Biosimilar corporate strategies in Argentina during the 2000s: technological and organizational learning for internationalization

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Abstract

Some Argentine biopharmaceutical firms managed to enter into the biosimilars segment of the global market at an early stage, as creative imitators of the first generation of biotechnological drugs during the first phase of the new paradigm. The transition from the first to the second generation of biosimilars implies new and greater challenges. In this document, we discuss the nature of these challenges, focusing on different institutional and corporate learning trajectories within the Argentine biosimilar industry, the technological and regulatory capabilities needed to enter second-generation biosimilar markets, and the existence (or the lack) of a common learning trajectory in the sector. For this purpose, we discuss the specificities of the learning process in biosimilars, and then analyse the institutional set-up, the S&T infrastructure, and the main characteristics of the biosimilar industry in Argentina.

Resumen

Algunas empresas biofarmacéuticas argentinas lograron competir en los mercados globales de biosimilares, en etapas tempranas, como imitadores creativos de la primera generación de drogas biotecnológicas, durante la primera fase del nuevo paradigma. La transición hacia la segunda generación de biosimilares implica nuevos y mayores desafíos. En este documento discutimos la naturaleza de esos desafíos, centrándonos en el análisis de las diferentes trayectorias de aprendizaje corporativo e institucional dentro de la industria de biosimilares, las capacidades regulatorias y tecnológicas necesarias para entrar en el mercado de biosimilares de segunda generación, y la existencia (o la ausencia) de una trayectoria común de aprendizaje en este sector. Para ello, discutimos las especificidades de los procesos de aprendizaje en biosimilares y analizamos la configuración institucional, la infraestructura en Ciencia y Tecnología y las principales características de la industria de biosimilares en Argentina.

Introduction

In the late 1980s, some Argentine biopharmaceutical firms managed to enter regional and global markets as creative imitators during the first phase of the diffusion of the new paradigm, initially producing recombinant proteins from the first wave of biotechnologies.

We argue that -following the hypothesis presented in Perez and Soete (1988) and Perez (2002) concerning the 'windows of opportunity' for catching-up that opened up for emerging countries in new technology-based industries during the initial emergence phase of the new paradigm-, the early entry of Argentine biotech firms into international biosimilar markets took place at a time when technological and regulatory entry barriers were not very high.

Notwithstanding, biotech firms had to develop particular innovative and learning capabilities related to the specificities of biological-based production processes and products, and to implement the analytical tools needed for assessing whether the new biosimilars were comparable with the original innovative products, in line with regulatory requirements.

As the biotech paradigm spreads and new waves of biotech drugs are produced– particularly larger, more complex molecules such as recombinant molecular antibodies – experience and regulatory barriers increase, and so do costs and production time. The transition from the first generation to the second generation of biosimilars requires new technological, organizational, and regulatory learning. Likewise, new challenges arise if companies are to succeed in the new high-cost, high-price biosimilar markets, in particular with regard to the required experience in biosimilar analytical techniques, which are one of the most important barriers to market entry.

In this paper, we discuss the learning process challenges that firms and institutions need to address if they are to successfully move from the first to the second generation of biosimilar recombinant proteins. To this end, we intend to answer the following questions:

What have the corporate learning trajectories of the Argentine biosimilar industry been like? Is technological experience a necessary and sufficient condition for

moving from the first to the second generation of recombinant drugs? Given the diversity of firms' strategies, is there a common learning trajectory in Argentina?

The paper is organized as follows. Section 1 discusses the specificities of the learning processes and reverse engineering in biosimilars. Section 2 presents the institutional set-up and the science and technology (S&T) infrastructure for the health biotech industry in Argentina, considering S&T opportunities, technological policies, intellectual property rights, and the regulatory framework. Section 3 presents the main features of the biosimilar industry in Argentina, analysing firms' international integration and industrial structure. In Section 4, we analyse the different learning trajectories in the Argentine biosimilar industry. Finally, in the conclusions, we summarize the main evidence included in this study.

1. Learning in biosimilars: what does it mean?

Several scholars have studied learning experiences in developing countries (Kim, 1987; Lee and Lim, 2001; Lee, 2005; Lee, *at al*, 2005). These works refer mainly to catching-up processes in the chemical and electronic industries. In these cases, learning was focused on process technology and resulted from reverse engineering. Early imitators had the advantage of skipping the research, design, and development stages by reverse engineering the manufacture process. The main technology sources were internal learning-by-doing and learning-by-using in relation to imported capital equipment and plant set-up. Several organizational and institutional innovations complemented this technological path: the creation of engineering departments in relatively integrated firms, weak intellectual property rights that were limited to process and a set of ad hoc government S&T institutes that were more or less structured around a top-down policy design. These complementary technological, organizational, and institutional learning processes were at the core of Asia's catching-up experiences and underlie the entry of new competitors into global oligopolies in several industries.

Catching-up in the biopharmaceutical industries does not replicate this learning pattern. It is difficult and costly to recreate biologics, because they are complex molecules that derive from living genetically modified organisms (Berkowitz, *et al*, 2012,). In contrast, small-molecule drugs produced by chemical synthesis can be easily replicated and are considerably less expensive to reproduce. Because of the variability between biological molecules, duplicative imitation is not possible. As biosimilars need

to be officially approved, versions of the original innovative products, which can be manufactured when the patent for these expires, are subject to domestic property rules and regulatory guidelines[1].

