Medicines under Exclusivity Situation Funded by the Ministry of Health: ANALYSIS OF THE PATENT SITUATION AND PUBLIC PROCUREMENT

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Rio de Janeiro

1ST Edition

A publication of

Ministério da Saúde
FIOCRUZ
Fundação Oswaldo Cruz

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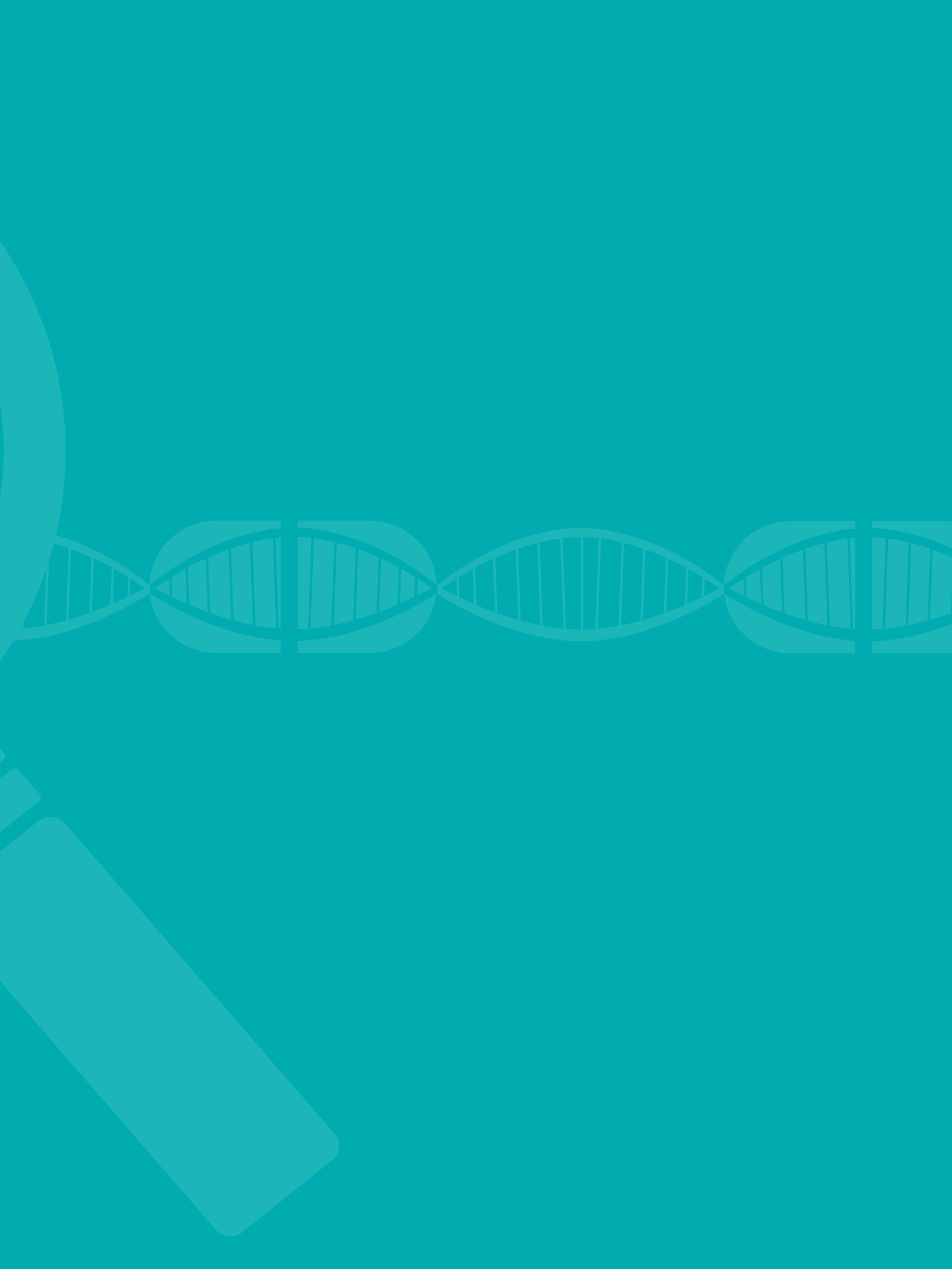

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This research is part of a series of arguments from accessibsa: Innovation & Access to Medicines in India, Brazil & South Africa, a project coordinated by Achal Prabhala and supported by the Shuttleworth Foundation.

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This publication is an English translation of the original version in Portuguese called *Medicamentos em situação de exclusividade financiados pelo Ministério da Saúde: análise da situação patentária e das compras públicas* published in December 2018.

Cataloguing

Fundação Oswaldo Cruz
Instituto de Comunicação e Informação Científica e Tecnológica em Saúde Biblioteca de Saúde Pública

M489m Medicines under exclusivity situation funded by the Ministry of Health: analysis of the patent situation and public procurement / Gabriela Costa Chaves, et al. – Rio de Janeiro : Fiocruz , ENSP, 2019.
200 p. : tab.

Translation from: Medicamentos em situação de exclusividade financiados pelo Ministério da Saúde: análise da situação patentária e das compras públicas.

ISBN: 978-85-9511-032-8

1. Intellectual Property of Pharmaceutic Products and Process. 2. Patents. 3. Drug Industry. 4. Public Sector. 5. Group Purchasing. 6. Pharmaceutical Services. 7. Right to Health. 8. Unified Health System. 9. Access to Essential Medicines and Health Technologies. I. Chaves, Gabriela Costa. II. Vieira, Marcela Cristina Fogaça. III. Costa, Roberta Dorneles F. da. IV. Vianna, Mariani Nunes Sadock. V. Title

CDD - 23. ed. – 615.19

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About the Project:
accessibsa: Innovation & Access to Medicines in India, Brazil & South Africa:

accessibsa is a tri-continental project enabled by a fellowship from the Shuttleworth Foundation. Our work expands access to life-saving medicines for those most in need. We make arguments for intellectual property systems that support public health — with safeguards for both sovereign human rights and genuine pharmaceutical innovation. For more, please see accessibsa.org

Acknowledgments

To Walter Britto Gaspar for the collaboration at the initial stages of the patent search, to Rafael Almeida da Silva for the collaboration in the data collection of public procurement and market authorization (registration), and, to Vitor Ido for the collaboration in the chapter about legal aspects.

To the experts that, during the discussions in the meeting on July 23, 2018, provided important comments and reflections that contributed to the improvement of this report.

We dedicate this report

To Inez Ribeiro Costa (*in memoriam*) and to Rosa Regina Dorneles Ferreira da Costa (*in memoriam*) for the lessons of love, care and resilience.

To Ana Paula Jucá Silva (*in memoriam*) for her kindness and contribution to public health, especially for her work dedicated to the promotion of access to medicines.

Summary

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List of acronyms

ADI	Direct Action of Unconstitutionality
Anvisa	Brazilian Health Regulatory Agency
APAC	Authorization of High Complexity Procedure
API	Active Pharmaceutical Ingredient
ARV	Antiretroviral
CAS	Chemical Abstracts Service
CEAF	Specialized Component of Pharmaceutical Services
CESAF	Strategic Component of Pharmaceutical Services
CF	Federal Constitution
CMED	Medicines Market Regulation Chamber
Conitec	National Commission for Health Technologies Incorporation
DAA	Direct-Acting Antiviral
Datasus	Information Technology Department of SUS
DTG	Diagnostic and Therapeutic Guidelines
E-sic	Citizen Information Service Electronic System
EPO	European Patent Office
FDA	Food and Drug Administration
IBGE	Brazilian Institute of Geography and Statistics
INN	International Nonproprietary Name
INPI	National Institute of Industrial Property
IPCA	Extended National Consumer Price Index
IPEA	Institute for Applied Economic Research
IUPAC	International Union of Pure and Applied Chemistry
LAI	Access to Information Law
LPI	Industrial Property Law
MPOG	Ministry of Planning, Budget and Management
PAHO	Pan American Health Organization
PCDT	Clinical Protocols and Therapeutic Guidelines
PDP	Partnership for Productive Development
PL	Draft Bill
RDC	Resolution of the Board of Directors
RENAME	National List of Essential Medicines
SIASG	Administration of General Services Integrated System
SIOPS	Information system on public health budgets
SISG	General Services System
STF	Supreme Federal Court
SUS	Unified Health System
TRIPS	Agreement on Trade-Related Aspects of Intellectual Property Rights
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WTO	World Trade Organization

Executive Summary

The Brazilian Unified Health System (SUS) is committed to ensuring universal access to medicines. Pharmaceutical services are part of the actions that promote the integrality of access to health in the country, guaranteed by the Federal Constitution. Increasingly, pharmaceutical spending has taken a leading role in health spending as a whole. Although one of the aspects that increase these expenses is related to the increase in the number of individuals treated, on the other hand, it can also mean an increase in expenses due to the incorporation of high-cost specialty medicines, driven by the possibility of commercialisation under monopoly. Medicines under exclusivity can be caused by the patent system and, in the absence of competition, a company has greater power to establish the price of its product despite measures taken to regulate prices.

SUS is marked by a history of under-funding, which has recently deepened with the approval of Constitutional Amendment 95/2016 aimed at freezing primary federal expenditures until 2037, thereby further reducing the budgets for the health and education sectors.

In this scenario there is a constant need to search for alternatives that can ensure a more affordable supply of medicines and prevent shortages. The guiding question of our study was to analyse determinants of the exclusivity situation of medicines related to patent protection, based on a list of medicines funded by the Ministry of Health.

Our initial assumptions were that the multiplicity of patent applications for the same active pharmaceutical ingredient (API) generate legal uncertainty and lack of clarity for public procurement in relation to patent monopolies on medicines. This occurs whenever the Ministry

of Health considers conducting competitive bidding processes in public procurement procedures. In addition, the uncertainty generated by the existence of multiple patent applications contributes to the absence of generic products in the Brazilian market even though they are available in the international market.

Our research focused on Group 1 medicines of the Specialized Component of Pharmaceutical Services (CEAF), as they account for a relevant percentage of the expenses with medicines; of antiretrovirals (ARVs), which are part of the Strategic Component of Pharmaceutical Services (CESAF), based on their history of sole source procurement; and cancer treatment medicines, which are also a significant part of public spending and are constantly growing.

From this list of medicines, the study involved four axes of analysis: (a) the identification of medicines in an exclusivity situation from the supply side, (b) analysis of the patent situation of the medicines included in the sample in Brazil, (c) analysis of public procurement of selected medicines and (d) the analysis of legal aspects that may contribute to an exclusivity situation, especially related to the pendency situation of patent applications from a comparative perspective.

The definition of an exclusivity situation from the supply side for selected medicines was the following: an active pharmaceutical ingredient (API) in its different pharmaceutical presentations available in the Brazilian market in December 2016 by a single supplier. The analysis of the patent situation of medicines included in the sample was carried out in three phases: a) identification of international patents and Brazilian correspondents, b) mapping of the status of applications in Brazil for December 2016 and c) analysis of the claims and classification of patents and patent applications (primary and secondary).

In the first section of the results, among the initial selection of 170 active pharmaceutical ingredients, 77 were found to be in an exclusivity situation from the supply side, 21 of CEAF 1A, 15 CEAF 1B, 14 CESAF and 33 cancer treatment. Of these, 74 active pharmaceutical ingredients were selected for a patent search, of which 54 were synthetic and 20 were biological ones.

In our search for patents we found 720 national patent applications (BR) related to 68 active pharmaceutical ingredients. Following a content

analysis, 80 applications were excluded, resulting in a total of 640 applications considered relevant for 68 active pharmaceutical ingredients (47 synthetic and 18 biologic active pharmaceutical ingredients). No patent application was found for 9 active pharmaceutical ingredients in Brazil, indicating that the exclusivity situation was not due to a patent barrier. The average number of patent applications per active ingredient is 7.2 for synthetic products and 16.7 for biological products.

The analysis of patent status was performed for a total of 640 patent applications. For another 6 active pharmaceutical ingredients, the analysis of the status of national applications also indicated that there was no patent barrier in force because they were classified as rejected, dismissed or expired. Considering only patent law monopoly situations, that is to say, those resulting from a patent granted in the country, of the 65 active pharmaceutical ingredients with patent applications identified in Brazil, only 26 had granted status patents and another 6 had expired or had been terminated, indicating that they had patents granted in the country which were no longer in force considering their situation in December 2016. This means that 33 active pharmaceutical ingredients in our sample have never had patent protection in Brazil. In addition to the 9 for which no relevant patent has been identified in Brazil and the other 3 considered as having no patent barrier because of generic production in the country, there were 45 active pharmaceutical ingredients without a "legal" patent barrier in December 2016 among the 77 in an exclusivity situation from the supply side, that is, in 58% of cases.

The results of our research, ranging from the selection of medicines under exclusivity situation from the supply side to the analysis of patent status - covering the identification of national applications, their status and the classification of claims – allowed us to generate strategic information both for the monitoring of pharmaceutical market trends as well as to identify specific policy options to address patent barriers and to promote competition in the context of efforts to increase access to medicines.

Among our findings, we highlight the low number of granted patents (33) when compared to the number of pending applications, which totalled 355 applications; which resulted in a significant number of pending applications, 10 times higher than applications granted. This

situation suggests that multiple patent applications, most of which are pending, may contribute to the exclusivity situation of medicines made available by SUS. CEAF 1A medicines had the highest number of pending patent applications (163 applications).

We analysed the content of 564 applications, out of which 301 applications refer to 47 active pharmaceutical ingredients of synthetic products and 263 to 18 biological products. In total, 174 applications were classified as primary or indicative that they would be primary; and 390 as secondary or indicative of secondary; a ratio of 2.25 secondary applications for every primary. This ratio is higher for chemical ones (2.76) than for biological ones (1.8).

Of the 21 medicines (synthetic products) that had at least one patent granted, only 14 of them were classified as primary, and for 11 of them patents were identified for the active ingredient itself (product) and for 3 process patents (product chemical synthesis) (relative to the active ingredient itself) and process 4 (product chemical synthesis). The vast majority of applications were classified as secondary (221 out of 301), which according to critical literature could not be considered innovative and therefore would not meet patentability requirements.

A high number of patent applications was also observed on biological products, an average of 16.7 applications per active pharmaceutical ingredient. In the analysis of the content of the claims, 94 applications were classified as indicative of primary, while 169 were classified as indicative of secondary, which is a ratio of 1.8 patent applications of secondary relative to primary ones. Only 5 of the biological active pharmaceutical ingredients had patents granted, of which 3 had patents classified as indicative of primary and 2 only as indicative of secondary. Thus, these results seem to indicate a Continued of the strategy of broad patenting in this technology segment, as documented for synthetic products, but with specific peculiarities for biological medicines, such as the patenting of biopharmaceutical-specific amino acid sequences.

Chapter 6 is devoted to SUS pharmaceutical procurement. The procurement analysis of 74 listed active pharmaceutical ingredients funded by the Ministry of Health from 2007 to 2016 (10 years) revealed an estimated total expenditure in excess of BRL 20 billion with values adjusted by inflation according to IPCA of 2016. The estimated spending

in 2016 alone was BRL 3.2 billion.

The share - in terms of procurement values - of the medicines that are under exclusivity from the supply side demonstrate that these procurements account for a significant part of budget of the Ministry of Health. For example, for CEAF medicines, the group responsible for high-cost medicines, the percentage of estimated expenditures for those listed in our research versus total component spending was 0.12% in 2007. By 2016, the same group accounted for 37.3%. It is worth mentioning that this percentage reached its highest value in 2011 when it was more than 50.8% of the established ratio. A 10-year expenditure ranking shows that the highest expenditure was with adalimumab, BRL 5,210,840,577.16, representing 35.1% of total expenditure. We also did a cross-sectional analysis for 2016, and the medicine with the highest expenditure in relation to medicines included in our study was sofosbuvir, R $ 721,617,868.83, about 25% of the total annual expenditure.

We mapped the medicines (CEAF 1A, ARV and cancer) whose patent status of the active pharmaceutical ingredients indicated that there was no patent barrier in December 2016 (including pending applications) or whose granted patent had been classified as a primary process patent or as a secondary patent, indicating a lower risk for the patent to be a barrier to generics. That is, only a primary patent granted to the product was considered as a barrier to eventual use of the generic version in Brazil. In this situation 40 active pharmaceutical ingredients were identified, among the 65 active pharmaceutical ingredients for which patent information was found in Brazil. We identified prices for generic or biosimilar alternatives available in the international market in order to compare with prices in Brazil in 2016 and estimate potential savings if these alternatives were available in the domestic market at the same prices.

For most medicines no alternative versions were available on the international market in 2016 or in the prior year, with the information identified only for 5 active pharmaceutical ingredients (5 medicines). The estimated saving was US $ 220,237,801.61 (approximately BRL 768,409,689.81) in 2016.

Chapter 7 presents an analysis of the legal aspects, addressing some points related to the patent system and the public procurement legislation of medicines that contribute to the exclusivity situation. In relation

to the patent system, Brazilian legislation establishes the payment of compensation to the holder even for acts committed before the patent was granted, and that the amount of such compensation can be quite high in comparison with that of other countries. On the other hand, the Brazilian industrial property law did not adopt measures that could protect eventual potential competitors against abuses committed by patent holders. Thus, we understand that Brazilian law creates disincentives to competition, since it imposes an excessive risk to third parties with respect to acts committed before a patent is granted.

Regarding the legislation on public procurement of medicines, Anvisa emphasised the requirement for market approval (registration) as well as recent changes in regulating exceptional imports of medicines without market approval in Brazil. We concluded that the market approval requirement in Brazil makes it difficult for generic / biosimilar producers that operate in the international market to take part in government procurement processes conducted by SUS. In addition, recent Anvisa regulatory changes prevent procurement of medicines without market approval in Brazil when there is at least one company with market approval in Brazil, making it even more difficult for the use of possible alternatives to increase competition.

Our approach is unprecedented because the initial selection of active pharmaceutical ingredients had as its starting point the identification of those in an exclusivity situation from the supply side. Our patent analysis of active pharmaceutical ingredients sought to go beyond the status identification and included claim analysis, allowing us to have more elements for evaluating whether the exclusivity situation of a product could be explained by a patent barrier. In addition, the breadth of research on patent applications related to 74 active pharmaceutical ingredients of interest to SUS, including international patent applications that do not have a corresponding one in Brazil, is also something not previously explored in literature.

Our final considerations point out the main limitations of our research study, as well as to some changes in the Brazilian pharmaceutical medicines market between the end of our research period (December 2016) and this report's preparation and release (June / July 2018). We believe that, even with all its limitations, the present research study

relates different dimensions that are usually addressed separately, bringing a novel contribution to the field. The discussion of medicines under an exclusivity situation in Brazil is far from exhausted, and our study brings new questions to the debate around the multifaceted field of government procurement of medicines in Brazil.

To conclude, we reflect on our findings that allow us to present some recommendations to the governmental institutions related to both the market strategies adopted by pharmaceutical companies to ensure marketing exclusivity as well as to the public procurement of medicines carried out by SUS, which is currently responsible for the health care of almost 80% of the Brazilian population. This report offers recommendations to the National Institute of Industrial Property (INPI), the National Agency of Sanitary Surveillance (Anvisa), the National Commission of Incorporation of Technologies in SUS, the Ministry of Health, Public and private sector manufacturers, academic institutions, the Government and political actors, and civil society.

1. Introduction

The present study was prepared with the main objective of contributing to a better understanding of the context in which government procurement of medicines occur in Brazil, especially those under the responsibility of the Ministry of Health. We investigated some of the determinants of the exclusivity situation (single source) of medicines in the national market, in an attempt to understand the role played by the patenting dynamics in the pharmaceutical sector.

Assuming that public administration procurement should, as a rule, be carried out by means of a bidding process, which presupposes the existence of different competitors, the study focused on medicines that do not follow this rule because they have only one supplier in Brazil. The situation we call as "exclusivity from the supply side" makes bidding impossible and may result in higher prices due to the lack of competition, placing a heavier burden on the public health system. Thus, we believe that a better understanding of the different elements that can lead to this situation of exclusivity can be useful to improve the processes related to government procurement of medicines, potentially leading to large savings for the public sector and to providing improvements to the public health services in the country.

In a context of chronic underfunding of the Unified Health System (SUS) - aggravated by policies aimed at freezing federal primary expenditures for 20 years,[1] including those in health and education - to seek alternatives that can ensure the supply of medicines at more affordable prices is a constant need.

The research considered four dimensions with the aim to understand and relate the different elements that make up the scenario of

public procurement of medicines in Brazil: (a) identification of medicines under exclusivity from the supply side, (b) analysis of the patent situation, including status and quality of the content of patent applications, (c) procurement by the Ministry of Health, including price analysis for comparison with alternatives available in the international market and, (d) legal aspects related to industrial property legislation and briefly, legislation related to public procurement of medicines. In the end, we seek to point out some ways that may help to overcome existing barriers to competition in Brazil that favour the exclusivity situation, especially those caused by the patent system in the pharmaceutical field, aiming at possible savings to public resources that may contribute to the sustainability of a public and universal health system.

This research represents an effort to include intellectual property in the debate on public procurement of medicines. It represents in particular, an invitation to a dialogue, which has already begun, between professionals specialised in intellectual property and health professionals with experience in public procurement and health regulation. We believe that complex issues demand views from different angles to open spaces for the emergence of the most creative solutions to the problems and that these may be reflected in the guarantee of the continuity of access to medicines policies at the Unified Health System.

1.1 Right to Health and Pharmaceutical Services in the Context of SUS

In Brazil, health is a fundamental human right guaranteed by the Federal Constitution (CF) as a right of all people and a duty of the State, which must be guaranteed through public policies of universal and equal access to actions and services aimed at its promotion, protection and recovery (article 6 and 196, CF). The "Sanitary Movement" - originated in the 1970s - played a fundamental role in the process that led to the constitutional recognition of the right to health in Brazil. In 1988 the foundations were laid for the establishment of a public health system in the Federal Constitution, regulated by law in 1990.[2]

Law 8.080 / 90 included the execution of integral therapeutic care

projects among SUS' scope, including pharmaceuticals (article 6, I, d). On the one hand, SUS was a great achievement for the Brazilian population. On the other hand, the challenge was to develop and implement a public health system that would follow fundamental pharmaceutical ingredients such as universality, integrality and equal access to health services at all levels of care, including pharmaceutical services.[3]

Law 8080/90 was amended through Law 12,401/11 and Decree 7.508/11 focusing on pharmaceutical services and the issue of technology incorporation into SUS as one of the ways needed to ensure integrality, considering the context of the launch of new technologies and judicialisation of the system to obtain those health technologies.[4]

Technology incorporation, including new medicines, has been an integral element in most health systems. The introduction of medicines that are potentially more effective for certain diseases happens at an accelerated pace and at varying levels and may contribute to prolonging life, alleviating pain, reducing the risk of illness, and improving or maintaining health conditions of populations.[5]

In recent years, there has been a worldwide trend of increased costs in health systems.[6] This trend can be associated with several factors. Among the most relevant ones is the incorporation of new technologies. These technologies are generally protected by an intellectual property system and marketed as under exclusivity at high prices.[7] Medicines are responsible for a significant part of health expenditures, accounting for 10 to 20 percent of health expenditures in developed countries, and more than 50 percent in developing countries.[8] High prices can exclude millions of people from access to technology and jeopardise the sustainability of public health policies aimed at ensuring access to medicines.

In recent years Brazil has seen a significant increase in public procurement of pharmaceuticals. The Ministry of Health spending on medicines increased by 74% between 2008 and 2015 (from BRL8.5 billion to BRL 14.8 billion), while the health care federal budget increased by only 36.6% in the same period.[9]

In a recent study, Vieira[10] analyses SUS spending on medicines between 2010 and 2016, considering the three levels of government. While in the period from 2010 to 2015, spending went from BRL14.3 billion to BRL20 billion (an increase of 40%), it fell to BRL18.6 billion

in 2016. Despite the observed fall in the last year, the Ministry of Health spending grew by 53% between 2010 and 2016 and those of the states and the Federal District and municipalities decreased by 27% and 23%, respectively.

Although increased public spending on medicines may reflect an increase in the number of treated individuals, this may also mean an increase in spending on high-cost medicines. Many of these medicines are in an exclusivity situation due to the patent system, as will be discussed below.

1.2 Intellectual Property and Access to Medicines

Several studies have linked high prices of medicines to monopolies established by the patent system.[11, 12] It has been demonstrated that the existence of a patent may raise prices because of market conditions in which a producer can operate with exclusivity. In the absence of competition, a producer has greater power to establish a good's price, even when it is considered essential for human life and health, as in the case of medicines and other health technologies.[8] Competition can significantly reduce prices and increase access[13-16]. In Brazil, generic medicines, which can only be marketed in the absence of a patent barrier, must be priced at least 35% lower than the originator medicine (called "reference medicine" in Brazil[17]), but in practice this difference can be much higher.

Patents of invention - a type of intellectual property protection - are granted by the State that gives exclusive rights to its holders, allowing them to prevent third parties from manufacturing, using, marketing, selling or importing patented products or processes. Possible private competitors and possible public producers are prevented from producing a particular product or using a particular production process during the established protection time (20 years as a general rule for patents[18]). Once the patent protection time is over, the "invention" goes into the public domain and anyone can exploit it.

That is, a patent grants its holder a temporary privilege to exploit the patented object under conditions of exclusivity, that is, without competition. The objective is to enable the patent holder to obtain the return

of the investments made to develop the object, in exchange for revealing the knowledge developed to society at large, so that everyone can exploit it after that knowledge enters the public domain, which occurs after the patent term. Thus, the holder has the possibility and the incentive to sell the product at the highest possible price during the patent term.[19]

The current Brazilian patent law (law 9,279/96), known as the Industrial Property Law (LPI), was enacted in 1996. The LPI amended previous legislation on the subject to bring the Brazilian legislation in line with the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS Agreement) of the World Trade Organization (WTO), signed in December 1994. The TRIPS Agreement is currently the main international treaty on intellectual property and all WTO member countries, including Brazil, are obliged to have a national legislation compatible with the obligations assumed under that agreement.

As some studies show, Brazil is often mentioned as one of the countries where fewer patents are granted in the pharmaceutical sector, as compared to other countries[20, 21]. Correa et al. (2013) compare pharmaceutical patents granted in Argentina, Brazil, Colombia, India and South Africa. According to the authors, in Argentina 951 pharmaceutical patents were granted between 2000-2007, in Brazil 278 patents were granted between 2003-2008, in India 2,347 from 2005-2008 and in South Africa 2,442 patents were registered only in 2008. The World Intellectual Property Organization (WIPO) data places Brazil in the last position among the 10 most important patent offices for the pharmaceutical sector between 2006 and 2016. [A]

The existence of a comparatively lower number of pharmaceutical patents granted in Brazil would indicate that medicines would be procured under a competition regime and that prices would be low. However, case studies of some high-cost medicines procured by the Ministry of Health have shown that those were procured under exclusivity though there were no patents granted in Brazil.

The antiretroviral (ARV) Tenofovir is one such case. The medicine was marketed exclusively for the Ministry of Health by Gilead from 2003 to 2010, even though there has been a generic alternative in the inter-

A World Intellectual Property Organization (WIPO) Statistics Database.

national market since 2006. There has never been any patent granted in Brazil but there were patent applications pending decision, which were all secondary. The main patent application related to Tenofovir disoproxil fumarate (TDF), a pharmaceutical form adopted by the Ministry of Health (MoH), was rejected in 2009 and a national generic version started to be commercialised as of 2011. It is estimated that from 2006 to 2010, the MoH has spent about USD $200 million more on the purchase of the Gilead version of Tenofovir.[22]

A study on public procurement of hepatitis C medicines from 2005 to 2015 signalled a similar situation in which the Direct Acting Antivirals (DAA) sofosbuvir and daclatasvir were marketed by transnational pharmaceutical companies exclusively to the Ministry of Health despite the existence of only pending patent applications in the country and cheaper generic alternatives on the international market.[23] Compared to international reference prices (Egypt and Indian generics), the treatment price in Brazil could be between 62% and 92% cheaper.

This situation of few patents granted, but several procurements under exclusivity due to a lack of competition is what we have called "the patent paradox in Brazil".[24] This question was analysed in a preliminary document, with the same title, in which we presented the background of the current research.

1.3 General Objective

To analyse the determinants of the exclusivity situation related to patent protection of a set of medicines financed by the Ministry of Health.

1.4 Specific Objectives

- To map medicines under exclusivity from the supply side in 2016 included in the Specialized Component of Pharmaceutical Services (Groups 1A and

1B), antiretrovirals and those indicated for oncological treatment;

- To analyse the patent situation of a set of medicines that were selected for being classified as under exclusivity from the supply side;
- To describe the procurement of a set of selected medicines from 2007 to 2016;
- To compare prices charged in Brazil with those in the international market for generic or biosimilar versions for some selected medicines;
- To analyse aspects of Brazilian industrial property legislation that may contribute to the exclusivity situation from the supply side even in the absence of a patent granted in the country; and,
- To point out possible ways to reduce public procurement without bidding processes due to the exclusivity situation from the supply side.

1.5 Assumptions

- The large number of patent applications for the same active pharmaceutical ingredient contributes to generate legal uncertainty and lack of clarity at the time of public procurement processes as to the monopoly status of a medicine and for bidding processes to develop.
- The uncertainty generated by the existance of several patent applications contributes to the absence of generic products in the Brazilian market even though they are available in the international market.

2. Theoretical Framework

2.1 Brief Characterisation about the Financing of Pharmaceutical Services in the Unified Health System

The financing of pharmaceutical services in SUS is complex. The three levels of government have responsibilities in relation to the financing and management of medicines. In summary, as of 2009, through Administrative Rule GM/MS No. 2,981 dated November 26, 2009, pharmaceutical services began to be organised by Components – divided into Basic, Strategic and Specialized Components, as described in Chart 1, with different responsibilities between the Ministry of Health, states and municipalities regarding funding and procurement.

The Specialized Component (CEAF) was first regulated by Administrative Rule GM/MS No. 2,981, of November 26, 2009 and, later, by Administrative Rule MS/GM 1,554/2013.[25] For medicines in Group 1A, the Ministry of Health was responsible for funding and procurement, while those in Group 1B were funded by the Ministry of Health, while procurement was the responsibility of the states.

In December 2017, GM Ordinance Number 3.992[26] was approved and from then funding of health actions ceased to be specific blocks (Primary Care, Outpatient and Hospital Medium and High Complexity Care, Pharmaceutical services, Health Surveillance, Management) and became known as the "Block of Costing Actions and Services on Health".

The supply as well as the responsibilities of the different entities of Basic, Strategic and Specialized Components of pharmaceutical services

has not changed and continue to be called this way. However, in terms of financial transfers, pharmaceutical services resources have become part of a single block that includes other health actions.

The Ministry of Health also had the responsibility for funding the Popular Pharmacy Program of Brazil in its two different parts (Own Distribution Network and "Here you find a Popular Pharmacy"). [27] Financing the enforcement of lawsuits is the responsibility of the three levels of government.[27]

Medicines for hospital use, such as those for cancer treatment, are funded by Ministry of Health transfers for Medium and High Complexity actions, such as the High Complexity Procedure Authorization (APAC). [27] In this way, the National Cancer Institute (INCA) has an annual budget for its own costing and specific for inputs[28] thereby responsible for procurement of medicines.

However, it is important to note that some medicines for cancer treatment such as imatinib are now centrally procured by the Ministry of Health in order to achieve better bargaining power for price reduction.[29]

In summary, it is important to differentiate procurement from funding. Although products selected for this research were funded by the Ministry of Health, it does not mean that the procurement of these products was also made by the Ministry. As mentioned, CEAF 1B products were procured by the states and most oncology medicines were procured directly by the hospitals themselves.

Chart 1 Brief Summary of the Components of Pharmaceutical Services and its Financing in Force in 2016

COMPONENT OF PHARMACEUTICAL SERVICES	PRODUCTS COVERED	FUNDING
BASIC	Medicines aimed at the prevalent and priority diseases of Primary Care, present in RENAME in force. It also includes the phyto-therapeutic medicines established in RENAME in force, homeopathic matrices and mother tinctures according to Brazilian Homoeopathic Pharmacopoeia, 3rd edition	Federal contribution is R $ 5.48 / inhabitant / year, and the state and municipal counterparts must be at least R $ 2.36 / inhabitant / year each
STRATEGIC	It is aimed at funding pharmaceutical services actions of the following strategic health programs: 1. Tuberculosis Control; 2. Hansen's disease Control; 3. Control of Smoking; 4. Focal Endemias; 5. Influenza; 6. HIV/Aids; 7. Prevention of Nutritional Deficiencies; 8 Blood and Hemoderivatives and 9. Child Health. They include medicines for tuberculosis, leprosy, malaria, leishmaniasis, Chagas disease, cholera, schistosomiasis, leishmaniasis, filariasis, meningitis, onchocerciasis, plague, trachoma, systemic mycoses and other diseases that are due to and perpetuate poverty. They also include medicines for influenza, HIV / AIDS, hematological diseases, smoking and nutritional deficiencies, vaccines, serums and immunoglobulins	Ministry of Health
SPECIALIZED	Comprised of 198 active pharmaceutical ingredients in 389 pharmaceutical presentations indicated for the treatment of the different evolutionary phases of the diseases contemplated	Group 1 - funding under the exclusive responsibility of the Union. It includes medicines of high financial impact for the Component, indicated for "more complex diseases, for cases of refractoriness or intolerance in the first and / or second line of treatment and for those included in productive development actions in the health industrial complex " Group 2 - funding responsibility of the State Health Secretariats Group 3 - responsibility for funding is tripartite

Source: Ministry of Health, 2016

2.2 Intellectual Property Rights and Patenting Trends in the Pharmaceutical Sector

The WTO TRIPS Agreement is the main international treaty related to trade in products subject to intellectual property protection. The main change the agreement brought in was the establishment of the obligation to protect intellectual property for all technological fields and the creation of international sanction mechanisms for cases of violations of the rights derived from this protection.

Prior to the TRIPS Agreement, many countries, such as Brazil[B] did not grant patents in sectors considered sensitive, such as pharmaceuticals and food sectors.[30] With the TRIPS Agreement, this was no longer possible, and Brazil was forced to change its legislation to comply with international rules.

TRIPS provided for a transitional period of 10 years, that is, until 2005, for the adequacy of the national laws of developing countries that did not grant patents in the pharmaceutical sector until then. However, Brazil did not use this period and modified its law by 1996 (Law No. 9.279 / 96). It also permitted the granting of patents for products that were already in the public domain in Brazil, since they could not be patented by previous legislation,[30] which was not mandatory under the TRIPS Agreement.

If under the previous patent legislation there was the possibility of competition through both private and public production of medicines, the change in the Brazilian patent law profoundly modified this scenario, creating a significant impact on medicine procurement policies by the SUS and on prices.

TRIPS introduced common rules for different WTO countries to adopt. However, it left the possibility of negotiating rules open for the provision of greater protection of intellectual property than those established by TRIPS. These measures are known as "TRIPS-plus". Among the most common measures are those that aim at extending a patent's term.

B Brazil adopted its first industrial property law in 1809. Brazilian legislation granted patent protection for inventions in the pharmaceutical and food areas until 1945, when inventions for products in these areas were no longer patentable in the country, and only a process patent was allowed. In 1969, one more legislative amendment excluded the possibility of patenting for the entire pharmaceutical area, which remained until 1996, with the adoption of the current LPI.

On the other hand, in order to minimise potential negative effects, the TRIPS agreement also provides WTO member countries with the means to take the necessary measures to protect public health and nutrition and to promote public interest in sectors of vital importance to their socio-economic and technological development (Article 8, TRIPS). In 2001, the "Doha Declaration on TRIPS and Public Health" was adopted, which reinforced the right of countries to adopt such protective measures, known as "TRIPS flexibilities". Among them: compulsory license; patent oppositions; and rigorous interpretation of patentability requirements necessary to obtain a patent in the country.

It should be noted that TRIPS Agreement provisions are not self-enforcing and depend on a country's legal frameworks. In addition, by the principle of territoriality of patents, a patent is only valid in the country in which it is granted, so that a certain object (such as a medicine) may have a patent granted in one country and not in another. TRIPS brings some general criteria, but it is up to each country to determine the appropriate way to implement the Agreement at the national level (Article 1.1, TRIPS).

