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Creative imitation at the front of pharma biotechnology opportunities: some lessons from late late industrialization countries[1]

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Given that high-cost biopharmaceutical drug patents have started to expire since the early 2000s, biotechnology opens up opportunities for developing countries to pursue an upgrading process by entering the sector as early imitators. Developing these opportunities was transformed on priority needs of health systems since the outbreak of COVID-19. Certain developing countries have advanced in a strategy of imitating biotechnological reference drugs once their patents have expired, opening a possibility for a catching up process.

Given that high-cost biopharmaceutical drug patents have started to expire since the early 2000s, biotechnology opens up opportunities for developing countries to pursue an upgrading process by entering the sector as early imitators. Developing these opportunities was transformed on priority needs of health systems since the outbreak of COVID-19. In the case of biotechnological therapeutics, there are currently numerous drugs that are being tested in clinical trials for COVID-19, sixteen of which are biotechnological, mainly monoclonal antibodies (AMC), interferons and recombinant fusion proteins. In most cases, these are drugs previously approved for other indications. Certain developing countries have advanced in a strategy of imitating biotechnological reference drugs once their patents have expired, opening a possibility for a catching up process.

The literature on late industrialization has emphasized the economic advantages of backwardness, which consist in the possibility of accelerated industrialization on the basis of technological imitation and institutional innovation processes (Gerschenkron, 1968; Hirschman,

[1] Summary version of P.J. Lavarello, S. Sztulwark, M. Mancini, & S. Juncal, "Imitación creativa frente a las oportunidades de la farmabiotecnología", *Revista Brasileira De Inovação*, v. 19 (2020), e020008. Available from https://periodicos.sbu.unicamp.br/ojs/index.php/rbi/article/view/8655699. This article was submitted to the South Centre on 24 May 2020.

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1980). In turn, Perez and Soete (1988) and Pérez (2001) emphasize that processes to close the technology gap for least developed countries depend on the life cycle and dynamics of technology in the framework of a new techno-economic paradigm. Successive new biological revolutions disrupted previous ones, increasing knowledge base complexity. Each new generation of biotechnological design required new process innovations modifying technical parameters and regulatory standards. Fluidity of new therapeutic targets, new molecule design, and new bioprocesses is coupled with a renewed dispute around regulatory approval between big pharma and newcomers into this industry.

This gives rise to the strategy called "creative imitation". Unlike previous latecomers' experiences, the learning process here seems to be focused not only on the manufacturing stage, as was the case with the "duplicative imitation" strategies of chemical drugs, but also on the product development stage.

The imminent expiry of patents for several second-generation biotech products taken together with the existence of production capacities in the field of biopharmaceuticals in developing countries provide a promising framework for making headway on understanding new upgrading processes based on "creative imitation", making it possible to build an autonomous learning path in any of the more dynamic fields of knowledge at the global level[4].

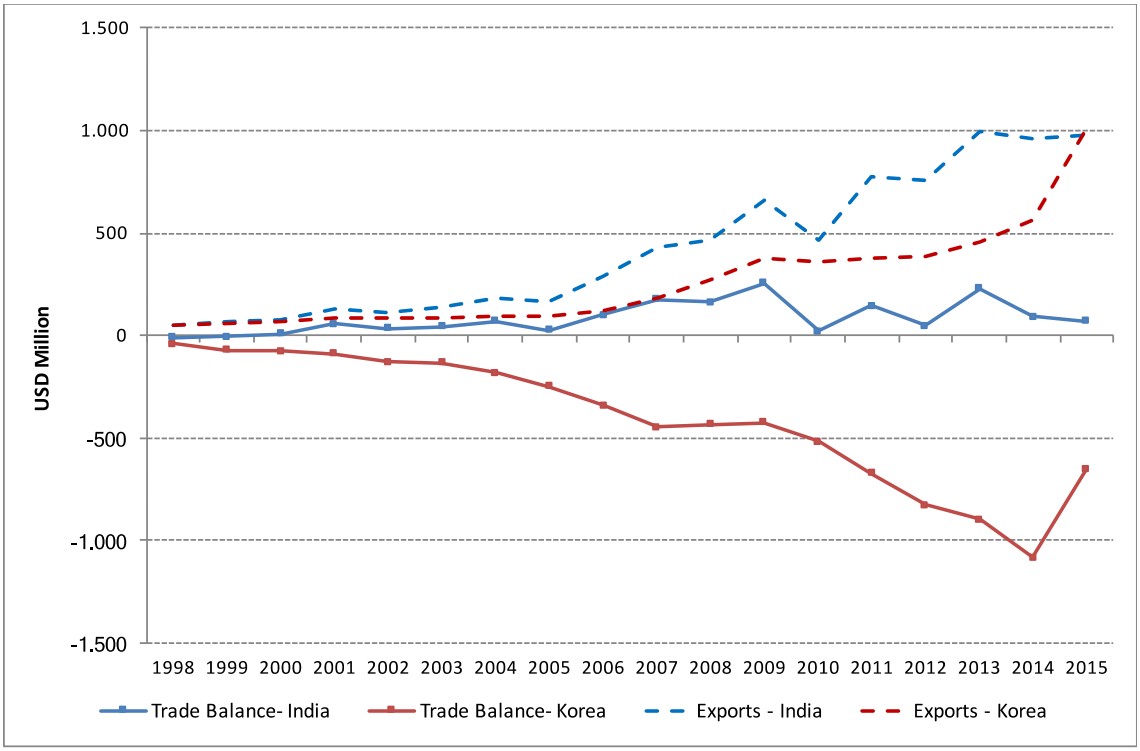
Over the past few years, after the expiration of patents of the main biotech molecules, certain countries, such as Korea and India, have adopted learning paths based on entry into second-generation biosimilars markets as creative imitators. Although they have adopted this common strategy, the sequence and the speed of entry have been different. While India has been characterized by export growth and trade surplus in biologics since the 1990s, Korea has exponentially increased its exports of biologics since 2015, partially reversing its trade deficit (Graph 1).

