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Article

Decline in Public Spending on Biopharmaceutics in Brazil

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Biopharmaceuticals, mainly monoclonal antibodies, and fusion proteins are drugs that have gained notoriety in the treatment of various chronic and inflammatory diseases and have high prices. The study aimed to verify which monoclonal antibodies and fusion proteins were most incorporated into the Unified Health System (SUS), which therapeutic indication most benefited from them and to analyze public spending on these biopharmaceuticals from January 2012 to September 2019. This study performed a qualitative and quantitative analysis of biopharmaceuticals incorporated by SUS. The data were collected on the websites of CONITEC and the Health Price Bank. The results demonstrated that subcutaneous adalimumab was most frequently incorporated, and the most requested therapeutic indication was rheumatoid arthritis. Public spending on biopharmaceuticals exceeded R$ 28 billion (more than US$ 140 billion). However, a downward trend was confirmed (-266.7%) in the period evaluated. Despite the increase in demand and public spending on biologics in general, in Brazil and worldwide, the results of this research show that there was a drop in public spending on the biopharmaceuticals studied in the last seven years.

Keywords: Incorporation. Health technologies. CONITEC. Biopharmaceuticals. Public spending.

INTRODUCTION

The 1988 Federal Constitution recognized health as a right of all and a duty of the State, in addition to establishing the foundations of the Brazilian Unified Health System (in Portuguese, *Sistema Único de Saúde*, or SUS). With this, the State was obliged to guarantee, through SUS, health care, including public financing that would allow universal and equitable access to medicines and other health technologies to citizens (Caetano *et al*., 2017). Health technologies are drugs, procedures, products, and protocols used in patient care (Santos, Frota, Martins, 2016).

In this scenario, Law No. 12.401/2011 changed Law 8.080/1990 (Organic Law of SUS) and instituted the National Commission for Incorporating Technologies in SUS (CONITEC). It is an organ of the regulatory structure of the Ministry of Health, which assists in the incorporation, exclusion, or alteration of new health technologies in SUS (CONITEC, 2014).

The incorporation of technologies has been the main cause for the increase in the costs of national health systems (Guimarães *et al*., 2019). It is noted that public spending on medicines has been growing in the world, year by year, mainly with biopharmaceuticals (Vieira, 2018).

Biopharmaceuticals, such as fusion proteins and monoclonal antibodies, are complex molecules produced by an organism or cell and are used in medicine to heal, treat, or restore health (Pimenta, Monteiro, 2019). These two groups of biopharmaceuticals have gained attention

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mainly in the treatment of chronic inflammatory diseases in the past two decades (Pinto, Domingos, Centeno, 2014).

It is essential to investigate which monoclonal antibodies and fusion proteins are being incorporated and their therapeutic indications, as these are health technologies that were introduced on the market more recently and have a higher cost compared to other groups of drugs. This information is of great relevance and serves to demonstrate how these technologies have acquired a place in public health in Brazil and how public spending on these technologies has reacted.

These biopharmaceuticals have been increasingly used for certain diseases, such as cancer, Alzheimer's disease, and others, consuming increasing portions of the Unified Health System's medication budget (Pinto, Domingos, Centeno, 2018).

The present study aimed to verify which monoclonal antibodies and fusion proteins have been most incorporated into SUS and the therapeutic indication most benefited, as well as to analyze the annual public expenditures on these biopharmaceuticals from January 2012 to September 2019.

METHODS

This is an exploratory, descriptive, retrospective study, with a qualitative and quantitative approach to the demands for biopharmaceuticals (monoclonal and fusion proteins) submitted to CONITEC in the period from January 1, 2012 to September 30, 2019, that is, the period between the start of CONITEC's activities and the development of this study. Data collection was carried out between March and October 2019. In the document analysis, different secondary data sources were used, mainly in the databases available for consultation on the CONITEC website (link: http://conitec.gov.br/) with the list of incorporated technologies. Regarding government spending data on biopharmaceuticals, it was used on the Health Price Bank website (link: http://www.saude.gov.br/gestao-do-sus/economia-da-saude/banco-de- prices-in-health), a system created by the Brazilian Ministry of Health with the objective of registering and making available online information on public and private purchases of medicines and health products.

