Mercosur-EU Free Trade Agreement:

IMPACT ANALYSIS OF TRIPS-PLUS MEASURES PROPOSED BY THE EU ON PUBLIC PURCHASES AND DOMESTIC PRODUCTION OF HIV AND HEPATITIS C MEDICINES IN BRAZIL

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The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) of the World Trade Organization (WTO) established the obligation to recognise patent rights in all technological fields. Patents guarantee a period of exclusivity in the market by excluding the participation of third parties in the different stages involving production and trade. In the absence of substitutes/ competitors, market exclusivity provides a monopolistic position that allows the power to set prices often very much higher than in a scenario with competition. In the pharmaceutical sector, patents have an impact on access and production of medicines and other technologies, with direct implication on public policies related to health and industrial development.

The TRIPS Agreement contains provisions that need to be applied by all WTO country members. Members are not obliged to provide more extensive protection than is required by TRIPS, but they are allowed to negotiate such provisions (known as TRIPS-plus) outside the WTO multilateral forum. The European Union (EU) and Mercosur countries are currently negotiating a free trade agreement (FTA) containing a chapter on intellectual property rights (IPR).

In the end of 2015, the former United Nation Secretary-General convened a High-Level Panel on Access to Medicines to address the policy incoherence between the justifiable rights of inventors, international human rights law, trade rules and public health in the context of health technologies. One of the many conclusions and recommendations of the final report released in September 2016 was for the development of public health impact assessments by governments engaged in trade and investment treaties in order to ensure that these agreements do not include provisions that interfere with their obligations to fulfil the right to health.

The present study aims to contribute to the assessment of the public health impact of the Mercosur-EU FTA by estimating the impact of TRIPS-plus measures proposed by the EU on public expenditure on medicines and sales of domestic production in Brazil. In this report, we present findings related to the antiretroviral (ARV) medicines used in the treatment of HIV/AIDS and to the medicines used for Hepatitis C.

A preliminary report of the study was released previously, in March 2017. That report analysed the EU proposal for the IPR chapter that was made publicly available in September 2016. The preliminary report identified three main TRIPS-plus provisions with implications for health policies: (i) mandatory adoption of regional or national exhaustion of intellectual property rights (IPR); (ii) extension of the period of protection conferred by a patent on medicinal products and (iii) exclusivity of data submitted to obtain market authorisation. The preliminary

report also made an estimation of the impact of one of those TRIPS-plus measures – patent term extension - on prices of selected medicines in Brazil. The calculations included six medicines that may have their patent protection extended under such provision: three for HIV (darunavir, etravirine, raltegravir), two for Hepatitis C (sofosbuvir, daclatasvir) and one for cancer (dasatinib). It was estimated that this extension would represent an **additional expenditure of nearly USD 444 million by the Brazilian Ministry of Health (MoH)**, in comparison with the lowest international prices.

In this report, we present the findings of a more comprehensive impact assessment of two of the TRIPS-plus provisions contained in the EU proposal: patent term extension and data exclusivity. As Brazilian law already adopts the national regime of exhaustion of IPR, the impact of that specific provision was not individually calculated in the study, even though it is considered in the base scenario. Taking the reality of the Brazilian market as a base for the calculations, we applied the Intellectual Property Rights Impact Aggregate (IPRIA) Model[b] in order to estimate the impact of such provisions on the public expenditure and domestic sales of medicines in Brazil.

The Model was applied only to the market segment comprised by ARV medicines indicated for the treatment of HIV and to the market segment of medicines for Hepatitis C, which are both exclusively public in Brazil. It was not applied to estimate the impact of IPR changes in the Brazilian pharmaceutical market as a whole, as was done in most of the other studies conducted to estimate the impact of TRIPS-plus provisions in health. The results of the study should be read with this in consideration.

The selection of the two case studies took into consideration the significant difference between them. In Brazil, the ARV market has been relatively stable over the past years in terms of public expenditure and included an important share of generic medicines, both imported and locally produced, mostly as a result of adoption of measures to challenge patent barriers (threat and issue of compulsory license, patent oppositions, experimental use/Bolar exception and voluntary license).

On the other hand, the Hepatitis C market has been sharply increasing; it is historically almost 100% under exclusivity. The strategies adopted to try to remove IPR barriers had not yet fully resulted in changes in the market as of 2016, resulting in a market in which the negative impact of IPR on public expenditure and local production can be measured in full.

For these reasons we consider the ARV market and the Hepatitis C market to be key case studies to simulate and illustrate the implications on public expenditure and sales by domestic producers with the adoption of TRIPS-plus provisions proposed by the EU in the FTA negotiations with Mercosur.

The IPRIA model is based on a “scenario methodology”: a base scenario - which reflects the market behaviour based on the selected parameters as well as the effects of legislation/regulation that has been already approved at the initial year of the period analysed - is compared with alternative scenarios that incorporate

the impact of the potential changes on IPR taking into account the behaviour of the Brazilian market. The study considered two main outcomes: (i) **changes in public expenditure** and (ii) **changes in the sales of domestic producers.** The latter was only calculated for the ARV market, as the sales of domestic producers in the Hepatitis C market in Brazil are only residual and represent around 0.01% of sales.

We used the prospective simulation to produce five different scenarios in order to estimate the impact of the inclusion of each of the above-mentioned TRIPS-plus provisions proposed by the EU both separately and together.

i. Base scenario – the evolution of the market if there are no changes on IP regulations in Brazil, therefore including TRIPS-plus provisions already adopted in Brazilian law;

ii. Alternative scenario 1 – the evolution of the market in the absence of the article 40, sole paragraph, of the current Brazilian patent law, which allows for patent term extension based on patent examination delay;

iii. Alternative scenario 2 – the evolution of the market in the case of adoption of patent term extension as a consequence of market authorisation delay;

iv. Alternative scenario 3 – the evolution of the market in the case of adoption of data exclusivity for a period of 5 and 8 years;

v. Alternative scenario 4 – the evolution of the market in the case of adoption of both data exclusivity (5 and 8 years) and patent term extension due to delay in regulatory market authorisation.

The main results can be summarised as follows:

i. The base scenario shows that without any change in the IP legislation:

a. The ARV expenditure would go from BRL 1.12 billion in 2015 to BRL 2.95 billion in 2050, considering a growth trend of 3% (adjusted for inflation) observed from 2008-2015 (Chart 24).

b. The Hepatitis C expenditure would go from BRL 1.02 billion in 2016 to BRL 2.05 billion in 2051. This was calculated using the very conservative market growth of 2% observed from 2015-2016 (Chart 25).

ii. Alternative scenario 1 shows that if Brazilian industrial property legislations were changed to remove the patent term extension due to patent examination delay:

a. For ARV, there would be savings of BRL 2.05 billion by the Brazilian MoH in the period of 2015 – 2050 (an average of BRL 58.7 million per year). It would also lead to an increase in the sales of domestic producers of BRL 92.3 million (Chart 26).

b. For Hepatitis C, the savings in public expenditure would be of BRL 16.32 billion in the period from 2016-2051, a simple average of BRL 481.7 million per year (Chart 27).

iii. Alternative scenario 2 shows that the adoption of the patent term extension due to market authorisation delay as proposed by the EU would lead to:

a. For ARV, an additional expenditure of BRL 1.25 billion by the Brazilian MoH in the period of 35 years (an average of BRL 35.8 million per year). It would also lead to a decrease in the sales of domestic producers of BRL 102 million (Chart 28).

b. For Hepatitis C, it would lead to additional expenditure of BRL 16.3 billion (an average of BRL 466.4 million) (Chart 29).

iv. Alternative scenario 3 shows that the adoption of data exclusivity would lead to:

a. For ARV, an additional expenditure by the Brazilian MoH in the period of 2015-2050 of BRL 2.42 billion if it was adopted for a period of 5 years (an average of BRL 70.1 million per year) or of BRL 3.74 billion if adopted for a period of 8 years (an average of BRL 106.8 million per year). It would also lead to a decrease in the sales of domestic producers in the same period of BRL 237.06 million if adopted for 5 years or BRL 423.7 million if adopted for 8 years (Chart 30).

b. For Hepatitis C, there would be an additional expenditure of BRL 31.45 billion from 2016-2051, an average of BRL 898.6 million per year (5 years data exclusivity); and, BRL 47.8 billion from 2016-2050, an average of BRL 1.37 billion per year (8 years data exclusivity) (Chart 31).

v. Alternative scenario 4 shows that the adoption of both TRIPS-plus provisions proposed by the EU would lead to:

a. For ARV, an additional expenditure by the Brazilian MoH in the period of 2015-2050 of BRL 3.7 billion if data exclusivity was adopted for a period of 5 years (an average of BRL 105.9 million per year) or of BRL 4.99 billion if adopted for a period of 8 years (an average of BRL 142.7 million per year). It would also lead to a decrease in the sales of domestic producers in the same period of BRL 393 million if adopted for 5 years or BRL 612 million if adopted for 8 years (Chart 32).

b. For Hepatitis C, there would be additional expenditure of BRL 46.6 billion in the accumulative from 2016-2051, an average of BRL 1.33 billion per year (5 years data exclusivity); and BRL 63 billion in the accumulative from 2016-2051, an average of BRL 1.8 billion per year (8 years data exclusivity) (Chart 33).

Chart 1 - Summary of the findings

Scenario	Time Period	Variation in ARV expenditure compared to base scenario (BRL)	Variation in expenditure on medicines for Hepatitis C compared to base scenario (BRL)
Alternative (Alt) 1	2015-2050 for ARV and 2016-2051 for Hepatitis C	-2,054,436,157.85	-16,862,109,838.52
Alt 2		1,255,011,241.61	16,326,989,040.47
Alt 3 (5-years DE)		2,452,784,149.22	31,451,189,948.91
Alt 3 (8-years DE)		3,740,179,503.19	47,861,780,962.03
Alt 4 (5-years DE)		3,707,795,390.84	46,639,086,730.75
Alt 4 (8-years DE)		4,995,190,744.80	63,049,677,743.86

The **discussion of the results** highlights the implications that changing the intellectual property law could have for policies of access to health and national development, summarised below:

(i) The public expenditure on ARV in Brazil has been relatively stable in the past years as a result of multiple strategies adopted to negotiate price and remove patent barriers, such as the use of public health TRIPS flexibilities, allowing for the treatment of more people with small increase in total expenditure;

(ii) The Hepatitis C market in Brazil is almost 100% under exclusivity between 2006 to 2016. The strategies to remove patent barriers were less adopted and the patent oppositions presented for sofosbuvir and daclatasvir have not shown full results yet. Public expenses have been increasing and treatment has not been available to all in need. The impact of exclusive rights is higher in Hepatitis C than in ARV as of today and will be even worse if more exclusive rights are adopted in the country;

(iii) The adoption of the TRIPS-plus measures proposed by the EU, besides the increase in public expenditure on medicines and reduction of domestic sales shown in the study, would also reduce the policy space currently available to adopt measures to reduce the negative impact of IPR on health

policies, such as the TRIPS flexibilities. That could lead to even higher increase in public expenditure and decrease of sales by national producers in the whole pharmaceutical market;

(iv) The removal of already existing TRIPS-plus provisions that extend the market exclusivity due to patent term extension would lead to savings of public money and increase in domestic sales;

(v) Public expenditure on medicines has been increasing in the past years, consuming rising shares of the total public health budget as a result of incorporating medicines under market exclusivity. Therefore, the adoption of new measures that increase market exclusivity is detrimental to the sustainability of the public health system.

Based on the results and discussions of the study, the authors make the following **recommendations:**

1. The rejection of any TRIPS-plus provision that extends market exclusivity as proposed by the European Union in the negotiation of the Free Trade Agreement with Mercosur, considering the negative impact of those measures on policies of access to health and national development in Brazil;

2. For the Brazilian government and other countries involved in the negotiation of the FTA to conduct an impact study in the field of public health and human rights, as recommended recently by the UN High-Level Panel on Access to Medicines. The impact studies should be conducted transparently and be made publicly available;

3. The negotiations of the FTA should be transparent and all draft texts and proposals from all parties involved should be publicly disclosed and public consultations should be held to allow the participation of all sectors of society;

4. For the Brazilian government to make all efforts necessary to exclude TRIPS-plus measures already foreseen in national IP legislation, especially the removal of the provision included in the sole paragraph of article 40 of the patent law that allows for patent term extension due to delay in patent examination.

1. Introduction

1. Introduction

The WTO TRIPS Agreement, which came into effect on 1 January 1995, changed the international system of intellectual property with the establishment of minimum protection standards. This Agreement significantly changed the levels of protection practised in developing countries, raising them, in most cases, to levels incompatible with their own stages of development.[1]

Resulting from an intensely private agenda, coordinated by a group of multinational companies,[c] and led by developed nations such as the United States, Japan and some European countries,[2] the TRIPS Agreement established the obligation to grant patent protection in all technological fields for a minimum duration of 20 years by all member members of the WTO. The Agreement does, however, factor in varying implementation deadlines (transition periods), according to the development classification of the member countries, a period not always fully enjoyed by the respective countries.

The negotiations of the Agreement did not occur without resistance from developing countries, which sought to minimise the negative impact by adopting provisions that would balance intellectual property rights abuses.[1] But for those who advocate the strengthening of global standards of intellectual property protection, the TRIPS Agreement fulfilled 95% of their expectations.[3]

The TRIPS Agreement was regarded as setting out the minimum standards for intellectual property protection, opening a window of opportunity to even higher standards – the other 5% – to be negotiated outside the WTO multilateral forum and in a context of increased asymmetry among countries involved. The so-called 'TRIPS-plus provisions' are those that go beyond the TRIPS Agreement, as a rule, strengthening the power conferred by intellectual property and restricting the space for the adoption of measures that minimise the effects arising from the abuse of monopoly powers awarded by intellectual property.

