Facing the coronavirus crisis: Opportunities and challenges in developing countries, the Argentina case

Graciela Gutman[1] and Pablo Lavarello[2]

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Track 1. Addressing the role of research and innovation in times of crises: institutional and individual responses over time

Introduction

This presentation discusses the structural opportunities and challenges that opened up for the biopharmaceutical industries of developing countries in the face of the current crisis.

COVID 19 outbreak has made visible some drawbacks of science-industry relationships that were already present since 1990s. In particular, they made evident the limits of a research and innovation model in which scientific knowledge and discoveries had become the base of new promises of asset valuation. We refer to major institutional changes in intellectual property regimes, science business model and massive market valuation of new starts ups (Coriat and Orsi, 2002). These changes manifested in particular in the pharmaceutical industry with the establishment of the biotechnology paradigm, resulting in great promises that are not yet reflected in R&D productivity (Pisano, 2006; Pammoli, et al, 2011; Lavarello, 2018).

The difficulty to transform the opportunities of science into new products on the market reopens the discussion about the windows of opportunity for the (very) late industrializing countries and the thresholds needed for a catching up strategy (Perez and Soete, 1988). In the installation phases of the technological paradigms, neither the production scale requirements nor the experience are high. Only the knowledge thresholds are important. That is, the requirements of a Science and Technology infrastructure of National Innovation Systems. But with the diffusion of the new technology, scale and experience becomes important. The biopharmaceutical industry has not been able to this transition from the emergence of the paradigm to its diffusion on a stabilized set of research and production trajectories. Each new wave of molecular biology results in a new emergency cycle of disease treatments and drugs that increases the complexity of the knowledge base, making it difficult to establish a limited set of R&D processes and heuristics. In this way, the pharmaceutical industry presents the dynamics of a "moving target" as pointed out by Perez (2001). This “technological fluidity” highlight the centrality of manufacturing in the innovative process and opened

[1] CEUR-CONICET, Argentina; gutman.graciela @conicet.gov.ar
[2] CEUR-CONICET, Argentina: plavarello@conicet.gov.ar

windows of opportunity for developing countries which had achieved the thresholds of knowledge and (productive and regulatory) experience (Lavarello, et al, 2018)

However, a catching up strategy in biopharma faces important challenges. The industrial organization of these industries is no longer similar to the one that existed until the 1980s. Financialization of science was accompanied by a concentration and centralization of capital in which the MNCs went from an integrated business model to one characterized by the fragmentation and selective internationalization of R&D and production activities (Chesnais, 1994). In this context, a small group of firms from very late industrializing countries adopted different modalities of insertion in world markets of new biopharmaceutical products, either as contract manufacturing organizations and / or as early imitators of the reference drugs.

COVID 19 has shown that individual firms' strategies can only be translated into catching up and upgrading processes to the extent that it is accompanied by the generation of internal conditions in terms of industrial policy and articulation with the health system.

This article inquire if, given the limits faced by the financialization of the articulation between science and technology, there are structural spaces for catching up for countries who have reached the thresholds of knowledge, production and regulatory experience, and what are the necessaries local conditions for the success of these processes.

In order to answer this question this presentation adopts an historic structure approach based on appreciative theory. That is, starting from the contemporary historical dynamics of the pharmaceutical industry at a global level, identify the structural spaces for the accumulation of opportunities and the challenges for developing. Based on this analysis of the international context, we discuss the internal conditions of Argentina, a country that has shown an early and incipient development of the biopharmaceutical industry. Research sources are based on a set of previous case studies of the biopharmaceutical industry in Argentina in the period 2003-2020. These studies were based on: 1) a survey of Argentine biotech companies looking for their innovative capabilities and strategies); 2) estimations of biopharmaceutical foreign trade and health systems' procurement expenses; and 3) in-depth interviews with R&D institutions and a selected group of biotechnology companies that adopted early imitation strategies in the face of different waves of biopharmaceuticals drugs; (Gutman et al , 2020; de la Puente, et al 2020 ; Lavarello et al , 2018; Gutman & Lavarello, 2014)

This paper is organized as follows: in Section 1 we present the historical and theoretical framework of this paper, focusing on the impacts of the financialization of science and technology relationships, the new configuration of the pharmaceutical global chains, and the new transitory windows of opportunities that the new competitive context open to developing countries, considering the actual COVID-19 pandemic.

Section 2 discusses the opportunities and challenges faced by the Argentinean biopharmaceutical industry, considering the industrial structure, the firm's productive and technological capabilities thresholds, and the country's achievements in the

knowledge base, regulatory and institutional thresholds. The strengths and weaknesses of this industry are highlighted, as well as the importance of building internal windows of opportunities inface to the COVIC-19 challenges.

Finally, Section 3 summarize the main findings and proposals of this paper and suggest some policy issues for a catching-up strategy.

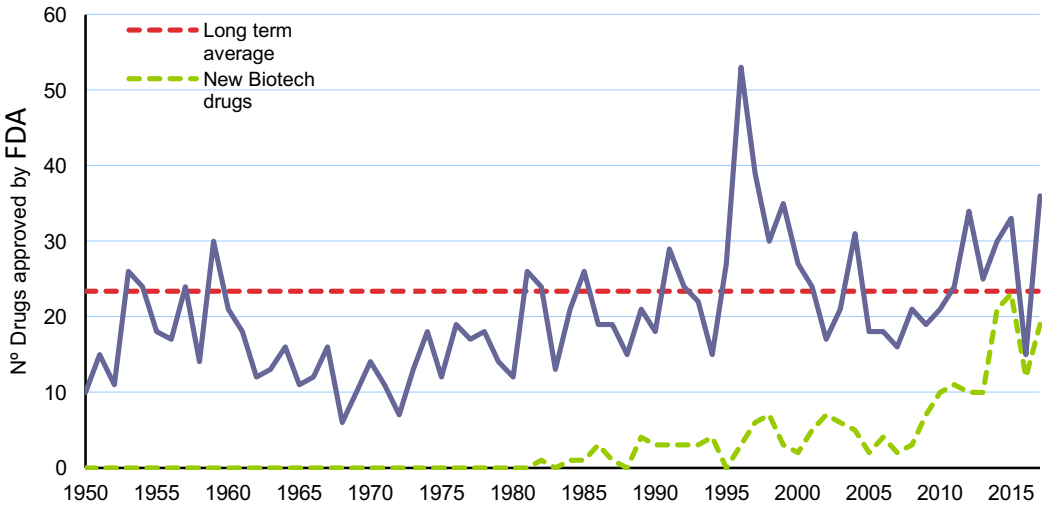
1.- Historical and theoretical framework

1.1. The (unachieved) opportunities of biotechnology: a financialized science technology relationship.

Since the beginning of the 1970s, it has been proposed that biotechnology could emerge as a new techno-economic paradigm understood as a constellation of technological systems based on the potential of the molecular biology revolutions (Freeman and Perez, 1988). Fifty years after these promises biotechnology has not replaced, but still coexists with the ICT paradigm (Tylecote, 2019). Alternatively, the concept of Technological Paradigm proposed by Dosi (1983), defined as a set of heuristics for solving techno-economic selected problems based on selected science source and their forms of appropriation, is more suitable for analyzing the sectoral dynamics.