What characterize these heterogeneous dynamics are the different policy sequences and previous technological trajectories followed by domestic industries. While India's national strategy has been predominantly based on a sequential trajectory taking advantage of its previous pharmaceutical specialization in chemical synthesis, Korea displays a stage-skipping strategy of entry into international biosimilar markets with firms acting as contract manufacturing organizations (CMO).

In the case of India, there has been a clear support to science and technology infrastructure with the strengthening of its national innovation system, building centers of excellence and university education support in biomedicine. In the early 1980s, in its *Sixth Five-Year Plan* 1980–85, India included the development of biotechnology in its official policies for the very first time. More recently, in 2007, the Department of Biotechnology launched its first *National Biotechnology Development Strategy*, which included specific guidelines for the development of this area, recognizing the growing importance of the biotech sector and following a National Innovation System approach.

[4] See P.J. Lavarello, G. Gutman and S. Sztulwark, *Explorando el camino de la imitación creativa: la industria biofarmacéutica argentina en los 2000,* 1a ed.– (Buenos Aires, PuntoLibro, 2018). Available from http://www.ceur-conicet.gov.ar/archivos/publicaciones/Industria_farmace%CC%81utica_FORMATO_Electro%CC%81nico.pdf.

Graph 1
Annual biopharmaceutical trade. Korea and India. 1998-2015.



Source: Own elaboration based on UN-Comtrade database

At the manufacturing stage, government intervention selectively supporting technology capability building is less evident. There is a clear leadership from the large groups that take advantage of prior accumulated learning in the manufacture of generic drugs and vaccines—in spite of the heterogeneous capabilities accumulated by the Indian pharmaceutical industry. Certain Indian firms have progressively moved from being traditional suppliers of vaccines to the national health system to integrate themselves as providers of international institutions of growing importance, under the expansion of immunization programs and schemes. In this context, big national companies have been the leading actors of the biotech entry strategy. They initially focused on first-generation biotech drugs such as erythropoietin and interferons and subsequently moved to second-generation molecules such as monoclonal antibodies. These strategies have been developed in association with Big Pharmas. Most of the bigger ones have made plans to launch first- and second-generation biosimilars in developed country markets in partnership with some major developed country firms. Such are the cases of the agreements between Biocon and the US firm Mylan, Dr. Reddy's and the German company Merck KGaA, and Intas and Apotex. The main orientation of Indian firms' strategies to develop biosimilars has been technology acquisition, accessing international markets and managing regulatory requirements.

Although Korea had been promoting biotechnology since the 1980s, it was mainly in the 1990s, with the Biotech 2000 program (launched in 1993), that government investment in biotechnology research and development (R&D) greatly increased. These initiatives encouraged venture capital to support the emergence of new science-based startups and novel patterns of

interaction among new biotechnological specialized firms, academies, and technological institutes. Notwithstanding the emergence of new small science firms and networking initiatives driven by this momentum in biotechnology at the national level, they have not been accompanied by bioprocessing capabilities building support. A number of leading Korean pharmaceutical companies within the domestic synthetic drug industry began to invest in biotechnology R&D in the 1980s but they found it difficult to break into the biotech paradigm. In a context of limited articulation between universities, public research institutes and the domestic private sector, bottom-up horizontal promotion of basic science undermined greater exploitation of scientific knowledge by pharmaceutical companies.