For the pharmaceutical sector, and especially multinational pharmaceutical companies, the protection of intellectual property is a key instrument of its commercial and innovation strategies, particularly of industrial property that

includes trademarks and patents and other market exclusivity privileges. Patents guarantee companies a period of exclusivity in the market for their products, excluding third parties, without their consent, from the different stages involving production and trade. In the absence of substitutes/competitors, market exclusivity provides a monopolistic position that allows them the power to set prices often much higher than in a scenario with competition. This privilege is justified on the grounds that it is required to recover their alleged cost for research and development (R&D). The argument goes on to state that without strong IPR there would be no R&D and hence no future innovation to address existing health needs. Branding contributes to product differentiation market strategies, which together with other strategies aimed at influencing prescription patterns, contribute to strengthening dominant market positions during and after the exclusivity period and, ultimately, to increased sales for these products.[4]

More recently, cases such as that of the new medicine sofosbuvir, a drug that can cure chronic Hepatitis C (above 90% efficacy rate) - initially marketed at USD 1,000 per tablet - as well as oncological medicines marketed at exorbitant prices, rekindled the debate on the limits of intellectual property protection in the face of lack of access to medicines that have the potential to save millions of lives.[5-8] These drugs are often unaffordable and financially unsustainable even to the health systems of the wealthiest countries.

On the other hand, the TRIPS Agreement also contains provisions that make it possible to safeguard public health, the so-called 'TRIPS flexibilities of public health protection', which allows for the removal of the exclusivity conferred by intellectual property rights. This allows for the entry of generic medicines, enabling competition to encourage price reductions.[9-10] In 2001, the "Doha Declaration on the TRIPS agreement and public health", adopted in the WTO framework, reaffirmed the right of countries to adopt such measures of public health protection.

At the international level, different organisations recommend caution with the adoption of TRIPS-plus provisions, as they may have a negative impact on the ability of states to provide essential medicines, a component of the obligation of the state for the realisation of the human right to health. Recently, in September 2016, a report was published by the United Nations Secretary-General's High-Level Panel on Access to Medicines that had, among others, a recommendation to countries to conduct preliminary public health impact studies[11] while negotiating trade agreements.

1.1. The Mercosur-EU FTA

Negotiations on a trade agreement between the European Union and Mercosur began in the year 2000. Intensive negotiations were held in 2004 with the objective of concluding the agreement by the end of that year. However, in October 2004, at a ministerial meeting in Lisbon, Portugal, both parties agreed that they would need more time to draft the agreement and the negotiations were suspended. In May 2010, negotiations were officially resumed and since then 28 rounds of negotiations have taken place (including the Bi-regional Negotiating Committee Meeting - BNC). The latest round with Mercosur was held in July 2017 in Brussels and the next one is planned to take place in Brasilia from 2 to 6 of October 2017.

The aim is to negotiate a comprehensive trade agreement covering not only trade in industrial and agricultural goods but also services and public procurement, as well as intellectual property and other technical barriers to trade. Unlike most trade agreement negotiations, the EU made the text proposed for some chapters of the agreement being negotiated public, including the one related to intellectual property rights,[d] which is the object of the present study.

An analysis of the last publicly available text of the EU proposal for the chapter on intellectual property (dated 23 September 2016) shows that it includes the following TRIPS-plus provisions:

- **Exhaustion of intellectual property rights** - Article 3 of the EU proposal addresses the exhaustion of intellectual property rights. Under the proposal, the parties would either adopt the national regime, or the regional exhaustion regime. Under the WTO TRIPS Agreement, countries may choose the exhaustion regime they consider most appropriate (Articles 6 and 28 of the TRIPS Agreement and Article 5d of the Doha Declaration on TRIPS and Public Health). Thus, by means of TRIPS, countries may also opt for the international exhaustion regime, which would not be possible if the EU proposal was accepted.

- **Extension of the period of protection conferred by a patent on medicinal products** - According to Article 8.3 of the proposal presented by the EU, countries should extend the term of validity of a patent for a medicinal product that has undergone an administrative authorisation procedure for its commercialisation. The extension period is 5 years less than the period between the filing of the patent application and the first authorisation to place the product on the national market. In the case of medicinal products for which studies for paediatric formulations have been carried out, countries should grant a further extension of the patent term for a period not specified in the proposal text. The same provision applies to patents on phytopharmaceutical products [plant-based products] (Article 8.5).

- **Exclusivity of data submitted to obtain an authorisation to put a medicinal product on the market** - In accordance with Article 10.2 of the EU proposal, the parties shall not allow any other manufacturer of the same or similar

product to obtain marketing approval based on a marketing approval granted to the manufacturer who provided the results of pre-clinical or clinical tests, for a period of […] years (the number of years is not specified in the proposal). An additional period, not specified in the proposal, would be granted in case of authorisation to one or more new therapeutic indications that may be considered of significant clinical benefit. In other FTAs it was adopted up to a minimum period of 5 years.

Prior to the FTA negotiations round held in March 2017, the Brazilian team of the "AccessIBSA project" (Shuttleworth Foundation) estimated the effects of one of the TRIPS-plus measures proposed by the EU in the IP chapter (extension of patent term) in the public expenditure by the Brazilian Ministry of Health (MoH)[e] That was a preliminary estimation and included only six medicines: three for HIV (darunavir, etravirine, raltegravir); two for Hepatitis C (sofosbuvir, daclatasvir); one for cancer (dasatinib). By estimating the patent extension of each selected medicine - considering the purchases made in 2015 (volume) and comparing the prices to those paid by the MoH with generic versions available in the international market - it was possible to estimate an **additional expenditure of nearly USD 444 million with the adoption of only this TRIPS-plus measure during the additional monopoly time brought by the extension of the patent term of each of those six drugs.**

In order to further estimate the impact of the FTA on the public purchases of medicines in Brazil, we conducted the present impact study, which estimates the impact of two of the TRIPS-plus measures proposed by the EU (patent term extension and data exclusivity). As Brazilian law already adopts the national regime of exhaustion of IPR,[f] the impact of that specific provision was not individually calculated in the study, even though it is considered as part of the base scenario.

There have been some estimates published on the impact of adopting TRIPS-plus provisions on the pharmaceutical market and medicines costs in Latin American countries (Colombia, Ecuador, Peru, Costa Rica and the Dominican Republic).[12-17] These studies were based on an economic model of measuring the impact of IPR changes[18] on access to medicines. These analyses considered three main outcomes: i) changes in the consumption of medicines, ii) changes in the expenditure with medicines, and iii) changes in the domestic market share.

The present study applies the same Intellectual Property Rights Impact Aggregate (IPRIA) Model used in the above-mentioned studies to estimate the impact of the adoption of two TRIPS-plus provisions proposed by the EU on purchases by the public health system in Brazil and the changes in the domestic market share. Initially, the model was applied only to the HIV antiretroviral (ARV) market and Hepatitis C market in Brazil that are exclusively public, as all these medicines are provided by the Unified Health System (SUS) and there are no sales in the private market. In this study, the Model was not applied to estimate the impact of IPR changes in the Brazilian pharmaceutical market as a whole, as done in most of the other studies conducted to estimate the impact of TRIPS-plus provisions in health. The results should be read considering this.

The analysis of the impact of changes in the intellectual property regulations in Brazil should take into account the fact that the Brazilian patent law already has adopted TRIPS-plus measures, with significant impact on prices of medicines as briefly described in the next section.

1.2. The Brazilian patent legislation is already TRIPS-plus

In relation to industrial property, as of May 1997, Brazil passed law number 9.279/96 to comply with the TRIPS Agreement, granting patent protection for pharmaceutical products in advance, therefore not taking advantage of the transition period allowed under TRIPS until 2005 for developing countries. In addition, the law incorporated a series of TRIPS-plus provisions that turned out to be harmful to access policies, especially under the Unified Health System (SUS). Among the TRIPS-plus provisions adopted in the Brazilian legislation are the mechanism of patent revalidation known as "pipeline" (articles 230 and 231), which allowed for the granting of patents retrospectively, and the sole paragraph of article 40, which allows for extension of patent term due to delay in granting by the Brazilian Patent Office (INPI). Both provisions had their validity questioned under the Brazilian constitution in the Federal Supreme Court (Direct Action of Unconstitutionality – ADI 4234 and ADI 5061 and 5529, respectively, which are still awaiting decision). There are two bills – PL 139/99 and PL 8091/2014 - ongoing at the National Congress to remove the provision of the article 40 of the Brazilian patent law.

In the last twenty years, the assurance of pharmaceutical services in the public health system has represented an important step forward in terms of expanding access to medicines for the Brazilian population,[19] and has also been the target of increasing challenges for the sustainability of policies on access to medicines.

These include the growing incorporation of new technologies under monopoly[20] and the growing expenditure on medicines by the federal, state and municipal levels of government.[21-22] The expenses on medicines by the Ministry of Health (the federal entity being responsible for the purchase of the most expensive technologies) went from 8.5 billion Reais (BRL) in 2008 to 14.8 billion Reais (BRL) in 2015.[23]

Furthermore, it is also possible to illustrate the monetary losses to SUS caused by the above-mentioned TRIPS-plus provisions adopted by the Brazilian patent law.

In the case of patents which were revalidated under the pipeline mechanism, Hasenclever et al.[24] estimated the extra amounts that the Ministry of Health paid, compared to the purchase of generic versions for six[9] antiretrovirals

(ARV) available in the international market, in different formulations, but which were protected by pipeline patents in Brazil. Looking at the purchased volume and the difference between prices paid and prices available from two different sources (the World Health Organization – WHO and Médecins Sans Frontières - MSF) in the 2001 - 2007 period, ***the loss was estimated at approximately USD 420 million (MSF minimum prices) and USD 519 million (WHO minimum prices).*** Another study[25] estimated that from May 2009 to December 2010, the Ministry of Health spent ***an extra BRL 123 million*** on the purchase of four medicines protected by pipeline patents (imatinib, lopinavir/ritonavir, olanzapine and atorvastatin) when compared to what it would have spent on generic versions of these products.

On patent term extension, article 40 of the Brazilian patent law has a sole paragraph that allows extension of patent term in case it takes more than 10 years to be granted in the country. A study[26] identified nine medicines purchased by the Ministry of Health[h] whose patent terms were extended or have patent applications that are pending analysis by the patent office for more than 10 years and, if granted, will have patent protection for a period of over 20 years. Based on the years of accumulated extensions up to January 2016 and the average volume of purchases of the last 3 years, the authors estimated how much more the government will pay for those nine medicines when compared to the possibility of buying generic versions and more affordable biosimilar medicines. ***The estimated amount was a total of BRL 2.14 billion or about BRL 933 million per year.***

These are some examples that illustrate the damage caused to SUS by the TRIPS-plus provisions already adopted in the Brazilian legislation, which are enough to support the understanding that these kinds of measures should not be adopted in any case in intellectual property chapters proposed in trade agreements involving Brazil. In the sections below, we will examine the estimation of further losses that would be caused to SUS in case the proposed TRIPS-plus provisions contained in the EU proposal are adopted.

2. Methodology

2. Methodology

2.1. Selection of the market in Brazil

For the purpose of this study, we selected two case studies to estimate the impact of the IPR changes in Brazil: (i) antiretroviral (ARV) medicines used for the treatment of HIV and (ii) medicines used for the treatment of Hepatitis C. In both cases, those medicines are only supplied by the public sector in Brazil, which means there is only a public market. We did not apply the Model to estimate the impact in the Brazilian pharmaceutical market as a whole, as done in most of the other studies conducted to estimate the impact of TRIPS-plus provisions in health. This choice was based on the fact that the variables considered in the Model can vary considerably when considering different market segments and we wanted the figures to be more accurate according to each specific disease segment and to the public market.

The selection of the two case studies took into consideration the significant difference between them. In Brazil, the ARV market has been relatively stable over the past years in terms of expenditure. Almost 35% of the market, in terms of sales, is under exclusivity (2015) and there is domestic production of generics. The Brazilian response to the HIV/AIDS epidemic has been based on the combination of prevention and care strategies, including access to treatment. Brazil was one of the first developing countries to provide access to treatment and pursued different policies to ensure the provision of those treatments, such as: local production of medicines, price negotiations with multinational companies and adoption of measures to challenge patent barriers (threat and issue of compulsory licenses, patent oppositions, experimental use/Bolar exception and voluntary license).[27] As a consequence of those initiatives, the public expenditure on ARVs have been kept relatively stable in face of the increase in the number of patients starting and under treatment.[28-29]

It should be noted, however, that it is unlikely this scenario will continue to be stable, as in 2013 the treatment guideline has changed to treat all people living with HIV,[30] which is expected to increase the number of people in treatment beyond variation in previous years, and because the newer ARVs are under exclusivity and are replacing current ARVs with generic alternatives. Considering

that the first ARVs were produced in Brazil due to the lack of grant of patents for pharmaceuticals before 1996, it should be expected that the proportion of the medicines under exclusivity should increase in relation to the historical data used as a base for this study.

On the other hand, the Hepatitis C market has been sharply increasing, the market is historically almost 100% under exclusivity (2006-2016). The strategies adopted to try to remove IPR barriers[i] had not yet fully resulted in changes in the market as of December 2016, resulting in a market in which the negative impact of IPR on public expenditure and local production can be measured in full.