In the particular case of the pharmaceutical industry, biotechnology would allow to overcome the limits of chemical synthesis technological paradigm in identifying new therapeutic targets for a reduced number of small molecules by random screening methods. Limits which can be illustrated by the systematic decrease of productivity of R&D since the 1950s (Pisano, 2006; Pammolli, et al, 2011, Lavarello, 2018). Faced with the scenario of falling productivity, biotechnology came was conceived as a potential tool for increasing the productivity of R&D through new techniques from genetic engineering to other DNA technologies as Gene Editing, reducing the production costs of the biological products from modern bioprocess techniques.

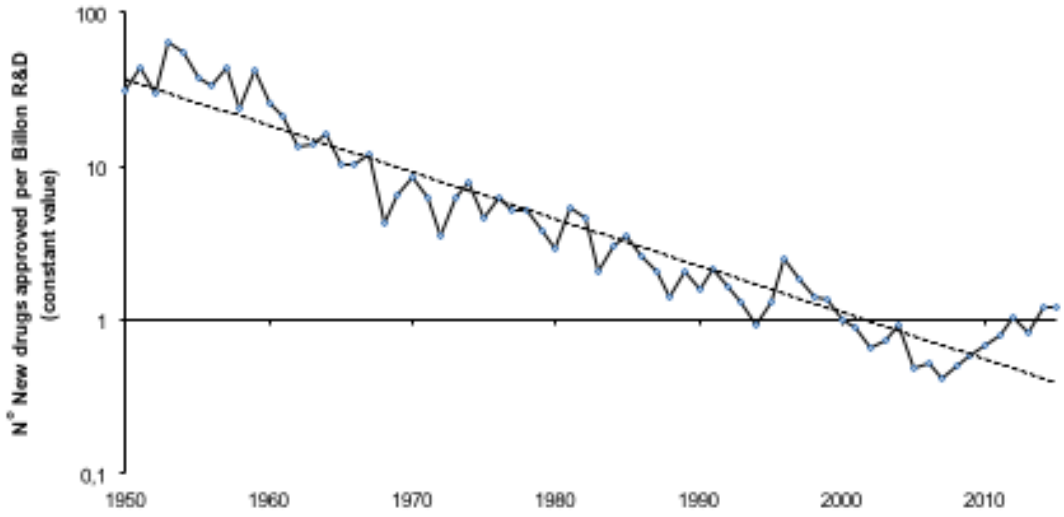
Graphic 1. FDA approvals of new drugs (in numbers)



Source: Lavarello (2018) based in Munos (2006) and FDA reports .

These promises, based on successive "waves" of revolutions in molecular biology (Pisano, 2006), did not reverse the trend towards falling R&D productivity (Lavarello, 2018). Graph Nº1 shows the new chemically synthesized drugs and the new biological drugs approved by the United States regulatory authority since the 1950s. Even if in 2010 the number of molecules began to grow, when the productivity of the R&D of the pharmaceutical industry is estimated (graph Nº2), it is possible to appreciate that its long-term decline has not yet been reversed.

Graphic 2 USA pharmaceutical industry. R&D productivity



Source: Lavarello (2018) based on Munos (2006) FDA reports

Despite the great promises of increased R&D productivity, and the acceleration in the number of new biotech molecules approved by the FDA, there is still no evidence of a drastic reduction in R&D costs that can overcome the limits of the paradigm of chemical synthesis (Lavarello, 2018).

Notwithstanding these (still) unfulfilled promises of biotechnology, they have attracted the interest of finance. Institutional changes enabled a change in the configuration between science and technology. As Coriat and Orsi (2002) pointed out, this new organizational form was only possible to the extent of the emergence of a set of regulatory changes in intellectual property regimes with the ruling of the Supreme Court in the Diamond vs. Chakrabarty case, the enactment of the Bay Dohle Act that opened the door to commercialize scientific knowledge, and regulatory changes in the financial markets that made it possible for start-ups to go public even when they did not have income.

As a consequence of these institutional changes, two type of organizations modified science and technology relationships. On the one hand, the increase in start-ups incubated around university campuses, and on the other hand, the development of a "venture capital" industry. Venture capitals are a new type of financial capital that participates in the management of excellent money capital financing biotechnological start-ups and the organization of the business model, in order to achieve the listing of companies in the market (Nasdaq).

This new configuration of financial link between science and industry did not reverse the secular decrease of R&D productivity of pharmaceutical industry. Pisano (2006) explains this process as the as the "monetization of intellectual propriety". That is the difficulty to coordinate an increasing multiplicity of different technologies needed to develop a new drug and its process by financial market relationships.

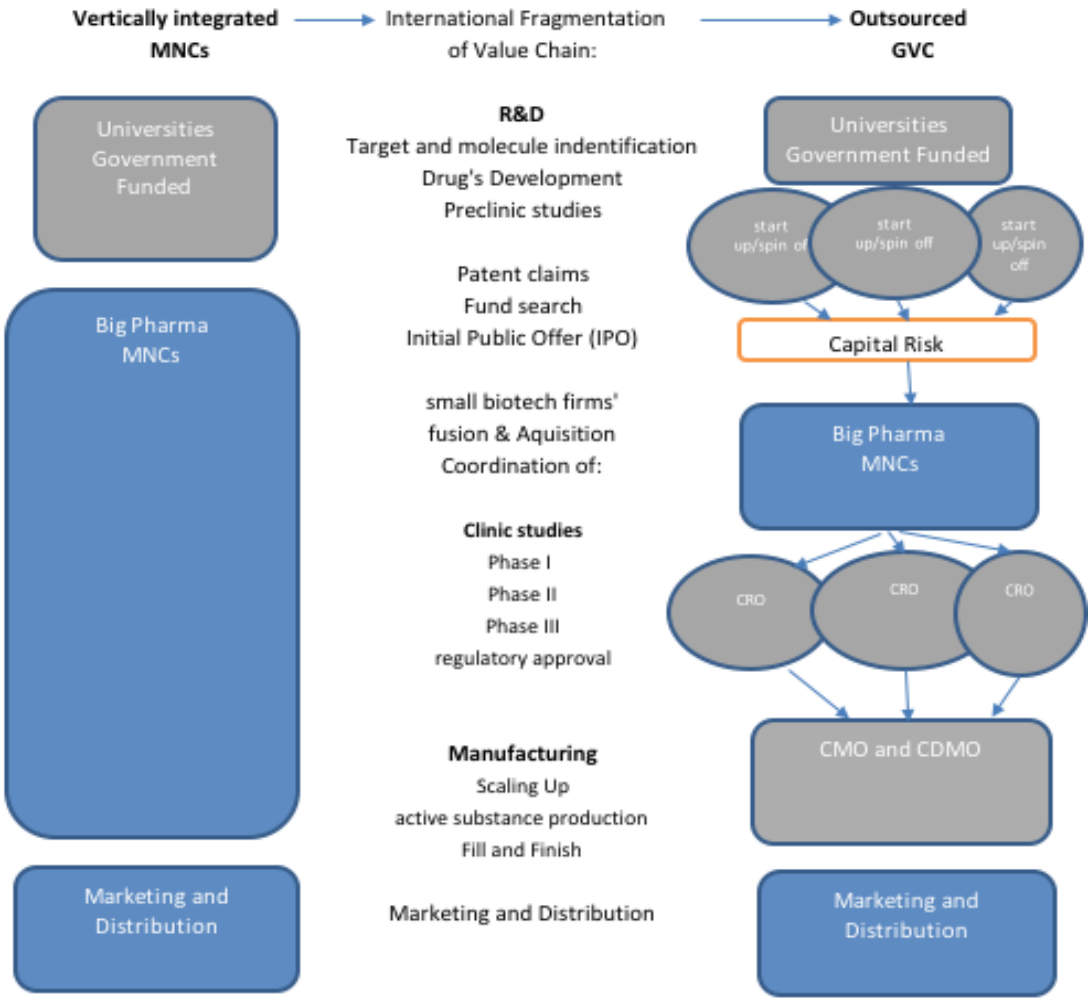
1.2. The new Global value chain configuration of Big Pharma