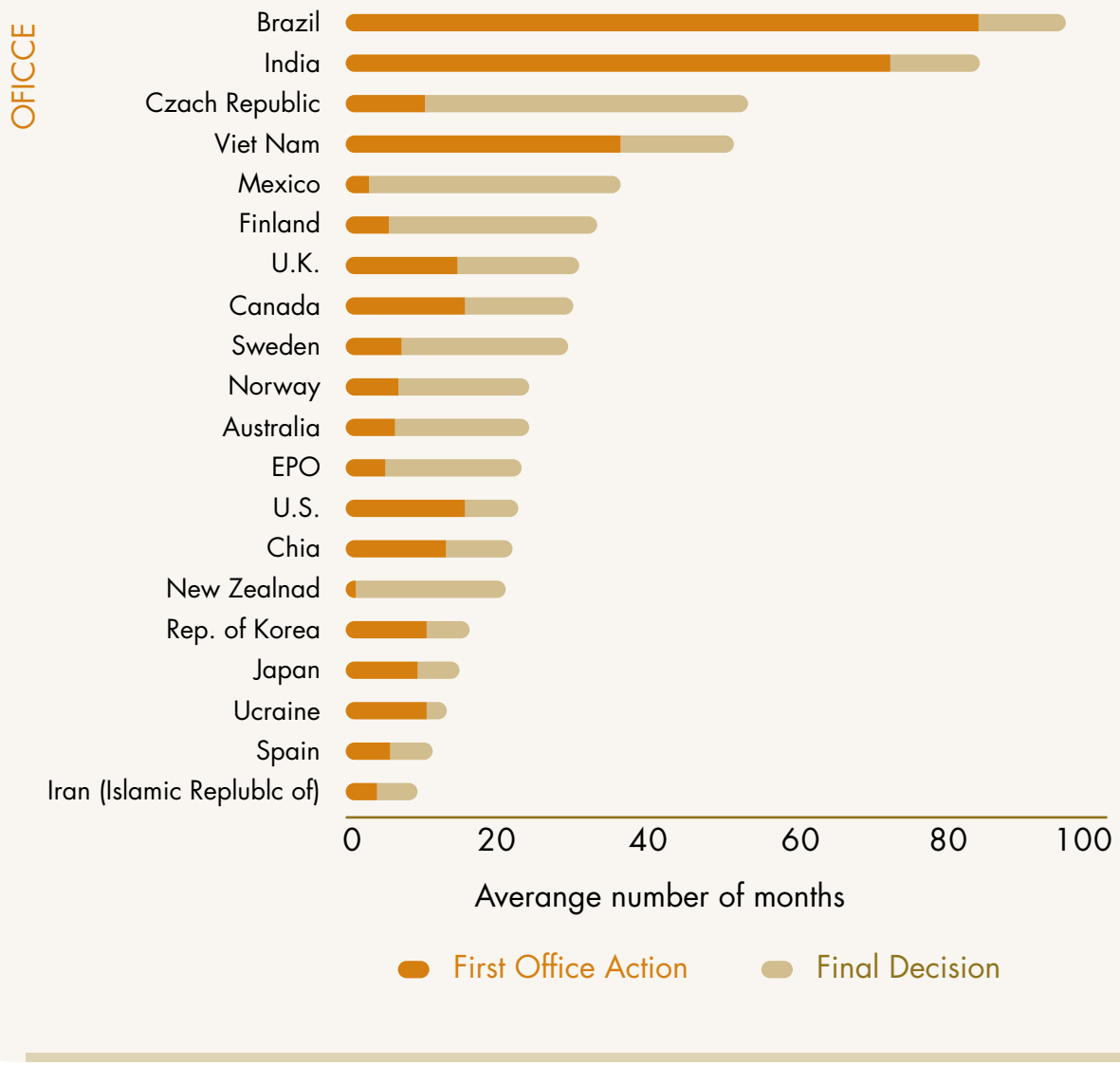
With regard to the patentability requirements, TRIPS establishes that an invention is patentable provided it is new, has an inventive step and industrial application (art. 27.1, TRIPS). However, it does not lay down criteria for interpreting those requirements, which are set by each country. A broader interpretation of the requirements may lead to a greater number of patents granted in the country, with more knowledge in the private domain and less in the public domain. On the other hand, a stricter interpretation of the requirements aims to ensure that only the content which in fact represents additional knowledge for society can be patented, preventing knowledge already in the public domain from being misappropriated.

2.3. *De facto* Monopoly and Evergreening Strategies (or perpetuation of patent exclusivity)

Several factors may lead to the existence of a single supplier of a pharmaceutical product in a given country. One of the main factors is related to the dynamics of the patent system. Even in the absence of patents granted, the patent system may create a "de facto monopoly", that is, a situation where there is no patent granted in the country for a particular product, but it is "subject to patent protection" due to one or more applications (s) that are still awaiting decision whether or not they will be granted. This situation creates "legal uncertainty" about the patent status of a medicine due to pending applications,[31] which is exacerbated by the possibility of third parties having to pay compensation to the patent holder, if it is granted. This and other legal aspects will be analysed in chapter 7.

This situation is worsened in the Brazilian context due to the time taken between filing a patent application and its examination, which is very high. Recent data[32] from the World Intellectual Property Organization (WIPO) show that Brazil is the country with the highest average waiting time (95.4 months), as shown in Figure 2.

Figure 1 – Average waiting time between initial application and final decision in selected patent offices (all sectors), 2016.



Source: WIPO, World Intellectual Property Indicators, 2017, p. 19.

A study specifically, for the pharmaceutical sector analysing 278 pharmaceutical patents granted in Brazil from 2003 to 2008 revealed

that more than 50% of pharmaceutical patent applications took at least 8 years to review and about 25% took more than 10 years[20].

More recent data from the Brazilian National Institute of Industrial Property (INPI) show that currently more than 65% of the granted patents are granted after 10 years from the filing date, [31] falling within the rule of the sole paragraph of article 40 of the LPI, and therefore having a term greater than the general rule of 20 years counted from the filing date. The average time for a decision by the INPI is 10.23 years and for pharmaceuticals, it is 13.4 years.[33]

This dynamic of the patent system is not specific to Brazil but reflects a reality of how pharmaceutical companies operate to maximise exclusivity in relation to their products through so-called "life cycle management" by pharmaceutical companies. Critics call this "evergreening". This type of approach increases the total number of patent applications to be processed by patent offices, contributing to increasing backlog, and increasing legal uncertainty regarding a medicine's patent status, and may influence decisions on production and procurement.

There is a growing debate about the quality of patents granted worldwide. Entities such as the Academy of Sciences and the Federal Trade Commission of the United States have already indicated that the quality of patents granted is deteriorating and that the standard of analysis of patentability requirements has become excessively low, making it possible to grant numerous patents of poor quality which unduly affect the public domain and have negative effects on competition and innovation.[34]

In the pharmaceutical area, it has been pointed out that there are several patent applications for modifications made to existing medicines, widely called incremental innovations, while decreasing the number of applications aimed at the protection of pharmaceutical inventions considered to be genuinely innovative.[20]

Considering the interpretations given to the concept of evergreening, we highlight some that were adopted as basis for the analyses in the present research.

According to Kapczynski et al:[35]

> *The flip side of this is the widespread allegation that secondary patents are part of firms' "evergreening" strategies to extend monopoly protection on existing products [10]. The term evergreening is used to refer to a range of practices. Some are independent of patent strategy [14]–[16], but others depend importantly on secondary patents. For example, such patents may be listed on the FDA's Orange Book and thus can provide opportunities for automatic injunctions against generic competitors [11].*
>
> (…)
>
> *To distinguish between such patents and those with purely secondary claims, we also determined which patents were "independent" secondary patents, those with secondary claims only. We make this distinction since patents with independent secondary claims are those that are most important for discussions of evergreening, since secondary claims in patents that also have chemical compound patents do not generate additional patent life.*
>
> (p. e49470, emphasis added in bold)

Pereira and Fiuza (2013)[36] summarise the main strategies adopted by transnational pharmaceutical companies identified in the European Pharmaceutical Sector Inquiry (2009) to delay the entry of generic medicines into the market. These may include the following strategies:

> *1) Defensive patenting strategies, such as **filing a large number of patent applications for a single drug (so-called patent clusters or patent thickets**). These strategies overlap patents focusing on various commercial aspects of the same medicine (processes, new salts, formulations, uses, combinations, polymorphs, etc.) and **increase legal uncertainty about the scope of protection** for that medicine.*
>
> *(…)*
>
> *6) Lifecycle strategies, also known as **evergreening** by innovative pharmaceutical laboratories (LFIs), through which a **LFI fosters a transition from prescribing medicines whose patents are close to expiring or about to be invalidated to second generation medicines derived from the original***

> ***medicine*** *and also known as follow on (see definition in section 3), still without generics - in this case, pharmacists cannot do the substitution at the time of dispensing*. (p. 28, emphasis added in bold, free translation)

According to Kapczynski et al.[35] evergreening refers to a strategy for extending the monopoly of products already available in the market, which includes, among other approaches, the filing of patent applications with "secondary" claims. These patent applications are called secondary "as they are assumed to come later in the sequence of innovation, and to offer less robust protection than a chemical compound claim", called the "primary" or "primary" patent" (p. 3). Secondary applications may include claims such as formulations, combinations, dosages, polymorphs, prodrugs, method of treatment and use (including second medical use).[20]

The claims of a patent application cover what the applicant intends to protect. It is the content of the application for which the industrial property law will be enforced in case the patent is granted. The content of the claims shall be based "on the descriptive report, characterising the particulars of the application and clearly and precisely defining the subject matter of the protection" (Article 25 LPI).

In the European Inquiry (*apud* Pereira and Fiuza),[36] evergreening focuses on the launch of second-generation products onwards, by the same pharmaceutical company, followed by patenting strategies. That is, the transition to the second or third generation would follow the expiration times of the first product patents, followed by subsequent patent applications for the following products. According to the authors:[36]

> *The (European) Commission understood follow-on as* ***second-generation products****, which are the result of* ***incremental*** *research and development (R & D), essentially based on existing products (first product) and essentially having a similar mode of action.* ***These secondary products may have the same active ingredient (AI)*** *as the initial version (e.g., secondary products involving inter alia new* ***formulations, crystalline forms, particle sizes or medical uses****) or a* ***different AI*** *(e.g.* ***combinations, salts, stereoisomers separated from mixtures or metabolites of an existing active ingredient****).* (p.29, emphasis added in bold, free translation)

Although approaches to the concept of evergreening converge in the two studies, the analytical approach differs in that the former seeks to analyse secondary patent applications in relation to the potential for extending the lifetime of a first patent for a particular product, while the second explores the types of second-generation products that enter the market and their relationship to the patenting process. In the present research study, we will adopt the Kapczynski et al (2012) approach.

In Brazil, a study on medicines for HIV/AIDS - in which 447 patent applications were identified for 20 antiretrovirals - showed an average of 22 applications for each medicine. About 25% of applications were abandoned for some reason during the administrative procedure and were never analysed on their merit. The author used this data as an indicator of the low importance of the patent and its use to generate uncertainty and block competition.[C 37]

Another study analysed 2,964 applications for pharmaceutical patents classified by the authors as "secondary" and revealed that about 60% of the applications were withdrawn or abandoned in Brazil before the examination.[21]

A study conducted in the United States shows that "secondary" patents add, on average, another six years of patent protection to a medicine. In Brazil, on average, 8.7 additional patent applications are made by the patent holder of the reference product for each medicine already patent protected.[36] In another study that analysed patent status of antiretroviral medicines in Brazil, an average of 6.5 years of additional patent protection was indicated as a result of secondary patents.[38]

C The author distinguishes between "incremental" and "trivial" innovation. The former means additional innovation and the latter means only an attempt to protect the market and expand a monopoly without any further innovation. This is an interesting approach to analysing secondary patents, however, in our view, incremental innovations that meet patentability requirements are still the exception rather than the rule, especially if the country adopts a restrictive interpretation of patentability requirements.

2.4 Synthetic/Semi-synthetic Products and Biological Products

Among the health technologies to be analysed in the present research are products called synthetic and biological. According to Anvisa, medicines with synthetic and semi-synthetic active pharmaceutical ingredients can be classified as new, generic and similar (RDC 200/2017).[39]

According to the RDC nº 55/2010, the products considered biological are: the vaccines, hyperimmune sera, blood products, biomedical products classified as: (a) medicinal products obtained from biological fluids or tissues of animal origin and (b) medicinal products obtained by biotechnological procedures, monoclonal antibodies, and medicinal products containing live, attenuated or dead microorganisms.

For regulatory purposes in Brazil the concept of a new biological product is the one that gets market approval registered first in the country.[40] [D] Biological products are "non-new or known biological medicine containing a molecule with known biological activity already with market approval (registered) in Brazil "(Art. 2, XV). [E] [40] The latter is known internationally as the biosimilar product.

Synthetic medicines originate from chemical synthesis, whereas biological medicines are the result of processes of biosynthesis of living organisms. [41] These two technologies can also be differentiated by the size of their active pharmaceutical ingredients. While synthetic medicines can be understood as small molecules, biological medicines are formed by large and complex molecules.[41] In this way, it is possible to classify medicines involving micro-molecules (synthetic and semi-synthetic) and macro-molecules (biological).

D Article 2, For the purpose of this Resolution, the following definitions are adopted:
XX - new biological product: it is the biological medicine that contains a molecule with known biological activity, not yet registered in Brazil and that has gone through all stages of manufacture (formulation, packaging, lyophilisation, labeling, packaging, storage, quality control and release of the batch of new biological medicine for use);

E Art. 2, For the purpose of this Resolution, the following definitions are adopted:
XV - biological product: it is the non-new or known biological medicine that contains a molecule with known biological activity, already registered in Brazil and that has gone through all stages of manufacture (formulation, packaging, lyophilisation, labeling, packaging, storage, quality control and release of the batch of biological product for use).

3. Methodology

The study involved four axes: (a) identification of products in exclusivity situation from the supply side, (b) analysis of the patenting situation of selected medicines in Brazil, (c) analysis of the public procurement of selected medicines and (d) analysis of legal aspects that may contribute to the exclusivity situation.

The different steps, analytical options and limitations are presented in Appendix 1. The adopted methodology will be summarised in this section.

The **selection of the active pharmaceutical ingredients** (API) **in the sample** considered the medicines that are financed by the Ministry of Health and involved the following categories: CESAF - only antiretroviral (ARV) medicines indicated for the control of HIV/AIDS infection; CEAF - Group 1 medicines, subgroups 1a (financing and centralised procurement at the federal level) and 1b (federal funding and decentralised procurement by the states); and medicines for cancer treatment present in the Clinical Protocols and Therapeutic Guidelines (PCDT). We selected medicines as per the Ministry of Health's documents available in 2016.

The definition of exclusivity situation from the supply side selected in the previous step was carried out considering the market situation in December 2016. To do so, we opted to consult the price list of the CMED (Medicines Market Regulation Chamber), referring to the "Medicines Prices for Public Procurement", published in January 2017

The analysis of a **patent situation of medicines** included in the sample was carried out in three phases: a) identification of international and corresponding patents in Brazil, b) mapping the status of patent

applications in Brazil for December 2016 and c) analysis of the claims and classification of patents and patent applications.

The **identification of international and corresponding patents in Brazil** involved the following sources: Orange Book (FDA) and Patent Register (Health Canada), scientific articles, Scifinder database, Integrity database, Patent Lens database, National Institute of Industrial Property (INPI) website for summary and titles, and other databases (Medicines Patents and License Database and Patent Opposition Database, requests for priority examination at INPI, lawsuits and other relevant documents available in existing literature).

We analysed the **patent status in Brazil** for **December 2016**. Applications were classified according to the following categories: granted, rejected, pending, expired, extinct and dismissed. The date of filing of each application in Brazil was also recorded to make a note of the time of the patent in the country and chronological analysis of the applications.

The **analysis of the claims** prioritised the most up-to-date claims table available on the INPI website. We attempted to identify applications directed to protect active pharmaceutical ingredients and processes - classified as "primary" - and other applications for various categories, classified as "secondary", as detailed in Chart 9 (Appendix 1). It is important to note that many applications included both primary and secondary claims.

For the identification of the active pharmaceutical ingredient of biological medicines (macromolecules), specific categories available on Scifinder® (see Chart 10, Appendix 1) have been adopted. However, the classification of "primary" and "secondary" for biological products were considered new, requiring complementary analysis. Therefore, we opted to classify the results according to the categories – "indicative of primary claim" and "indicative of secondary claim".

The **history of public procurement of the medicines** selected for the research involved different public databases, namely, the Integrated System of Administration of General Services (SIASG) for CEAF 1A, ARV and cancer medicines and, Public Health Budgeting Information System (SIOPS) for CEAF medicines 1B. The information was also supplemented by data obtained from the Electronic System of the Citizen Information System (e-sic). At this stage of the study, data was collected

on procured quantities (volume) and unit prices from 2007 to 2016, in addition to the procurement modality. Prices were adjusted for inflation - with 2016 as the base year - according to the Extended National Consumer Price Index (IPCA).

In order to estimate potential savings in medicines procurement in a competitive scenario, the prices of generic or biosimilar versions marketed internationally were used. As there is no single source for obtaining this information for all products, we used different studies, which in itself constitutes a limitation for this stage of our research study. Prices charged in Brazil were converted to the average dollar of the year. [42]

The analysis of the legal aspects related to exclusivity situation of medicines focused on pending patent applications and considered industrial property legislation in Brazil compared to legislation of other selected countries available on the WIPO webpage, as well as comments available in specialised literature. The search for jurisprudence in Brazil considered the Federal Justice unified search system.

A preliminary version of the report was discussed with experts from different fields in a meeting on the 23 of July 2018 at ENSP/Fiocruz (Program – Appendix 2). The inputs to the study contributed to its improvements and adjustments, included in this final version which is the exclusive responsibility of the authors.

4. Results

This research study involved a series of steps, from the selection of medicines in exclusivity situation from the supply side to content analysis of patent applications (claims) identified in Brazil.

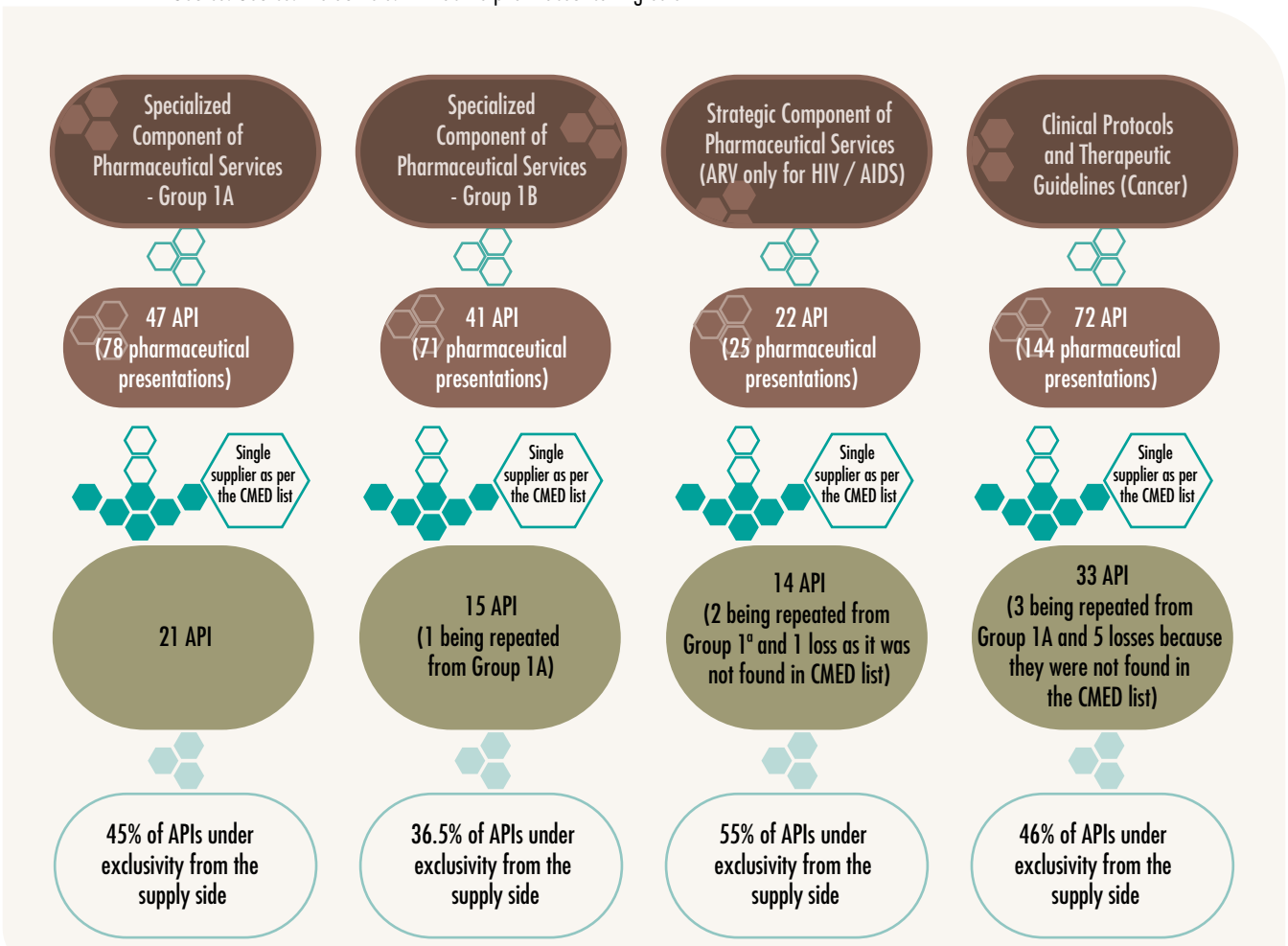
The results are presented in the order of steps taken so as to have the following final overview of the analysis in relation to medicines in exclusivity situation: (a) total active pharmaceutical ingredients with patent barriers, (b) total patent applications analysed according to status in December 2016 and, (c) total applications analysed in relation to the content (claims).

4.1 Selection of Active Pharmaceutical Ingredients in Exclusivity Situation from the Supply Side for the Patent Search

A total of 170 active pharmaceutical ingredients (API) were identified (excluding duplicates among components) from both the selected lists and the Clinical Protocols and Therapeutic Guidelines (PCDTs),, of which 77 were in exclusivity situation from the supply side in 2016 (based on the Medicines Market Regulation Chamber (CMED) list). This represents a total of 45% of API in exclusivity situation among the API of the initial sample. The distribution of the API among the different components is detailed in Figure 2.

Figure 2 – Selection of active pharmaceutical ingredients in exclusivity situation from the supply side according to medicines groups (2016). Brazil, 2016.

Source: Source: the authors. API=active pharmaceutical ingredient



The same 77 API were checked in relation to their market approval (registration) at the Brazilian Health Regulatory Agency (Anvisa), considering the 2016 situation (Table 1). We considered the API by itself and not disassembling in its different pharmaceutical presentations. For one API - asparaginase - no record was found in Anvisa. For 11 API, we found Anvisa market approval from more than one company. As was done with the CMED list, a preliminary search was carried out to verify if the companies belonged to the same group or if there had been mergers/acquisitions,

indicating that it was in fact a single company[F], which constitutes an exclusivity situation. Following this analysis, six API represented more than one company with an Anvisa's market approval. For the other 70, the exclusivity situation was confirmed in both modalities (CMED list and Anvisa's market approval).

Table 1 – Comparison of active pharmaceutical ingredients (API) in exclusivity situation between CMED list and Anvisa's market approval (registration) (2016). Brazil, 2016.

	COMPONENT 1A	COMPONENT 1B	ARV	CANCER MEDICINES
Total API in exclusivity situation based on the CMED list (excluding repetitions)	21	14	12	30
Total of API in exclusivity situation based on the CMED and Anvisa's market approval lists	20	14	10	26*
API in exclusivity situation on the CMED list, but with more than one company with an Anvisa's market approval	anti-hepatitis B immunoglobulin	-	didanosine and lopinavir / ritonavir	cyclophosphamide, etoposide and exemestane

* For 1 API (asparaginase) no Anvisa's market approval was found in 2016, and, therefore, it was not possible to cross-reference it.

Source: the authors, based on Anvisa website data.

The existence of more than one company with market approval by Anvisa suggests the possibility of competition. It should be noted that Brazilian industrial property law provides for the so-called *Bolar exception*, which allows a company to obtain the approval of a medicine even during the term of a patent (article 43, VII, LPI). In these cases, even if more than one company owns the market approval, the existence of a granted patent prevents the commercialisation of the product by other companies. While the patent barrier to commercialisation remains, it does not exist for market approval by Anvisa. On the other hand, it may also mean that

F We considered the same company: i) Abbott and Abbvie; ii) Pfizer, Wyeth, Evolabis and Hospira; iii) Sandoz and Novartis; iv) Ipsen and Beaufour.

there is no patent barrier and the exclusivity situation from the supply side on the CMED list is due to other factors.

Considering that the comparison showed that 91% of 77 active pharmaceutical ingredients are under exclusivity status in both sources, we considered that the option to select products based on the CMED list was satisfactory for the purposes of this research study.

Thus, the 77 selected API in exclusivity situation underwent a preliminary analysis to verify whether their exclusivity situation was generated by a patent barrier or not. Despite having a single supplier in the country, three active pharmaceutical ingredients were produced in generic versions by domestic companies (amandatine, saquinavir and thalidomide), suggesting that exclusivity was not a result of patent barrier. These ingredients were therefore excluded from our patent search.

Accordingly, we selected a total of 74 API for the patent search, of which 54 were of synthetic chemical origin and 20 of biotechnological origin (biological products).

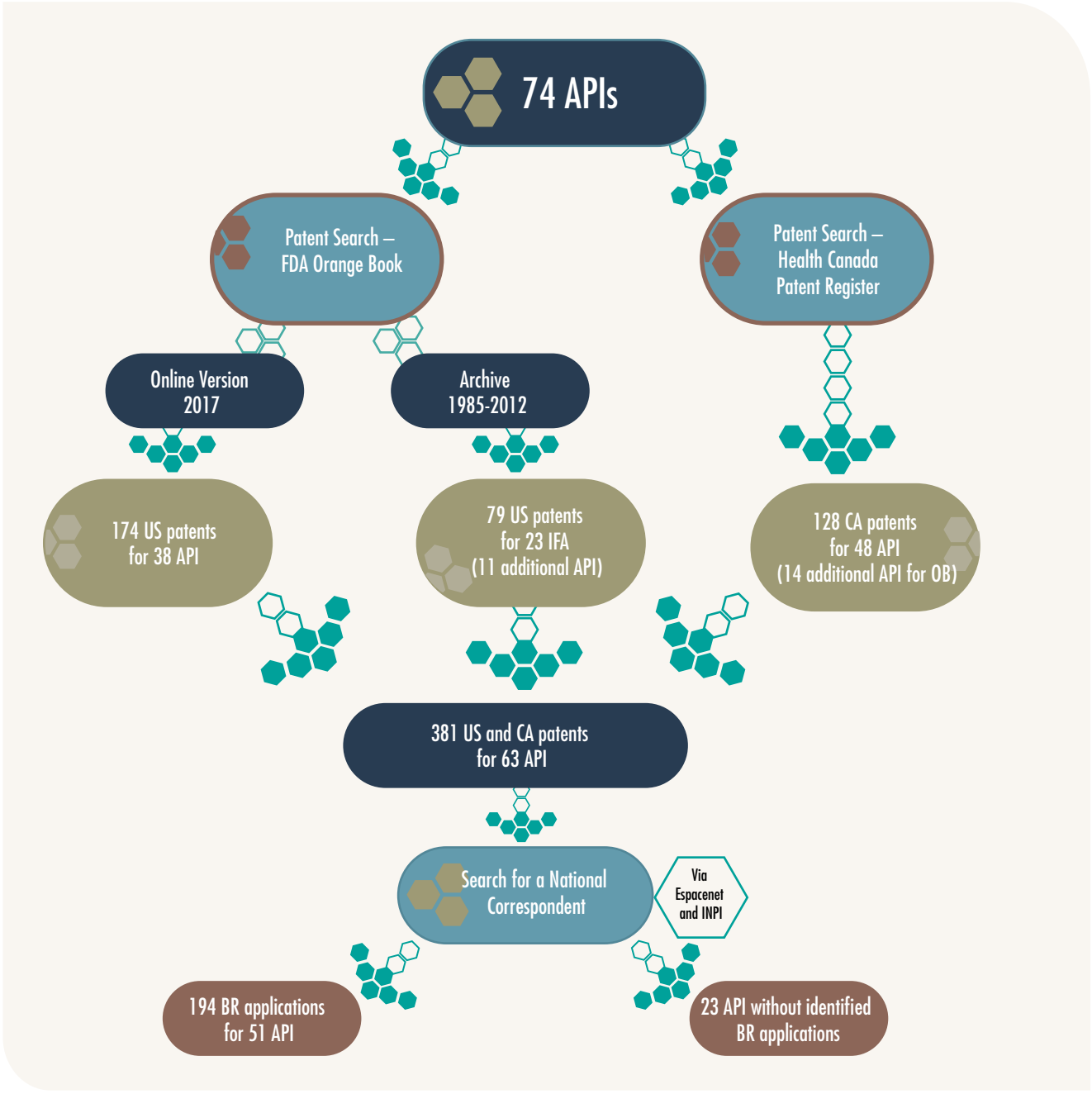
4.2 Patent Search and Identification of Patent Applications in Brazil

In the first stage of our search, 253 US patent applications were found for 49 active pharmaceutical ingredients in the FDA Orange Book and 128 CA applications for 48 active pharmaceutical ingredients in the Health Canada Patent Register. 14 of them - 13 biological products and one chemical – were not found in the US database. In this way, 381 US and CA patent applications were found for 63 active pharmaceutical ingredients and the national correspondents (BR) were found on *Espacenet* or on the INPI website. Of this universe, 194 BR applications were identified for 51 active pharmaceutical ingredients. Thus, there were 23 active pharmaceutical ingredients that had no BR patent application found by this method (Figure 3).

We prioritised these active pharmaceutical ingredients in complementary search strategies, which were also used to deepen our search

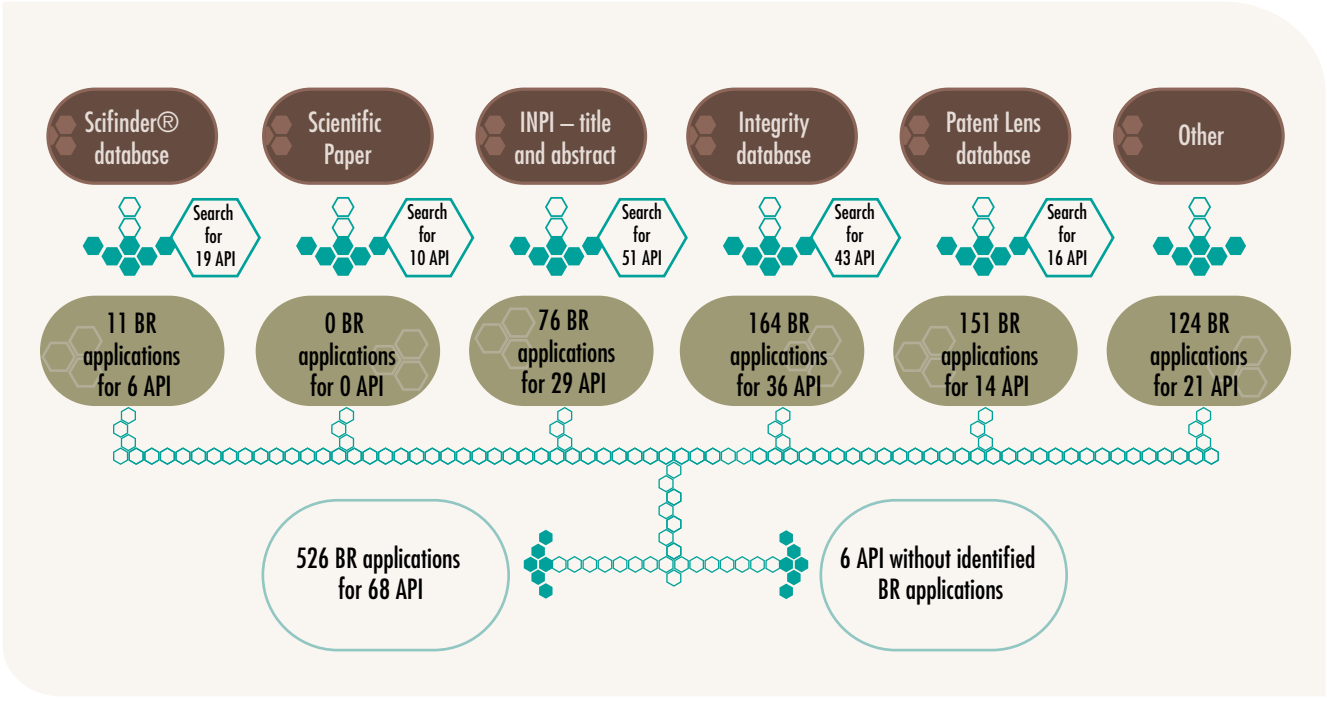
for the other active pharmaceutical ingredients. A complementary search had six other search strategies, described in the methodology section, which together resulted in 526 patent applications in Brazil related to 68 active pharmaceutical ingredients (Figure 4).

Figure 3 – Patent applications identified from the first search strategy based on the FDA Orange Book and Health Canada Patent Register



Source: authors.

Figure 4 – BR patent applications identified by different complementary search strategies



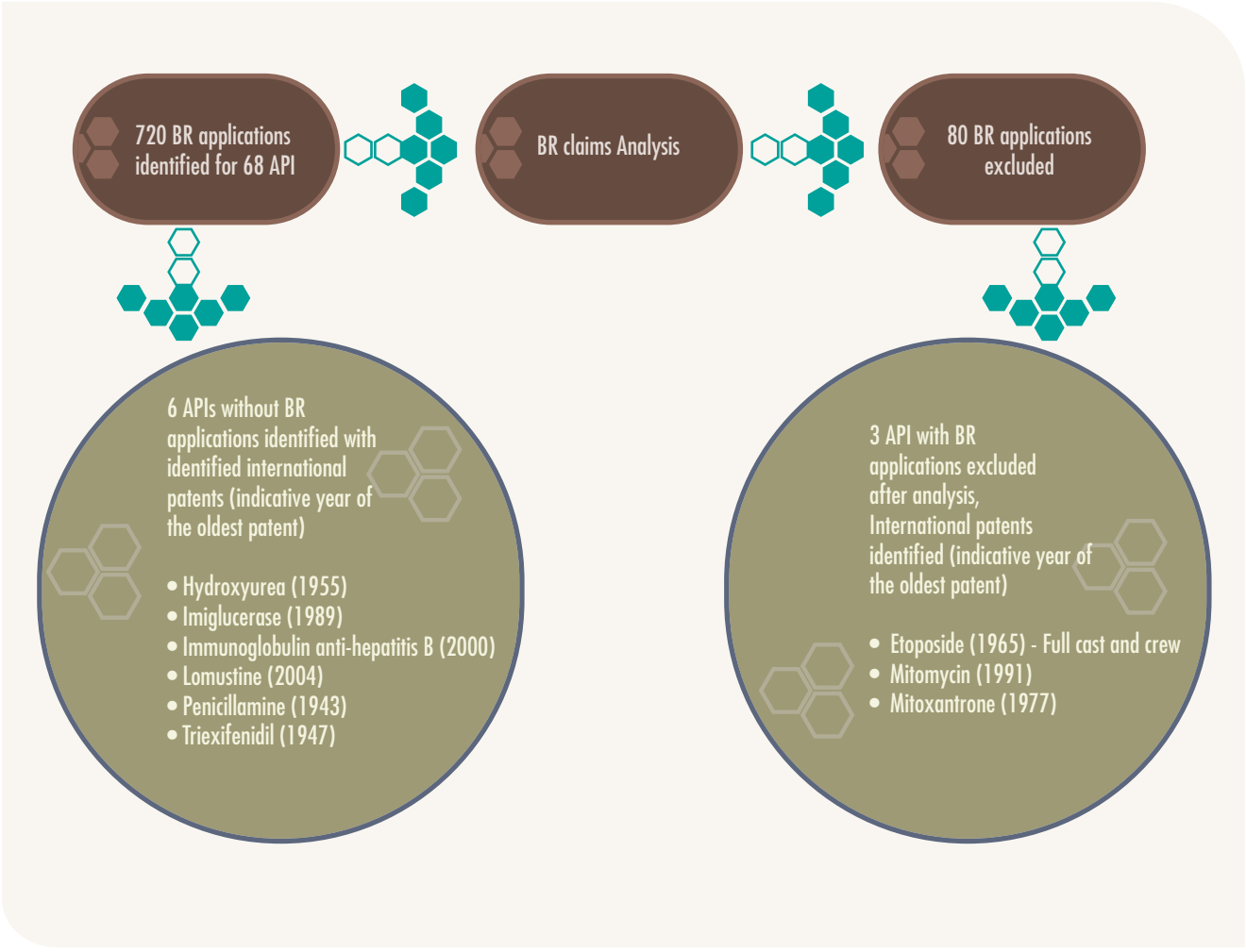
Source: authors.