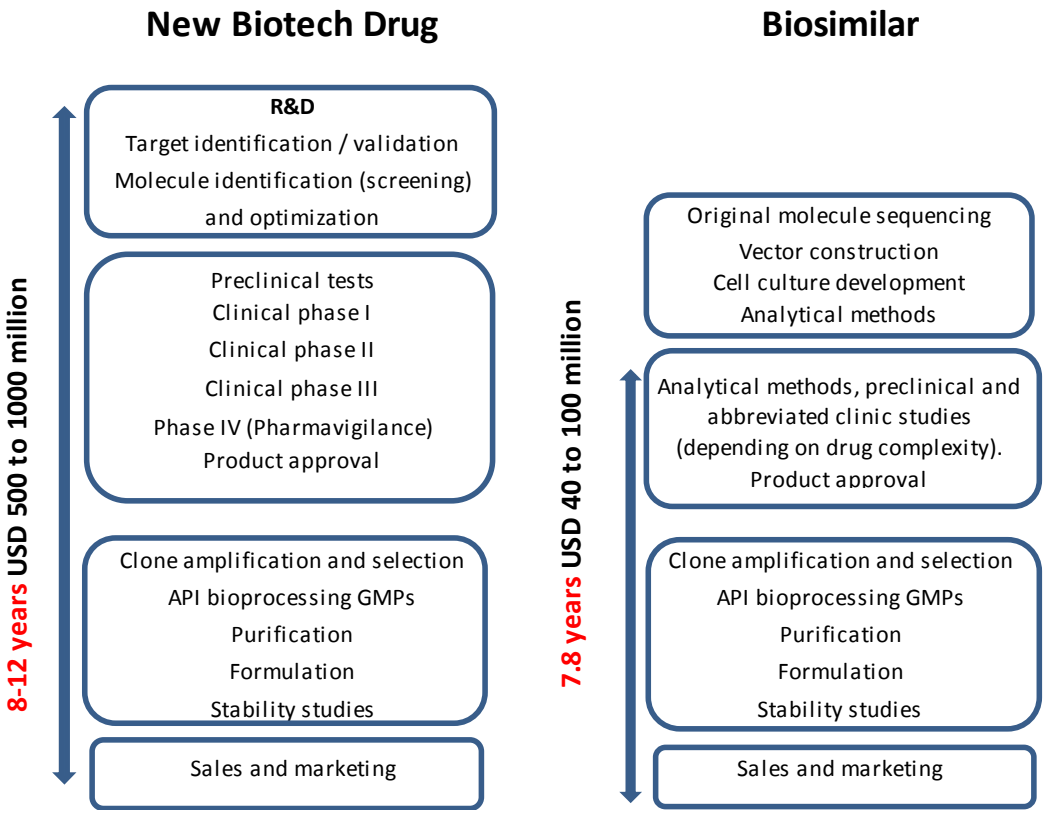
Reverse engineering in biosimilars involves both product and process learning. Product imitation implies developing a drug that is sufficiently similar to the original in terms of quality, efficacy, and safety. Unlike small-molecule chemical synthesis drugs, biotechnological drugs generally exhibit high molecular complexity, and can be quite sensitive to changes in manufacturing processes. Molecular complexity is greater in high price second-generation biotechnological products like monoclonal antibodies (MABs), than in erythropoietin (EPO), insulin, and other first-generation biotech drugs. Reproducing the original drug requires biotech capabilities in order to replicate the original molecule through DNA sequencing. It requires also experience in laboratory, biological, and chemical analytical capabilities, to ensure that the biosimilar molecule has the same characteristics as the original at several stages of the innovation and manufacturing processes.

Furthermore, achieving a similar molecule at the laboratory stage does not ensure its productive efficiency. Culture development involves the selection of those clones whose DNA sequencing best codifies the protein's characteristics and functions. Last but not least, the upstream and downstream manufacturing stages involve knowing which combination of the expression system, bioprocessing method, and purification system can be adopted.

Knowledge sources in this case involve not only internal manufacturing and regulatory learning but also different external knowledge sources, including local and international institutions and international contract research organizations (CROs) specializing in different stages of development. The recombination of external knowledge distinguishes biosimilar firms from traditional duplicative imitators.

[1]It is mandatory for biosimilars to undergo both non-clinical analytical testing and clinical testing to enable the detection of differences between the biosimilar and the reference products in terms of human pharmacokinetics (PK) and pharmacodynamics (PD), efficacy, safety, and immunogenicity.

Figure 1. The development of original biotech drugs and biosimilars



Developing biosimilars enables some stages in the process to be skipped: the identification of the target protein, molecule development, preclinical studies, and some of the costly clinical studies (Figure 1). Although this implies an advantage for imitators and for the catching-up process, this cannot be assimilated into a duplicative imitation strategy, as is the case in other industries, including chemical drugs. The legal requirements of approval pathways, together with the costly clinical and scaling-up processes, increase the costs for developing biosimilars to a range of between USD 40 to USD 100 million (Bourgoin, *et al* 2013, Fanfan-Porter *et al*, 2014, Sekhon et al, 2011). Even more stages may be skipped in cases where the biosimilar firm decides to outsource the cell development stage and acquire the productive optimized molecule, focusing on scaling up, and the upstream and downstream manufacturing stages.

A biosimilar is essentially a 'regulatory good'. The approval of a biosimilar is subject to regulatory pathways, which are the result of the co-evolution of technological advances in analytical tools, public-private learning between governmental agencies and

firms, and changes in competitive strategies between innovators and imitators. In recent years, there have been significant advances in the analytical techniques used to characterize molecules and determine their similarity. As such, regulatory pathways have been changing, opening up the possibility of entering biosimilar markets without completing all the clinical and pre-clinical analyses. As approval requisites and technology co-evolve, only those firms that are able to manage both regulatory and technological learning can profit from the patent's expiration in progress. Management of this co-evolving processes requires the development of organizational learning and a flexible network structure which combines the advantages of an integrated structure with those of the outsourced one and, more importantly, selectively internalizes those stages that ensure that the firm has mastered the entire innovation process. In this context, domestic bottom-up policies should be complemented by deliberate top down strategies that aim to create focused technological capabilities and institutional and regulatory learning so as to be able to take on new challenges.