While this model has not created the conditions for an increasing productivity of R&D, it allowed large pharmaceutical companies to "rejuvenate" their development and product portfolios in the face of the fall of many of its patents on drugs with large market share (blockbusters). The new institutional and organizational model is then consistent with the needs of large pharmaceutical groups to outsource highly risky R&D phases in areas of knowledge in which they do not have capabilities. In this way, large pharmaceutical firms manage to reconcile their need to reduce the mass of immobilized capital by acquiring stakes in venture capital companies instead of increasing their investment in highly uncertain R&D phases and by acquiring those firms when their development is already in an advanced stage. This explains why as share prices collapsed beginning in 2015, mergers and acquisitions in the pharmaceutical industry grew both in number and dollar amount.

This context of technological and institutional changes based on finance, has not only enabled capital centralization but also led to a reconfiguration of the global value chains of large pharmaceutical companies. There is a transition from an integrated GVC model

to another based on networks of contract manufacturing organizations (CMO), contract development and manufacturing organizations (CDMO) and Contract Research Organizations (CRO)[3] (see Graphic 3).

Graphic 3. Big Pharma's Global Value Chain reconfiguration



Source: own elaboration in base Lavarello, Gutman and Sztulwark (2018)

Large pharmaceutical companies, or "Big Pharma", have centralized the intellectual property and distribution phases, orienting their pipeline towards high-cost

[3] A contract manufacturing organization (CMO), and a contract development and manufacturing organization (CDMO), are companies that serves other companies in the pharmaceutical industry on a contract basis to provide services from drug development through drug manufacturing. A contract research organization (CRO) is a company that provides support to the pharmaceutical, biotechnology, and medical device industries in the form of research services outsourced on a contract basis. A CRO may provide, among other services, biologic assay development, commercialization, preclinical research, clinical research, clinical trials management, pharmacovigilance.

blockbusters drugs. These companies searched to outsource the manufacturing stage taking advantage of economies of scale, and used specialized manufacturing knowledge to bring their medicines and vaccines to the global market. These contractors have not only provided filling and finishing work, but have also contributed to the production of Active Pharmaceutical Substances (APIs).

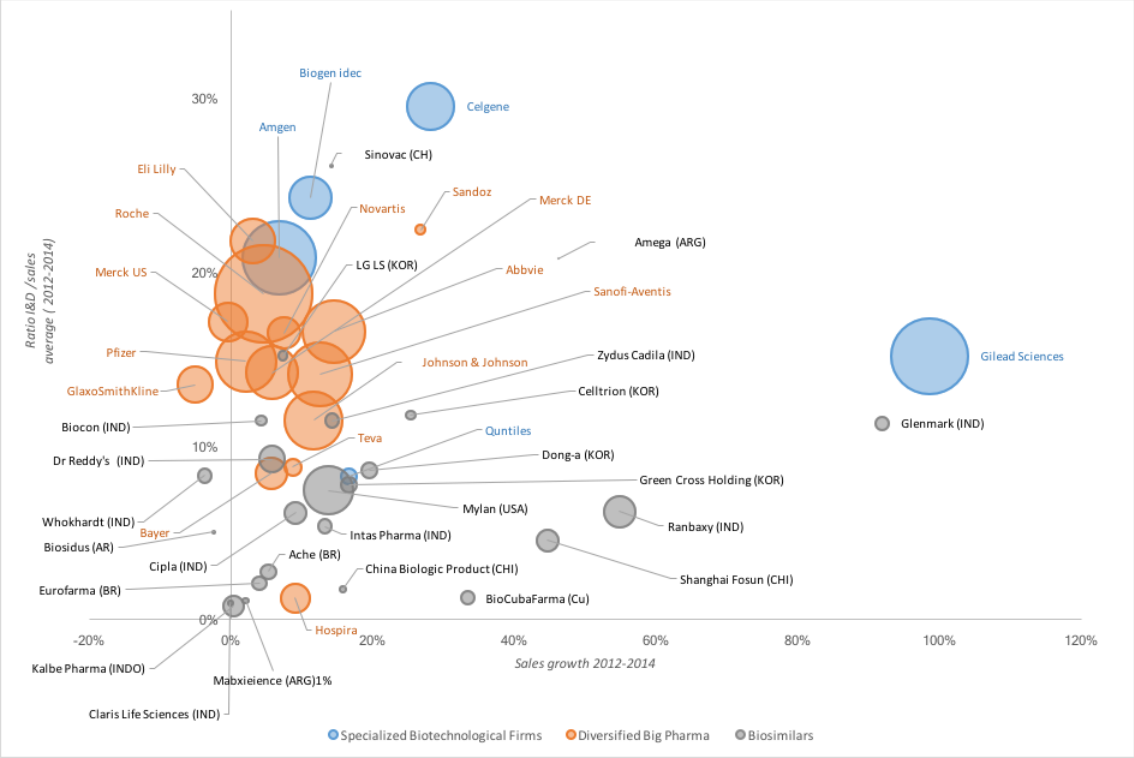
1.3. New competitive framework: the (transitory) windows of opportunity for developing countries' firms

The new competitive framework included, on the one hand, new players from developing countries that enter as biosimilar[4] producers and those companies that originally manufacture (CMO) or carry out clinical research activities (CRO) under contract with the world's leading companies, among which are Korean and Indian companies stand out respectively, and also, generic companies that operate in developed countries in the vaccine segments, and that recently started the production of biosimilars with similar R&D coefficients as specialized biotechnology firms.

As can be seen in Graphic 4, incumbent big pharmaceuticals such as Roche and big dedicated biotechnological firms such as Amgen, Gilead, and Celgene invest a huge share of their revnues in the development of new drugs.

[4] Biosimilars are imitative biotechnological drugs, active pharmaceutical inputs (API) and other biotech products and services, that can be introduced in the markets once the original products' patents expire.

Graphic 4. Biopharma world competitive landscape: originators and imitators
(The size of bubbles indicates sales)



Source: Lavarello, Sztulwark, Mancini and Juncal (2021)

As graphic 4 shows, biosimilar firms show less R&D intensity than original biopharmaceutical firms due to the lower technology and regulatory barriers they face. As was discussed in Lavarello et al (2021) this shows how backwardness advantages have emerged since the early 2000s. While biosimilar firms invest less in R&D in terms of revenue than innovators, their growth rate is not necessarily lower. Certain biosimilar firms such as Glenmark, Ranbaxy and Celltrion have achieved growth rates higher than 20% between 2012 and 2014.

