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When access to drugs meets catch-up: insights from the use of CL threats to improve access to ARV drugs in Brazil

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Abstract

Access to affordable lifesaving medicines is considered a human right. This leads to a question largely understudied in the catch-up literature on accumulation of industrial capabilities. Can the need to improve access to an essential commodity impact the sectoral catch-up trajectory of the corresponding industry? In 1996, Brazil initiated a policy of universal and free access to highly-active ARV therapy, which put an enormous pressure on the Brazilian Ministry of Health (MoH). In order to ensure an adequate supply of ARVs in the public healthcare system with a limited budget, MoH started negotiating price reductions for high-cost patented drugs, often deploying the threat of using compulsory licensing. Through a scoping review of the literature and construction of the Brazilian case study, the paper explores how the need to access is impacted by prior catch-up in the pharmaceutical sector and triggers in turn future sectoral catch-up. It shows that price negotiations may or may not impact both catch-up and access positively. Catch-up can provide bargaining strength in price negotiations and have a positive

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inter-temporal impact on both future catch-up and access. However, results suggest that only successful catch-up can lead to long term access, as the capabilities accumulated in aborted catch-up are not sufficient for large scale production of low cost essential medicines. Thus, industrial policy and health policy can impact one another and twining between catch-up and access can be helpful.

Key-words

Access to medicines; technological catch-up; pharmaceutical industry; Brazil; compulsory license; window of opportunity

1. Introduction

Catch-up theories of industrial capability build-up, like macro-economic theories of growth, focus on the supply side. Sectoral catch-up studies describe pathways by which local firms accumulate capabilities within their sectoral and national innovation systems, expand their markets, and contribute to economic growth (Abramovitz, 1986; Malerba and Nelson, 2011). Catch-up is important for policy makers, because of the underlying implicit assumption that if production is increased, then its trickle-down benefits would improve access to commodities, in terms of their availability and affordability. For most products, these trickle-down benefits are left to be determined by markets, with the state being held accountable for catch-up in terms of the technological, innovative and industrial capabilities upstream, and the quality and safety of goods reaching final consumers downstream. However, for some essential commodities and services, access is also deemed to be the responsibility of the government, and not to be left to markets alone. For example, access to food, water, sanitation, medicines, education etc. as embodied in the 17 Sustainable Development Goals (SDGs), are considered as human rights, and hence, important policy goals. This leads to a question largely understudied in the catch-up literature. Can the need to improve access to an essential commodity impact the sectoral catch-

up trajectory of the corresponding industry? In order to throw light on this issue, the present paper takes a bottom-up perspective instead of a top-down view and enquires if access goals of the state can impact catch-up.

Drugs for life threatening diseases are essential commodities, whose universal accessibility is important for inclusive growth. For middle and low-income countries, which have to catch-up in pharmaceuticals, this challenge is most daunting. The manufacturing of small molecule drugs involves two main operations in decreasing levels of complexity and knowledge intensity: production of 'active pharmaceutical ingredients' (API)[2] and drug formulation[3]. The wider the scope of technological capabilities over the production process, the higher the catch-up in pharmaceutical manufacturing. The World Health Organization reports that there are at least 126 developing countries without API production capabilities and 42 in this set have limited, or no competence in drug formulation, relying exclusively on imports to satisfy their demand (WHO, 2011).

When a country is faced with a high disease burden and has to improve access to the corresponding drug, its response is affected by its level of catch-up and whether or not the drug is patented. For emerging countries with limited API production capabilities, the problem may become untenable, if drug manufacturers are unwilling to supply adequate quantities at acceptable prices and/or the corresponding technology cannot be licensed from the supplier and developed independently by other firms. In such cases, Target 3b of Goal 3 of SDG affirms that

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[2] These are the core therapeutic components of drugs. Industrial production of APIs involves development and optimization of the chemical synthesis.

[3] It is the preparation of final pharmaceutical products (e.g. tablets, capsules, injections, parenteral solutions). It is a relatively simple manufacturing activity wherein inputs go through a physical transformation process.

governments have the right to use, to the full, the provisions in the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) regarding flexibilities to protect public health, and, in particular, provide access to medicines for all in accordance with the 2001 Doha Declaration on the TRIPS Agreement and Public Health. This includes the possibility of issuing a compulsory license.

Compulsory license or CL is a flexibility contained in TRIPS, whereby a government can permit third parties to produce the patented product without the consent of the patentee. This is a measure that has been purposefully introduced to minimize the potential negative impact of patents on access to medicines. Scholars have confirmed that the CL option empowers developing countries to negotiate prices with pharmaceutical companies more aggressively (Beall et al., 2015; Beall and Kuhn, 2012; Ramani and Urias, 2015).

Under this context, the central questions of our paper can be redefined as follows. *For an emerging country with limited manufacturing and innovation capabilities, what are the possible inter-temporal impacts of sectoral catch-up in pharmaceuticals on access to life saving drugs and vice versa? Furthermore, what insights can be gained from the interrelationships between price negotiations of essential patented drugs, access and catch-up?*

For our research queries, the Brazilian catch-up experience in the production of antiretroviral (ARV) drugs required by HIV/AIDS patients presents itself as an ideal trajectory to study. In 1996, Brazil initiated a policy of universal and free access to highly-active ARV therapy (HAART) (or simply Universal Access Policy), which put an enormous pressure on the Brazilian Ministry of Health (MoH). In order to ensure an adequate supply of ARVs in the public healthcare system with a limited budget, MoH started negotiating price reductions for high-cost patented drugs, often deploying the threat of using CL. In this context, the paper

explores how the need to improve access in Brazil was impacted by prior catch-up in the pharmaceutical sector and in turn triggered future sectoral catch-up.

A mixed methodology is applied to answer our central questions. The literature is first examined and its main findings on catch-up and access are summarized as theoretical constructs through figures. Then the Brazilian case study is built using multiple sources of data. Its implications for the interrelationships between catch-up and access are validated through expert interviews. At each stage, results are inferred, and then in the final section, they are combined together to provide a broader analytical insight. The case study method is applied, because it is suitable for studying complex contemporary social phenomena, when boundaries between a phenomenon and its context are not clearly evident (Yin, 1994). Moreover, since the number of observations of CL threats in Brazil is not sufficiently high to justify a statistical analysis, the case study method is more appropriate.

The rest of the paper is organized as follows. Section 2 presents a scoping review of the literature and summarizes its main findings through theoretical constructs (Figure 1 and Figure 2). Section 3 starts by tracing the Brazilian catch-up trajectory and then presents a detailed study of the use of CL in price negotiation episodes for ARVs in Brazil. Section 4 discusses the main results obtained, and the refinement they provide of the earlier frameworks (Figure 3). Finally, section 5 concludes the paper.

2. A brief review of the literature

The term catch-up has been used broadly to study the comparative or individual experiences of communities (countries, regions or firms) in terms of the evolution of their income, productivity, capabilities or other economic variables (Hartnett and Russell, 2002; Nayyar, 2013). The focus is either on patterns of (lack of) convergence of economic variables in a set of regions or over time (Verspagen, 1991) or on the tracing of the strategy-outcome paths

of economic actors (Lee and Malerba, 2017; Odagiri et al., 2010). In the latter, a sub-stream centres on the dynamics of knowledge and capability accumulation within an innovation system applying qualitative inductive research methods such as case studies (Malerba and Nelson, 2011; Ramani, 2014). The present paper situates itself in this niche of evolutionary economics. However, even a comprehensive survey of this sub-stream is beyond the scope of this article. Hence, we briefly discuss the influential theoretical constructs on technological catch-up and then look into the role of access in this literature.

Technological catch-up in production of a commodity can be defined as the acquisition of knowledge, savoir faire, equipment, personnel, infrastructure etc. i.e. all the capabilities, required to manufacture the product in terms of a targeted quantity and quality. Empirical studies demonstrate that even technological catch-up is not technologically deterministic, either in terms of the drivers, the processes or the final state, for the evolutionary trajectory is formed of a series of systemic outcomes, crucially marked by initial conditions and path dependencies (Kline and Rosenberg, 1986; Rosenberg, 1994). Besides being catalysed by science push or demand pull, innovation is induced by systemic changes such as resource scarcities, changing relative prices and productivity challenges (Binswanger et al., 1978; Ruttan and Hayami, 1984). State investment, policy initiatives and the functioning of public agencies play a pivotal role in the performance of national innovation systems. For instance, public investment in developing an educated work force with social capabilities (Abramovitz, 1986) and a dynamic public research network (Nelson, 1993) are crucial. Entrepreneurial firms can thrive only if there are financial institutions that can support the costs of risky investment (Gerschenkron, 1962). Finally, all of the above must be steered by a benevolent and rational government policy to create an enabling environment for industrial capacity building (Freeman, 1995; Lundvall, 1992). Indeed, inadequate institutional capabilities such as rule of law and contract enforcement alongside widespread corruption are cited as the main obstacles to catch-up of developing countries

(Keefer and Knack, 1997). Thus, technological catching-up cannot be taken for granted; a variety of necessary and complementary capabilities are required under an enabling environment for effective absorption of available technological knowledge and its transformation into industrial capabilities (Ramani and Szirmai, 2014).