Cost data used in the study was taken only from public expenditures made by the union, states, and municipalities during the research period. Data were used from all types of purchases, such as auctions, exemption from bidding, or unenforceable bidding. That is, expenses arising from lawsuits are also included, which justifies spending by states and municipalities in the purchase of some medications under the responsibility of the Union.

As this is a historical series of data on public spending, it was necessary to correct them using the Broad Producer Price Index, according to the Processing Stages (IPA-EP). The amounts were in reais, the currency of Brazil, with the US dollar quoted at R$ 5.28 (exchange rate of March 24, 2020).

The specific demand/technology unit was established to account for each required technology. This means that although a technology has been presented more than once, it has been demanded for different reasons, including (1) different presentation or therapeutic indication than the previous ones; (2) having been requested by different claimants at more than one point in time; or (3) demanded readjustment of use or having been denied in previous analyses.

The data were analyzed descriptively using absolute frequencies and percentages for categorical variables. Soon after, the expenses of states, the federal district and municipalities were added. Federal expenditures were accounted for separately. After being arranged in an Excel spreadsheet, the amounts of each biological medication were added together separately and per year. The data were entered into Excel spreadsheets and the IBM SPSS version 23 program was used to obtain the statistical calculations and generate graphs and tables.

As this is research involving secondary data taken from the websites of public agencies not involving human beings, there was no need for submission to a Research Ethics Committee.

RESULTS

Regarding the class of drugs of interest in the study, it was found that in the period evaluated, 13 monoclonal antibodies and 3 fusion proteins became part of the list of SUS technologies, totaling 16 biologicals, 7 of which

were incorporated more than once and indicated for more than one disease. This led to a count of 29 incorporations (specific demand/technology).

Adalimumab was demanded nine times and incorporated four times. The most frequent demand was for rheumatoid arthritis (Table I).

TABLE I - Anatomic Therapeutic Chemical (ATC) classification, therapeutic indications and the year of incorporation. Brazil, 2012 to 2019

Technology	ATC classification*	Therapeutic indication	Year of incorporation
Trastuzumab[a]	L01XC03	Advanced breast cancer	2012
		Early breast câncer	2012
		HER2-positive metastatic breast câncer	2017
Golimumab[a]	L04AB06	Rheumatoid arthritis	2012
		Ankylosing spondylitis	2016
		Psoriatic arthritis	2016
Certolizumab pegol[a]	L04AB05	Rheumatoid arthritis	2012
		Axial spondyloarthritis	2017
		Moderate to severe Crohn's disease	2018
Rituximab[a]	L01XC02	Rheumatoid arthritis	2012
		Non-hodgkin's lymphoma	2014
Abatacept IV[b]	L04AA24	Rheumatoid arthritis	2012
Tocilizumab[a]	L04AC07	Rheumatoid arthritis	2012
Infliximab[a]	L04AB02	Rheumatoid arthritis	2012
Adalimumab SC[a]	L04AB04	Rheumatoid arthritis	2012
		Non-infectious uveitis	2018
		Psoriasis	2018
		Moderate to severe active suppurative hidradenitis	2018
Etanercept[b]	L04AB01	Rheumatoid arthritis	2012
		Psoriasis	2018
Palivizumab[a]	J06BB16	Respiratory syncytial virus infection	2012
Abatacept SC[b]	L04AA24	Moderate to severe rheumatoid arthritis	2015
Pertuzumab[a]	L01XC13	HER2-positive metastatic breast cancer	2017
Eculizumab[a]	L04AA25	Paroxysmal Night Hemoglobinuria	2018
Ustequinumab[a]	L04AC05	Psoriasis	2018

TABLE I - Anatomic Therapeutic Chemical (ATC) classification, therapeutic indications and the year of incorporation. Brazil, 2012 to 2019

Technology	ATC classification*	Therapeutic indication	Year of incorporation
Secuquinumab[(a)]	L04AC10	Psoriasis	2018
		Ankylosing spondylitis	2018
		Psoriatic arthritis	2019
Brentuximab vedotine[(a)]	L01XC12	Hodgkin's lymphoma	2019

ATC *: Chemical Therapeutic Anatomical Classification; (a): monoclonal antibodies; (b): Fusion proteins; Caption: IV- Intravenous; SC- Subcutaneous.
Source: Own elaboration based on data from CONITEC.