The growth of biosimilar firms is a sign of the high competitive pressure in biotechnological markets. With second-generation more complex biosimilars, certain firms have invested in large scale bioprocess plants seeking to enter the market as big manufacturers. This is the case of some new big players from Korea and India which are entering the market.

As several high-cost biopharmaceutical drug patents have started to expire since the early 2000s, biotechnology opens up transitory opportunities for these firms to pursue an upgrading process by entering the sector as early imitators (Wechsler, 2011; Niosi, 2017). But unlike traditional pharma-chemical generics, where imitation have been duplicative, imitative strategy in biotech requires higher knowledge and regulatory barriers (Lavarello, et al, 2018). While low scale and learning thresholds offer advantages to latecomers, the costs of imitation could be rather high in the absence of a science and technology infrastructure, which is taken for granted in mature industrialized

countries. Whether developing countries develop these infrastructure thresholds or not depends on the presence of national systems of innovation and on the nature of the new waves of technology pervading the system, as was suggested by Freeman (2002).

1.4. COVID 19: new opportunities and challenges for developing countries

These trends in the biotech market are put in tension with the outbreak of the pandemic. Before the COVID-19 pandemic, the big pharmaceutical companies did little investment in vaccines for global diseases and viruses. It was just not profitable. But the COVID-19 pandemic has changed the strategy of the large pharmaceutical multinationals. About 14 billion doses are necessary, more than three times the production in "normal times", to provide effective vaccines to governments and health systems. In just under a year, after having defunded vaccine R&D projects, the industry was able to respond. How was this possible?

In the first place, in the USA, the National Institutes of Health (NIH), the Biomedical Advanced Research and Development Authority (BARDA) of the Department of Defense (DoD), and federally funded academic laboratories conduct basic research on vaccines[5]. It is interesting to note that this public-private partnership differs from the financialized model described above. A deliberate industrial policy characterized the United States's response. BARDA, created in 2006 in response to the SARS-CoV-1 pandemic (and other health threats), provided financing to businesses, but also participated in public-private partnerships and coordinated state agencies with a "mission" approach. A specific part of BARDA is bringing technologies to go through the "valley of death" between creation and commercialization, a task that the venture capital model has not effectively accomplished for these developments.

A second major change in the policy approach has been a deliberate support to capabilities' investments. This included selective support to big pharmaceutical companies in several developments, upstream, downstream production and fill and finish facilities. Thanks to this support, big pharma as Pfizer have established networks of CROs and CMOs around the world. This policy approach has been adopted by European countries.

The following companies were identified as the main production sites for the COVID 19 response initiatives[6]:

- **Emergent BioSolutions** which is articulated in a public-private partnership which includes BARDA, AstraZeneca, Johnson & Johnson, Novavax and Vaxart. BARDA disbursed $ 628 million to Emergent to scale production of targeted COVID-19 vaccine candidates to make "tens to hundreds of millions" of doses available

[5] The vaccines manufactured by Pfizer and Moderna are based on largely on two pivotal discoveries that emerged from federally funded research: the NIH-engineered viral protein; and the RNA modification concept first developed at the University of Pennsylvania (Mazzucato and Li, 2020).

[6] These paragraphs is based on International Federation of Pharmaceutical Manufacturers and Associations (https://www.ifpma.org) and Fierce Pharma (https://www.fiercepharma.com/special-report/top-10-manufacturers-fight-against-covid-19)

through 2021. The contract was part of the "Operation Warp Speed" development initiative of the Trump administration to accelerate promising COVID-19 vaccines through clinical trials and their mass production.

- **Catalent** which developed partnerships for vaccine development and manufacture with Johnson & Johnson, Moderna, and AstraZeneca. One of the largest global CDMOs, Catalent has pushed in recent years to rapidly boost its cell and gene therapy platforms, some of which use the same viral-vector delivery systems as leading mRNA-based coronavirus shot candidates. That portfolio made Catalent a clear partner to tap in the COVID-19 outsourcing effort.
- **Lonza** which has developed partnerships with Moderna and AstraZeneca. One of the largest contract manufacturers in the world, Switzerland's Lonza was a natural target for the biggest players in the race for a COVID-19 vaccine. Moderna has contracted Lonza to reserve two of the CDMO's facilities to boost production of Moderna's mRNA vaccine candidate. But Lonza hasn't only been involved as CMO with vaccine players, it also participated in new developments of next generation mRNA vaccines.
- **Oxford Biomedica** was the initial partner of AstraZeneca. In the early days of the pandemic, before pharma industry began signing off on supply deals for their COVID-19 vaccine hopefuls, a small group of manufacturers helped provide clinical supply of key candidates. As part of a consortium with the University of Oxford, the U.K.'s Oxford Biomedica joined AstraZeneca's vaccine developments at initial stages and will continue working with the MNC into the future.
- **Fujifilm Diosynth Biotechnologies'** CMO partnerships with Novavax and Eli Lilly. Among the major contract manufacturers in the COVID-19 fight, most players have focused on chipping in on only one front—i.e. vaccines, antibodies, or generics medicines. Fueled by its specialization in novel therapy manufacturing, including monoclonal antibodies and viral vector transports, Fujifilm is working with big pharma Eli Lilly and biotech Novavax on COVID-19 fighting antibodies and vaccines, respectively, from its facilities in Denmark and the U.S.
- **Phlow Corporation** public private partnership with BARDA. In May, BARDA revealed a $354 million contract with Virginia-based Phlow Corporation to build a generic medicine and active pharmaceutical ingredients (API) plant in Richmond, Virginia and supply COVID-19 treatments produced there. The contract can be expanded up to 10 years and a total of $812 million one of the largest in BARDA's history.
- **The Serum Institute of India** (SII), that have developed partnerships with AstraZeneca, Novavax, Codagenix, Bill & Melinda Gates Foundation, CEPI[7], and Gavi[8]. As part of a big contract with AstraZeneca and a coalition of global

[7] The Coalition for Epidemic Preparedness Innovations (CEPI) is a foundation that takes donations from public, private, philanthropic, and civil society organizations, to finance independent research projects to develop vaccines against emerging infectious diseases (EID).

[8] GAVI (Global Alliance for Vaccines and Immunization) is a public–private global health partnership with the goal of increasing access to immunization in poor countries. GAVI brings together developing country and donor governments, the World Health Organization, UNICEF, the World Bank, the vaccine industry in both industrialized and developing countries, research and technical agencies, civil society, the Bill & Melinda Gates Foundation and other private philanthropists.

nonprofit organizations, the Serum Institute of India has planned to manufacture more than 1 billion doses of licensed COVID-19 vaccines to low- and middle-income countries, including in India itself.

- **CSL agreement** with AstraZeneca, University of Queensland, CoVIg Plasma Alliance, which is focused to provide Australia's domestic vaccination. CSL has signed licensing deals with both the University of Oxford—which has partnered with AstraZeneca on a COVID-19 vaccine—and the University of Queensland to supply a combined 81 million doses of those vaccines to Australian patients.
- **mAbxience of Argentina Laboratorios Biomont of Mexico and Astra Zeneca** includes supply of 400 million doses to countries in Latin America (excepted Brasil). Mabxience. which is de biotechnological division of INSUD Group produces the active substance and Biomont makes fill and finish. The Argentina and Mexico deal with funding from the Carlos Slim Foundation, is expected to produce approximately 150-250 million doses to distribute across Latin America and the Caribbean in the first half of 2021. Like United States, Argentina, and Mexico deals with AstraZeneca, set a vaccine price of around $3-$4 per dose for distribution throughout Latin America and Caribe.