Following Abramovitz (1986), technological catch-up goes through four phases: entry, catching-up, forging ahead, and falling behind. Triggers for thrust into any of the stages may emanate in the innovation system in the form of new problems, actors, knowledge, discovery, technology or innovation, and finally, new policy initiatives (Lee, 2005; Perez and Soete, 1988). Some important triggers for catch-up in the pharmaceutical sector in emerging countries have been changes in the intellectual property rights (IPR) system (Guennif and Ramani, 2012), bandwagon effects of inter-organizational learning (Athreye et al., 2009), reverse brain drain of engineers trained in the USA and Europe (Kale et al., 2008), access to foreign know-how via joint-ventures and alliances (Lee and Kim, 2010) and import of technology and materials (Ren and Su, 2015).

Catch-up by a firm starts with entry through investment in the build-up of absorptive capabilities necessary to learn about existing and superior technologies. Then it continues through learning and integration of the most efficient technologies in the production process. Thereafter, market shares are expanded and market power is established. Finally, as new entrants armed with better innovations penetrate the market, earlier entrants lose their market leadership. Lee et al. (2016) refer to these four phases as the ‘standard’ catch-up cycle with three other possible variants: ‘aborted catch-up’ when only entry occurs (i.e. only first phase); ‘sustained leadership’ when incumbents are able to retain their leadership over time even with entry and catching up (i.e. only first two phases); ‘coexistence of leaderships’, when the last phase fails to materialize (i.e. only first three phases). Diverse patterns are possible because absorption and

subsequent integration depend on a range of institutional characteristics, technological and social capabilities (see Fagerberg and Godinho, 2005; Lee, 2013 for overviews).

2.1 Meta-Analysis of abstracts via a scoping review

Under the broad setting of catch-up, in order to identify the salient findings of the existing literature on catch-up triggers, the role of policy and its interrelationship with access, a scoping review of the literature was carried out and followed with an analysis of the article abstracts. A scoping review of the literature is suitable whenever the objective is to broadly explore a theme in order to identify the sub-themes covered and the gaps. Here, the search is done on a well-defined corpus using search equations with the inclusion/exclusion criteria being developed *iteratively* after initial search results (Armstrong et al., 2011). Following this methodology, for the purposes of our research query, three search equations were applied on SCOPUS the standard abstracts and citation database in the subject area: 'all social sciences', to extract a corpus of abstracts. The first equation was, 'catch up' OR 'catching up' OR 'catch-up' in either title, key words or abstract of the article. The second was 'indus*' AND 'pharm*' AND 'access'; while the third was 'indus*' AND 'pharm*' AND 'Brazil'. Considering each abstract as a data point, a meta-analysis was then carried out manually by reading through abstracts and retaining only those that provided responses to our research queries (Poth and Ross, 2009). We turn to the results covering works not discussed so far.

2.2 Role of 'access' for firm and regional catch-up: Needs for local consumption practically invisible

With respect to access, first and foremost, according to our corpus, in the catch-up literature, access has been considered uniquely with respect to the firm or public laboratory striving to catch-up. Access to global knowledge and technology pools including the most

advanced is helpful to catch-up in knowledge intensive industries (Abraham, 2014; Colli and Corrocher, 2013; Dadush, 2008; Park and Lee, 2006; Schiller, 2011); so is access to global resources and market opportunities (Fan, 2011). Access to latest foreign technology is deemed important (Lee et al., 2005, 2011) and this can also be in the form of imported capital goods (Ahmad and Lee, 2016). Access to internet coverage and ICT platforms (Campisi et al., 2013; Conte, 2001; Gruber, 2001) and access to finance (Pšeničny et al., 2014) can be crucial for catch-up. However, similar access configurations need not lead to similar catch-up trajectories as the latter is determined by a host of other factors such as public policy and focus, infrastructure, managerial capabilities and culture (Raven et al., 2007). For effective exploitation of available access, local firms must have absorptive capabilities (Faucher, 1991; Park, 2011). Access can be enhanced through cross border inventions (Giuliani et al., 2011) as well as social networks (Salavisa and Fontes, 2012). Access to large markets promotes foreign direct investment (Poelhekke and van der Ploeg, 2009). For instance, under the aegis of sectoral industrial policy fine-tuned for catch-up, market access has been used to negotiate technology sharing for catch-up successfully in China (He and Mu, 2012). Multinationals can use such opportunities and not obstruct access to know-how for local firms, if the IPR system can guarantee protection of their innovations (Archibugi and Filippetti, 2010; Kiedaisch, 2015). To close, the catch-up literature confirms that profit driven firms which make or are enabled to make an astute use of accessible knowledge, resources and markets, can benefit from technological learning.

For the state, according to our corpus, the primary objective of sectoral catch-up is to strengthen industrial capabilities. Policy triggers for catch-up can be a combination of two types of actions focusing on the supply side sectoral actors: building an enabling innovation system or intervening through specific initiatives to build capabilities (Giesecke, 2000). Most scholars give more weight to the former for catch-up, as a pluralist approach is required to develop capabilities in new knowledge areas that require closer links with science, while addressing social

apprehensions about environmental problems and poverty (Romijn and Caniëls, 2011). Illustrations of each type are provided below.

Table 1
Illustrations of policy triggers for catch-up

Policy initiatives to nurture an enabling innovation system	Interventionist Initiatives
Investment in human capital and infrastructure (Archibugi and Filippetti, 2010; Choi, 2011; Co, 2002; Dadush, 2008; Furman and Hayes, 2004)	Promotion of national champions (Barbieri et al., 2013; Chu, 2009);
A strong patent system (Aghion et al., 2001)	Targeted policies and projects for specific technologies and standards (Choung et al., 2012; Fan, 2010; Khan, 1999)
Industrial policy that promotes a broad economic and social nurturing environment for innovation and technology capabilities accumulation (Filippetti and Peyrache, 2017; Intarakumnerd and Charoenporn, 2010; Mu and Lee, 2005; Oshima, 1984; Thacker-Kumar and Campbell, 1999; van Dijk and Szirmai, 2006; Zhang and Zhou, 2016)	Organizations and institutions for targeted facilitation (Choung et al., 2006; Goldman et al., 1997)
Reform of the public research and university system (Kwon, 2011; Lehrer and Asakawa, 2004) and promotion of knowledge transfers between university and firm (Kwon, 2011)	National R&D programmes and Consortiums (Ahn and Mah, 2007; Hutschenreiter and Zhang, 2007; Lucchini, 1998)
Stimulation of firms' participation in frontier innovation activities (Rasiah, 2010, 2013)	Cluster development (Klochikhin, 2013); Regional development (Iosif and Tăchiciu, 2016); Sector development (Wang, 2013)
Building managerial capabilities (McKendrick, 1992)	Improving public sector enterprises (Klochikhin, 2013)
Promotion of FDI (Camilla et al., 2013; Perkins and Neumayer, 2008)	Public financing and procurement (Siaroff and Lee, 1997)
International technology cooperation (Sawada et al., 2012)	Promote short cycle technologies (Lee, 2012)
Appropriate labour market policy (Lange and Marrocco, 2012)	Active control and guidance of the market by the state (Soofi, 2016)

To summarize, as in Figure 1, the catch-up literature portrays it as a process within the production space of an innovation system. Catch-up is the outcome of the actor-strategies designed to augment profit or growth on the supply side of the market, as a function of the nature of demand. But, actors and processes in the consumption space, and the need to improve access of commodities to local final users are not perceived as the drivers of catch-up strategies. Indeed, just as macroeconomic theories of growth and catch-up frameworks of income convergence implicitly assume that the quality of life of the poor is likely to improve through

trickle down effects, similarly sectoral studies seem to assume that access for local consumption will improve through catch-up.