The number of biopharmaceuticals incorporated by therapeutic indication per year varied considerably (Figure 1). The largest number of incorporations occurred in 2012, adding up to 11. In 2013 there was no incorporation and in the following years they increased slightly to a new peak in 2018, with nine technologies. In 2019 it fell again, though the data collection ended in September of that year.

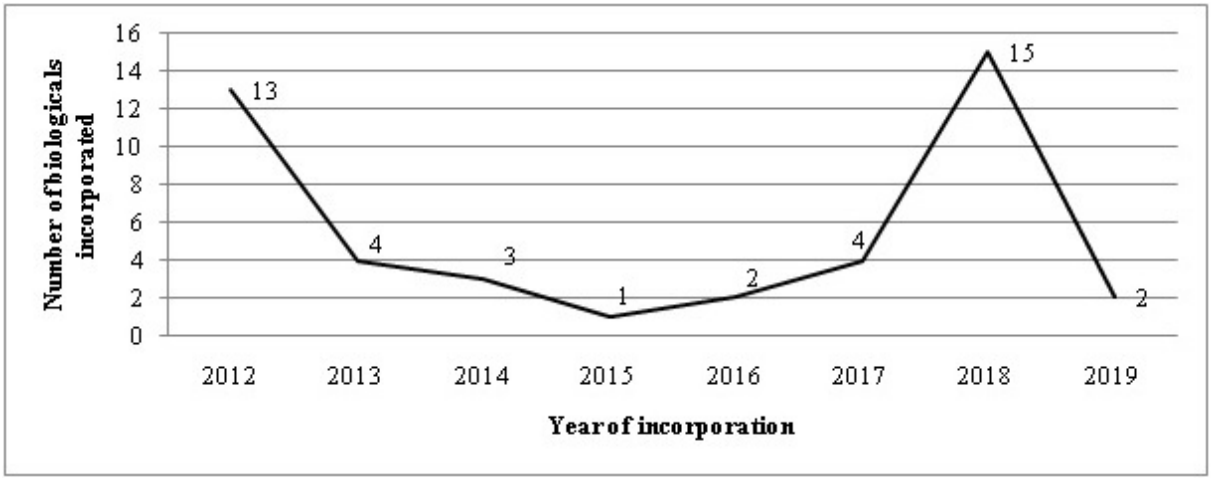

FIGURE 1 - Number of biologics incorporations. Brazil, 2012 to 2019.

Public spending by the three federative levels of government was about R$ 28 billion during the studied period (Supplement material, Table I). In 2015, the largest contribution of resources was obtained, in the order of R$ 5 billion. After 2017, there was a progressive decrease in investments (Figure 2).

