more systemic approach oriented to the establishment of public-private consortiums and "biotechnological poles" has complemented the horizontal policies from 2003 onwards[4].

Argentina's institutional configuration show several constraints: i) it is still characterized by an absence of risk capital markets and large-scale public procurement programmes; ii) the Health System is fragmented into three levels – public, private and union's subsystems- restricting the role of the State in the orientation of the domestic market; iii) the approval of new drugs in Argentina is a laborious, costly, and time spending process, as a result of the time required to local firms to patent a product and the incipient development of local regulations on biosimilars.

Within this industrial and regulatory framework, a relatively concentrated industrial structure began to emerge, where the main active ingredients are imported, and the galenic development, formulation, and marketing are carried out locally. There are significant entry barriers in biosimilar markets. Local firms – including large local groups – are unable to afford R&D or investment costs on the same scale as leading global firms, since they are not consistent with the time horizon and the size of the local market. Given these structural limitations, the biosimilars market allows specific – and sometimes complementary – innovations and diversification processes, which can lead to innovative niches. We turn to these innovations and processes in the following sections.

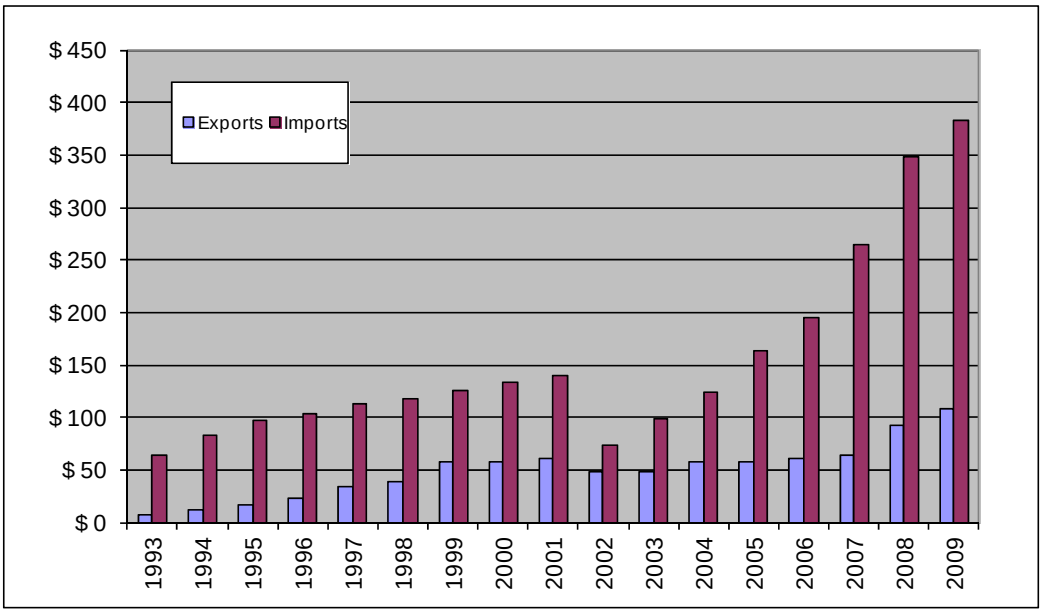
[4] In recent years, S&T public authorities have fostered both the organization of different individual demand-pull projects into clusters, and the focusing of private-public initiatives on R&D efforts. In vaccines, oncologic drugs and biosimilars, some projects have been encouraged by the CONICET and university laboratories working in networks with national firms and MNFs. In biosimilars, public and private initiatives promoted the creation of a Biotech Cluster in Rosario in 2000. In oncologic products, the biotechnological Group Chemo and the Universidad Nacional de Quilmes have initiated the development of a new product (see section 4). In vaccines, the government promoted an alliance between Chemo and the MNF Novartis for technology transfer and local production.

3.2. Size of the local biotech market

Local health biotech sector show a negative trade balance since de eighties. In 2009, it achieved a trade deficit of U$ million 275 (see Figure N°1). Local biotech production satisfies domestic demand only marginally; most of the supply is imported by MNF, particularly monoclonal antibodies and recombinant insulin.

