Biosimilars and Heterogeneous Technological Trajectories in the Argentine Biopharmaceutical Industry

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Abstract: This paper will review the strategies and learning trajectories followed to tap the opportunities opened by the successive waves of biotechnologies: early imitators followed by late imitators in the first generation of biosimilars (erythropoietin, insulins, interferons), and then sequential entry and skipping stages during the second generation (monoclonal antibodies).

Section 1: Introduction

This article aims to reflect on the main lessons arising from recent experiences of emerging trajectories of biotech-based companies with early imitation strategies of bio-pharmaceuticals developed in central countries. The global pharmaceutical industry forms a stratified oligopolistic market led by a group of large multinational companies that have maintained their position in the face of molecular biology revolutions. In recent decades, this industry has undergone a restructuring process, with the emergence of specialized companies in the new (bio) technological waves and the entry of companies from developing countries due to the expiration of patents for the first two generations of biotech products. However, this increased competition is not exempt from new entry barriers that are reconfiguring themselves throughout the diffusion of these products, including higher scientific and technological knowledge thresholds, regulatory uncertainty, and increasing economies of scale and experience in bioprocesses with higher financial requirements.

Given the transient nature of entry opportunities, our study analyzes the window of opportunity between 2003 and 2019 for firms in the emerging biopharmaceutical industry of semi-industrial countries such as Argentina. In this study, we aim to explain how the opportunities and challenges facing firms in these countries change with the diffusion of different biotech waves, leading to different strategies and trajectories of technological learning.

Previous studies have analyzed national catching-up strategies based on biosimilars in India, Korea, Brazil, and Cuba.[1] These countries had a minimum threshold of knowledge in molecular biology and prior technological learning in biologics development. Each strategy assumed different degrees of generality or focused on their actions and instruments regarding scientific and technological opportunities, firm

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learning generation, and selectivity of support for local firms, defining these states' industrial and technological policy. While Korea and Cuba adopted a set of deliberate actions and instruments in specific directions, India and Brazil opted for a facilitating role of their intervention supported by a previous industrial base and local group leadership.

In Argentina, the bio-pharmaceutical market reached approximately $1.29 billion in 2019. Therefore, like worldwide, biologics/biotech has become a key segment for the future performance of the pharmaceutical industry.

In 2005, biotechnology products represented only 12% of the pharmaceutical market, but by 2013, they had grown to 27%.[2] In 2019, biotech products surpassed 30% of the national pharmaceutical market.[3] The bio-pharmaceutical sector offers opportunities for catching up by imitating original drugs via biosimilars.

need to distinguish between productive and innovative capacities.[6] According to neo-Schumpeterian literature on technological change, the most significant opportunities for semi-industrialized countries to enter the market occur during the transition phase between two technological paradigms when investment and learning thresholds in production are temporarily low. However, technological uncertainty is high during this early stage of technology diffusion, and innovative capacity thresholds assume a critical character.[7]

Building on this theoretical framework, some studies have addressed the specificity of the opportunities available in biotechnology for developing countries. Argentina is among the semi-industrialized countries that can insert themselves as "creative imitators" due to the pre-paradigmatic nature of these technologies.[8] The creative nature of innovation is reflected in the impossibility of separating R&D, productive scaling,

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This article is organized as follows: Section 2 presents the conceptual and methodological framework, drawing from literature on the experiences of very late industrialization, an analysis of the policy actions that characterized the development of the Argentine bio-pharmaceutical industry, including the strategic approach to regulatory and intellectual property matters discussed in section 3. Section 4 presents a typology of bio-pharmaceutical firms and the selection of a case study, while section 5 analyzes and discusses the cases presented. Finally, the study's main findings and conclusions are presented in section 6.

Section 2: Conceptual and Methodological Framework[4]

The article draws on historical literature examining the possibilities for industrial ascent in countries with (very) late industrialization through a strategy of imitating pioneer countries.[5] From this perspective, industrial ascent occurs during the maturity phases of technologies, with institutional and industrial policy actions focused on reaching financial thresholds for investment in new production capacities. With new technologies based on microprocessors emerges the and regulatory approval activities, which enables the efficient development and innovation of activities nationally.