After focusing on their National Innovation System during the 1990s, the government has recently adopted a selective and explicit policy that attempts to boost the development of second-generation biosimilars through setting-up large-scale plants. Paradoxically, this deliberate "top-down" strategy is the result of an accelerated institutional learning process about successful domestic "bottom-up" strategies. Given this institutional learning process, the national strategy focuses on massively developing critical missing assets as well as large-scale facilities and on encouraging investment alliances with foreign companies.

Celltrion, a biotech firm founded in 2002, was the exception. It was initially a joint venture with an ex-subsidiary of Genentech (Vaxgen) specialized in vaccine manufacturing and biosimilars, and whose goal was to fund the development of new biologics. This strategy enabled this firm to quickly (in little more than a decade) circumvent technological and regulatory barriers, and to enter the segment of leading biosimilar firms at the global level. Celltrion was the first company from an emerging country to obtain the European Medicines Agency's (EMA) approval for its biosimilar infliximab. On 5 April 2016, the Food and Drug Administration (FDA) also approved infliximab, which makes it the second biosimilar to gain approval in the US. In order to accelerate the emergence of a new biotechnology sector, since the mid-2000s, these policies were supplemented by a top-down approach, which combined more targeted science with bioprocess capabilities. Under this new policy framework, Korea attempted to replicate Celltrion's experience. In this sense, the government pursued an imitative strategy oriented towards an aggressive entry into the biopharmaceutical industry through the international integration of manufacturing.

In 2006, Korea launched its second biotechnology plan, Bio-Vision 2016 (for the period 2007–2016) with a more selective top-down approach. The total budget outlay for Bio-Vision 2016 was in excess of USD 15 billion over a period of 10 years. In the same vein, but with a specific focus on the production of selected biosimilars, in 2010 the Ministry of Knowledge Economy (MKE) launched an industrialization plan that aimed to turn Korea into a world leader in biosimilar markets over the course of a decade. This plan was ambitious: it aimed to achieve a 20% share of the world market for biosimilars with five companies operating on a global scale. Drawing on the successful experience of Celltrion, Korea adopted a stage-skipping pathway and decided to directly enter more regulated countries as a provider of second-generation biosimilars.

To ensure the effective and rapid achievement of this objective, the Korean government created state-owned organizations and firms. It was with this aim that the state agency called Korea Biotechnology Commercialization Center (KBCC) was created in 2007. KBCC is more than a commercialization agency; it is a CMO which acquired manufacturing experience working with global pharmaceutical leaders as clients. In the same year, the government established the Korea National Enterprise for Clinical Trials (KoNECT) with the idea of making Korea a leading clinical trial center at the global level by providing it with the appropriate infrastructure and staff training.

The Korean government showed to be aware of how demanding high investment thresholds are for bioprocess innovation and the high-risk regulatory thresholds that have to be met to produce second-generation biosimilars. Therefore, targeted industrial support measures were reinstated orientating *chaebols'* strategies. Having declared the biopharmaceutical industry as one of the new-generation growth engines in 2009, the Korean government designated companies such as Samsung and LG as major biosimilar manufacturers and supported their R&D investments in order to break into biosimilar production.

Though biosimilars still constitute the main structural space of this strategy, strengthening of this strategy is needed to leverage the process development platform for the development of new biotechnological drugs. The question remains whether Korea could meet regulatory and R&D thresholds to move towards innovative strategy. Or if, with the appearance of a new generation of biopharma, the gap could widen again and Korea remains locked in previous trajectories.

The main lesson to be drawn from this comparative analysis is that horizontal national strategies, not targeted towards specific structural spaces (or individual big firms), have not the speed and strength required by a catch up strategy facing the fluidity of biotech revolutions. In contrast, they reduce the "lock-in" risks of a wrong choice, leaving open the possibility of accumulating capabilities in next-generation innovative products and processes. In contrast, a more targeted creative imitation strategy, with selective infrastructure and process capability building, offers greater backwardness advantages but it constrains industrial upgrading to some products.

Which national strategy will be successful and which will not is still an unanswered question. Success will depend on biosimilars market growth and the evolution of the competitive environment over the next years, taking into account production capacities, overaccumulation, and increasing regulatory uncertainty.

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