A preliminary estimate of the size of the domestic market in 2008 (excluding output and imports of vaccines) reached almost US$ 390 million, including domestic output of recombinant proteins, and imports of proteins, insulin, and monoclonal antibodies. The domestic production of formulated products and active ingredients intended for the domestic market is near US$ 32 million, which amounts to only 8 percent of demand. Around 80 percentof the local output intended for the domestic market is produced by two local firms, which nevertheless direct most of their output to the international market: between 75 and 85 percent of their output is exported to Latin American and Asian countries with flexible regulations. Though Argentina represents only 0,15 percent of world exports, it's the second biotech exporter of Latin America after Brazil and it has increased its share in global exports from 0,11 percentin 2007 to 0,15 percent in 2009.

Figure N°1. Health Biotech sector in Argentina: Trade balance of health biotechnological products (Millions US$)



Source: COMTRADE Database

The Argentinean biopharmaceutical industry is thus characterized by a small production capacity for the domestic market, and follows the typical pattern of pharmaceutical industries as importers of 'active ingredients' and formulators of pharmaceutical products, but shows, at the same time, an early integration of its exports into the biosimilars market segment.

3.3 Biopharmaceutical firms in Argentina[5]

The Argentinean biopharmaceutical industry of the early 2000s consisted of no more than 19 firms producing biotechnology drugs, reagents, and inputs. On average, biotechnology products accounted for 33 percent of sales by these firms, which were strongly export oriented. Though there were significant inter-firm differences, average annual sales per firm were at US$ 6 million, and sales of biotechnology products at US$ 2 million, which reveals that local biotechnology firms are considerably smaller than their international counterparts. Although investment in R&D is quantitatively lower in local firms than in those based in developed countries, the former are notably innovative within the local context, since their investments represent 5 percent of sales (the figure for the industry as a whole being below 0.5 percent) and they show significant coordination with the S&T public infrastructure (data for 2003, Bisang, Gutman, Lavarello et al., 2006).

There were 26 biopharmaceutical firms in 2010. National firms fall into three types: some of the more recently established firms are corporate spin-offs or university start-ups focused on R&D stages, without reaching the commercial stage yet ; others are specialized biotech firms articulating with large local pharmaceutical firms through technology, production and trade cooperation; others are diversified pharmaceutical firms, traditional pharmaceutical laboratories which have invested in biotechnology but whose main income derives from the production of conventional drugs (tables 1 and 2).

Table 1: Argentinean Biotechnology Firms in 2010
By type and date of foundation

FIRM (Type)	Before the 1980s	1980s	1990s	2000s	TOTAL All firms
SBS	0	0	1	6	7
SBF	1	3	3	0	7
DPF	6	2	2	1	11
MNF	0	0	1	0	1
TOTAL All firms	**7**	**5**	**7**	**7**	**26**

Notes: SBS: Specialized local biotech start-up;
SBF: Specialized local biotech firm;
DPF: Diversified pharmaceutical firm;
MNF: Multinational firm.
Source: Gutman, G. and Lavarello, P, Database of the project entitled "Biotecnología y desarrollo industrial en Argentina".

Specialized local biotech start-ups (SBSs) and specialized local biotech firms (SBFs) account for 58 percent of the health biotechnology sector, while 38 percent are diversified pharmaceutical firms (DPFs) and there is only one multinational firm (MNF). Most SBSs were established in the 2000s and were focused on the R&D stage of the value chain (see table 2). Two of these firms are part of techno-financial holdings or groups.[6]In contrast, SBFs were established in the 1980s and 1990s, and focused on

[5] Traders, importers and distributors of these products are excluded.

[6] A holding which profits from financial advantages and a set of cross-section technologies (Lavarello, 2004).

the production of first-generation proteins and on in-vitro diagnostics. These firms use DNA-based biotechnology in the R&D and production stages. Four firms are part of techno-financial groups or holdings with established pharmaceutical firms. The first and most important biopharmaceutical firm in Argentina is Bio Sidus. Finally, DPFs are longer-standing and belong to the leading national pharmaceutical groups. Some national pharmaceutical groups, like Romikin and Roemmers, were not directly involved in local biotech production or research, but they have diversified towards these activities.