This requires the local existence of a long trajectory of learning in bioprocesses, and that the country is close to the threshold of core knowledge in molecular biology, which opens up opportunities for local firms to advance in the development and manufacture of high-cost drugs similar to the originals.[9]

Biotechnology has been nourished by different waves of revolutions in molecular biology.[10] Different waves make it difficult to consolidate a stable paradigm, resulting in a low degree of coherence in the knowledge bases of large pharmaceutical corporations.[11] This makes the industry dynamic "reopening" windows of opportunity for creative imitators.[12] Given their pre-paradigmatic and finance led nature,[13] these possibilities are conditioned by a high uncertainty in the regulatory framework in the biosimilar approval phase, product specificities, and national healthcare systems.

This article proposes as a starting hypothesis the absence of a dominant strategy for Argentine bio-pharmaceutical companies, seeking to analyze how

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different strategies were delineated based on previous trajectories in the face of different waves of biotechnology diffusion and changing entry barriers. For this, the accumulated capabilities of different types of firms and the specificities of the country's regulatory and policy context will be considered.

The methodological approach to answer this question is based on a multiple case study of Argentine biopharmaceutical firms. Different firm strategies are identified from a survey of biotechnology companies.[14] The case study allows a deeper understanding of how different types of creative imitator firm strategies are associated with different learning trajectories in a specific regulatory context. The multiple case study is the most appropriate for analyses in which it is not possible to separate the cases and the context, that is, the firm strategies and the competitive dynamics in which they are inserted, and where there is no control by the researchers of the events analyzed.[15]

Section 3: The Regulatory Context, Technological and Industrial Policies

The regulatory, technological, and industrial policies context is very important for developing an innovative industry such as biosimilars in Argentina. The high regulatory barriers at a global level, as well as the budgetary constraints on science and technology policies in the country, have hindered the consolidation of an institutional framework based on market arrangements that could expand the variety of innovative start-ups, further reinforced by the weakness of the local capital market. Thus, it is essential to consider the regulatory and policy framework that enabled the embryonic development of the biosimilars sector in Argentina.

Regarding the strategic approach to intellectual property, different works have analyzed how developing countries can take advantage of the degrees of freedom in this area.[16] For example, Argentina has limited the strategies of spurious patenting by multinational companies,[17] enabling incremental innovation of biosimilar companies.[18] In 2012, a joint resolution between the Ministries of Health, Science and Technology, Industry, and Economy established guidelines that require inventive height for chemical synthesis products.[19] Although this regulation did not indicate detailed criteria in the case of biologicals, it recommends extrapolating these inventive height requirements for each case. Furthermore, in Argentina, there is no link between patents and health approval as in Europe, avoiding the blocking of local imitative strategies. Therefore, Argentina is one of the countries that has sustained a strategic approach to intellectual property that enables the development of local capacities consistent with ADPIC.

The regulatory requirements constitute the main hurdle for pharmaceutical companies to enter the national and international markets. Institutional learning in regulatory matters has resulted from a long process of public-private interaction initiated in the early 1990s during the first wave of biotechnology. The central regulatory authority in the country is the National Administration of Drugs, Food and Medical Technology (ANMAT), a decentralized body of the Ministry of Health created in 1992. ANMAT has adopted international guidelines per the World Health Organization (WHO) recommendations. The approval of biosimilars is based on comparability with innovative reference drugs, with high-quality standards regarding good manufacturing practices and quality control of medicines. Like European regulatory agencies, Argentina has adopted a case-by-case criterion, where the requirements for conducting human clinical trials are associated with the complexity of the biotechnology products involved. Recent advances in analytical methods for comparability analyses, as in developed countries, have reduced the requirements for human clinical trials due to their ethical implications and high costs.[20]

On the other hand, the use of government procurement as a tool for promoting industry is an area in which Argentina has not made progress at a similar pace to that of intellectual property and regulatory approval. Only in 2018, Law 27,437 on Argentine Purchasing and Supplier Development generated possibilities to institutionalize and generalize this type of experience. Government and state social security purchases are highly fragmented, limiting the possibility of achieving the necessary scale. An exception to this high fragmentation of government procurement was the supply of vaccines for H1N1 flu, in which the national government ensured Advance Market Commitent new vaccine for five years and required the transfer of technology to the local company to formulate biologicals for an additional five years.[21]

In summary, institutional learning in regulatory approval of new medicines and the incipient advances in government procurement as a tool for technology transfer generate opportunities for developing the biosimilars industry in Argentina.

