

# Biosimilars in Brazil: The Beginning of an Era of Broader Access

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## Abstract

Cancer is a major public health issue worldwide, especially in the developing world where 70% of the cancer-related deaths occur. During the last three decades, with the advent of targeted therapies using monoclonal antibodies, patients' survival and quality of life have dramatically improved. Unfortunately, these great accomplishments came at the expense of high financial costs which most of the population living in low-and middle-income countries cannot afford. Biosimilars (biotherapeutic products that are similar to an already licensed reference biotherapeutic product in terms of quality, safety and efficacy) have been successfully used in Europe and in US with a substantial reduction in price of around 30%. Brazil is about to have trastuzumab as the first biosimilar available to treat cancer patients in the country. Based on strict regulatory legislations, biosimilars are expected to deliver affordable yet effective and safe treatment options all over the world, expanding the access to cancer treatment and reducing inequalities.

## Keywords

Cancer Therapy, Biosimilar, Trastuzumab, Herceptin, Breast Cancer

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## 1. Introduction

Cancer is deemed to be the cause of 1 at every 8 deaths worldwide. In 2015, cancer was the second leading cause of death (only behind cardiovascular diseases).

It was responsible for 17.5 million cases and 8.7 million deaths. If the rates continue to rise in these proportions, it is expected 21.7 million new cases of cancer and 13 million deaths by 2030 [1] [2]. According to the World Health Organization (WHO), approximately 70% of the deaths occur in low- and middle-income countries (LMICs) [3]. For instance, in Brazil, it was estimated the occurrence of about 600,000 new cases of cancer and 190,000 deaths for 2016 [4] [5]. The higher cancer burden in LMICs is partially explained by the lack of well-established cancer prevention strategies and the underfunding of the health systems [6] [7].

Understanding the hallmarks of cancer was critical for the development of novel and effective treatment approaches, such as targeted immunotherapies. Although cutting-edge therapies and personalized medicine have tremendous impact on cancer survival, these treatments are costly and almost inaccessible for most part of the population living in LMICs [2] [8]. This reality can be seen in Brazil, a country in which approximately 75% of the population is assisted by the public Health System (*Sistema Único de Saúde—SUS*), an underfunded health system in which access to high-cost medications is scarce. In many situations, the only way to have access to gold standard drugs (such as monoclonal antibodies) is via law suits against the government, a practice that has been exponentially growing over the years [9] [10]. Since the Brazilian constitution guarantees universal medical care to all Brazilian citizens, the outcome for the majority of these legal disputes is in favor of patients [11]. It is estimated that government expenditures for the acquisition of judicialized drugs increased from approximately US\$ 785,000 in 2005 to US\$ 92.5 million in 2012 and these numbers are only expected to rise more and more [9].

In Brazil, the Federal government purchases approximately 60% of the biotherapeutic products (also known as biologics). Although biologics represent only 4% of the drugs distributed through *SUS*, they account for 51% of the governmental expenditures with medications [12]. Due to their high budget impact, access to these medications is restricted in the Brazilian Public Health System. For instance, it has been reported that almost half of the oncologists from Mexico, Turkey, Russia and Brazil would be able to prescribe trastuzumab (an anti-HER2 targeted therapy) to more patients if the cost of the monoclonal antibody was lower [13].

Thus, it is clear that affordable yet effective options for biotherapeutic products are an urgent unmet need in LMICs. Considering that many of the reference products' patents have already expired or will soon expire, "biosimilars" stand out as viable options to broaden access to high-cost medications in these countries. Biosimilars can be defined as "biotherapeutic products that are similar to an already licensed reference product in terms of quality, safety and efficacy" [14] [15].