Nowadays, there is only one MNF subsidiary in the biotech sector in Argentina with R&D and production investments, Aventis Pharma, (belonging to Sanofi-Adventis Group), specialized in the production of recombinant vaccines and veterinary products[7]. The major global pharmaceuticals firms have commercial and /or distribution channels in the country. Even though external markets are the main target of domestic firms, local competition with MNF refers to the health system acceptance of biosimilar drugs versus innovative imported ones. In fact, domestic production of recombinant proteins (excluded vaccines) oriented to the local market represent only the 8 percent of domestic demand, as pointed out in section 3.2..

The analysis of the origins of specialized biotech firms in the country reveals that many of them have emerged as spin-offs of **Bio Sidus**, a firm that has early incorporated Argentinean scientists and technologists in its laboratories. Bio Sidus (a formerly Sidus Group member) has been directly or indirectly responsible of the establishment of seven specialized biotech firms through a series of spin-off processes

Box 1: Bio Sidus, the main source of spin-offs in human health biotechnology in Argentina

Bio Sidus has been involved in the establishment of several specialized biotech firms which arose after Bio Sidus technologists left the firm. In the early 1990s, some Bio Sidus researchers formed a small SBF and, together with Laboratorios Pablo Cassará, in 1995 founded PC-GEN, a firm that specialized in the production of recombinant proteins. Later on, in association with the German pharmaceutical firm Rhein Inmuno BV, PC-GEN created American Rhein to develop the human hepatitis B recombinant vaccine. This firm was subsequently acquired by the Fench MNF Aventis Pharma. PC-GEN also contributed to the establishment of Zelltek, another biotech start-up. As from 2005, PC-GEN and Zelltek became members of the Amega Biotech Group. Likewise, two PC-GEN partners founded Immunotech, which is devoted to vaccine production. Incubatech and Protech Pharma, also members of the Amega Biotech Group, were created as spin-offs of Zelltech in 2004. And in 2008, R&D PharmaAdn was created by former Genargen researchers and other partners.

Source: interviews with firms and specialists.

The following table shows the products made by biopharmaceutical firms and the application of DNA-based technology in the different stages of the value chain.

[7] Since 1985/1990, many MNF with subsidiaries in Argentina were relocated in Brazil, as a result of the weak regulatory system prevailing in those years in the country, concerning intellectual property of new molecules.

Table 2. Argentinean Biotech Firms in 2010
By type, biotechnological techniques used in the value chain, and type of product

FIRM (Type)	DNA-based technology			Type of product			TOTAL All firms
	R&D and Production	R&D	Production	Biopharm. product	Divers.	Other [1]	
SBS	2	5	0	2	0	5	7
SBF	4	2	1	4	3	0	7
DPF	4	6	1	2	2	7	11
MNF	0	0	1	1	0	0	1
TOTAL All firms	**10**	**13**	**3**	**9**	**5**	**12**	**26**

Notes: SBS: Specialized local biotech start-up;
SBF: Specialized local biotech firm;
DPF: Diversified pharmaceutical firm;
MNF: Multinational firm.
(1) Firms that use biotechnology techniques only in the R&D stages – but do not market their products – or that produce drugs by chemical synthesis.
Source: Gutman, G. and Lavarello, P, Database of the project entitled "Biotecnología y desarrollo industrial en Argentina".

These firms use recombinant DNA technology in either the R&D or production stages (including quality control), or in both, in order to produce active ingredients as well as drugs. They have modern production processes (cutting-edge equipment, qualified human resources) and they have obtained international quality standard certifications. Although most of them produce biosimilars, some have made incursions into innovative niche products by means of local and international alliances.

From this brief diagnosis, it can be argued that, even if small, there is a critical mass of biotech firms in the human health sector in Argentina, coexisting with specialized R&D start-ups and with downstream firms devoted to the manufacture and launch of products. An analysis of case studies of firms that are representative of the sector will serve to identify the different strategies and value chain forms of organization pursued by pharmaceutical firms.