In addition to advances in the regulatory framework, local firms have been supported by policies that promote their technological capabilities through non-reimbursable credits and contributions to innovation. Notably, the science and technology programs implemented by the National Agency for the Promo-

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Table 1
Argentina: Companies with Biotechnological Capabilities, 2020

		Typology of Strategies				
Type of Companies	**N° of Companies 2020**	**1st Generation Biosimilars**	**2nd Generation Biosimilars (may include 1st)**	**Formulation, fill and finish**	**Niches (diagnostic kits)**	**R&D Platforms**
New Biotechnology Companies	34	0	0	0	10	24
Specialized Biotechnology Companies	7	2	0	3	2	0
Diversified Pharmaceutical Companies	19	1	2	9	3	4
Foreign subsidiaries of Large Pharmaceutical Companies	11	0	0	7	3	1
Total	**71**	**3**	**2**	**19**	**18**	**29**

Source: Own elaboration based on Survey of biopharmaceutical companies CEUR-FONCyT project "Business strategies facing the biotechnological revolution: the case of the bio-pharmaceutical industry in Argentina."

tion of Science and Technology have laid the scientific and manufacturing foundations of the local industry, including the two plants with the capacity to generate second-generation biosimilars.[22]

These programs have demonstrated significant institutional learning in designing and implementing their financing instruments since their creation in 1996. Initially, with the creation of the Argentine Technology Fund (FONTAR), the instruments included non-reimbursable contributions and tax credits with a horizontal approach in which biotechnological activities were not prioritized. As a result of this learning, a more advanced instrument was launched in 2010, funded by the Argentine Sectoral Fund (FONARSEC), which was more selective and systemic. This financing supported the generation of biotechnological platforms for the national production of vaccines and recombinant proteins.

In summary, Argentina has established a policy and regulatory framework that has facilitated firms in carrying out imitative strategies in biotechnology markets. The main actions aim to generate a framework of incentives that limits the protectionist actions of large multinational companies and allows for exploiting the advantages of lagging behind by quickly adopting new biotechnological waves. On the other hand, it has implemented a set of instruments to support the accelerated generation of technological capabilities of firms.

Section 4: Typology of Firms: Selection of Cases

To investigate how the national business base responded to this policy context, we drew on previous studies in which different strategies were identified based on a survey of companies in the Argentine biopharmaceutical industry.[23]

Table 1 characterizes 71 companies with biotechnological capabilities in the human health sector, considering a broad definition of biotech companies that have R&D, analytical, formulation, and in some cases, production capabilities for active pharmaceutical ingredients (APIs). It is possible to distinguish between different types of companies and the strategies they adopt depending on whether they have advanced towards the production of first or second-generation biosimilar APIs or whether they are companies that formulate and fill, focus on niches (mostly diagnostic kits), or are R&D platforms that license their developments or provide services to other firms.

A highly volatile number of these companies (34 firms) were new biotech companies in 2020 that had not yet advanced to the manufacturing phase, many of which were spin-offs from pharmaceutical laboratories, universities, or technological institutes, showing a high turnover of entry and exit. Their strategies mainly focus on licensing their technologies and providing R&D services or manufacturing in small batches aimed at product niches with lower regulatory thresholds (Diagnostic Kits).

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Secondly, 19 pharmaceutical companies and subsidiaries of national pharmaceutical groups have diversified into biotechnological activities, mainly in the final stages of formulation, filling, and final conditioning of therapeutics and vaccines with imported IFAs or bulk drugs. Also in this segment were Mabxience of the local INSUD group and Zelltek of the Amega group, two companies that advanced towards the total integration of biotech production, from biotech IFAs to formulation in their subsidiaries in Uruguay, with significant investments since the mid-2000s.

Thirdly, six biotech companies specializing in biotechnology were consolidated before the segment of Pharmaceutical Group subsidiaries. Their development originated in the early 1990s, among which are the pioneering Biosidus company and the Pablo Cassará laboratory with a high integration in the production of first-generation biosimilars, and a set of companies specialized in niches of diagnostic kits, among which the Wiener group stands out.

Finally, 11 subsidiaries of large foreign pharmaceutical companies are present in this industry segment, most locally performing analytical and clinical trial activities to achieve regulatory approval for their imported products.