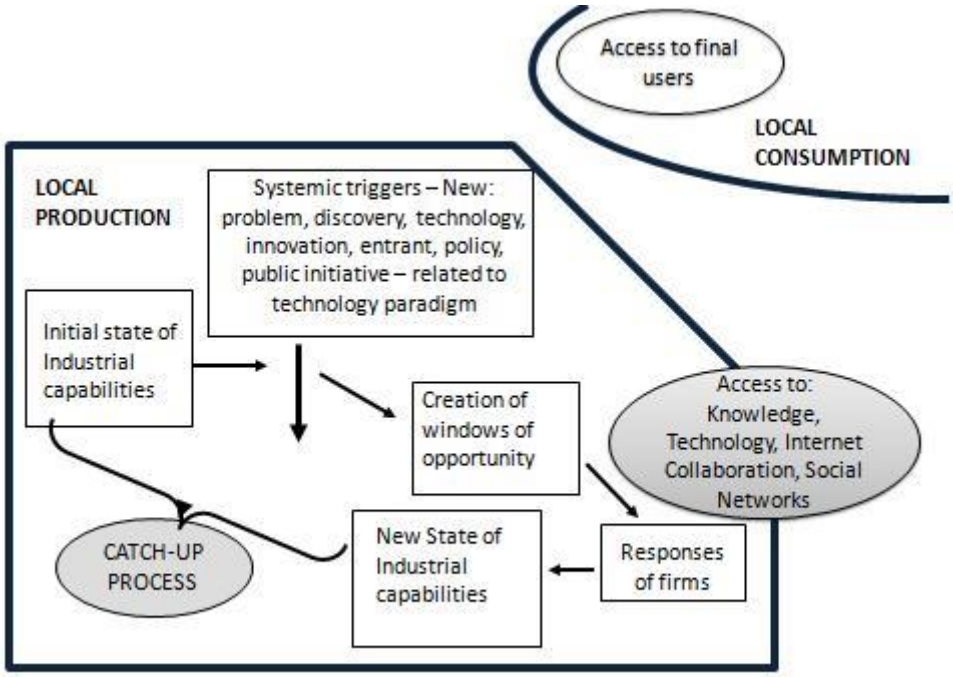

Fig. 1. Catch-up as an outcome of the strategies of supply-side actors

2.3 Role of catch-up and industrialization on access to medicines: Always helpful when it happens

Turning to the other two corpuses on the interrelationships between the industrialization process in pharmaceuticals and access to medicines and then the specificities with respect to Brazil, we however get a different view as depicted in Figure 2.

The different perspective seems to stem from the fact that medicines are an essential commodity to ensure a good quality of life via health. There is a demand from civil society that essential commodities, including medicines, should be provided by the state to all citizens as a fundamental human right. Such a movement has been particularly strong for medicines in Brazil

(Loyola, 2009). Civil society pushed the Brazilian government to ensure access to drugs for HIV/AIDS via interventions in the production space (Flynn, 2008; Veras, 2014). Intergovernmental agencies such as World Health Organization, World Intellectual Property Organization, and World Trade Organization have created programmes that aim at promoting access and innovation in drugs for HIV/AIDS and other selected diseases simultaneously (Nilsson, 2017).

The state can address the access challenge in various ways with or without successful catch-up. In Africa, access to medicines was satisfied through imports of low-cost generics from India and China (Chaudhuri et al., 2010; Haakonsson, 2009). In India, during the 1960's the government invested in the creation of a network of public sector firms and technology transfer from international agencies to provide access to essential medicines; and when it proved insufficient, the IPR regime was changed in 1972 to permit local firms to re-engineer branded drugs resulting in both catch-up and much improved access (Ramani and Venkataramani, 2001; Sampat, 2010). In addition to public investment and policy changes, a government can also engage in direct negotiations with drug manufacturers to establish the primacy of access over patent rights. For instance, CL has been used as a bargaining tool in Thailand and Brazil to improve access (Ford et al., 2007; Shadlen and Fonseca, 2013; Rosenberg, 2014).

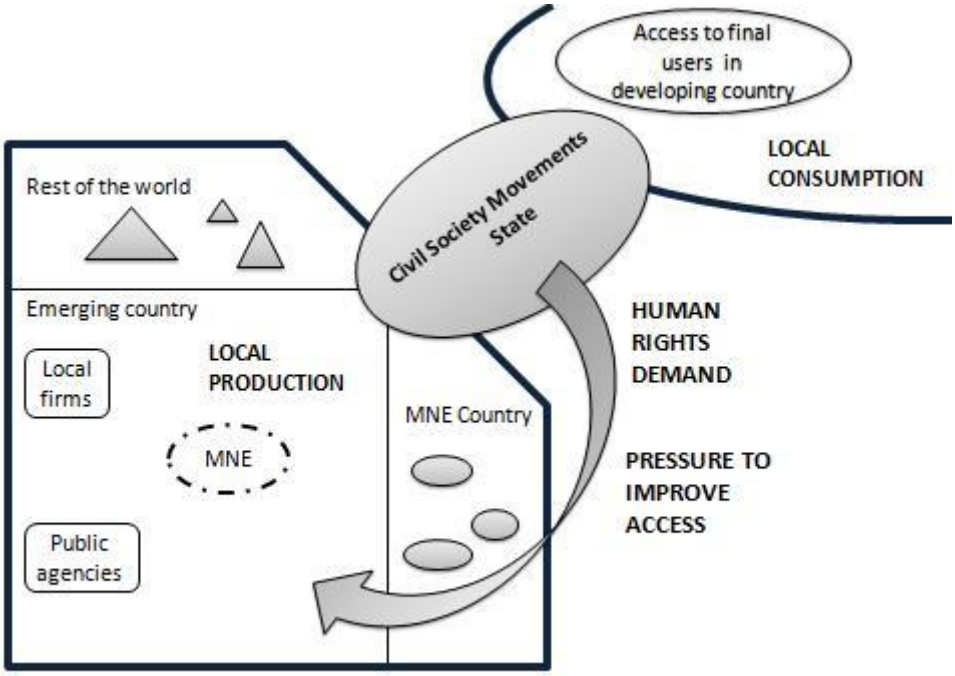

Fig. 2. Bridging consumption and production systems through access as human right

To conclude, the literature is not clear about the conditions under which access needs can stimulate technological catch-up or the impact of prior catch-up on the possible alternatives to improve access to essential commodities like medicines. While the need for universal access to essential commodities by actors that bridge production and consumption spaces is putting pressure on actors in the local production system to increase output, this may not always happen. Imbalances between components and systemic constraints may trigger exploration for corrective action along the technological trajectory (Rosenberg, 1978), but systemic challenges may or may not induce institutional changes to promote a more efficient resource allocation (Ruttan and Hayami, 1984). To gain insight on such issues, we turn to the Brazilian case study.

3. Brazilian need to improve access to ARVs and its impact on Catch-up

Brazil's first AIDS case was reported in 1982 and, by the end of the decade, there were approximately 76,000 people living with HIV in the country (Levi and Vitória, 2002; Nunn, 2009). Faced with this crisis, while most developing countries focussed on prevention of new cases, Brazil became a trailblazer by taking the stance that all its citizens would be ensured access to medicines as a human right. In 1996, Brazil initiated a well-structured official policy of universal and free access to HAART through its public health system. The availability of ARVs to people living with HIV/AIDS was to be ensured through local formulation of generic drugs in state-owned laboratories and imports of branded drugs from research-based pharmaceutical multinational enterprises (MNEs). It is worth noting that local production of ARVs in Brazil could be considered only because of prior catch-up in pharmaceuticals (Urias, 2015).

3.1. Catch-up efforts from 1969 – 1990s

Between 1969 and 1984, local production of pharmaceuticals in Brazil was nurtured by a variety of policies among which three particularly are noteworthy.

Abolition of patent protection in 1969: This move was expected to enhance the competitiveness of indigenous companies and improve access to medicines (Frenkel et al., 1978). Local firms responded by importing generic APIs to reduce their production costs (Rebouças, 1997). Thus, while the loose intellectual property regime fostered price competition and improved access to medicines, it did not stimulate accumulation of technological capabilities for industrial production of APIs.

Creation of institutional technology suppliers: In 1976, a public-private entity called CODETEC was founded to promote accumulation of technological capabilities in private

companies of several sectors via support provision in product and process R&D. In pharmaceuticals, its mandate was to reverse engineer APIs and then transfer the technology to local private companies. CODETEC mastered the synthesis process of about 80 APIs, and local companies were able acquire the knowledge and skills necessary to scale up and commercialise 25% of them (de Cerqueira Leite, 2008).