2.2. Data and information sources

The data related to prices, volume of purchases and suppliers of ARV medicines in the period of 2008 to 2015 used in the application of the IPRIA Model was supplied by the Brazilian Ministry of Health (MoH) through the Access to Information Act.[j] The data related to Hepatitis C medicines was also obtained from the MoH for the year 2016. For the period of 2006-2015 we used data available in a previous study recently published by one the authors.[34]

Data related to regulatory market authorisation was obtained at the official website of Anvisa *(Agência Nacional de Vigilância Sanitária)*.[k] Data related to patents was obtained at the official website of the Brazilian Patent Office - INPI *(Instituto Nacional de Propriedade Industrial)*.[l]

2.3. IPRIA Model and scenario method: Base and Alternative scenarios

The IPRIA Model is based on the "scenario method". Information on the medicines market selected is obtained by comparing alternative scenarios to a base scenario. The impact is the result of the difference between a basic scenario - which, in the prospective simulation, describes the current situation and its possible evolution if there are no changes in IP regulation - and different alternative scenarios that describe possible evolutions according to different changes in IPR.

The data used for the base scenario is the state of the market in the first year of the simulation (2015 for ARV and 2016 for Hepatitis C). The variables that characterise the initial year of the simulation are the same in the baseline scenario and in all alternative scenarios. These variables are based on actual data as far as they are available. If not so, they must be estimated outside the model by extrapolating previous figures and trends or by expert opinion. In order to simulate posterior years of the baseline and of the alternative scenarios it is necessary to populate the model with the parameters requested by it. The values of these parameters can be based on an extrapolation of past trends or on justified assumptions on the future evolution of the market.

There were two main outcomes considered for this study: (i) changes in public expenditure; and (ii) changes in the sales of domestic producers. The latest was only calculated for the ARV market, as the sales of domestic producers (only ribavirin) in the Hepatitis C market in Brazil are considered residual.

The simulation of each scenario is based on a series of parameters (Chart 2). These are: (i) fixed parameters, which are the same for every scenario; (ii) scenario-specific parameters, which describe the projected changes in each scenario; and (iii) annual input data, which give the simulations substance in order to produce predictions based on actual market behaviour. Therefore, the Model uses the historical market parameters to simulate different future scenarios keeping the same market parameters to simulate the impact of the changes in IP regulations.

Chart 2 - Description of the parameters

Fixed parameters	Description
YI	The initial year of simulation.
YL	The final year of simulation.
TAPto	Number of medicines on the first year of the simulation.
MVto	The value of the market on the first year of the simulation.
A	Annual growth rate of the market.
D	Discount rate.
kde	Market share of domestic industry in market under exclusivity.
kdc	Market share of domestic industry in market under competition.
Scenario-Specific	**Description**
YP	Year of the introduction of product patents.
YDP	Year of the introduction of data exclusivity.
PD	The term of a patent in years.
DT	Average time from patent application and market registration.
PDE	Extension of patent term due to marketing approval or patent examination delay.

Scenario-Specific	Description
pPDE	The proportion of medicines obtaining an extension of patent term due to delay in market approval.
TTC	The time lag between the expiry of a patent of an originator product and entry of generics.
DE	The period of data exclusivity.
RPec	The price differential between the average price of a drug under market exclusivity and that under competition.
e	Price-elasticity of demand.

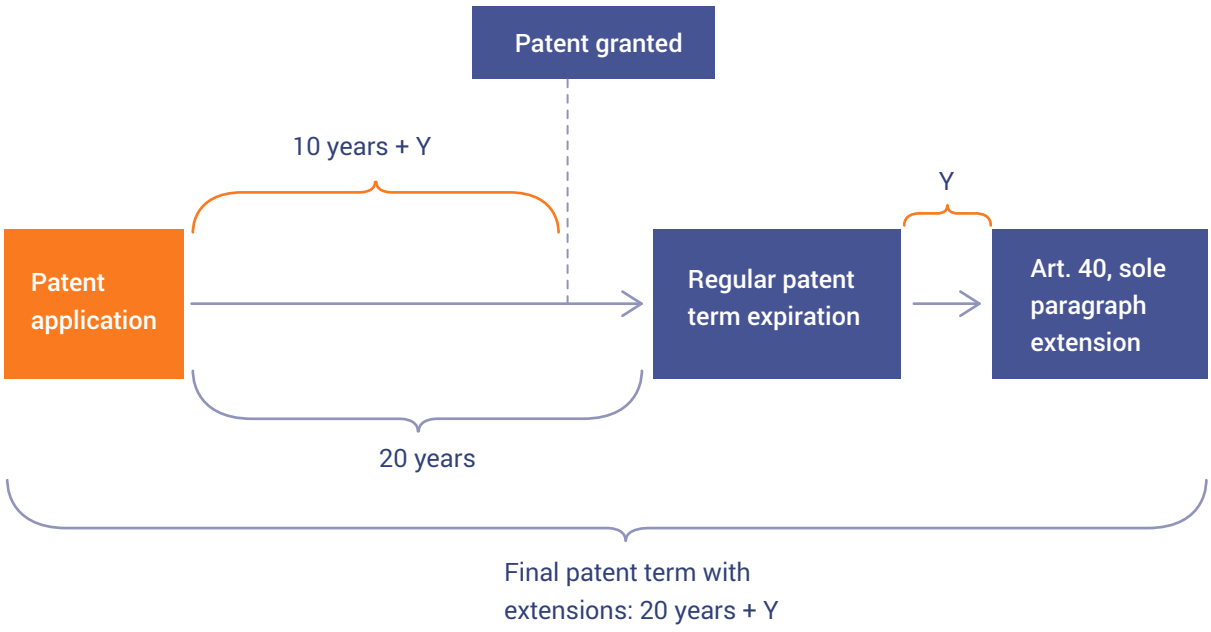
Annual Input Data	Description
Ali	The number of new medicines entering the market in a particular year.
AOI	The number of medicines exiting the market in a given year.
AIPPi	The number of medicines that enter the market in a particular year with (product) patent protection.

Source: Rovira (2009)

2.3.1. Alternative scenario 1 - Patent term extension due to delay on patent examination

Brazilian patent law allows for patent term extension when a patent application takes more than 10 years to be granted. The extension will be of Y years, where Y is the number of years that surpass 10 years after the date of application in the country (Figure 1). That is, a patent application that takes 11 years to be granted will have a total patent term of 21 years counting from the application date, instead of 20.[m] This period begins from the application date, that is, it is retroactive. **In the model, this extension is incorporated into the base scenario and an alternative prospective scenario** without it is simulated in order to estimate its impact.

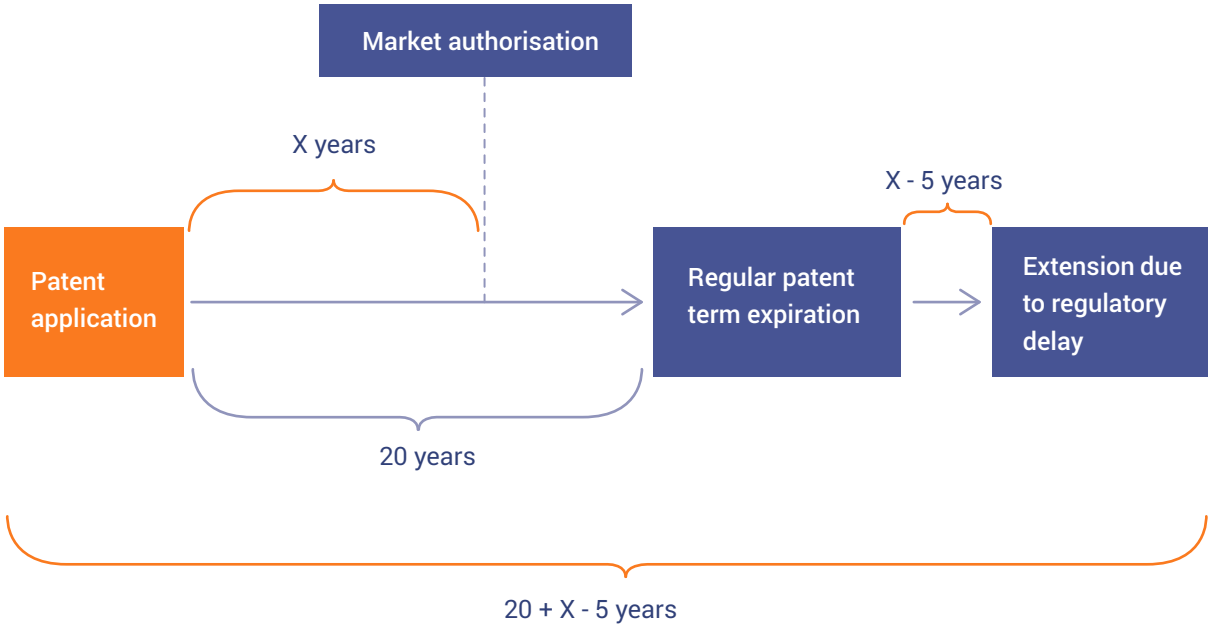
Figure 1 – Patent term extension due to delay on patent examination under article 40, sole paragraph of the Brazilian patent law



2.3.2. Alternative scenario 2 - Patent term extension due to delay in obtaining market authorisation

The EU FTA proposal establishes the adoption of a new patent term extension not yet adopted in Brazil: an extension to patent term due to the time lag between patent application and market approval (Figure 2). This would be calculated as the time between filing a patent and obtaining market approval minus 5 years.

Figure 2 - Patent term extension due to delay in obtaining market approval as proposed by the EU on the negotiations of the Mercosur-EU FTA



For the purpose of this study, we estimated the average time frame between the filling of the oldest patent application for each medicine (either granted or pending) in the country and the date of obtaining the first sanitary registration, and reduced the 5 years mentioned in the proposal (Chart 3). Granted patents and pending applications were considered assuming the chance of those pending of being granted and the de facto monopoly created by the legal uncertainty.

Chart 3 - Estimates of patent term extension due to delay in patent examination (Brazilian law) or in the delay to obtain market authorisation (EU proposal for the FTA)

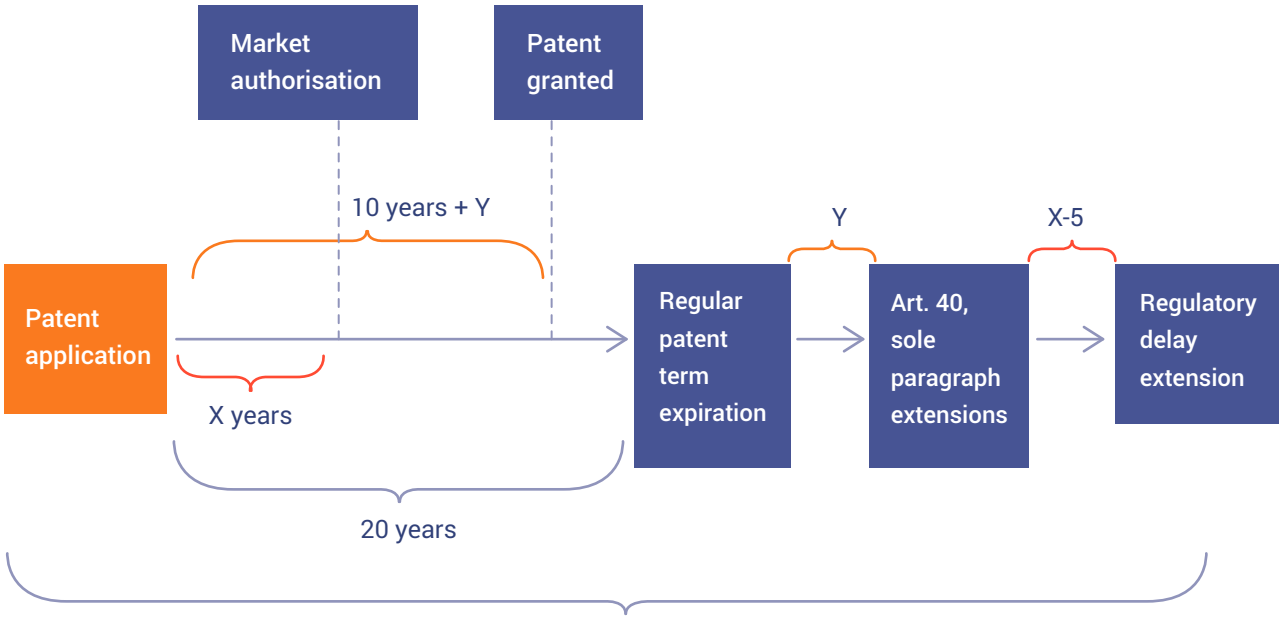
	ARV		Hepatitis C	
	Years	**Proportion of patent applications in which the provision was applied**	**Years**	**Proportion of patent applications in which the provision was applied**
Average patent term extension due delay in patent examination*	5.61 (rounded to 6)	0.27	4.3 (rounded to 4)	0.43
Average patent term extension due to delay in regulatory market authorisation	4.52 (rounded to 5)	0.45	5.2 (rounded to 5)	0.71

* The average was calculated based in real terms for patents already granted and for patents still pending we considered the last days of December 2015 and 2016 for ARV and Hepatitis C medicines respectively.

Considering the base scenario takes into consideration the current Brazilian patent law, including the TRIPS-plus provision that provides for patent term extension due to delay in patent examination, it was estimated the cumulative effect of patent extension by both delay in patent examination and regulatory market authorisation (Figure 3).

The wording provided by the EU text suggests this additional protection period will begin after the lawful patent term – or, to be more precise, it would be added to the final patent term even if it had already been extended by other provisions, such as the one in article 40 of the Brazilian law.[n]

Figure 3 - Patent term extension based on the cumulative effect of extension due to delay in patent examination and delay in market authorisation



2.3.3. Alternative scenario 3: Data exclusivity

Data exclusivity is another of the TRIPS-plus measures contained in the EU proposal. This would grant exclusivity over the test data required for sanitary registration of medicines to the first registering company (Figure 4). The period is not defined in the proposal, but in other agreements the EU has set it to a minimum of 5 years and 8 years. Thus, we have simulated both cases - 5 and 8 years - as the period of exclusivity for the alternative scenarios where data exclusivity would be implemented in Brazil.