In total, after all search routes, 720 BR patent applications related to 68 active pharmaceutical ingredients were found. These applications were then submitted to a status analysis and a claims analysis, which resulted in the exclusion of 80 applications, as detailed in section 4.4.

For the six API - hydroxyurea, imiglucerase, Hepatitis B immunoglobulin (HBIG), lomustine, penicillamine and triexifenidil - no national patent application was found (BR applications), but international patents were found without corresponding patents in Brzil. For three other active pharmaceutical ingredients (etoposide, mitomycin and mitoxantrone), BR patent applications were found that were excluded after analysis (Figure 5). It should be noted that the content of international patents without corresponding patents in Brazil can be considered as being in the public domain.

To better understand the market dynamics of these nine API with a single supplier in the Brazilian market, but without an apparent patent barrier, it would be opportune to investigate other factors that may generate exclusivity situation. The existence of old patents in some other countries (Figure 5) may be an indicator that these products are old and in the process of being replaced by newer medicines for the same medical indication(s) and therefore be in danger of disContinued in the market, with little interest in producing them. It was beyond the scope of this research, however, to track further explanations for these situations.

Figure 5 – Total BR patent applications identified by different search strategies before and after exclusions



4.3. Patent Status Analysis in 2016

The 640 patent applications that were considered relevant to the 65 API of the sample were checked in relation to their status as of December 2016 on the INPI website (Table 2).

Table 2 – Overview of patent applications status in December 2016 according to medicine groups. Brazil, 2016.

GROUP OF MEDICINES	GRANTED	PENDING	DISMISSED*	REJECTED	EXPIRED
CEAF 1A	7	163	87	22	5
CEAF 1B	2	11	16	8	1
CESAF (ARV)	13	31	33	23	3
CANCER MEDICINES	11	150	38	14	2
TOTAL	33	355	174	67	11

Source: authors. * In most cases, it includes "dismissed before analysis" (168) and "dismissed after analysis" cases (6)

We identified that the number of applications with pending status is almost 10 times greater than the number of patents granted. Of the total analysed, 27% of the applications were dismissed, 10.5% of applications were rejected and there was an average of 0.51 granted by API.

The low number of patents granted - equivalent to almost half of the total number of active pharmaceutical ingredients analysed - added to the large number of pending applications. This seems to corroborate the assumption of this research study that multiple patent applications, most of which are pending, contribute to exclusivity situations in Brazil for medicines procured by SUS.

Tables 3, 4, 5 and 6 present patent status by active ingredient according to medicine group, respectively CEAF 1A, CEAF 1B, ARV and cancer medicines. The average number of patent applications per active ingredient is 7.2 for products of chemical origin and 16.7 for biological products.

It should be noted that there is a difference between the two technological groups of more than twice the average number of patent applications per active ingredient, suggesting a deepening of the pat-

enting strategy for products of biotechnological origin by transnational pharmaceutical companies.

Pharmaceutical companies' approach on the marketing of biological products have been perceived not only as a transition to a new technology niche, but also as a consequence of the market potential that these technologies can bring from their time of exclusivity in the market.[43] Among the arguments is that exclusivity is not only due to patent protection, but mainly because of high development costs and due to regulatory requirements for the approval of biosimilar products.[44] Nevertheless, the results of the present research study suggest that patenting strategies continue to be important, demanding further analysis to understand its role in market dynamics.

Table 3 – Patent status in December 2016 for CEAF 1A active pharmaceutical ingredients. Brazil, 2016.

API (CEAF 1A)	TOTAL GRANTED PATENTS	TOTAL PENDING APPLICATIONS	OTHER STATUS (REJECTED, DISMISSED, EXPIRED)	TOTAL NUMBER OF BR PATENT APPLICATIONS
SYNTHETIC PRODUCTS (MICROMOLECULES)				
Adefovir	1	1	3	5
Sirolimus	1	2	28	31
Simeprevir	1	6	1	8
Glatiramer	1	10	3	14
Entecavir	0	3	2	5
Daclatasvir	0	10	0	10
Sofosbuvir	0	20	1	21
Miglustate	0	0	2	2
BIOLOGICAL PRODUCTS (MACROMOLECULES)				
Adalimumab	2	22	9	33
Peginterferon alfa-2a	1	4	10	15
Golimumab	0	2	0	2
Peginterferon alfa-2b	0	3	8	11
Natalizumab	0	3	4	7
Tocilizumab	0	5	3	8
Alphavelaglycerase	0	6	0	6

Continued Table 3

API (CEAF 1A)	TOTAL GRANTED PATENTS	TOTAL PENDING APPLICATIONS	OTHER STATUS (REJECTED, DISMISSED, EXPIRED)	TOTAL NUMBER OF BR PATENT APPLICATIONS
Etanercept	0	9	6	15
Rituxmab	0	14	29	43
Abatacept	0	16	3	19
Certolizumab	0	27	2	29
TOTAL	7	163	114	284

Source: authors, based on the INPI patent database Legend: Darker color, active pharmaceutical ingredients with at least one patent granted; lighter color, active pharmaceutical ingredients without patent granted; no color, active pharmaceutical ingredients without patent granted or pending application.

Table 4 – Patent status in December 2016 for CEAF 1B active pharmaceutical ingredients. Brazil, 2016.

API (CEAF 1B)	TOTAL GRANTED PATENTS	TOTAL PENDING APPLICATIONS	OTHER STATUS (REJECTED, DISMISSED, EXPIRED)	TOTAL NUMBER OF BR PATENT APPLICATIONS
SYNTHETIC PRODUCTS (MICROMOLECULES)				
Tolcapone	1	0	0	1
Deferasirox	1	2	6	9
Danazol	0	3	0	3
Bromocriptine	0	2	3	5
Ambrisentana	0	1	3	4
Deferiprone	0	1	1	2
Iloprost	0	0	1	1
Gosserelin	0	0	2	2
Lanreotide	0	0	6	6
BIOLOGICAL PRODUCTS (MACROMOLECULES)				
Dornase alfa	0	2	3	5
TOTAL	2	11	25	38

Source: authors, based on the INPI patent database. Legend: Darker color, active pharmaceutical ingredients with at least one patent granted; lighter color, active pharmaceutical ingredients without patent granted; no color, active pharmaceutical ingredients without patent granted or pending application.

Table 5 – Patent status in December 2016 for ARVs active pharmaceutical ingredients. Brazil, 2016.

API (CESAF ARV)	TOTAL GRANTED PATENTS	TOTAL PENDING APPLICATIONS	OTHER STATUS (REJECTED, DISMISSED, EXPIRED)	TOTAL NUMBER OF BR PATENT APPLICATIONS
SYNTHETIC PRODUCTS (MICROMOLECULES)				
Didanosine	1	0	5	6
Tipranavir	1	1	6	8
Etravirine	1	7	1	9
Fosamprenavir	2	0	8	10
Maraviroc	2	0	6	8
Abacavir	3	1	9	13
Lopinavir / ritonavir	3	5	7	15
Enfuvirtide	0	1	6	7
Raltegravir	0	3	2	5
Dolutegravir	0	4	1	5
Darunavir	0	9	8	17
TOTAL	13	31	59	103

Source: authors, based on the INPI patent database. Legend: Darker color, active pharmaceutical ingredients with at least one patent granted; lighter color, active pharmaceutical ingredients without patent granted; no color, active pharmaceutical ingredients without patent granted or pending application.

Table 6 – Patent status in December 2016 for active pharmaceutical ingredients of Cancer treatment medicines. Brazil, 2016.

API (CANCER)	TOTAL GRANTED PATENTS	TOTAL PENDING APPLICATIONS	OTHER STATUS (REJECTED, DISMISSED, EXPIRED)	TOTAL NUMBER OF BR PATENT APPLICATIONS
SYNTHETIC PRODUCTS (MICROMOLECULES)				
Cyclophosphamide	1	0	0	1
Degarelix	1	1	1	3
Lapatinib	1	1	1	3
Vandetanib	1	3	3	7
Erlotinib	1	3	5	9
Temsirolimus	1	4	1	6
Sorafenib	1	5	3	9
Eribulin	1	10	1	12

Continued Table 6

API (CANCER)	TOTAL GRANTED PATENTS	TOTAL PENDING APPLICATIONS	OTHER STATUS (REJECTED, DISMISSED, EXPIRED)	TOTAL NUMBER OF BR PATENT APPLICATIONS
Pazopanib	0	1	1	2
Cladribine	0	1	1	2
Enzalutamide	0	2	0	2
Melphalan	0	2	2	4
Abiratenone	0	3	0	3
Sunitinib	0	3	8	11
Dasatinib	0	3	1	4
Gefitinib	0	4	0	4
Vemurafenib	0	4	2	6
Nilotinib	0	15	1	16
Exemestane	0	0	3	3
BIOLOGICAL PRODUCTS (MACROMOLECULES)				
Trastuzumab	1	21	9	31
Bevacizumab	1	24	4	29
Pertuzumab	1	24	2	27
Cetuximab	0	15	4	19
L-asparaginase	0	1	0	1
Aldesleukin	0	0	1	1
TOTAL	11	150	54	215

Source: authors, based on the INPI patent database. Legend: Darker color, active pharmaceutical ingredients with at least one patent granted; lighter color, active pharmaceutical ingredients without patent granted; no color, active pharmaceutical ingredients without patent granted or pending application.

In analytical terms, the patent status of an API already allows us to assess whether its exclusivity situation in Brazil can be explained by a patent barrier. As shown in Tables 3, 4, 5 and 6, it is possible to group active pharmaceutical ingredients into at least three groups: those having at least one granted patent, those with only pending applications with or without applications with other statuses, and those that only have dismissed, rejected, extinct or expired applications.

For the first group, there is a greater likelihood of a patent barrier, even though it is worth analysing the content (claims) to assess whether the patent protects the API or its synthetic process (primary patent) or

if it is secondary. This influences the scope of the protection and consequently affects the options of action. In the second group, exclusivity can be explained by a pending situation for some applications, which requires as a second step a content analysis (claims) for a risk assessment for the production and the possibilities of procurement. The third group suggests that there is no patent barrier of any kind to the current API.

4.4 Analysis of the Content of Claims of Patent Applications

In the claims content analysis step, we sought to separate patent applications that included the API or its synthetic process (primary claims) from those considered to be secondary, according to specific modalities. A patent application is broadly structured in two main parts: a descriptive report, wherein the invention is presented, and the claims, which contains the content for which patent protection is requested.

This analysis was performed for patent applications of all active pharmaceutical ingredients (synthetic and biological). For synthetic products, this distinction can be made from parameters and definitions well described in specialised literature. For biological products, the same approach (primary and secondary) was applied, and preliminary results of the claims analysis of these applications are presented as "indicative of primary claim" and "indicative of only secondary claim" to illustrate early efforts. They are also presented in a specific section (section 4.5).

The synthetic and biological products claim analysis led to the exclusion of 80 patent applications that were considered not directly related to the active pharmaceutical ingredients of the sample. We believe that this information makes an important contribution to our research field, as these applications were initially identified as related to a given medicine and may eventually be listed in other patent mapping studies, suggesting a larger number of patent applications around a given medicine and increasing uncertainty over its patent status.

Of the remaining 640 applications - 74 did not have their claims analysed because they were identified at the most advanced stage of the research and had already been dismissed at the INPI, and 2 were not anal-

ysed because their claims were not found in any national or international source. 96 dismissed applications were also analysed because they were identified in the initial stages of our research study. [G]

A total of 564 patent applications were analysed for their claims, of which 301 applications refer to the active pharmaceutical ingredients of synthetic products whose analyses will be presented in this section. The results for biological products will be presented in the next section. Table 7 shows the distribution of filed applications according to the "primary" and "secondary" categories. The ratio of applications with only secondary claims to primary claims is 2.7.

Table 7 – Classification of patent applications by claim analysis of synthetic active pharmaceutical ingredients.

GROUP OF MEDICINES	APPLICATIONS WITH PRIMARY CLAIMS	APLICATIONS WITH ONLY SECONDARY CLAIMS	APPLICATIONS NOT REVIEWED
CEAF 1A	18	58	20
CEAF 1B	3	24	6
ARV	25	75	3
Cancer	34	64	9
TOTAL	80	221	38

Source: authors.

Tables 8, 9, 10 and 11 present a cross-checking exercise of the quality of patent applications with their respective statuses in December 2016. This information enhances the interpretive potential on the exclusivity situation as a result of the primary patent (s) granted or secondary patents granted, as well as allows for a deeper analysis of pending applications and their potential to block competition. Of the 21 active pharmaceutical ingredients that had at least one patent granted, only 14 were classified as primary, that is, covering the active ingredient (11) or only its chemical synthesis process (3) (Chart 2).

It is worth mentioning that, as a rule, a product patent covering an active pharmaceutical ingredient has a greater potential to block

G We decided not to analyse dismissed patent applications identified later because throughout our research work process these applications were deemed as not relevant to the subsequent analysis of ingredient API monopoly situation.

competition against generic medicines than a patent for the synthetic process, as it may be possible to obtain the same active ingredient by different synthesis processes.

Chart 2 – Active pharmaceutical ingredients of synthetic products with at least one granted patent (primary or secondary). Brazil, 2016.

API	TYPE OF PRIMARY PATENTE GRANTED	TYPES OF CLAIMS OF SECONDARY PATENTS GRANTED	TYPE OF PRIMARY APPLICATION PENDING
Abacavir	Synthesis process (PI9813048-0)	Combination, use, method of treatment, others (packing) (PI9607851-0) Compound, Marksuh formula, isomer, synthetic processo f the compound, synthesis intermediate) (PI9810472-1)	0
Adefovir	API (PI1100467)	0	0
Ciclofosfamida	Synthesis process (PI9814266-6)	0	0
Deferasirox	API (PI97099732)	0	0
Degarelix	API (PI 9808523-9)	0	0
Didanosina	0	Composition, formulation, synthesis process not involving the API (PI9815861-9)	0
Eribulina	API (PI 9911326-0)	0	0
Erlotinibe	API and synthesis process (PI 9601200-5)	0	0
Etravirina	API and synthesis process (PI9915552-4)	0	API and synthesis process (PI0609291-8)
Fosamprenavir	0	Compound, composition, combination, method of treatment, use, synthetic process of the compound (PI9912156-5); composition, route of administration, synthetic process not involving the API (PI9708238-4)	0
Glatiramer	0	Composition, use, route of administration (PI9807076)	Synthesis process (PI0515033-7 e BR112012027753)
Lapatinibe	API (PI 9906904-0)	0	0

Continued Chart 2

API	TYPE OF PRIMARY PATENTE GRANTED	TYPES OF CLAIMS OF SECONDARY PATENTS GRANTED	TYPE OF PRIMARY APPLICATION PENDING
Lopinavir/Ritonavir	API (PI1100661-7) API and synthesis process (PP1100397-9)	Compound, composition, selection patent, combination, formulation (PI9714310-3)	API and synthesis process (PI0108146-2 e PI0512970-2)
Maraviroque	API (PI9917007-8); API and synthesis process (PI0110955-3)	0	0
Simeprevir	0	Use, synthetic process of other compound, composition, esters, ethers and salts (PI1008918)	API/ synthesis process (PI0614654-6); API (PI0923393)
Sirolimo	0	Composition, doses, synthetic process not involving the compound (PI9801120)	Synthesis process (PI0509852)
Sorafenibe	0	Compound, composition, ester, ethers and salts (PI 0007487-0)	API (PI 0017535-8)
Tensirolimo	API and synthesis process (PI 95073230)	0	0
Tipranavir	0	Composition, formulation (PI9810729-1)	0
Tolcapona	Synthesis process (PI9800426)	0	0
Vandetanibe	API and synthesis process (PI9711302-6)	0	0

Source: Authors.

Cross-checking patent status with patent applications content is extremely important information, since it reinforces that patent status analysis is insufficient to confirm that the protected active ingredient is blocked or not against competition.

Secondary patent applications, on the other hand, may also constitute a barrier to competition in specific situations. This is because some active pharmaceutical ingredients may be marketed in new pharmaceutical forms and presentations and such modifications may be accompanied by secondary patent applications granted in the country, contemplating related claims, which eventually result in a barrier to competition for such medicines, as described in other research studies.[35-38]

When presenting their preliminary results for the Brazilian Inquiry on Competition in the Pharmaceutical Sector Pereira and Fiuza (2013)[36] pointed out that:

> *As patent activity intensifies in the last few years preceding the expiration of the primary patent, a broad network of patent clusters is created, which is developed around the original invention and makes it difficult to delimit the protected material content and scope. Because of this uncertainty, the development of generic versions of the original or incremental product is made more difficult or less attractive by generic laboratories ". (p. 35, free translation)*

The granting of a secondary patent does not protect against the active pharmaceutical ingredients in its first pharmaceutical form and presentation. A secondary claim may protect what the authors called second-generation products. Thus, it is possible that one particular pharmaceutical form of the same medicine is in a patent monopoly situation and another is not.

We can illustrate this situation with two documented cases of ARVs - didanosine and lopinavir/ritonavir - whose pharmaceutical forms have been replaced in the market and whose respective secondary patent applications could allow the extension of the company's exclusivity rights over the product (See Chart 3).

However, applications for secondary patents, if not objectively followed by second generation products in the market, may not constitute a barrier to the entry of generics in relation to the first product that entered the market, and are seen as causing confusion about the product patent status in the market.

Chart 3 – Secondary patent applications and their relationship to new pharmaceutical forms of ARVs

Didanosine was originally produced locally in Brazil in the 1990s as it did not have patent protection of the active pharmaceutical ingredient. However, an enteric coating didanosine was later launched by Bristol-Myers Squibb, as a secondary patent covering this form was granted, and this pharmaceutical form was then adopted by the Ministry of Health. Thus, the company sells enteric coating didanosine exclusively to the Ministry of Health. Another pharmaceutical form without patent protection continued to be produced and supplied by public manufacturers.

Lopinavir-ritonavir was released as a refrigeration-dependent gel capsule and was protected in Brazil by a pipeline patent which expired in March 2017. In 2005, the Ministry of Health adopted the heat-stable tablet form, which was not dependent on refrigeration, and had a new pending patent application for analysis which, if granted, would expire in 2024. This patent application got an Anvisa[H] prior non-consent in 2014 and subsequently the first rejection decision by INPI in October 2015. The company filed an administrative appeal and the rejection was upheld in October 2017. Had this secondary patent been granted, it could have prevented the marketing of a generic version of the heat-stable form until at least 2024, seven years after the expiration of the patent that protected the gel capsule form and the active pharmaceutical ingredient

Source: Adapted from Villardi[38] and Scopel[44]

H The LPI establishes that the granting of a patent in the pharmaceutical area depends on Anvisa's prior consent (article 229-C). The content of the prior consent is in dispute, with two main interpretations: one that understands that Anvisa must verify if the patent application meets all the requirements established in the LPI so that it can be granted and another that understands that Anvisa should only analyse whether the content of the application presents a health hazard or not. Currently, the last regulation on the subject establishes that Anvisa's market approval in itself should only analyse sanitary risk, but that Anvisa has the option to present considerations on the fulfilment of patentability requirements as a third-party observations to the INPI. This ordinance has been challenged in court by the Federal Public Prosecutor's Office regarding its legality, since it understands that the LPI requires Anvisa to analyse all the necessary requirements for the granting of a patent (public civil action number 87409-43.2014.4.01.3400, 16th Federal Court of the Federal District).

Table 8 – Cross-check of patent application classification with status in December 2016 for synthetic active pharmaceutical ingredient for CEAF 1A group. Brazil, 2016.

API	TOTAL NUMBER OF PRIMARY PATENT APPLICATIONS		STATUS OF PRIMARY APPLICATIONS		TOTAL NUMBER OF SECONDARY PATENT APPLICATIONS	STATUS OF SECONDARY APPLICATIONS	TOTAL NUMBER OF DISMISSED AND NON--REVIEWED APPLICATIONS	TOTAL NUMBER OF BR APPLICATIONS
	PRODUCT	PROCESS	PRODUCT	PROCESS				
Adefovir	1	0	1 Granted	N/A	4	1 Pending; 3 Rejected	0	5
Simeprevir*	1	2	1 Pending	2 Pending	6	1 Granted; 4 Pending; 1 Dismissed	0	8
Sirolimus	0	1	N/A	1 Pending	12	1 Granted; 1 Pending; 3 Rejected; 7 Dismissed	18	31
Glatiramer	0	2	N/A	2 Pending	11	1 Granted; 8 Pending; 1 Rejected; 1 Dismissed	1	14
Daclatasvir	1	2	1 Pending	2 Pending	7	7 Pending	0	10
Entecavir	1	2	1 Expired	2 Pending	2	1 Pending; 1 Dismissed	0	5
Sofosbuvir*	3	4	3 Pending	4 Pending	16	15 Pending; 1 Dismissed	0	21
Miglustate	1	0	1 Rejected	N/A	0	N/A	1	2

Source: authors based on search at INPI database. Legend: *Product and process claims in the same patent application.
N/A – not applicable

Table 9 – Cross-check of patent application classification with status in December 2016 for synthetic active pharmaceutical ingredient for CEAF 1B group. Brazil, 2016.

API	TOTAL NUMBER OF PRIMARY PATENT APPLICATIONS		STATUS OF PRIMARY APPLICATIONS		TOTAL NUMBER OF SECONDARY PATENT APPLICATIONS	STATUS OF SECONDARY APPLICATIONS	TOTAL NUMBER OF DISMISSED AND NON--REVIEWED APPLICATIONS	TOTAL NUMBER OF BR APPLICATIONS
	PRODUCT	PROCESS	PRODUCT	PROCESS				
Deferasirox	1	0	1 Granted	N/A	4	2 Pending; 2 Dismissed	4	9
Tolcapone	0	1	N/A	1 Granted	0	N/A	0	1
Ambrisentan	0	0	N/A	N/A	4	1 Pending; 3 Dismissed	0	4
Deferiprone	0	0	N/A	N/A	2	1 Pending; 1 Rejected	0	2
Bromocriptine	0	0	N/A	N/A	5	2 Pending; 1 Rejected; 1 Dismissed	0	5
Danazol	0	0	N/A	N/A	3	3 Pending	0	3
Gosserelin	0	0	N/A	N/A	2	2 Rejected	0	2
Iloprost	0	0	N/A	N/A	1	1 Dismissed	0	1
Lanreotide	1	0	1 Rejected	N/A	3	1 Rejected; 1 Dismissed; 1 Expired	2	6

Source: authors based on search at INPI database. Legend: *Product and process claims in the same patent application.
N/A – not applicable

Table 10 – Cross-check of patent application classification with status in December 2016 for ARV active pharmaceutical ingredient. Brazil, 2016.

API	TOTAL NUMBER OF PRIMARY PATENT APPLICATIONS		STATUS OF PRIMARY APPLICATIONS		TOTAL NUMBER OF SECONDARY PATENT APPLICATIONS	STATUS OF SECONDARY APPLICATIONS	TOTAL NUMBER OF DISMISSED AND NON--REVIEWED APPLICATIONS	TOTAL NUMBER OF BR APPLICATIONS
	PRODUCT	PROCESS	PRODUCT	PROCESS				
Abacavir	0	1	N/A	1 Granted	12	2 Granted; 1 Pending; 2 Rejected; 6 Dismissed; 1 Expired	0	13
Lopinavir / ritonavir *	4	3	2 Granted; 2 Pending	1 Granted; 2 Pending	10	1 Granted; 3 Pending; 5 Rejected; 1 Dismissed	1	15
Etravirine *	2	2	1 Pending; 1 Granted	1 Granted; 1 Pending	7	6 Pending; 1 Dismissed	0	9
Maraviroc*	5	1	2 Granted; 2 Rejected; 1 Dismissed	1 Granted	2	2 Dismissed	1	8
Didanosine	0	0	N/A	N/A	6	1 Granted; 2 Rejected; 2 Dismissed	0	6
Fosampre-navir	2	1	1 Rejected; 1 Expired	1 Rejected	6	2 Granted; 2 Rejected; 2 Dismissed	1	10
Tipranavir	1	0	1 Dismissed	N/A	7	1 Granted; 1 Pending; 2 Rejected; 3 Dismissed	0	8
Darunavir	1	2	1 Dismissed	2 Pending	14	7 Pending; 2 Rejected; 5 Dismissed	0	17
Dolutegra-vir *	1	3	1 Pending	3 Pending	2	1 Pending; 1 Dismissed	0	5
Enfuvirtide	2	1	1 Rejected; 1 Dismissed	1 Dismis-sed	4	1 Pending; 1 Rejected; 2 Dismissed	0	7
Raltegravir	0	0	N/A	N/A	5	3 Pending; 2 Dismissed	0	5

Source: authors based on search at INPI database. Legend: *Product and process claims in the same patent application.
N/A – not applicable.

Table 11 – Cross-check of patent application classification with status in December 2016 for synthetic active pharmaceutical ingredient for cancer medicines. Brazil, 2016.

API	TOTAL NUMBER OF PRIMARY PATENT APPLICATIONS		STATUS OF PRIMARY APPLICATIONS		TOTAL NUMBER OF SECONDARY PATENT APPLICATIONS	STATUS OF SECONDARY APPLICATIONS	TOTAL NUMBER OF DISMISSED AND NON--REVIEWED APPLICATIONS	TOTAL NUMBER OF BR APPLICATIONS
	PRODUCT	PROCESS	PRODUCT	PROCESS				
Cyclophos-phamide	0	1	1 Granted	N/A	0	N/A	0	1
Temsirolimus *	1	1	1 Granted	1 Granted	5	4 Pending; 1 Rejected	0	6
Degarelix	1	0	1 Granted	N/A	2	1 Pending; 1 Dismissed	0	3
Lapatinib	2	0	1 Granted; 1 Rejected	N/A	1	1 Pending	0	3
Vandetanibe	2	3	1 Granted; 1 Rejected	1 Granted; 1 Pending; 1 Rejected	4	1 Pending; 3 Dismissed	0	7
Eribulin	1	2	1 Granted	2 Pending	9	8 Pending; 1 Rejected	0	12
Erlotinib *	1	5	1 Granted	1 Granted; 1 Rejected; 3 Dismissed	4	3 Pending; 1 Rejected	0	9
Sorafenib	1	0	1 Pending	N/A	7	1 Granted; 4 Pending; 2 Dismissed	1	9
Abiraterone	0	1	N/A	1 Pending	2	2 Pending	0	3
Vemurafeni-be *	2	2	1 Pending; 1 Dismissed	1 Pending; 1 Dismis-sed	4	3 Pending; 1 Dismissed	0	6
Dasatinibe	1	0	1 Pending	N/A	3	2 Pending; 1 Dismissed	0	4
Sunitinibe	2	0	1 Pending; 1 Dismissed	N/A	4	2 Pending; 2 Dismissed	5	11
Enzalutami-de *	2	1	2 Pending	1 Pending	0	N/A	0	2
Gefitinib	1	2	1 Pending	2 Pending	1	1 Pending	0	4
Nilotinib*	2	3	2 Pending	3 Pending	12	12 pending	1	16

Continued Table 11

API	TOTAL NUMBER OF PRIMARY PATENT APPLICATIONS		STATUS OF PRIMARY APPLICATIONS		TOTAL NUMBER OF SECONDARY PATENT APPLICATIONS	STATUS OF SECONDARY APPLICATIONS	TOTAL NUMBER OF DISMISSED AND NON--REVIEWED APPLICATIONS	TOTAL NUMBER OF BR APPLICATIONS
	PRODUCT	PROCESS	PRODUCT	PROCESS				
Cladribine	0	0	N/A	N/A	2	1 Pending; 1 Dismissed	0	2
Pazopanib	1	0	1 Rejected	N/A	1	1 Pending	0	2
Melphalan	0	0	N/A	N/A	2	2 Rejected	2	4
Exemestane*	1	2	1 Expired	2 Dismissed	1	1 Rejected	0	3

Source: authors based on search at INPI database. Legend: *Product and process claims in the same patent application. N/A – not applicable

Table 12 presents the frequency of different categories of secondary claims found in the analysed patent applications according to pharmaceutical classifications. Four categories (compositions, method of treatment, use and Markush formula) accounted for 46.42% of all categories identified.

Table 12 – Frequency of secondary claims of analyzed patent applications for active pharmaceutical ingredients of synthetic products.

TYPE OF SECONDARY CLAIM	TOTAL	PERCENT IN RELATION TO TOTAL (%)
Composition (formulation)	232	17.86%
Other molecules that are not the API	159	12.24%
Method of Treatment	139	10.70%
Use	132	10.16%
Other	123	9.47%
Markush Formula	100	7.70%
Other process of molecules that are not the API	88	6.77%

Continued Table 12

TYPE OF SECONDARY CLAIM	TOTAL	PERCENT IN RELATION TO TOTAL (%)
Selection Patent	64	4.93%
Doses	63	4.85%
Combination	59	4.54%
Sysnthesis intermediate	37	2.85%
Polyform	29	2.23%
Route of Administration	23	1.77%
Esthers, ethers and salts	22	1.69%
Enantiomers	11	0.85%
Product by process	10	0.77%
Pro-drugs/metabolites	8	0.62%
TOTAL OF CLAIMS	1,299	100.0%

Source: authors.

4.5 - Brief Considerations on the Patenting of Biological Products in Brazil

Very little is understood regarding the market dynamics of biological products, as well as the role played by patent protection and the main trends in patenting. In this research study, we sought to identify different patent applications for these active pharmaceutical ingredients and to analyse patent status in December 2016 and the content of the claims. In the claims analyses we applied the same criteria as for synthetic products classification – primary and secondary. However, it is unclear whether these criteria are best suited for the analysis of patent applications for biologicals. This requires further analysis that could be the subject for a

research study in the future.

For this reason, and in order to contribute to a still emerging field in patent literature, we have chosen to present the analysis performed to date, seeking to identify whether claims are indicative of being classified as primary and secondary or not (as detailed in Tables 13, 14 and 15).

Table 13 – Patent applications classification according to active pharmaceutical ingredients claims analysis for biological products.

GROUP OF MEDICINES	APPLICATIONS WITH CLAIMS INDICATIVE OF PRIMARY	APPLICATIONS WITH CLAIMS INDICATIVE OF SECONDARY	NON-REVIEWED APPLICATIONS
CEAF 1A	48	105	35
CEAF 1B	5	0	0
cancer medicines	41	64	3
% IN RELATION TO TOTAL NUMBER OF PATENT APPLICATIONS	94 (31.2%)	169 (56.1%)	38 (12.6%)

Source: authors.

Table 14 – Cross-check of patent application classification with status in December 2016 for biological active pharmaceutical ingredients for CEAF 1A and 1B. Brazil, 2016.

API (CEAF 1A AND 1B)	APPLICATIONS WITH CLAIMS INDICATIVE OF PRIMARY	STATUS OF PATENT APPLICATIONS WITH CLAIMS INDICATIVE OF PRIMARY	TOTAL OF APPLICATIONS WITH CLAIMS INDICATIVE OF SECONDARY	STATUS OF PATENT APPLICATIONS WITH CLAIMS INDICATIVE OF SECONDARY	NON-REVIEWED APPLICATIONS	TOTAL OF BR APPLICATIONS
Abatacept	2	Pending	16	14 Pending; 1 Rejected; 1 Expired	1	19
Adalimumab	13	2 Granted; 8 Pending; 1 Rejected; 2 Dismissed	20	14 Pending; 6 Dismissed	0	33
Peginterferon alfa-2a	1	Granted	13	4 Pending; 2 Rejected; 7 Dismissed	1	15
Peginterferon alfa-2b	0	N/A	11	3 Pending; 3 Rejected; 5 Dismissed	0	11
Alphavelaglycerase	1	Pending	5	Pending	0	6
Certolizumab	13	Pending	14	Pending	2	29
Etanercept	6	Pending	3	Pending	6	15
Golimumab	2	Pending	0	N/A	0	2
Natalizumab	0	N/A	4	3 Pending; 1 Rejected	3	7
Rituximab	9	8 Pending; 1 Expired	13	6 Pending; 6 Rejected; 1 Expired	21	43
Tocilizumab	1	Expired	6	5 Pending; 1 Dismissed	1	8
Dornase alfa	5	2 Pending; 3 Rejected	0	N/A	0	5

Source: authors.

Table 15 – Cross-check of patent application classification with status in December 2016 for biological active pharmaceutical ingredients for cancer medicines. Brazil, 2016.

API (CANCER)	APPLICATIONS WITH CLAIMS INDICATIVE OF PRIMARY	STATUS OF PATENT APPLICATIONS WITH CLAIMS INDICATIVE OF PRIMARY	TOTAL OF APPLICATIONS WITH CLAIMS INDICATIVE OF SECONDARY	STATUS OF PATENT APPLICATIONS WITH CLAIMS INDICATIVE OF SECONDARY	NON-REVIEWED APPLICATIONS	TOTAL OF BR APPLICATIONS
Aldesleukin	0	N/A	1	dismissed	0	1
Bevacizumab	9	8 pending; 1 rejected	20	1 granted; 16 pending; 1 rejected; 2 dismissed	0	29
Cetuximab	14	pending	5	1 Pending; 3 Dismissed; 1 Expired	0	19
L-asparaginase	1	pending	0	N/A	0	1
Pertuzumab	7	1 granted; 6 pending	20	18 pending; 1 dismissed	1	27
Trastuzumab	11	10 pending; 1 dismissed after analysis	18	1 Granted; 11 Pending; 5 Rejected; 1 Dismissed	2	31

Source: authors.

Results indicate that there are 16.7 patent applications on average, per active ingredient and 1.8 secondary application claims for each primary application. These results reinforce the importance of patenting strategies for biological products. On the other hand, considering the dynamics of the entry of biosimilars in the international and national markets, some case studies show that there is no clarity about the role of the patent granted and applications as a potential barrier to competition of each patent.

Table 16 shows the most frequent categories of claims indicative of secondary applications for biological products. With the exception of those classified as "other" (27.13%) because they included, among others, specific aspects to this type of technology, the most frequent categories were "method of treatment" (19.09%), "composition" (19.69%) and "use" (12.12%), totalling to about 50% of the claims.

It should be noted that these categories were also the most frequent for synthetic products, accounting for 38.72% of the claims analysed and classified as secondary (see Table 12). This result suggests that patenting strategies adopted for synthetic products are also applied to biological products.

Table 16 – Frequency of indicative secondary claims of analyzed patent applications for active pharmaceutical ingredients of biological products

TYPE OF CLAIM INDICATIVE OF SECONDARY	TOTAL	% IN RELATION TO TOTAL
Method of Treatment	159	19.09%
Composition (formulations)	164	19.69%
Use	101	12.12%
Doses	50	6.00%
Other macromolecules that are not the API	38	4.56%
Route of administration	29	3.48%
Combination	27	3.24%
Markush Formula	15	1.80%
Selection Patent	13	1.56%
Other modalities (polyphorms, esters / ethers / salts, isomer, intermediate, product by process, metabolite / prodrug)	11	1.32%
Others*	226	27.13%
TOTAL OF CLAIMS	833	100.0%

Source: authors. *Claims with specifics of biological products.

4.6 - The Problem with Multiple Patent Applications

Multiple patent applications for a single medicine in different statuses, generate legal uncertainty about the patent situation of the medicine. This uncertainty affects the performance of potential competitors in the domestic market, contributing to exclusivity situation from the supply side in the country. This is the main problem that this research study aims to analyse.

Although patent evergreening has already been widely studied, the extensiveness of this practice in the medicines procured by the Unified Health System, together with patent status analyses and claim content analyses is most probably unprecedented in the Brazilian context.

The results presented allow the identification of four categories for sample classification, two of which indicate that the active pharmaceutical ingredients included in them do not have a patent barrier and, therefore, exclusivity situation occurs due to other factors (see Figure 7). Most of the active pharmaceutical ingredients in the sample (59 out of 74), however, fall into those categories with at least one patent granted or with at least one pending patent application under review. We can deduce that legal uncertainty is not only characterised by the existence of multiple patent applications for a single product, but also by pending patent status. If the multiple applications went through a faster review process, there would be less uncertainty generated.

If we take into consideration only a patent monopoly, that is to say, resulting from a patent granted in the country in December 2016, we will see that of the 65 active pharmaceutical ingredients with patent applications identified in Brazil, only 26 have patents with granted status and six others with expired or extinct status. This means that the other 33 active pharmaceutical ingredients have never had patent protection in Brazil. In addition to the other nine, for which no relevant patent was identified in Brazil and the other three considered as not having a patent barrier because of generic production in the country, we have the situation of 45 active pharmaceutical ingredients without a “legal” patent barrier in December 2016 (that is, in 58% of cases).