This analysis has allowed us to identify five firms that emerged between the mid-1990s and the mid-2000s and entered into developing and manufacturing biosimilars by integrating the manufacture of IFAs. We will focus on four differentiated cases.

- Case of early imitator in first-generation biosimilars (Biosidus): This pair of independent pharmaceutical firms that initially specialized in chemical synthesis processes and advanced early in the 1990s towards international markets for first-generation biosimilars, such as erythropoietin, insulin, and interferons.

- Case of late imitator in first-generation biosimilars (Denver): This is a pharmaceutical group specializing in formulating generic chemical synthesis drugs that diversified late into biosimilars in the second decade of the 2000s, with incremental development of improvements in first-generation biosimilars (such as analog insulin).

- Case of sequential entry from first to second-generation biosimilars (Zelltek of the Amega biotech group): Like the two previous cases, it started with an insertion in international markets for first-generation biosimilars between the 90s and 2000s but then ascended in product and process complexity towards those of the second generation.

- Case of entry by "stage skipping" into second-generation biosimilars (Mabxience of the Insud Group): This is a group that adopts a more offensive strategy of direct entry into the imitative segment of more complex products towards the second half of the 2000s, without having gone through the development or production of simpler biological molecules.

Based on this selection of cases, the following sections investigate how companies have faced (changing) thresholds of knowledge, experience, and regulatory requirements at different stages of diffusion of the biotechnological paradigm through various learning trajectories and changes in organizational forms.

Section 5: Analysis and Discussion

In this section, we analyze companies' entry strategies and organizational structures throughout their development, followed by the stylization of learning trajectories and the accumulation of technological capabilities. These results are summarized in Table 2.

Based on these four cases, it is possible to analyze how stylized strategies and organizational structures are associated with particular specific learning trajectories that allowed them to respond to the opportunities in the biosimilars market and new regulatory barriers.

5.1. Early Imitators in the Face of the First Wave of Biotechnology: Incremental Learning in First-Generation Biosimilars

The company positioned itself as a global provider of first-generation biosimilars (erythropoietin and Interferon Beta) at the beginning of the installation of the first biotechnology wave. In this way, it achieved international insertion as a supplier of high-quality, customized, and low-cost products to meet the specific demands of the markets in developing countries.

This company's entry in the early 1990s required certain thresholds of scientific knowledge and experience in biologics production, utterly different from the knowledge accumulated in its previous trajectory as a company formulating chemically synthesized drugs. Towards the end of the 1970s, the pharmaceutical group (Sidus) decided to venture into biotechnological research simultaneously with the launch of the first biotech companies in the United States. In 1983, the achievements obtained led to the creation of a special-

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Table 2
Entry Strategies and Learning Trajectories

Strategy	Case 1: Early imitator (first generation)	Case 2: Late imitator (first generation)	Case 3: Sequential entry (first to second generation)	Case 4: Stage skipping (second generation)
Paradigm phase of entry	First generation emergence (80-the 90s)	First generation maturity (2009-2015)	First generation maturity/ second generation installation (2007-2015)	First generation maturity/ second generation installation (2007-2015)
Market	International market for high-quality, low-cost biosimilars	Local market for low-cost biosimilars	Local and regional market for high-margin biosimilars	Local and regional market for high-quality biosimilars
Organizational structure	Integrated	Integrated	Integrated Group	Networked Group
Relevant entry barrier	R&D	Scale, learning, and regulatory	Development and regulatory	Development and regulatory
Learning trajectory	Incremental improvements to first-generation biosimilars	From chemical synthesis to first-generation biosimilars	From first to second-generation biosimilars	From biological formulation to second-generation biosimilars
Core capabilities	Development of cell cultures and bacterial bioprocesses	Access to government procurement	Development of cell cultures and bacterial bioprocesses	Clinical capabilities and formulation
Secondary capabilities	Regulatory requirements and distribution in developing countries	Galenic development capabilities (formulation)	Development of cell cultures for complex molecules	Bioprocess capabilities in animal cells

Source: Own elaboration based on interviews from the CEUR-FONCyT project "Business strategies in the face of the biotechnological revolution: the case of the bio-pharmaceutical industry in Argentina."

ized biotechnology company (Biosidus)[24] that would become an independent company with high degrees of vertical integration from the 2000s onwards. By 1990, this company had already reached its first biosimilar product, erythropoietin. By the end of the first decade of the 2000s, the company marketed seven recombinant proteins for human health, domestically and internationally.

