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A problemática global do diabetes e o contexto brasileiro dos antidiabéticos glibenclamida e insulina: a contribuição de um laboratório farmacêutico oficial para a saúde pública.

The global problem of diabetes and the Brazilian context of antidiabetics glibenclamide and insulin: the contribution of the official pharmaceutical laboratory for Health System.

El problema mundial de la diabetes y el contexto brasileño de glibenclamida y la insulina: la contribución de un laboratorio farmacéutico oficial para una salud pública.

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RESUMO: Pensar o diabetes como emergência global, se traduz em um grave problema de saúde pública, haja vista ser a doença que mais mata no mundo com 5 milhões de óbitos em 2014. Acomete mais de 400 milhões da humanidade e há previsão de um aumento de 60% até 2040. No Brasil haverá cerca de 65 milhões de diabéticos, necessitando dos pilares do SUS brasileiro. Nesse sentido, milhares de pesquisas científicas e tecnológicas apontam grande avanço no cenário farmacêutico, contribuindo para melhor controle desta emergência, como se observou nos artigos científicos e patentes na área. Da mesma forma o cenário mercadológico brasileiro movimenta cerca de 500 milhões de reais. Políticas públicas, como a participação na atenção farmacêutica pelos laboratórios farmacêuticos oficiais, ainda que numa escala pequena, tem sido evidenciado na contribuição da sustentabilidade do SUS. Na RENAME foram identificados 66 produtos, dos quais

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29% são associações. Os países líderes em papers e patentes são EUA, Japão, China e Alemanha. Já as empresas líderes são Novo Nordisk, Merck and Co. e Sanofi-Aventis.
Palavras chave: Antidiabéticos. Laboratório Farmacêutico Oficial. Saúde Pública.

ABSTRACT: Thinking of diabetes such as a global emergency translates into a severe public health problem. Diabetes is the world's most deadly disease with 5 million deaths in 2014. It attacks more than 400 million of humanity and is predicted to increase by 60 % By 2040. In Brazil, there will be about 65 million diabetics in the pillars of Brazilian Health System. In this sense, thousands of scientific and technological research points to a great advance in the pharmaceutical scenario, contributing to a better control of this scenario. This overview is observed in the scientific articles and pharmaceutical patents. In the same way, the Brazilian market scenario reaching around 500 million reais. Public policies in pharmaceutical care such as producing medicines in official pharmaceutical laboratories, albeit on a small scale, have been evidenced in the Health System sustainability. Brazilian National List of medicines has 66 diabetes products which 29% are associations. The Top countries in scientific papers and patents are USA, Japan, China and Germany. The leading companies are Novo Nordisk, Merck and Co. and Sanofi-Aventis.
Keywords: Antidiabetics. Official Pharmaceutical Laboratory. Public health.

RESUMEN: Pensar en la diabetes como una emergencia global se traduce en un grave problema de salud pública. La diabetes es la enfermedad más mortal del mundo con 5 millones de muertes en 2014. La diabetes ataca a más de 400 millones de la humanidad y se prevé que aumente en un 60% el año 2040. En Brasil habrá unos 65 millones de diabéticos en los pilares del Sistema Brasileño de Salud. En este sentido, miles de investigaciones científicas y tecnológicas apuntan a un gran avance en el sector farmacéutico, contribuyendo a un mejor control de este escenario. Este panorama se observa en los artículos científicos y patentes farmacéuticas. Del mismo modo, el mercado brasileño alcanza los 500 millones de reales. Las políticas públicas de atención farmacéutica, como la producción de medicamentos en laboratorios farmacéuticos oficiales, aunque a pequeña escala, se han evidenciado en la sostenibilidad del Sistema de Salud. La Lista Nacional de Medicamentos de Brasil tiene 66 productos de diabetes y el 29% son asociaciones. Los principales países en papeles cientificos y patentes son EE.UU., Japón, China y Alemania. Las empresas líderes son Novo Nordisk, Merck y Co. y Sanofi-Aventis.
Palabras clave: Antidiabéticos. Laboratorio Farmacéutico Oficial. Salud pública.

INTRODUCTION

The improvement in the quality of life of humanity has contributed to a healthier ageing process and a longer life expectancy. Among other factors, the increase in the population age is the result of the availability of new drug discoveries for treating various chronic diseases, such as diabetes, hypertension, and dyslipidaemia [1,2].