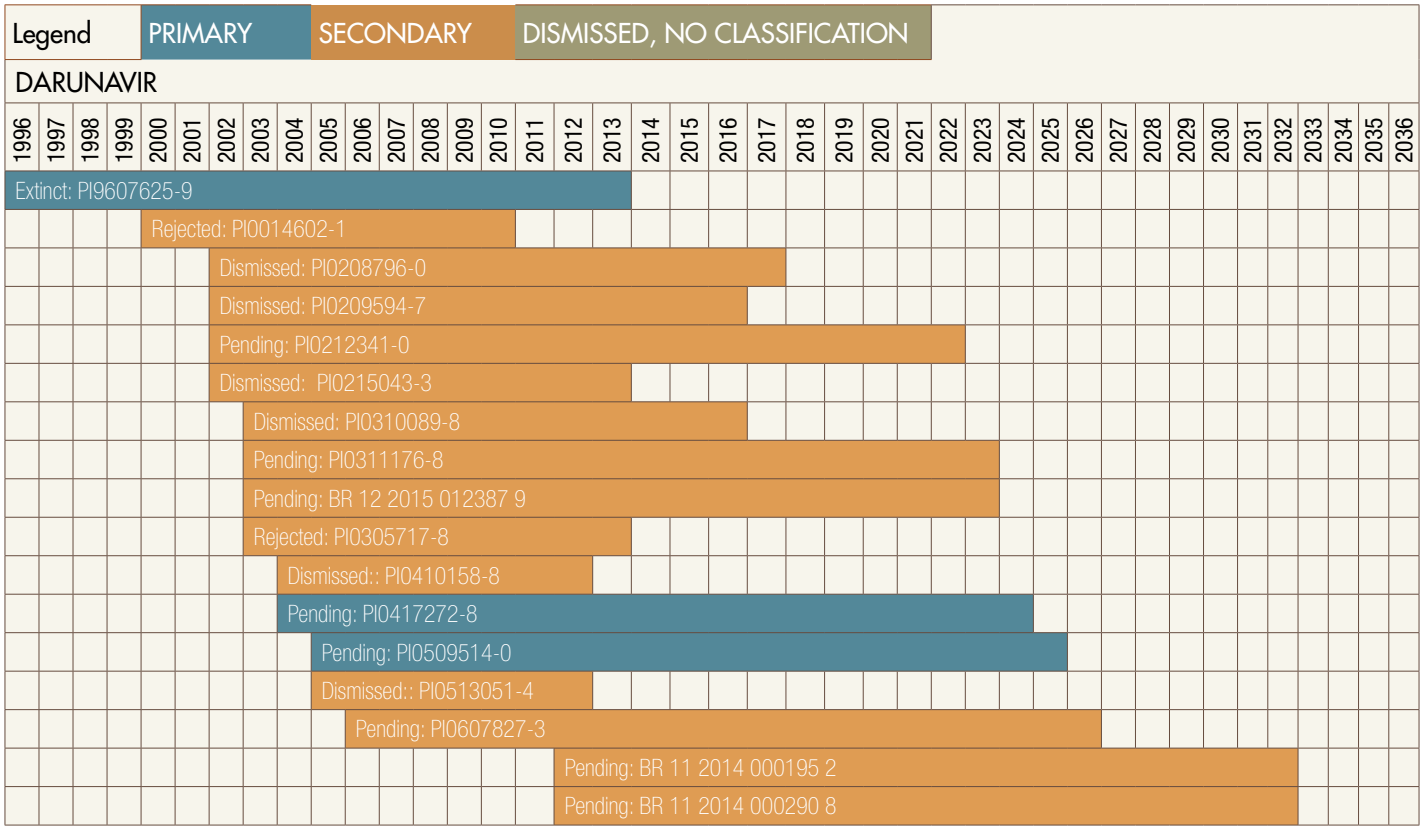
Our analytical effort sought not only to provide an overview of the patenting situation of the active pharmaceutical ingredients of the sam-

ple, but also to present a reflective path in which layers of interpretation were added by analysing the status and then the claims.

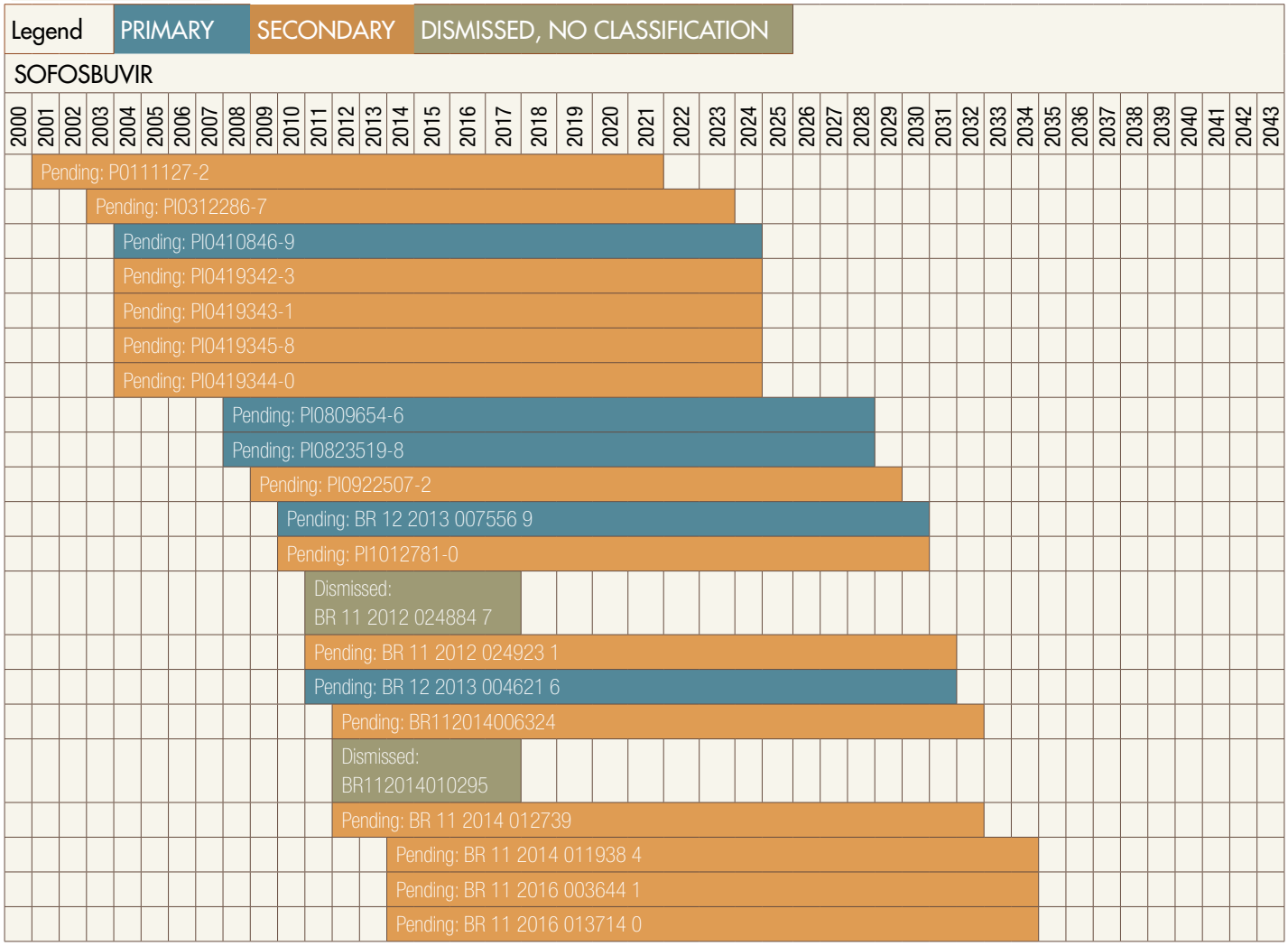
These layers were necessary, first, because there is more than a merely linear or binary view, such as "there is or there is no patent" type, for each situation. Secondly, they also made it possible to identify measures to be taken in order to overcome patent barriers, as illustrated by the list of patent applications candidates for priority examination and for patent oppositions (in Brazil, known as third party observation).

A third analytical layer was developed based on the chronology of patent filings by active ingredient (Figure 8) which, besides illustrating the effect of evergreening, critically appraise the cases that had more than one application classified as primary. Applications classified as primary at a much later stage following initial filings should be considered as potentially missing the "novelty" and / or "inventiveness " patentability requirements.

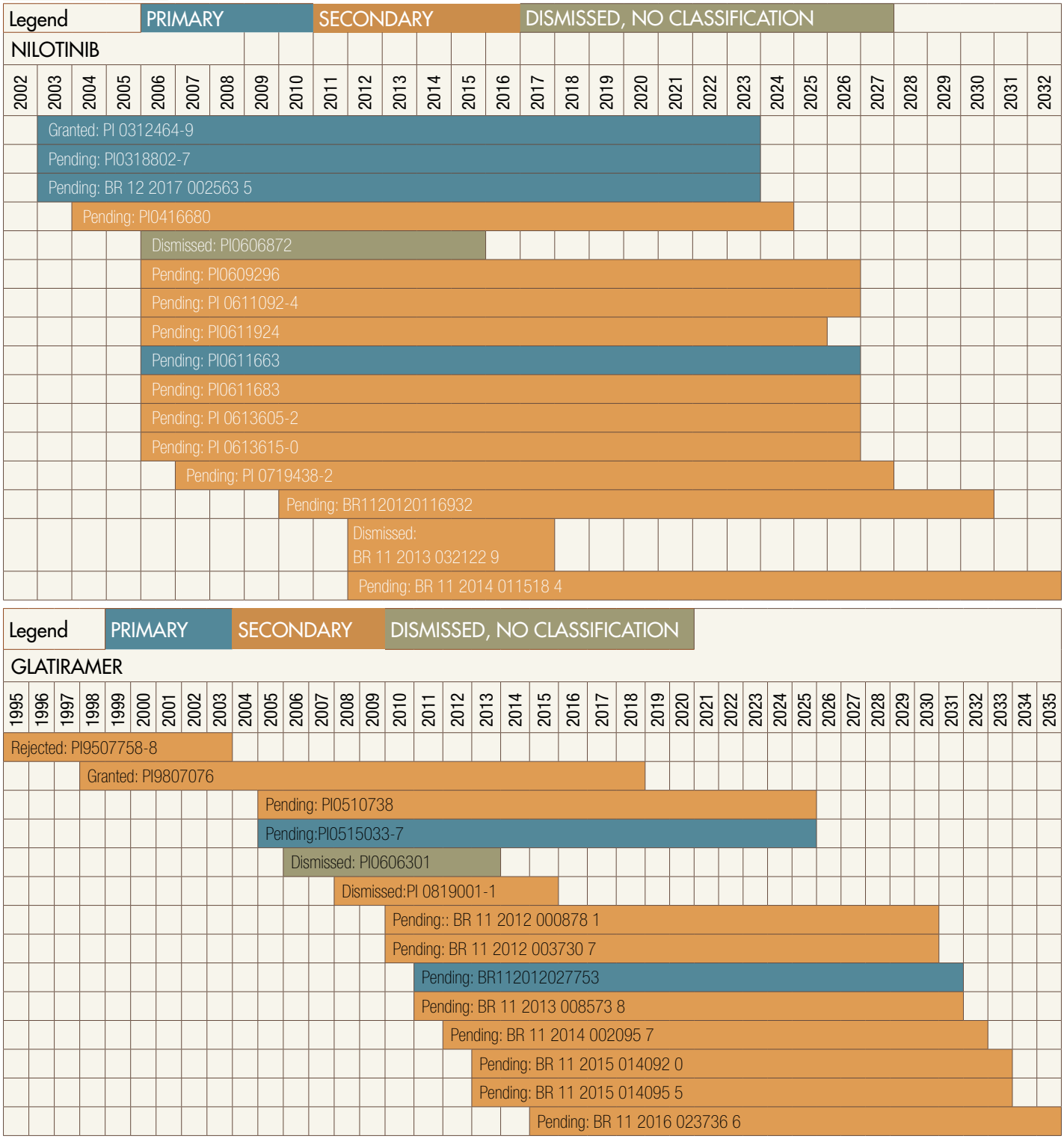
Figure 6 – Chronology of patent applications in Brazil for 4 active pharmaceutical ingredients (darunavir, sofosbuvir, nilotinib and glatiramer) according to status in 2016.



Continued Figure 6



Continued Figure 6



Source: authors. Blue - applications with claims classified as primary. Orange - applications with claims classified as secondary. The timeline takes into account the general 20-year term rule for patents from the date of filing, not considering possible extension due to the time of analysis of the application, as provided in article 40 caput and sole paragraph of the LPI.

5. Translation of Patent Data into Strategic Information for Access to Medicines Policies

The results presented so far, ranging from the selection medicines in exclusivity situation from the supply side to the analysis of patent situation - covering the identification of national applications, their status and the classification of claims - generate strategic information for both the monitoring of pharmaceutical market trends as well as the identification of specific policy options for overcoming patent barriers and to promote competition as part of the efforts to increase access to medicines.

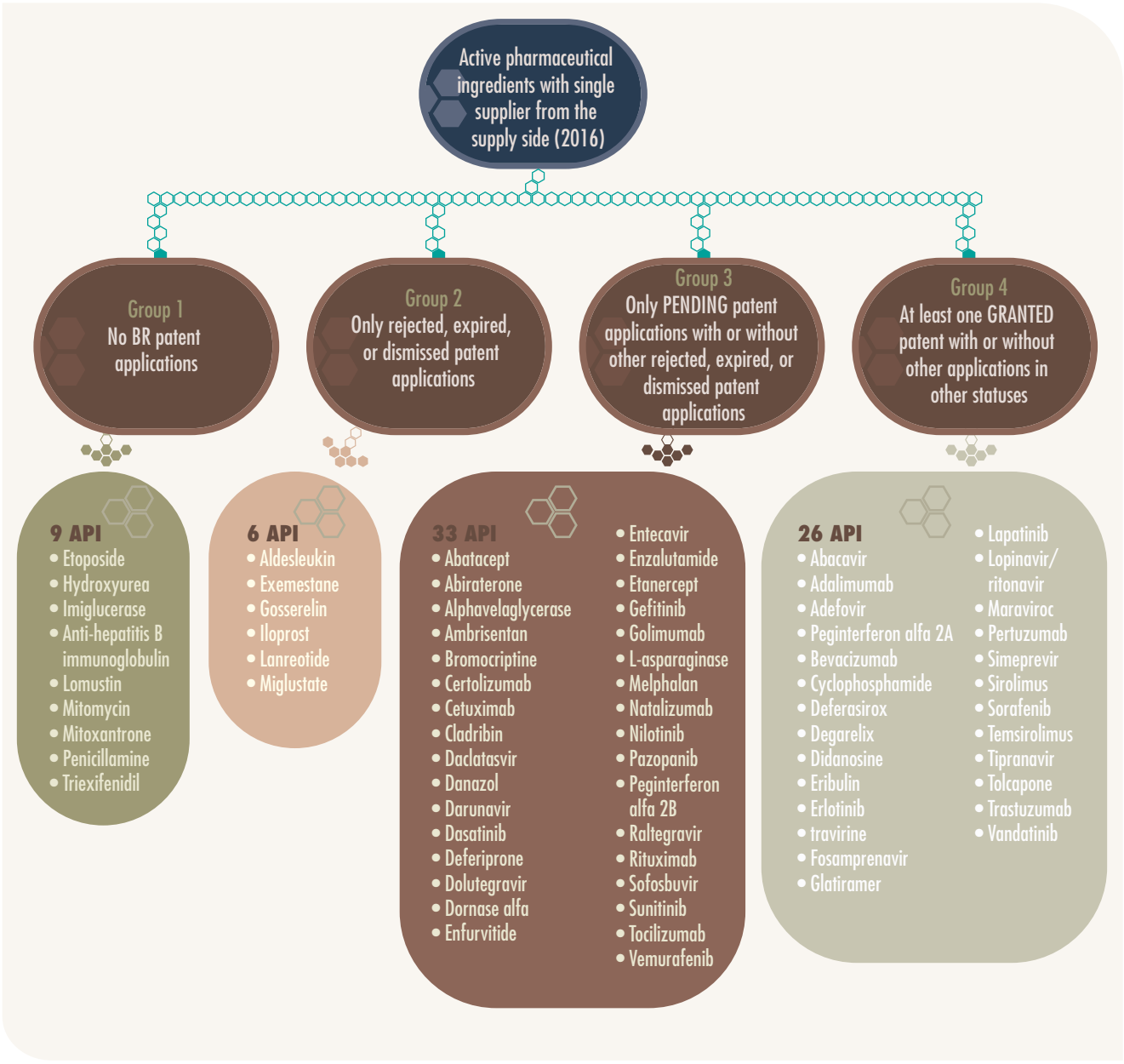
By mapping national patent applications and analysing their patent status, we were able to classify the 74 active pharmaceutical ingredients into four categories, as shown in Figure 7. Those without applications found in Brazil (Group 1) or with national applications in rejected, dismissed, expired or extinct status (Group 2) were considered to be without a patent barrier in the country. Therefore, the exclusivity situation is a result of other factors in the market dynamics of these products that are not explained by their patent situation.

The active pharmaceutical ingredients classified in Group 3 (from a total of 33) were those whose patent applications are pending or in other statuses (rejected, expired, dismissed, extinct) and without any granted patent. This was the most represented group in our sample, and which motivated the present research.

The active pharmaceutical ingredients classified in Group 4 (from a total of 26) are those that had at least one patent granted as of December 2016. As will be discussed below, the existence of a granted patent, without due consideration to the content of the claims, may prove insufficient to judge whether it is a barrier to the entry of competitors, and it is also necessary to evaluate the content of the application for a better risk assessment.

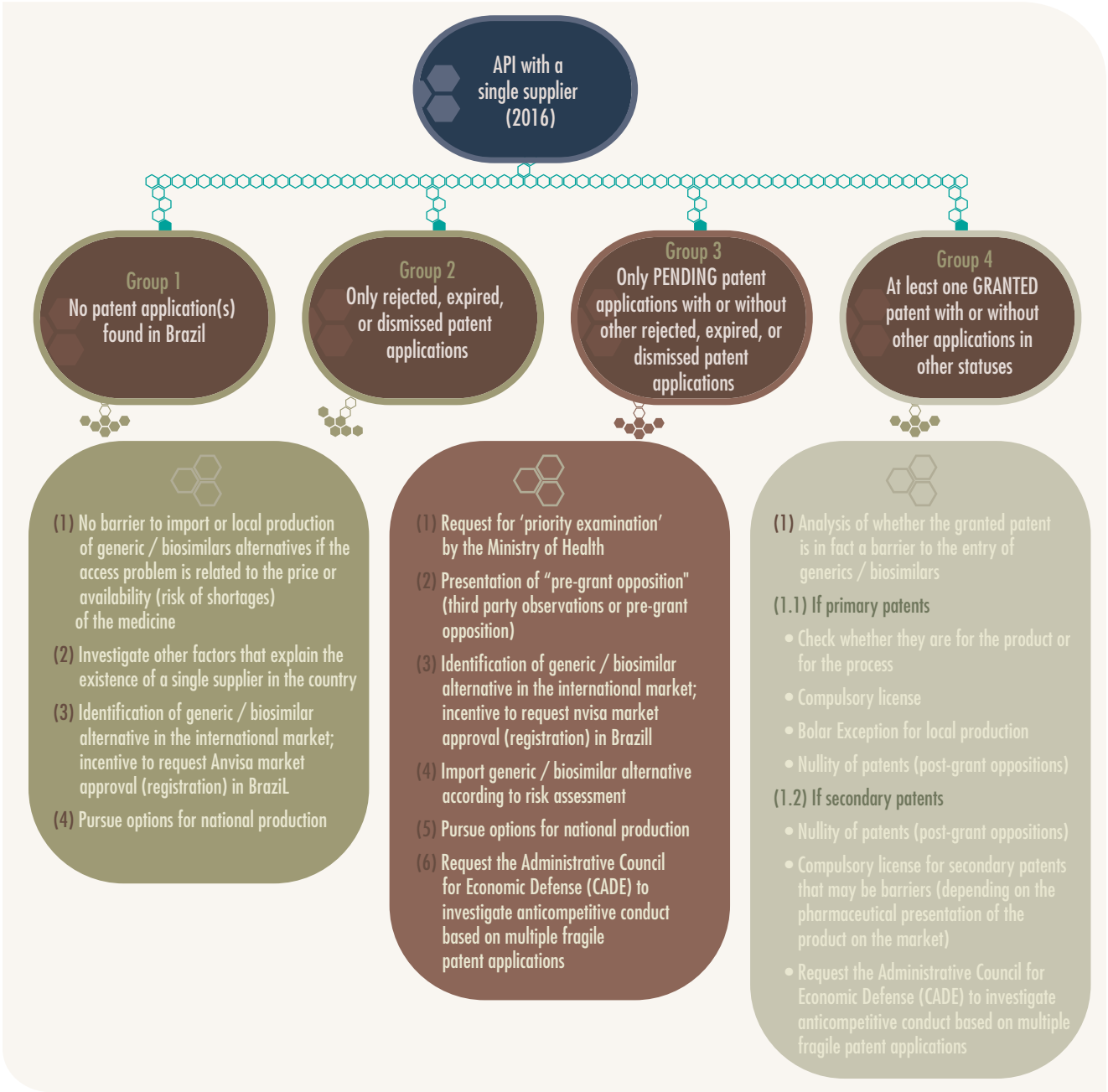
Figure 8 presents initiatives and policy options that might be considered from the results of patent status analysis of applications identified in the country.

Figure 7 – Synthesis of patent situation as of December 2016 of the 74 active pharmaceutical ingredients of the sample



Source: authors, based on the INPI patent database.

Figure 8 – Options of initiatives and policies to be considered from the mapping and analysis of the patent status of the active pharmaceutical ingredients of the sample.

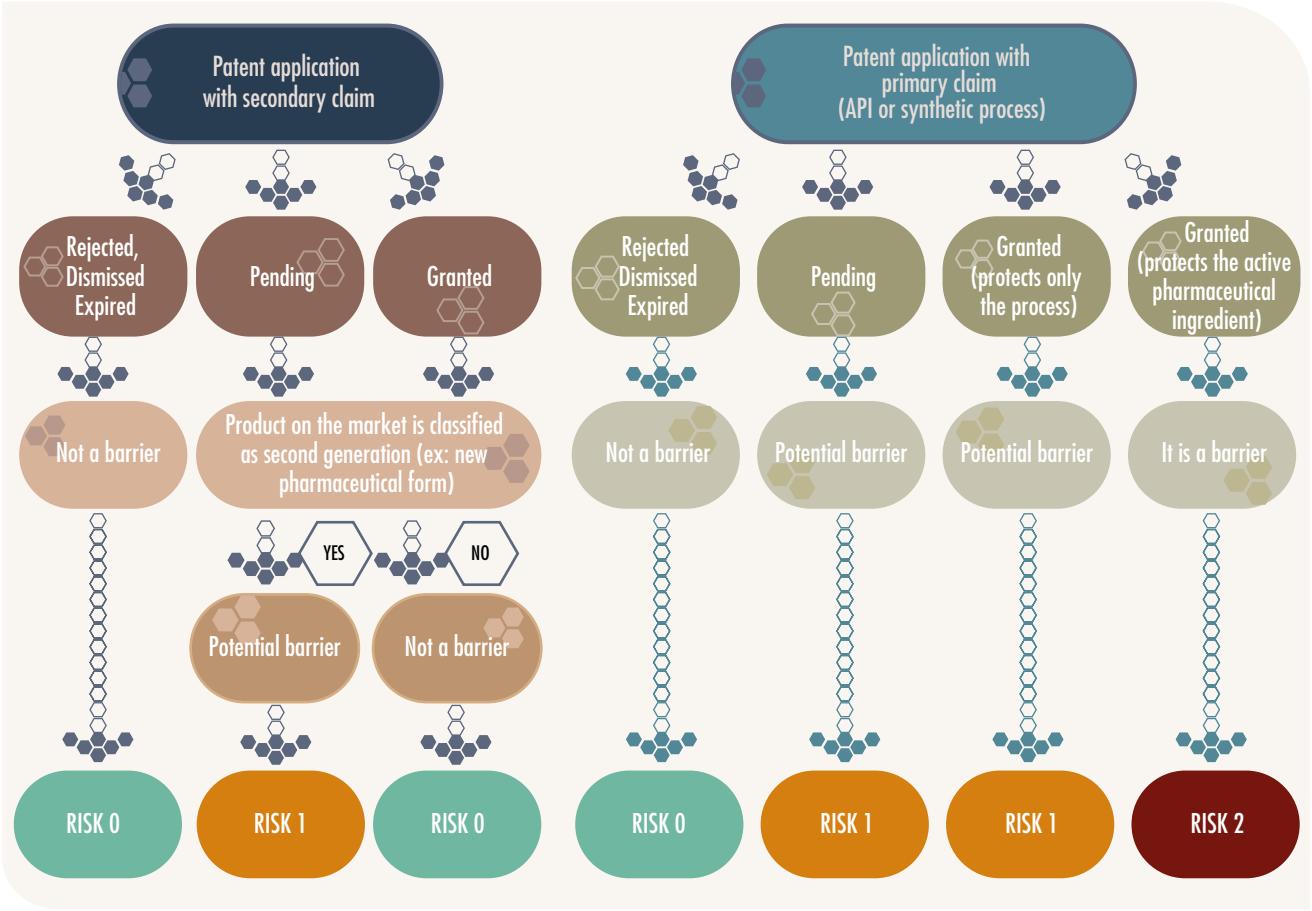


Source: authors.

Cross checking patent status with the analysis of the content of the claims can generate strategic information. First, it allows for a deeper examination of the risk of whether or not a patent application or a granted patent constitutes a barrier to competition.

In Figure 9 we look at whether a ranking for risk assessment of patent applications would be a barrier to generic/biosimilar medicine entry into the market. We assume that there are differences between primary process claims and product claims, considering that in the absence of a product patent, a competitor may adopt a synthetic route to get to the product without necessarily infringing patents related to the synthesis process.

Figure 9 – Ranking for risk assessment of a patent application being a barrier to the entry of generic / biosimilar medicines in the market.



Source: authors.

Another relevant deduction from the "status and claim" cross checking is the identification of applications that may be the subject of a request for priority examination by the Ministry of Health and pre-grant opposition (in Brazil, known as "third party observation") They are applications classified as primary and that are still pending examination, especially those related to products. The patent applications identified for each active pharmaceutical ingredient in this situation are listed in Chart 4.

Regarding pre-grant oppositions, it is necessary to make a more detailed analysis of the applications classified as primary to verify if they potentially fulfil the requirements and conditions of patentability stipulated by the LPI. In case of non-compliance, they must be considered as priority candidates for pre-grant oppositions that may contribute to the patent not to be granted unduly. Secondly, applications classified as secondary should also be considered for pre-grant opposition, to avoid the extension of the monopoly situation resulting from evergreening strategies.

Chart 4 – List of patent applications classified as primary and pending of synthetic active pharmaceutical ingredients in December 2016 selected as candidates for the request for priority examination and submission of pre-grant opposition to the INPI

ACTIVE PHARMACEUTICAL INGREDIENT	NUMBER OF THE PATENT APPLICATION	TYPE OF PRIMARY PATENT	OTHER PRIMARY PATENTS GRANTED
Glatiramer	PI0515033-7	Process	
	BR112012027753	Process	
Simeprevir	PI0614654-6	product and process	
	PI0923393	Process	
Sirolimus	PI0509852	Process	
Daclatasvir	PI0716483-1	Product	
	PI0815611-5	Process	
	BR 11 2012 011134 5	Process	
Entecavir	PI0317255-4	Process	
	PI0510743	Process	

Continued Chart 4

ACTIVE PHARMACEUTICAL INGREDIENT	NUMBER OF THE PATENT APPLICATION	TYPE OF PRIMARY PATENT	OTHER PRIMARY PATENTS GRANTED
Lopinavir/ritonavir	PI0108146-2	product and process	PP1100397-9 (product and process)
	PI0512970-2	product and process	
Etravirine	PI0609291-8	product and procedure/Process	PI9915552-4 (product and process)
Darunavir	PI0417272-8	Process	
	PI0509514-0	Process	
Dolutegravir	PI0610030	product and process	
	BR 11 2013 002461 5	Process	
	PI0923217	Process	
Vandetanib	PI 0015203-0	product and process	PI9711302-6 (product and process)
	PI0616715	Process	
Eribulin	BR 11 2012 018232 3	Process	PI 9911326-0 (product)
	BR 11 2016 009452 2	Process	
Sorafenib	PI 0017535-8	Product	
Gefitinib	PI 9608082-5	Product	
	PI0314238-8	Process	
	PI0308023	Process	
Nilotinib	PI 0312464-9	product and process	
	PI0318802-7	product and process	
	PI0611663	Process	
Sunitinib	PI 0108394-5	Product	
Vemurafenib	BR 11 2012 002251 2	product and process	
Dasatinib	PI 0009721-7	Product	
Abiraterone	BR 11 2015 023629 4	Process	

Source: the authors.

Chart 5 – List of patent applications classified as indicative of primary and pending of biological active pharmaceutical ingredients in December 2016 selected as candidates for the request for priority examination and submission of pre-grant opposition to the INPI

ACTIVE PHARMACEUTICAL INGREDIENT	PATENT APPLICATION NUMBER	TYPE OF PATENT INDICATIVE OF PRIMARY
Adalimumab	PI9715284-6	Product and Process
	PI 0508761-9	Product and Process
	BR 11 2016 015140 2	Product
	BR 11 2014 003769 8	Product and Process
	BR 11 2015 018248 8	Product and Process
	BR 11 2015 017800 6	Product and Process
	PI 0819693-1	Product and Process
	PI0307837	Product and Process
Dornase alfa	BR 11 2017 014433 6	Product and Process
	BR 11 2014 019117 4	Product
Alphavelaglycerase	BR 11 2017 015348 3	Process
Bevacizumab	PI 9816350-7	Product and Process
	PI 0919663-3	Product and Process
	BR 11 2012 024287 3	Product and Process
	BR 11 2012 024312 8	Product and Process
	BR 11 2015 012538 7	Product and Process
	PI0516299-8	Process
	BR 11 2017 010555 1	Process
	BR 11 2016 007547 1	Process
	BR 11 2017 000389 9	Process

Continued Chart 5

ACTIVE PHARMACEUTICAL INGREDIENT	PATENT APPLICATION NUMBER	TYPE OF PATENT INDICATIVE OF PRIMARY
Certolizumabe	PI 0106682-0	Product and Process
	BR 11 2014 000341 6	Product
	BR 11 2015 014768 2	Product and Process
	BR 11 2012 030179 9	Product and Process
	BR 11 2017 012509 9	Product
	BR 11 2012 021926 0	Product and Process
	BR 11 2017 019559 3	Product and Process
	PI 1012560-4	Product and Process
	PI 0412637-8	Product and Process
	BR 11 2012 006670 6	Process
	BR 11 2012 016808 8	Process
	BR 11 2012 016807 0	Process
	BR 11 2012 017425 8	Process
Etanercept	BR 11 2016 017698 7	Product
	BR 11 2017 008525 9	Product
	BR 11 2015 021708 7	Product and Process
	PI 0821604-5	Product and Process
	BR 11 2013 008459 6	Process
	BR 11 2014 003670 5	Process
Golimumab	BR 12 2013 012507 8	Product
	PI 0113110-9	Process

Continued Chart 5

ACTIVE PHARMACEUTICAL INGREDIENT	PATENT APPLICATION NUMBER	TYPE OF PATENT INDICATIVE OF PRIMARY
Pertuzumab	BR 11 2014 022932 5	Product and Process
	BR 11 2014 028368 0	Process
	BR 11 2014 032193 0	Process
	BR 11 2012 012983	Process
	BR 11 2015 003938 3	Process
	PI0516299-8	Process
Rituximab	BR 11 2015 021921 7	Product and Process
	PI 0410031-0	Product
	PI 0510674-5	Product
	BR 11 2015 003459 4	Product
	BR 11 2016 004768 0	Product
	BR 11 2016 015875 0	Process
	BR 11 2016 024895 3	Process
	BR 11 2013 018130 3	Process
Trastuzumab	BR 11 2017 001513 7	Product and Process
	BR 11 2015 006368 3	Product and Process
	PI0412879	Product
	PI0516284	Product and Process
	BR 11 2015 023589 1	Process
	BR 11 2015 025106 4	Process
	BR 11 2012 011980 0	Process
	BR 11 2014 015933 5	Process

Source: the authors.

5.1 Case Studies: Effects of the Patent Status of Multiple Patent Applications

We selected a few active pharmaceutical ingredients that reflect different situations - thus pointing to different options for government responses - to illustrate how multiple statuses of patent application and evergreening influence the risk assessment of the existence of a patent barrier. For this section, some data has been updated with information available through August 2018.

We sought to emphasise the patent status of primary applications and differentiate them on the content of the claims - whether in reference to the synthesis process of the API or the API itself (product). We started with the premise that those related to "process" are less likely to set up a barrier to competitor entry than "product"-related ones. This is because a competitor may seek other synthetic routes to obtain the active pharmaceutical ingredient, whereas if the patent is for the active ingredient itself, there is no alternative.

Etravirine - primary product and process patent granted and other pending applications

For this API, nine applications filed in Brazil were identified, of which only two were classified as primary. The only patent granted (PI9915552-4) from 1999, is primary and covers both product and synthesis process. The other primary application (PI0609291-8) in 2006, covers both the API (product) and its synthetic process and is still pending. This application also identified claims for the synthetic intermediates (product).

According to the proposed risk assessment classification (Figure 9), we suggest that primary product applications be classified as "risk level 2" as they block competition. The other application, which covers both process and product, was filed many years after the first filing, and is still pending, and there is no certainty that it will be granted. In our risk classification, this application is classified as level 1, since it is still pending. Pending applications, although not real barriers, have been classified as representing potential risk because of the possibility of engendering retroactive compensation payments to the patent owner in case the

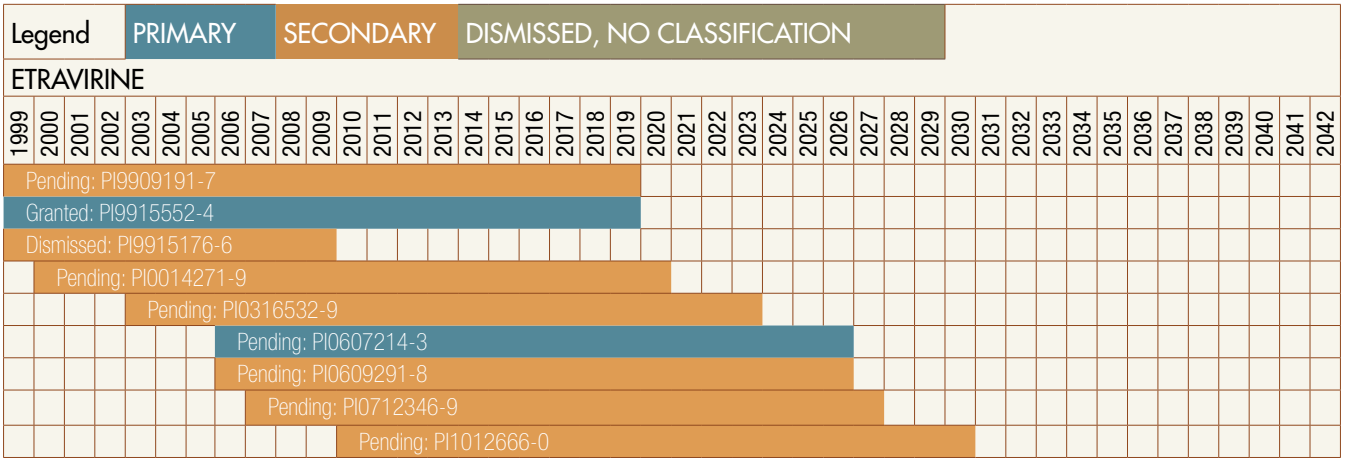
application is granted. It should also be kept in mind that applications filed many years later, even when classified as primary, may not fulfil the criterion of novelty, necessary for the patent to be granted.

Among immediate measures to reduce patent status uncertainty and promote competition are: a) a request for prior examination by the Ministry of Health, ii) Pre-grant opposition, again prioritising the primary application and later the secondary ones that generate uncertainty while pending and iii) efforts for industrial development to obtain the market approval (registration) in the country, since the LPI allows both development and registration even during the patent term of the granted patent, which expires in November 2023 in Brazil. There is also the option of issuing a compulsory license, which would allow the sale of a generic product even before 2023.