In the same year, Farmanguinhos was founded as part of a network of stated-owned laboratories to supply affordable medicines to the public sector (Hamilton and Azevedo, 2001). In 1979, Farmanguinhos set up a research laboratory for chemistry synthesis of APIs (Vieira, 2005). The objective was not to manufacture APIs, but to build the technological capabilities for reverse engineering of APIs and transfer the necessary knowledge and skills to local companies (Hamilton and Azevedo, 2001; Vieira, 2005).

Interventions to build technological capabilities in pharmaceuticals during 1980's: The objective of an industrial policy called *Projeto Fármaco* initiated under the aegis of CODETEC, was to provide technical and scientific support to indigenous pharmaceutical companies in order to reduce imports of APIs. Several policy instruments provided support to *Projeto Fármaco*, including tariff and non-tariff barriers to trade and fiscal and financial subsidies to local firms. In turn, *Projeto Fármaco* fostered formal and informal collaborative arrangements between local firms and state-owned laboratories, often supported by public funding schemes (Queiroz, 1993; Rebouças, 1997). Universities were critical nodes of such a system, not only through supply of skilled scientists and chemical engineers, but also via collaboration to assist in reengineering of drugs (Cassier and Correa, 2008).

As a result of these initiatives, during the 1980's there was finally a steady accumulation of technological capabilities in API production, demonstrating that lack of IPR alone is not sufficient for catch-up (Guennif and Ramani, 2012; Queiroz, 1993; Rebouças, 1997). Queiroz

(1993) provides a wealth of facts to confirm such catch-up: (i) between 1984 and 1990, 12 R&D labs and several pilot-plants for API development and production were opened; (ii) the mean time for process development of APIs in CODETEC decreased from 7.5 months in 1984 to 4.5 months in 1990; (iii) finally, between 1982 and 1987, the real value of local API production increased by 95%, while the exports of APIs increased by 40% between 1985 and 1990.

The Brazilian pharmaceutical industry, however, did not move to the forging ahead phase after catch-up for diverse reasons. During the 1990s, most of the companies could not exploit the economic opportunities created, because public support was abandoned due to financial constraints. Further, protection to the local industry was discontinued by the mid-1990s; tariff and non-tariff barriers were removed and CODETEC was shut down. Consequently, local API production fell drastically and the local pharmaceutical industry remained confined to drug formulation and distribution activities (Queiroz, 1995). Finally, under a macroeconomic context of import substitution, extremely high protection proved to be indiscriminate and exaggerated; and incentives put no emphasis on exports or innovation capabilities, stalling the forging ahead phase (Suzigan and Furtado, 2006). However, such an aborted catch-up cycle enabled accumulation of knowledge and skills in a few niches, such as the production of ARVs. Indeed, the local producers of ARVs active in the new millennium had built their technology capabilities through collaboration with either CODETEC or Farmanguinhos, mainly under *Projeto Fármaco*.

3.2. Catch-up in ARVs in the 1990s

In 1991, MoH included imported ARVs in the public health system with the distribution of zidovudine (AZT) capsules (Teixeira et al., 2004). In 1992, Microbiológica, a university spin-off founded in 1981 and supported by CODETEC since 1983 (Rabi, 2007), became the first local company to synthetize the API of AZT, and one year later, Microbiológica started

supplying AZT to a state-owned laboratory (Cassier and Correa, 2003; Orsi et al., 2003). However, with implementation of the Universal Access Policy in 1996, there was an immediate need to increase access multifold

For this purpose, MoH targeted increased local production of ARVs as the main pillar of support for the Universal Access Policy (Orsi et al., 2003). Then, MoH assigned Farmanguinhos the task of being the main supplier of generic ARVs. When CODETEC was shut down by the Federal Government in the early 1990s, one of its leading chemists, Benjamin Gilbert was seized by Farmanguinhos to be its scientific director. In Farmanguinhos, Gilbert created an R&D department for reverse engineering of pharmaceutical processes (Vieira, 2005). This allowed Farmanguinhos to develop imitative capabilities for reverse engineering the synthesis processes of the several drugs, including second-generation ARVs such as Efavirenz, Nelfinavir and Lopinavir (Cassier and Correa, 2008).

Between 1997 and 2002, the accumulation of technological capabilities allowed a sevenfold increase in production volume at Farmanguinhos, notably due to ARV production (Cassier and Correa, 2003). Nevertheless, Farmanguinhos and other state-owned laboratories responsible for local production of ARVs, remained specialized in drug formulation. Only a few private companies developed their own technological capabilities to produce APIs (Fortunak and Antunes, 2006), and therefore the public sector was dependent on imports of these critical inputs. More than 90% of the public demand for APIs were satisfied by Indian and Chinese firms (Orsi et al., 2003; Pinheiro, 2012).

3.3. Challenge to access posed by TRIPS and possible solution pathways

The sustainability of the Universal Access Policy was severely constrained by high prices of newer ARVs due to premature compliance with the TRIPS Agreement. In 1997, the

patentability of pharmaceutical products and processes was re-introduced in the country as Brazil had waived the ten years adaptation period for developing countries.

Different countries in Latin America retained different features of TRIPS flexibilities in their local IPR regime (Correa, 2015). For instance, Brazil opted to retain CL and the experimental use of patented inventions (also known as 'Bolar exemption'), but opted out of permitting parallel imports and included a provision for 'pipeline patents'[4]. Such choices had a strong bearing on the ability of the country to cope with the potential negative impact of patents on access to ARVs.

The challenge became even more daunting with the major depreciation of the local currency in 1999 that led to a 64% rise in the cost of antiretroviral drugs in Brazil as compared to 1998 (Grangeiro et al., 2006). An increasing number of AIDS patients, the introduction of high priced, newly patented ARVs, and the need to ensure the success of the Universal Access Policy, while answering to its own government and other societal stakeholders put an enormous pressure on MoH. Fenced in by these diverse constraints, MoH sought price reductions for the patented drugs, threatening at times to issue a CL (Galvão, 2002; Nunn et al., 2007, 2009). What was their effect on access and catch-up? We turn to this question now.

4. Role of catch-up in Price Negotiations and Impact on Access

4.1. Primary and Secondary Data Collection

The ARV price negotiations were identified by applying designed search criteria to our secondary data. These secondary sources included: scientific articles; official documents,

[4] Brazil automatically granted patents of inventions that were already patented abroad, provided that the product covered by the foreign patent was not made commercially available anywhere (Mitsuuchi Kunisawa, 2009)

national and international reports; Web portal of the STD/AIDS Department at MoH of Brazil, available at: http://www.aids.gov.br/; Official Gazette of the Federal Government of Brazil, available at: http://portal.in.gov.br/); MoH of Brazil: administrative documents, proposals, progress reports, and other internal records, available at http://portalsaude.saude.gov.br/ and finally, newspaper clippings and other articles appearing in the press and digital media. The search criteria spotted negotiations between MoH and pharmaceutical companies for patented ARVs that involved at least one of the following factors: CL threat, voluntary license request, rejection of patent claim and patent nullification. Thus, we inferred that between 2001, when MoH began price negotiations over ARVs, and 2014, there have been at least 14 episodes of price negotiations involving 6 different ARVs (see Table 2) that fitted our search criteria.

Table 2:
Price negotiations of ARVs in Brazil

Episode	Drug	Pharmaceutical MNE	Start
1A	Efavirenz	Merck & Co. (USA)	Jan/2001
1B	Nelfinavir	Roche (Switzerland)	Jan/2001
2A	Efavirenz	Merck & Co. (USA)	Jul/2003
2B	Nelfinavir	Roche (Switzerland)	Jul/2003
2C	Lopinavir/Ritonavir	Abbot Laboratories (USA)	Jul/2003
3A	Lopinavir/Ritonavir	Abbot Laboratories (USA)	Mar/2005
3B	Efavirenz	Merck & Co. (USA)	Mar/2005
3C	Tenofovir	Gilead Sciences (USA)	Mar/2005
4	Atazanavir	Bristol-Myers Squibb (USA)	Nov/2006
5	Efavirenz	Merck & Co. (USA)	Nov/2006
6	Tenofovir	Gilead Sciences (USA)	Apr/2007
7	Tenofovir	Gilead Sciences (USA)	Aug/2008
8A	Raltegravir	Merck & Co. (USA)	Sep/2010
8B	Atazanavir	Bristol-Myers Squibb (USA)	Sep/2010

This data was complemented by primary data obtained from 26 semi-structured and exploratory interviews[5] with academics, politicians, lawyers, activists and businesspersons

[5] The choice for using both semi-structured and exploratory interviews is justified by several variations in the circumstances in which interviews took place, such as the background of the person interviewed, the time available for the interview and personal knowledge of the subject.

familiar with the Brazilian experience in price negotiation for ARVs. The selection of the first experts to be interviewed was based on online research. Furthermore, we also used a 'snowball sampling' technique, asking interviewed people to give referrals to other possible subjects. These interviews were conducted in Portuguese, between January and March 2012. Additional primary sources were also used, such as personal communication (via e-mail) with personnel of both STD/AIDS Department and Department of Science, Technology and Strategic Resources at MoH and Data requested via the 'Portal for Access to Public Information'[6], available at http://www.acessoainformacao.gov.br/.