Figure 4 – Data exclusivity for a period of 5 or 8 years

2.4. Description of the parameters adopted

2.4.1. ARV market

The evolution of the ARV pharmaceutical market in Brazil was based on data collected from the Ministry of Health based on expenditure from 2008 to 2015. This aggregate annual data was adjusted to the inflation of 2015 by adopting the IPCA - Índice Nacional de Preços ao Consumidor index (Chart 4).

The Model considers the parameters of historical data to simulate prospective scenarios based on the market behaviour and not on the specific information of individual drugs available in the first year of the simulation. That is, the Model considers the inclusion and exclusion of new products, the proportion of products under exclusivity or on competition, the status in which new products enter into the market and so on in order to simulate the behaviour of the market in future years.

Chart 4 - Estimated public expenditure on ARV and the number of people under treatment. Brazil, 2008 to 2015.

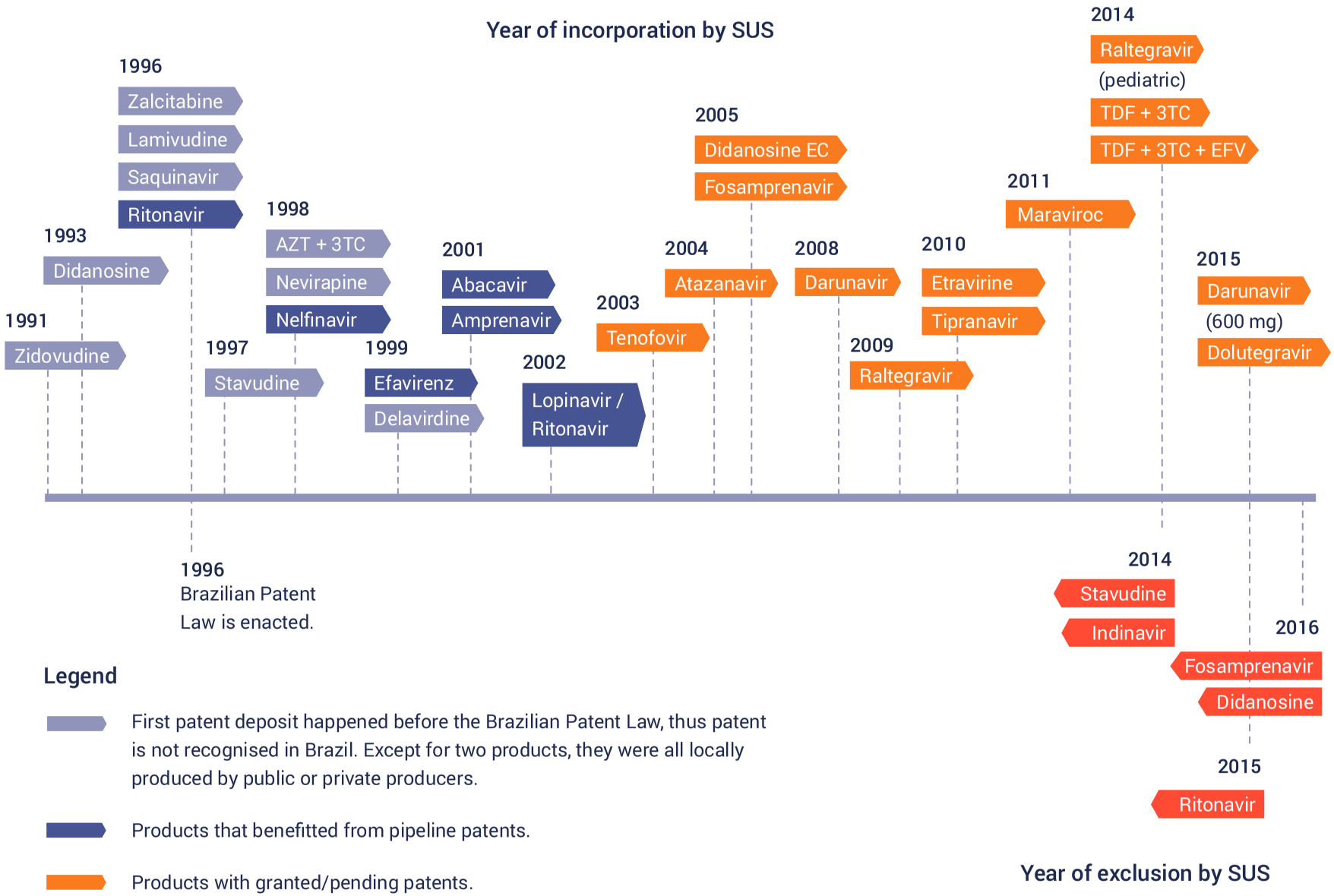
Year	Total expenditure in current values (unadjusted) (BRL) A1	Total expenditure adjusted to the inflation* (BRL) A2	Number of people on ARV treatment B	Variation in number of people on ARV treatment	Expenditure per person on treatment (unadjusted) (BRL) (A1/B)	Expenditure per person on treatment (adjusted) (BRL) (A2/B)
2008	593,478,608.93	921,757,635.10	190,506	-	3,115.47	4,838.47
2009	671,304,484.71	999,551,733.50	231,146	21.33%	2,904.24	4,324.33
2010	830,297,809.46	1,167,300,448.20	257,000	11.18%	3,230.73	4,542.02
2011	795,000,612.47	1,049,461,753.00	284,390	10.65%	2,795.45	3,690.22
2012	734,868,139.04	916,555,440.60	313,175	10.12%	2,346.50	2,926.65
2013	728,767,666.39	858,225,568.40	354,519	13.20%	2,055.65	2,420.81

Year	Total expenditure in current values (unadjusted) (BRL) A1	Total expenditure adjusted to the inflation* (BRL) A2	Number of people on ARV treatment B	Variation in number of people on ARV treatment	Expenditure per person on treatment (unadjusted) (BRL) (A1/B)	Expenditure per person on treatment (adjusted) (BRL) (A2/B)
2014	870,806,581.05	963,721,643.20	403,970	13.94%	2,155.62	2,385.62
2015	1,119,149,617.60	1,119,149,617.60	454,615	12.53%	2,461.75	2,461.75
Annual rate of market increase	9.5% (rounded to 9%)	2.8% (rounded to 3%)				

* Values adjusted to inflation according to IPCA 2015.
Source: Ministry of Health, Brazil. Access to information law.

From these values, we calculated the average growth rate of the market. This is expressed in Brazilian Reais (BRL). A Compound Annual Growth Rate (CAGR) formula was adopted and estimated considering the evolution of the market adjusted and not adjusted by the inflation, as follows: (a) CAGR (2008, 2015) = 2.8% (adjusted); CAGR (2008, 2015) = 9.5% (not adjusted).

The average of inclusions and exclusions of ARV in the market was based on historical data of ARV, as shown in Figure 5. The ARV market in 2015 was composed of 22 APIs that were purchased by the MoH, including a drug that had been excluded from treatment guidelines in the previous year, considering that this would more adequately reflect the market scenario. It is important to note that fixed-dose combinations (FDC) were considered as one API, as they behave in the market as a single API. First market registrations were obtained in the dates described in Figure 6.

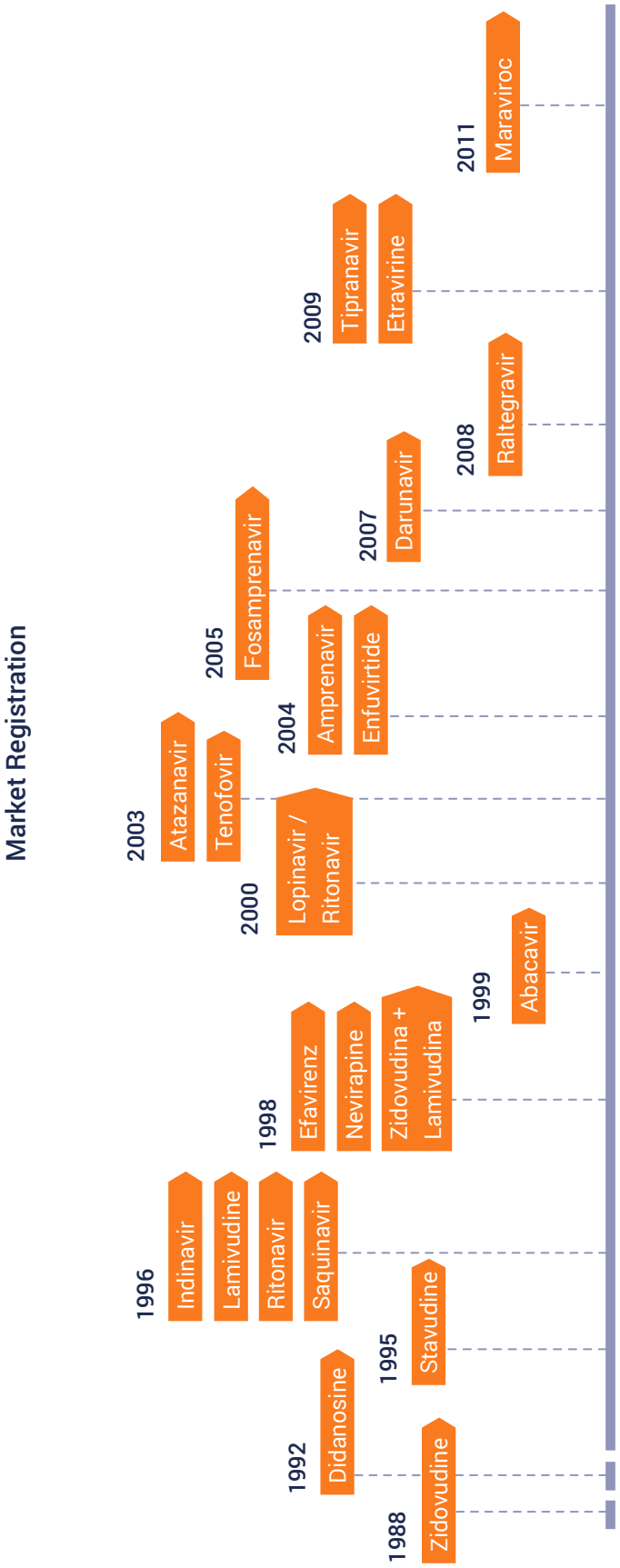


Legend

- First patent deposit happened before the Brazilian Patent Law, thus patent is not recognised in Brazil. Except for two products, they were all locally produced by public or private producers.
- Products that benefitted from pipeline patents.
- Products with granted/pending patents.
- Products excluded by SUS

Figure 5 - Inclusions and exclusions of ARV on SUS, 1991 - 2015

Figure 6 - Dates of market approval of ARV in Brazil, 1988-2015



2.4.2. The complexity of patent situation and market exclusivity in the Brazilian pharmaceutical market

The ARVs market is also illustrative of a complex configuration in the Brazilian pharmaceutical market. According to several studies on patent landscape of ARV in Brazil,[31-33] for all ARVs adopted by the national therapeutic guidelines there are related patent applications. However, this does not necessarily mean that all ARVs are under exclusivity in the country.

We observe at least four main situations:

a) ARVs adopted by SUS between 1991 and 1998 that was subjected to domestic production. This allows the interpretation that the industrial property law 9.279, enacted in 1996, did not apply to the initial patent applications related to those medicines, leading to a situation of competition even if late after there were other secondary patent applications related to the medicine;

b) ARVs in which the first patent in the country was granted through the pipeline mechanism, as mentioned before, a TRIPS-plus provision in the Brazilian law which allowed for retroactive patent protection in the country through the revalidation of patents granted abroad, were generally under exclusivity;

c) ARVs in which patents granted or pending create a monopoly situation for the product. In the case of products with pending patent applications this can be the result of competitors not willing to take the risk of entering the Brazilian market or public purchasers interpreting that the product is under monopoly;º

d) Fixed-dose-combinations in which active pharmaceutical ingredients (API) are in public domain, but there are pending patent applications for the combination. The MoH is purchasing the generic version of those products.

The ARV exclusivity situation was assessed on the basis of the above-mentioned criteria as well as on the trend in public procurement from one or more producers (Chart 5).