These manufacturers have settled big contracts to fight the virus, and each of them is likely to play a significant role in the wave of global biosimilar and vaccine launches to come. This would surely imply a greater knowledge and scale threshold for new entrants. Only a selective club of *late late* industrializing countries like India, Brasil, Argentina, India and Mexico are among those countries which could take advantage of this process. As we will illustrate in next section, Argentina is one of the countries that has the opportunity to develop a catching up process.

2.- Argentina. Opportunities and challenges for a catching-up strategy in the pharmaceutical industry.

As we discussed in section 1 of this paper, in the ongoing processes of centralization and financialization in the global pharmaceutical markets, exacerbated by the pandemic, some fragile and transitory windows of external opportunities are available for some developing countries. They are those who managed to reach the minimal capability thresholds required to face the new pandemic challenges. Argentina, along with India, Brazil and other few developing countries, is part of this small group. These are volatile and transitory opportunities that arise in a context of increased competitions in global markets (Lavarello, et al, 2021).

Not only bioprocessing and technological thresholds are necessary to participate in these markets; knowledge base, regulatory and institutional ones are also important. Clearly, these opportunities are associated with the development of biosimilars drugs and vaccines and with the actual reconfiguration of the pharmaceutical GVC with the geographical dispersion of some of the chain stages, that allowed some domestic argentine pharmaceutical firms to participate as biosimilar producers in international markets or to became CMO, CDMO or CRO of big global pharmaceutical corporations engaged in vaccine productions.

In order to transform these volatile windows of opportunities in more stable and permanent ones, looking for creation and the improvement of the innovative capabilities of domestic biopharma firms, the consolidation of internal windows of opportunities are required. They are associated with radical developments in the scientific and technological capabilities bases; the scaling up of the bioprocess stages generating economies of scale, the articulation within the national health systems – including public and private health demands; medical equipment and other strategic inputs suppliers- and the integration into productive, scientific and technological regional and global networks.

2.1. Productive and technological capabilities thresholds. The Argentinean biosimilar sector. Firm technological strategies

Biosimilar production in Argentina started at about the same time as in the central countries (late 1980 decade), showing a similar share in the total pharmaceutical industry, about 23% in 2015, and, equally, a larger dynamism than the rest of the traditional pharmaceutical production (Gutman & Lavarello, 2014, Lavarello, et al, 2018).

Argentina has developed a specialized manufacturing knowledge in biosimilar drug production, as early imitator of first biopharma drugs, with R&D and bioprocessing capabilities in the bio pharmaceuticals industry not only in fill and finish activities but also in the production of first generation active pharmaceutical ingredients (API). More recently, has started the development of capabilities in second generation of complex recombinant proteins (monoclonal antibodies, MAB). These are necessary capabilities to adopt a catching up strategy based on creative imitation of biotech drugs, which is expressed in the opportunity to manufacture DNA and RNA based vaccines and to develop therapeutic drugs for COVID-19.

At the beginning of the 2020 decade, the biopharmaceutical industry of the country involved 73 firms. As Table 1 shows, they conform a heterogeneous group of firms of different type and dissimilar involvement in the sector`s value chain (Gutman and Lavarello 2018, 2020). The more numerous ones are small biotechnology companies (NBF) focused on R&D activities and some biotechnology services such as invitro diagnosis, which do not weigh on sectoral turnover but are relevant given their technological capabilities and development potential. NBF's segment is very volatile and its number is associated to Government funding. Diversified pharmaceutical companies (DPF) follow in numerical importance, their participation in the biosimilar medicines segment has been usually limited to regulatory and formulation activities and they have a strong orientation towards the domestic market. The specialized or dedicated biotechnology firms (DBF) and the domestic group subsidiaries (DGS) show a high share of biosimilars in their total sales and a strong export orientation frequently coupled by integration of API manufacturing. These two types of companies account for most exports and R&D efforts in biotechnology in Argentina.

Multinational subsidiaries (MNC) restrict their local activities to the use of biotechnological techniques for some analytical phases in order to accomplish regulatory requirements, with the exception of one MNC in the production of vaccines using recombinant techniques which is integrated in a Global production network. However, they play a central role in the Argentinian biopharmaceutical market as main suppliers of imported highly complex biopharmaceutical drugs, as significant suppliers of these drugs to the public health sector, and they are, along with some DGS, one of the main players in the definition and implementation of the domestic regulatory context.

A few public laboratories focused on biological vaccines complete the biopharma segment.

Table 1 Argentina. Biopharmaceutical Firms (*). 2020

Type of biotech firms (1)	Number of firms 2021	Product Typology		
		Therapeutics	Vaccines	Others (2)
NBF-**R&D intensives**	34	0	0	34
DBF	6	3	0	3
DPF	14	8	1	5
DGS	6	5	2	1
MNC	8	7	1	1
PL	5	3	2	3
Total (3)	**73**	26	6	47

Notes:
(*) Includes biologics and biotechnological (biosimilar) products
(1): NBF: New Biotech Firms; DBF; Dedicated Biotech Firms; DPF: Diversified Pharmaceutical Firms; DGS: Domestic Group Subsidiary; MNC: Multinational companies; PL: Public Laboratories
(2) Focused on the R&D stage of the value chain. In vitro diagnosis, protein and genomic platforms, cell culture, and other products.
(3) Some Biotech firms have a diversified portfolio. That's why vertical and horizontal numbers of firms of each type may not match
Source; Own elaboration based on CEUR-CONICET Biosimilar Database and author's previous researches

Even though Argentina currently has twenty six firms producing therapeutic drugs and six in the manufacture of vaccines, only a small set of local firms have achieved the minimum thresholds of technical capabilities in recombinant DNA, cell culture and bioprocesses necessary to overcome the international regulatory barriers and become an international player integrating API's development and manufacture through a creative imitative strategy. The remaining companies are either engaged in the final stages of the value chain, are in preliminary attempts to produce recombinant drugs, or are focused on biological (not biotechnological) productions

At present, only six domestic biotech firms can be considered as creative imitators ; they concentrate most of the country production and exports of biotech drugs. The biggest ones are subsidiaries of pharmaceuticals groups: mAbxience (Insud Pharma), Zelltek

and Gemabiotech (Amega Biotech) and Biosidus (Biosidus Group). The remaining forty seven firms are positioned as R&D platforms, providers of technological services, innovative niches (*tests* diagnostics) or as API formulators (Gutman and Lavarello, 2014 Lavarello et al 2018).

Domestic biotech firms showed different strategies and capacities to advance in biosimilar production and import substitution of drugs and active pharmaceutical ingredients. Networks with international and national partners are the predominant form of firm's organization. Two learning paths in the biosimilar trajectory of these firms are important, a distinction that is relevant for the implementation of a catching-up strategy. On the one hand, firms based on a stage skipping strategy, focused on manufacturing capacities in more complex drugs. On the other hand, those based on a sequential entry from the less complex to the most complex drugs, seeking to undertake locally the entire R&D and production chain. Each of these trajectories involves different forms of articulation between the public infrastructure of Science and Technology and the business sector, with implications on the speed of R&D. While the first one involves insertion in international and national networks with a temporary advantage in the development of imitative drugs, the second one is more focused on local networks with a greater impact on local capacities but a lower learning speed (Lavarello, Gutman y Sztulwark, 2018).