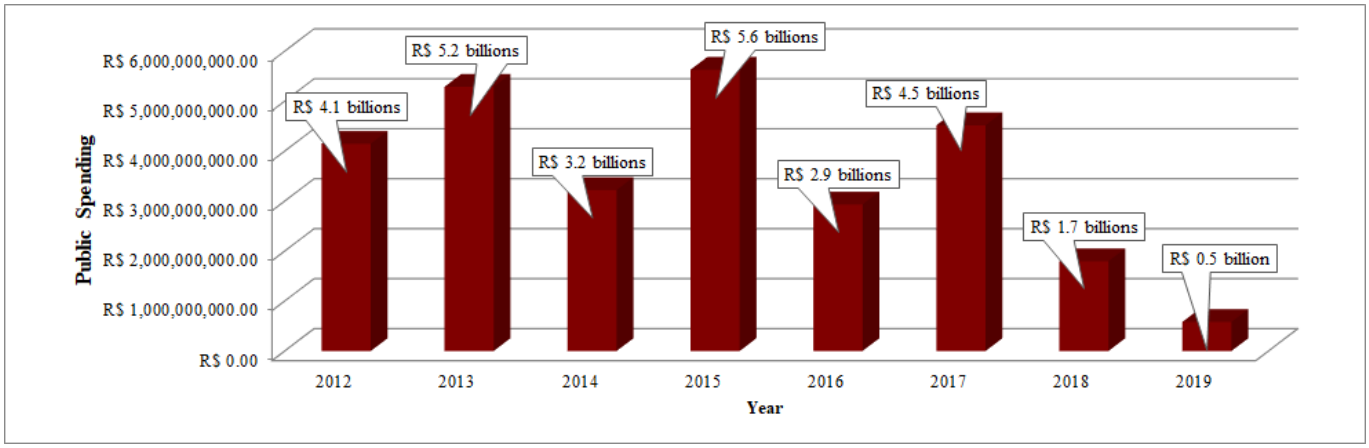

FIGURE 2 - Public spending in billion Reais on biopharmaceuticals by the three governmental Federative levels Brazil, 2012 to 2019.

Legend- The amounts are in reais, Brazilian currency, with a dollar exchange rate of R$ 5.28 (exchange rate of March 24, 2020).

Figure 3 shows three spending trend curves. The blue curve represents the average total spending of the three levels of government during the period evaluated (R$ 175,6 million) (Supplement material, Table II). The red curve shows the average spending of the three levels of government per year, with their respective percentage changes in relation to the average of total spending. Average spending was higher in 2013 (+ 0.3%) and 2015 (+ 6.8%), while it then declined in 2018 (-65.9%) and 2019 (-89%). The black curve reflects the linear trend of the average spending per year, which varied -266.7%.

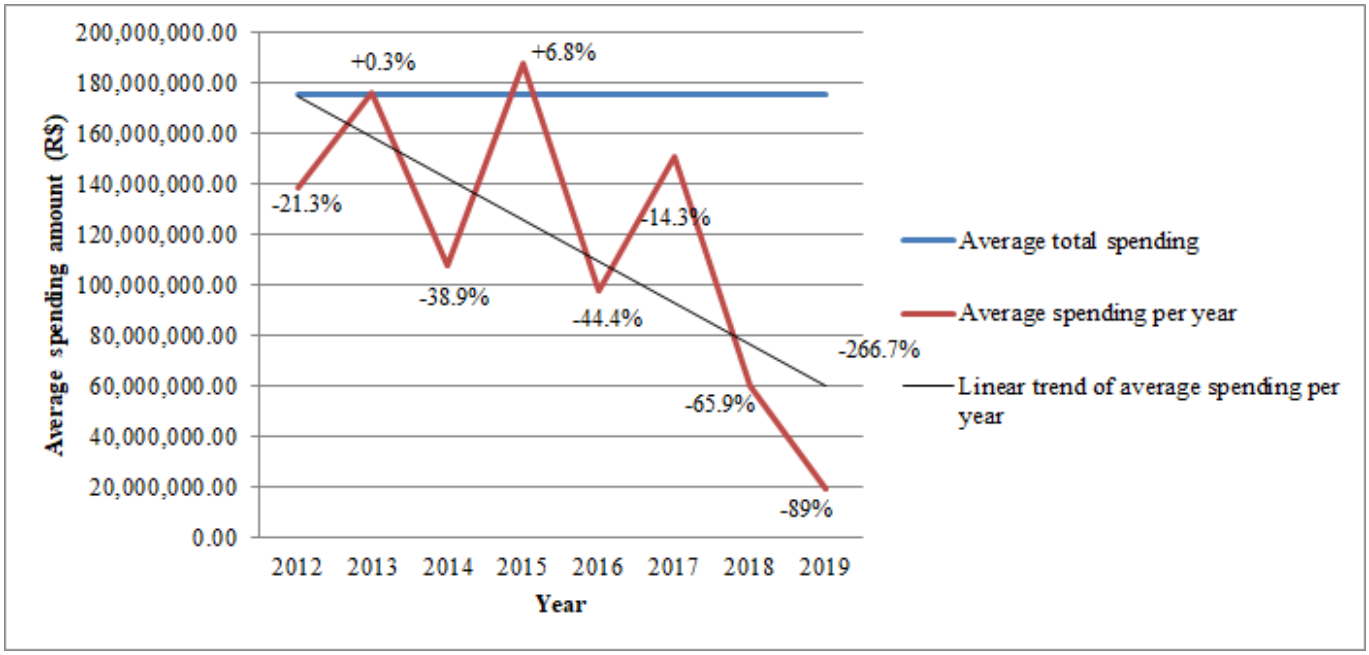

FIGURE 3 - Trend in public spending on biopharmaceuticals. Brazil, January 2012 to September 2019.