With the increase in regulatory and investment thresholds since the 2000s, this strategy faced new challenges that prevented it from advancing in the process of "upgrading" towards second-generation biosimilars, focusing on a strategy of incremental innovations in first-generation biosimilars. Although Biosidus still explains most of Argentina's biosimilar exports, the main challenges of this strategy since those years are the decrease in profit margins of first-generation biosimilars and the technological transfer requirements associated with import substitution policies adopted by developing importing countries.

5.2. Late Imitators Based on Accelerated Learning: From Chemical Synthesis to First-Generation Biosimilars

In the face of greater cost competition and higher regulatory thresholds in international biosimilar markets, the possibility of new "latecomers" entry depends fundamentally on preferential access to the local market in an import substitution scheme.

The case analyzed is that of a company with capabilities initially focused on formulating and filling a wide variety of generic therapeutic drugs, diagnostics, and niche health products for the social security system with a high presence in state tenders. With these significant assets based on the formulation and distribution of health products with significant scope economies, in the 2000s, they formulated local insulin from an initial agreement with a European company from which they purchased the IFA.

In 2009, the company under analysis obtained regulatory approval, becoming the only national com-

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petitor to multinational importers of the already formulated product (Eli Lilly, Sanofi, Novonordisk). The late entry of the analyzed company was made possible thanks to access to state purchases, allowing them to monetize 18 years of development of recombinant insulin from an R&D laboratory acquired from another local firm (Laboratorios Beta). With the incorporation of these new R&D and insulin manufacturing capabilities, the company developed a "platform" that went beyond therapy, encompassing all application complements (application devices, diagnostic strips).

sity R&D institutes with capabilities in developing cell cultures. The acquisition of a company with these capabilities enabled a process of "reverse engineering" of complex molecules from previous experience in continuous bioprocessing techniques and developing their own cell cultures, in which the university-company alliance was crucial. Thus, developing cell cultures and bioprocessing is undoubtedly the central capacity of this strategy and its learning trajectory.

In this case, the knowledge thresholds, production experience, and investment were overcome by resort-

The comparative case study shows that the strategy changes according to the degree of opportunity opened by each wave, the capabilities developed by the firms, and the articulation with the national regulatory framework in a direction and organization consistent with the firms' strategies. The case of the second generation of biosimilars shows that there are two possible trajectories. On the one hand, sequential entry is supported (and reproduced) by the National Science and Technology infrastructure. On the other hand, the stage jump enables faster entry with the possibility of consolidating among global players from emerging countries. Both trajectories face risks.

5.3. Sequential Entry (and Learning): From First-Generation Biosimilars to Second-Generation Biosimilars

In the face of new biotechnological waves at the beginning of the 2000s and the development of monoclonal antibodies, the transition from first- to second-generation biosimilars requires high thresholds of learning in regulatory and technological aspects in which the ability to develop their cell lines gives companies versatility in identifying those cells that produce proteins with safety and efficacy requirements, as well as production efficiency. These capabilities result from cumulative processes that cannot be generated at the speed required to meet the shortened life cycles of each biosimilar. In this framework, this third trajectory involves technological learning, centralization, and corporate restructuring.

The sequential entry from the first to the second generation of biosimilars combined centralization through the acquisition of various specialized biotechnology companies incubated in universities and spin-offs from other groups, adopting existing bioprocess capabilities, with the linkage with the National Institute of Industrial Technology (INTI) in the scaling stage,[25] and long-term articulation with univer-

ing to the advantages of their group organization and systematic support from the S&T policy through the FONTAR program and mainly the FONARSEC. However, these public efforts do not guarantee the success of the chosen trajectory in a short period, given the low support from regulatory agencies. In this sense, regulatory requirements for the development of complex drugs were changing towards the end of the project, delaying its approval two years longer than planned.