With the use of biosimilars, costs with monoclonal antibodies are projected to fall about 30%. Trastuzumab is expected to be the first monoclonal antibody to treat cancer patients with a commercially available biosimilar in Brazil. It is estimated to be launched in market until 1Q2018 by Libbs, a Brazilian pharma

company which works in partnership with Biocon and Mylan to bring this technology to the country. Trastuzumab (Herceptin®) was made available for patients in the public health system in the adjuvant and neoadjuvant scenarios only in 2013 due to financial issues [16] [17]. In order to decrease costs, the government centrally buys all the medication and distributes through the country, which creates an additional logistic challenge due to the continental dimensions of Brazil. However, in the palliative setting, trastuzumab is not yet available for patients treated at public health system due to the prohibitive budget impact that its inclusion would bring to the country. Hopefully, this situation is about to change because the Brazilian National Committee for Incorporating Technologies at SUS (“CONITEC—Comissão Nacional de Incorporação de Tecnologias no SUS”) has approved the use of trastuzumab in the palliative setting on August/2017 and the drug should be made available within six months after the official publication of the decision. In this scenario, the introduction of biosimilars will represent an opportunity to reduce the access gap that prevents patients treated at the Brazilian Public Health System to benefit from the great accomplishments brought by science into medicine.

## 2. Monoclonal Antibodies (mAbs)

### 2.1. History

The German scientist Paul Ehrlich was the first to develop the concept of “magic bullet”, more than 100 years ago. Ehrlich’s research identified the presence of specific receptors in different tissues that could be used as targets paving the way for the modern era of targeted therapies [18]. However, the concept of targeting a specific antigen as a therapeutic strategy could not be widely used in medicine until 1975, when César Milstein and Georges J. F. Köhler developed the technique for the production of monoclonal antibodies (mAbs), which lead them to be awarded the Nobel Prize in Physiology or Medicine in 1984 [19].

With the advent of these discoveries, medicine has moved into a new era of personalized therapies, where the use of monoclonal antibodies takes the main role. The first therapeutic monoclonal antibody, muromonab-CD3, was approved for prevention of kidney transplant rejection in 1986. Since then, the market for monoclonal antibodies is expanding rapidly, with them being now used to treat an extensive range of diseases, from rheumatoid arthritis to cancer. Currently, mAbs represent the group of biotechnology molecules with the fastest growth in clinical trials [20] [21]. In 2016, one-third of the top 15 best-selling drugs were monoclonal antibodies and it is expected that the global expenditures with biologics in oncology will be around US\$ 50 billion in 2018 [13] [22].

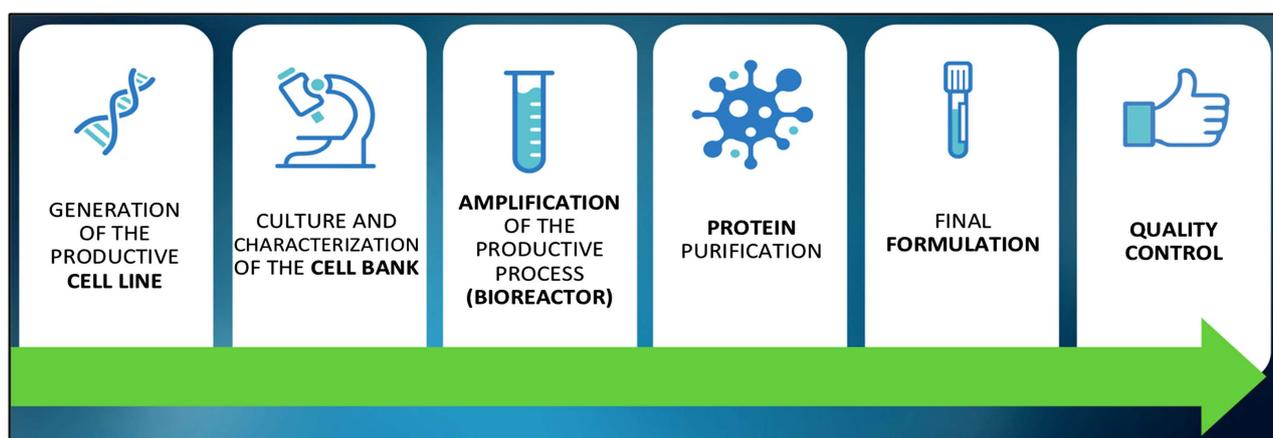
### 2.2. Definition of mAbs and Production Peculiarities