Legend- The amounts are in reais, Brazilian currency, with a dollar exchange rate of R$ 5.28 (exchange rate of March 24, 2020).

When assessing the origin of these public expenditures, federal expenditures were clearly higher than those of the states and municipalities combined. Federal spending alternated periods of increases and decreases successively, the highest in 2015, totaling about R$ 5 billion. In the last two years there has been a downward trend, converging with state and municipal spending, which showed a linearity between 2012 and 2015. In 2016 states and municipalities experienced a peak in spending, with a total of about R$ 811 million, but in the following years their expenditure decreased (Figure 4).

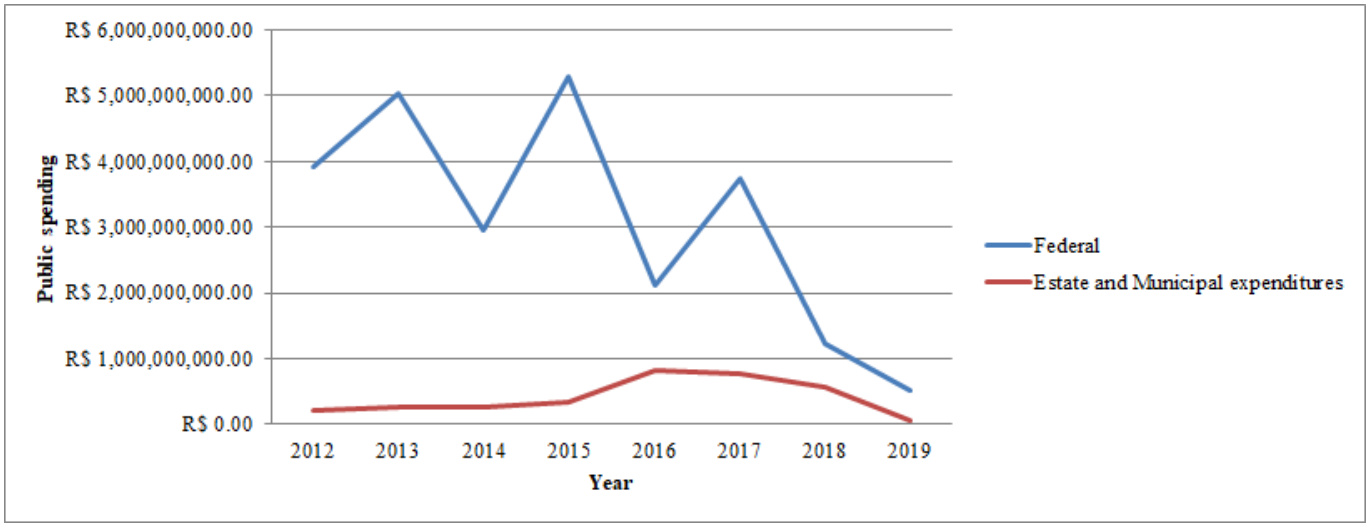

FIGURE 4 - Federal spending x State and Municipal spending.

Legend- The amounts are in reais, Brazilian currency, with a dollar exchange rate of R$ 5.28 (exchange rate of March 24, 2020).

DISCUSSION

The subcutaneous adalimumab was the most often desired medication, and the most requested therapeutic indication was rheumatoid arthritis. The average public expenditure per patient in Brazil with adalimumab for the treatment of rheumatoid arthritis in 2019 was US$ 3,652.64. This figure exceeds, for example, the average expenditure on other biologicals, such as etanercept, which was US$ 3,351.92 (Dos Santos, 2019).

To give you an idea, in 2016 the Ministry of Health spent R$ 15.5 billion on medicines. Of this amount, R$ 4.7 billion (30%) went for the purchase of ten pharmaceutical products with higher costs. Among them was adalimumab with R$ 621.9 million, corresponding to approximately 4% of the total spent. (Vieira, 2018).