After summarizing the interview results, we also submitted an online survey to all the interviewed subjects to reduce the importance of personal opinion and to obtain a greater level of generalization. The rate of response was 21 out of 26 (81%).

4.2. Price negotiations as a process within a complex system

Though price negotiations are bilateral in principle, in practice they are actually a multi-player game whose outcomes emerge through strategic play within a complex system as shown in Box 1.

There are two loose coalitions around the public agency of the developing country and the pharmaceutical MNE respectively. For instance, in the Brazilian case, one coalition comprises MoH supported by state-owned laboratories, notably Farmanguinhos, a few local companies, and Indian generic manufacturers. MoH's bargaining strength is built upon the technological capabilities in fine chemicals accumulated at Farmanguinhos and local firms.

[6] This portal provides general data on financial expenditures and contracts, programmes, actions, projects and other public works at the city, state, and national levels.

Indeed, all the indigenous companies that support both MoH and Farmanguinhos, that is Cristália (episodes 3A, 5, 6, 7), Nortec (episodes 3B, 6, 7, 8A, 8B), Blanver (episodes 5, 6 and 7), Microbiológica/Genvida (episode 3C), and Globe Química (episode 5) benefited from technological transfers from CODETEC in the past.

The other coalition revolves around pharmaceutical MNEs and their governments. The bargaining strength of the MNEs rests upon the ability of their home governments to inflict costly reprisal whenever there is a conflict of interest. For example, in 2005 (during episodes 3A, 3b and 3C) the US Government threatened Brazil, using its 'Special 301 Report' to impose trade sanctions against Brazilian exports and to remove preferable trade partner status (Galvão, 2002; Love, 2008; Nunn, 2009). Such pressure may make emerging country actors fear that a CL may provoke MNEs to seek a more business-friendly legal climate elsewhere and lower the flows of foreign direct investment, trade and technology transfer.

Tensions between the two coalitions can be attenuated by other sectoral actors. For example, when international pressure is too strong, then the Ministry of Development, Industry and Trade (MoDIT) may put pressure on the MoH against CL. In Brazil, MoDIT is in charge of the country's innovation policy and it sees CL as an impediment to the creation of an 'innovation-friendly' environment. Moreover, MoDIT is under pressure from other economic sectors that believe that CL may cause loss of exports and/or foreign investments. The outcomes of the price negotiations are presented in Table 3. Out of the 14 episodes of price negotiations, 1 was a failure (i.e. 3B), 10 led to price discounts (i.e. 1A, 1B, 2A, 2B, 2C, 3A, 3C, 4, 6, 7), 2 led to public-private partnerships (PPP) through licensing (i.e. 8A, 8B) and 1 triggered a CL (i.e. 5).

Box 1:
Summary of actors' involvement in price negotiations (besides MoH and MNEs)

Actor/Episode	1A, 1B	2A, 2B, 2C	3A	3B	3C	4	5	6	7	8A, 8B
MoDIT	Not involved	Not involved	Took over the negotiation to avoid CL	Took over the negotiation to avoid CL	Took over the negotiation to avoid CL	Not involved	Did not oppose to CL	Did not oppose over rejection of patent claim	Did not oppose over rejection of patent claim	Co-sponsor of PPPs for local production
International Generics Suppliers	Supply of small quantities for 'experimental use'	Supply of drugs until local production commences in case of CL	Supply of drugs until local production commences in case of CL	Supply of drugs until local production commences in case of CL	There was no generic available for imports	There was no generic available for imports	Supply of drugs until local production commences in case of CL	There was no generic available for imports	There was no generic available for imports	There was no generic available for imports
Local Firms	Not involved	Not involved	Cristália would supply of API under PPP in case of CL (16 months to commercial scale)	Nortec would supply of API under PPP in case of CL (14 months to commercial scale)	Genvida-Microbiológica would supply of API under PPP in case of CL (12 months to commercial scale)	Not involved	Blanver, Globe Química and Cristália would supply of API under PPP in case of CL	Blanver, Cristália and Nortec would supply of API under PPP	Blanver, Cristália and Nortec would supply of API under PPP	Technology for API production to be transferred to Nortec within 5 years
Public Labs	Reverse engineering by Farmanguinhos (process in pilot scale already developed).	Reverse engineering by Farmanguinhos (process in pilot scale already developed).	Reverse engineering by Farmanguinhos (process in pilot scale already developed). Formulation and distribution in case of CL.	Reverse engineering by Farmanguinhos (process in pilot scale already developed). Formulation and distribution in case of CL.	Formulation and distribution in case of rejection of patent claim (reverse engineering of process yet to be developed)	Formulation and distribution in case of CL. (reverse engineering of process yet to be developed)	Reverse engineering by Farmanguinhos (process in pilot scale already developed). Formulation and distribution in case of CL.	Formulation and distribution in case of rejection of patent claim (reverse engineering of process yet to be developed)	Formulation and distribution in case of rejection of patent claim by FUNEDE and LAFEPE (reverse engineering of process yet to be developed)	Technology for drug formulation to be transferred to Farmanguinhos and LAFEPE within 5 years
Foreign Government	Strong opposition from US Government	No opposition due to Doha Declaration	Strong opposition from US Government	Strong opposition from US Government	Strong opposition from US Government	Not involved	Not involved	Not involved	Not involved	Not involved

Table 3
Summary of the negotiation episodes (prices in US$)

Episode	Drug	Initial Price	Final price after negotiation	Lowest price of patent holder (A)	Price of cheapest imported generic version (B)	Price if locally produced	Final price discount achieved	Final price relative to A	Final price relative to B	Other concessions
1A	Efavirenz (200 mg)	2.05	0.84	0.46	0.44	1	-59%	1.84	1.9	
1B	Nelfinavir	1.07	0.64	0.74	0.42	0.6	-41%	0.86	1.52	
2A	Efavirenz (600 mg)	2.1	1.59	0.95	1.27	0.87	-24%	1.67	1.83	
2B	Lopinavir + Ritonavir	1.5	1.3	0.23	0.9	0.68	-13%	5.7	1.91	
2C	Nelfinavir	0.52	0.47	0.26	0.31	0.53	-10%	1.81	1.51	
3A	Lopinavir + Ritonavir	1.17	0.63	0.23	0.72	0.41	-46%	2.76	1.54	
3B	Efavirenz (600 mg)	1.59	1.59	0.95	0.92	0.87	0%	1.67	1.83	
3C	Tenofovir	7.68	3.8	0.57	1.00[1]	*	-51%	6.7	3.8	
4	Atazanavir (200mg)	3.13	3.04	0.48	**	n/a	-3%	6.28	n/a	
5	Efavirenz (600 mg)	1.59	-	0.65	0.46	0.6	-	-	-	CL
6	Tenofovir	3.8	3.25	0.57	0.42[2]	*	-14%	5.73	7.83	
7	Tenofovir	3.25	2.54	0.57	0.42[2]	*	-22%	4.48	6.12	Patent rejection and PPP
8A	Raltegravir	8.04	7.53	0.93	**	*	-6%	8.14	n/a	PPP and Voluntary license
8B	Atazanavir (200mg)	1.98	1.85	0.68	0.48[1]	*	-7%	2.73	3.83	PPP and Voluntary license
	Atazanavir (300mg)	3.58	2.8	1.13	0.69[1]	*	-22%	2.48	4.08	

* There was no cost estimation for local production.

** There was no generic available for imports

[1] Generic manufacturers were unable to export to Brazil due to contractual arrangements with the patent holder

[2] Generic manufacturers were unable to export to Brazil due to lack of regulatory approval by local authorities.