Chart 5 - Patent status of ARV and assessment of exclusivity situation in 2015 in Brazil

Product	Number of patent applications in Brazil	Patent status in 2015	Market situation in 2015	Justification
Abacavir	17	3 granted (1 expired); 5 pending; 2 rejected; 7 filed before analysis	Exclusive	3 granted patents and 4 pending applications. Public procurements supplied by the multinational company (GSK), except in 2012 (Aurobindo)
Amprenavir	1	Expired	Not available	Not applied
Atazanavir	7	1 granted; 2 pending; 2 rejected; 2 filed.	Non-Exclusive	Since 2015, there is a generic version available from Farmanguinhos (national public producer) developed under a technology transfer and voluntary license with BMS.
Darunavir	15	1 granted (currently abandoned); 8 pending; 2 rejected; 4 filed before analysis	Exclusive	1 granted patent (currently abandoned); 8 pending application. Public procurements supplied by the multinational company (Janssen-Cilag)
Didanosine EC	2	1 granted; 1 rejected	Exclusive	1 patent granted related to the enteric-coated formulation. Public procurement supplied the multinational company (BMS)

Product	Number of patent applications in Brazil	Patent status in 2015	Market situation in 2015	Justification
Efavirenz	21	3 granted (1 expired); 3 pending; 3 rejected; 12 filed	Non-exclusive	Product under a compulsory license since 2007. Public procurements supplied by Indian generic companies and/or Brazilian public manufacturers.
Enfuvirtide	8	1 pending; 2 rejected; 5 filed before analysis	Exclusive	Although most applications are rejected or filed, there is one pending application. All public procurements were supplied by the multinational company (Roche)
Stavudine	6	Not applied (locally produced since 1990)	Not available	Locally produced since 1990 decade
Etravirine	8	1 granted; 6 pending; 1 filed before analysis	Exclusive	1 granted patent; 6 pending applications. Public procurements supplied by the multinational company (Janssen-Cilag)
Fosamprenavir	13	2 granted (1 expired); 1 pending; 5 rejected; 5 filed before analysis	Exclusive	1 granted patent; 1 pending application. Public procurements supplied by the multinational company (GSK)
Indinavir	13	Not applied (locally produced since 1990)	Non-exclusive	Locally produced since 1990 decade
Lamivudine (3TC)	27	Not applied (locally produced since 1990)	Non-exclusive	Locally produced since 1990 decade

Product	Number of patent applications in Brazil	Patent status in 2015	Market situation in 2015	Justification
Lopinavir / ritonavir	12	1 granted; 7 pending; 3 rejected; 1 filed before analysis	Exclusive	1 granted patent; 7 pending applications. Public procurements supplied by the multinational company (Abbott/Abbvie)
Maraviroc	7	2 pending; 1 rejected; 4 filed before analysis	Exclusive	2 pending applications. Public procurements supplied by the multi-national company (GSK)
Nevirapine	4	Not applied (locally produced since 1990)	Non-exclusive	Locally produced since 1990 decade
Raltegravir	5	2 pending; 3 filed before analysis	Exclusive	2 pending applications. Public procurements supplied by the multi-national company (MSD)
Ritonavir	22	Not applied (locally produced)	Non-exclusive	Locally produced
Saquinavir	14	Not applied (locally produced since 1990)	Non-exclusive	Locally produced since 1990 decade
Tenofovir	16	3 rejected; 11 pending; 2 filed	Non-exclusive	Main patent rejected. Public procurements supplied by public manufacturers since 2011
TDF+3TC	Not found	Not applied.	Non-exclusive	Public procurements supplied by public manufacturer (Farmanguinhos/Fiocruz)

Product	Number of patent applications in Brazil	Patent status in 2015	Market situation in 2015	Justification
TDF+3TC+EFV	Not found	Not applied.	Non-exclusive	Public procurements supplied by PAHO Strategic Fund
Tipranavir	8	1 granted; 2 pending; 2 rejected; 3 filed before analysis	Exclusive	1 granted patent; 2 pending applications. Public procurements supplied by the multinational company (Boehringer)
Zidovudine (AZT)	1	Not applied (locally produced since 1990)	Non-exclusive	Locally produced since 1990 decade
AZT+3TC	Not found	Not applied (locally produced since 1990).	Non-exclusive	Locally produced since 1990 decade

To estimate the average of price reduction (RPec) after generics enter the market, we identified three ARV which had generics first registered in Brazil in the period from 2008 to 2015. The table below shows the difference between the price of the branded-version in the year immediately before the generic version was purchased and the price of the generic in the first year it entered the market (Chart 6). However, as atazanavir is being produced under a voluntary license of the patent in a context of a public-private partnership for technology transfer from BMS to Farmanguinhos, it cannot be considered under generic competition in the same way as the cases for efavirenz and tenofovir. Therefore, to estimate the average of price reduction after generics enter the market we considered only the case of efavirenz and of tenofovir. This resulted in an average of price reduction of 55.6% (Chart 6).

It should be noted that the generic production of tenofovir was possible in a context in which the patent application was denied by the Brazilian patent office in 2009 following patent oppositions filed by generic producers and civil society organisations. The generic production of efavirenz was possible under a compulsory license issued in 2007, which is by definition non-exclusive. Therefore, in both cases the generic version could be introduced to the Brazilian market before the initial expected patent expiration due to the adoption of strategies to remove the patent barrier.

Chart 6 - Estimated price reduction of selected ARVs

Product	Situation	Originator price (BRL) (year)*	Generic price (BRL) (year)*	Reduction (%)
Efavirenz 600 mg	Compulsory license issued in 2007	6.43 (2006)	1.47** (India, 2007)/2.1 (Brazil, 2009)	77%/67%
Tenofovir 300 mg	Patent application rejected by the Patent Office in 2009. First generic procurement in 2011	9.45 (2009)	5.31 (2011)	44%
Atazanavir 300mg	Voluntary license and technology transfer to a public manufacturer (Farmanguinhos) in 2014.	6.57 (2013)	6.04 (2014)	8%
Average reduction (without atazanavir)				55.6% (rounded to 56%

* All prices were adjusted to inflation according to IPCA 2015
** There were purchases from both Ranabaxy and Aurobindo, same volume. Indicated price was the average of each: R$ 1.46 and R$ 1.47.

Elasticity was set to zero (0) because the government has a duty to provide medicines as a component of the constitutional right to health and there is a specific law on the obligation to provide treatment for HIV (Law 9,316/96), so it is assumed amounts purchased would not be greatly reduced in the face of price increases.

The time horizon for this prospective simulation is 35 years, from 2015 to 2050, allowing enough time for the projected policy changes to produce effect.

To calculate the average time between patent expiry and generic entry in the market, we looked at the generics registrations first obtained during the time frame of the study. As the registration was made before patent expiry, so the period between one

and the other was set to 0 considering that generics would have been able to enter the market as soon as the patent expired (Chart 7). It should also be noted that Brazilian IP law has adopted the Bolar exception (Article 43, VII Law 9279/96) which allows generic drug manufacturers to prepare all necessary documents for regulatory approval during the validity of the patent, allowing the generic to be put in market just after the patent expiries or the exclusivity is removed. Some of the cases were also possible because the patents were licensed compulsorily (efavirenz) and voluntarily (atazanavir).

Chart 7 - Estimated price reduction of selected ARVs

Active ingredient	Patent expiry	First generic registration
Atazanavir*	22/04/17	2014
Efavirenz**	09/04/17	2009
Lopinavir+ Ritonavir	30/04/17	2016

*The generic entry was made possible before the patent expiration because there was a voluntary license granted by BMS to Farmanguinhos/Fiocruz in the context of a technology transfer agreement.

**The generic entry was made possible before the patent expiration because there was a compulsory license issued in 2007.

The average time between patent application and regulatory approval (DT) was estimated based on the data of the first market approval in Brazil and the oldest patent application in the country (Chart 8).

Chart 8 - Time between patent application and market registration of ARV (years)

Product	Brazilian patent number	Patent filing date	Market registration date	Time lag: patent filing / market registration (years)
Abacavir	PI9506667-5	02/03/1995	16/03/1999	4.04
Atazanavir	PI9701877-5	22/04/1997	18/09/2003	6.41
Darunavir	PI9607625-9	03/07/1996	21/05/2007	10.88
Didanosine EC	PI9106503-8	05/08/1991	11/06/1992	0.85
Efavirenz	PI9608839-7	21/05/1996	03/11/1998	2.45
Enfuvirtide	PI9609152-5	06/06/1996	31/05/2004	7.98
Etravirine	PI9915176-6	11/04/1999	02/02/2009	9.82
Fosamprenavir	PI9608032-9	18/04/1996	26/12/2005	9.69
Indinavir	PI9406503-9	24/03/1994	01/04/1996	2.02
Lamivudine	PI9507499-6	21/04/1995	13/05/1996	1.06
Lopinavir/ ritonavir	PP1100397-9	30/04/1997	09/10/2000	3.44
Maraviroc	PI9916585-6	12/01/1999	07/02/2011	12.07
Raltegravir	PI0011939-3	22/06/2000	28/01/2008	7.60

Saquinavir	PI9006264-7	12/10/1990	26/02/1996	5.37
Tenofovir	PI9205661-0	20/02/1992	07/06/2003	11.30
Tipranavir	PI9507615-8	05/04/1995	20/04/2009	14.05
	Average			**6.82**

The average of inclusions (Ali) and exclusions (AOi) was estimated based on the number of inclusions (27) and exclusions (7) in 24 years (1991-2015) as in Chart 9. For the purpose of the baseline data, we considered this average for the period of 2017-2050. For 2016, we considered the inclusion of one ARV (dolutegravir) and exclusion of two ARVs (fosamprenavir and DDi EC). However, there were procurements of excluded ARVs in the following years. So, this figure was used to estimate the variables Ali and AOi.

Chart 9 - Average of inclusions and exclusions of ARVs, Brazil, 1991-2015

Data	Number	Average of inclusion/exclusion per year
Number of inclusions of ARVs from 1991-2015	27	1.12
Number of exclusions of ARVs 1991-2015	7	0.29

In order to estimate the number of APIs losing patent protection, we considered the oldest granted patent or pending patent application, as shown in Chart 10.

Chart 10 - Estimate of ARVs losing patent protection in Brazil

Products	Patent number	Estimated expiring year
Abacavir	PI9506667-5	2015
Atazanavir	PI9701877-5	2017
Darunavir	PI9607625-9	2013 (not included)
Didanosine EC	PI9815861-9	2018
Enfuvritide	PI0312889-0	2017 (withdrawn)*
Etravirine	PI9915552-4	2019
Fosamprenavir	PI9708238-4	2017
Lopinavir/ritonavir	PI1100397-9	2017
Maraviroque	PI9917007-8	2026
Raltegravir	PI0213522-1	2027
Tipranavir	PI9507615-8	2015

*As we assumed pending applications created an exclusivity situation, we also considered the year of withdrawn as rejected

All these parameters are summarised in the table below, referring to the various scenarios calculated in the prospective simulation (Chart 11).

Chart 11 - Prospective simulation, parameters used for ARV market

Fixed param.	Base scenario	Alternative scenario 1 (w/o art. 40 ext.)	Alternative scenario 2 (reg. delay ext.)	Alternative scenario 3 (data exclus.)	Alternative scenario 4 (base + data excl. + reg. ext.)
YI	2015	2015	2015	2015	2015
YL	2050	2050	2050	2050	2050
TAPto	22	22	22	22	22
MVto	R$ 1,119,149,617.60	R$ 1,119,149,617.60	R$ 1,119,149,617.60	R$ 1,119,149,617.60	R$ 1,119,149,617.60
α	0.03	0.03	0.03	0.03	0.03
d	0.03	0.03	0.03	0.03	0.03
k_{de}	0	0	0	0	0
k_{dc}	0.84	0.84	0.84	0.84	0.84
Scenario-Specific	**Base scenario**	**Alternative scenario 1**	**Alternative scenario 2**	**Alternative scenario 3**	**Alternative scenario 4**
YP^{p}	1997	1997	1997	1997	1997
YDP^{q}	2050	2050	2050	2015	2015
PD	20	20	20	20	20

Scenario-Specific	Base scenario	Alternative scenario 1	Alternative scenario 2	Alternative scenario 3	Alternative scenario 4
DT^r	7	7	7	7	7
PDE	6	0	11	6	11
pPDE	0.3	0	0.3	0.3	0.3
TTC	0	0	0	0	0
DE	0	0	0	5 / 8	5 / 8
RPec	2.3	2.3	2.3	2.3	2.3
e^s	0	0	0	0	0
Annual Input	**Base scenario**	**Alternative scenario 1**	**Alternative scenario 2**	**Alternative scenario 3**	**Alternative scenario 4**
Ali^t	1.125	1.125	1.125	1.125	1.125
AOI	0.29	0.29	0.29	0.29	0.29
AIPPi	0.9	0.9	0.9	0.9	0.9

Domestic and foreign industry values were estimated based on the supplier for each product in 2015 (Chart 12 and Chart 13). There were 11 products under exclusivity and 11 without exclusivity. In markets without exclusivity, there were 6 national producers (including public and private), which amounted for approximately 84% of the market without exclusivity (Chart 13).

Chart 12 - Market share of foreign and national companies in ARV market in 2015

Product	Market situation in 2015	Market-share in 2015 (in monetary values)	Supplier in 2015
Abacavir	Exclusive	0.26%	GSK
Atazanavir	Exclusive	12.70%	Farmanguinhos/Fiocruz (ongoing technology transfer with BMS)
Darunavir	Exclusive	7.14%	Janssen-Cilag
Didanosine EC	Exclusive	0.30%	BMS
Efavirenz (EFV)	Non-exclusive	0.01%	Aurobindo
		6.73%	Farmanguinhos/Fiocruz
		0.04%	MSD
Enfuvirtide	Exclusive	0.81%	Roche
Stavudine	Non-exclusive	0.02%	Cristália
Etravirine	Exclusive	1.66%	Janssen-Cilag
Fosamprenavir	Exclusive	1.43%	GSK
Lamivudine (3TC)	Non-exclusive	1.42%	Lafepe, Iquego, Furp
		0.10%	Aurobindo

Product	Market situation in 2015	Market-share in 2015 (in monetary values)	Supplier in 2015
Lopinavir/ ritonavir	Exclusive	13.90%	Abbvie
Maraviroc	Exclusive	0.66%	GSK
Nevirapine	Non-exclusive	0.64%	Farmanguinhos/Fiocruz
		0.01%	Aurobindo
Raltegravir	Exclusive	8.74%	MSD
Ritonavir	Non-exclusive	4.35%	Abbvie
Saquinavir	Non-exclusive	0.10%	Cristália
Tenofovir (TDF)	Non-exclusive	3.08%	Funed
		5.13%	Lafepe
TDF+3TC	Non-exclusive	11.53%	Farmanguinhos/Fiocruz
TDF+3TC+EFV	Non-exclusive	5.90%	PAHO
Tipranavir	Exclusive	0.14%	Boehringer
		0.10%	Farmanguinhos/Fiocruz
Zidovudine (AZT)	Non-exclusive	0.01%	Cristália
		0.05%	Lafepe

Product	Market situation in 2015	Market-share in 2015 (in monetary values)	Supplier in 2015
AZT+3TC	Non-exclusive	13.25%	Lafepe, Iquego, Furp, Farmanguinhos/ Fiocruz

Chart 13 - Market share of ARV according to the exclusivity situation in 2015

Market share of API under exclusive market	35.04%
Market share of API on non-exclusive market	65.17%
Market share of domestic industry under exclusive market	0
Market share of domestic industry under non-exclusive market	84%

2.4.3. Hepatitis C market

Since 1980, the Brazilian government has implemented policies related to viral Hepatitis. Different initiatives were incorporated in the response, such as: compulsory notification, prevention, diagnosis and treatment. In relation to Hepatitis C, it is estimated that there are 1.5 million of people infected with the virus (HCV) in Brazil. The first therapeutic guideline was published in 2000. Initially, treatment involved conventional alfainterferon 2a and 2b monotherapy; then, peginterferon 2a or 2b plus ribavirin regimen (since 2000).[34]

In 2012, the new direct-acting antiviral drugs (DAA) – boceprevir and telaprevir – were included as part of the therapeutic regimen. In 2015, three additional DAA were incorporated – sofosbuvir, daclatasvir and simeprevir. The adoption of DAA in the treatment has been a landmark in terms of the increase of the Ministry of Health expenditure, as shown in Chart 14, highlighting real concerns related to the sustainability of the access policy.