2. Institutional set-up and S&T opportunities

Three institutional characteristics of the biotechnological innovation system in Argentina – which differs significantly from those of developed countries – affect the emergence of biotech firms (Gutman and Lavarello, 2014a and 2014b): i) the absence of risk capital markets and large-scale public procurement programmes, ii) the fragmented health System, and iii) the fact that domestic regulatory agency still being consolidated.

In this context, Argentina has succeeded in developing minimal thresholds in scientific and technical knowledge, and has generated the conditions for technological learning processes at the manufacturing stage and, more recently, in intellectual property rights and regulatory frameworks, allowing biotech firms to compete in biosimilar markets.

2.1. Science and technology opportunities

High educational standards and achievements in scientific and technological research achievements are two factors that have opened up important opportunities for the development of biotechnology in Argentina.

Argentina has developed levels of excellence in graduate and postgraduate academic education in disciplines related to biotechnology (medicine, biology,

biochemistry, and pharmaceutics). This has placed the country in a privileged position for dealing with the knowledge barriers to biotech development, and ensured the availability of highly qualified human resources for the R&D, analytical, and manufacturing phases of biotech firms' value chain. Argentina has also a long tradition in R&D activities: university laboratories and S&T research centres such as those of the National Scientific and Technical Council (CONICET); the Leloir Institute; the National Institute of Industrial Technology (INTI); the National Institute of Agricultural Technology (INTA); and health institutions with medical research capabilities, such as the Roffo Hospital, among others, have been carrying out relevant basic and focused research activities, providing important S&T infrastructure.[2]

According to the annual S&T surveys carried out by the Ministry of Science and Technology (MINCyT), 12% of publicly funded research projects in 2013 were related to the medical sciences (around 3500 projects involving more than 11,000 researchers). The recent National Survey on Biotech Research Groups carried out by the same Ministry showed that 83% of these groups in 2015 belonged to the network of universities and S&T centres, and that more than half of these projects were oriented towards the area of human health (MINCyT, 2015) These significant sources of innovation resulted in relevant processes of learning by interaction, strengthening the competitive advantages of biotech firms.

2.2 Technological policy: institutional learning

Today, biotechnology is one of the priority areas for public support programmes and policies focusing on technological development. Among the MINCyT policies and instruments that are oriented towards supporting firms' technological capabilities, three are particularly important: the Argentine Technology Fund (FONTAR), the Support Programme for Technology-Based Firms (PAEBET), and the Argentine Sector Fund (FONARSEC).

The aim of FONTAR is to support R&D&I and firm technology modernization projects.[3] Although most of the country's biotech firms have been incorporated into this programme, in practice, there is a high concentration of subsidies among the few larger

[2] In 2011, Argentina had the highest number of researchers per employed person in Latin America: 3.06/1000 employed people (Gutman and Lavarello, 2012).
[3]Within the total portfolio of FONTAR subsidies, human health biotech projects represented 4% in 2006–2012.

firms: between 1996 and 2012, 63% of these subsidies were concentrated in only five firms.

PAEBET, which started in 2011, supports the initial pre-competitive activities of start-up firms based on the results of scientific or technological research, with capabilities for the creation and transfer of technology. This has policy boosted the emergence of numerous small biotech firms, a point we will return to in Section 3, but they showed a high rate of rotation.

These two programmes were implemented as horizontal instruments to support firm capabilities and are considered bottom-up policies.

The FONARSEC programmes are a new systemic approach that have been in place since 2005. They have enabled public S&T authorities to foster the creation of public-private biotech arrangements (*consorcios*) through a more selective approach, opening up a stage of new and more focused top-down institutional learning in technology policies for the sector. Though these instruments have increased the number of projects and firms in the sector, only a few domestic pharmaceutical holding groups with organizational advantages have profited from them. Specifically, some projects relating to vaccines, oncological drugs, and biosimilars have received support from CONICET and university laboratories working in conjunction with domestic firms.

Overall, these programmes have marked the start of an institutional learning path that is gradually moving towards more focused, selective policy instruments.

2.3. Intellectual property rights regime and regulatory framework

Like many developing countries, for many decades Argentina adopted a patent regime which protected the methods or processes for making a given product but excluded the final product itself. In the case of chemical synthesis, these rules opened up opportunities for process learning. Since virtually any chemical compound can be made through a variety of processes, the scope of patent protection was greatly reduced. Thus started the era of reverse engineering, when firms innovated by changing their production processes. Argentine pharmaceutical firms moved into the area of manufacturing formulations by importing active pharmaceutical ingredients (APIs), while a limited number of firms followed with backward integration into the production of bulk drugs.

Patent protection was extended to include products themselves following the signing of TRIPs in 1995 and the congressional sanction of Law 24,481 and the decrees that regulated its implementation. After the transition period allowed by the TRIPS, Argentina started to grant product patents in 2001. Since then, pharmaceutical patents have represented around 30% of total patents. Only 2.5% of applications have been from domestic companies, with the majority instead coming from multinational corporations (MNCs). Certain authors show that a large proportion of these patents are new forms or minor changes in formulations and do not include new molecules (Correa, *et al*, 2011)

Although patents were extended to include products, there are many flexibilities and grey areas in international legislation that increase the policy space for developing countries (Correa, 2011). Argentina has not yet utilized health-related patent flexibilities such as compulsory licensing, parallel imports, the exhaustion of rights, and the research and early working exemptions. Conversely, since 2012 it has adopted tougher standards of patentability, making it harder to obtain a patent for 'inventions' which offer little to no real improvement over existing drugs. Under TRIPs, countries are free to determine for themselves their criteria for novelty, inventiveness, and usefulness.