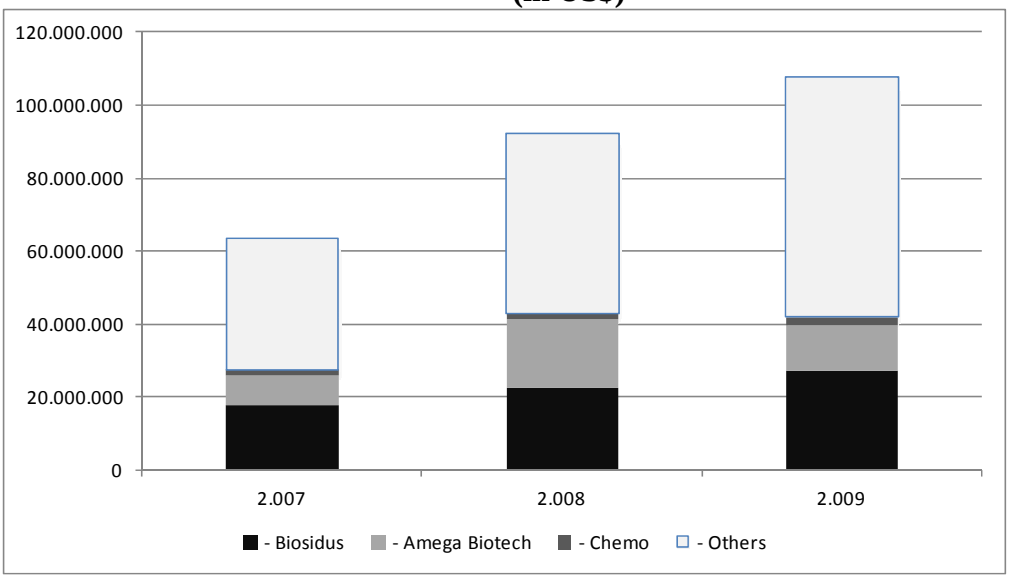
IV. Argentinean biotech firms' business strategies

The multiple case studies presented – which exemplify three forms of organization that are representative of the sector (ideal-type method) – seek to answer the core question raised by this paper: what forms of organization prevail in the main firms (or groups) of the pharmaceutical sector that are making inroads into biotechnology, and what factors determine these forms of organization in view of scientific, economic, and institutional opportunities? The case studies chosen are as follows:

- A leading local specialized biotech firm (SBF) producing biosimilar recombinant proteins: Bio Sidus.
- A domestic group organized as a network of several specialized biotech start-ups and spin-offs (SBS) and specialized biotech firms (SPF): Amega Biotech.
- A Diversified Biotech Group (DBF) named Chemo , dealing with human and animal health and organized on a global network: the alliance between Romikin, Laboratorios Elea, Biogenesis-Bagó and the National University of Quilmes.

These three enterprises represented almost 40 percent of Argentine's exports in 2009. Bio Sidus has been clearly the export leader since de 90's. In recent years, this leadership has been challenged by others groups. In Figure N°2 we present the health biotechnology exports of Bio Sidus, Amega Biotech and Chemo Groups. Whereas Bio Sidus and Amega Biotech are specialized in health biotechnology, Chemo has a clear specialization in Animal Health and has recently entered to this market.

Figure N°2. Health Biotechnology industry in Argentina: Firms' exports share in total domestic exports (in US$)



Sources: Database of the project entitled "Biotecnología y desarrollo industrial en Argentina".

Table 3 shows a stylization of the main organizational features of the three cases under analysis:

Table 3: Argentinean biotech firms' strategies and forms of organization. Selected cases.

	Bio Sidus (SBF)	Amega Biotech (Domestic Network of SBS and SBF)	Chemo (DBF)
Strategy	Final biosimilar products export specialization	Biosimilars API export specialization	Human and animal health diversification
Production	7 rADN Proteins (EPO, 3 interferon, G-CSF, Somatropin, Lenograstim)	9 rADN Proteins (EPO, 4 interferon, FSH, interleukin, Somatropin, G-CSF)	Vaccines, rADN proteins and small molecules.
Innovative Trajectories	Incremental/major Product imitation Process innovation	Incremental Product imitation Process innovation	New and imitative products New process innovation
Knowledge base and complementary assets	Internal R&D Production, Regulatory and international customer learning Branding	Internal D Regulatory and customer learning	External R&D Regulatory and biomedical learning
Chain value configuration	Vertically integrated	Quasi-integrated	Global Network

Source: Own elaboration based on interviews with firms.