4.3. From catch-up to access via price negotiations

Reorganizing the information in Box 1 and Table 3, we derive Table 4, which shows that even basic catch-up or absorptive capacity can improve access.

Table 4
Final prices relative to the most affordable generic alternative and small-scale local capacity

Episodes wherein reverse engineering had not been carried out	Final price relative to the best international price	Episodes wherein reverse engineering had been carried out	Final price relative to the best international price
3C	3,8	1A	1,9
		1B	1,52
4*	6,28	2A	1,83
		2B	1,91
6	7,83	2C	1,51
		3A	1,54
7	6,12	3B	1,83
Average	6,01	Average	1,72

In an extensive survey of the literature on the use of CL in price negotiations, Ramani and Urias (2015) highlight that local technological capabilities and import possibilities have an important influence on outcomes of price negotiations evoking CL. In episodes 3C, 4, 6, and 7, local manufacturing capacity posed a challenge by its total absence. Furthermore, Brazil could not import the drug from third parties even if a CL had been granted (See Table 3, notes 1 and 2). However, the MoH was able to negotiate discounts in all these cases. In episodes 3C, 6, and 7, a local public-private consortium announced that it could manufacture Tenofovir within 12 months (see Box 1), even though there had been no previous reverse engineering effort. Therefore, what seems to matter is not only actual technological and manufacturing capabilities, but also the potential for building these, as suggested by a former Director of STD/AIDS Department, who led three price negotiation episodes:

'*The simple fact that Brazil masters the technology and knowledge necessary for API and drug production has resulted in price reductions. Actually, the patent holder may reduce its*

prices just to make the local production less attractive and, therefore, avoid the creation of local productive capacity.' (Interview with STD/AIDS Department at MoH[2]).

Table 4 also illustrates how investment in public R&D in the 1980s, coupled with application of TRIPS flexibilities, led to catch-up and better access to ARVs in the 2000s. Prices were relatively lower for drugs wherein the technological capabilities had been previously built by local actors. MoH paid, on average, six times the lowest international price for the drugs on which no reverse engineering effort had been carried out. Moreover, the impact on access was higher when technological capabilities for production on a small scale were already developed, as MoH was able to negotiate better prices – on average, 1.7 times the lowest international price (i.e. Efavirenz (1A, 2A, 3B); Nelfinavir (1B, 2B); and Lopinavir (2C, 3A)). This was possible because, in 2001, MoH authorized Farmanguinhos to use the 'Bolar exemption' to reverse engineer the production technology of these three APIs to strengthen its position in the negotiation with pharmaceutical MNEs (Cassier and Correa, 2008). The existence of technological capabilities for reverse engineering a given drug means that local production can commence in less time and, therefore, increases the country's bargaining strength in the negotiation as explained by an interviewee.

'*The issue of technological capacity is complex. Brazil does have technological capacity to produce ARVs, including APIs. However, there are many steps involved, such as drug deformulation, development of an alternative synthesis route, regulatory approval to ensure that the generic drug has the same quality and efficiency, as does the original drug. This process is not straightforward. This is not like an electrical power that you just have to plug into the wall socket. The capacity building takes time.*' (Interview with Local Company [1]).

4.4. From CL to catch-up and access

The first – and only – CL was issued in 2007 after failing to achieve any significant price reduction for Efavirenz with the patent holder (episode 5). The drug was initially imported from Indian suppliers, but local production had to be arranged, because the Brazilian IPR law allows parallel imports only for 12 months after a CL. Then, a public-private consortium was set up, wherein three local private enterprises were responsible for the development and production of the API – Cristália, Nortec and Globe Química, while two state-owned laboratories (LAFEPE and Farmanguinhos) were in charge of the formulation and distribution. This public intervention to foster local production of ARVs was an important policy window for accumulation of technological capabilities necessary for developing a synthesis route for Efavirenz and to scale up production to a commercial scale.

While CL can boost catch-up it may not always improve access. For example, MoH granted a CL for Efavirenz in 2007 and the local production of the drug started in 2009. Since then, the price of the local generic manufactured version has not changed while the lowest international price has reduced by 77% (see Table 5). The CL allowed MoH to save around US$103.5 million of the resources otherwise needed for the period 2007–2012 (Correa, 2015). If only imports had been considered, then MoH could have saved approximately 25% more. Therefore, even though CL improved access to the drug, such improvement was less than it could have been, due to the lack of competiveness of local producers.

Table 5
Price comparison of Efavirenz after CL in Brazil (US$ 2007 constant)

Year	Best generic price[1]	CL price (Imported)[2]	CL price (Farmanguinhos)[2]
2007	0.47	0.46	
2008	0.42	0.30	
2009	0.27		0.69
2010	0.14	0.14	0.69
2011	0.14		0.69
2012	0.12		0.69
2013	0.11		0.69

Sources: [1] MSF; [2] MoH of Brazil, STD/AIDS Department

4.5. Post-CL PPP: another pathway for catch-up and access

From 2005, when MoH was considering CL for three ARVs (See Box 1, episodes 3A, 3B, 3C), the PPP model was viewed as the solution that would be implemented if ever a CL was issued. However, a PPP came to be formed with three local private enterprises and two state-owned laboratories only in 2007 when a CL was actually issued after episode 5 and it proved to be successful. With this, came policy learning of PPP management induced by CL issuance and the PPP model was extended for a wider range of drugs leading to further catch-up[1]. This was confirmed by a MoH staff member directly involved with these partnerships:

"The model of CL for efavirenz was the base, a kind of pilot project, for the existing partnerships for technological transfer supported by the Ministry of Health." (Interview with MoH [1])

In 2009, 11 PPPs for local production of high-cost drugs – including their APIs – were launched, with assured procurement by MoH. These included, two consortia of local companies (Blanver, Nortec and Cristália) and state-owned laboratories (FUNED and LAFEPE) for local production of a generic Tenofovir, only a few months after the Brazilian Patent Office overruled

[1] Officially, these PPP are called 'Partnerships for Productive Development', or PDPs in the Portuguese acronym.

its patents (episode 7). Finally, episodes 8A and 8B resulted in PPPs as part of a set of institutional changes implemented by both MoH and MoDIT aimed at making voluntary license agreements a more attractive alternative to pharmaceutical MNEs. The 2009 policy window of opportunity for catch-up in form of PPPs also included national R&D programmes and consortiums, international technology cooperation, and promotion of national champions (Del Campo, 2016)

Presently there are 83 ongoing PPPs for local production of 38 synthetic drugs, 24 biologicals (including biosimilars and vaccines) and 21 medical devices (Ministry of Health of Brazil, 2016). As of march 2017, 35 consortia were already supplying the respective product to MoH, generating a total savings of US$ 1,5 billion in drug acquisitions for the public health system (Ministry of Health of Brazil, 2017).

Again, though PPPs are meant to improve access via catch-up, they can also backfire, as illustrated by the case of Tenofovir after episodes 6 and 7. In 2011, the first batch of Tenofovir supplied to MoH by the two public-private consortia mentioned above was eleven times more expensive than the lowest international price. In addition, after two years, these consortia reduced the price by 5%, while the lowest international price fell 30% during the same period. Thus, as in the case of the local generic Efavirenz, local production of Tenofovir resulted in a suboptimal access to the drug as compared to importing generics.

5. Discussion of results

We discuss the results at two levels, in terms of what they add to our understanding of the nature of the reciprocity between catch-up and access; and also inferences that can be made from the Brazilian case study on effective policy instruments to attain both. Our arguments are summarized in Figure 3, which also shows how the case study refines the preceding theoretical constructs (Figures 1 and 2).