This regulatory change explains a reduction in the ratio between granted patents and applied patents, which is particularly notable in the case of second-generation biotech drugs. Of 3289 patent applications for MABs since 2010, only 155 were granted (5%). Spurious patenting limitations enable domestic firms to develop biosimilars as soon as patents expire. This change shows how it is possible to set up a strategic approach to intellectual property rights in the context of the new rules of the game, enabling institutional learning in the face of new technological paradigms.

More than patent guidelines, the real entry barriers to international markets are the complex regulatory requirements that are established once original patent protection has expired (Niosi *et al*, 2012). Some first-generation biotechnological products – such as recombinant insulin and recombinant human growth hormone – can be well characterized by established analytical approaches, which have facilitated the regulatory approval of biosimilar versions under abbreviated pathways (based on data from the original drug, analytical data, and, in some cases, limited clinical data) (Berkowitz, *et al*, 2012).

Argentina entered the simpler biosimilar drugs markets early on, and domestic firms have accumulated significant experience in analytical techniques. However, many biotech drugs, such as MABs and other recombinant therapeutic proteins, are larger and more complex. As we discussed in Section 2, the extent to which existing analytical technologies can be used to support the likelihood of clinical comparability is much more limited. Consequently, a key challenge for the development of biosimilars is learning how much and what kind of data is needed to establish the fact that the differences between similar (but not identical) products are not clinically significant. This challenge requires a co-evolution between domestic regulatory agencies and firms' learning on analytical techniques and international regulatory changes.

In recent years, ANMAT, the domestic regulatory agency, began developing its own abbreviated pathway for biosimilars by adopting WHO guidelines. Like the European Medicines Agency (EMA), ANMAT has adopted a case-by-case regulatory standard of comparability which is higher for complex molecules and lower for simple first-wave biologics. Between 2011 and 2012, 99 biological-biotechnological drugs were approved for commercialization, 30 of which were domestically produced biosimilars. Only one MAB biosimilar developed by a domestic firm was authorized.

The regulatory agency approach seeks to find a solution to the trade-off between setting a high bar for comparability (which discourages the entry of small and medium domestic firms into the biosimilar market) and setting too low a bar (in which case the drug's efficacy and patient safety could be in jeopardy, inhibiting an international catching-up process). Simultaneously, as we will discuss in Section 4, those enterprises seeking to enter the international biosimilars arena are partnering with CROs and health organizations with experience designing and conducting biosimilar clinic trials.

3. The biosimilars market in Argentina: international insertion and industry structure[4]

Argentina developed biotech molecules early on, launching its first molecule shortly after the commercialization of these drugs in developed countries, during the initial pre-paradigmatic diffusion period for these new technologies when, although high knowledge thresholds were required, there were not yet high regulatory thresholds or relevant learning processes in manufacturing.

[4] This section is based on Gutman and Lavarello (2014a, 2014b, and 2015).

Two important features distinguish the health sector from the other biotech sectors in Argentina: the majority presence of domestic private firms in the domestic market, and its early internationalization, which explain its gradual but systematic production and the regulatory learning process.

3.1. Domestic markets and firm internationalization

The Argentine biopharmaceutical industry is characterized by a small production capacity for the domestic market, and follows the typical pattern of the country's pharmaceutical industries as importers of APIs and formulators of pharmaceutical products.

The size of the domestic market was about USD 1200 million in 2013, including domestic production of recombinant proteins and imports of proteins, insulin, and MABs (the production and importing of vaccines are not included in this estimation). As is the case elsewhere in the world , the Argentine biotech market shows high growth rates, shifting from 12% of total pharmaceutical sales in 2005 to almost 27% in 2013. Total domestic production of both APIs and final drugs was near USD 55 million in 2013, which represents only 4% of domestic demand. Around 80% of local output aimed at the domestic market comes from three local firms/holdings whose commercial strategy is, however, oriented towards international markets: between 75% and 80% of their output is exported to Latin American and Asian countries with flexible regulation standards.

The sector shows a high and growing trade deficit, stemming from the importing of both original biotech drugs and of the main APIs. With the growth in the domestic market, the negative balance of biopharmaceutical trade notably increased, moving from a deficit of about USD 18 million in 2003 to one of more than USD 463 million in 2013. Imports of second-generation original biopharmaceutical products, mainly MABs, are the main explanation for this growth in trade deficit: between 2010 and 2013, imports of MABs reached almost 81% of the total trade deficit for biopharmaceuticals. Imports of drugs and APIs are the main activity of the MNC subsidiaries operating in the country, which are responsible for 96% of the sector trade deficit balance in 2015 (Lavarello et al., 2015).

Notwithstanding this trade deficit, since the mid-1990s, Argentina has been able to achieve a surplus in relation to first-generation biopharmaceuticals and has high

chances for import substitution of the latest developments in first-generation molecules (Interferon beta-1a, interferon beta-1b, and Peginterferons) (Lavarello and Goldstein, 2014).

3.2 Industrial structure

Several factors have shaped the structure of the biopharmaceutical sector in Argentina: changes in the domestic and international regulatory context over the last two decades, increased competition in the global biologics markets, the technological and organizational competences of firms, and the trajectory of the pharmaceutical industry.

The sector is a relatively dynamic, albeit concentrated, one. Between 2009 and 2015, the number of firms in it increased from 26 to 55, which in 2015 amounted to 45% of the total biotech firms in Argentina. Only eight firms manufacture domestically produced biological APIs, of which six firms produce APIs for therapeutic use. Until now, these firms have focused on the production of first-generation recombinant biosimilar proteins, including drugs, APIs, and in vitro diagnosis. One of them has launched its first MAB biosimilar and another is making progress on the production of another MAB biosimilar.