A brief description of these three cases reveals additional evidence to that shown in the above table. **Bio Sidus**, the largest Argentinean specialized biotech firm, is domestically owned and belonged to Sidus Pharmaceutical Group (SPG), a strongly export-oriented pioneer in the production of medicines and active ingredients from biosimilar proteins. In 1983, Bio Sidus was established as an autonomous biotech business unit controlled by the Sidus Group, but in 2011 was disengaged from its mother group. It became the first biotech firm in Argentina and Latin America, preceding its local successors by ten years in the production of recombinant proteins, and commercialized its products almost at the same time as ground-breaking biotech firms at the global level did.

Its current portfolio of seven biosimilar recombinant therapeutic proteins are made using cell culture or bacterial fermentation techniques, and it also produces an intestinal prebiotic. Seventy percent of Bio Sidus's sales correspond to erythropoietin (EPO), being the largest supplier of EPO in the local market - where it competes with Amega Biotech- and the seventh producer at the global level. Exports of the firm account for 80 percent of its sales. In 2009, Bio Sidus explained 25 percent of Argentine's health biotech products, being the first exporter of this sector. Its 2009 turnover reached US$ 40 million, 10 percent of which was invested in R&D. Its payroll is in the order of 350 people (45 percent of whom are professionals and technicians).

As is the case with other local biotech firms, Bio Sidus's competitive strategy is based on exports of inexpensive high-quality products tailored to meet the demands of markets with flexible regulations and intellectual property regimes. Its main competitors are MNFs and distributors of brand products or biosimilars.[8]

The financial advantages derived from assuming the Group form were crucial to the emergence and consolidation of Bio Sidus. Subsequently, public funding granted through National Agency FONTAR subsidies was key to developing R&D activities. Bio Sidus has obtained loans from state-owned banks as well as subsidies from the Argentine-Brazilian Biotech Centre (CABBIO, the acronym of its name in Spanish).

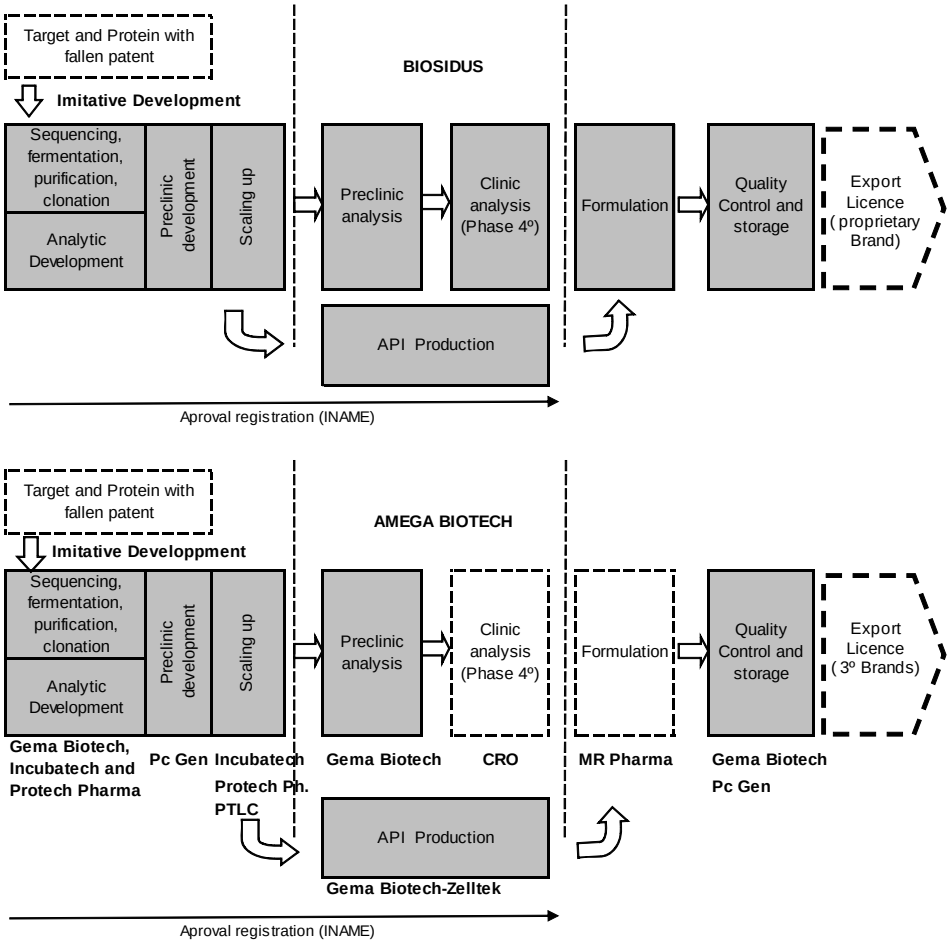
However, the growth of this firm has not been solely determined by its financial advantages. These have enabled Bio Sidus to develop technology and production capabilities along the value chain. It has integrated I&D, preclinical and clinical studies, and manufacturing activities as well as pre-clinical and clinical trial stages on biosimilar proteins (see figure 3). Its two manufacturing plants in Buenos Aires meet US (FDA) and European (EMEA) regulations and standards. Its interaction with Argentinean regulatory agencies has favoured learning processes both for the firm and the system as a whole.