Monoclonal antibodies are laboratory-created proteins with complex structures and high molecular weight (>10,000 Da) which have the ability of binding to

only one specific antigen (the so called “target”). They are also named “biotherapeutics” or “biologics” because their production process involves the use of recombinant technology to clone and express the heavy and the light chain antibody genes in cells of living systems such as bacteria, yeast or mammalian cell lines. They are produced by identical cells that are clones of an immunized B cell fused with a myeloma cell, known as hybridoma. For this technique, the B cells are immunized against a certain epitope so the hybridomas will synthesize and secrete identical highly specific antibodies [20]. Monoclonal antibodies production in mammalian cells involves a long process that comprises steps such as the choice of the cell host (expression system) and the transfection of the gene of interest into the cells followed by cloning, selecting, maintaining, and growing the cell line in bioreactors to finally separate, purify, and characterize the final products [13] [23] [24] (Figure 1).

The Chinese hamster ovary (CHO) cells are, by far, the cell line most frequently used to achieve stable large-scale production of biologicals, accounting for over 70% of biopharmaceutical proteins. After choosing the expression system, the cells need to be transfected with expression vectors (usually plasmids) to transfer the gene of interest. The next step is the selection of the clones expressing the gene marker. The selected cells are then expanded and evaluated regarding growth and mAb production. The higher mAb-producing clones are then selected for another round of cultivation and tests. The next step is to subject these cells to adaptation processes to the new conditions brought by the large-scale production that involves cell growth in suspension and the use of serum-free or protein-free medias [23] [24] [25].

Biologics, including mAbs, can have differences in the sugars on their surfaces (*i.e.*: glycosylation) or folding patterns, according to how they are produced. There is evidence demonstrating that the glycosylation profile can alter the properties of a recombinant protein, such as stability, half-life, and immunogenicity [25] [26]. Because monoclonal antibodies are much more sensitive than chemically synthesized drugs to manufacturing changes, they are strictly regulated by the health authorities [26] [27]. In a study published at Nature Biotech-



**Figure 1.** Biological medicines' productive process.

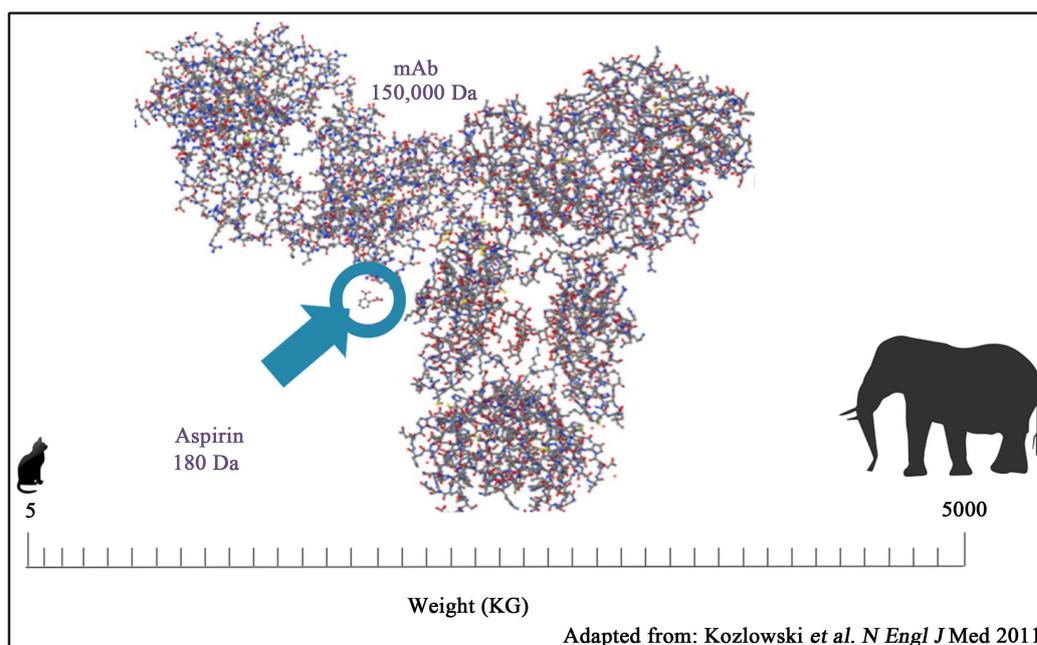
nology in 2011, significant changes in quality parameters of the reference rituximab were identified since it was first launched in market, but these alterations did not lead to any change in the product's label [27]. It does not mean that there is lack of quality control for the production of biological products, on the contrary, while chemical drugs usually have 40 to 50 critical tests, biologicals might have 250 [26]. This means is that biological products inevitably vary even within different products batches from a reference monoclonal antibody.