2.2.- Not only technological thresholds are necessary. Knowledge base, regulatory and institutional thresholds

In the context of an institutional configuration of Science and Technology severely affected by institutional changes[9], Argentina has managed to reach minimum knowledge thresholds, with a clear orientation to medical and biologic scientific opportunities. This is expressed in the presence of highly qualified professionals in the disciplines associated with the development of modern biotechnology (molecular biology, medicine, biochemistry, computer science, among others) at undergraduate and graduate training levels, creating the conditions for carrying out the technological learning processes.[10] Biomedical research is one of the main orientations of Argentina's knowledge base. According to MinCyT data, in 2013, 12% of publicly funded research projects were related to medical sciences, some 3500 projects encompassing more than 11,000 researchers.

This is explained by a long national trajectory of R&D activities carried out in university laboratories and research centers in science and technology, and an important background in medical science and biotechnology research in specialized institutions (such as the Malbrán Institute, the Leloir Institute Foundation and the National Council on Science and Technology Research, CONICET), with developments in cell cultures,

[9] In particular, after a period of important institutional learning and support for S&T between 2007 and 2015, between 2016 and 2019 the Ministry of Science, Technology and Innovation was eliminated and financing for R&D infrastructure was discontinued.

[10] In 2011 it showed the highest level in Latin America of the indicator of researchers per active person: 3.06/1000

molecular biology and other closely associated research subjects. A survey conducted by this Ministry in 2015 indicated that 83% of the biotechnology research groups were part of universities and research centers in Science and Technology networks, and more than half of them were oriented to the area of human health (Gutman and Lavarello, 2017).

This important knowledge base in the government sphere has been accompanied by government support for firms to reach these thresholds in technological capabilities. The pharmaceutical industry has received significant momentum from the state in recent decades, through the the National Ministry of Science and Technology (MinCyT, acronym in Spanish) and the National Agency for Scientific and Technological Promotion.

Starting in 2007, Argentina implemented a set of selective tools to support the generation of technological capabilities in human biotechnology. Since 2010, policies aimed at stimulating and promoting the development of biotechnology received additional impetus through various MinCyT funds: on the one hand, those aimed at supporting the generation of scientific opportunities for the sector (FONCyT),and on the other hand those aimed at supporting the generation of technological capabilities of companies. The second ones include different instruments. The main ones in relation to biotechnology were: the Argentine Technological Fund (FONTAR), focused on subsidies and credits at subsidized interest rates for R&D and technological modernization firm projects; EMPRETECNO , for the development of technology-based companies.. More recently, the Argentine Sector Fund (FONARSEC) a more selected instrument oriented toward the development of general purposes applied research projects and technology transfer through public/ private consortia. The larger companies in the sector, in particular the subsidiaries of economic groups, were the main beneficiaries of this policy instrument.

In addition to the knowledge and skills thresholds, Argentina has reached a certain degree of regulatory thresholds regarding patents and sanitary standards. Thas is, the institutional capacities in establishing a strategic approach to intellectual property, sanitary approval and management of public procurement. Argentina has carried out a strategic approach to intellectual property rights, has implemented an incipient policy of public procurement of drugs and vaccines, and has implemented stringent regulatory standards for first and second generation of biosimilars. The main regulatory changes began in the 1990s enabling the achievement of quality standards, good manufacturing practices and drug control, in line with WHO recommendations (Lavarello and Gutman, ECLAC 2020). This process involved important learnings between government agencies and a dynamic set of firms. However, a high degree of heterogeneity persists in the ability of smaller firms to meet regulatory thresholds. a fact that is reinforced by the increases in regulatory thresholds associated with the second generation of biosimilars.

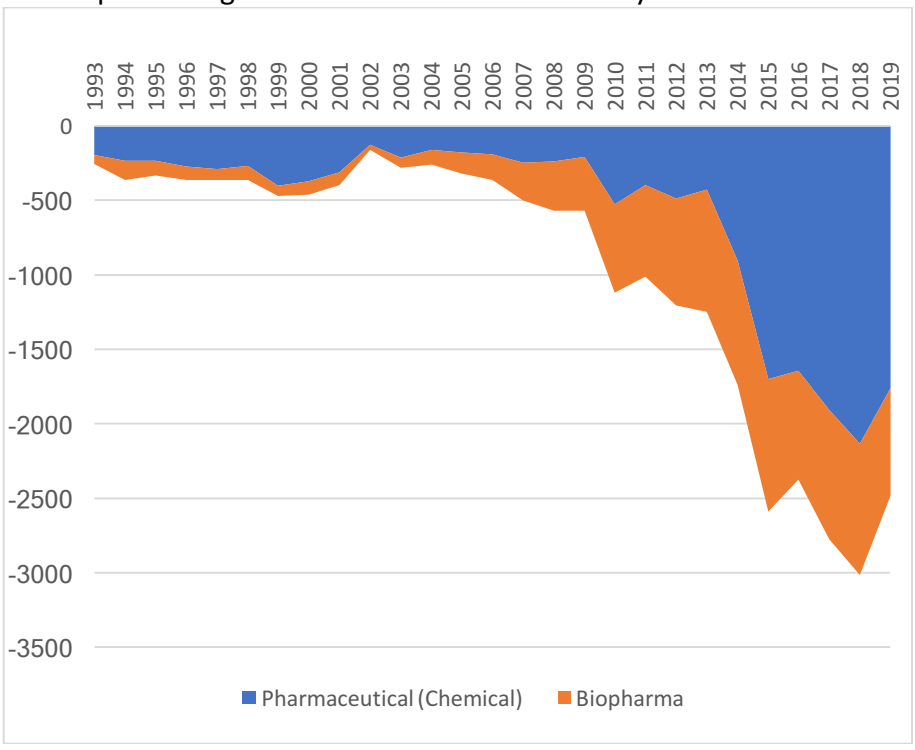
2.3.- Strengths and weaknesses of the Argentinean biotech industry

As we discussed in previous sections, thanks to the infrastructure in Science and Technology, the national regulatory framework, and the trajectories of the biotechnological firms, Argentina has managed to generate a domestic business base with technological capabilities to participate in international markets as early imitators of biotechnological molecules of the first wave of recombinant proteins, and advance towards the second generation of biosimilars. Minimal capabilities thresholds were reached and a small (although potentially growing) number of domestic firms are gaining competitiveness in these fields.

The high heterogeneity among firms concerning their technological and regulatory capabilities, coupled with the strong participation of MNC in the public procurements of highly price complex drugs, are in the origin of the following important features in the recent dynamics of the biopharmaceutical industry that may become obstacles for a catching-up strategy, namely i) the high balance of trade deficit shown by the pharmaceutical industry; and ii) the low coverage of domestic public and private drug demand by domestic production

Concerning the trade deficit of pharmaceuticals goods, it has been growing steadily since the 1990s, reaching US$2.43 billion in 2019. Biopharmaceutical drug imports rises at a higher speed, increasing from 20 per cent of the total pharmaceutical deficit in the 1990s to 40 per cent in 2019. (Graphic 5).