According to IMS Health (2019), second generation monoclonal antibodies have caused a real therapeutic revolution in the areas of oncology, rheumatology, and endocrinology. Adalimumab has been the most commercialized biopharmaceutical in the world, and in 2018 it accumulated US$ 19.9 billion in global sales and US$ 18.4 billion in 2017 (Medscape, 2019).

Adalimumab is a biopharmaceutical with considerable therapeutic relevance worldwide. The pharmaceutical industry has always looked for new alternatives to improve the treatment of several diseases that presented unsatisfactory therapies. With the appearance of biological molecules, the search for new therapeutic options has been intensified. Monoclonal antibodies and fusion proteins, for example, appear as a great opportunity for therapeutic use, but also as a great economic and financial risk due to high prices (Costa, 2015).

Rheumatoid arthritis is a systemic inflammatory disease that mainly affects the joints, but can also affect

the lungs, heart, and other organs. It is estimated that this disease affects 0.2% to 1% of the population in Brazil (Borssatto, 2019). This represents 2 million people, and although it is a low prevalence, that number exceeds the population of several countries, such as Iceland, Montenegro, and Timor-Leste (Costa, 2019).

Regarding the variation in the number of biologicals included per year, the highest volume of biological incorporations in 2012 occurred because only in that same year, five new biologicals were incorporated into SUS for the treatment of rheumatoid arthritis. This was in addition to the three others that were already approved but that expanded the use for this same disease. Therefore, in 2012 rheumatoid arthritis had eight (72.7%) biologicals among the 11 medications incorporated (CONITEC, 2019). This expansion was possible only because since 2002 the SUS has had a clinical guideline for the treatment of rheumatoid arthritis, which has been constantly updated due to the emergence of new approaches and treatments (Costa, 2019).

This large number of added medications for rheumatological diseases may be related to the strength of the plaintiffs. The association of groups of rheumatological patients has been the most successful in its demands among external claimants in the last years. It is worth mentioning that in Brazil, the process of incorporating technologies is subject to public consultation. It is an indispensable tool in promoting advertising and transparency by allowing society to issue criticism, opinions, and information about their experience with that technology (CONITEC, 2019).

In 2013 no new biologicals were incorporated because, according to CONITEC (2013), despite there being 15 demands for biologicals, eight of them were not approved due to the fragility of the evidence of efficacy and safety presented and their inadequacy in proving their respective effects. The other seven demands were related to biologicals that were to be excluded (CONITEC, 2013).

In 2018 the increase in the number of biologicals incorporated was driven by the update of therapies for psoriasis, with four (44.4%) of the nine biologicals incorporated this year. Psoriasis is a chronic disease that affects quality of life and increases mortality. A considerable part of patients afflicted with a more severe form of this disease did not respond to the drugs available in SUS. After analyzing the demands with studies proving the safety and efficacy for the treatment of the disease in question, adalimumab, etanercept, ustequinumab, and secuquinumab were incorporated (CONITEC, 2018).

Between October and December 2019, six biopharmaceuticals (infliximab, vedolizumab, aflibercept, certolizumab, emicizumab, and omalizumab) were also incorporated for five different indications, including rectocolitis, diabetic macular edema, psoriatic arthritis, hemophilia, and asthma.

This research revealed significant amounts of public spending over the past seven years on the analyzed biopharmaceuticals. The three levels of government spent about R$ 28 billion between January 2012 and September 2019. This market for organic products represented around 20% of the global pharmaceutical industry in 2018 and has been growing continuously. The global commercialization of biopharmaceuticals has been increasing every year and projections indicate that it will exceed US$ 300 billion by 2021 (Salerno, Matsumoto, Ferraz, 2018).

There was a continuous oscillation in the sums spent during the whole period as observed year by year, and there were successive rises and decreases between 2012 and 2017, that last year being followed by a pattern of decrease. This oscillation may be related to the changes that occurred in the treatment of diseases over the period, interfering in the types and quantities of biologicals acquired by the three levels of government (Mega, 2019).

In 2015, the highest volume of expenses occurred, totaling about R$ 5 billion, because 2015 was the year with the greatest expenditure of resources for biologicals for rheumatoid arthritis. The further cause was that the technologies were only fully implemented in 2014 and 2015, since the PCDT (in Portuguese, *Protocolos Clínicos e Diretrizes Terapêuticas*) was also approved in 2015. The PCDTs are protocols published by the Brazilian government that aim to guide the use of technologies of interest to public health (Mega, 2019).