Table 1. Argentine biotech firms by organizational form, products, and main activity. 2015.

Organizational form	Number of firms	Type of products				Main biotech activity		
		Therapeutics	IVD	Services	Others [1]	R&D	API	Drug Formulation
SBF	5	2	2	1	0	1	2	2
SBS	26	6	1	14	5	25	1	0
DPF	10	7	1	1	1	3	1	6
DGS	10	10	0	0	0	3	3	4
MNC	3	3	0	0	0	0	0	3
PL	1	1	0	0	0	0	1	0
Total	55	29	4	16	6	32	8	15

Notes: SBS=specialized biotech start-up; SBF=specialized biotech firm; DPF=diversified pharmaceutical firm; DGS=domestic group subsidiary; MNC=multinational corporation; PL=public laboratory.
IVD=in vitro diagnostic; R&D=research and development; API=active pharmaceutical ingredient
(1) Gene therapy, cell culture, others
Source: Gutman and Lavarello, 2014; PICT Project CEUR-CONICET 'Innovative strategies in face of the diffusion of biotechnology: the biopharmaceutical industry in Argentina' 2013–2016.

As shown in Table 1, only three firms are MNC subsidiaries, and focus on imports, drug formulation, and sales in the domestic market. These firms contract specialized companies or local R&D institutes for clinical or analytical studies only when necessary to comply with local regulatory requirements.

With regard to domestic firms, the structure of Argentina's biotech industry today consists of 52 firms that are heterogeneous in terms of their main activity, organizational forms, market orientation, and value chain configuration. These include **specialized biotech firms (SBFs)** established in the 1980s and 1990s, which focus on the production of first-generation proteins and in-vitro diagnostics. They rely on the scientific opportunities provided by CONICET and the national universities, from which their scientific and technical staff come. From 2000 to 2010, these firms became the main source of spin-offs in the sector. The majority of these were **specialized biotech start-ups and spin-offs (SBSs),** young firms that developed with the support of public programmes focusing on technology-based firms. Their future is uncertain: they may be integrated into domestic pharmaceutical holdings as group subsidiaries; alternatively, in what is a more difficult and unlikely trajectory, they may become specialized biotech firms, or, more probably, they may cease to exist. **Diversified pharmaceutical firms (DPFs)** are generic drug producers which are diversifying into biotech production, which represent a small part of total sales. As we will analyse in the next section, some SBFs and SBSs have been integrated into the value chain of diversified pharmaceutical holdings, thus becoming **domestic group subsidiaries (DGSs).** This integration has implied a subsequent selective restructuring of the entire value chain in order to obtain vertical coherence. Finally, only one of the three **public laboratories (PL)** with capacities for producing traditional vaccines and other extractive biological products would be potentially capable of producing recombinant proteins.

To sum up, taking into account firms at the business unit level, independent SBF and controlled SBS, the country's core biotech firms, represent about two-thirds of the total biotech firms in the health sector in Argentina. However, until now, only a few of these have successfully developed all the stages of the value chain (directly or through their integration into domestic holdings), and acquired the production and regulatory capabilities and know-how needed to compete in local and global markets.

These firms developed different learning trajectories in connection with the production of first-wave biosimilars and, in some cases, they were able to enter production of second-wave biosimilars, as we discuss in the next section.

4. Learning trajectories

Argentine firms have adopted different learning trajectories depending on the strategies, organizational structure, and capabilities they have accumulated. Strategy choice is based on different economic and technological trade-offs between the level of the technological opportunity and market and regulatory uncertainty, between the speed of capital rotation and the time needed to develop a biosimilar, and between the level of fixed costs and the flexibility needed to face the shortening of biosimilar life cycles. A change in strategy may also require a change in organizational structure, and changing the structure of a firm is harder than it may seem. By this, we are referring to the company's management, and how to ensure a governance structure that allows the strategy to be implemented. Given that the strategy defines a firm's structure, it is then possible to define a structure that supports different learning patterns.

4.1. Market, technology, and productive strategies

Before analysing the learning trajectories of the Argentine biosimilar industry, we should first acknowledge the four main stylized strategies and associated organizational structures adopted by Argentina's biotech firms to respond to biosimilar market opportunities and new regulatory barriers.

1. The first strategy, adopted by some independent SBFs based on exports of first-generation biosimilars, was the international insertion as suppliers of high-quality low-cost products. A highly integrated organizational structure supports this strategy. The most notable of the firms following this strategy is Biosidus, the first Argentine family firm to enter the biosimilar medicines market in the early 1990s and which became a global supplier of erythropoietin and interferon beta. With the increasing regulatory and investment thresholds that have been established since the early 2000s, this strategy became less successful. Although it continues to explain the majority of Argentina's biosimilar exports, the main challenges to this strategy since the 2000s have been the decreasing profit margins for first-generation biosimilars and the technology transfer requirement associated with the import substitution policies adopted by importing developing countries.

- The second strategy has mainly been adopted by local diversified pharmaceutical firms (DPFs) specializing in generic chemical synthesis drugs. This strategy looks to take advantage of their access to public procurement,

entering the markets for first-generation biosimilars such as insulin (and its analogues) and in vitro diagnostics for certain diseases. These market segments are characterized by lower regulatory requirements and knowledge and bioprocessing scale thresholds than those of the high-quality biosimilars associated with the first strategy.