National production efforts would be timely especially considering the absence of generic alternatives in the international market in 2017 and 2018. [45,46]

The other seven applications, classified as secondary, cover claims such as packaging, Markush, doses, formulation, combinations, polymorph, uses and routes of administration, and according to the risk classification are initially considered as risk 0 for the pharmaceutical form currently in the market (Figure 10). A more detailed analysis of each application is necessary for a better risk assessment in case the patents are granted.

Figure 10 – Timeline of etravirine patent applications in Brazil according to status in 2016.



Source: authors. Blue - applications with claims classified as primary. Orange - applications with claims classified as secondary. The timeline takes into account the general 20-year patent term rule for patents from the date of filing, not considering possible extension due to the time of analysis of the application, as provided in article 40 caput and sole paragraph of the LPI.

Didanosine enteric-coated capsules – product secondary patent granted

Didanosine, one of the first ARVs adopted by SUS, was incorporated in 1993 and produced by the Brazilian industry (public and private). In 2005, a new pharmaceutical form was launched[47] – enteric-coated capsules (DDi EC) - and it has since then been marketed exclusively by Bristol Myers-Squibb (BMS).

Of the six patent applications found for didanosine in Brazil, three were rejected, one dismissed, one expired and only one granted (PI9815861-9). The expired patent (PP1100041-4) - granted through a pipeline mechanism – has the year 1993 as priority date and expired in December 2013. The only granted patent in December 2016 refers to the pharmaceutical form involving enteric coating and it expired in August 2018. Among the three applications rejected, one of them (PI9815948-8) also refers to the enteric coating.

This case is illustrative of an evergreening situation in which a second-generation product characterised by a new pharmaceutical form is followed by a secondary patent covering it. It also illustrates a practice

wherein the previous pharmaceutical forms available in the market were not marketed in exclusivity situation, that is, evergreening "re-established" a situation of exclusivity for the active pharmaceutical ingredient, as the new pharmaceutical form adopted was protected by another patent.

Thus, in this specific situation a secondary granted patent configures a barrier to competition for the pharmaceutical form adopted by SUS, therefore classified as "Risk level 2" (Figure 9).

Among the policy options that could be adopted to avoid this type of situation is the stricter patent application guidelines in order to restrict the granting of patents considered secondary, especially when the active ingredient is already in the public domain.

One option to enable competition in cases where the patent is already granted is the issue of a compulsory license for import or local production. In this particular case, the patent has expired, so this measure would not be necessary, since there is no current patent barrier. However, enteric-coated didanosine was excluded from the SUS medicines list in December 2016 and there were no further purchases of this medicine.

Darunavir - primary patent of the active pharmaceutical ingredient dismissed and primary pending applications of process

There were 17 patent applications in Brazil related to darunavir, of which only three were classified as primary. The oldest application (PI9607625-9), dated 10 March 1995, covered the active pharmaceutical ingredient and had the status of dismissed after being granted in December 2016. This patent was granted on October 23, 2007 and lost its validity on April 24, 2013, due to a default on the annual payment. The two other primary applications with pending status cover only synthetic processes (PI0417272-8 and PI0509514-0) and are from 2004 and 2005 respectively.

Of the 14 applications classified as secondary, six have been dismissed (5) and rejected (1), therefore leaving eight pending applications.

Considering the importance of this medicine in Ministry of Health ARV procurement, policy options should include encouraging generic producers to register their product[s] in the country or seek exceptional importing mechanisms. This assessment is based o n the existence of a generic alternative in the international market,[48] that the primary patent

for the API has been dismissed ("Risk 0"), and that pending applications refer only to process (primary) or secondary applications ("Risk 1").

To illustrate the potential savings for SUS, darunavir (600mg) was sold by Janssen-Cilag in exclusivity situation in 2018 at a price of BRL 6.91[I] per tablet. We were unable to find the generic price in 2018, but in 2017 the Aurobindo generic, pre-qualified by the WHO, was priced at BRL 2.97 (US $ 0.90),[46] that is, 57% lower. Considering the procured volume in 2018, if the generic had been purchased, the Ministry of Health would have saved more than BRL 132 million. In 2018, two Phase I PDP projects for the domestic production of darunavir were approved, but there is no news of when the national version will be available.[49]

Raltegravir - pending or dismissed secondary applications but no primary patent found

For this active pharmaceutical ingredient, 5 BR applications were identified, two of which were dismissed (prior to analysis) and three were pending as of December 2016. All these applications were classified as secondary, and therefore, not blocking the active ingredient or its synthesis process. We consider the range of risk from 0 to 1 for such applications to be a barrier to competition (from no barrier to potential barrier risk). That is, we evaluate that the risk for entry of competitors in the domestic market is low and national production or imported options should be considered.

Up to August 2018, Merck was the only company had an Anvisa registration for this medicine. They sell to the MoH under exclusivity, although there is a WHO pre-qualified generic version by Hetero available in the international market. This generic is produced under a voluntary license signed via the Medicines Patent Pool[50] and cannot be marketed to countries outside the geographical scope of the license - as in the case of Brazil - if there is a patent barrier in force in the country. However, it can be marketed in the absence of a patent barrier, which is the case in Brazil at present. In 2017, Merck's price in Brazil was BRL 14.16 per tablet (400mg), while Hetero's price was BRL 3.21, that is, 77%

I LAI, 2018, Application 25820000449201882

lower. If the generic version been procured in 2017 it would represent savings of more than BRL 49 million to SUS. No PDP projects related to raltegravir were found.

Dolutegravir – all primary applications pending

This ARV belongs to the integrase inhibitors class and is recommended by WHO's 2016 HIV guidelines as a first-line option for adults and adolescents over 12 years. It is also indicated for rescue treatment in adults.[48] In Brazil, the medicine was included in the SUS list in 2016.[51]

Five national patent applications were identified, of which four are pending and one has been dismissed. Three pending applications were classified as primary, the oldest (PI0610030) covering the API and its synthetic process. The other two only cover synthetic processes (PI0923217 and BR1120130024615). It is important to mention that in May 2018 there was a first INPI technical opinion for the rejection of PI0610030, and a final decision is still pending.

Among the policy options, there are the request for priority examination[J] and pre-grant opposition, besides those already presented by civil society organisations and by Blanver Farmacêutica in 2017. In 2016, there were no alternative generic versions in the international market,[48] but in subsequent years the scenario began to change and options for importing could have been considered, as there has been a WHO prequalified generic since October 2017.

In 2017, GSK marketed the medicine for BRL 4.86 (US$1.50) per tablet - in non-requirement of bidding mode - while the generic price for the Aurobindo tablet was BRL 0.52 (US$ 0.16), almost 90% lower. We should mention that the Aurobindo generic version is produced under a voluntary patent license which does not include Brazil among the countries eligible for the procurement of the generic version. However, the license allows exporting in the absence of a patent barrier in the country, even for countries outside the geographical scope of the license.[52] In 2018, Phase I PDP projects for domestic dolutegravir production were announced.[49]

J - The pharmaceutical company ViiV Healthcare requested priority examination for the application PI0610030.

Sofosbuvir - primary and secondary applications - all pending

The hepatitis C treatment medicine sofosbuvir is another example of an exclusivity situation generated only by pending applications. Twenty-one patent applications related to this active pharmaceutical ingredient were identified in Brazil, and as of December 2016 one had been dismissed and another 20 were pending. Among them, 15 were classified as secondary and 5 as primary, of which 3 cover the product and 2 only cover the process.

These medicines were incorporated by SUS in 2015 and in 2016 SUS spent BRL 721.6 million on sofosbuvir, representing the highest estimated expenditure on an API in the year for all API of the sample of this research (Table 19), as will be discussed in chapter 6.

Among the measures already taken to overcome this patent barrier, we have identified the following: i) request for priority examination by the Ministry of Health,[53] ii) presentation of pre-grant opposition by public and private manufacturers, by the association representing private national manufacturers and civil society organizations,[51,54] and iii) efforts for local production.[55]

There are WHO pre-qualified sofosbuvir generic versions available in the international market for US$ 2.14 per tablet,[56] but until recently none had a market approval by Anvisa in Brazil. In March and May 2018, Blanver and Fiocruz obtained an Anvisa registration for the generic version of the medicine produced in Brazil. The last purchase was made in 2017 from Gilead - via a non-requirement of bidding modality - at BRL 160 (US$ 48.50) per tablet,[57] that is, a 95% difference from the generic one.

In July 2018, the Ministry of Health held a meeting with companies holding Anvisa registrations to negotiate the price of medicines for hepatitis C.[58] As a result, the lowest price was that of the Brazilian generic that would cost around BRL 33 (US$ 8.50) per tablet, about 80% lower than the Gilead price. This process was the subject of opposition that questioned the Ministry of Health strategy, which in turn issued a communiqué with more information that defended the process.[58]

Adalimumab - granted patents indicative of being primary and various pending applications

Adalimumab is a CEAF 1A biological medicine used in the treatment of rheumatoid arthritis and other medical indications. In Brazil, it has been exclusively marketed by Abbvie / Abbott since 2005, when it was included in the SUS procurement list.

In total, 47 patent applications were identified in Brazil, 14 of which were excluded after analysis because they were not directly related to the API. Of the remaining, 1 was rejected, 8 were dismissed, 22 were pending, and 2 were granted (PI9707379-2 and PI9715219-6). Both the granted ones were classified as indicative of primary, 1 being of product and i of process. The 2 granted patents were filed in 1997 but are still valid in Brazil due to the provision in the sole paragraph of article 40 of the LPI, which extended the patent term until November 2019 and February 2020, respectively.

We identified initiatives for the national production of the medicine. The first PDP was launched in 2015.[49] However, Abbvie sent out an extrajudicial notice to potential competitors on the grounds that the production could constitute a violation of its patents and requested the INPI for an examination of all pending applications on priority, on grounds of possible infringement.[59]

In view of the existence of a patent granted to a primary product, the risk classification is 2. We emphasise that LPI allows the development and obtaining of market approval by Anvisa even during the term of a patent, but marketing is not possible while the patent is valid. Issuing a compulsory license for public interest provides greater legal certainty for local production and allows marketing of the product before the patent expires. This option also makes it possible to import biosimilars that are already approved by the FDA and the EMA.

Another measure to be adopted in this case - considering that a request has already been made for priority examination of the pending applications in the INPI - is the presentation of pre-grant oppositions (in Brazil, called “third party observation”). Among the pending applications,

14 were classified as indicative of secondary and 9 as primary, all of which involve the product and the synthesis process.

In 2016, the price in Brazil was BRL 659 per syringe, totalling to BRL 621,880,336.00, which represented 25% of CEAF1A's total expenditures in that year.

Etanercept

Unlike the previous cases, the etanercept and trastuzumab cases seek to relate the dynamics of the entry of biosimilar products in the market to the patent landscape found in the research.

Etanercept was licensed for marketing in the United States in November 1998 and in the European Union in February 2000. The first patent application related to the medicine dates back to 1989,[60] for which we could not identify a corresponding application in Brazil. According to a website specialised in biological products,[44] the reference product ("originator") expiry date in the European Union was August 2015. It is expected to expire in the United States in 2028 following a new patent grant in the country.

The first etanercept biosimilar, according to information available on the same page, was launched in India in April 2013. There is no patent information related to the product in the country.

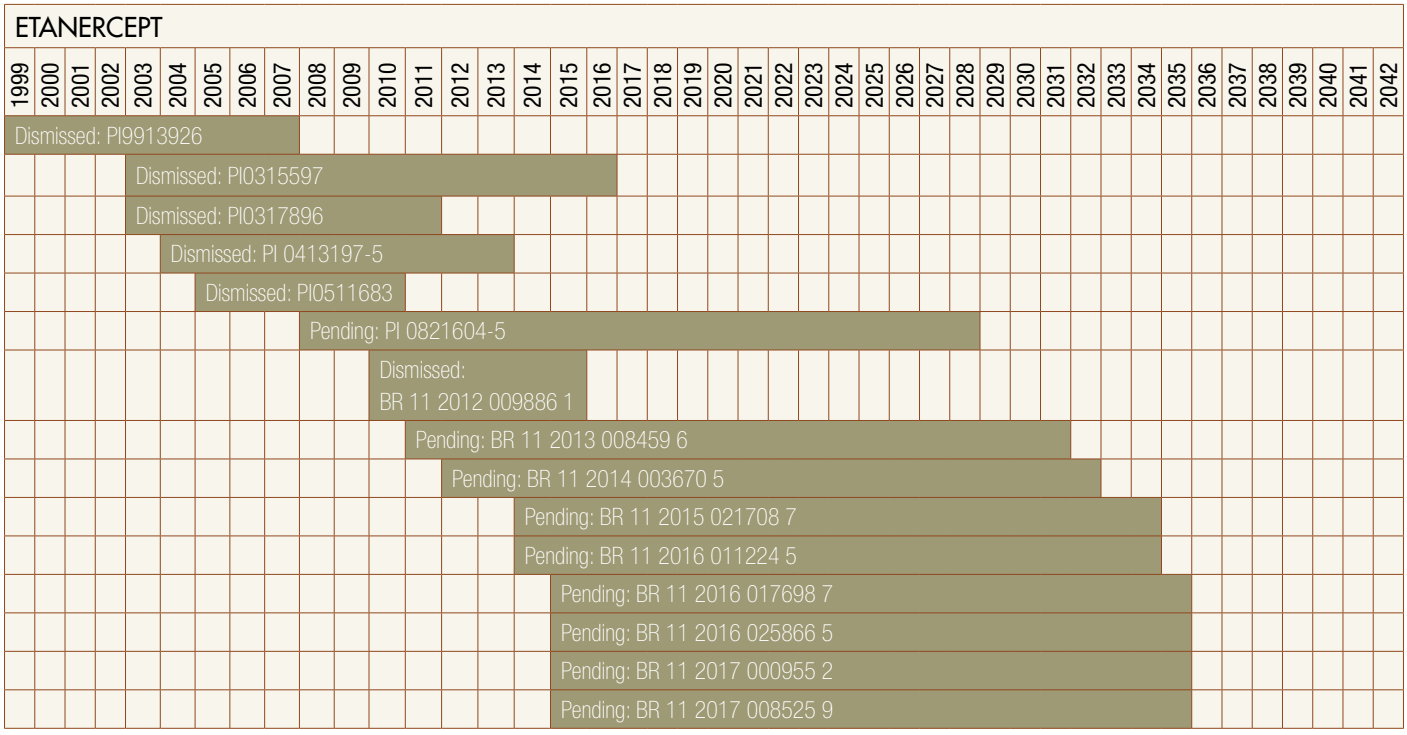
We were able to identify that in August 2016, Sandoz obtained approval for marketing an etanercept biosimilar by the regulatory authority of the United States, the Food and Drug Administration (FDA).[61] The first etanercept biosimilar was approved in Europe in January 2016, manufactured by Samsung Bioepis.[62]

In Brazil, 15 patent applications related to etanercept were identified. 5 of them with the oldest filing dates had a dismissed status in 2016. Among the remaining applications filed from 2008 to 2015, 1 was dismissed and the other 9 were pending (Figure 11). Among them, 6 were classified as indicative of being primary, 4 involving the product and 2 only for process.

The pending applications do not appear to be blocking the entry of alternative versions in Brazil, since the biosimilar version of the medicine marketed by Samsung Bioepis got market approval by Anvisa in

December 2017 and is currently on the CMED list among the suppliers - including Pfizer[K] - of the medicine in Brazil.

Figure 11 – Timeline of etanercept patent applications in Brazil according to status in 2016.



Source: authors. The timeline takes into account the general 20-year term for patents from the date of filing, not considering possible extension due to the time of analysis of the application, as provided in article 40 caput and sole paragraph of the LPI.

Trastuzumab

The first patent application identified in our research related to this medicine dates back to 1989 (WO8906692, without correspondent in Brazil). According to a specialised website,[63] the patent in the European Union expired in July 2014. It will expire in June 2019 in the US.

Our research has identified that in December 2017, Mylan GMBH obtained FDA approval for marketing a trastuzumab biosimilar.[61] On

K When we consulted the CMED price list of May/15/2018, there was another company besides Pfizer marketing etanercept - Samsung Bioepis BR Pharmaceutical LTDA.

the Anvisa website[64], we were able to identify the health record of a trastuzumab biosimilar approved in December 2017 owned by Libbs Farmacêutica LTDA, a private Brazilian company.

In Brazil, we identified 31 patent applications related to trastuzumab filed from 1996 to 2016.[L] Considering their status in December 2016, there were the following situations: a patent, classified as indicative of primary product was extinct (since May 2014), one patent was granted (classified as indicative of secondary), 20 applications were pending, 6 were rejected and 3 were dismissed. Of the 21 pending applications, 10 were classified as primary, 6 of which involve the product.

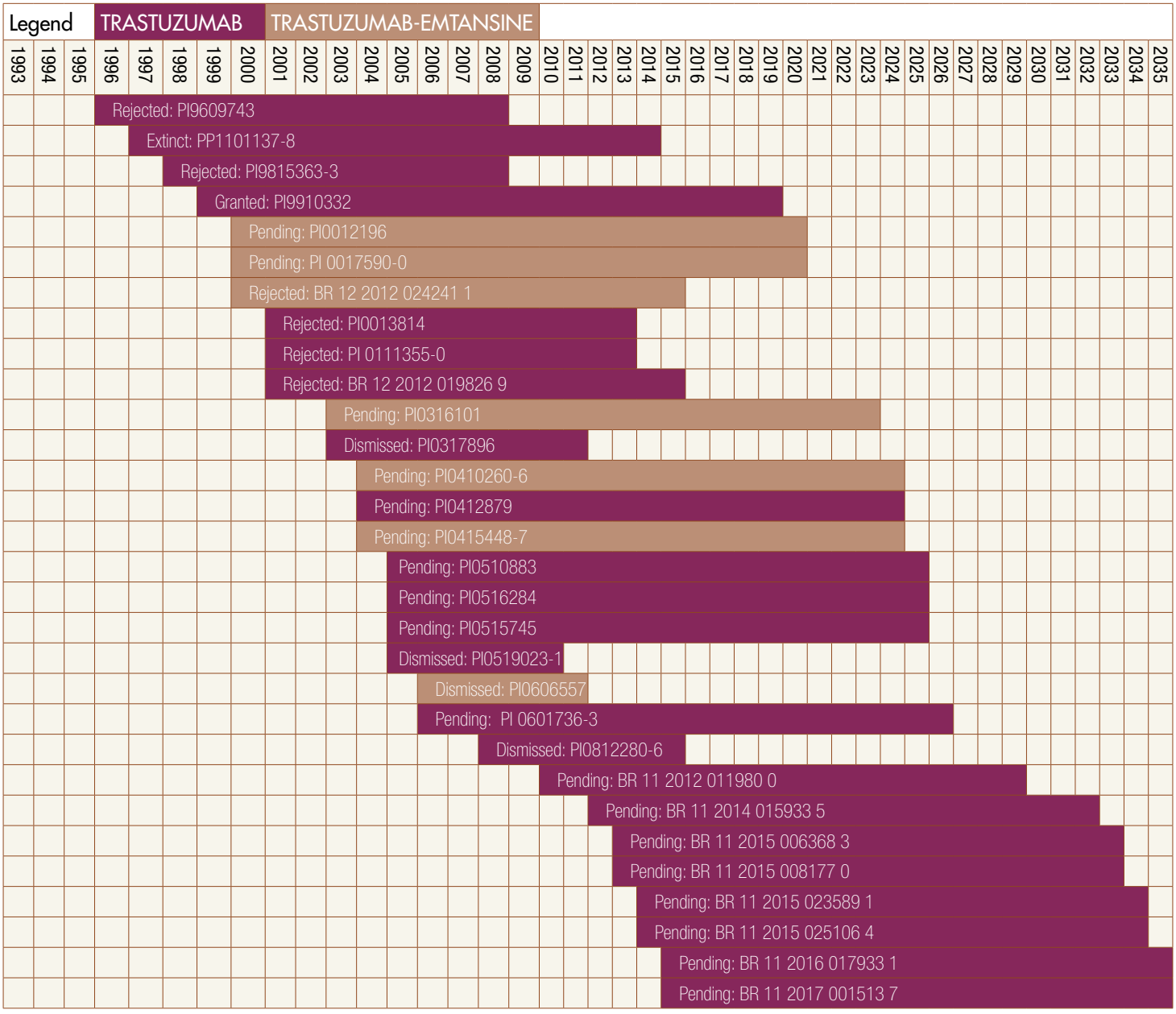
The scenario of multiple applications in different statuses (Figure 12) does not appear to have prevented a competitor from entering the Brazilian market in 2018, concurrently with the approval of the first biosimilar in the US by another company.

According to Anvisa's website, the first market approval in Brazil for trastuzumab (Herceptin®) by Roche was in 1999. Roche registered trastuzumab with pertuzumab (Perjeta HER®) and trastuzumab-emtansine (Kadcyla®) in 2013 and 2014 respectively. The latter refers to an antibody-drug conjugate, the emtansine being a synthetic product.

In this way, these last two medicines are examples of second-generation products that can also be identified in the company's patenting strategy, classified as evergreening. Of the 31 applications identified for trastuzumab, 7 are related to trastuzumab emtansine, with applications made long after the first application for the API and 3 for trastuzumab and pertuzimab.

L Possible applications after 2016 were not included in the research.

Figure 12 – Timeline of Trastuzumab patent applications in Brazil according to status in 2016..



Source: authors. In purple applications related to trastuzumab and in beige related trastuzumab-emtansine. The timeline accounts for the general rule of patent term of 20 years from the date of filing, not considering possible extension due to the time of analysis of the application, as provided in article 40 caput and sole paragraph of the LPI.

6. Public Procurement of Medicines Included in Research Sample

The last dimension investigated in our research was an exploratory analysis of the public procurement of medicines related to the 74 active pharmaceutical ingredients selected for the patent search in the period from 2007 to 2016. The evolution of the price per unit was analysed for the period between 2012 and 2016. We selected a set of medicines that had the greatest weight in the sample's total procurement, by group, within which we identified those with indicated no patent barrier in December 2016 based on specific criteria. We compared their prices with generic or biosimilar versions available in the international market, to estimate the potential economy for the SUS if this alternative were available in Brazil.

In relation to public procurement, Table 17 presents an estimate of the Ministry of Health expenditure for a 10-year period (2007 to 2016) for the sample selected for patent search. No procurement records were found throughout the period for the following active pharmaceutical ingredients of the 74 investigated: alphavelaglycerase (CEAF 1A), degarelix (cancer) and eribulin (cancer).

We also estimated the percentages of expenditures for the selected active pharmaceutical ingredients against the total expenditure of the Ministry of Health with the Specialized Component of Pharmaceutical services (budget action 4705) and Medicines for AIDS (budget action 4370) made available by the Access to Information Law. It was not possible to estimate this percentage for the medicines indicated for cancer treatment because there was no total (denominator) available.

There are some limitations in this type of analysis involving public procurement of medicines. The first of these refers to the overlap of active

pharmaceutical ingredients between the groups. Peginterferon Alfa-2A and 2B and rituximab are present in CEAF1A and are also indicated in oncology. As it was outside the scope of this study to separate procurement by therapeutic indication, we chose to account for these medicines in the CEAF 1A procurement. Although anti-hepatitis B immunoglobulin is also present in groups 1A and 1B of CEAF, we decided to include it in the first group only.

As of 2009, procurement of medicines included in the sample, in their different pharmaceutical forms and presentations, represented more than BRL 1 billion/year (in values adjusted to inflation 2016, according to IPCA). In 2016, expenses almost tripled, reaching BRL 3.2 billion.

It is important to consider that in the period between 2007 to 2015, there were other medicines in exclusivity situation that are not included in the sample of the present research. This means that the proportion of the expenses of products in exclusivity situation in those years may have been even greater than the values found.

Table 17 – Estimate of Ministry of Health expenditure (BRL) for the set of medicines selected for the patent search. Brazil, 2007-2016.

GROUP OF MEDICINES	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
CEAF 1A*	1,055,759.05	425,557,650.04	385,992,913.04	1,332,774,782.61	2,397,121,301.11	970,856,743.96	1,730,156,407.71	1,411,325,799.47	2,255,163,701.89	2,308,663,858.22
CEAF 1B	3,051,867.06	77,661,835.50	94,381,067.86	114,534,208.73	112,907,369.15	114,897,753.64	120,897,777.87	111,945,469.97	111,945,469.97	146,850,330.88
Percentage of expenditure in relation to the total budget execution of the Ministry of Health with CEAF (%)	0.12%	13.26%	11.47%	29.78%	50.80%	20.06%	29.71%	26.48%	37.97%	34.37%
CESAF (ARV only)	420,481,053.16	148,185,603.39	515,819,792.52	591,967,372.21	418,881,015.66	308,295,387.95	278,714,911.21	627,409,142.36	423,133,714.14	264,507,574.59
Percentage of expenditure in relation to the total budget execution of the Ministry of Health with AIDS medicines (%)	34.0%	14.8%	44.1%	65.4%	37.1%	28.3%	28.9%	61.8%	36.3%	24.1%
Cancer	1,124,668.25	34,070,050.38	43,123,136.48	114,268,652.43	70,753,375.02	156,053,364.17	705,654,280.95	603,819,656.10	284,554,905.65	504,753,052.19
TOTAL SPENDING ON THE 4 GROUPS	425,713,347.52	685,475,139.31	1,039,316,909.90	2,153,545,015.98	2,999,663,060.94	1,550,103,249.72	2,835,423,377.74	2,754,500,067.90	3,074,797,791.65	3,224,774,815.88

Source: authors based on information provided by the Ministry of Health through the Access to Information Law. Values adjusted by the IPCA 2016. * Includes active pharmaceutical ingredients also present in CEAF 1B and cancer. As a result, they were not counted twice. BRL - Brazilian Real

In order to further investigate the ones with the greatest financial weight in the sample, the ten active pharmaceutical ingredients with the highest expenditure in the year 2016 and in the last 10 years were ranked in decreasing order (Tables 18 and 19). We observed that several products that were among the heaviest expenditure in 2016, were also among the heaviest over in the 10 previous years analysed for all groups.

Table 18 – Ten active pharmaceutical ingredients with the highest expenditure (BRL) in the sample, by medicines group, from 2007 to 2016

CEAF 1A	10-YEAR TOTAL	CEAF 1B	10-YEAR TOTAL	ARV	10-YEAR TOTAL	CANCER	10-YEAR TOTAL
Adalimumab	5,210,840,577.16	Deferasirox	450,341,251.07	Lopinavir/ ritonavir	1,609,845,337.21	Trastuzumab	1,582,451,429.11
Etanercept	1,449,016,750.90	Goserelin	310,136,152.22	Raltegravir	902,734,068.85	Dasatinib	293,619,858.88
Sofosbuvir	1,232,115,287.91	Dornase alfa	165,862,250.54	Darunavir	560,117,247.44	Nilotinib	148,647,535.06
Peginterferon alfa 2a	1,069,987,437.97	Hydroxyurea	25,137,689.71	Enfuvirtide	314,379,559.39	Sunitinib	102,562,479.61
Glatiramer	642,877,536.87	Deferiprone	23,262,231.69	Dolutegravir	188,092,813.50	Cetuximab	58,922,562.04
Peginterferon alfa 2b	572,119,681.96	Bromocriptine	18,283,246.78	Fosamprenavir	154,026,035.99	L-asparaginase	58,716,509.37
Imiglucerase	451,647,545.22	Lanreotide	12,146,956.92	Etravirine	92,815,476.50	Sorafenib	50,762,562.32
Rituximab	431,407,163.36	Penicillamine	7,899,789.83	Abacavir	60,702,096.62	Abiraterone	31,141,639.58
Daclatasvir	398,019,030.41	Danazol	3,257,606.84	Didanosine	53,040,307.59	Erlotinib	25,542,764.65
Sirolimus	341,014,239.10	Tolcapone	2,804,982.28	Maraviroc	51,935,037.44	Cladribin	23,302,404.90
TOTAL	11,799,045,250.86	TOTAL	1,019,132,157.88	TOTAL	3,987,687,980.53	TOTAL	2,375,669,745.50

Source: authors based on the data collected. BRL – Brazilian Real

Table 19 – Ten active pharmaceutical ingredients with the highest expenditure (BRL) in the sample, by medicines group, in 2016

CEAF 1A	YEAR 2016	CEAF 1B	YEAR 2016	ARV	YEAR 2016	CANCER	YEAR 2016
Sofosbuvir	721,617,868.83	Deferasirox	65,805,836.62	Dolutegravir	188,092,813.50	Trastuzumab	374,003,094.00
Adalimumab	621,880,336.00	Dornase alfa	43,426,637.18	Raltegravir	51,149,265.00	Dasatinib	64,161,225.60
Etanercept	339,489,682.44	Goserelin	23,288,771.05	Maraviroc	20,874,325.54	Nilotinib	27,509,820.80
Daclatasvir	215,144,116.34	Lanreotide	7,232,990.78	Darunavir	3,232,800.00	Cetuximab	19,660,286.01
Glatiramer	135,646,552.00	Hydroxyurea	3,236,609.28	Tipranavir	1,097,420.80	Sunitinib	4,341,558.60
Entecavir	108,412,779.61	Deferiprone	2,614,273.20	Fosamprenavir	60,949.75	Exemestane	3,632,598.04
Rituximab	86,775,122.70	Bromocriptine	237,767.10			Gefitinib	2,609,934.00
Golimumab	85,104,332.10	Danazol	111,508.59			Cyclophosphamide	1,260,351.20
Tocilizumab	49,378,817.21	Tolcapone	82,207.50			Vemurafenib	961,691.36
Natalizumab	39,387,815.85	Iloprost	25,331.02			Erlotinib	858,772.80
TOTAL	2,402,837,423.08	TOTAL	146,061,932.32	TOTAL	264,507,574,59	TOTAL	498,999,332.41

Source: authors based on the data collected. BRL – Brazilian Real

Although many of the high-expenditure products in the sample are present both in 2016 and in the sum of the ten years analysed, an analysis of price evolution over the six-year period (Tables 20, 21 and 22) points to price reductions for many of the medicines, despite the lack of competition through multiple suppliers. These results suggest a potential positive effect of centralised procurement, aligned with price-negotiation efforts between the Ministry of Health and transnational pharmaceutical companies. Another possible explanation is that there may be competition through the existence of therapeutic alternatives, reducing prices over time, which would require further analysis involving treatment protocols and utilisation profiles. Other factors may also contribute to the observed price reduction, such as exchange variation, but it was beyond the scope of the research to delve deeper into this field.

For the CEAF1A medicines group - with the highest expenditure in 2016 in the sample - the reduction in the six-year period ranged from 81.3% (rituximab 10mg / mL in a 10mL bottle) to 9.8% (tocilizumab) (Table 20).

For the ARV group - with the highest expenditure in 2016 in the sample - price reduction occurred in the period for most of them, with the exception of fosamprenavir 700mg and raltegravir 100mg (Table 21). Reductions ranged from 44.4% (darunavir 150mg) to 5.9% (darunavir 600mg).

For the most expensive set of cancer medicines in 2016 in the sample, there were price reductions in the period for most of them, except for sunitinib (capsules 12.5mg and 25mg) and erlotinib (tablet 100mg). Reductions ranged from 66.4% (dasatinib 20mg tablet) to 8.8% (erlotinib 100mg).

Table 20 – Price evolution (BRL) of the medicines whose active pharmaceutical ingredients accounted for the largest expenditure in the sample in 2016 for CEAF 1A. Brazil, 2016.

API	PRESENTATION	2011	2012	2013	2014	2015	2016	PERCENTAGE REDUCTION IN THE PERIOD (%)
Rituximab	10mg / ml sol, Injectable vial 10ml	**1,924.07**	**1,525.62**	**1,912.52**	**495.22**	**901.82**	359.06	81.3%
Tocilizumab	20 mg/mL injectable (per vial - 4 mL ampoule)	**588.19**	**570.18**	**403.91**	433.67	**198.62**	175.40	70.2%
Rituximab	10mg/ml sol, 50ml injectable vial	**5,926.32**	**4,365.52**	**3,439.33**	**2,320.20**	**2,131.79**	1,798.15	69.7%
Adalimumab	40 mg injectable (filled syringe)	**1,810.55**	**1,371.68**	**1,100.84**	**961.21**	**824.93**	**659.68**	63.6%
Etanercept	50 mg injection (per vial or filled syringe)	864.32	-	-	-	1,252.54	330.85	61.7%
Etanercept	25 mg injection (per vial)	432.16	**328.07**	-	**752.83**	1,450.86	165.43	61.7%
Glatiramer	20 mg injection (per vial or filled syringe)	**102.43**	89.03	79.86	68.30	59.86	54.34	46.9%
Entecavir	0,5 mg (per tablet)	13.68	13.12	11.45	**10.05**	11.55	8.54	37.6%
Natalizumab	300 mg (per vial)	3,430.60	**3,823.33**	**3,015.69**	**2,733.64**	2,395.79	2,186.39	36.3%
Sofosbuvir	400mg (per coated tablet)	-	-	-	-	268.83	173.36	35.5%
Golimumab	50 mg injection (filled syringe)	-	-	-	1,649.19	1,415.68	1,276.98	22.6%
Daclatasvir	60 mg (per coated tablet)	-	-	-	-	99.71	84.48	15.3%

Continued Table 20

API	PRESENTATION	2011	2012	2013	2014	2015	2016	PERCENTAGE REDUCTION IN THE PERIOD (%)
Tocilizumab	20 mg/mL injectable (per vial - 10 mL ampoule)	**1,474.10**	**1,434.54**	**1,460.65**	**1,314.39**	**1,330.36**	-	9.8%
Entecavir	1 mg (per tablet)	**21.19**	23.64	19.69	-	-		7.1%
Daclatasvir	30 mg (per coated tablet)	-	-	-	-	-	42.24	N/A

Source: authors based on data collected. * Prices in **bold** refer to the Weighted Average Price (PMP) estimates for more than one purchase in the year. Price adjusted for the inflation according to IPCA 2016. BRL – Brazilian Real.

Table 21– Evolution of the price (BRL) of medicines whose active pharmaceutical ingredients accounted for the largest expenditures in the sample in 2016 for ARVs. Brazil, 2016.

API	PRESENTATION	2011	2012	2013	2014	2015	2016	PERCENTAGE REDUCTION IN THE PERIOD (%)
Darunavir	150 mg tablet	5.07	-	-	2.82	-	-	44.4%
Darunavir	300 mg tablet	10.14	7.86	-	5.65	-	-	44.3%
Fosamprenavir	50 mg / mL	-	231.50	-	127.16	126.39	154.69	33.2%
Tipranavir	250 mg capsule	-	11.36	9.14	8.33	7.38	7.63	32.8%
Raltegravir	tablet 400 mg	20.60	18.06	17.09	**15.50**	14.36	14.16	31.3%
Tipranavir	100 mg/ML, oral suspension (vial)	-	493.16	419.07	378.77	-	354.20	28.2%
Maraviroc	150mg	-	-	22.12	17.84	**17.51**	17.20	22.2%
Darunavir	600 mg tablet	-	-	-	10.20	-	9.60	5.9%
Fosamprenavir	700 mg tablet	4.52	4.08	4.15	4.00	**4.58**	-	-1.3%
Raltegravir	tablet 100 mg	-	-	-	5.48	-	5.82	-6.2%
Dolutegravir	tablet 50 mg	-	-	-	-	-	4.86	N/A

Source: authors based on data collected. * Prices in **bold** refer to the Weighted Average Price (PMP) estimates for more than one purchase in the year. Price adjusted for the inflation according to IPCA 2016. BRL – Brazilian Real. The minus sign (-) for raltegravir and fosamprenavir indicates price increase in the period.

Table 22 – Evolution of sample medicines prices (BRL) whose active pharmaceutical ingredient accounted for the largest expenditure in 2016 for cancer medicines. Brazil, 2016.