The articulation of knowledge built up inside and outside the firm, together with learning processes triggered by the production of leukocyte interferon and subsequently enhanced by the development of recombinant proteins, enabled Bio Sidus to diversify into more complex biotech platforms.[9]

[8] The firm estimates that the global market comprises 60 firms spread over 15 countries making products similar to theirs.

[9] Its main technology platforms are bacterial fermentation, cell culture, genetically modified animals, and gene therapy (protein replacement therapy).

Figure 3: Biotechnology value chain: Bio Sidus and Amega Biotech



Amega Biotech[10] is a strongly export-oriented biotech firm that specializes in the production of active pharmaceutical ingredients (APIs). It belongs to a locally owned group with a minority share held by German capitals. It was established in 2005 by the Mega Pharma holding, a network of pharmaceutical firms located in Montevideo, Uruguay.

Amega Biotech is a medium-sized/large company – as per local market and specialized biotech firm standards – with a payroll of around 230 people, 34 percent of whom are involved in production stages, while another 32 percent works in R&D. The firm's 2009 turnover added up to US$ 10 million (one-fourth of Bio Sidus's) and grew very dynamically; its investment in R&D is substantial, nearing 35 percent of sales. Since 2009, the firms controlled by Amega Biotech explain 21 percent of health biotech exports, placing this group as the second biotech exporter from Argentina.

As happened in the previous case, this group's financial advantages have been a distinctive feature since the start, but unlike Bio Sidus, Amega Biotech gained technological advantages by acquiring existing firms. Between 2005 and 2008, this group acquired a R&D biotech firm (Gema Biotech) and two major domestically-owned

[10] This case study is based on interviews held with the firm, previous researches , and data from specialized magazines. For an in-depth analysis of this case, see Gutman and Lavarello (2010).

biotech firms specializing in the production of recombinant proteins (Zelltek and PC-GEN). Thanks to its merger-and-acquisition-based growth strategy, Amega Biotech needed a very short time to expand. After these acquisitions, the firms were thoroughly restructured, rearticulating and redistributing activities such as R&D (now focused on development), API production, pre-clinical trials, quality control, and marketing, and also expanding their production capacity significantly. The economic group technology strategy is aimed at expanding its recombinant protein production by developing new technology platforms.

In contrast to Bio Sidus, Amega's value chain is only partially integrated (see figure 1). At present, clinical trial and final-product formulation stages, as well as some marketing and commercialization activities, are either subcontracted by the group and/or developed in association or networking with other firms.

The forms of organization adopted by the group as well as its networks with local university laboratories and its alliance and acquisition strategies have enabled it to make very rapid progress in terms of the learning processes and organizational innovation needed to expand its production and marketing strategy.

Lastly, **Chemo** is pharmaceutical diversified group owned by an Argentinean family, whose main product lines are active ingredients (APIs) and final products for human and animal health. It was founded in Spain 30 years ago and has been in Argentina since the late 1980s.