The pharmaceutical industry is the sector of the economy that is considered the most dynamic and intense in terms of research and development [3,4]. The pharmaceutical world market is expected to reach approximately US $ 1.3 trillion by 2018. In this scenario, the United States of America represents the largest drug market in the world, but it had a 10% decrease in its global market share in 2015 (31% of participation), compared with 2005, where it held 41% of the global market share. For Europe, it was approximately 19% in 2015, which is lower than the 27% growth in 2005. For emerging countries, such as Brazil, the share of global sales reached approximately 28% in 2015, up from 12% in 2005 [5,6].

The pharmaceutical market has advanced, even in the face of global crises, maintaining investments in studies on the order of 20% of total revenues. For Brazil, it can be seen that over the last five years, the country moved from 10th to 6th place in the world market in terms of sales. Brazil has had pharmaceutical growth on the order of US $ 10 billion/year, with projections of reaching R $ 87 million in revenues in 2017 [6–8]. The pharmaceutical industry acts in all areas of human therapy. It is important to highlight the major areas of investment: oncology and diabetes. The latter had sales growth on the order of 4-7% between 2011 and 2015, totalling approximately US $ 50 billion. Similarly, it is estimated that the expenditures on antidiabetics in 2016 were between US $ 48 and 52 billion[5].

According to the International Diabetes Federation (IDF) (2015), there are approximately 400 million diabetics worldwide, with 4.9 million deaths in 2014 alone. It is estimated that by the year 2040, there will be 642 million diabetics (IDF, 2015) [9]. According to King, Aubert & Herman (1998), the increase in the number of diabetics will occur mainly in developed countries located in the Americas and most likely in the age group between 45-64 years. In South and Central America, where Brazil is located, the increase will be 65% [10].

The disease Diabetes Mellitus (DM) distinguishes itself as a metabolic disorder that is triggered by several factors. It is characterized by increased glycaemia and metabolic disorders of carbohydrates, proteins and fats that result from defects in insulin secretion and/or action [11]statistical models that assess a patient's risk of diabetes progression, are popular tools in clinical practice for prevention and management of chronic conditions. Most, if not all, models currently in use are based on gold standard clinical trial data. The relatively small sample size available from clinical trial limits these models only considering the patient's state at the time of the assessment and ignoring the trajectory, the sequence of events, that led up to the state. Recent advances in the adoption of electronic health record (EHR.

The growing number of cases of DM in the world goes hand-in-hand with scientific and technological disease research. On the biomedical literature database of MEDLINE, PubMed (https://www.ncbi.nlm.nih.gov/pubmed), there are more than 100,000 indexed documents. In terms of technologies, the World Intellectual Property Organization (WIPO) patent database, PatentScope, has more than 57,000 patents. There is a trend in Research, Development and Innovation (R, D

& I) to study technologies for treating diabetes that use oral insulin, stem cells, drugs with renal action, intelligent insulin infusion, vaccines and new insulin[12]. This R, D & I intensity in the pharmaceutical sector has provided a constant supply of new Active Pharmaceutical Ingredients (API) and medicines for the world population [8].

When one observes the Economic and Industrial Health Complex (CEIS – Brazilian term), it is noted that a set of sectors is being developed via productive activities in the health field, where inter-sector relations are maintained to undertake R, D & I activities, production, purchase and sale of services and to develop knowledge and technology [13,14]. This paradigm considers the need to articulate the social, sanitary, economic and innovation logic of the health sector [13,15].