API	PRESENTATION	2011	2012	2013	2014	2015	2016	PERCENTAGE REDUCTION IN THE PERIOD (%)
Dasatinib	20 mg tablets	**47.35**	**44.74**	**42.25**	**29.54**	**22.33**	15.89	66.4%
Nilotinib	20 mg tablets	**50.96**	**48.14**	**42.42**	**31.15**	**28.23**	23.02	54.8%
Cetuximab	5mg / ml injectable solution 100ml	-	**4,656.93**	**2,907.41**	**3,252.27**	**2,531.93**	2,568.83	44.8%
Cetuximab	5mg / ml injectable solution 20 ml	**889.61**	**695.45**	**709.19**	**655.54**	**573.75**	577.69	35.1%
Gefitinib	250 mg tablets	**147.75**	**108.84**	**124.20**	**99.44**	**97.68**	**96.13**	34.9%
Trastuzumab	150mg	-	-	**1,454.90**	1,199.84	-	989.40	32.0%
Dasatinib	100 mg tablets	-	-	-	116.45	99.97	79.47	31.8%
Sunitinib	50 mg capsules	**652.50**	**535.09**	**578.80**	**556.73**	**505.23**	**459.40**	29.6%
Dasatinib	50 mg tablets	**95.10**	**89.86**	**84.84**	**79.73**	**72.01**	-	24.3%
Exemestane	25mg	23.38	**18.01**	**17.18**	**18.14**	**16.28**	**18.37**	21.4%
Vemurafenib	240 mg Coated Tablets	-	-	**114.91**	**109.99**	**99.61**	**90.38**	21.3%
Cyclophos-phamide	200 mg powder extemporaneous injection	**11.58**	**11.80**	**11.23**	**12.19**	**9.92**	-	14.3%
Cyclophos-phamide	1 g extemporaneous injectable powder	**41.45**	**48.04**	**42.60**	**42.76**	**41.51**	35.70	13.9%
Erlotinib	150 mg tablets	**252.80**	**184.57**	**225.42**	**195.48**	**195.87**	198.79	21.4%
Trastuzumab	440 mg	**11,516.21**	**5,396.07**	**10,969.94**	**11,133.22**	**10,208.44**	-	11.4%
Erlotinib	25 mg tablets	-	-	63.79	-	58.19	-	8.8%
Sunitinib	12.5mg capsules	126.63	123.32	**145.50**	**113.18**	**130.21**	-	-2.8%
Sunitinib	25 mg capsules	253.28	246.63	**290.90**	**225.66**	**261.27**	**262.17**	-3.5%
Erlotinib	100 mg tablets	166.17	164.21	**200.45**	-	**180.09**	-	-8.4%

Source: authors based on data collected. * Prices in **bold** refer to the Weighted Average Price (PMP) estimates for more than one purchase in the year. Price adjusted for the inflation according to IPCA 2016. BRL – Brazilian Real. The minus sign (-) for sunitinib, erlotinib and trastuzumab indicates price increase in the period.

Regarding the modalities of procurement of the medicines in the sample (CEAF 1A, ARV and cancer), Chart 6 presents an overview of those that took place in 2016 and Chart 7 presents the scenario in the period from 2007 to 2016. This analysis was not applied to the CEAF 1B medicines, as it is a part of the Brazilian central government fund for pre-defined transfers to states.[25]

For 2016, we observed that Group 1A and ARV medicines in the sample were procured via non-requirement of bidding modality, possibly confirming the existence of only one supplier in the domestic market. For cancer medicines, only dasatinib and nilotinib were in the same situation.

The scenario for procurement modalities from 2007 to 2016 (Chart 7) demonstrates a somewhat more complex situation. We have identified procurements in all modalities, including electronic trading session, for CEAF1A and cancer medicines, which suggests that there was a period in the analysed timeframe that there was more than one supplier in the national market. For ARV medicines, only those that did not require bidding and those waived from bidding were identified.

It should be noted that the procurements made via non-requirement of bidding modality were in greater volume. Those carried out by waiving of bidding or electronic trade sessions were mostly for small volumes, suggesting that they were carried out only to meet demands from lawsuits.

Chart 6 – Overview of procurement modalities for medicines involving the active pharmaceutical ingredients of the sample in the year 2016

PROCUREMENT MODALITY (IES) - 2016	MEDICINES
Non-requirement of bidding	**CEAF1A:** Abatacept 250mg vials; Adalimumab 40 mg injection; Adefovir 10 mg; Certolizumab pegol 200 mg / mL injection; Daclatasvir 60mg; Entecavir 0.5 mg; Entecavir 1 mg; Etanercept 25 mg injection; Etanercept 50 mg injection; Golimumab 50 mg injection; Glatiramer 20 mg injection; Miglustate ** 100 mg; Natalizumabe 300 mg; Simeprevir 150mg; Sirolimus 1mg; Sirolimus 2mg; Sofosbuvir 400mg; Tocilizumab 20 mg / mL injection (vial ampoule 4mL); Rituximab 10mg / ml sol., Injection bottle 10ml; Rituximab 10mg / ml sol., Injection bottle 50ml **ARV:** Darunavir 600mg; Dolutegravir 50 mg; etravirine 100 mg tablets; Fosamprenavir 50 mg / mL; Maraviroc 150 mg; Raltegravir tablet 400 mg; Raltegravir Tablet. coated 100 mg; Tipranavir 250 mg. Capsule; Tipranavir 100 mg / mL bottle Cancer: Dasatinib 20mg; Dasatinib 100mg; Nilotinib 200mg
Waiver of bidding	**Cancer:** Bevacizumab 25mg / ml solution injection 4ml; Bevacizumabe 25mg / ml solution injection 16ml; Cetuximabe 5mg / ml solution injection 100ml; Pazopanib hydrochloride ** 200 mg; Lapatinib Ditosylate 250mg; Sunitinib malate 25mg; Sunitinib malate 50mg
Trading session	**Cancer:** Cetuximabe 5mg / ml solution for injection 20ml; Cyclophosphamide 1g extemporaneous injectable powder; Erlotinib hydrochloride 150mg; Mitoxantrone hydrochloride * 2mg / ml solution for injection; Exemestane ** 25 mg; Lomustine * 40mg
Non-requirement of bidding+ waiver of bidding	**Cancer:** Pertuzumab 420mg injection solution.
Waiver of bidding + trading session	**Cancer:** Etoposide * 20mg / 5ml solution for infusion; Gefitinib 250mg

Source: authors. * No patent application identified in Brazil; ** All BR applications expired, rejected or dismissed

Chart 7 – Overview of procurement modalities for medicinal products involving active pharmaceutical ingredients in the sample from 2007 to 2016

PROCUREMENT MODALITY (IES) FROM 2007 - 2016	MEDICINES
Non-requirement of bidding	**CEAF1A:** Certolizumab pegol 200 mg / mL injection; Daclatasvir 60mg; Golimumab 50 mg injection; Imiglucerase * 400 U injection; Immunoglobulin anti-hepatitis B * 600 IU injection; **ARV:** abacavir tablet 300mg; abacavir 20mg / mL bottle; darunavir 150mg; darunavir 75mg; darunavir 600mg; didanosine capsules 250mg; didanosine capsules 400mg; enfuvirtide flask - ampoule 90mg / mL; enfuvirtide flask - ampoule 180mg / mL; etravirine tablets 100mg; fosamprenavir 700mg; fosamprenavir 50 mg / mL; lopinavir + ritonavir tablets (200mg and 50mg); lopinavir + ritonavir flasks (80mg / mL E 20mg / mL); raltegravir tablet 400 mg; Raltegravir Coated Tablets. coated 100Mg **Cancer:** Dasatinib 100mg
Trading session	**Cancer:** aldesleukin ** 18 MUI, lyophilic powder for injection; Etoposide * 100mg; Lomustine * 10mg; Lomustine * 40mg
Non-requirement of bidding + waiver of bidding	**CEAF1A:** Adefovir 10 mg; Peginterferon alfa 2B 80 mcg; Peginterferon alfa 2B 120 mcg; Entecavir 0.5 mg; Entecavir 1 mg; Etanercept 25 mg injection; Etanercept 50 mg injection; Glatiramer 20 mg injection; Miglustate ** 100 mg; Nataluzimab 300 mg; Simeprevir 150mg; Sirolimus 2mg; Sofosbuvir 400mg; Immunoglobulin anti-hepatitis B * 500 IU injection **ARV:** Darunavir 300mg; Maraviroc 150mg; Tipranavir 250 mg. capsule; Tipranavir 100 mg / mL vial **Cancer:** Pertuzumab 420mg injection solution.
Non-requirement of bidding + waiver of bidding+ trading session	**CEAF1A:** Abatacept 250mg vials; Adalimumab 40 mg injection; Alfapeginterferone 2a 180 mcg; Alfapeginterferone 2b 100 mcg; Sirolimus 1mg; Tocilizumab 20 mg / mL injection (vial ampoule 4mL); Tocilizumab 20 mg / mL injection (per 10 mL vial); Rituximab 10mg / ml sol., Injection bottle 10ml; Rituximab 10mg / ml sol., Injection bottle 50ml **Cancer:** Bevacizumabe 25mg / ml solution injection 4ml; Bevacizumabe 25mg / ml solution injection 16ml; Cetuximabe 5mg / ml solution injection 20ml; Cetuximabe 5mg / ml solution injection 100ml; Erlotinib hydrochloride 150mg; Dasatinib 20mg; L-asparagase 10,000 IU inj. powder for dilution; Lapatinib Ditosylate 250mg; Sunitinib malate 12.5mg; Sunitinib malate 25mg; Sunitinib malate 50mg; Nilotinib 200mg
Waiver of bidding+ trading session	**Cancer:** Abiraterone acetate 250mg; Cyclophosphamide 200mg extemporaneous injection powder; Cyclophosphamide 50mg extemporaneous powder injection; Cyclophosphamide 1g extemporaneous injection powder; Cladribine 1mg / ml Injection solution: vial ampoule 10ml; Erlotinib hydrochloride 100mg; Erlotinib hydrochloride 25 mg; Mitoxantrone hydrochloride * 2mg / ml solution injection; Pazopanib hydrochloride ** 200 mg; Pazopanib hydrochloride ** 400 mg; Dasatinib 50mg; Etoposide * 20mg / 5ml solution for infusion; Etoposide * 50mg; Exemestane ** 25mg; Gefitinib 250mg; Melphalan 2mg; Melphalan 50mg; Mitomycin * 5mg injection solution
non-requirement of bidding + trading session	**CEAF 1A:** Immunoglobulin anti-hepatitis B * 100 IU injection

Source: authors. * No patent application identified in Brazil; ** All BR applications expired, rejected, extinct or dismissed

Finally, among the 65 active pharmaceutical ingredients for which we were able to identify patent information in Brazil, we sought to map CEAF 1A medicines[M], ARV and cancer treatment groups. We identified the ones whose patent status of synthetic and biological active pharmaceutical ingredients pointed out that there was no patent barrier in December 2016, including pending applications, or whose granted patent has been classified as process primary or as secondary only to synthetic active pharmaceutical ingredients, suggesting a lower risk for the patent to be truly a barrier to the generic version. In other words, only a primary patent granted to the product was considered as a barrier to eventual use of the generic version in Brazil.

In this situation, 40 active pharmaceutical ingredients were identified.[N]

For these products, we sought to identify generic or biosimilar alternatives available in the international market in order to compare them with prices in Brazil in 2016 and to estimate the potential savings if these alternatives were available in the domestic market at the same prices (Table 23). Prices were collected from diverse, publicly available sources.[65,66,48]

On one hand, this is a rather limited estimate, especially since other costs related to transport and distribution are not considered if these generic / biosimilars were imported. In addition, it was not easy to find 2016 prices. On the other hand, our effort to estimate these prices contributes to signal that there are other reference prices in the international market, to reinforce the question as to why these options are not available in Brazil and to illustrate the potential effects of the legal uncertainty generated by the existence of multiple patent applications pegged to pending applications.

We were able to identify prices of generic alternatives for only 5 active pharmaceutical ingredients (5 medicines) that were priced in 2016 or some previous year (Table 23). The estimated savings generated was US$ 220,237,801.61 (approximately BRL 768,409,689.81).

M The CEAF 1B group medicines were excluded from this estimate because prices were previously defined.

N According to those criteria, we included the following API: abacavir, abatacept, abiraterone, aldesleukin, Peginterferon alfa 2b, alphavelaglycerase, certolizumab, cetuximab, cyclophosphamide, cladribin, daclatasvir, darunavir, dasatinib, didanosin, dolutegravir, enfuvirtide, entecavir, enzalutamide, etanercept, exemestane, fosamprenavir, gefitinib, glatiramer, golimumab, l-asparaginase, melphalan, miglustat, natalizumab, nilotinib, pazopanib, raltegravir, rituximab, simeprevir, sirolimo, sofosbuvir, sorafenib, sunitinib, tipranavir, tocilizumab, vemurafenib.

Table 23 – Difference between the expenditure in 2016 of selected medicines in the sample in relation to the estimated cost involving generic biosimilars prices available in the international market. Brazil, 2016.

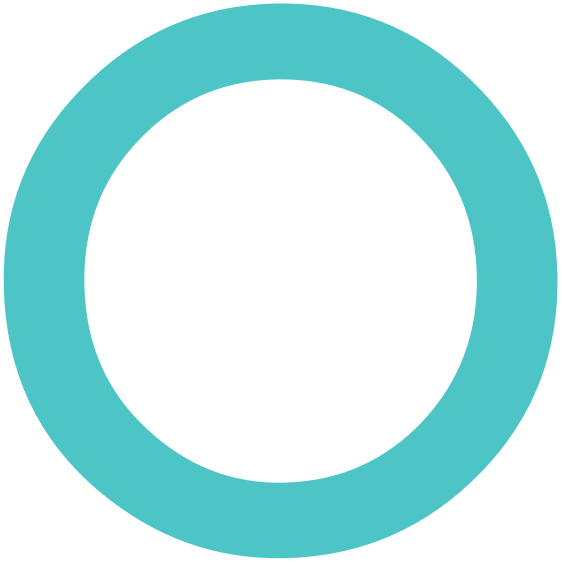
ACTIVE PHARMACEUTICAL INGREDIENT	UNIT PRICE (US$) PAID IN BRAZIL IN 2016 (A)	VOLUME (QUANTITY PROCURED IN 2016) (B)	ESTIMATE OF TOTAL EXPENDITURE L IN 2016 (US$) (C=A X B)	ALTERNATIVE PRICE (US$) AVAILABLE IN THE INTERNATIONAL MARKET (D)	EXPENDITURE ESTIMATE TOTAL IN 2016 BASED ON THE GENERIC VERSION PRICE (E = BXD)	ESTIMATED SAVINGS (US $) (C-E)
Daclatasvir (60 mg)*	24.21	2,407,440	58,283,573.92	2.18	5,244,780.00	53,038,793.92
Darunavir (600 mg)**	2.75	3,367,500	9,264,364.52	0.90	3,034,117.50	6,230,247.02
Entecavir (0,5 mg)***	2.45	12,692,160	31,062,056.57	1.17	14,849,827.20	16,212,229.37
Raltegravir 400mg**	4.06	3,600,000	14,608,396.62	1.33	4,788,000.00	9,820,396.62
Sofosbuvir (400mg)*	49.68	2,944,704	146,294,278.68	3.86	11,358,144.00	134,936,134.68
TOTAL						220,237,801.61

Source: authors. SIASG and LAI for the Ministry of Health's estimates of purchases. Commercial exchange rate for purchase: Real (BRL) / US dollar (US $) - 2016 average = 3.4895. * Generic price: http://hepcasia.com/generic-daas-pricing/ - Price divided by 28 because it deals with packaging with 28 units); ** Source of generic price: MSF Untangling the Web of ARV Price Reduction, 2016 *** Source of the entecavir 0.5mg generic price (Indian generic). US427 for 1-year treatment (to reach the unit price, 1 tablet of 0.5mg per day for 365 days was considered) Hill et al. 2015

7. Legal Aspects[o]

O Vitor Ido collaborated with the drafting of the first version of this chapter. The final version is the responsibility of the authors.

7.1 Comparative Legal Aspects Related to the Pendency Period of Patent Applications



Our analysis of the status showed that many medicines do not have a patent granted in Brazil, but still only have one supplier in the country, leading to sole source procurement by the Government, and without any bidding.

Different factors may lead to this situation. One of the main aspects addressed by the research is related to the patent system, which can generate a "de facto monopoly" prior to the "monopoly by law" arising from a patent granted for a particular product / medicine. We understand that "de facto monopoly" occurs when a technology is "subject to patent protection", that is, when there is an expectation of right arising from a patent application that has been filed but is still pending resolution in the administrative realm. This resolution may be the dismissal of the application resulting from failure to comply with any of the legal formalities, abandonment for failure to perform any act of the applicant's responsibility (before or after the examination, which leads to the status of dismissed or extinct, respectively) or rejection or grant of the application after examination of the merit by the competent authorities. We call this period between the filing and the resolution in the administrative realm, the pendency period.

Legally, during the pendency period, it is possible for third parties not authorised by the applicant to produce and market a medicine in the country, but this rarely occurs. Again, different factors can influence this situation. One such factor is that the patent law grants some rights to the patent applicant even during the pendency period. These rights vary from country to country. Next, we analyse some aspects related to this subject in Brazilian Law, in the WTO TRIPS Agreement and in the law of some other selected countries. Some examples of concrete cases are mentioned in order to illustrate the application of the law by the courts.

The main points to be analysed are: (i) measures which may prevent marketing during the pendency period ii) compensation that the patent owner may be entitled to for the commercialisation that occurred during the pendency period.

Brazil

1) Measures to prevent exploitation by unauthorised third parties during the pendency period

a precautionary measure, in general, is a judicial proceeding aimed at preventing, preserving, defending or ensuring the effectiveness of a right. In this regard, in some cases, the applicant/patent holder may file for preventive measures to be adopted to avoid possible intellectual property rights violations. In the present subject matter, the most relevant possibility would be the patent applicant obtaining a measure that would prevent the marketing of a medicine produced by a third party without his authorisation during the pendency period.

There are no specific provisions in the Industrial Property Law (LPI) regarding precautionary measures prior to the granting of the patent. Thus, although they may be applied for under the general rules provided for in the Code of Civil Procedure, they will be granted exclusively based on the violation of expectation of a right, not a right conferred specifically for that purpose. So in Brazilian Law there is no specific right to prevent the commercialisation of a certain product on the grounds of patent infringement during the pendency period as the patent does not yet exist.

The Brazilian jurisprudence found on the subject is unanimous in affirming the character of mere expectation of a right before the granting of a patent and the non-admission of precautionary measures to prevent the exploitation by third parties during the patent application pendency period.[P 67]

2) Compensation for exploitation by unauthorised third parties during the pendency period

We have also seen that the LPI (Brazilian Industrial Property law) - when dealing with the protection conferred by the patent - specifically provides for the right to obtain compensation for the improper exploitation that occurs during the pendency period of an application, should the patent be granted.

P Among others: "the right of patentability is not guaranteed by an application fee mere expectation of right, and not acquired right" TFR AMS nº 88580 / RJ of 03/27/1985 in RTFR 126 / 327-329 apud BASTOS, Aurelio Wander. *Propriedade Industrial: política, jurisprudência, doutrina* São Paulo: Liber Juris, 1991. p. 46; «Request for granting of privilege by INPI. Patent not yet granted. A mere expectation of rights that does not authorise the interested party to prevent exploitation by a third party, even though it assures the right to obtain compensation for the improper exploitation between the date of publication of the application and that of the granting of the patent, according to the law. " (TJSP Vote No. 1930 Instrument Award: 097.277.4 / 2 District: Lapa Regional Court. Agte: Omnitek Tecnologia Ltda. Agdo: Samapre Indústria de Máquinas Ltda.); The simple filing of the patent application does not give the applicant the rights attached to it. This will be subject to a certain procedure to verify the fulfilment of the legal requirements, in terms of articles 19 to 37 of Law 9.279 / 96 and after such evaluation will be granted or not. Only after such decision is taken will the applicant become the holder of the right and may prevent the use of the invention without his consent.
In fact, the fee generates an expectation of the right to the applicant, since the invention is exploited even before the privilege is granted, but after the grant, the right to compensation will have to be paid in respect to that period. However, it is recalled that there will be only a right to reparation for damages caused if the patent is obtained.
According to article 333, I of the Code of Civil Procedure, the author is responsible for proof of the constitutive fact of his right and for the defendant to prove the existence of an impending, modifying or extinguishing fact of the author's right.
In this case, the appellant has only confirmed the filing of the application for an invention privilege and not the actual grant of the patent.
The defendant, on the other hand, proves that the author's request was archived, due to the provision of article 33, sole paragraph of Law 9.279 / 96, definitely, information not rejected by the author who insists that from the application for registration of the patent with the INPI, the inventor has the right to exploit the invention.
In this way, the author is not properly discharged of the burden that was his, failing to prove the effective granting of the patent on which he bases his right, the appealed decision was correct by dismissing the claim of compensation "(<t8 /> APELACAO 0072732-35.2004. 8.19.0001 – Judge-Rapporteur: MARIO ASSIS GONCALVES - Judgment: 10/11/2010 - THIRD CIVIL COURT Date of Judgment: 10/11/2010); "The simple filing of the patent application, addressed to the INPI, does not in itself confer on the applicant the right of exclusivity of the product, but mere expectation of such right, and only after the granting of the patent, will result in the right of its owner to prevent third parties from producing the patented product, and may also claim indemnification in the event of any undue exploitation, ex exegesis of articles 42 and 44 of Law 9,279 / 96 "(<t10 /> TJMG Civil Appeal (s): GUDIM INDÚSTRIA METALÚRGICA LTDA., BOABEDIL DE OLIVEIRA ALVES - ME - GALVANIZADOS ALVES JÚNIOR and Subject of the appeal: the same persons Rapporteur: Des. (a) SILAS VIEIRA Date of the meeting: 306.342-3, District of GUARANI, Judgment: 05/16/2000 Publication date: 06/17/2000); "<T11 /> Trademarks and patents - Absence of use of counterfeit product - Cause of application based on patent application with INPI - Mere expectation of right that does not allow to prevent third party from exploring similar product - Decision maintained - Remedy not available <t12 />. n.
9122179-12.2002.8.26.0000, TJSP, 7ª Câm. Dir. Priv., Judge-Rapporteur Luiz Antonio Costa, J., 03.02.10.

> *Art. 44, LPI. To the patent holder is guaranteed the right to obtain indemnification for the improper exploitation of the object of the patent, including that which occurs between the date of publication of the application and that of the patent grant.*

According to the LPI, the right to obtain compensation starts on the date of publication of the patent application (art. 44, caput, LPI) or of the beginning of the use, if the offender was aware of the content of the application prior to publication (art. 44, §1º, LPI). It should be stressed that the indemnification will only be due after the patent is granted, as prior to it there is only an expectation of a right. If the expectation of a right is confirmed by the granting of the patent, it will be possible to obtain compensation retroactively to the pendency period. If the patent is not granted, there is no indemnification owed to the applicant. It is also important to remember that the indemnification only applies to improper use, that is, it does not include the acts provided for in article 43 of the LPI.[Q] And that the indemnification is limited to the content of the patent in the form in which it is granted (art. 44, §3º, LPI). This last point is extremely important because there is the possibility that the claims initially filed are substantially different from the actual protection by the patent granted.

But what constitutes this compensation? This is where Brazilian law differs more substantially from the legislation of other countries. In relation to most of the national legislations analysed, the LPI contains one of the most broad compensation provisions, providing for a high indemnification quantum that applies even to the period prior to the grant of the patent, with no explicit difference in the amount payable due to facts occurred before or after the granting,[R] as seen in other countries.

The compensation is provided for in the chapter of the general provisions of the LPI, articles 208, 209 and 210, which stipulate: (i) compensation for damage caused (ii) damages for acts of violation of IP rights

Q Among others, article 43 of the LPI allows the experimental use related to studies or scientific and technological research (item II) and the Bolar exception, which makes it possible to practice acts necessary to obtain market authorisation by the health regulatory agency (section VII).

R It is possible to interpret that only Article 208 of the IPL would apply to acts committed before the granting of patents, while Articles 20 and 210 would apply to acts committed after the granting of the patent.

and acts of unfair competition not provided for by the LPI (art. 209, LPI), and (iii) loss of profits. Additionally, it stipulates the following criteria for calculating indemnification:

- the indemnification is determined by the benefits that the injured party would otherwise have obtained (art. 208, LPI);
- the stipulation of loss of profits by the criterion most favourable to the injured, among the following: (i) the benefits that the injured party would have received had the violation not occurred; or (ii) the benefits that were obtained by the author of the violation of the right; or (iii) the remuneration that the perpetrator of the violation would have paid to the owner of the right violated had a license been granted that allowed the perpetrator to legally exploit the property (art. 210, LPI).

As seen above, the jurisprudence reviewed by our research is unanimous in stating that there is no measure to prevent exploitation of the object of a patent application prior to its grant, but that there is compensation for acts of improper exploitation occurred during the patent application pendency period if the patent is granted. However, the exact amount to be paid is stipulated in the execution process. Most cases in Brazilian courts have not even been finalised at this stage, so there was no specific jurisprudence found on the amount of compensation applied to cases of patent infringement, whether occurring before or after the granting.

It should also be mentioned that the LPI has a specific chapter on crimes committed against patents (Chapter I of Title V), which allows for possible violations of rights to be dealt with in the criminal law field, in addition to civil law remedies. However, the legislative wording is explicit in the sense that crimes are against patents (articles 183, 184, 185 and 186, LPI), thus not extending to acts committed before the patent was granted.

Finally, it is possible to return to the explanatory statement of the patent law to make additional considerations about the legislative policy adopted. The Explanatory Memorandum states that:

> *25. With regard to procedural matters, legislators sought to provide the bill with clear and precise provisions, so as to provide interested parties with a better knowledge of the rules to follow in the exercise of their rights and fulfilment of their obligations. (...)*

The legislative option, therefore, was to provide - in the case of infringements of industrial property rights - predetermined criteria for compensation, on the grounds of providing greater legal certainty and predictability.

However, by setting the criteria for possible compensation excessively high, and by not specifically differentiating the appropriate compensation in cases of improper exploitation occurred before or after the grant of the patent, the Brazilian law creates great disincentives to innovation and competition, since it imposes an excessive risk to third parties. As will be seen below, these criteria are far above similar provisions in the TRIPS Agreement and other national legislation on the subject.

In the specific case of this research, the LPI creates a system that limits access to medicines and, consequently, the right to health. It provides excessive protection to the patent applicant, even if the patent is often not granted, making affordable access to medicines - including by the public health system - more difficult.

International Comparison: the LPI is TRIPS-plus and more restrictive than US, EU, India, Thailand and Argentina laws

As stated above, Brazilian law provides greater protection to patent holders and to applicants than that determined by the WTO TRIPS Agreement of the WTO. We will briefly analyse the relevant provisions of TRIPS and the national/regional laws of the United States, European Union, India, Thailand and Argentina.

TRIPS

The TRIPS Agreement sets out the main parameters on intellectual property that must be followed by the national laws of WTO member countries.

With regard to preventive measures, Article 41 of TRIPS requires countries to legally ensure procedures for the enforcement of intellectual property protection rules in order to allow effective action against any violation of the rights provided for in the Agreement, including procedures to prevent infringements. The same article states that these procedures should be applied in such a way as to avoid creating barriers to legitimate trade and to provide safeguards against their abusive use (art. 41.1). It also states that procedures for the enforcement of intellectual property rights must be "fair and equitable" (art. 41.2).

Furthermore, Article 50 stipulates that judicial authorities shall have the power to determine prompt and effective provisional measures to prevent the occurrence of a violation of any intellectual property right. And the same article states that the applicant must pay a fee that is sufficient to protect the defendant and avoid abuse.

Regarding compensation for infringement of an intellectual property right, TRIPS, in its Article 45.1 states that an intellectual property infringer must pay "adequate damages to compensate for the injury" to the right holder. TRIPS does not define "adequate damages". TRIPS provides that "the term of protection available shall not end before the expiration of a period of twenty years counted from the filing date" (article 33), but there is no specific reference to the payment of compensation for acts committed before the patent is granted.

In this sense, we can argue that the measure imposed by Brazilian law far outweighs *adequate* compensation, since it provides for a total compensation for all damages. Additionally, damages and loss of profits set in the most beneficial criterion in favour of the patent holder, which could, if applied literally, be even much higher than any gain earned by the infringer. This is even worse where the same damages can be obtained by acts committed before the granting of the patent. In other words, both the amount of indemnification provided for by the Brazilian law and the fact of providing compensation for acts committed prior to the granting of the patent are measures that exceed the parameters imposed by TRIPS, thus being TRIPS-plus.

In addition, the LPI does not foresee any measure that would prevent the abuse of procedures relating to a possible patent infringement by the patent holder or applicant or the creation of undue barriers to trade,

as determined by Article 41.1 of the TRIPS Agreement. The Brazilian legal system foresees the abuse of intellectual property rights as an infraction of the economic order punishable by law (article 36 of Law 12,529 / 2011, which deals with the Brazilian System for the Defence of Competition), but there is no provision in the industrial property law itself.

It is also important to note that Article 48 of TRIPS provides for the possibility of compensation not only for the holder of an intellectual property right, but also for the person wrongly accused of violation by abusive measures or threats. This caution, as we will see below, is foreseen in the Indian and Argentine laws, but is not specifically provided for in the Brazilian Industrial Property Law (although it may characterise, under other Brazilian laws, a hypothesis of abuse of right subject to compensation).

Argentina

In Argentina, the patent law provides for the possibility of requesting certain measures in court prior to the granting of a patent, "under such precautions as the judge deems necessary". In relation to patents already granted, article 83, II provides for precautionary measures only in a restrictive manner: either to avoid patent infringements, especially to prevent the entry of certain goods into the market (art. 83, II, 1), or to preserve evidence relating to an offense (art. 83, II, 2). However, the following conditions are required: (i) that there is a reasonable likelihood that the patent, if challenged as void, will be declared valid; ii) that any delay in granting precautionary measures would result in irreparable damage to the patent holder; iii) that the damage caused to the owner is greater than the damage of the alleged offender if such a measure is granted erroneously; iv) that there is a reasonable likelihood of patent infringement.

In addition, Argentine law also provides that in all cases involving precautionary measures, the judge will request the applicant to provide a security fee sufficient to protect the defendant and to avoid abuses.

Regarding compensation, Article 81 of the same law provides for the possibility of action to prohibit the Continued of unlawful exploitation and to obtain "compensation for loss suffered" to the patent holder. It is a measure exclusively open to the patent holder (and not to the applicant), and which is limited to the reparation of the damage suffered.

This is unlike Brazilian law, which stipulates damages, losses and damages and loss of profits, all of which stipulate high amounts.

Thailand

Thai Patent Law states that acts committed prior to the grant of a patent do not constitute an infringement of rights unless they relate to an already published patent application and that the infringer is aware that a patent has been filed or if the infringer was informed in writing that there was a pending patent application for the invention. In such cases, the patent holder, once the patent has been granted, may file a lawsuit for the infringer to pay damages for acts committed before the patent was granted but after the application has been published.

Article 77ter of the Thai Patent Law provides some parameters that must be observed by the judges in quantifying the damage, such as the seriousness of the infringement and the loss of profits, but these parameters only apply to the patent holder, for acts committed after the patent has been granted. Thus, there are no established parameters for the quantification of damages for acts committed during the pendency period.

As regards precautionary measures, Thai Patent Law guarantees patent holders the right to seek a court order to stop or prevent an infringement of rights by third parties. The law mentions "patent holder" and there is no specific provision extending that right to a mere applicant.

India

In India, the Patent Law provides that from the date of publication of a patent application, the applicant enjoys the same rights as if the patent had been granted. After the grant of the patent, the holder acquires the right to file lawsuits for violations of rights, including those that happened before the granting. However, prior to the grant, no court action may be requested by the applicant.

As far as compensation is concerned, the Indian Patent Law is explicit in providing for "or compensation for damage caused or a portion of the profits". Further, the same law provides that there will be no compensation against the accused of infringing patents that prove not to be aware, or would not have reasonable conditions, to know of the existence of a patent.

Finally, India's Patent Law provides for protection against unwarranted threats of lawsuits for infringement of patent rights by the patent holder, the applicant of a patent application, or any person who is threatening, including damages to the person who suffered the threat.

United States of America

In the United States (US), where the law and jurisprudence are typically highly protective of intellectual property rights, the expected indemnification parameter in case of a breach occurring during the pendency period is the payment of "reasonable royalty," which is well below the criteria established by Brazilian law. Even after the granting of the patent, the criteria for fixing the indemnification are more restricted than those provided by the Brazilian LPI. The US law establishes the payment of damages "not less than reasonable royalties" and expressly provides that compensation for damages that may be increased by the judge does not apply to acts committed before the grant of the patent.

What is broader than in Brazilian law is the possibility of granting precautionary measures before the granting of a patent. However, judicial practice (case E-bay v. Merc-Exchange, 2006), imposes strict conditions for the granting of precautionary measures in such cases, and the following elements must be proven:

i. That there was irreparable damage;

ii. That the available legal instruments (such as a posteriori indemnity) are inadequate to compensate for the damage;

iii. Consider the balance between the inequalities between the holder of intellectual property rights and the infringer, so that an equitable instrument is used;

iv. The public interest cannot be violated by a permanent injunction.

European Union (EU)

In the EU, the rights of the patent applicant, that is prior to the grant of the patent, only provide for the payment of "reasonable" compensation, pursuant to Article 67 (2) by the European Patent Convention.

There is no specific provision on legal measures that may be granted during the patent application pendency period.

Conclusion

This brief survey of global legal provisions, both in regions of industrialised countries (the United States and the European Union) and in countries technologically similar to Brazil (Argentina, Thailand and India), demonstrates that Brazilian law is extremely disproportionate in relation to the amount of compensation due for possible violations of patent rights even when they occur after the granting of the patent. Applying the same compensation for acts that occurred before the grant goes beyond what is determined by the WTO TRIPS Agreement and the national legislation of any other country reviewed in this study. The LPI unduly restricts the possibility of competition during the patent application pendency period by excessively protecting the (perhaps future) holder of the patent and imposing excessive risks on other actors, which is inefficient and disproportionate vis-à-vis the stated objectives of the intellectual property system which are to promote innovation and to serve the public interest.

At the same time, Brazilian Industrial Property Law paradoxically lacks mechanisms such as those provided in other jurisdictions to protect third parties from undue threats by patent holders or applicants.

7.2 Brief considerations on non-patent barriers to competition

Our research study identified 77 active pharmaceutical ingredients in a situation of sole source procurement on the supply side, out of a universe of 170 initially analysed. In view of this situation, we tried to address different aspects that may lead to sole source procurement procedures. The focus of the study was patent barriers, including the *de facto* monopoly generated by pending patent applications and the compensation for acts committed during the pendency period as a factor that discourages competition from possible generic producers during this period (as discussed in the previous section).

However, other elements besides the patent system can also act as a barrier to competition, contributing to the situation of sole source procurement on the supply side. We have already briefly mentioned the issue of older medicines being replaced by new ones, and therefore generating less market interest for different suppliers. Replacement of the first-generation medicine with a generic by the pharmacist is impaired as it is no longer prescribed, but the condition for the launch of the generic is that an innovative medicine without patent protection is available. The launching period for second generation products - usually a few years before the expiration of the primary patent - is considered critical for a successful sales transition from the original to the second-generation medicine.[36] In this section, we will briefly discuss issues related to the public procurement process and obtaining market approval (registration) of medicines.

As a rule, a public administration procurement process must be carried out through a public tender process (bidding) (article 37, XXI, FC). Public tender processes are regulated by Federal Law 8.666/1993,[68] also known as the Public Tendering Law.

The Public Tendering Law foresees situations where bidding can be waived (article 24) or not required (article 25). The waiver refers to cases in which there is no need for a bidding process for reasons of public interest (including procurement carried out to comply with judicial decisions). Bidding is not required in cases where competition is not possible, such as when there are no competitors.

One of the situations for a waiver is the procurement of strategic products for the SUS when there is technology transfer (art. 24, XXXII). One of the provisions of the law for when bidding is not required is that the object can only be supplied by one producer, company or exclusive commercial representative (art. 25, I). The same legal provision establishes the following: (i) need to present a certificate attesting the exclusivity of supply, (ii) the waiver or non-requirement of bidding must be ratified by a higher authority (art. 26) and (iii) the use of waiver or non-requirement of bidding outside the possibilities of the law or non-compliance with the formalities is considered a crime (art. 89).

The procurement of the medicines identified in the research as being in exclusivity situation from the supply side could possibly not

require bidding if only one supplier exists in the national market. Nevertheless, Law 8.666 / 93 provides for the possibility of international tendering (bidding), with the participation of foreign companies that do not operate in the country, but which must have legal representation in Brazil (art. 32, §4). At first, this option could be applied to the procurement of products that have a sole supplier in Brazil, but that have more than one supplier in the international market. It is important to note that the Public Tendering Law establishes the possibility of having a preference margin of up to 25% for products that meet Brazilian technical standards (art. 3º, §5º) and for products resulting from development and technological innovation carried out in the country (art. 3, paragraph 7). The margin of preference may also be extended to products originating in Mercosur countries (art. 3º, §10).

In addition, the same law also provides for the possibility of a waiver of bidding for the acquisition of goods - in terms of specific international agreements - when the conditions offered are clearly advantageous to the Government, provided that such agreement is approved by the National Congress (art. 24, XIV). Specific rules also apply in the case of goods acquired with financing from an international financial institution or a foreign cooperation agency (art. 32, §6).