According to Vezer, *et al.*, the manufacturing process of several biologicals used in oncology have changed over time leading to “high risk changes”, but authorities maintained their approval after the drugs passed the requested tests. For instance, from the moment it was first marketed until October 2014, the reference trastuzumab has had 26 manufacturing changes (two of them classified as “high risk changes”) with no approval withdraw or label change according to the European Public Assessment Reports [28].

### 3. Biosimilars

#### 3.1. Definition of Biosimilar

Biosimilars can be defined as “biotherapeutic products that are similar to an already licensed reference biotherapeutic product in terms of quality, safety and efficacy” [14] [15]. However, it is of paramount importance to differentiate biosimilars from generics. While generic medicines are identical copies of their original chemical molecules; biosimilars are complex proteins that might show small variations in relation to their reference biotherapeutic product (RBT) (Figure 2).



**Figure 2.** Comparison between the molecular weights of biological medicines and a chemically synthesized drug (Aspirin).

### 3.2. Regulatory Process to Approve Biosimilars

Because of the inherent variability that exists in the manufacturing process of biotherapeutic products, it is impossible to characterize the biosimilar and the reference product as identical products (as it is done with generic medicines). To solve this impasse, specific regulatory standards were created in order to define the criteria that would have to be evaluated before stating that an allegedly similar biotherapeutic product has similar properties in terms of efficacy, safety and quality when compared to a reference biotherapeutic product [13].

Biosimilars are better established in Europe than in the United States (US). While European countries have approved 37 biosimilars since 2006, US had only 5 by early August/2017 (**Table 1**) [29]. In order to speed the development and approval of biosimilars by the FDA (Food and Drug Administration), the Biologics Price Competition and Innovation Act (BPCIA) was passed in 2010 as part of the Patient Protection and Affordable Care Act in US [30]. Since then, distinct but overlapping regulatory legislations for biosimilar approvals have been developed by the FDA and the EMA (European Medicines Agency). The main point is that both jurisdictions recognize that biologics must be treated in a different way from generic medicines because of their complex structures and susceptibility to manufacturing variations. In general lines, the critical issues evaluated in the regulatory process of biosimilars is based on a stepwise process starting with analytical and nonclinical comparison of structural and *in vitro* functional characteristics as well as *in vivo* animal studies, including assessments of toxicity. Once a biosimilar candidate is approved in these first steps, adequately powered clinical tests are required in order to demonstrate the equivalence in terms of efficacy, safety and immunogenicity. **Table 2** summarizes the main documents regulating biosimilars in the world.

### 3.3. Pivotal Studies for Trastuzumab Biosimilars

The HERITAGE trial (NCT02472964), led by Hope, *et al.*, was first presented at the ASCO Annual Meeting/2016 and had its final results published at the Journal of the American Medical Association (JAMA) in January 2017 [32]. It is a multicenter randomized clinical trial designed to compare the efficacy in terms of overall response rate (ORR) and the safety of a proposed trastuzumab biosimilar and the reference trastuzumab after 24 weeks of follow-up in the first-line treatment of patients with metastatic HER2-positive breast cancer. ORR was defined as the achievement of complete or partial response according to RECIST criteria. The study was successful in achieving the pre-established equivalence boundaries of 0.81 - 1.24 for ORR ratio and  $\pm 15\%$  for ORR difference resulting in an ORR ratio of 1.09 (90%CI 0.97 to 1.21) and a ORR difference of 5.53 (95%CI -3.08 to +14.04). The treatments were also considered equivalent in other efficacy outcomes of interest such as overall survival, progression-free survival and time to tumor progression. The safety profile, as well as the pharmacokinetics, pharmacodynamics and immunogenicity studies were also similar between the two groups.