Chemo is a majority shareholder of other firms and undertakes joint ventures and technology cooperation agreements. Thanks to this form of organization, the internationalization of its production and the diversification of technology have unfolded rapidly. The firm has developed a global network operating in 24 countries and carrying out a range of activities, from R&D and manufacture of chemical synthesis APIs to the formulation and marketing of these products. Its payroll adds up to 2,800 employees and its 2009 turnover exceeded 450 EUR million. Chemo annually invests between 5 and 10 percent of its turnover in R&D to develop new drugs. In Argentina, exports of the group achieved U$S 32 millions. While only US$ 2 millions correspond to health biotechnological products, 12 millions were associated to animal health biologic and biotechnological products.

The group owns several manufacturing plants producing APIs by chemical synthesis for the production of generic and synthetic drugs in different locations (Spain, Italy, Argentina, and China). Building on the expertise gained by producing APIs, and on patented developments, they have achieved highly complex formulations of their own. They have located their production of veterinary biologics and some new chemical synthesis product lines in Argentina, where associations and joint ventures with other long-standing human and animal health-related firms prevail (Roemmers, Familia Sielecky and Bagó).

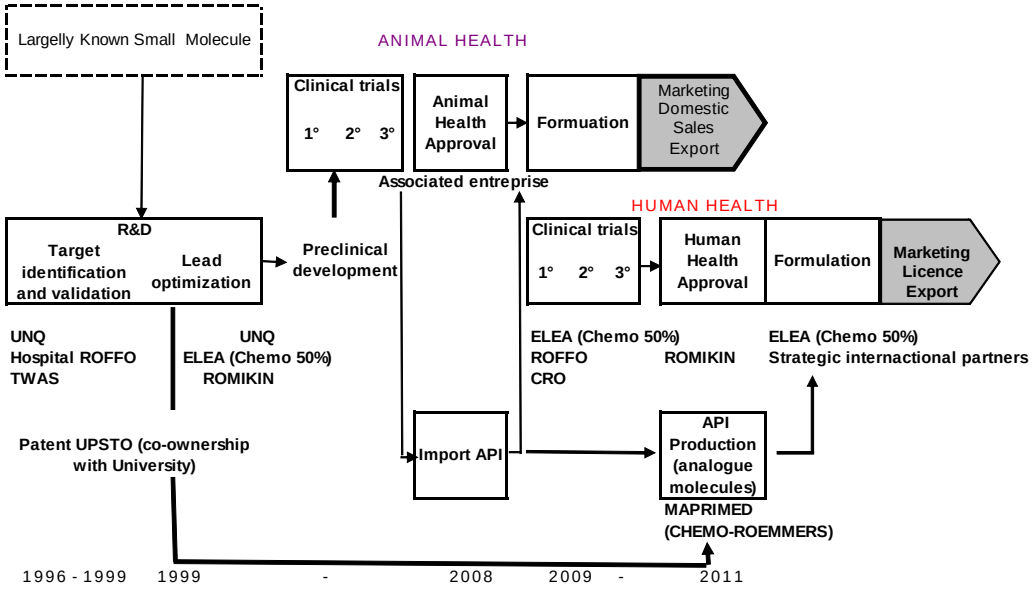
In view of recent breakthrough discoveries in the field of molecular biology, the group support its developments in external sources of scientific knowledge and oriented basic research. By incorporating ground-breaking advances in molecular biology from universities and scientific institutes, Chemo has been able to make the leap from empirical to molecular methods in oncology developments[11].

[11] Among R&D projects, it is worth noting the development of veterinary desmopressin carried out by the National University of Quilmes (UNQ), Romikin and Biogénesis-Bagó as a first step taken towards it use in humans. What is new is that UNQ scientists have identified a biological mechanism by which a widely

Chemo has teamed up with local and international firms and institutions to undertake further joint projects, in which each part has played a different role in the R&D chain: (i) universities initiate developments up to different stages according to the project; (ii) through Romikin, the firm articulates the network of projects and co-finances them from initial developments to product approval and marketing; (iii) other linked pharmaceutical firms lead pre-clinical and clinical stages of developments; (iv) joint-ventures with other local groups (Biogénesis-Bagó, Maprimed) provide technology and production capabilities that meet international quality standards for the production of active ingredients for new developments; (v) a dense network of international strategic partners and subsidiaries take charge of clinical stages in exchange for the technology licence of Chemo's patents.