Figures obtained in March 2018 from Datasus/MS and from the IMS-PMB Health database show that 40% of the public budget for pharmaceuticals is used to purchase biological medicines at SUS, to serve around two

percent of the total number of SUS patients. Rheumatoid arthritis was considered the most responsible reason for the consumption of these drugs in Brazil (Cuber, 2018).

In general, there has been a downward trend in public spending on these biomedicals in Brazil. Despite the alternating periods of expenditure increases and decreases, it was noticed that with each year of increase, this expenditure was lower than the previous period of increase, except for the year 2015. In the present study, the periods of falls followed the same trend. In addition, after 2017 there was a decreasing spending curve. Overall, there was a 266.7% drop in spending on these technologies.

It is necessary to consider the impact of the economic crisis that started in 2008. It was responsible not only for the decrease in tax revenue but also for the reduction of the expenses of states and municipalities. These were in addition to the restriction of expenses that the Union has been implementing in Brazil. A study by Vieira (2018) demonstrated that between 2014 and 2016 the public health expenditures decreased by two percent in the case of the Union, seven percent for states and three percent for municipalities.

In Brazil, a study showed that there was an increase in public spending on biologicals in general between 2010 and 2015; however, a decrease was observed from 2016 onward due to the current economic crisis and the freezing of the minimum investment in public actions and services generated by the Constitutional Amendment 95/2016. This is a Constitutional Amendment that limits public spending for 20 years, approved during the government of President Michel Temer in Brazil (Agência Senado, 2016).

The results of this research show that federal spending was much higher than that of states and municipalities. This superiority was already expected, considering the centralized purchase of medicines by the specialized component of the Ministry of Health (Vieira, 2018). A large component of biological medicines is included in this group, such as abatacept, adalimumab, etanercept, infliximab, secuquinumab, certolizumab, and golimumab (BRASIL, 2019).

Products considered strategic (but expensive) are purchased centrally by the federal government in Brazil. At the outpatient level, medications are purchased for some clinical situations, mainly chronic conditions, with higher or more complex treatment costs (Reis, Pieroni, Souza, 2010). Even so, there were expenditures by states and municipalities for these drugs, which can be attributed to acquisitions resulting from legal demands. All these aspects caused the federal spending curve to impact the total public expenditure curve, showing the same trend.

Since 2008, there has been an increase in SUS demand not only for chemical-based drugs, but also for bio-based drugs (Tanaka, Amorim, 2014). Between 2005 and 2010 the costs associated with biologicals increased by 37%. It should be noted that biological products accounted for 60% of public spending on medicines, involving only 12% of the amount spent on medications (Salerno, Matsumoto, Ferraz, 2018)

According to the same authors, this representativeness of biologicals is due to their high cost of production and consequent commercialization. Other data that point to this trend is described in the Pharmaceutical Market Statistical Yearbook 2016 (ANVISA, 2017), according to which biological products represented 19% of the total revenue of medicines in Brazil in 2016, although they were responsible for less than 5% of the total of units sold. The report points out that this category was the one that grew most in sales and in units sold between 2015 and 2016 (ANVISA, 2017).

When comparing information obtained in other studies and the results obtained in this research, it appears that there was an increase in the demand for biologicals in general, as well as an increase in public spending on them. However, for the biopharmaceuticals researched in this study, the same was not noticed. They have not kept up with the worldwide trend of increased spending, but it is known that demand for them has been increasing continuously.

CONCLUSION

The study allowed the demonstration of the relevance of the biologicals studied not only for public health in Brazil but also for public expenditures, which constitute an important part of the expenditures on medicines. Understanding these expenditures is important to enable decision-making by managers, as well as to guide the incorporation of technologies in SUS in Brazil in a

balanced way. Despite the increase in demand and public spending on biologics in general, in Brazil and worldwide, the results of this research showed that there was a drop in public spending on the studied biopharmaceuticals in the past seven years. This fact requires more studies to analyze how these expenses will present themselves in the coming years and the reason for such a decline.

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