The period considered for this is study is related to the beginning of centralisation of the purchases of Hepatitis C medicines by the Ministry of Health in 2006 until 2016.

The Hepatitis C market has been sensitive to adoption of newer technologies. Since

2006 and 2007, the increase in expenditure was reflected by the procurement of peginterferon 2a and 2b and also by the increase in volume. Due to price reductions of those technologies between 2007 and 2011, it was possible to have a decrease in expenditure followed by an increase in volume purchased. The adoption of DAA had a significant increase in expenditure, as shown from 2012 to 2016. In 2015, the procurement of only four DAA achieved BRL 1 billion. Considering only sofosbuvir, the volume purchased in 2015 and 2016 was equivalent, respectively, to 31,956 and 35,056 treatments (considering 84 tablets per treatment).

The evolution of the Hepatitis C pharmaceutical market in Brazil was based on data collected from the Ministry of Health based on expenditure from 2006 to 2016. From the period 2006 to 2014, this did not include data on procurement direct from the public manufacturer on ribavirin. However, according to Chaves et al. (2017), the weight of ribavirin in the cost of the treatment is residual compared to the weight of other medicines such as peginterferon and later DAAs in therapeutic regimens. For 2015 and 2016, as the data was collected directly from Access to Information Law, there was no procurement of ribavirin from any supplier.

This aggregate annual data was adjusted to the inflation of 2016 by adopting the IPCA index (Chart 14). From these values, we calculated the average growth rate of the market. A Compound Annual Growth Rate (CAGR) formula was adopted and estimated considering the evolution of the market adjusted by the inflation, as follows: (a) CAGR (2006, 2016) = 33%. However, for the purpose of this study, we applied the annual rate of market increase observed from 2015-2016 (2%), considering the inclusion of newer DAA in 2015 and the historical tendency of smaller market increase in years following big changes in treatment guidelines.

Chart 14 - Estimated public expenditure on Hepatitis C medicines in Brazil, 2006-2016.

Year	Total expenditure in current values (unadjusted) (BRL)	Total expenditure adjusted to inflation* (BRL)	Annual variation of public expenditure on Hepatitis medicines (%)
2006	33,270,968.71	60,759,684.23	
2007	256,493,132.28	448,410,508.67	638%
2008	241,256,933.87	398,275,768.88	-11%
2009	226,397,587.44	358,302,575.40	-10%

Year	Total expenditure in current values (unadjusted) (BRL)	Total expenditure adjusted to inflation* (BRL)	Annual variation of public expenditure on Hepatitis medicines (%)
2010	213,405,327.60	318,894,056.09	-11%
2011	260,874,119.62	366,034,950.74	15%
2012	239,213,713.38	317,123,043.62	13%
2013	165,318,477.85	206,931,286.65	35%
2014	372,872,988.60	438,614,758.43	112%
2015	945,554,000.84	1,005,027,205.75	129%
2016	1,024,694,075.88	1,024,694,075.88	2%
Annual rate of market increase			33%

* Values adjusted to inflation according to IPCA 2016.
Source: Ministry of Health, Brazil. SIASG for 2006 to 2014, apud Chaves et al. 2017. From 2006 to 2014, the data does not include information about procurement direct from the public manufacturer on ribavirin. 2015 and 2016 data was available from the Access to Information Law.

The calculation of the average of inclusions and exclusions of medicines for Hepatitis C was based on historical data available in the national therapeutic guidelines (Chart 15 and Chart 16). For purpose of the base scenario, we considered those averages for the period of 2017-2051. For 2016, we considered the exclusion of two DAA (boceprevir and telaprevir).

Chart 15 - Inclusion and exclusion of new medicines for Hepatitis C. Brazil, 2000-2016

Year	Inclusion	Entry with exclusivity	Exclusion
2000	3	0	-
2001	-	-	-
2002	-	-	-
2003	-	-	-
2004	-	-	-
2005	-	-	-
2006	2	2	-
2007	-	-	-
2008	-	-	-
2009	-	-	-
2010	-	-	-
2011	-	-	-
2012	2	2	-
2013	-	-	-

2014	-	-	-
2015	3	3	-
2016	-	-	2

Chart 16 - Average of inclusions and exclusions of Hepatitis C medicines in Brazil, 2006-2016

Data	Number	Average of inclusion/ exclusion per year
Number of inclusions 2006 - 2016	10	0.59
Number of exclusions 2006 - 2016	2	0.12

From the total of eight medicines available for Hepatitis C in 2016, only three were non-exclusive (conventional alfainterferon 2a and 2b and ribavirin) (Chart 17). Ribavirin was the only one identified as locally produced.

Chart 17 - Assessment of market exclusivity situation for Hepatitis C drugs in 2016 in Brazil

Product	Patent status in 2016	Market situation in 2016
Alfainterferon 2a	-	Non-exclusive
Alfainterferon 2b	-	Non-exclusive
Alfapeginterferon 2a	Granted	Exclusive

Product	Patent status in 2016	Market situation in 2016
Alfapeginterferon 2b	Withdrawn	Exclusive (only one producer with market approval and purchases under exclusivity regime)
Ribavirin	-	Non-exclusive
Boceprevir	Pending patent application	Exclusive
Telaprevir	Pending patent application	Exclusive
Sofosbuvir	Pending patent application	Exclusive
Daclatasvir	Pending patent application	Exclusive
Simeprevir	Pending patent application	Exclusive

In order to estimate the number of API losing patent protection (AOPPi), we considered the oldest granted patent or pending patent application (Chart 18).

Chart 18 - Estimate of API of Hepatitis C medicines losing patent protection in Brazil

Product	Patent number	Estimated expiry (year)
Alfapeginterferon 2a	PI9703421	01/06/2017
Alfapeginterferon 2b	PI9809425	27/04/2018
Sofosbuvir	PI0111127-2	31/12/2026

Daclatasvir	PI0716483-1	08/08/2027
Simeprevir	PI0506945	31/12/2026

Although in 2016, procurements were only for three exclusive products, there were eight products available for the treatment according to the therapeutic guideline. In the historical data, it can be observed that the government purchased medicines in alternate years, considering stocks from previous years. For this reason, we considered the market of 2016 as having eight medicines.

The proportion of sales under exclusivity was based on historical available data (Chart 19). From 2006 to 2016, the exclusive market had been 99-100%, which is a major difference from the ARV market. It is important to highlight that, from the data available, the non-exclusive market-share in terms of sales is nearly residual (Chart 20). As this data is only used to simulate changes in the domestic industry, which was not applied for the Hepatitis C case, we assumed the share of domestic production as 0%. This does not interfere at all in the simulation of changes in expenditure.

Chart 19 – Market-share (%) of exclusive and non-exclusive products for Hepatitis C in Brazil, 2006-2016.

Product	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Alfainterferona 2a	1.19	0.001	0.001	0.006				0.014	0.001		
Alfainterferona 2b	1.00						0.008				
Alfapeginterferona 2a	97.71	39.69	51.41	49.50	99.99	65.18	0.014	65.92	34.71		
Alfapeginterferona 2b	1.00	60.30	48.57	50.48		34.81		34.05			
Ribavirin	0.04	0.007	0.004	0.001	0.001	0.001	0.001				
Boceprevir							21.48			2.51	

Product	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Telaprevir							78.48		65.28		
sofosbuvir										71.79	72.68
daclatasvir										18.19	23.31
simeprevir										7.49	4.00
% non-exclusive	2.23	0.008	0.005	0.007	0.001	0.001	0.009	0.014	0.001		
% exclusive	98.71	99.99	99.99	99.99	99.99	99.99	99.99	99.98	99.99	100	100

Chart 20 – Assumption of market share of Hepatitis C according to the market exclusivity situation in 2016

Market share of API under exclusive market	99%
Market share of API on non-exclusive market	1%
Market share of domestic industry under exclusive market	0%
Market share of domestic industry under non-exclusive market	0%

To estimate the average of price reduction (RPec) after generics enter the market, we considered the prices of generic versions available in the international market, as there were no generics for Hepatitis C medicines available in Brazil. If patent barriers were overcome in 2016, the only generic options would have been those from the international market. For this reason, we estimated an average difference (Chart 21) between the price paid by the Brazilian government in 2016 and the price of an Indian generic option for sofosbuvir and daclatasvir, the ones that had information available, and found an average reduction of 92%; which means brand price if 12.5 times higher than the generic.

Chart 21 - Estimated price reduction of selected Hepatitis C medicines

Product	Brazil unit price (2016) BRL	Generic unit price (2016) BRL (1)	Price difference (%)
Sofosbuvir 400mg			91.88%
Daclatasvir 60mg	252.92	19.19	92.41%
Average reduction	93.81	7.61	92.14% (rounded to 92%)

* All prices were adjusted to inflation according to IPCA 2016
** Exchange rate:US$1= R$3.49
(1) HepCAsia, Generic DAAs pricing, Market price, 2016.

The average time between patent application and regulatory approval (DT) was estimated based on the data of the first market approval in Brazil and the oldest patent application in the country (Chart 22).

Chart 22 - Time between patent application and market registration of Hepatitis C medicines in Brazil

Product	Brazilian patent number	Patent application date*	Market registration date	Time lag: patent application / market registration (years)
Alfapeginterferona 2a	PI9703421	02/06/1997	27/12/2001	4.57
Alfapeginterferona 2b	PI9809425	28/04/1998	02/01/2006**	7.69

Product	Brazilian patent number	Patent application date*	Market registration date	Time lag: patent application / market registration (years)
Boceprevir	PI0112540	19/07/2001	25/07/2011	10.02
Telaprevir	PI0911673	23/04/2009	31/10/2011	2.52
sofosbuvir	PI0111127	23/05/2001	27/03/2015	10.94
daclatasvir	PI0716483	09/08/2007	06/01/2015	7.42
simeprevir	PI0506945	28/01/2005	11/03/2015	10.12
Average				**7.61 (rounded to 8)**

*The oldest patent application in Brazil for each product was considered.
**The market authorisation currently available on the Anvisa website was obtained on 03/01/2011. However, the product was incorporated in the 2006 treatment protocol, which makes the 2011 date incoherent for obtaining the first market authorisation. Therefore, we assume that the first market authorisation was obtained in 2006.

All these parameters are summarised in the table below, referring to the various scenarios calculated in the prospective simulation (Chart 23).

Chart 23 - Prospective simulation, parameters used for ARV market

Fixed param.	Base scenario	Alternative scenario 1 (w/o art. 40 ext.)	Alternative scenario 2 (reg. delay ext.)	Alternative scenario 3 (data exclus.)	Alternative scenario 4 (base + data excl. + reg. ext.)
YI	2016	2016	2016	2016	2016
YL	2051	2051	2051	2051	2051
TAPto	8	8	8	8	8
MVto	BRL 1,024,694,075.88	BRL 1,024,694,075.88	BRL 1,024,694,075.88	BRL 1,024,694,075.88	BRL 1,024,694,075.88
α	0.02	0.02	0.02	0.02	0.02
d	0.03	0.03	0.03	0.03	0.03
k_{de}	0	0	0	0	0
k_{dc}	0	0	0	0	0
Scenario-Specific	**Base scenario**	**Alternative scenario 1**	**Alternative scenario 2**	**Alternative scenario 3**	**Alternative scenario 4**
YP	1997	1997	1997	1997	1997
YDP	2051	2051	2051	2051	2051
PD	20	20	20	20	20

Scenario-Specific	Base scenario	Alternative scenario 1	Alternative scenario 2	Alternative scenario 3	Alternative scenario 4
DT	8	8	8	8	8
PDE	4	0	9	4	9
pPDE	0.4	0.4	0.4	0.4	0.4
TTC	0	0	0	0	0
DE	0	0	0	5/8	5/8
RPec	12.5	12.5	12.5	12.5	12.5
e	0	0	0	0	0
Annual Input	Base scenario	Alternative scenario 1	Alternative scenario 2	Alternative scenario 3	Alternative scenario 4
Ali	0.58	0.58	0.58	0.58	0.58
AOI	0.11	0.11	0.11	0.11	0.11
AIPPi	0.41	0.41	0.41	0.41	0.41

3. Results: the impact on ARV and Hepatitis C public expenditure and domestic production sales of ARV

3. Results: the impact on ARV and Hepatitis C public expenditure and domestic production sales of ARV

The results were obtained by comparing the base scenario to the alternative scenarios. The base scenario considers the market in 2015 for ARV and in 2016 for Hepatitis C and no change in the IP regulation in Brazil. Therefore, the base scenario includes the patent term extension due to patent examination delay contained in the sole paragraph of article 40 of Brazilian patent law. The period of 35-years was adopted to allow the necessary time for the changes in IPR to take full effect in the pharmaceutical market.