Regarding the public procurement of medicines, the Inter-ministry Ordinance 128/2008[69] establishes that national tenders will be preferred in procurement of medicines by the public administration (art. 2) and that it is compulsory to present the product registration certificate (market approval) issued by Anvisa (Brazilian regulatory health agency) (art. 2, §1). It should also be noted that Law 12,401 / 11, which amended Law 8.080 / 90, prevents the supply of medicines in the public health system (SUS) without market approval by Anvisa (art. 19-T, II). Regarding the margin of preference for national products provided for in the Public Tendering Law, this was established by Decree 7,713/2012[70] for the acquisition of medicines, with applications until March 30, 2017.

To illustrate this situation, we requested documents - via the Access to Information Law (LAI) - to prove the situation of exclusivity of supply of some of the medicines being investigated, namely: a) direct-acting antiviral medicines used in the treatment of hepatitis C (simeprevir, daclatasvir and sofosbuvir) and b) HIV / AIDS medicines. Only informa-

tion related to hepatitis C medicines was sent.[S] Documentation regarding ARV medicines was denied on the grounds that the request would be disproportionate and would require additional work by public servants (art. 13, II and III, LAI).[T] In the documents obtained, the justification presented in the three cases, for procurements made in 2015, 2016 and 2017, was the existence of only one company with market approval by Anvisa. Thus, it is understood that the lack of market approval by Anvisa can be an impediment to the participation of foreign companies in possible medicines procurement tenders, thereby further reducing the possibility of opening international tenders.

In an attempt to identify ways to promote competition and reduce the price of medicines purchased by the public health system (SUS), we investigated the possibility of competition between suppliers who may hold market approval issued by other health regulatory agencies, but not the Brazilian agency.

Anvisa's foundation law provides for the possibility of exemption from registration (market approval) of medicines in the country when acquired through international multilateral organisations for use in public health programmes by the Ministry of Health and its related entities (article 8, §5, Law 9,782/99).[71] This was the case, for example, in the purchase of the generic medicine efavirenz imported from India shortly after the patent compulsory license was issued in 2007. A purchase was made through the Pan American Health Organization (PAHO)[72] while the production of the generic medicine was in progress in the national territory. This was also the case for the procurement of the generic medicine darunavir, purchased through the PAHO Strategic Fund under the Mercosur joint procurement mechanism in early 2016. It is important to note that generic medicines purchased via PAHO are prequalified by the WHO.

However, a purchase without market approval in Brazil is the exception and was the subject of debates within Anvisa, culminating in a new regulation on the subject. The new resolution (RDC 203/17)[73] seems to prevent possible alternatives to increase competition, even on an exceptional basis, by restricting the possibility of importing medicines without

S E-SIC, Application n. 25820000711201899, replied on 08/03/2018.

T E-SIC, Application n. 25820000711201899, replied on 08/03/2018.

market approval by Anvisa via international multilateral organisations. That possibility now applies only to cases of "unavailability on the domestic market" that is, when there is no one with market approval in the country (art. 3, I). The resolution also mentions cases of "public health emergency of national importance", in which the import of products without market approval by Anvisa could be carried out independently of international mechanisms and independently of the existence of anyone else with market approval issued in the country (art. 3, II).

However, the resolution does not mention cases of public interest, which exists in other national legislation, for instance when dealing with the possibility of issuing compulsory licenses in cases of national emergency or public interest (art. 71, LPI). We can interpret that RDC 203/17 precludes the purchase of medicines without market approval in Anvisa even in case of compulsory license for public interest when there is at least one company registered in Brazil. This situation further complicates the use of this important public health safeguard under the patent system.

RDC 203/17 also made it unfeasible to procure medicines without market approval by Anvisa that could occur under the Mercosur joint procurement mechanism prior to the new regulation. In 2015, Mercosur countries launched a joint mechanism for the procurement of selected high-cost medicines, which includes the possibility of buying medicines via PAHO from generic producers prequalified by the WHO. Darunavir, as mentioned above, was one of the medicines included in the procurement list. Data from the Ministry of Health shows that in 2016 the medicine was partially procured from Janssen, at a price of BRL 9.60 (USD 2.75), and partially from Aurobindo through PAHO, for BRL 4.34 (USD 1.24)[U]. Considering the volume purchased from Aurobindo[U], this purchase resulted in savings to the Brazilian public health system of more than BRL 42 million. However, in 2017 darunavir was once again solely procured from Janssen under the provision of non-requirement of bidding. The only company with a market approval for darunavir in Brazil is Janssen-Cilag. We can speculate that the interruption of procurement of the generic

U Brazil, Ministry of Health, Department of STD, HIV Aids and Viral Hepatitis. 2017. Information obtained through the Access to Information Law. Request 2058558. In 2016, 8,038,200 units were procured from Aurobindo and 3,367,500 from Janssen. Available at http://portalquivos2.saude.gov.br/images/pdf/2017/agosto/03/LICITACOES-2017.pdf <t1 /> (last consulted on 06/20/2018).

version via PAHO is linked to the lack of market approval in Anvisa and that this case is one of the factors that have led to the new regulation on the subject. There is no patent granted for darunavir in Brazil and pending patent applications are either secondary or are process (not product) primary.

It is also worth mentioning that one of the ARV medicines identified as being in the exclusivity situation from the supply side in 2016 is lopinavir / ritonavir. We did not have access to documents that justified the purchase without bidding for this medicine, but currently there are three companies with a market approval valid in Brazil: i) Abbvie, with the current registration obtained on 10/27/2014; ii) Cristália, with registration obtained on 07/07/2016 and iii) Furp, with registration obtained on 03/03/2017, according to information available on the Anvisa website. On June 22, 2017, an electronic auction session (n.35 / 17) was opened with the aim of procuring the medicine, but the result was "deserted" as indicated on the Ministry of Health website.[74] The "desert" result occurs when no one applies for the tendering process, which may later justify the waiver of bidding. This case indicates that even when there is more than one supplier with market approval in Brazil, other factors may lead to sole source procurement, that is via a waiver or non-requirement of bidding.

Finally, it would be advisable to investigate the reasons that may lead to the absence of requests for market approval in Brazil by foreign companies that have approval in other countries, especially in the case of generic medicines approved by other regulatory agencies that have parameters similar to that of Anvisa, as they would have conditions to participate in public tendering for medicines procurement if they have market approval in Brazil. Medicines regulation is a central factor in the pharmaceutical market and can increase or restrict access to medicines. However, this issue is beyond the scope of this study.

8 Discussion

The present research project investigated in depth some determinants of the exclusivity in the national market for medicines procured by the Unified Health System, seeking to understand mainly the role played by multiple patent applications filed in Brazil for the same product and to analyse those situations involving pending applications.

The approach we adopted is unprecedented for many reasons. First, because the initial selection of active pharmaceutical ingredients had as its starting point the identification of those in exclusivity situation. Second, because our analysis of the patent situation of the active pharmaceutical ingredients tried to go beyond the identification of the status and included the analysis of the patent claims, which allowed us to bring more elements to evaluate if the exclusivity situation of the product could be explained by patent barriers. In addition, the extension of the patent applications related to 74 active pharmaceutical ingredients of interest to SUS, including international patent applications without correspondents in Brazil[v], is also unprecedented.

Third, we analysed public procurement of selected medicines, considering both their relevance in the context of the Ministry of Health's expenditures in pharmaceutical services, as well as an overview of procurement modalities and the intersection with the patent situation of each one of them. Finally, we analysed some legal aspects that can contribute to exclusivity situations examined in our research, especially regarding pendency of patent applications, a focus of our research.

V A patent application without a correspondent one in Brazil suggest its specific content is in the public domain in the country.

Our results revealed many important lessons learned and reinforced the contribution of the methodology embraced.

Regarding exclusivity situations from the supply side, we found that for some medicines the only supplier in Brazil was a national generic medicines company (3 active pharmaceutical ingredients). Following the patent search, it was also possible to identify a group of medicines that had no patent application filed in Brazil (9 active pharmaceutical ingredients). These two situations, without patent barriers, deserve other types of research to understand the reasons why these medicines had only one supplier in the national market and to explore possible governmental responses to overcome potential risks of shortages and possible alternatives for price reduction. For the active pharmaceutical ingredients with patent applications identified in Brazil there was also a group whose status in 2016 ranged from expired, extinct, rejected and dismissed, suggesting there is no patent barrier for them (6 active pharmaceutical ingredients). With the exception of exemestane, whose procurement was among those with the highest expenditure for our cancer medicines sample in 2016, no active pharmaceutical ingredient with indication of not having a patent barrier or even potential had procurements of amounts proportionally significant in relation to the analysed sample, both in 2016 and in the period from 2007 to 2016.

The results also made it possible to identify that 59 active pharmaceutical ingredients had at least one patent granted and the others were expired, extinct, rejected and dismissed (total 26) and at least one pending application and others (expired, extinct, rejected and dismissed) (total 33), confirming the study's assumptions that multiple patent applications, especially those pending, could generate legal uncertainty that would contribute to the exclusivity situations for certain medicines in the country.

The classification of applications by active pharmaceutical ingredient, based on the filing date in the country, graphically illustrates the hypothetical extent of exclusivity situation of the product if all applications are granted and are interpreted as a barrier to competition. This reinforces the risk of multiple patent applications.

The analysis of patent applications claims for active pharmaceutical ingredients of chemical-synthetic origin also made it possible "to sort the

wheat from the chaff" regarding the quality of patents. This confirms the practice of evergreening as the main driver of the multiple applications presented by companies. We also emphasised the proportion of applications dismissed (26.7% of the total analysed and included in the research) before the examination. In other reviews of pharmaceutical patents in Brazil, Sampat and Shadlen[21] found 60% were dismissed applications, but they analysed only those classified as secondary. Reis[37] found 25% of ARV medicines applications dismissed.

The analysis of the estimates of the purchases financed by the Ministry of Health allowed us to rank active pharmaceutical ingredients that represented the greater part of the expenditures in the sample, which are mostly those with at least one pending application and at least one secondary patent granted or primary process, but without the primary patent granted. This result suggests that many high-cost medicines for SUS are in an exclusivity situation among other reasons, as a consequence of the *de facto* monopoly situation generated by pending patent applications or from a granted patent that does not necessarily block competition with generics. This indicates the possibility to adopt practices that can stimulate competition and reduce prices.

Despite the situation of exclusivity found and the significant weight that these medicines have in terms of Ministry of Health expenditure on pharmaceutical services, our analysis of unit price evolution points to price reductions for most of them over six years, reinforcing the importance of centralised purchasing and other mechanisms - such as negotiation with multinational suppliers - that have been adopted to achieve price reduction.

On the other hand, although the evolution of unit prices is recognised as an improvement in terms of efforts to reduce it, total expenditure on various medicines over a ten-year period has been high. The comparison of prices charged in 2016 for medicines whose active pharmaceutical ingredients were pending patent applications or were classified as secondary patent granted, compared to prices charged by generic alternatives available in the international market point to an even greater potential for resource savings. This finding supports the notion of the importance of integrating the analysis of the patent situation of medicines procured by SUS in public procurement processes. It also reinforces the importance

of considering an active search for the existence of alternative sources of generic/biosimilars in the international market to be used as price reference and potential supplier in the absence of a patent barrier.

8.1 Governmental responses to reduce prices of medicines under exclusivity in SUS

The results of this research are intended primarily to start a dialogue with different health professionals on the role of patents as a relevant determinant to high-cost medicines in exclusivity situation for SUS. The effort is to carry out a comprehensive methodological approach aimed at demonstrating that it is possible to incorporate the patent component in a systematic way as a variable of analysis of the market dynamics of these medicines.

A number of strategies have already been adopted by the Ministry of Health to reduce prices of medicines procured under exclusivity, including measures to address patent barriers.[75] However, we believe that the latter can be expanded to a wider range of medicines procured by SUS that are in the same situation, since most of the work in the specific field of patents is related to HIV/AIDS medicines and more recently to hepatitis C. It is important to emphasise that government strategies have also involved initiatives from other public entities - such as a Public Manufacturer (Farmanguinhos / Fiocruz) - and that non-governmental stakeholders, including civil society organisations of public interest - such as the Working Group on Intellectual Property of the Brazilian Network for the Integration of Peoples (GTPI / Rebrip) - have a long history of activism in this area.

Among the strategies espoused by the Ministry of Health to reduce prices is pooled procurement (centralised) of medicines to increase bargaining power based on the consolidation of the volume and price negotiation with pharmaceutical companies.

A recent study[76] signed by Ministry of Health managers, presents price reduction strategies for a set of medicines whose sourcing and procurement from monopoly producers was incorporated between 2012 and 2015. These belong to CEAF and CESAF and centrally procured

antineoplastic medicines. It was not mentioned measures to address the patent barrier, among the presented strategies.

Among the strategies which resulted in savings, are the following: pooled procurement of some products; pricing agreement with manufacturers who compare of the effectiveness and price of technologies already adopted by SUS for the same therapeutic indication; application of the Price Adequacy Coefficient (CAP) to define a Maximum Sale Price to the Government (PMVG) for almost all CEAF medicines; petitions to the National Council for Treasury Policy of the Ministry of Finance for tax exemption for SUS listed medicines; and, local production and technology transfer initiatives through Productive Development Partnerships.

For HIV/AIDS medicines, the government's bargaining power was strengthened in price negotiations through the adoption of reference prices established on the basis of estimates of production costs and signalling of capacity to produce locally. including with signals that measures could be taken to remove patent barriers if necessary, with, for instance, issuance of public interest compulsory license.

From 2005 to 2008, more direct measures to address patent barriers were adopted by government and state entities, such as the presentation of third-party observations (patent opposition) of ARV patent applications (tenofovir and lopinavir / ritonavir) by Farmanguinhos / Fiocruz; request for priority examination of patent applications, which when rejected allowed the use of locally produced generics (tenofovir) [22]; and issuing a compulsory license (efavirenz) for importation and subsequent local production of a generic version of the medicine.[75, 77] While these measures may be considered limited to specific and temporary events in relation to the number of medicines covered, they have played a very important role in reducing prices and increasing access to specific medicines. Similar measures could be adopted for other medicines in a patent monopoly situation[W] in order to direct the debate on patents and medicines as a whole.

An industrial policy focused on the Health Industrial Complex was implemented in 2009. Since then, as some studies indicate, other

W Among others, the speech by the President of the Federative Republic of Brazil, Dilma Rousseff, in the United Nations (UN) High Level Meeting of the General Assembly on the prevention and control of non-communicable diseases in 2011.

measures to overcome patent barriers were adopted with the objective of nationalising the production of strategic medicines for SUS.[78,79] Among them was the adoption of voluntary licensing of patents for technology transfer (atazanavir). It should be noted however, that questions have been raised about voluntary licenses, in relation to their effectiveness for significant price reductions, especially if compared to previously adopted measures such as compulsory licensing, as well as to the necessity and efficiency of the technology transfer.[78,80]

Regarding the existence of occasional experiences on addressing patent barriers by government entities, there is no evidence as to how systematically they are adopted for all medicines supplied by SUS under exclusivity situation.

In 2016 and 2017, the Ministry of Health requested priority examinations[81] for several patent applications of active pharmaceutical ingredients included those in our sample. In 2016, the Ministry of Health made the same request for sofosbuvir, daclatasvir, simeprevir and ledipasvir. In 2017, the Ministry of Health requested patent priority examinations[53] for patent applications related to adalimumab, atazanavir, pramipexole, sirolimus, formoterol fumarate dihydrate + budesonide, bevacizumab, glatiramer acetate, raltegravir, trastuzumab, clozapine, infliximab, everolimus, imatinib.

We also identified third-party observations (pre-grant oppositions) for applications for sofosbuvir (PI0410846-9), daclatasvir (PI0716483-1) and dolutegravir (PI0610030-9) by civil society organisations (GTPI / Rebrip), Farmanguinhos / Fiocruz and private companies from 2015 to 2017.

In terms of local production efforts, we identified project proposals for PDP (Phase I) and PDP Projects (Phase II) for various active pharmaceutical ingredients of our research sample, both before and after 2016. We were unable to find any Phase III PDP, this being the phase in which the transfer of technology itself occurs and the beginning of the supply of the medicine to SUS (Ordinance 2531/2014) [82] by the company transferring the technology to the public manufacturer. Thus, even if the patent barrier is being targeted, local production is non-existent.

According to the survey presented in Chapter 6, there were a few generic and biosimilar versions found in the international market

for most of the active pharmaceutical ingredients in the sample. This reinforces the importance of national industrial development of these alternatives not only to promote competition in the price negotiation processes, but also to ensure timely availability when patent barriers are overcome. However, the difficulties in identifying these alternatives does not necessarily mean that they do not exist. This limitation underscores the importance of creating and updating a public and transparent database on the international availability of sources and prices of generic and biosimilars alternatives.

We identified PDP Projects (Phases I and II) for the following active pharmaceutical ingredients of synthetic products: daclatasvir (2018), darunavir (2018), dasatinib (2018), dolutegravir (2018), erlotinib (2018), glatiramer (2018), sirolimus (2010, 2016), sofosbuvir (2018), simeprevir (2018), gosserelin (2012), hydroxyurea (2018).[49] We found PDP (Phase I and II) proposals for the following biologicals: adalimumab (2018), bevacizumab (2017), etanercept (2013, 2017), golimumab (2018), imiglucerase (2018), rituximab (2013, 2017), tocilizumab (2018), and trastuzumab (2017).

Most PDP projects for technology transfers involve private companies. We found some cases of biological products in which multinational companies are not the applicants and/or the holders of the patent applications, suggesting that this segment of the pharmaceutical industry is also competing for a share of the biosimilars market. We found a small number of PDP projects involving multinational companies that had filed patent applications related to the technology in question, which may indicate that there is some negotiation regarding the licensing of the patent involved.

Finally, it is worth mentioning other public policy initiatives that are more comprehensive which apply to the whole patent system and especially to medicines of interest to SUS. We consider it relevant to mention 3 of these initiatives, but without going into further detail as they are out of the scope of this research study: i) Anvisa's prior consent; ii) INPI examination guidelines and iii) patent law reform.

In 1999 a provisional measure in the Industrial Property Law introduced the need for Anvisa to grant prior consent for a patent to be granted in the pharmaceutical sector (Article 229C). It became a law in 2001.

Prior approval was established with the main objective of performing the best possible technical examination for patent applications in a sector considered to be of extreme public interest, both from the point of view of health access policies and industrial and technological development policies.

Over the years, Anvisa's prior consent played a key role in not consenting patent applications or reducing the content scope of patents granted when they did not meet the criteria. However, this measure was subject to questioning and was recently subject to a new regulation that reduces the strength of Anvisa's decisions. Their decisions were considered as support to the INPI examination regarding compliance with the patentability requirements (Joint Ordinance n. 1, of April 12, 2017, ANVISA / INPI). [83] Nevertheless, it is believed that having a governmental organisation of the health sector with the attribution of analysing patent applications for medicines of interest to SUS and conducting systematic pre-grant oppositions is an extremely valuable measure for addressing patent barriers in the sector.

Regarding INPI's patent examination guidelines, there was a long process to update guidelines in the chemical-pharmaceutical field, which went on until the beginning of 2018, when the new INPI guidelines specifically aimed at this sector were published. The publication revoked an earlier document dating from 1995 (Resolution INPI / PR n. 208, of December 27, 2017). It is beyond the scope of our research study to analyse the content of these guidelines, but it should be remembered that examination guidelines play an essential role in detailing what may or may not be subject to patent protection and has enormous potential to restrict the granting of secondary patents to medicines analysed in our research.[84]

With regard to patent law, a number of bills are currently being drafted in the National Congress. They propose several changes in the legislative text, both towards extending the rights of patent holders and in expanding and facilitating the adoption of measures to restrict rights and minimise abuse.[85] The merit of the proposals is beyond the scope of this study, but it is important to mention that those initiatives are underway and can change the context around the issue. [85]

8.2 Measures to reduce INPI patent application decision backlogs

The backlog issue, that is, the number of patent applications awaiting an INPI decision, is by no means new. INPI has taken a number of measures aimed at reducing the time required to obtain a decision on a patent application, thereby reducing the backlog and application pendency time. As seen in the course of our research, the backlog contributes to legal uncertainty about the patent status of a medicine, influencing the decision of potential competitors as well as buyers. Among the most recent measures, we can highlight: i) workforce recruitment, totalling a 25% staff increase in the last two years ii) increase in production per examiner, which in the pharmaceutical area was up 60% compared to 2015 (iii) investment in computerisation and digitisation systems and (iv) simplification and automation of some administrative procedures. [30]

However, other measures are still needed, given that the average decision time in the pharmaceutical patents field in 2017 was still 13.4 years. [30]

Although a more detailed analysis of patent applications identified is beyond the scope of this research study, a quick look at the data reveals that many applications remain without any dispatch being published by INPI for years. So in addition to measures related to the examination of the merits of the application, it seems necessary to reinforce measures to reduce the timeframe of processes carried out prior to the examination itself, such as, publication of patent applications, notification of entry for the national phase of the Patent Cooperation Treaty (PCT) application and preliminary formal examination. Many pending status orders had no annuities paid for several years, and yet did not have a dismissing dispatch published by INPI. So the efforts made to automate processing of the dismissing of patent applications for which no required payments or other mandatory actions by the applicant have been made deserve special mention.

In the context of patent backlogs, it is worth mentioning the proposal by Abreu[86] for the prospecting methods to identify patent applications for technologies of interest to SUS as candidates for priority examination requests.

Another side of the backlog issue is related to the increase in the number of patent application filings. Greater clarity on what may or may not be patented in Brazil could be of great use in reducing the number of patent applications that have a low probability of being granted in the country, especially with regard to secondary applications. In this context, it is important to mention that in January 2018 INPI published New Guidelines for Patentability Examination of Patent Applications directed to Chemical Inventions (Resolution 208/2017).[84] However, it is outside the scope of this research to analyse the content of the new guidelines.

Finally, a proposal for a simplified procedure for the granting of patents is currently under discussion. This proposal, if approved, would not apply to the pharmaceutical sector. It is believed that such measures should be avoided, since they may lead to the granting of low-quality patent applications which do not meet patentability requirements, adversely affecting competition even in the absence of any contribution to innovation.[87]

8.3 Research limitations and difficulties for interpretation of findings

this study contributes to the debate by trying to analyse the connections between the supply of a medicine under exclusivity situation in the Brazilian market, its patent situation and public procurement. Although it is a daring step from the point of view of the scope of analysis, it also has a number of limitations.

In methodological terms, these limitations can be related both to the limits of the data sources themselves and to the uncertain nature of the dynamics being investigated.

We prioritised the selection of a set of medicines available on public lists in the year 2016. However, on one hand, it is known that medicines are not necessarily procured every year, especially for high-expenditure products.[23] On the other hand, products that have been formally excluded in previous years may have surplus purchases in subsequent years. In addition, different sources of procurement data were often inconsistent (missing purchase registration not available in one, present in another) or incomplete (procurement modality).

We have attempted to compare the CMED list - adopted as a source for the medicine supply situation in the Brazilian market - with product market approval (registration). However, this comparison was also limited because the existence of a record is not a guarantee of immediate product availability in situations where it has been obtained in using the *Bolar* exception safeguard.

In the case of patent search, it is known that the evergreening strategy encourages companies to file patents over years. As the cross-section of this study was centred in 2016, we only focused on applications as well as patent status made up to that year. However, the following facts are known: (i) for some products selected in this study new patent applications were made in 2017 and 2018 or (ii) the patent situation has already changed to the point of having generic alternatives / biosimilars in the Brazilian market or (iii) initiatives for local production (Partnerships for Productive Development) were launched involving only private companies and public manufacturers or requests for priority examination by the Ministry of Health.

Once these limitations are recognised, our analytical effort sought to "**take a picture**" of the monopoly situation of the selected medicines in the **year 2016**. The changes in the dynamics of these products in subsequent years validate the importance of monitoring the variables selected here in order to increase government bargaining power in medicine procurement that represent high expenses for SUS.

Being a dynamic process, the situation found in 2016 is not necessarily the situation in 2017 or 2018. Their status may have changed, the availability of generic versions may have changed, SUS prices may have changed, and some medicines may already have been excluded from SUS (such as adefovir, lopinavir, fosamprevanir, didanosine).

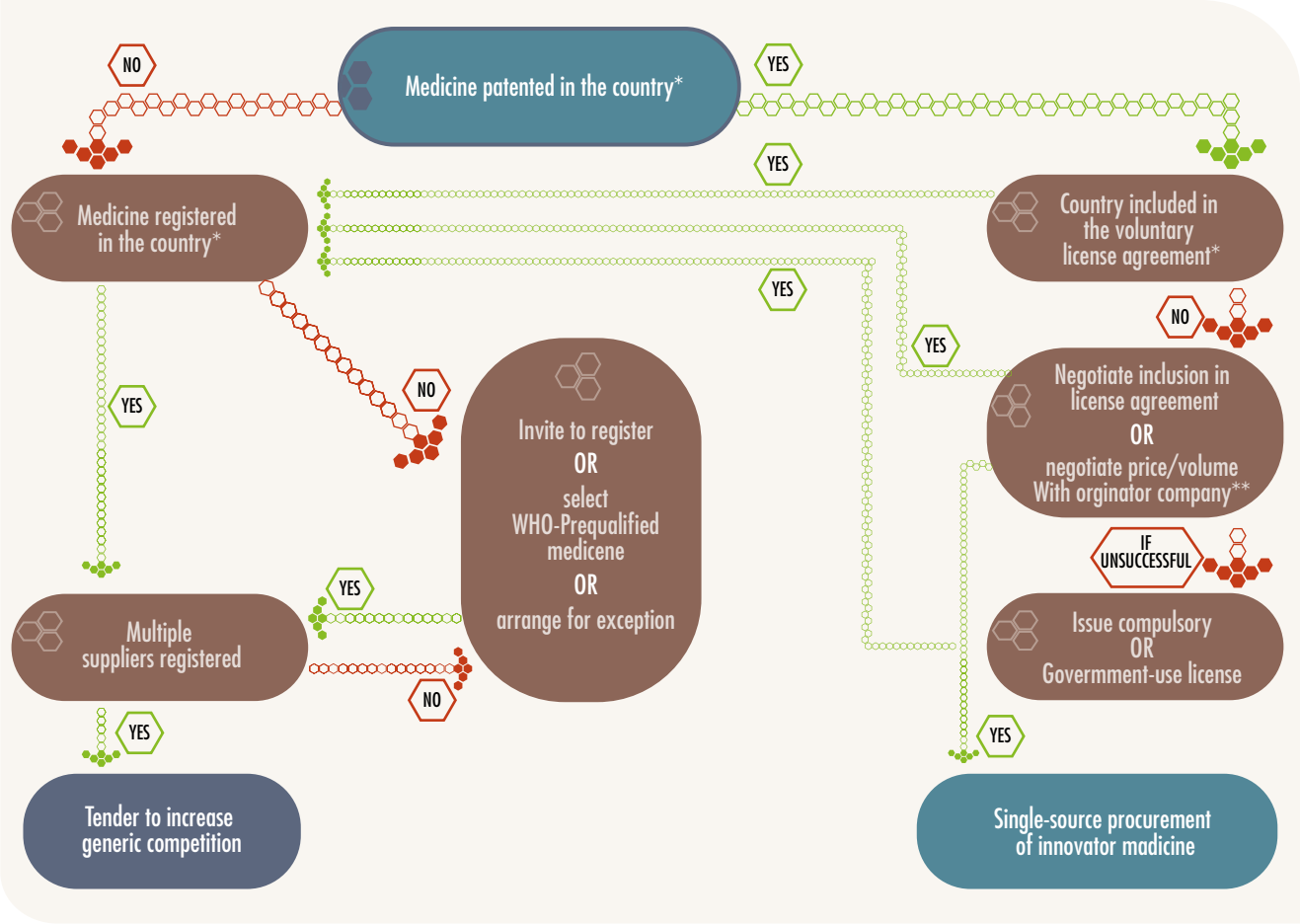
The study also showed that 44% of the active pharmaceutical ingredients of the sample that were subject to patent search had a patent pending status, suggesting that this is the barrier for other companies to place generic versions on the market, including national companies. They all face uncertainty about whether a patent will be granted and the possibility of having to pay compensation to the holder if applicable. However, there is no guarantee that this is in fact the reason why these companies do not do it. This investigation is worthy of further research.

9.Recommendations

We can systematise key action optionsaddressed in the research with a flowchart published recently in a WHO report on access to treatment for hepatitis C[88] (Figure 13). The chart brings different paths for action according to the patent situation of each medicine. Broadly speaking, the first question to be asked is whether the medicine is patented in the country (Note: we are referring only to a granted patent and not to a pending patent application). If the answer is yes, we can verify whether Brazil is included in the geographical scope of any existing voluntary licenses for the medicine (as Brazil is generally excluded from internationally negotiated voluntary licenses). If the country is not included in any voluntary license, WHO recommends either negotiating inclusion in the scope of the license or negotiating the price of the medicine with the manufacturer of the original version. And if those negotiations are unsuccessful, it suggests the issuing a compulsory license.

The second main question is whether the medicine has a market approval (registration) in the country. If there is no market approval whatsoever, or there is only one, we recommended the adoption of measures to allow bidding between different competitors. Thus, interested companies can be invited to obtain market approval in the country or to procure from suppliers prequalified by WHO, or to provide market approval exception in the country.

Figure 13 – Choosing a course of action to make medicines widely available



Source: WHO, 2018. Original title of the figure "Choosing a course of action to make direct-acting antivirals widely available". Legend from the original figure: * Check on www.medspal.org; ** WTO TRIPS Agreement does not require previous negotiations for government-se licenses. This figure is found in the WHO report from the figure originally proposed by the *Medicines Law and Policy - https://medicineslawandpolicy.org*

Our research sought to contribute to the understanding of the context in which the procurement of medicines of high cost by the SUS occur, especially those in an exclusivity situation from the supply side. It is a complex and multifaceted issue and involves different fields of knowledge and different stakeholders.

Without having the ambition of being prescriptive or exhausting the theme, some recommendations that are presented could be taken

into account in the collective effort to act in the field of patenting in the pharmaceutical sector in order to minimise the negative impact on sustainability of the SUS in relation to the procurement of medicines in exclusivity situation in the national market.

The first concerns transparency in relation to patent applications and patenting of medicines. We consider that different government agencies could play a relevant role in identifying patent applications filed in the country for each medicine, seeking to ensure that companies provide this information to the government, thereby facilitating the evaluation of production and procurement options for each medicine.

INPI

- Adopt measures that reduce patent application waiting time, without, however, giving up or reducing the quality of technical examination of requirements and conditions of patentability carried out by INPI.
- Adopt patent examination guidelines that provide greater clarity about what may or may not be the subject of patent protection in Brazil, in order to provide greater security for risk analysis by potential competitors during an application pending period.
- Adopt examination guidelines that reduce the possibility of granting patents for secondary / trivial innovations.

Anvisa

- Request companies' information on patent applications filed in the country related to the medicine at the time of request and renewal of the market approval (registration).
- Contribute towards the provision of risk assessments to produce specific medicines, especially in the case of a *de facto* monopoly generated only by pending patent applications.
- Consider amending RDC 203/2017 to include the possibility of importing medicines without an Anvisa registration, but with international registration that ensures the quality of the product according to article 4 of RDC 203/2017. This would be of relevant public interest in the following

cases: (i) when there is only one supplier in the country, especially when the medicine available in the domestic market is imported or (ii) where the medicine produced in Brazil exceeds the difference in price of the margin of preference established by law for the procurement of domestic products.

Conitec (National Commission for Technology Incorporation in SUS)

- Request companies' information on patent applications filed in Brazil at the time of applying for technological incorporation in SUS.
- Consider the existence of generic versions in the international market in the elaboration of cost-effectiveness analysis for technological incorporation in SUS.

National public and private producers

- Consider the production of generic versions of medicines without patent granted in the country, including for those that only have pending applications.

Public, private, academic institutions and civil society organisations

- Prepare pre-grant opposition to pending patent applications related to medicines of interest to SUS and with the potential of inclusion SUS list in the future.

Ministry of Health

- Establish a platform for monitoring patent situation of the medicines of interest to SUS to subsidise price negotiations, as well as clarify monopoly situations resulting from the patent system for potential producers.
- Submit requests to INPI for priority examination of pending patent applications related to medicines of interest to SUS.
- Consider issuing compulsory licenses in the case of patents granted related to medicines of interest to SUS.

- Map potential international producers of generic and biosimilars versions. Consider the possibility of importing where patent statuses indicate an absence of a patent barrier including when there are only pending applications, or cases of removal of patent barrier through the use of public health safeguards.
- Strengthen incentive measures for domestic producers of generic and biosimilar versions during pending patent application periods or other situations in which there are no patent barriers.
- Avoid strengthening de facto monopoly generated by patents not yet granted in the country and avoid extending exclusivity situations beyond the patent term by eventually negotiating voluntary patent licenses.
- Strengthen joint procurement mechanisms with other countries in the region, such as the one created under Mercosur, especially for medicines in exclusivity situation from the supply side in Brazil and without a patent barrier in the country.

Government / National Congress / Judiciary / other institutional stakeholders

- Not to implement measures that extend the patent term (as proposed in the framework of the negotiations of the trade agreement between the European Union and Mercosur, and in a bill in progress in Congress - PL 6869/17).
- Make every effort to exclude measures already included in national legislation that allow for the extension of exclusivity situation generated by a patent, especially the removal of the sole paragraph of article 40 of the industrial property law (LPI). This paragraph allows the extension of patent term due to the time necessary for examining the application (as proposed in bills in progress in Congress - PL 3944/12 and PL 5402/13 - and in a direct action of unconstitutionality in process in STF - ADI 5529).
- Promote the amendment of the LPI with respect to the payment of compensation for acts committed during pending patent application periods, which currently favour the applicant. Establish third party protective measures that

are unfairly subject to notifications / threats based on patent applications still under review by the INPI in accordance with Article 48 of the WTO TRIPS Agreement.

- In order to judge possible cases of patent infringement, especially in relation to actions that occurred during the pending period, promote a systematic interpretation of the law considering the public interest involved in the case such as - the constitutional right to health (art. 6 and 196, CF) in cases related to medicines for use in SUS, and the constitutional principle of free competition as the basis of the economic order (article 170, IV, CF). 170, IV, CF)..
- Consider opening procedures to investigate crimes against the economic order related to possible abuses committed by applicants / patent holders in the pharmaceutical sector.

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Appendix1 – Detailed Methodology

The study involved four axes:

1. Identification of products in exclusive situation from the supply side;
2. Analysis of the patenting situation in Brazil of the medicines selected;
3. Analysis of public procurement of medicines selected; and,
4. Legal analysis of pending patent applications from a comparative perspective.

1 Selection of active pharmaceutical ingredients in the sample

We chose to consider medicines financed by the Ministry of Health, assuming that this would be a representative universe of both the products accounting for the highest expenses in pharmaceutical services in the SUS,[90] compared to the expenses of other subnational levels, and of products under monopoly procured by the public sector[80]. Thus, the selection involved three categories:

- CESAF - only antiretroviral (ARV) medicines prescribed to control HIV / AIDS infection;

- CEAF - Group 1 medicines, subgroups 1a (financing and centralized procurement at the federal level) and 1b (federal funding and decentralized procurement by the states); and,
- Medicines for cancer treatment.

For medicine selection, we consider the documents in force in 2016 as Ministry of Health sources. For the selection of ARV medicines, the National List of Essential Medicines of 2014 was used, updated in June 2015,[90] which was in force until August 2017. We used the list provided in Annex I of Administrative Rule 1554/2013, updated on January 4, 2017[91] for the selection of CEAF medicines.

Regarding cancer treatment medicines, there was no specific list of medicines systematised in the scope of SUS pharmaceutical services. For the selection of these medicines, we started with pharmacological treatment options informed in the Clinical Protocols and Therapeutic Guidelines (PCDT) for different types of cancers.

Initially we used the "Clinical Protocols and Therapeutic Guidelines in Oncology"[92] released by the Ministry of Health in 2014, which includes all documents available from November 2014. After that date, the selection of medicines was updated with the Diagnostic and Therapeutic Guidelines (DDT) for specific cancers: esophageal carcinoma (December, 2014), cell carcinoma renal (December 2014), (May 2016), cancer of the head and neck (June 2015), multiple myeloma (August 2015), breast carcinoma (September 2015), adenocarcinoma of the prostate (May 2016). The guidelines were published from November 2014 to December 2016 on the National Commission for Incorporation of Technologies in SUS' (Conitec) website. Finally, the selection of products for oncology was complemented by a search for the decisions on the incorporation of technologies in the SUS that occurred in the period from October 2015 to December 2016, referring to cancer medicines on the Conitec website.