- A third strategy is followed by the biopharmaceutical group AMEGA, controlled by an association between international investors and a domestic pharmaceutical holding (Roemmers). This strategy seeks to advance from first-generation biosimilars to more complex, second-generation ones. This strategy is based on the acquisition of different SBSs and SBFs which developed in the early 2000s as exporters and main local suppliers of first generation APIs for formulating domestic firms. After these acquisitions, the firms were thoroughly restructured, leading to the rearticulation and redistribution of activities such as R&D (now focused on development), API production, pre-clinical trials, quality control, and marketing, and significantly expanding their production capacity. The group's technology strategy is aimed at expanding its recombinant protein production by developing new technology platforms.
- The fourth strategy is that of Mabxience, a specialized global biotech firm controlled by CHEMO, a pharmaceutical chemical synthesis and animal health biologics holding whose capital is controlled by Argentine families. This strategy is aimed at entering into MAB biosimilar markets. Although the price of the biosimilar would be between 60% and 80% lower than that of the reference drug, this strategy ensures high profit margins after patents expire. Unlike the third strategy there is a lower degree of integration of R&D activities, which implies lower development and regulatory time requirements for approval. These opportunities are closely connected to high regulatory standards and market uncertainty, which requires an organizational structure that is flexible enough and a portfolio of capabilities that is broad enough to adapt to a changing technological and regulatory environment.

Table 2. Firm strategies and learning trajectories.

	From chemical synthesis to first-generation biosimilars		From first-generation to second-generation biosimilars	From biologics to second-generation biosimilars
Strategy	International low-cost high-quality specialized early imitators	Domestic market low-cost latecomer imitators	Regional high-quality high-profit-margin biosimilar exporters	Global high-profit-margin biosimilar exporters
Organization Structure	Integrated	Integrated	Quasi-integrated	Network
Core Capabilities	Cell culture development and bioprocessing	Public procurement market access	Cell culture development and bioprocessing	Biotechnological drug clinical and formulation capabilities
Secondary Capabilities	Developing countries drugs distribution requirements	Drug Formulation capabilities	DNA innovator capabilities	Animal health bioprocessing and formulation
External Knowledge sources	University molecular biologists, hospital biomedical teams	International drug licenses and R&D private labs acquisition	University long-term partnership	International and local university partnerships, CROs, and new (disposable) bioprocessing equipment
Technological learning	Incremental product development, simple protein cell culture, low-scale bioprocess optimization	Analogue (incremental) product development and low-scale bioprocessing	Complex protein cell culture technologies, product and bioprocess optimization	Upstream and downstream bioprocess optimization
Regulatory learning	First-generation analytical techniques and regulatory agency learning-by-interaction	First-generation analytical techniques	New analytical techniques and regulatory agency learning-by-interaction	New analytical techniques and regulatory agency interaction
Organizational Learning	International partnership development	R&D and manufacture restructuring	Corporate reorganization from conglomerate holding to internal specialization	Corporate reorganization from conglomerate holding to network global organization

Source: prepared by authors.

As we will analyse in the next section, by implementing routines around each organizational structure, firms have adopted different learning trajectories. New routines involve technological, organizational, and, notably, regulatory learning, which will differ depending on the strategy and organizational structure adopted by the firms.

4.2. Learning trajectories: technological, organizational, and regulatory capability accumulation

Three main learning trajectories can be identified in association with the strategies analysed above. First, the trajectory based on the transition from chemical synthesis production to first-generation biosimilars, which was implemented early by high-quality low-cost exporters like Biosidus and subsequently adopted by other local producers. Second, the transition from first-generation to second-generation biosimilars by an accumulative trajectory; and third, entry into second-generation biosimilar production without previous manufacturing experience in first-generation biosimilars. The following subsections explore these trajectories in more detail.

4.2.1. From chemical synthesis to first-generation biosimilars

Biotech products are made up of totally different scientific knowledge bases, technological expertise, and regulatory requirements than chemical synthesis drugs. This learning trajectory has partly been made possible by the fact that scale, production expertise, and regulatory thresholds were low at the beginning of the biotechnology paradigm. During the early stages of diffusion of the biotechnological paradigm, a small enterprise which wanted to wager on this new market only required low scale roller bioreactors and abbreviated analytic (non-clinical) studies.

However, at the beginning of the first wave of the biological revolution, knowledge thresholds were high, and public biomedical and biological knowledge enabled this pioneering trajectory. Early entry of local biotechnological firms was possible due to the extensive biomedical expertise of teams at public hospital and highly qualified biochemists and molecular biologists. These public infrastructure sources could not have been transformed into new developments without the production-oriented research taken on by firms such as Biosidus. Local imitative development required notable internal learning-by-doing in simple cell culture development and the scaling up of bioprocessing.

As the first wave of the molecular biology revolution became better known and public knowledge thresholds became less constraining, several generic chemical firms adopted this learning trajectory. The successful entry of latecomers depended on low competitive pressure in domestically regulated markets. Those firms wanting to compete in international markets adopted a cost-reducing and incremental product

trajectory. In recent years, this trajectory has depended more on cost reduction through learning-by-doing in highly disseminated bioprocessing techniques than on the development of new molecules. Product development was limited to incremental innovations in first-generation biosimilars. However, this incremental innovation strategy also requires regulatory learning and interaction with domestic patent offices as big MNCs tend to extend the patent life of previously approved drugs through minor innovations.

4.2.2. From first-generation biosimilars to second-generation biosimilars

This trajectory is characterized by cumulative technological and regulatory learning at all stages of the value chain. As we discussed in Section 1, the path from first-generation to second-generation biosimilars implies an accelerated learning process in the technological and regulatory aspects of the process. This includes not only DNA technologies but notably expertise in complex cell culture technologies and product and process optimization.

This is the case of AMEGA Biotech, a domestic holding whose financial advantages enabled an accelerated learning process. The firm's initial core capabilities were simpler cell culture technologies and low-scale bioprocess learning. Between 2005 and 2008, AMEGA restructured an R&D biotech firm with analytical capabilities and two domestically owned biotech firms specializing in cell culture development and in recombinant protein bioprocessing. This acquisition-based growth strategy required significant organizational learning and restructuring. This enabled technology learning in complex cell development, process optimization, and multiple analytical techniques.