**Table 1.** Biosimilars approved in Europe and US [29] [31].

Europe*	US*
Adalimumab (Amgen)**	Adalimumab-atto (Amjevita-Amgen)
Adalimumab (Amgen)**	Andetanercept (Erelzi-Sandoz)
Adalimumab (Samsung Bioepis)	Infliximab (Samsung Bioepis)
Enoxaparin sodium (Pharmathen)	Infliximab (Jansen Biotech)
Enoxaparin sodium (Tehdow Europe)	Filgrastim (Sandoz/Novartis)
Epoetin alfa (Medice Arzneimittel Pütter)	
Epoetin alfa (Hexal)	
Epoetin alfa (Sandoz)	
Epoetin zeta (Hospira)	
Epoetin zeta (Stada Arzneimittel)	
Etanercept (Samsung Bioepis)	
Etanercept (Sandoz)	
Filgrastim(Accord Healthcare)	
Filgrastim(Apotex)	
Filgrastim (CT Arzneimittel)	
Filgrastim (Hexal)	
Filgrastim (Hospira)	
Filgrastim (Ratiopharm)***	
Filgrastim (Ratiopharm)***	
Filgrastim (Sandoz)	
Filgrastim (Teva Generics)	
Follitropin alfa (Finox Biotech)	
Follitropin alfa (Teva Pharma)	
Infliximab (Celltrion)	
Infliximab (Hospira)	
Infliximab (Samsung Bioepis)	
Insulinglarginine (Eli Lilly/Boehringer Ingelheim)	
Insulin glarginine (MSD)	
Insulin lispro (Sanofi-Aventis)	
Rituximab (Celltrion)****	
Rituximab (Celltrion)****	
Rituximab (Celltrion)****	
Rituximab (Sandoz)*****	
Rituximab (Sandoz)*****	
Somatropin (BioPartners)	
Somatropin (Sandoz)	
Teriparatide (Gedeon Richter)	
Teriparatide (Stada Arzneimittel)	

\*By early August/2017; \*\*two different approved product names: Amgevita and Solymbic; \*\*\*two different approved product names: Filgrastim ratiopharm and Ratiograstim; \*\*\*\*three different approved product names: Ritemvia, Truxima and Tuxella; \*\*\*\*\*two different approved product names: Rixathon and Riximyo.

**Table 2.** Main regulatory documents for biosimilars.

Agency	Document Title	Available at
World Health Organization (WHO)	Guidelines on Evaluation of Similar Biotherapeutic Products	<a href="http://www.who.int/biologicals/areas/biological_therapeutics/BIO_THERAPEUTICS_FOR_WEB_22APRIL2010.pdf">http://www.who.int/biologicals/areas/biological_therapeutics/BIO_THERAPEUTICS_FOR_WEB_22APRIL2010.pdf</a>
World Health Organization (WHO)	Good manufacturing Practices for Biological Products	<a href="http://www.who.int/biologicals/areas/vaccines/Annex_2_WHO_Good_manufacturing_practices_for_biological_products.pdf?ua=1">http://www.who.int/biologicals/areas/vaccines/Annex_2_WHO_Good_manufacturing_practices_for_biological_products.pdf?ua=1</a>
EMA—European Medicines Agency	Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies—non-Clinical and Clinical Issues	<a href="http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf">http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf</a>
FDA—United States Food and Drug Administration	Scientific Considerations in Demonstrating Biosimilarity to a Reference Product	<a href="https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf">https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf</a>
FDA—United States Food and Drug Administration	Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product	<a href="https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf">https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf</a>
FDA—United States Food and Drug Administration	Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product	<a href="https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf">https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf</a>

Results from two other proposed trastuzumab biosimilars (CT-P6 and SB3) were presented at the ASCO Annual Meeting/2017 and proved to be as safe and effective as the reference trastuzumab in the neoadjuvant setting [33] [34]. These studies have in common the fact that different proposed trastuzumab biosimilars have proven to be as safe and effective as the reference drug in different clinical scenarios establishing a robust body of evidence that supports the use of these medications in clinical practice.

## 4. Biosimilars in Brazil

### 4.1. Production and Regulatory Process

The Brazilian national regulatory agency (ANVISA—Agência Nacional de Vigilância Sanitária) issued its first guideline about biosimilar submissions in 2010 (RDC 55-2010) [35]. This document states the basis of the regulatory process for biologics and biosimilars in Brazil. Most of the main issues addressed are in concordance with the EMA (European Medicines Agency) and WHO (World Health Organization).