It is important to mention some limitations to this methodology. The first is that PCDTs cite treatment possibilities, but it does not necessarily mean that all medicines have already been incorporated via Conitec. Neither is there any guarantee that public procurement has already taken place, unless it has been through a judicial process, in that

case, beyond the scope of this research. The National List of Essential Medicines (Renames)[91] update further ensures the list of products that have been incorporated via Conitec over time, but this may not be an option for the selection of cancer treatment medicines.

1.1. Definition of products in exclusivity situation from the supply side

The second step consisted in the definition of single supplier purchase situation (sole source procurement) medicines selected in the previous step was carried out considering the market situation in December 2016. To do so, we opted to consult the price list of the Medicines Market Regulation Chamber (CMED), referring to the "Medicines Prices for Public Procurement", a spreadsheet updated in January 2017.[93]

For methodological purposes, **we assumed** that the CMED price list included all products available in the Brazilian market, including its suppliers. In this way, we used the CMED price list to identify the active pharmaceutical ingredients that had a single supplier for all existing pharmaceutical presentations, characterising what we call **exclusivity from the supply side**. From the selection of products in this situation, we set out to search for patents related to them.

Another way considered to identify the exclusivity situations of the active pharmaceutical ingredients from the supply side was to look at the information from the 2016[64] active market approvals (registration). However, we found a limitation in Anvisa's registration database: active registrations in 2016 may not necessarily mean that all products are available on the market or could be marketed, since by the "Bolar exception" (Article 43, VII, of Law 9.279 / 96)[X 18] it is possible to carry out the necessary tests to obtain the market approval of a patented product to place it in the market once the patent expires.

X Art. 43. The provisions of the previous article do not apply: (...)
VII - acts committed by unauthorised third parties related to the invention protected by patent, exclusively for the production of information, data and test results, aiming at obtaining the registration for commercialisation, in Brazil or in another country, for the exploitation and commercialisation of the product object of the patent, after the expiration of the periods stipulated in art. 40. (Included by Law No. 10,196, of 2001) ".

The cross-listing of the CMED with the market approvals by Anvisa validated, in most cases, the relation of the medicines considered to be in sole-sourcing situation (exclusive on the supply side). In the few cases where there was any inconsistency, we decided to keep the selection from the CMED price list as an option for defining the list of active pharmaceutical ingredients selected for patent search.

1.2. Patenting situation of selected medicines

Considering that patent barriers may be a central element for the exclusivity situation of a medicine in the market, the second phase of the research consisted in mapping selected medicines patent situation in Brazil by the criteria of the previous phase.

It is important to note that the active pharmaceutical ingredients that had a single supplier for all pharmaceutical presentations, and therefore were under exclusivity, but the supplier was a national public or private producer, were excluded from the patent search. Our interpretation is that such products were not under exclusivity due to their patent status, since they were being produced as generic medicines.

The elaboration of patent situation of medicines was carried out in three phases: a) identification of international patents and Brazilian correspondents; b) survey of the status of applications in Brazil for December 2016 and c) analysis of the claims and classification of patents and patent applications.

The search for patent applications involved a series of steps which will be detailed below. We started from a common path for all medicines from the consultation of public databases available internationally. We adopted differentiated and complementary paths, especially when, from the common starting point for all active pharmaceutical ingredients, no results were found. In some situations, we found international applications without correspondents at the national level, and in others we could not find any international applications.

We performed complementary searches throughout the research process itself and assumed specificities and arbitrations for each patent database consulted. We sought to carry out the most complete search

possible within the limitations of the methodology adopted, however, **the results found in the present research may have limitations on the total of existing patent applications in the country involving the active ingredient (s) in question.**

We attempted to circumvent this limitation in part by examining the claims of applications found and identifying the primary application (the active pharmaceutical ingredient or its synthetic process) and the secondary application (s). We assumed that the primary application was the most important as a patent barrier to competition. Thus, when it was identified, it indicated that the patent search was satisfactory even if not all secondary patent applications were found by the adopted routes.

In any case, the limitation of this interpretation is also recognized, since in some cases secondary patent applications may, on their own, set a barrier to certain technologies in the market, especially second- and third-generation technologies.[36]

1.2.1. Identification of international and corresponding patents in Brazil

Orange Book (FDA) and Patent Register (Health Canada)

The first stage of the search considered the free access public electronic bases of regulatory authorities of medicines of the United States of America and Canada. The first is called the *Orange Book,*[94] made available by the *US Food and Drug Administration* (FDA), and the second, *the Patent Register,*[95] made available by *Health Canada*. The main advantage of the Patent Register is that it also includes information on biological medicines, which are not included in the *Orange Book*.

The choice to make them the first option for the search is related to the fact that these are easy-access public databases, in which it is possible to search from the name of the active pharmaceutical ingredient.

Both databases are linked to the agencies responsible for market approval (registration) of products in their respective countries, so the search is facilitated by the use of the *International Non-proprietary Name* (INN). The step-by-step approach was initially based on the methodologies described by Villardi[38] and the patent search manual, with small variations that became necessary throughout our search process [38,96].

Both databases have limitations that should be highlighted. The

Orange Book only has patents granted in the US, leaving out applications that are pending, rejected or expired. In ingredient, it only includes applications related to the active ingredient, not including those related to synthetic process or intermediates. And, the *Orange Book* only lists applications for products of chemical origin. Although the so-called *Purple Book* is for biological products, no related patent applications are available. As the query of the Orange Book electronic database only gives access to patents in force at the moment of the search, the search was complemented using previous archives of the Orange Book for the period of 1985 to 2012[Y]. This survey allowed us to find patents that were in the Orange Book previously, but which were no longer available because they were no longer valid in the US at the time of the main search. The Health Canada database has the same limitation in relation to patents in force, but no files from previous periods were found for reference.

The second step was to verify if the applications identified in those two countries had correspondents in Brazil. The electronic database of the European Patent Office (EPO) –*Espacenet*[97] was also used for this stage, which is also available free of charge. In this database it is possible to search the previously identified U.S. or Canada patent number and access the International Patent Documentation (INPADOC patent family), which provides the corresponding patent number in different countries, including Brazil. However, Brazilian patents are not always listed in the patent family. Thus, in cases where Brazilian correspondents were not present, the search focused on additional information available in the database: the WO (World Intellectual Property Organization) or the priority.

As the INPI - National Institute of Industrial Property website does not allow direct search by WO, it is necessary to previously identify the corresponding PCT number (Patent Cooperation Treaty), which can be done using the WIPO Patentscope[98] database. With the PCT or the priority it is possible to search the Brazilian correspondent in the advanced patent search of the INPI[59] website. It should be mentioned that not all patents necessarily have Brazilian correspondents.

The detailing of the search path is described in Chart 8.

Y The spreadsheet was kindly put at our disposal by Professor Bhaven Sampat, Columbia University.

Chart 8 – Detailed path for patent search at FDA Orange Book and Health Canada Patent Register

SOURCE	STEP BY STEP
FDA Orange Book https://www.accessdata.fda.gov/scripts/cder/ob/	• Identify approved medicines • Look up "Proprietary Name", "Active Ingredient or Application Number", using the INN • Click on "application number" (appl no) only for products whose code starts with N (check all products with code that starts with N because sometimes the information appears differently depending on the pharmaceutical form / presentation) • Click on "patent and exclusivity information" • Select US Patent Number
Health Canada Patent Register https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/patent-register.html	• Look up "search criteria" • Search for the active ingredient in "medical ingredient" • Select the CA patent number
Espacenet https://worldwide.espacenet.com	• Go to "Smart search" - enter the patent number found in the Orange Book or Patent Register (include US or CA, e.g. US6703396 or CA2289753) • Go to "INPADOC patent family" and search in the "publication info" application that begins with BR (there may be more than one BR application or there may be no application) • If there is no BR order, select the order number WO • If there are no BR or WO applications, select the priority number (s)
PatentScope (WIPO) https://patentscope.wipo.int	• **Only when no BR application have been found in Espacenet from the application number US or CA.** • Select WO number and go to PatentScope • Maintain English language interface • Select option "ID / number" and enter WO number • Select "international application number PCT"
USPTO https://www.uspto.gov/	• **Only when no BR or WO applications have been found on Espacenet and no information has been found by the priority number. Applies only to US applications identified in the Orange Book.** • Search for "patents"à USPTO Patent Full-Text and Image Database (PatFT) à Searching Full Text Patents (Since 1976) à Quick search • Enter the patent number found in the Orange Book; "Field 1: select patent number" • Option 1: For US priority number, select application number. • Option 2: For priority number outside the US, select the application number or PCT number, when available (sometimes only images), in "foreign application priority data"

Continued Chart 8

SOURCE	STEP BY STEP
National Institute of Industrial Property www.inpi.gov.br	• In this step, the search for internationally mapped applications at the national level begins. • Register for free to have access to documents. • **Option 1:** from the BR application identified in the Espacenet. • Quick access> search> patent> quick search (in Portuguese Acesso rápido > faça uma busca > patente > pesquisa rápida) • Enter BR number obtained on Espacenet (replace BR with PI, for example: PI9205661) • **Option 2:** when there is only PCT number • Quick access > search > patent > advanced search (in Portuguese *Acesso rápido > faça uma busca > patente >pesquisa avançada*) • Enter PCT application number (without PCT, no bars - for example, US2004000832 or EP1997003315 - for USPTO, sometimes, a PCT/EP97/03315 format comes up - in such cases, you will need to adjust that to the other format, including adding 0 so as to get 6 digits after the year) • **Option 3:** when there is only the priority number (priority only in cases where there is no PCT) • For cases in which there is no PCT (warning: for cases that there was a PCT, but no BR patent was found, it is no use to do priority search because you will not find it either) • Enter country / priority number (in US13 / 440,246 or US440,246 or US440,246 or US440,246 formats) (note: on Espacenet the format that appears is US201213460452 20120512). Ignore numbers that appear after the space, because it is the priority date in the format yyyy.mm.dd) • Caution: If you do not enter a number before the bar, you may see results that do not match the priority you want. In those cases, check if the IPC code A61K or A61P or C07 appears and the title and summary are similar • When priority is not US, put in the format that appears in the same USPTO (ex: 1593/96) and try your luck! (check if the IPC code A61K or A61P or C07 appears and the title and summary are similar)

Search in scientific articles

To complement the survey of primary patents involving medicines in a monopoly situation procured by SUS, we also carried out a survey in scientific articles. Our focus was on finding references present in the articles that describe the synthesis and the development process of the compounds with pharmacological response. It is possible to find data in

these studies that refer to the code of the molecule with pharmacological activity. It is also possible to find references to the information about the patent applications for the active molecules. We have used this form of search primarily for medicines that we were unable to find in the Orange Book and/ or Health Canada.

We started our search from the ChemSpider (http://www.chemspider.com/) and PubChem (https://pubchem.ncbi.nlm.nih.gov/) databases, where we could use medicines to obtain information regarding the structure of the compound and official nomenclature, according to the International Union of Pure and Applied Chemistry (IUPAC).

This information contributed to the construction of a literature search, in which key words were added, such as: structure-activity, synthesis, crystallography and pharmacological activity.

From this, we selected articles focusing on those involving the names of the first authors responsible for the citations and for describing the compound in literature. With this, we arrived at the patent of the compounds and the following steps were to carry out a search in the Espacenet, as previously described.

Seacrh on the SciFinder® database

SciFinder® is the *Chemical Abstracts Service* (CAS) research tool, which enables the researcher to retrieve and analyse information about patent applications from a single place making use of information from different CAS databases in various areas, among them, Organic Chemistry and Pharmacology. This tool gathers information from more than 61 patent authorities including patents prior to 1907 (CAPES, available at: http: // www-periodicos-capes-gov, accessed: 08/15/2017). Access is restricted and is available in Brazil on the CAPES Journals website.

We chose the chemical structure for researching medicine patents. First, we performed a search on the *PubChem*[Z] [99] and *ChemSpider*[AA] [100]

Z *PubChem* is a database of molecules operated and maintained by the National Center for Biotechnology Information (NCBI), which is part of the National Library of Medicine, which in turn integrates the National Institutes of Health of the United States of America. Anyone can use it for free through the internet (NCBI, available at: https://pubchem.ncbi.nlm.nih.gov/, accessed on 08/15/2017).

AA *ChemSpider* is a free chemical structure database that gives you quick access to more than 58 million structures, properties, and associated information, owned by the Royal Society of Chemistry. This tool builds on the sources you collect by adding additional properties, related information, and links back to the original data sources. (Royal Society of Chemistry, available at: http://www.chemspider.com/AboutUs.aspx, accessed: 08/15/2017).

websites for recognition of the chemical structure of the active pharmaceutical ingredien. Next, we had a model of the chemical structure in the corresponding field. From this, the results passed through some filters, such as: patent, name of the active pharmaceutical ingredient", therapeutic class, chemical structure and synthesis.

Next, we selected the patents referring to the structure of the active compounds, the molecules and the process of synthesis. This is because the focus for using this tool was to find primary patents referring to medicines.

The next step was to conduct a search on Espacenet, the European patent office, as described previously.

Search on the Integrity℠ database

Integrity℠ is a private database, a subsidiary of Thomson Reuters, available in Brazil on Capes Journals (https://integrity-thomson pharma.ez68.periodicos.capes.gov.br/integrity/xmlxsl/). We searched for the name of the active ingredient and use filters, such as: "applicants", to select the transnational company that markets the product and its subsidiaries or companies resulting from mergers and acquisitions; "Subject matter"; and, in "condition", to select the scope of therapeutic indications. Once these filters were applied, we selected each patent application where it was possible to identify the patent family by INPADOC, redirecting it to *Espacenet's* address.

Search using the Patent Lens database

Patent Lens (https://www.lens.org/) is a private, open access database that we used to complement the patent search for biological products.

First, we identified the amino acid sequence of the macromolecule (active ingredient) on DrugBank (https://www.drugbank.ca/). Thereafter, the sequence was looked up on the Patent Lens, considering the period up to 12/31/2016, and the results were filtered from the WO patents applications filed by transnational companies that markets the product.

Search based on summary and title on the INPI website

This search involved access to the INPI website (www.inpi.gov.br) and, after registration, the following path: "quick access" → "search" →"patent" → "advanced search" (from the terms in Portuguese) "acesso rápido"-->"faça uma busca"-->"patente"-->"pesquisa avançada").

We searched by the name of the active ingredient in the field "title" or "summary" separately" (from the terms in Portuguese "título" and "resumo").

Then, we select the applications whose applicants were transnational companies that market the medicine.

Others

In our search for patents for selected medicines we also used other sources such as the *Medicines Patents and License Database* (http://www.medspal.org/), which includes medicines for HIV / AIDS, hepatitis C and cancer, and applications cited in upport to examinations (also known as third-party observations or pre-grant opposition) available on the *Patent Opposition Database* (https://www.patentoppositions.org/). In some cases, we also included patent applications cited in priority examination requests made to INPI or in lawsuits involving disputed patents around a medicine.

1.2.2 Mapping of patent status in Brazil

Once the Brazilian applications were identified from the different databases and methodologies described above, the patent status of the medicine in Brazil was surveyed. To do so, we considered the situation in December 2016. Applications were classified according to the following categories: granted, rejected, pending, expired and dismissed (before or after the INPI examination). The patent filing date for each application in Brazil was also recorded. Following that, the application was downloaded with the descriptive report and the claims for the step for claim's analysis and classification.

1.2.3 Analysis of the patent claims

The analysis of the claims privileged the most up-to-date claims available on the INPI website. For applications that were not available on the INPI page, they were requested directly from the Institute. They were uploaded on the website subsequently. However, the content of some of the applications was not made available and in order to avoid this issue, we decided to work with the international application document (WO) made available on *Espacenet,* with the provision that there could be changes in the Brazilian application.

We sought to identify applications aiming to protect of the active pharmaceutical ingredient and its preparation process - classified as "primary" - and the other applications for various categories, classified as "secondary", as detailed in Chart 9. It is important to note that many applications included claims of the primary and secondary type.

For identification of the molecule of the active ingredient, especially when the claim was of the *Marksuh* type, we used the IUPAC molecular structure and nomenclature available on ChemSpider®.

The separation of primary and secondary patents is widely used in literature as a form of classification for purposes of analysis. However, it should be noted that secondary claims, if the application is granted, can actually represent barriers to the entry of competitors into the market, such as those related to pharmaceutical forms and prodrugs.

For the identification of the API of biological medicaments (macromolecules) specific categories available on Scifinder were adopted and are described in Chart 10. However, the separation of "primary" and "secondary" for this type of technology has required other analyses that will be the object of a future publication. In any case, the analysis of the claims according to these criteria served to exclude applications for patents not related to the medicines in the sample.

Chart 9 – Definitions adopted for the interpretation of the claims of the patent applications

CATEGORY	DEFINITION
PRIMARY	
Active pharmaceutical ingredient	Any substance or mixture of substances intended to be used in the manufacture of a medicine and that, when used in the production of a medicine, becomes an active pharmaceutical ingredient of the medicine product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or function of the body.[101]
Process for the synthesis of the active pharmaceutical ingredient	The process for the synthesis can be considered as the basis of the project activity,[102] it involves identification of the processing route to produce the desired product, investigation of the necessary chemical reactions, selection and design of the operations involved in the processing route, as well as calculations of requirements of utility, waste and emissions into the environment and many more.[103]
SECONDARY	
Compositions (formulations)	They may encompass active pharmaceutical ingredients and pharmaceutically acceptable carriers or excipients. Many may contemplate active pharmaceutical ingredients already known. The preparation of pharmaceutical compositions (formulations) requires the use of techniques and compounds commonly known to a person skilled in that field (p.10).[104]
Markush claims	They consist of a generic chemical structure with multiple alternatives that allow for the protection, under a single patent, of several variants of a claimed invention (p.21).[104] Corresponds to claims involving compounds claimed in the form of structures containing multiple and functionally equivalent radical chemical entities attached to one or more parts of a basic skeleton (p.39).[105]
Selection patents	In some cases, a subgroup of elements is selected from a larger group and claimed on the grounds that a new, unexpected property has been found. For instance, if a Markush claim was admitted in relation to a set of pharmaceutical compounds, the patent owner might later file a new patent application covering one or more of such compounds. Thus, the patent owner may obtain a further 20-year monopoly simply by picking one or more compounds out of the generic formula (p.23).[104]
Doses	Some patent applications claim independently, or as part of a broader claim, the dose for administrating a particular drug (p.36).[104] It is interpreted that claims over the dose of a drug fail to comply with the industrial applicability requirement and they should be treated as a method of medical treatment (p.10).[104]

Continued Chart 9

CATEGORY	DEFINITION
Polymorphs	Polymorphism refers to the possibility of molecules having different crystal structures when they are in the solid state. It is considered an inherent property of a substance. Polymorphs of drug substances are obtained through standard crystallization methods. In some cases, polymorphs can occur unintentionally during production or storage of a drug (p.25).[104]
Salts, ethers and esters	Salts are generally sought when the drug is not sufficiently soluble or stable, or when it is difficult to purify, handle or process during manufacturing. The preparation of pharmaceutically suitable salts is a mature technical field and are familiar to any person with ordinary training in the formulation of pharmaceuticals. Different salts may lead to different solubility, bioavailability and efficacy (p.29).[104] Ethers and esters are sometimes used in pharmaceutical products and are generally more lipid soluble than salts. However, they would not generally enhance the therapeutic efficacy of a drug. The preparation of ethers and esters of a compound is part of the common knowledge of a person skilled in pharmaceuticals (p.32).[104]
Combinations	When two (or more) known drugs are combined in a single product, and patent protection over the combination is claimed (p.38).[104]
Enantiomers	Enantiomers are chiral molecules, meaning they are mirror images of one another. They have identical physical characteristics (energy, solubility in typical achiral solvents, boiling and melting points, NMR and IR spectra, etc.) except for their ability to rotate plane-polarized light (optical activity). The techniques applicable to separate enantiomers in a racemic mixture are well known (p.28).[104] Being different molecules, one enantiomer can present pharmacological activity and another one does not, or each one can present different activities. Isolated enantiomers should not be deemed patentable when the racemic mixture was previously disclosed. Processes for the separation and purification of enantiomers may only be patented if novel and inventive (p.9).[104]
Intermediates	Refers to intermediates in relation to a route of synthesis for the production of a particular compound. Thus, the intermediate is produced at some stage between the starting compound and the final product (active compound) (p.39). [105]
Product-by-process	Claims for inventions of products reciting manufacturing processes of the products.[106]
Prodrugs / Metabolites	Prodrugs: A prodrug is a precursor of a drug, which undergoes a chemical conversion by metabolic processes in the body before becoming therapeutically active. Many medicines are commercialized as prodrugs. Prodrugs are often claimed independently from the active drug when a patent on the active drug has expired or is about to (p.39).[104] Metabolites: An active metabolite is the compound that remains after a drug is metabolised by the body. An active metabolite retains most, if not all, of the properties of its parent drug. Active metabolites may be identified, synthesized and commercialized as a product different from the parent drug. Often, patent applications on specific active metabolites are filed. In some cases, however, generic references to 'all metabolites' are included in patents claiming an active ingredient (p.41).[104]

Continued Chart 9

CATEGORY	DEFINITION
Method of treatment	Some patent applications involve methods of therapeutic treatment, including prophylaxis, cure, diagnosis or surgical methods. Such claims do not involve a product per se, but the way in which it is used to obtain certain effects (p.30).[105]
Use (second medical use)	Some countries allow the first therapeutic indication of a known product to be patented. The second therapeutic indications are also accepted in some patent laws. However, the granting of a patent to a new use for an already known product including, in particular, second indications, increases the scope of protection inconsistently with the novelty requirement (p.30).[105] Claims over a new medical use of a known medicine (often called 'second use claims') are usually filed when a patent on the active ingredient is about to expire or has expired, as an attempt to extend monopoly by applying for patents for one or more new therapeutic uses of an active ingredient (p.42).[104]
Route of administration	A route of administration is the path by which a drug is taken into the body.

Chart 10 – Categories considered to identify and analyse biological products

ACTIVE PHARMACEUTICAL INGREDIENT	RELATED CODES
Aldesleukin	2-133-Interleukin 2 (human reduced), 125-L-serine- (9CI) 2-133-Interleukin 2 (human clone pTIL2-21a protein moiety reduced) 125-L-serine- Aldesleukin L 2-7001 Proleukin
Dornase alfa	Nuclease, deoxyribo- (human clone 18-1 protein moiety) (9CI) Deoxyribonuclease (human clone 18-1 protein moiety) Dornase alfa Dornase alpha Pulmozyme
Peg-interferon alfa 2a	Interferon λ1 (synthetic human) 20-kilodalton pegylated Peginterferon lambda-1ª
Peg-interferon alfa 2b	Interferon λ2 (synthetic human)

Continued Chart 10

ACTIVE PHARMACEUTICAL INGREDIENT	RELATED CODES
Certolizumab	Immunoglobulin, anti-(human tumour necrosis factor α) Fab' fragment (human-mouse monoclonal CDP870 heavy chain) disulfide with human-mouse monoclonal CDP870 light chain pegylated CDP 870 Certolizumab Certolizumab pegol Cimzia PHA 738144
Bevacizumab	Immunoglobulin G1, anti-(human vascular endothelial growth factor) (human-mouse monoclonal rhuMAb-VEGF γ1-chain), disulfide with human-mouse monoclonal rhuMAb-VEGF light chain, dimer (9CI) Anti-human vascular endothelial growth factor immunoglobulin G1 with dimeric human-mouse monoclonal rhuMAb--VEGF γ1-chain disulfide with human-mouse monoclonal rhuMAb-VEGF light chain Avastatin Avastin Bevacituzumab Bevacizumab HyBEV rhuMAb-VEGF
Cetuximab	Immunoglobulin G1, anti-(human epidermal growth factor receptor) (human-mouse monoclonal C225 γ1-chain), disulfide with human-mouse monoclonal C225 κ-chain, dimer C 225 Cetuximab Cituximab EGFR antibody Erbitux IMC 225 IMC-C 225

Continued Chart 10

ACTIVE PHARMACEUTICAL INGREDIENT	RELATED CODES
Etanercept	1-235-Tumor necrosis factor receptor (human) fusion protein with 236-467-immunoglobulin G1 (human γ1-chain Fc fragment) (9CI) Other Names Embrel Enbrel Etacept Etanercept Recombinant human TNF TNFR-Fc TNFR:Fc rhu TNFR:Fc
Golimumab	Immunoglobulin G1, anti-(human tumor necrosis factor α) (human monoclonal CNTO 148 γ1-chain), disulfide with human monoclonal CNTO 148 κ–chain, dimer CNTO 148 Golimumab Simponi
Natalizumab	Immunoglobulin G4, anti-(human integrin α4) (human-mouse monoclonal AN100226 γ4-chain), disulfide with human-mouse monoclonal AN100226 light chain, dimer (9CI) protein Antegren Natalizumab Tysabri
Pertuzumab	Immunoglobulin G1, anti- (human neu (receptor)) (human-mouse monoclonal 2C4 heavy chain), disulfide with human-mouse monoclonal 2C4 κ-chain, dimer 2C4 Omnitarg Perjeta Pertuzumab rhuMAb 2C4

Continued Chart 10

ACTIVE PHARMACEUTICAL INGREDIENT	RELATED CODES
Rituximab	Immunoglobulin G1, anti-(human CD20 (antigen)) (human-mouse monoclonal IDEC-C2B8 γ1-chain), disulfide with human-mouse monoclonal IDEC-C2B8 κ-chain, dimer Manual Registration GP 2013 IDEC 102 IDEC-C 2B8 Immunoglobulin G 1 (human-mouse monoclonal IDEC-C2B8 γ1-chain anti-human antigen CD 20), disulfide with human-mouse monoclonal IDEC-C2B8 κ-chain, dimer Kikuzubam MabThera RITUXIN Reditux Retuxin Rituxan
Tocilizumab	Immunoglobulin G1, anti-(human interleukin 6 receptor) (human-mouse monoclonal MRA heavy chain), disulfide with human-mouse monoclonal MRA κ-chain, dimer Actemra Atlizumab MRA R 1569 RoActemra Tocilizumab
Trastuzumab	Immunoglobulin G1, anti-(human p185neu receptor) (human-mouse monoclonal rhuMab HER2 γ1-chain), disulfide with human-mouse monoclonal rhuMab HER2 light chain, dimer Herceptin Immunoglobulin G 1 (human-mouse monoclonal rhuMab HER2 γ1-chain anti-human p185c-erbB2 receptor), disulfide with human-mouse monoclonal rhuMab HER2 light chain, dimer Trastuzumab rhumAb 4D5

Continued Chart 10

ACTIVE PHARMACEUTICAL INGREDIENT	RELATED CODES
Abatacept	Fusion protein with an extracellular domain of human cytotoxic T-lymphocyte-associated antigen (CTLA-4) and modified Fc domain of human immunoglobulin G1 DMARD BMS-188667 CTLA-4Ig Orencia
Adalimumab	Immunoglobulin G 1 (human monoclonal D2E7 heavy chain anti-human tumor necrosis factor), disulfide with human monoclonal D2E7κ-chain, dimer (WHO) L04AA17,L04AB04 Tumor necrosis factor alpha (TNF–α) inhibitor D 2E7 0331731-18-1 Humira

Source: Authors based on consultation of several sources

1.3 Public procurement analysis

For our analysis of the Brazilian Ministry of Health public medicines procurement system we looked at different public databases, namely: The Integrated General Services Management System (SIASG) for CEAF 1A, ARV and cancer medicines; and, the Public Health Budgeting Information System (SIOPS) for CEAF medicines 1B. The information was also supplemented by data obtained through the Electronic System of the Citizen Information Service (e-sic). At this stage of the study, we collected data on quantities procured and unit prices from 2007 to 2016, in addition to procurement modality.

1.3.1 Information system on public health budgets (SIOPS)

Access to the SIOPS is done through the website of the Department of Information Technology of the Brazilian National Health System (Datasus), at http://www2.datasus.gov.br/DATASUS/index.php. This system

gives us access to the amount submitted by the State Health secretariats (SES), the quantity and value approved by the Ministry of Health, the processing period, and the geographical location of the resources transferred for the medicines that are part of the CEAF group 1B.[AB]

We searched for the area of Health Care (from Portuguese "Assistência à Saúde"), [AC 107] seeking outpatient production by place of residence. We then completed some important information to obtain the data: medicine amounts and quantities approved for each of the years covered by the period (2005 - 2016); procurement modality and company. Following that, we selected procedure codes, which have ten digits referring to the procedure group (medicines - 06), subgroup (CEAF - 0604), and the specific codes of the pharmaceutical presentations related to the scope covered by our study. For the mapping of transfers carried out prior to the creation of the Specialized Component of Pharmaceutical services (CEAF), the codes referring to the deactivated Exceptional Dispensing Medicines Component were also used.

1.3.2 General Services Management System (SIASG)

The Health Prices Bank (BPS from the Portuguese name "Banco de Preços em Saúde") is a system created by the Ministry of Health that aims to register and make available online information on public and private medicine and health products procurement since 1998. BPS is free, and any citizen, organ or public or private institution can access it for consultation.

In this database it is possible to have access to SIASG, created by Decree No. 1,094, dated March 23, 1994, as an auxiliary of the General Services System (SISG), with the function of digitizing and operationalizing SISG. The system is under the responsibility of the Ministry of Planning, Budget and Management (MPOG).

AB Medicines financed by the Ministry of Health through the transfer of financial resources to the Secretariats of Health of the states and the Federal District for acquisition, programming, storage, distribution and dispensing for treatment of the diseases contemplated under the Specialized Component of Pharmaceutical services.

AC TABNET application is a generic public domain tabulator that allows you to organize data quickly according to the query you want to tabulate. It was developed by DATASUS to generate information from the databases of the Unified Health System (Secretariat for Strategic and Participatory Management / MS) available at: http://www2.datasus.gov.br/DATASUS/APRESENTACAO/TABNET/Tutorial_tabNet_FINAL.pptx_html /html/index.html#5

This system has information on sourcing about commitments of procurement made by the federal government, its contractors and institutions that use the Federal Government Procurement System.

In this database we selected medicine procurement made by the MoH logistics department, as well as federal hospitals, and national institutes.

We observed acquisitions related mainly to CEAF group 1A medicines, medicines used in the treatment of cancer, and strategic medicines, since in these cases both financing and procurement are the responsibility of the MoH.

We note that in SIASG it is also possible to find some procurements of group 1B of CEAF, for two distinct reasons (1) the medicines may have migrated from the list over the period studied; (2) procurements may occur from other procurement modalities.

Another point that deserves to be highlighted regarding this data source is that the acquisitions based on partnerships for productive development (PDP) are not available in this system.

1.3.3 Access to Information Law (LAI)

The Access to Information Law(LAI), [AD 108] through the Electronic System of the Citizen Information Service (e-sic - https://esic.cgu.gov.br/), was used to obtain data on medicine purchases of ARVs for HIV / AIDS, Direct Acting Antivirals for hepatitis C, and of the Ministry of Health budget execution in pharmaceutical services divided by funding component. We also sought data related to other medicines to complement the procurement record.

1.3.4 Analysis of medicines expenditures

The data obtained from the different databases were systematised in Excel® worksheets to estimate the federal spending from these MS

AD Law No. 12,527, enacted on November 18, 2011, has the purpose of regulating the constitutional right of citizens to have access to public information and its provisions are applicable to the three Powers of the Union, States, Federal District and Municipalities. Among its objectives the democratization of information, also actions to prevent corruption in the country. It allows for greater popular participation and social control of the governmental actions. Societal access to public information paves the way for improvements in public management. Available at: http://www.acessoainformacao.gov.br/sistema/site/acesso_info.html.

purchases, multiplying the quantity purchased with the price charged.

In order to allow the comparability of the values obtained over the years of analysis, considering the 10-year period of data collected, and the importance of monetary updating of the values for trend evaluation, the annual expense figures were corrected for 2016. We used the annual variation of the Extended Consumer Price Index (IPCA), calculated by the Brazilian Institute of Geography and Statistics (IBGE) and made available by the Institute of Applied Economic Research (IPEA), available at http: //www.ipeadata. gov.br/. The option for this index was based on Law no. 10.742 / 2003, which establishes the regulatory norms for the pharmaceutical sector, and defines the IPCA for adjustment in medicine prices in the country. [109]

1.3.5 Estimates of savings in public procurement

To estimate potential savings in public medicines procurement, we used prices of generic or biosimilar versions commercialised in the international market, mainly in the Indian market. As a data source, we considered different published studies, as we were unable to find a homogeneous source to obtain all information for all products, which in itself constitutes a limitation of this stage of our research study.

For the purpose of comparing prices in Brazil with that of the version available in the international market, we selected the price in the purchase of the largest quantity in the country for the conversion to the average dollar of the year, based on IPEA-DATA[AE] numbers. We gave priority to procurement years compatible with generic or biosimilar version data available in the international market.

The savings estimate was based on the difference of the Ministry of Health spending in a given year with the product and the estimated cost if it had been obtained with the same quantity with the price of the generic / biosimilar version available in the international market.

AE www.ipeadata.gov.br/

Appendix 2
Medicines under exclusivity situation funded by the Ministry of Health: analysis of patent situation and public procurement

JULY 23, 2018

SEMINAR

MEDICINES UNDER EXCLUSIVITY SITUATION FUNDED BY THE MINISTRY OF HEALTH: ANALYSIS OF THE PATENT SITUATION AND PUBLIC PROCUREMENT

PROGRAMME

9 AM TO 9:30 AM – OPENING

- **HERMANO CASTRO,** director Sergio Arouca National School of Public Health (ENSO) / Fiocruz
- **JORGE BERMUDEZ,** head of the Department of Medicine Policy and Pharmaceutical Services (NAF) – ENSP
- **ACHAL PRABHALA,** Accessibsa (Innovation and Access to Medicines in India, Brazil and South Africa) representative, funded by the Shuttleworth Foundation

9:30 AM TO 12H30 PM – PANEL 1 - MEDICINES UNDER EXCLUSIVITY SITUATION FUNDED BY THE MINISTRY OF HEALTH: ANALYSIS OF THE PATENT SITUATION AND PUBLIC PROCUREMENT

- Coordinator: **JORGE BERMUDEZ**

9:35 – 10:10 AM – RESEARCH RESULTS PRESENTATION:

- **GABRIELA COSTA CHAVES,** NAF/ENSP/Fiocruz

10:10 – 11:30 AM – DISCUSSANTS

- **MARIA ANGÉLICA BORGES DOS SANTOS,** Healthcare Logistics and Technology Center (NUTEC), ENSP/FIOCRUZ
- **FABÍOLA SUPINO VIEIRA,** Social Policies and Studies Department (Disoc), The Institute for Applied Economic Research (Ipea)
- **EDIANE BASTOS,** National Center for Healthcare Economics (NUNES), Department of Healthcare Economics, Investments and Development (DESID), Ministry of Health
- **LUCIENE AMARAL,** General Coordination of Regulatory Affairs, Department of Industrial Complex and Innovation in Health (Deciis) of the Secretariat of Science and Technology and Strategic Inputs (SCTIE) / Ministry of Health

11:30 – 12:30 – DISCUSSANTS

12:30 – 1:30 PM – LUNCH (AT THE VENUE)

1:30 – 4:30 PM – PANEL 2 – LEGAL ASPECTS RELATED TO PUBLIC PROCUREMENT OF MEDICINES UNDER EXCLUSIVITY SITUATION

- Coordination: **JUSSANÃ ABREU**, Brazilian Health Regulatory Agency (Anvisa)

1:35 – 2:10 PM – RESEARCH RESULTS PRESENTATION

- **MARCELA CRISTINA FOGAÇA VIEIRA,** Accessibsa

2:10 – 3:30 PM – DEBATERS

- **ELAINE LAZZARONI,** National Cancer Institute (Inca)
- **PEDRO MARCOS NUNES BARBOSA,** Denis Borges Barbosa Law Firm
- **RICARDO MEDEIROS DE CASTRO,** Department of Economic Studies (DEE), Administrative Council of Economic Defense (Cade)
- **MARCO TULIO DE BARROS E CASTRO**, Office of Innovation, Center for Technological Development in Health (CDTS), Fiocruz

3:30 – 4:30 PM – DISCUSSANTS

4:30 PM – CLOSING

A PUBLICATION OF

Ministério da Saúde
FIOCRUZ
Fundacão Oswaldo Cruz

ESCOLA NACIONAL DE SAÚDE PÚBLICA SERGIO AROUCA
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WITH THE SUPPORT OF

SHUTTLEWORTH FELLOWSHIP

Medicines under Exclusivity Situation Funded by the Ministry of Health: ANALYSIS OF THE PATENT SITUATION AND PUBLIC PROCUREMENT

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1ST Edition

A publication of

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