In contrast to the first trajectory, the rigorous regulatory pathways for approval demanded a broad range of analytical techniques to ensure comparability to the original drug. Given the multiplication of analytical techniques that have reshaped regulatory pathways, internal learning has been coupled with learning-by-interaction with international CROs. This interaction has become a necessary condition for launching second-generation biosimilars in a more selective and contestable market.

4.2.3. Fast track to second-generation biosimilars.

In contrast to the cumulative and sequential learning trajectory adopted by AMEGA, there is a second fast-track learning trajectory. This trajectory, which was adopted by

Mabxience, involved skipping the complex stages of cell culture development. An optimized MAB clone was acquired from specialized international biotechnological firms with regulatory experience in markets with high regulatory standards. This trajectory has allowed the firm to specialize in the upstream and downstream bioprocessing stages where it has accumulated previous experience.

Buying the optimized clone required a certain level of absorptive capabilities in DNA sequencing and analytical characterization. Nevertheless, the main learning focus has been the optimization of the bioprocessing and analytical techniques needed to ensure quality and cost efficiency. One of the key aspects of this learning trajectory is achieving the combination of expression system, bioprocessing, and purification that is most compatible with a short product cycle and a flexible strategy. Being among the early MAB imitators has required an abbreviated learning process and more flexible equipment, such as disposable (or single use) bioreactors.

As was the case with the previous trajectory, technological learning is coupled with organizational learning. Mabxience has developed organizational advantages due to having already internationalized its production. This allowed the firm to take advantage of the national innovation system and at the same time to expand to other countries. A domestic specialized biotechnological start-up (PharmAdn) became the first API manufacturing facility for the production of MAB biosimilars, and was well suited to integrating into the Mabxience global value chain as a scaling-up facility. However, as Mabxience became a global player, this plant did not reach the necessary productive capacity threshold, so CHEMO complemented this investment with another acquisition in Spain. In this global organizational structure, Argentina has become a global scaling-up centre, and a fill-and-finish location at CHEMO's other state-of-the-art local plant, SINERGIUM Biotech.

Conclusions

Given the imminent expiry of patents and health budget constraints in developed countries, growth in the biosimilar market is opening up new opportunities for imitative firms from developing countries (Huzair et al, 2011). However, as we have discussed in this article, the transition from first-generation biosimilars to high-cost, high-price, second-generation biosimilars implies new and greater challenges and will require higher scale and regulatory thresholds.

Thanks to the national S&T infrastructure and firms' biotechnological trajectories, Argentina has early accumulated knowledge and learning advantages which have allowed firms to enter the first-generation biosimilars market. Moving towards second-generation biosimilars will require high levels of investment and production expertise if firms are to succeed in global MAB markets; greater articulation between domestic and international markets so as to increase minimum scale thresholds; higher national regulatory status coupled with firms' regulatory experience; and finally, regulatory thresholds that involve an autonomous and efficient regulatory authority.

We have identified three main learning trajectories for pharmabiotech firms in Argentina in connection with their specific corporate strategy. First, the trajectory based on the transition from chemical synthesis production to first-generation biosimilars which required a totally new knowledge base. Second, the accumulative trajectory based on the transition from first-generation to second-generation biosimilars, which is characterized by cumulative technological and regulatory learning at all stages of the value chain. Third, the learning trajectory we identify as the 'fast track to second-generation biosimilars', which consists of directly entering second-generation biosimilar markets without previously having manufactured first-generation biosimilars by acquiring specialized firms and collaborating with international partners, a trajectory adopted by firms with global strategies.

Taking into account these different learning trajectories, technological experience in first-generation biosimilar production is not a necessary nor sufficient condition for moving from first- to second-generation recombinant biosimilar drugs. It is not a sufficient condition because some firms which have developed first-generation biosimilars have not managed to develop second-generation biosimilars. This transition requires regulatory and new technology learning because of increased regulatory and technology barriers. Likewise, it is not a sufficient condition because firms can directly enter the market segment for second-generation biosimilar drugs despite not having previous experience in recombinant drug manufacturing. However, country-level technological experience in first-generation biosimilar production *is* one of the necessary prerequisites for a firm to successfully catch up in this field. Without the acquisition of small SBS spin-offs from first-generation biosimilar producers, the fast track to second-generation biosimilars would have been impossible.

In keeping with these heterogeneous learning trajectories and capabilities, there is tension between the emergence of a biotechnological innovation system fostering a national catching-up process and individual firms' strategies. A biotechnological innovation system focused on catching-up requires coherent interaction between public S&T infrastructure and all stages of the innovative value chain, an incremental upgrading of domestic regulatory standards, public procurement for innovation policy coupled with society's needs, and an inclusive public health system. Although over the last 30 years a set of more or less continuous initiatives has fostered individual firms' learning processes, coherence has not yet been achieved in this field in Argentina. S&T infrastructure and technology policy is mainly oriented towards I&D capabilities, while increasing regulatory barriers would require analytical and bioprocessing capabilities. Recent institutional learning by local regulatory agencies has not been coupled with a widespread (but nationally selective) interaction with domestic market-oriented biotechnological firms. Only three firms or holdings have profited from this technological and institutional learning, and only one of them has been able to overcome the 'empty boxes' in the technology and regulatory learning processes due to previous internationalization. This explains why in Argentina the learning trajectory from first- to second-generation biosimilars is a firm-level phenomenon and not a national one.

References

Berkowitz, Steven A., John R. Engen, Jeffrey R. Mazzeo, and Graham B. Jones. 2012. "Analytical Tools for Characterizing Biopharmaceuticals and the Implications for Biosimilars." *Nature Reviews Drug Discovery* 11 (7): 527–40. doi:10.1038/nrd3746.