The regulatory timeline in ANVISA is known to be longer when compared to other agencies. For instance, when compared to FDA, approvals in Brazil are, in average, 8.6 months longer. However, ANVISA is taking actions in order to improve the flaws on its regulatory process. Since 2008, ANVISA has adopted a policy of prioritization, which accelerates the analysis of some products considered strategic, such as first available generic drugs and products developed as public-private partnerships [36] [37]. The efforts made by ANVISA in order to improve its own processes are paying off, and the agency is now recognized as part of the ICH (International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use) [38].

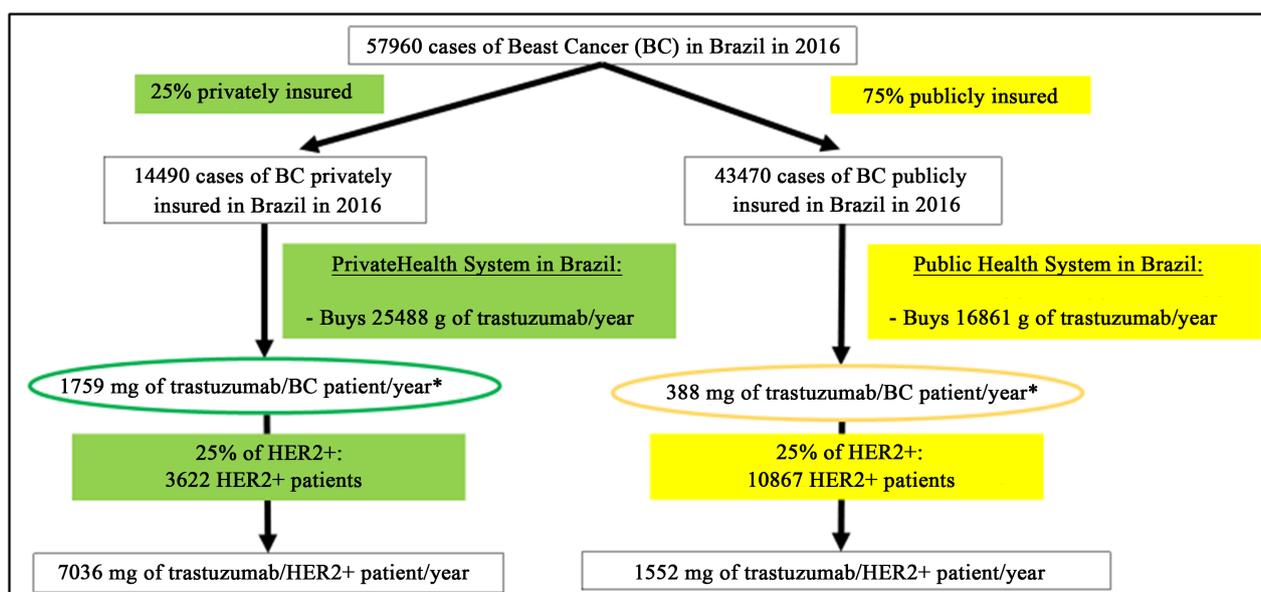
## 4.2. Expected Savings for the Public Health System in Brazil

To the present, the only monoclonal antibody that has a biosimilar marketed in Brazil is infliximab, which allowed a cost reduction of approximately 35% [39]. Among the monoclonal antibodies used in cancer treatment, there has been no approved biosimilars yet in Brazil, but based on the infliximab experience, savings are expected to be around 30%. Considering that in 2016 the Brazilian government expended U\$ 35 million with trastuzumab for neo/adjuvant indications and assuming a constant demand, it is expected an initial economy around US\$ 10 million per year with the introduction of biosimilars [40]. Considering that trastuzumab will be also offered in the palliative setting, savings are expected to be a greater magnitude.