The alternative scenarios in the prospective model were as follows:

a) Alternative scenario 1 – the absence of the article 40, sole paragraph, related to patent term extension based on patent examination delay;

b) Alternative scenario 2 – the adoption of patent term extension due to market authorisation delay;

c) Alternative scenario 3 – the adoption of data exclusivity for a period of 5 and 8 years;

d) Alternative scenario 4 – the adoption of both data exclusivity (5 and 8 years) and patent term extension due to delay in market authorisation.

3.1. Base scenario

Chart 24 - Base scenario: evolution of ARV expenditure and domestic production market, 2015-2050

Year	Proportion of API under exclusivity (pei)	ARV market in expenditure (BRL) (MVi)	Domestic production market in sales (BRL) (MVDi)
		Adjusted to inflation	Adjusted to inflation
2015	0.36	1,119,149,617.60	598,236,341.05
2050	0.27	2,952,875,834.63	1,818,848,610.65

The figure of approximately BRL 1.1 billion spent on ARV medicines was obtained from the Brazilian MoH. Considering an average growth of 3% from 2008 to 2015 (adjusted to inflation), it is estimated that without any change in the current industrial property legislation, the ARV market will nearly triple in 2050 in comparison to 2015. Domestic production sales would have an increase of BRL 1.8 billion in 2050 compared to 2015 (Chart 24).

For Hepatitis C, considering an average growth of 2% in the government expenditure with medicines would go from BRL 1.02 billion in 2016 to BRL 2.49 in 2051 (Chart 25).

Chart 25 - Base scenario: evolution of Hepatitis C expenditure, 2016-2051

Year	Proportion of API under exclusivity (pei)	Hepatitis C market in expenditure (R$) (MVi)
2016	0.67	1,024,694,075.88
2051	0.25	2,049,274,977.03

3.2. Alternative scenario 1: Base scenario without the patent term extension due to patent examination delay

This simulation was conducted in order to estimate the impact on government spending in ARV and Hepatitis C and in the participation of domestic production in the ARV market in case of exclusion of the patent term extension due to patent examination delay provided for under article 40 (sole paragraph) of the Brazilian patent law.

Chart 26 - Alternative scenario 1: evolution of ARV expenditure and domestic production market, 2015-2050

Year	Proportion of API under exclusivity (pei)	ARV market (BRL)		Domestic production market (BRL)	
		Base scenario	Variation in expenditure	Base scenario	Variation in domestic production sales
2015	0.36	1,119,149,617.60		598,236,341.05	
2050	0.24	2,952,875,834.63	-113,450,287.64	1,818,848,610.65	609,235.12
Cumulative (2015-2050)			-2,054,436,157.85		92,371,220.99

If this TRIPS-provision was excluded from Brazilian law, there would be a reduction in total spending with ARV of almost BRL 113 million in 2050 alone. **The cumulative reduction between 2015 and 2050 would be more than BRL 2.05 billion.** Domestic production would benefit from this change in the patent law, as ARV sales would be BRL 92 million higher than the base scenario from 2015 to 2050 (Chart 26).

For Hepatitis C medicines, savings would be of BRL 747 million in 2051 alone and achieve BRL 16 billion from 2016-2051 (Chart 27).

Chart 27 - Alternative scenario 1: evolution of expenditure on Hepatitis C medicines, 2016-2051

Year	Proportion of API under exclusivity (pei)	Market for Hepatitis C medicines (BRL)	
		Base scenario	Variation in expenditure
2015	0.67	1,024,694,075.88	
2050	0.22	2,049,274,977.03	-742,781,710.26
Cumulative (2016-2051)			-16,862,109,838.52

3.3. Alternative scenario 2: Base scenario with the adoption of patent term extension as consequence of delay in regulatory market authorisation

Alternative scenario 2 assumes the adoption of a patent term extension due to a delay in obtaining regulatory market approval, as proposed in the EU proposal. In practice, this is the cumulative effect of the existing patent term extension due to delay in patent examination already contained in the Brazilian law (sole paragraph of article 40) and the extension due to market authorisation delay. This scenario assumes there would be a patent term extension for market authorisation delays beginning in the year 2015 for ARV and in 2016 for Hepatitis C medicines.

As shown in Chart 28, **the cumulative increase in ARV expenditure from 2015 to 2050 would be around BRL 1.25 billion,** while the decrease in the market-share on sales from domestic production would be around BRL 102 million (Chart 28).

For Hepatitis C medicines (Chart 29), **the cumulative increase in expenditure from 2016 to 2051 would be around BRL 16 billion.**

Chart 28 - Alternative scenario 2. Evolution of ARV expenditure and domestic production market, 2015-2050

Year	Proportion of API under exclusivity (pei)	ARV market (BRL)		Domestic production market (BRL)	
		Base scenario	Variation in expenditure	Base scenario	Variation in dom. production sales
2015	0.36	1,119,149,617.60		598,236,341.05	
2050	0.29	2,952,875,834.63	94,541,906.37	1,818,848,610.65	-4,810,604.71
Cumulative (2015-2050)			1,255,011,241.61		-102,019,013.39

Chart 29 - Alternative scenario 2. Evolution of expenditure on Hepatitis C medicines, 2016-2051

Year	Proportion of API under exclusivity (pei)	Market for Hepatitis C medicines (BRL)	
		Base scenario	Variation in expenditure
2016	0.67	1,024,694,075.88	
2051	0.29	2,049,274,977.03	928,477,137.82
Cumulative (2016-2051)			16,326,989,040.47

3.4. Alternative scenario 3: Base scenario with the adoption of data exclusivity of 5 or 8 years

This scenario assumes there would be data exclusivity in Brazil beginning in the year 2015 for ARV market analysis and in 2016 for Hepatitis C medicines. As there is no specific time set in the EU proposal, we considered the minimum time of 5 years established in some FTA and 8 years in others.

From 2015 to 2050, the adoption of 5 years data exclusivity would result in a cumulative **increase in ARV expenditure of BRL 2.4 billion** and a reduction in sales from domestic industry of BRL 237 million. When simulating with the 8 years of data exclusivity, for the same period, the cumulative **increase in ARV expenditure would be around BRL 3.7 billion** and a reduction in sales of the domestic industry of around BRL 423 million (Chart 30).

From 2016 to 2051, the adoption of 5 years data exclusivity would result in a cumulative **increase in Hepatitis C medicines expenditure of BRL 31 billion.** When simulating with the 8 years of data exclusivity, for the same period, the cumulative **increase in Hepatitis C medicines expenditure would be around BRL 47 billion** (Chart 31).

Chart 30 - Alternative scenario 3: Evolution of ARV expenditure and domestic production market, 2015-2050

Year	Proportion of API under exclusivity (pei)	ARV market (BRL)		Domestic production market (BRL)	
		Base scenario	Variation in expenditure as consequence of 5y data exclusivity	Base scenario	Variation in dom. prod. sales as consequence of 5y data exclusivity
2015	0.36	1,119,149,617.60		598,236,341.05	
2050	0.29	2,952,875,834.63	87,538,802.19	1,818,848,610.65	-4,320,116.33

Cumulative (2015-2050)			2,452,784,149.22		-237,064,189.84
Year	Proportion of API under exclusivity (pei)	Base scenario	Variation in expenditure as consequence of 8y data exclusivity	Base scenario	Variation in dom. prod. sales as consequence of 8y data exclusivity
2015	0.36	1,119,149,617.60		598,236,341.05	
2050	0.30	2,952,875,834.63	140,062,083.51	1,818,848,610.65	-8,521,953.72
Cumulative (2015-2050)			3,740,179,503.19		-423,690,419.73

Chart 31 - Alternative scenario 3: Evolution of expenditure on Hepatitis C medicines, 2016-2051

Year	Proportion of API under exclusivity (pei)	Market for Hepatitis C medicines (BRL)	
		Base scenario	Variation in expenditure as consequence of 5 years data exclusivity
2016	0.67	1,024,694,075.88	
2051	0.29	2,049,274,977.03	873,570,516.39
Cumulative (2015-2050)			31,451,189,948.91

Year	Proportion of API under exclusivity (pei)	Base scenario	Variation in expenditure as consequence of 8 years data exclusivity
2016	0.67	1,024,694,075.88	
2051	0.31	2,049,274,977.03	1,428,806,014.09
Cumulative (2016-2051)			47,861,780,962.03

3.5. Alternative scenario 4: Base scenario with the adoption of patent term extension due to market authorisation delay and data exclusivity for 5 or 8 years

This alternative scenario simulates the effect of all previous provisions together. This is what would happen if the EU's proposed text was approved as it is and no other changes are made at the current Brazilian IP law.

Considering 5 years of data exclusivity plus extension of patent term for regulatory delay, **additional spending on ARV would reach BRL 182 million in 2050 alone, and BRL 3.7 billion in aggregate from 2015 to 2050** (Chart 32). Domestic industry sales would decrease by BRL 12 million in 2050 and BRL 393 million in aggregate in the same period. If the period of 8 years for data exclusivity was adopted, **there would be BRL 4.99 billion in additional spending from 2015 to 2050 and BRL 612 million in losses for the domestic industry in the same period.**

For the Hepatitis C market, considering 5 years of data exclusivity plus extension of patent term for regulatory delay, **additional spending would reach BRL 1.7 billion in 2051 alone, and BRL 46 billion in aggregate from 2016 to 2051** (Chart 33). If the period of 8 years for data exclusivity was adopted, **there would be BRL 63 billion in additional spending from 2016 to 2051.**

Chart 32 - Alternative scenario 4: Evolution of ARV expenditure and domestic production market, 2015-2050

Year	Proportion of API under exclusivity (pei)	ARV market (BRL)		Domestic production market (BRL)	
		Base scenario	Variation in expenditure – reg. ext + 5 years data exclusivity	Base scenario	Variation in dom. production sales reg. ext + 5 years data exclusivity
2015	0.36	1,119,149,617.60		598,236,341.05	
2050	0.31	2,952,875,834.63	182,080,708.56	1,818,848,610.65	-12,752,698.13

Cumulative (2015-2050)			3,707,795,390.84		- 393,412,112.51
Year	Proportion of API under exclusivity (pei)	Base scenario	Variation in expenditure – reg. ext + 8 years data exclusivity	Base scenario	Variation in dom. production sales reg. ext + 8 years data exclusivity
2015	0.36	1,119,149,617.60		598,236,341.05	
2050	0.33	2,952,875,834.63	234,603,989.87	1,818,848,610.65	-19,127,721.77
Cumulative (2015-2050)			4,995,190,744.80		- 612,635,671.97

Chart 33 - Alternative scenario 4: Evolution of expenditure on Hepatitis C medicines, 2016-2051

Year	Proportion of API under exclusivity (pei)	Base scenario	Variation in expenditure as consequence of patent extension due to market authorisation delay + 5 years data exclusivity
2016	0.67	1,024,694,075.88	
2051	0.33	2,049,274,977.03	1,737,270,179.48
Cumulative (2016-2051)			46,639,086,730.75

Year	Proportion of API under exclusivity (pei)	Base scenario	Variation in expenditure as consequence of patent extension due to market authorisation delay + 5 years data exclusivity
2016	0.67	1,024,694,075.88	
2051	0.35	2,049,274,977.03	2,292,505,677.18
Cumulative (2016-2051)			63,049,677,743.86

4. Discussion of results and implications for health policies

4. Discussion of results and implications for health policies

In 2015, the United Nations Secretary-General established a High Level Panel (HLP) on Access to Medicines in order to address the policy incoherence between the rights of inventors, international human rights law, trade rules and public health in the context of health technologies. One of the recommendations of the report,[11] published in 2016, was as follows:

"Governments engaged in bilateral and regional trade and investments treaties should ensure that these agreements do not include provisions that interfere with their obligations to fulfil the right to health. As a first step, they must undertake public health impact assessments. These impact assessments should verify that the increased trade and economic benefits are not endangering or impeding the human rights and public health obligations of the nation and its people before entering into commitments. Such assessments should inform negotiations, be conducted transparently and made publicly available" (p.9).

The HLP also recommends the adoption of measures to avoid undue commercial pressure from the private sector in the negotiation of any change in IPR that can lead to undermining the use of TRIPS flexibilities (p.9), which is the case of some measures proposed by the EU that increase market exclusivity.

The present study aims at providing additional evidence on the effect that adopting the TRIPS-plus provisions proposed by the EU during the negotiations of a free trade agreement with Mercosur could have, for guaranteeing universal access to medicines in Brazil.

This study adds to previous ones by allowing a prospective simulation comparing four possible scenarios, including the cumulative effect of TRIPS-plus provisions proposed by the EU, with an already TRIPS-plus scenario enforced by the sole paragraph of article 40 in Brazilian industrial property legislation that allows for patent term extension due to delay in patent examination. The present study also provides an estimation of the effect of adopting the data exclusivity provision for a period of 5 and 8 years in ARV expenditure and domestic production sales, as

well on Hepatitis C medicines expenditure, which has not been done so far in previous studies.

The purpose of analysing two disease groups of medicines is to show the difference between the two markets, from where the simulation starts, and the level of risks that TRIPS-plus provisions might have on each scenario.

The ARV market and generic competition has been possible thanks to local production, before the adoption of the new patent law, and to the use of public health TRIPS flexibilities – compulsory license and patent oppositions – for some patented medicines. The issue of a compulsory license of efavirenz allowed generic competition 6 years before the patent expiration date. Price reductions of medicines under exclusivity have also been possible thanks to strategies of price negotiations, by using estimates of cost of production by national public laboratories and threats to issue a compulsory license.

The use of patent oppositions for tenofovir patent applications overcame the *de facto* monopoly created by pending applications. It also contributed to the adoption of generic fixed-dose-combinations containing TDF in 2014.