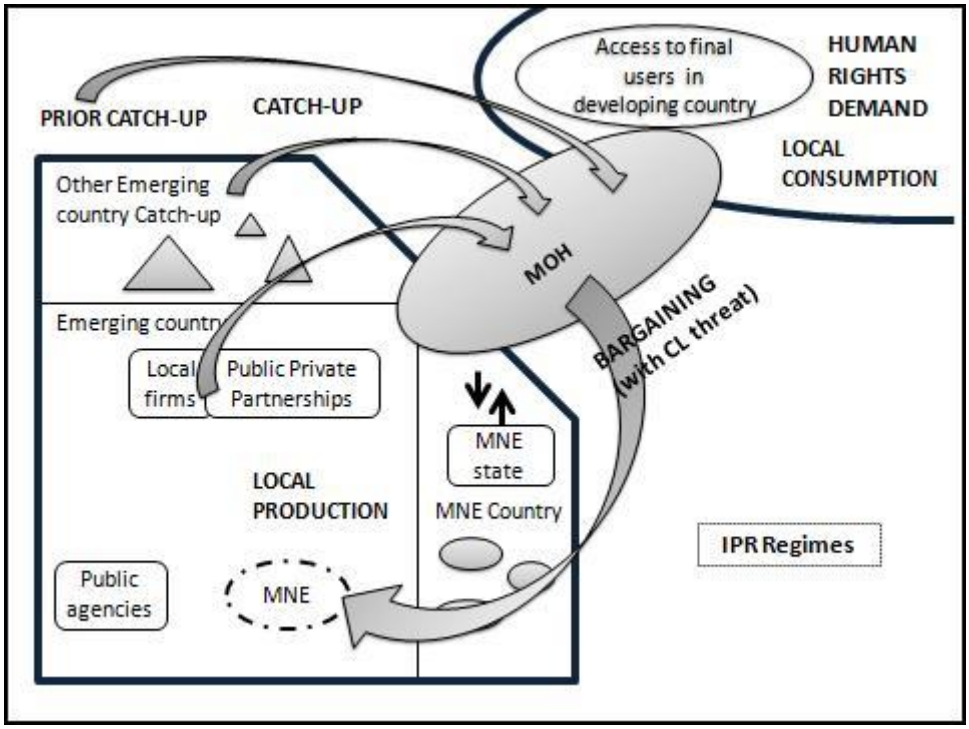

Fig. 3. Interrelationships between catch-up in pharmaceuticals and access to drugs

There are five main inferences on the reciprocity between catch-up and access. First, catch-up in the manufacturing of an essential commodity need not automatically lead to better access, but public agencies can play a crucial in creating such synergies (e.g. MOH as connector in Fig. 3). In the economic growth literature, it has been repeatedly pointed out that growth benefits may not trickle down to improve poverty alleviation unless the system, especially the state and public agencies, nurture structural changes and capability building for pro-poor growth (Kakwani et al., 2000; Nussbaum and Sen, 1993). Similarly, for catch-up to improve local access to essential commodities, going beyond markets, there is a need for public actor bridging of the production and consumption sub-systems. In the Brazilian case, the MoH served that role. Furthermore, while the literature mainly covers catch-up triggers in the form of novelty in the innovation system, either as a new technology, an entrant, a new macroeconomic or industrial policy or some form of external shock that directly impacts local firms, the Brazilian experience

demonstrates that it is possible for public agencies focussing on access rather than on knowledge or firm capabilities enhancement to do the same.

Second, with respect to an essential commodity like medicines, sectoral catch-up can have a strong inter-temporal relationship with access (See arrow from 'Prior Catch-up' in Fig. 3). Past catch-up, even if aborted, can nurture better access in the future. Similarly, present need to improve access can trigger future catch-up. The Brazilian industrial policy implemented since the 1970s to build technological and innovation capabilities was directly responsible for the success of the Brazilian health policy to tackle the HIV/AIDS epidemics, even though there is a consensus that this policy failed to build a competitive pharmaceutical industry and reduce trade deficits in pharmaceuticals. Skills in fine and organic chemistry accumulated locally, notably at Farmanguinhos and in a handful of private companies in the 1980s, created absorptive capability and prior knowledge bases for the local production of ARV drugs. Furthermore, CL enabled accumulation of technological capabilities for API and formulation of efavirenz, only because of absorptive capabilities developed over prior aborted catch-up.

Third, the synergies or trade-offs between catch-up and access are dependent upon both exogenous or relatively unchangeable systemic features (e.g. IPR in Fig. 3) as well as actor-strategies (e.g. of MNEs, local firms, MOH etc. in Fig. 3) An example of the former is international product accessibility under TRIPS and the latter is organisational learning of firms and public agencies.

Catch-up of other emerging countries can boost access, but only if the IPR regime permits it. The MoH of Brazil could issue a CL and import Efavirenz from India, only because India had made full use of the transitional period allowed by TRIPS to developing countries. Therefore, generic versions of drugs developed before 2005, such as Efavirenz, are available for exports in India (Babovic & Wasan, 2011). However, drugs developed after 2005 are subjected

to patent protection in India, thus their exports would demand a CL under the Paragraph 6 system of TRIPS Agreement. The Paragraph 6 system allows producers to export drugs produced under CL to countries without technological capabilities. However, very few generic manufacturers regard such a system as an useful option, because it involves enormous procedural challenges and hence not considered worthwhile (Gehl Sampath, 2005). Therefore, the use of a CL – or of the threat of issuing one – is not only limited by the existing local technological capabilities but also by importing possibilities under the present IPR regime. This is a challenge that must be addressed to promote both catch-up and access.

Organisational learning is an important source of catch up. Individual firms require considerable time to build and accumulate technological capabilities and the associated organizational learning. Effort needs to be invested to acquire tacit knowledge that underlies effective performance (Bell and Pavitt, 1993; Kim, 1999; Lall, 1992). Therefore, given the long-term nature of technological capabilities, for an industrial policy to be a mechanism to promote change, it is necessary to have in place a stable institutional framework to facilitate long-term planning and continuous private investment (Chang, 1994). For this purpose, PPPs can be an effective instrument.

In Brazil, PPPs are driving several trends towards the accumulation of technological capabilities in biotechnology. Local companies such as Cristalia, Orygen, Bionovis, Libbs, decided to establish their own in-house R&D programmes to develop biosimilars. To accelerate this process, these companies are collaborating closely with foreign organizations to sources knowledge and technology know-how (see Table 6). These trends are similar to those in India (Ramani and Guennif, 2014; Sampat, 2010) and South Korea (Lee and Kim, 2010). Such accumulation of technological capabilities through international sourcing seems essential to improve access to the respective drugs. This is because, unlike the case of Tenofovir and other

small molecule drugs, there are no low-price international suppliers of biosimilars. Thus, a competitive PPP is necessary to break the existing monopolies to reduce prices and facilitate better access.

Table 6

Access to foreign know-how in biotechnology

Local Company	Foreign Partner	Biosimilar drugs
Cristália	Alteogen (South Korea)	Etanercept; Trastuzumab
Libbs	Mabxience (Spain)	Adalimumab; Bevacizumab; Etanercept; Rituximab; Trastuzumab
Bionovis	Janssen-Cilag (USA)	Infliximab
	Merck Serono (Germany)	Adalimumab; Etanercept; Rituximab; Bevacizumab; Trastuzumab
Orygen	Alteogen (South Korea)	Rituximab; Infliximab; Bevacizumab

Indeed, PPPs are regarded as the main solution for the present shortages of biopharmaceuticals in the Brazilian health care system in many other chronic diseases (Moura, 2016). Furthermore, the role of PPP and government procurement in catch-up is likely to increase as more new drugs emerge as biopharmaceuticals, as they are much more complex than ARVs or other conventional chemical entities, more difficult to replicate, and at the same time, claim a rising share in the public healthcare expenditure (Tanaka and Amorim, 2014). However, to realise this potential from local firms and PPPs, it is necessary to implement an environment that builds international competitiveness for forging ahead.

Fourth, under complex systemic settings with actor and actor-group interactions and struggle, the impact of instruments used to ensure access can be nuanced and not clearly favour either access or catch-up (see Table 7). In turn, with respect to the ongoing debate about whether promoting catch-up in the pharmaceutical sector is likely to be harmful for access to medicines,

or whether the two can be complementary, the table indicates that neither argument can be generalized. Evaluation has to occur on a case by case basis even within the same country.