Graphic 5. Argentina. Pharmaceutical industry balance of trade



Source: own estimation based on COMTRADE Database.

This balance of trade trend is related to the launch of second generation of biopharmaceutical drugs, focused on complex and costly pathologies (cancer, multiple sclerosis, rheumatoid arthritis, among others). These drugs are responsible, at the same time, for much of the growth of the public spending on health since the early 2000s.

The recent local production of second generation biosimilars, (rituximab, bebacizumab, etanercept) by domestic capital groups specializing in biotechnology, shows the path of possibilities for an import substitution process. The actual achievements in this way is the result of investments made in the processing stage (manufacturing) of the biotech value chain and, in some cases, in the imitative development of molecules, based on a set of support public actions in the field of technological policy, regulatory framework policies, promotion of infant capacities, and forms of R&D organization based on public-private articulation , (CEPAL 2020; Gutman and Lavarello , 2017).

Considering the low articulation between the domestic biotech production and the domestic market, only a small part of the domestic public and private demand of biotech drugs is covered by local production (about 25 per cent), including both first generation biopharmaceutical drugs and a few complex ones. As a consequence, public procurement of complex drugs is covered mainly by MNE imports.

A recent research on public procurements of complex drugs by the country's main Decentralized Government Health Institutions, focusing on the purchase of oncology drugs and medicines for special treatments (chronic and/or low-prevalence diseases) shows the high participation of biological drugs, both biotechnological and extractive, in the total amount of medicines purchased by these Institutions, an amount that includes the segment of small molecules (54% versus 46% respectively) (Gutman et al, 2020)

In this public procurement, innovative drugs produce and imported by MNC have the greatest share. Considering only the biological/biotechnological segment of this public procurements , biosimilars participate only with the 10 per cent; the remaining 90 per cent are original biotechnological drugs provided by MNC. Biosimilars are supplied almost entirely by domestic capital companies (91 per cent), a majority that remains slightly reduced, considering in addition the two highest-weight biosimilar monoclonal antibodies (MAB) in these purchases, recently developed in the country.

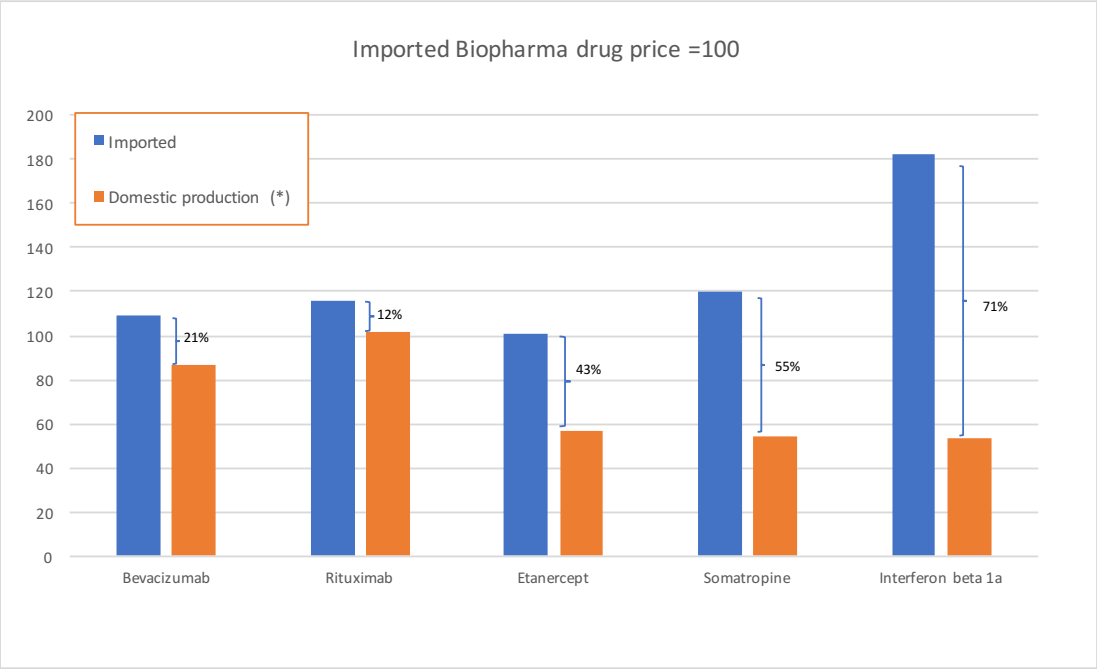
The observed low participation of biosimilars in the government purchases of complex medicines is partly explained by the export orientation of domestic production of first-generation biopharmaceuticals, but mainly by the MNC strong market control of patent-protected drugs. A different case in terms of market orientation is the latest local developments of second-generation biosimilars, with a greater orientation towards the domestic market (Gutman et al 2020; Lavarello et al., 2018).

The potential of a public procurement policy aimed at stimulating domestic production and simultaneously advance in the coverage of the public health systems with these productions and in the decline of the trade deficit is presented in Figure 2, which present

an estimation of the price differentials between biosimilars and original drugs in the purchase of selected molecules (Gutman, et al , 2020)

There are significant price differences in the public purchase of biosimilars and original drugs

Graphic 6 Argentina public procurement. Price differences between biosimilars and original drugs.



(*) Drugs produced with domestic API

Source: Gutman, Lavarello and Pita (2020)

Estimates presented in Graphic 6 shows that, in the case of second-generation molecules, where two groups of domestic capital compete with large foreign multinational companies (the monoclonal antibodies Rituximab, Bevacizumab and Etanercep), the price difference varies between 12 per cent and 43 per cent, according to the degree of biosimilar development in the country and the pressure that biosimilars exercise to lower the price of original or innovative drugs. In the case of Somatropin and Interferon beta 1, first generation molecules, price differences are more noticeable, showing that there are important areas of intervention to promote greater competition from domestic capital firms in the domestic market.

This price differential analysis illustrate that a national purchasing policy is a crucial tool with important budgetary and market impact to foster local techno-productive capabilities.

2.4. Challenges in face to the coronavirus crisis. The importance of building internal windows of opportunities

Argentina has achieved the minimal knowledge, manufacturing and regulatory thresholds requirements and a short (but potentially increasing) number of domestic capital biopharma firms engaged in biosimilar production, to face the challenges posed by de coronavirus pandemic.

As mentioned before, over the past 20 years, a small though relevant number of domestic companies have reached the capabilities required for the development of complex biotech API and for drug manufacturing (among them, monoclonal antibodies), in close articulation with national scientific institutions, and with varying degrees of integration into international R&D and production networks.

The COVID 19 crises has opened for a few Argentinian biotech firms, highly specialised in the production of recombinant proteins and with high quality standards, the possibility to participate in GVC, developing, in local and global networks, some of the value chain stages of the vaccines actually in production to face the pandemic. This are at present the cases of three domestic laboratories: mAbxience, the biotechnology division of Insud Group, is producing de active substance – in association with Astra Zeneca and the Mexican laboratory Biomont-; ; Synergium Biotech, also part of the Insud Group, in the fill-finishing stage of the Chinese vaccine Sinopharm, and in its initial, preliminary phases, the agreement of Richmond Laboratories to participate in the fill finishing stage of the Russian vaccine SputniK V. All this three laboratories have received important public subsidies in developing their process and technological capabilities.