This form of organization of the value chain enables a wide range of knowledge and competences to be incorporated (from therapy target discovery and validation to approval of the resulting drug in different international markets) and it also makes it possible to bear the high financial costs entailed by these projects. Thanks to the articulation between hierarchical and market forms, the firm can profit from specialization advantages, which are constantly being redefined by increasing necessary competences.

Figure 4: Biotechnology value chain: Chemo Holding



In short, Chemo bases its strategy on sequentially entering from a series of niche markets with low barriers to entry, taking advantage of the convergence between synthesis technology and modern molecular biology tools, and then moving into more complex segments at a later stage.

known molecule interacts with the cancer-cell target that spreads the disease after surgery – in metastases –, thus prolonging patient survival. It is not only inexpensive but also has potential to be used in other types of cancer, and there are great chances it can be extended it to all endoscopic procedures and biopsies in which tissue removal involves risk of spreading cancer cells.

V. Conclusions

Successive waves of molecular biology advances have given rise to local experiences on the part of Argentinean firms that have developed their own autonomous strategies to enter the biotech products market. Out of the three study cases analysed, Bio Sidus entered the market as an imitator in the initial stage of the diffusion of biotechnology, and thus became the local industry's leading exporter of biotech products. In spite of setting up in this business ten years later, Amega has been able to rapidly establish itself in international biosimilars markets by means of an aggressive strategy of acquisition of university spin-offs and other firms. Lastly, Chemo's involvement in biotechnology took place rather late; and it then profited from its synergies with S&T infrastructure and local production of veterinary biologics in order to "rejuvenate" previous developments in chemically synthesized small molecules, which enabled the firm to lay the foundations for the production of recombinants.

Although these microeconomic dynamics have failed to compensate for the deficit trade balance of this sector, they reflect certain systemic effects that, if generalized, may foster the emergence of a local biotech industry able to adopt (and adapt) – at an early stage –molecules already in the market or to develop products for niche markets.

This evolution shows considerable systemic differences with that which occurred in developed countries, mainly in terms of the size of the goods and capital market and public science and technology budgets. Nevertheless, it is worth noting certain features of the local configuration, which could be taken as a model for other emerging countries with certain potential for the production of biopharmaceuticals:

1. Apart from providing firms with competent human resources in the field of molecular biology and related technologies, science institutes and universities have enabled the formation of highly qualified research groups devoted to the discovery and development of new drugs, as proved by the three cases analized
2. If the capital and risk capital market is absent or weak, established firms (incumbents) play a key role in the early stages, directly articulating with spin offs since they emerge from the universities incubators (an idiosincratic type of spin offs, not necessarily having patents at that stage) by contributing the necessary financial resources and taking over the stages of final formulation, commercialization, and marketing of medicines (strategic assets downstream in the value chain).
3. The form of organization varies according to technology maturity, complexity of molecules, degree of involvement in the discovery and date of entry in this activity. While the pioneer Bio Sidus has adopted a highly integrated model as an early imitator of first wave molecules, the followers adopted network organizations searching to accelerate the diversification towards this new activity: Amega outsources some clinical and production activities, and Chemo is half-way between the two in that it divides labour through joint-ventures with local and international firms.

The evidence gathered in this paper provides a better understanding of the factors that define successful forms of organization in the field of biotechnology applied to human health. Although there are some particular determining factors – such as product mix and emergence at different stages of the technology lifecycle – the three cases show some common features in terms of the pre-eminence of financial advantages and articulation with the local knowledge base as a starting point for their evolutionary

paths. In turn, they raise new questions regarding the feasibility of these types of strategy in view of the increasing barriers to entry into biosimilars markets and the likelihood of their spreading to all firms in the sector. These potential scenarios represent new political and institutional challenges in terms of intellectual property rights strategies, medicine approval procedures, and configuration of the public health system in order to foster the structuring of an innovative system in the sector and the competitive integration of firms into global markets.

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