5.4. Stage Skipping: The Fast Track to Second-Generation Biosimilars

In contrast to the cumulative and sequential learning trajectory adopted by the previous case, the fourth trajectory is based on the combination of learning and hiring of services from international companies for the most complex stages within a stage-skipping strategy. The stage-skipping strategy includes moving to second-generation biosimilar production without going through the previous experience of manufacturing first-generation biosimilar APIs and skipping stages in local clone development. The feasibility of this trajectory is associated with quickly reaching high

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regulatory standards thresholds and reducing high market uncertainty through a network organization.

To achieve this, in the absence of previous experience in production and development, the starting point of the trajectory was access to specific preclinical and clinical capabilities resulting from the group's linkage with universities and hospitals. In this way, they gained access to biomedical capabilities in oncology and animal testing, allowing them to prepare the dossiers for the clinical phase. In this sense, previous experience using recombinant DNA techniques to develop small oncology proteins for animals and humans will play a central role in the company.

Conclusion: Primary Evidence and Findings

The case analyses allow us to answer the question of this article regarding the existence of a multiplicity of learning trajectories from biotechnology. Even among those strategies of creative imitation, different sequences and learning patterns are evident according to the diffusion stage of each biotechnology wave in which the company enters and the different configurations of entry barriers that firms face.

- In the early stages of the emergence of the (bio) technological paradigm, under low regulatory and bioprocess learning thresholds, the main barriers were based on scientific knowledge. Therefore, early access to knowledge of molecular biology and capabilities in biotechnological techniques based on DNA specific to the National Science and Technology infrastructure was crucial for entering firms from developing countries to compete in international biosimilar markets.

- When the rapid diffusion phase of first-generation biopharmaceuticals is reached, the barrier to access to molecular biology knowledge is no longer the main limitation but rather the experience in scaling and production. As a result, the possibility of new firms entering this segment was highly disputed in international markets. In this context, entering first-generation biosimilars required government purchase support as a condition for accelerated absorption of development and production capabilities.

- With the maturity of the first generation of biosimilars in the mid-2000s, a period was inaugurated in which opportunities opened after patents had expired of the second generation of biosimilars opened the possibility of valuing experience in the production and development of biotechnology in Argentina. The entry barriers are found in the development and scaling stage and the high uncertainty regarding the requirements of costly clinical trials. The sequence of patent expiration accelerates, and with it, the launch cycles of biosimilars shorten. Faced with this, two possibilities are evident: to gain the capacity to develop new molecules imitatively by developing their clones or to acquire clones from international companies and focus on their productive optimization, more easily overcoming regulatory and clinical thresholds.

The comparative case study shows that the strategy changes according to the degree of opportunity opened by each wave, the capabilities developed by the firms, and the articulation with the national regulatory framework in a direction and organization consistent with the firms' strategies. The case of the second generation of biosimilars shows that there are two possible trajectories. On the one hand, sequential entry is supported (and reproduced) by the National Science and Technology infrastructure. On the other hand, the stage jump enables faster entry with the possibility of consolidating among global players from emerging countries. Both trajectories face risks. On the one hand, aiming for the integrated national sector strategy may require longer times than those offered by the acceleration of biosimilar cycles. On the other hand, targeting the entire national strategy in the rapid entry may end up disrupting national science and technology potentialities in the face of the delocalization of technology-intensive activities.

The dispute over the orientation of industrial and technological policy is the field in which the competition between the major national pharmaceutical groups was decided in 2015-2020. However, this experience of transient autonomy may be truncated in the face of growing pressure from large multinational groups for "rapid" patenting and regulatory approval mechanisms, reorientating R&D support to specific stages of clinical development strategies, and recovering privileged access to government procurement. In the face of this, beyond some punctual success in international markets, local companies would see their national knowledge base disrupted, aspiring at most to be intermediaries in the global process of appropriating extraordinary profits and knowledge, selling their productive capacities to foreign groups. Overall, in case of not expanding the local productive base, this can weaken country's scientific infrastruc-

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ture and ability to independently generate and harness scientific knowledge.

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24. Initially, the company operated as a specialized entity under the pharmaceutical group.
25. The National Institute of Industrial Technology (INTI) possesses a bioprocess plant where firms carry out product developments to facilitate technology transfer. In addition, activities such as production scaling and implementing quality systems in existing processes are conducted. The plant is designed to accommodate a wide range of microorganisms and processes for applications in producing raw materials for biopharmaceuticals, food additives, and other industrial processes.

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