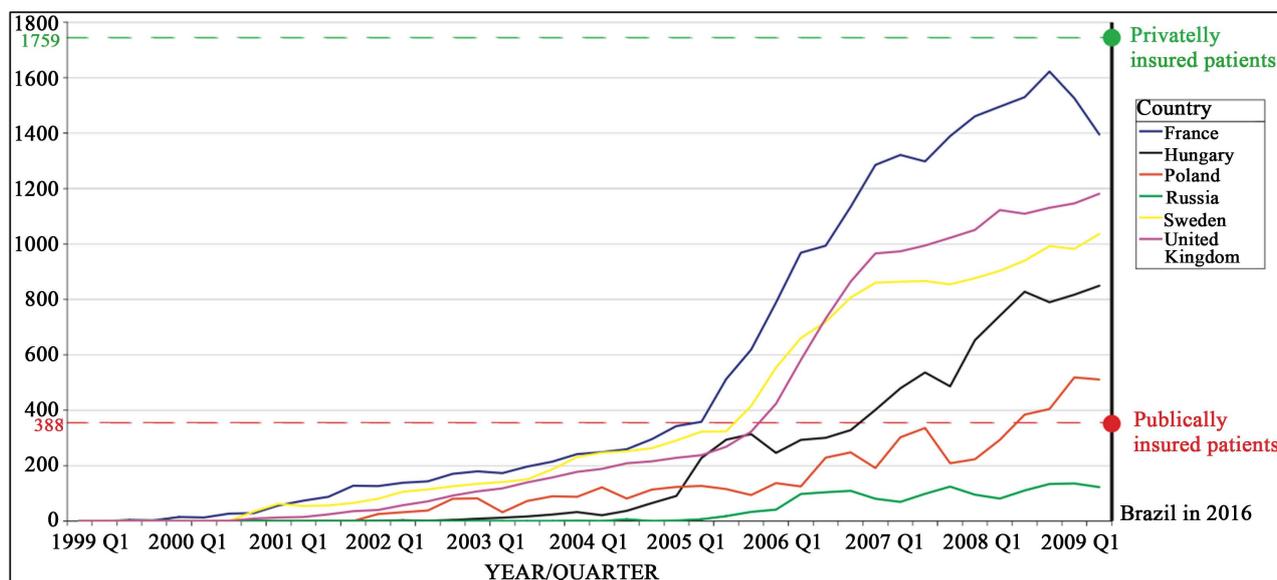
The main benefit that is expected to be achieved with the incorporation of the biosimilar trastuzumab in Brazil is the opportunity it offers to reduce the access gap that exists separating the public and the private health systems in the country. The fact is that there are two very distinct scenarios in Brazil: while breast cancer patients who have access to private health insurance receive an average of 1.759 mg of trastuzumab per case (which is more than it was dispensed in France in 2009), their counterparts treated at the public health system receive only 388 mg of trastuzumab per breast cancer patient (an average use that falls between the dispensed in Poland and Russia in 2009) [40] [41]. All these estimations are summarized in **Figure 3** and **Figure 4**.

## 4.3. Technology Transfer

In order to reduce costs, manufacturing and technological dependencies, and also promote technology development, Brazil launched public-private partner-



**Figure 3.** Estimation of trastuzumab consumption (mg/patient/year) in Brazil [5] [40]. \*trastuzumab sales for the private system were estimated using data from an audit that captures one out of the three sale channels that are expected to be equivalent.



**Figure 4.** Comparison of consumption of trastuzumab in Europe from 1999 to 2009 and Brazil in 2016. Adapted from [41].

ships known as productive development partnerships (PDPs). Producing biologics locally will create jobs; avoid problems and delays related to importation; increase population access to these therapies and lower the expenses for the Ministry of Health. Therefore, the PDP program is a double win: development of country's technology and improvement of patients' healthcare [16] [17].

## 5. Conclusions and Future Perspectives

Targeted therapies using monoclonal antibodies have significantly impacted cancer treatment and became essential weapons in the war waged by humanity against it. However, these great accomplishments came with high financial expenditures that impose prohibitive costs to most of the population living in low- and middle-income countries.

In order to fulfill the ultimate science's mission of improving people's lives, the benefits that the use of biologics brought to cancer patients must be made available to as much people as possible. In this sense, biosimilars have recently started to be part of the history of the mankind war against cancer and we do believe they will foster a new era of broader access to high-cost medications in oncology. In Brazil, the first step will be given with trastuzumab.

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