Table 7
Drivers and Impact of Price Negotiations on Catch-up and Access

Drivers of pathway	Public agency pathway	Bargaining Outcome (Episodes)	Impact on access	Impact on catch-up
Prior investment in basic absorptive capabilities	Price negotiations (neither CL nor importing generic was possible)	Price discounts from MNE (3C,4, 6, 7)	Positive	Incremental
Prior investment in reverse engineering capabilities with institutional support	Price negotiations	Price discounts from MNE (1A, 1B, 2A, 2B, 2C, 3A	Positive (could have been more with CL)	Incremental
Prior investment in reverse engineering capabilities with institutional support	Price negotiations	Status-quo (3B)	None	Incremental
Prior investment in reverse engineering capabilities with institutional support	Price negotiations	Compulsory licensing (5)	Positive (could have been more with import of generics)	Significant
Policy learning from compulsory licensing	PPP with MNEs (neither CL nor importing generic was possible)	MNEs agree to voluntary licensing to avoid CL risk (8A, 8B)	Positive	Significant
Policy learning from compulsory licensing	PPP with local firms and labs	Local production increases and diversifies with catch-up	Positive (could have been more with import of generics)	Significant

Fifth, lack of access can be a necessary condition to trigger catch-up, though it need not be sufficient. In order to ensure access to essential commodities like medicines, countries with the requisite resources and capabilities engage in gradual build-up of industrial capabilities. However, if the need is urgent, alternative corridors are available, with one of them being CL. The rationale for the state's choice to explore the alternative pathway can be understood in terms of Hirschman's (1963) framework of 'Exit and Voice'. There can be exit from standard pathways if the concerned stakeholders have a voice. To have a voice in our context means:

(i) *Access to medicines must be a core criterion to evaluate industry performance on the supply side:* Public decision makers must accept only a narrow latitude in standards of performance. In other words, whenever the catch-up strategy does not improve access, it must be revisited. Synergy between access and catch-up requires an enabling environment, a political will to invest in capability building and the local firms have the absorptive capacity.

(ii) *Lack of access must trigger strong public concerns on the demand side:* On the user/demand/consumer side, whenever the lack of access is intolerable, it must trigger visible and impactful protests, complaints, and criticism demanding efficiency. And the political will of the public agencies must be aligned to the demand for access.

In the Brazilian case, both conditions were satisfied. Non-universal access to ARVs was not an option either for the public or the MoH and the latter was able to mobilise the needed resources to implement the alternative.

Once initiated, CL can contribute to technological catch-up via two pathways: (i) through technological capabilities build-up; (ii) through policy learning that comes from the efforts to issue and implement the CL through PPP, as highlighted by the Brazilian case study.

Sixth, politics matter. The impact of access drivers on catch-up may be obstructed by power struggles between actors, or simply politics. Whenever the alternative pathway is chosen for catch-up, a bargaining process is set into motion between actor-groups. Improved access may emerge with catch-up only if such an outcome is compatible with systemic configuration. As Ruttan and Hayami (1984) suggest, this could be the existing configuration of power distribution among vested interest groups and the local cultural tradition and ideology, all of which make the associated institutional arrangements acceptable to all stakeholders.

In the Brazilian case, there was tension between the coalition led by the MoH and the other supported by the US Government. The pressure of possible retaliation was strongly indicated in episodes 3A, 3B and 3C. Thus, the first best solution for MoH was to accept price reductions instead of issuing CLs. In these episodes, both the MoDIT and the US Government

were actively mobilized by pharmaceutical MNEs to put pressure on MoH against CL. As presented in Table 1, a strong patent system is considered important for triggering catch-up. Therefore, this tension between MoH and MoDIT is a consequence of a wide-spread assumption that the use of compulsory licensing will hurt future innovation and, subsequently, hinder future catch-up attempts. However, research findings suggest that such an assertion that CL harms innovation is probably wrong (Baten et al., 2017; Chien, 2003).

5. Conclusion

The literature on sectoral catch-up does not address if and how local users/consumers will have better access to the final goods, seeming to assume that it will somehow happen through trickle down. Although this is not a major concern when analysing catch-up trajectories of typical consumer goods, we point out that access to essential commodities, such as medicines, should not be left to market forces alone. Furthermore, even the broader literature on the economic, social, and environmental trade-offs of technological change does not address the fact that development trajectories and the underlying market mechanism often fail to provide access to essential goods to the population (see Massa (2015) for review). Therefore, our objective was to explore the possible inter-temporal impacts of catch-up in pharmaceuticals on access to medicines and vice versa. The Brazilian success story in making with ARVs available free of charge to all HIV/AIDS patients through prices negotiations with patent holders lent itself as an ideal case study to draw insight on the research query, because it was intimately linked to prior catch-up by local firms and those from other emerging countries. A scoping review of the literature on catch-up was complemented by a detailed study of the Brazilian catch-up in ARVs production and price negotiations with patent holders between 2001 and 2010. The evidence provided a better understanding of the mechanisms, which initiate and direct a development

trajectory that tries to reconcile access to medicines with accumulation of industrial capabilities in pharmaceuticals.

Our findings indicate that catch-up is neither necessary nor sufficient for improving access, but it is favourable. The existence of absorptive capacity for reverse engineering can be enough to improve access through price negotiations. Moreover, when local actors master the savoir-faire to produce generic versions of the drug, then price discounts are likely to be greater.

It does seem that ultimately only forging ahead can lead to sustainable and large-scale access. An aborted catch-up experience may improve access in certain specific contexts, such as in price negotiations of patented drugs. However, by definition, such an experience means that companies have failed to reach the technological frontier of the industry. At the same time, the impact of investment in catch-up on access to medicines will take time to materialise, as in the initial learning stages, local actors will operate below the international technological frontier. On the other hand, it is imperative that policy and market mechanisms are in place to reduce the risk of an eventual negative impact on access to medicines due to prolonged inefficiency of local actors. This leads to three recommendations for emerging countries.

First, emerging countries with basic technology and innovation capabilities ought to invest in closing the knowledge gap in essential drugs production. The Brazilian case study indicates that given the paramount role of local technological capacity in bargaining with patent holders, public policy should support technological capacity building. This is even more critical for biopharmaceuticals, as these products face lower competition even after patent expiration due to their technological complexity and regulatory challenges. Countries with no previous capabilities should also invest in creation of absorptive capacity and reverse engineering skills, as these two can already be sufficient to obtain more affordable prices, when negotiating prices of patented drugs with research-based pharmaceutical MNEs.

Second, for emerging countries, there can be real trade-offs between catch-up and access. As the Brazilian case study amply illustrates, price discounts by MNEs for their patented drugs improve access, but they slow down catch-up, because then it becomes even more challenging for local firms to become equally competitive. Similarly, following a CL or initiation of a PPP, while there will be catch-up, access might be improved more by importing cheap generics than by procuring costlier locally produced drugs.

Third, especially for emerging and developing countries, a strong public sector would be a good source of bargaining power. It is not necessary for the public sector to undertake manufacturing of drugs, this can be left to the private sector. However, the public sector must have state of the art technological and innovation capabilities so that it can transfer technology to local firms whenever necessary. Thus, emerging countries must invest in the development of well performing public sector entities to close the knowledge gap in drugs production for their important disease burdens.

Our paper points to at least three research avenues for a broader and deeper understanding of the role of policy instruments to promote access and their possible synergy with catch-up.

The present evidence on catch-up and access inter-relationships in other emerging countries and other knowledge intensive industries is very mixed. In other words, further research is necessary to investigate the interdependencies between technological catch-up and access in other countries and sectors, as well as the roles played by IPR in these processes.

India is hailed as a successful catch-up example in pharmaceuticals, but despite lower prices of medicines as compared to the international prices, at least 50% of the Indian population is not able to access essential medicines (Maiti et al, 2015). On the other hand, South Korea has successfully combined a universal immunization of infants programme with technological catch-

up on rDNA hepatitis B vaccine. The Korean strategy was to gain access to foreign knowledge and technology through joint ventures, in combination with export incentives to ensure international competitiveness of the local product (Lee & Kim, 2010).

Similarly, in the knowledge intensive industry of genetically modified (GM) seeds, in India, joint-ventures with MNEs and licensing of IPR has resulted in both catch-up, exports and large-scale access to GM cotton (Thutupalli and Iizuka, 2016; Glover et al., 2015). However, in Argentina, absence of IPR protection accelerated access to GM soya, but local firms failed to accumulate technological capabilities in plant biotechnology (López, 2010).

The contextual politics and their influence on the patterns of price negotiations and CL usage also call for a deeper examination. For instance, a number of other countries like Ecuador, Thailand, and Malaysia have issued CL in the name of access, and others like India and Colombia have evoked the threat of using it and their comparative experience can be analysed. Further, the role of instruments to improve access to patented innovations evoked in this paper such as price negotiations, voluntary licenses and PPPs can also be examined in other essential commodity sectors, with respect to their impact on catch-up and access.

To conclude, catch-up, access improvement and price negotiations are processes that involve multiple and parallel discourses within a complex system, which taken together impact both catch-up and access. There can be positive as well as negative externalities due to unforeseen outcomes arising from interaction of different policies. This can give rise to a systemic risk such that improved access is not embedded effectively in the catch-up trajectory. To minimize this risk, emerging countries must continue to invest in technology catch-up and also pay attention to governance and the coordination between different national policies such as health and industry.

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