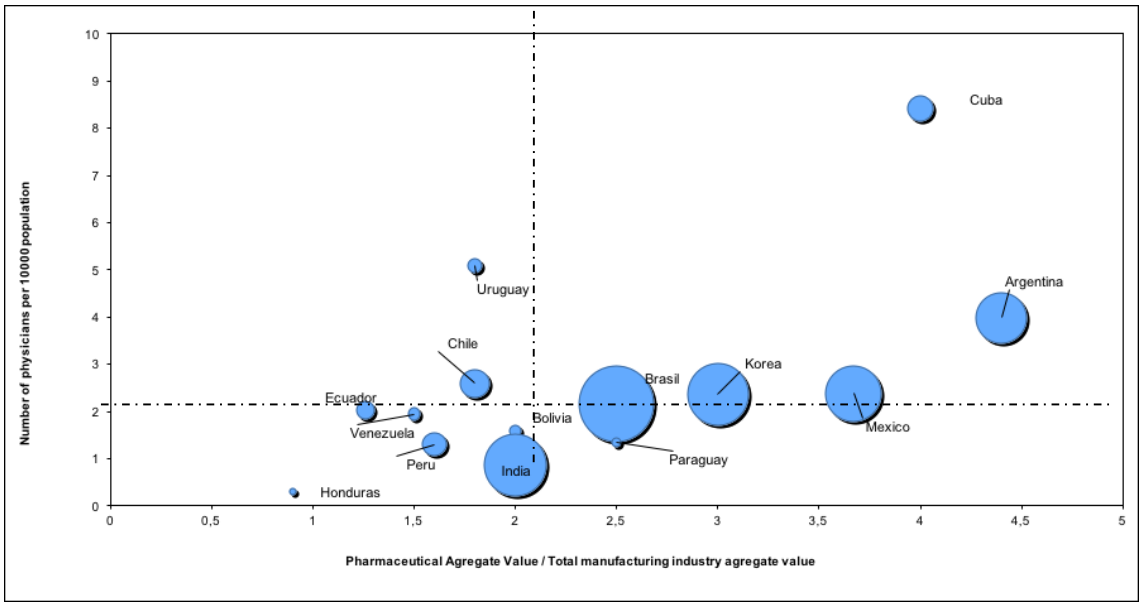
To deepen Argentina's adoption of biotechnology in the future, in particular in recombinant and new mRNA vaccine's production, new thresholds are required and new scientific, technological and regulatory challenges are at play, as well as a greater articulation between domestic and international markets. Then, we can see once again how the biotech paradigm is a "moving target" (Perez, 2004). It is revealed how the continuous appearance of new waves of biotechnologies, and the non-consolidation of the technological paradigm, requires expand the knowledge base towards new advances in gene therapies, new manufacturing processes that combine bioprocesses with nanotechnology and an adaptation of regulatory frameworks to the times and demands of the new context of health crisis.

Several developed countries that have made health a cross-cutting axis of their productive and social development, managed to combine industrial density, spending and public provision in health (access and coverage), through the articulation between public procurement policy, industrial and technological policy and the demands of their health systems. CoVID-19 global response illustrates the potentials of articulating scientific-technological policy and health policies.

Several international experiences highlight the importance of considering simultaneously the countries' productive capabilities, the public sector demands and the access to or coverage of health systems. However, the heterogeneity observed in the Argentinian biotech industry opens new questions on how to coordinate science opportunities, local technological capabilities and public procurement in order to overcome the strong commercial deficit of the industry, and to enhance the health system coverage.

Graphic 7 shows Argentina's positioning in these three variables, relative to Latin American countries and selected cases in Asia.

Graphic 7 Industrial capacity, access to health and state purchasing power in selected countries



Notes: The vertical axis of Figure 3 reflects access to health and uses the density of doctors every thousand inhabitants as an approximate variable. The horizontal axis signals the involvement of the pharmaceutical industry in manufacturing value added, based on the productive capacities of the industry. The size of the circles indicates the magnitude of public health spending estimated at thousands of dollars of purchasing power parity, as an indicator of the state purchasing power of the selected countries
Source: CEPAL (2020)

Many of the Latin American countries are located in the lower left quadrant of this graphic, a situation that shows low degrees of access to health services, an underdeveloped pharmaceutical industry, and a weak public demand role. This configuration reduces the possibilities of the local pharmaceutical sector to become a lever for productive development, at least in the short term.

On the other hand, Argentina is located in the upper right quadrant with the potential for virtuous complementation between the three selected variables, in line with what is observed in Brazil, South Korea or India. It is only surpassed by Uruguay and Cuba in terms of access to health, but it is the country that reveals the greatest weight of

pharmaceutical value added relative to the national total manufacturing value added. Argentina, in average values, has managed to rank among the countries of Latin America and Asia better positioned in terms of access to health and pharmaceutical value added.

This configuration show that, despite the high fragmentation and decentralization of the Argentinean public health procurements, state purchasing power can become a decisive tool for the development of the biopharmaceutical sector and to encourage a caching-up strategy in face to the coronavirus.

3.- Conclusions and policy issues

The coronavirus crisis has exposed tensions in the global pharmaceutical industry within the framework of an unprecedented concentration and centralization of capital, highlighting countries interest in having domestic capabilities to respond to pandemic demands. The collapse of the private led manufacture and distribution system, underlines the need for global scientific cooperation and health sovereignty, requiring scientific internationalization, national technological catching up and industrial policy actions on a national or regional basis.

As the pandemic revealed prompt response of developed countries industrial policies, temporarily overcoming the institutional imbalances between scientific opportunities and manufacturing base in new biotechnology fields, the new context opens transitory and small windows of opportunity for a limited number of developing countries which had achieved knowledge and technological capabilities thresholds. They can consolidate their insertion as early imitators at lower costs than big pharma in new waves of biotechnology, profiting from backwardness advantages (Gerchenkron, 1962).

Given the knowledge thresholds achieved by Argentine's scientific base in molecular biology, the learning and R&D thresholds achieved by the actual public and private technological capabilities, and the productive experience in bioprocesses and in biosimilars, domestic biotech companies have a chance to continue an updated import substitution process and to face the challenges posed by the pandemic.

As it was discussed in studies that analyzed industrial policy experience, this requires advances in three areas of intervention (Abeles, et al, 2017; Gutman and Lavarello, 2017). The strengthening and updating of biotechnology opportunities in close cooperation with the international scientific community; ii) support for the accelerated learning in new manufacturing technologies that are being developed with the new vaccines (subject to performance requirements by firms); and (iii) the strategic role of public procurement in enhancing local production of complex drugs, guiding scientific and technological developments to meet the needs of the public health system, and boosting local production of medicines (subject to a requirement of prices lower than those imported).

In short, the COVID 19 challenge opens up the possibility (driven by the health crisis), of building strategic high-cost drug development and manufacturing capabilities for the

public health system of developing countries. This requires articulating a deliberate action of international North South and South-South scientific cooperation with existing actions and instruments into "big structuring projects" at a national scale.

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