Bourgoin, A. F., and B. Nuskey. 2013. "White Paper: An Outlook on U.S. Biosimilar Competition." *Drugs of Today (Barcelona, Spain: 1998)* 49 (6): 399–410. doi:10.1358/dot.2013.49.6.2012938.

Correa, Carlos, Cynthia Balleri, Marina Giulietti, Federico Lavopa, Carola Musetti, Gastón Palopoli, Tomás Pippo, Catalina De la Puente, and Vanesa Lowenstein. 2011. "Patentes, Suministro de Medicamentos Y Protección de La Salud Pública." *Rev Argent SaludPública* 2 (7): 19–27.

Correa, Carlos M. 2011. "Pharmaceutical Innovation, Incremental Patenting and Compulsory Licensing." 41. Reseach Papers. South Centre.

Farfan-Portet, María-Isabel, Sophie Gerkens, Isabelle Lepage-Nefkens, IrmgardVinck, and Frank Hulstaert. 2014. "Are Biosimilars the next Tool to Guarantee Cost-Containment for Pharmaceutical Expenditures?" *The European Journal of Health Economics* 15 (3): 223–28. doi:10.1007/s10198-013-0538-4.

Gutman, Graciela, and Pablo Lavarello. 2012. "Building Capabilities to Catch up with the Biotechnological Paradigm. Evidence from Argentina, Brazil and Chile Agro-Food Systems."*International Journal of Learning and Intellectual Capital* 9 (4): 392–412. doi:10.1504/IJLIC.2012.049616.

———. 2014a. "Biopharmaceuticals and Firm Organisation in Argentina: Opportunities and Challenges." *International Journal of Technology and Globalisation* 7 (3): 159–78. doi:10.1504/IJTG.2014.064740.

———. 2014b. *Biotecnología Industrial En Argentina. Estrategias Empresariales Frente Al Nuevo Paradigma*. Buenos Aires: Letra Prima.

———. 2015. "Early Imitators in the Context of the New Technological Paradigm: The (incipient) Experience of Argentina's Biopharmaceutical Industry." In . Havana.

Huzair, Farah, and Dinar Kale. 2011. “Emergence of the Biosimilar Sector and Opportunities of Developing Country Suppliers.” Working Paper 94.Innogen. http://www.genomicsnetwork.ac.uk/media/Innogen%20Working%20Paper%2094.pdf.

Kim, Linsu. 1997. *Imitation to Innovation: The Dynamics of Korea’s Technological Learning*. Harvard Business Press.

Lavarello, Pablo. 2014. “Convergencia de Paradigmas Biotecnológicos Y Estrategias de Los Grupos Líderes Mundiales.” *Problemas Del Desarrollo* 45 (177): 9–35. doi:10.1016/S0301-7036(14)70861-2.

Lavarello, Pablo, and Evelin Goldstein. 2015. “Inserción Comercial Y Potencial de Sustitución de Importaciones de La Industria de Biofármacos En Argentina.” In .

Lee, Keun. 2005. “Making a Technological Catch-up: Barriers and Opportunities.” *Asian Journal of Technology Innovation* 13 (2): 97–131. doi:10.1080/19761597.2005.9668610.

Lee, Keun, and Chaisung Lim. 2001. “Technological Regimes, Catching-up and Leapfrogging: Findings from the Korean Industries.” *Research Policy* 30 (3): 459–83. doi:10.1016/S0048-7333(00)00088-3.

Lee, Keun, Chaisung Lim, and Wichin Song. 2005. “Emerging Digital Technology as a Window of Opportunity and Technological Leapfrogging: Catch-up in Digital TV by the Korean Firms.” *International Journal of Technology Management* 29 (1-2): 40–63. doi:10.1504/IJTM.2005.006004.

Lesser, Neil, Colins Terry, James Wu, Jacques Mulder, and Kevin Dondarski. 2016. “In the Face of Uncertainty: A Challenging Future for Pharmaceutical Innovation.” Deloitte.Accessed March 4. http://www2.deloitte.com/content/dam/Deloitte/lu/Documents/life-sciences-health-care/us_consulting_Inthefaceofuncertainty_040614.pdf.

MINCYT. 2014. “Encuesta Nacional de Grupos de Investigación En Biotecnología, Resultados Generales.” Documentos de trabajo 1. Buenos Aires: Ministerio de Ciencia, Tecnología e Innovación Productiva, Secretaría de Planeamiento y Políticas.

Niosi, Jorge, Petr Hanel, and Susan Reid. 2012. “The International Diffusion of Biotechnology: The Arrival of Developing Countries.” *Journal of Evolutionary Economics* 22 (4): 767–83. doi:10.1007/s00191-012-0284-2.

Perez, Carlota. 1988. “New Technologies and Development.” In *Small Countries Facing the Technological Revolution*, edited by Chistopher Freeman and Ben-AkeLundvall. London: Pinter.

———. 2002. “Technological Change and Opportunities for Development as a Moving Target.” In *Trade and Development: Directions for the 21st Century*, edited by J. F. J. Toye. Edward Elgar Publishing.

Perez, Carlota, and Luc Soete. 1988. “Catching up in Technology: Entry Barriers and Windows of Opportunity.” In *Technical Change and Economic Theory*, edited by Giovanni Dosi, Chistopher Freeman, Richard Nelson, Gerald Silverberg, and Luc Soete, Priter. http://pub.maastrichtuniversity.nl/f14dacb4-f33a-44f4-9283-fb9b7a541200.

Sekhon, Bhupinder Singh, and Vikrant Saluja. 2011. “Biosimilars: An Overview.” *Biosimilars* 1 (1): 1–11.