The Hepatitis C market has a completely different panorama. From 2006 to 2016, its market-share (expenditure) has been almost a 100% with products under exclusivity, with significant increases in expenditure. The most recent one was from 2014 to 2015, from BRL 438.6 million in 2014 to BRL 1 billion in 2015 due to the adoption of the newer DAA sofosbuvir, daclatasvir and simeprevir, with therapeutic regimens costing per treatment USD 8,742 (sofosbuvir+daclatasvir) and USD 8,802 (sofosbuvir+simeprevir).

The market-share of non-exclusive products has been residual and there has not been generic competition. In 2016 and 2017, civil society groups and a public manufacturer filed patent oppositions for sofosbuvir patent applications, but so far it has not resulted in overcoming patent barriers and promotion of generic competition. **Therefore, the use of public health TRIPS-flexibilities have not resulted in effective generic competition yet.**

Recent estimates assumed that if the 1.4 million people with HCV were eligible for the SOF + DAC treatment (USD 8,732), the resources required to treat everyone in need would be USD 12.2 billion or BRL 40.7 billion. This amount represents 3.3 times the amount the Brazilian Ministry of Health spent on medicines (R$ 12.4 billion) in 2014. Therefore, the prices of the newer DAA are really threatening the commitment of SUS of universal access to treatment.[34]

The challenges of ensuring access to Hepatitis C medicines are not only for developing countries, but also for developed countries. In France, it was estimated that if all the 127,700 people eligible were treated with sofosbuvir, the cost would be higher than the budget for the Public Hospital System of Paris (Assistance Publique des Hôpitaux de Paris) in 2014.[35] This is because the cost per treatment when DAAs were launched in France was € 56,000; therefore, the total spending of treatment would reach 7.15 billion Euros.

In the present study, for the ARV simulation of the impact of TRIPS-plus provision, the estimates were conservative by adopting an annual growth rate of 3% of the ARV market. This was estimated from ARV expenditure from 2008 to 2015 adjusted to inflation. This is coherent with historical data on ARV expenditure in Brazil which shows that annual spending has been relatively stable against the annual increase of people living with HIV on treatment. However, this is likely to change as of 2013 onwards, as a new treatment guideline was adopted in the end of 2013 to treat everyone living with HIV regardless of CD4 count. This is reflected in Chart 4, where the number of people under treatment increased more in 2014 and 2015 than in previous years.

However, even using a conservative estimation, the results shown in the previous session of the present study are impressive.

Alternative scenario 4 shows the potential impact of the adoption of the EU proposal on the public expenditure only related to ARV in Brazil, which would lead to an increase of BRL 4.9 billion in a 35-years period, or a simple average of BRL 142 million per year (regulatory delay and 8 years data-exclusivity). **This is equivalent to the annual public expenditure on health of 100,517 persons in Brazil.**[u] Considering that the provisions adopted at the FTA would impact the entire pharmaceutical market in Brazil, the increase on public expenditure of medicines would be much higher.

When analysing the effects of TRIPS-plus provisions in the **participation of local manufacturers in the ARV market**, relevant information is also obtained with different scenarios simulated by this study. The results show that if both TRIPS-plus provisions were adopted as proposed by the EU, **there would be a decrease in domestic production of BRL 393 million (5 years DE) and BRL 612 million (8 years DE) from 2015 to 2050.**

For the Hepatitis C market, considering 5 years of data exclusivity plus extension of patent term for regulatory delay, a**dditional spending would reach BRL 1.7 billion in 2051 alone, and BRL 46 billion in aggregate from 2016 to 2051** (Chart 33). If the period of 8 years for data exclusivity was adopted, **there would be BRL 63 billion in additional spending from 2016 to 2051.**

The four alternative scenarios simulated in this study show that all the three TRIPS-plus provisions have negative impact on the sales of domestic produced medicines, besides increasing public expenditure.

The estimate of the effects of TRIPS-plus provisions in the ARV and Hepatitis C markets provides only a snapshot of the implications of those provisions on the market share of domestic production and on the public expenditure of medicines by the public health system, considering that ARV and Hepatitis C medicines are a fraction of the medicines provided by SUS in Brazil.

For example, the Ministry of Health spending with the Specialized Component of Pharmaceutical Services (CEAF), which includes newer and high-price medicines, has increased from BRL 3.5 billion in 2008 to BRL 6 billion in 2015.[v] Spending on immunobiological products has increased from BRL 977 million in 2008 to

BRL 2.5 billion in 2015.[w] **If the IPRIA model had been applied to those groups of medicines, the effects of the adoption of TRIPS-plus provisions would be even more impressive.**

In the past years, there has been a significant increase in public spending on medicines, most of which are under exclusivity in Brazil.[x] In 2015, the MoH spending on medicines accounted for 13.7% of its entire budget. While federal spending on medicines increased by 74% from 2008 to 2015 (from BRL 8.5 billion to BRL 14.8 billion[y]), the federal health budget only increased by 36.6% in the same period.[23]

While increasing public spending on medicines may reflect an increase in the number of individuals being treated, on the other hand it can also mean an increase in spending on high-price drugs, many of which are under monopolistic situations because they are subject to patent protection (pending patent applications or granted patents).

Second, in 2016, a new tax regime was approved (EC 95/2016) and it will freeze the primary expenditure from the federal government for 20 years, directly affecting health financing. The budget will only be adjusted by inflation and will not follow changes in the Gross Domestic Product (GDP), such as it was in the previous regime. Estimates of losses on federal health financing, considering an increase of 2% of the GDP per year and comparing with the previous tax regime, achieves the total of BRL 415 billion from 2017 to 2036 (an average of BRL 20.7 billion per year).[36] On the other hand, the present study reveals a scenario of increase in public expenditure due to changes in IPR under negotiation in the FTA with the EU, which has an even more harmful effect in light of cutting in health expenditure.

The effects of TRIPS-plus provisions should not only be measured in terms of changes in medicines expenditure and in domestic production. **Their adoption will also reduce the policy space for the use of public health TRIPS flexibilities and other complementary initiatives Brazil has relied on to guarantee universal access to ARV treatment since 1990**, including the participation of local production to estimate costs of production and to supply a significant proportion of the ARV.

The reduction on the domestic production as consequence of the adoption of TRIPS-plus provisions can also undermine the efforts in the past years related to the implementation of industrial policies initiatives to stimulate the local production of API and final products.

Admitting the limitations of the present study, the data is still relevant to illustrate the significant impact of TRIPS-plus provisions on access to medicines policies and provides the basis for Brazil to reject all those provisions during negotiations with the EU on the FTA with Mercosur.

The increase in spending, reflecting challenges in the incorporation of high price monopoly medicines, as well as the potential reduction in the federal financing on health, present an already difficult agenda for achieving sustainability of access

to medicines policies. Therefore, any agreement that presents provisions directly affecting those policies must be rejected, considering the human right to health and the State's assumed obligation to implement progressive policies to fulfil the right to health, and the prohibition of retrocession.

5. Recommendations

5. Recommendations

The estimated additional expenditure of BRL 4.9 billion in the period of 35 years only for medicines used to treat HIV/AIDS and of BRL 63 billion for Hepatitis C medicines with the adoption of two of the TRIPS-plus provisions proposed by the EU is clear evidence of the harmful effect of these measures on public policies that aim at fulfilling the right to health in Brazil. The average of BRL 142.7 million of additional expenditure for ARV per year is equivalent to the HIV treatment of 57,975 people per year. Furthermore, the adoption of those measures would also have a negative impact on domestic industry, reducing sales and going against national development.

The Brazilian government determines the protection of industrial property with the aim of achieving economic and technological development, and promoting social interest (article 5, XXIX). The adoption of the TRIPS-plus measures proposed by the EU are against both those objectives. Considering the need for coherence between public policies in different areas we recommend the non-adoption of any TRIPS-plus provision that extends market exclusivity by Mercosur in its Free Trade Agreement with the European Union.

We also recommend that the Brazilian government and other countries involved in the negotiation of the FTA conduct an impact study in the field of public health and human rights, as recommended recently by the UN High Level Panel on Access to Medicines. The impact studies should be conducted transparently and be made publicly available.

The negotiations of the FTA should be transparent and all draft texts and proposals from all parties involved should be publicly disclosed and public consultations should be held to allow the participation of all sectors of society.

Furthermore, we recommend that the Brazilian government make all efforts necessary to exclude TRIPS-plus measures already foreseen in national IP legislation, especially the removal of the provision included in the sole paragraph of article 40 of the patent law that allows for patent term extension due to delay in patent examination. This recommendation is due to the huge negative impact it has on policies of universal access to health and national development.

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End Notes:

[a]The authors would like to thank Dr. Joan Rovira and Miguel Cortes, developers of the IPRIA Model, for their valuable advice, review and comments on the application Model that was used in this study to estimate the impact of changes in intellectual property regulations. However, the authors are responsible for the collection and selection of the data used to feed the Model and for running it, as well as for all the assumptions made along the study and are solely responsible for the results, analysis and police recommendations made in this report.

[b]Guide to the IPRIA (Intellectual Property Rights Impact Aggregate) Model (2009). Available at https://www.ictsd.org/sites/default/files/event/2010/03/guide-to-the-ipria-model.pdf

[c]During the negotiations of the TRIPS Agreement, in the Uruguay Round of GATT, the Intellectual Property Committee (IPC) advised the United States, in conjunction with other developed countries. The IPC was composed of the following companies: Bristol-Myers, CBS, Du Pont, General Electrics, General Motors, Hewlett-Packard, IBM, Johnson & Johnson, Merck, Monsanto, Pfizer (Sell, 2003).

[d]Available at: http://trade.ec.europa.eu/doclib/docs/2016/november/tradoc_155070.pdf. Last accessed on 21/08/17.

[e]For the full version of the preliminary report, please see: http://accessibsa.org/media/2017/12/EU-Mercosur-Free-Trade-Agreement.pdf (English version) and http://accessibsa.org/media/2017/12/Tratado-de-Livre-Come%CC%81rcio-Unia%CC%83o-Europeia-Mercosul.pdf (Portuguese version).

[f]The WTO TRIPS Agreement allows countries to choose the regime of exhaustion of IPR they will adopt. Brazilian patent law adopted the regime of national exhaustion of IPR (article 43), therefore restricting parallel imports. There are 2 bills ongoing at the National Congress proposing to change the regime of exhaustion of IPR to the international regime (PL 139/99 and PL 8091/2014).

[g]The six ARVs analysed were: abacavir, amprenavir, efavirenz, lopinavir/ritonavir, nelfinavir and ritonavir.

[h]The nine medicines were: adalimumab, erlotinib, maraviroc, raltegravir, cinacalcet, sofosbuvir, trastuzumab emtansine, gefitinib, etravirine. The study considered the price difference between the Brazilian price and the lowest generic price, when available, or a 40% difference in the absence of generics in the international market.

[i]There have been patent oppositions filed in Brazil against patent applications

related to sofosbuvir and daclatasvir, by Farmanguinhos/Fiocruz and GTPI/Rebrip – Intellectual Property Working of the Brazilian Network for the Integration of the Peoples, a group of Brazilian civil society organisations. A final decision from the Brazilian patent office is still pending in both cases.

[j]We also looked at two other sources: the Public Transparency Portal (Portal da Transparência), which gathers information on public spending by all branches of the Federal Administration; and the Health Prices Bank (Banco de preços em saúde), an online repository of public purchases of medicines. These two were abandoned in favour of the former because in the data provided by the MoH the information was more complete, especially since the previously mentioned databases don't include information of purchases from public laboratories.

[k]www.anvisa.gov.br

[l]www.inpi.gov.br

[m]It should be noted that during the time in which the patent application is pending analysis, there is a de facto monopoly due to the risk of entering the market and facing litigation or the payment of damages in case the patent is granted. This will be further developed in another study under the accessibsa Project.

[n]This interpretation is based on existing regulations on the subject: e.g., U.S. law: "patent term extension that may be available under 35 U.S.C. 156 for premarket regulatory review is separate from and will be added to any extension that may be available under former and current 35 U.S.C. 154".

[o]This issue is currently under development in another study of the accessibsa project and results are expected to be released early 2018.

[p]The current patent law, which establishes product patents for pharmaceuticals, was enacted in 1996 and went into effect in 1997. It should be noted that the law allowed for the granting of pharmaceutical patents retrospectively, through the mechanism known as "pipeline". The model takes into consideration patents in force before the base year.

[q]Exclusivity of test data doesn't exist under the current Brazilian law for health products of human use. Thus, the year for its introduction was initially set to the final simulation year, so it wouldn't affect the final result. This is changed in alternative scenarios to simulate the effect of adopting data exclusivity.

[r] This data was calculated case by case for the 24 ARV based on patent and sanitary registration information, and then an average was calculated.

[s]Considering that provision of antiretroviral is mandated by law, we expect demand not to vary with price hikes, thus it is inelastic, that is, its price-elasticity equals zero.

[t]This number was estimated based on the average of inclusions in 24 years (27 inclusions). The data on entries and exits were obtained from public therapeutic

protocols.

[u]The Brazilian public expenditure on health in the year 2014 was of BRL 1,419.85 (USD 604.20) per person, according to a study publish by the Conselho Federal de Medicina (CFM). Available at: https://portal.cfm.org.br/index.php?option=com_content&view=article&id=25985:2016-02-18-12-31-38&catid=3.

[v]Values were adjusted to inflation 2016.

[w]Values were adjusted to inflation 2016.

[x]Another study under the IBSAccess Project is analysing the exclusivity status of high-cost medicines purchased by the public health system in Brazil. First results are expected to be released by early 2018.

[y]Values adjusted to the inflation of 2016 (David et al.2016)

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About the project:

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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

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Gabriela Costa Chaves, Walter Gaspar Britto and Marcela Fogaça Vieira

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