In the context of CEIS [16]”source”:”www.bv.fapesp.br”,”abstract”:”Os Sistemas de Gerenciamento de Bases de Dados (SGBD, the Brazilian government maintains and promotes the public production of medicines by the Official Pharmaceutical Laboratories (LFO – Brazilian term). They act not only in manufacturing but also in policy-making and the research and development of formulations and new drugs. OFL produces medicine for the Unified Health System (SUS) and primarily produces medicines for basic care and neglected diseases [17]”container-title”:”PLoS Me d”,”page”:”e1001218”,”volume”:”9”,”issue”:”5”,”source”:”PLoS Med”,”abstract”:”As part of a cluster of articles leading up to the 2012 World Health Report and critically reflecting on the theme of “no health without research,” Suerie Moon and colleagues argue for a global health R&D treaty to improve innovation in new medicines and strengthening affordability, sustainable financing, efficiency in innovation, and equitable health-centered governance.”,”DOI”:”10.1371/ journal.pmed.1001218”,”shortTitle”:”Innovation and Access to Medicines for Neglected Popula tions”,”journalAbbreviation”:”PLoS Med”,”author”:[{“family”:”Moon”,”given”:”Suerie”},{“fa mily”:”Bermudez”,”given”:”Jorge”},{“family”:”Hoen”,”given”:”Ellen”,”non-dropping-particle”:- ”’t”}],”issued”:{“date-parts”:[[“2012”,5,15]]}}],”schema”:”https://github.com/citation-style-language/schema/raw/master/csl-citation.json”} , i.e., medicines for which there is no interest from private pharmaceutical companies due to non-profitability because the medicines treat diseases such as malaria, leishmaniasis, and tuberculosis [18]. The Ministry of Health (MS) also acts as a regulator of prices in the national market, as observed by their performance in 2005. The MS announced that it holds the technological competence to produce antiretroviral (ARV) Efavirenz, Nelfinavir and Lopinavir. This announcement led to a reduction of these drugs’ prices in private laboratories by 59%, 40% and 46%, respectively[19]”publisher”:”INTERCIENCIA”,”number-of-pages”:”209”,”source”:”Google Books”,”abstract”:”O setor farmacêutico nacional atravessa um período estimulante. Impulsionado por um expressivo crescimento do segmento de medicamentos genéricos, a participação das empresas nacionais vem se elevando de forma significativa ao longo dos últimos quatro anos. Contudo, parece apresentar-se aos produtores de genéricos e similares um desafio estratégico de longo prazo. Como manter rentabilidades adequadas em segmentos industriais de intensa concorrência, onde margens e crescimento parecem andar em sentidos opostos? A resposta deverá vir através da aposta clara e consistente na inovação.”,”ISBN”:”978-85-7193-202-9”,”shortTitle”:”Oportunidades em medicamentos genéricos”,”language”:”pt”,”editor”:[{“fami

ly":"Antunes, AMS","given":""},{"family":"Magalhaes, JL","given":""}],"issued":{"date-parts":[["2008"]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} .

Considering the public health problem of DM and the State Policy in maintaining and expanding drug access to the Brazilian population, it is worth identifying the scientific and technological scenario of antidiabetics and the respective contributions of the LFO to the SUS in the context of the Brazilian market.

METHODOLOGY

A survey of state-of-the-art pharmaceutical research was conducted in scientific journals indexed in the databases SCOPUS, Scielo and PubMed. In addition, official databases such as the health portal of the Ministry of Development, Industry and Foreign Trade (MDIC – Brazilian term); the Ministry of Science, Technology and Innovation (MCTI – Brazilian term); and the National Health Surveillance Agency (ANVISA – Brazilian term) were searched. The terms used for the searches were a) in English: active pharmaceutical ingredient (API), medicines, drugs, diabetes, diabetes mellitus, glibenclamide and insulin and b) in Portuguese: Insumo Farmacêutico Ativo - IFA, medicamentos, drogas, diabetes, diabetes mellitus, glibenclamida and insulina.

Concerning technological trends, patents were identified and extracted through the Integrity database through the Periódicos Capes Portal (http://www.periodicos.capes.gov.br/) [21] and through the database of the National Institute of Industrial Property (INPI)[22]. For the market trends for drugs and medicines, each diabetes-related substance present in RENAME and their respective trends of those substances were searched using the basis of the Foreign Trade Secretariat (SECEX – Brazilian term) of the MDIC, known as AliceWeb2. In the same way, to identify possible suppliers of these API, the database of the Directory of World Chemical Producers (DWCP) was consulted [23].

After the data were extracted, they were "mined" in free software such as CarrotLingo3G and GoPubMed. In the same way, the data inherent to the market were plotted in Grapheur software using Microsoft Office Excel® version 2013.

To determine whether there is a record of antidiabetics for SUS in its portfolio and its respective contribution to the market scenario of the system, the LFO used for this case study was based on the choice of the largest LFO linked to MS, Farmanguinhos [24,25].

RESULTS AND DISCUSSIONS

The WHO reports that diabetes is among the ten most deadly diseases in the world. According to King et al. (1998), the number of individuals with diabetes was 35 million in the year 2000, and it is projected to reach 64 million in 2025. In developed countries, the increase will occur mainly in more advanced age groups due to the increase in life expectancy and population growth. In

developing countries, the increase will be observed in all age groups, particularly in the 45-64 age group, where the prevalence of diabetes is expected to triple, and it will double in the age groups of 20-44 and 65 onwards[10].

Sixty-six diabetes-related products listed in RENAME 2014, which was published in 2015, were identified. These may be associated with each other (Table 1). Of this total, 19 are associated drugs, and 47 are single drugs. In graph 1, we can see the quantities imported and exported by Brazil in the period from 1997 to 2015, according to the AliceWeb2 system.

Table 1. Antidiabetic medicines in RENAME.

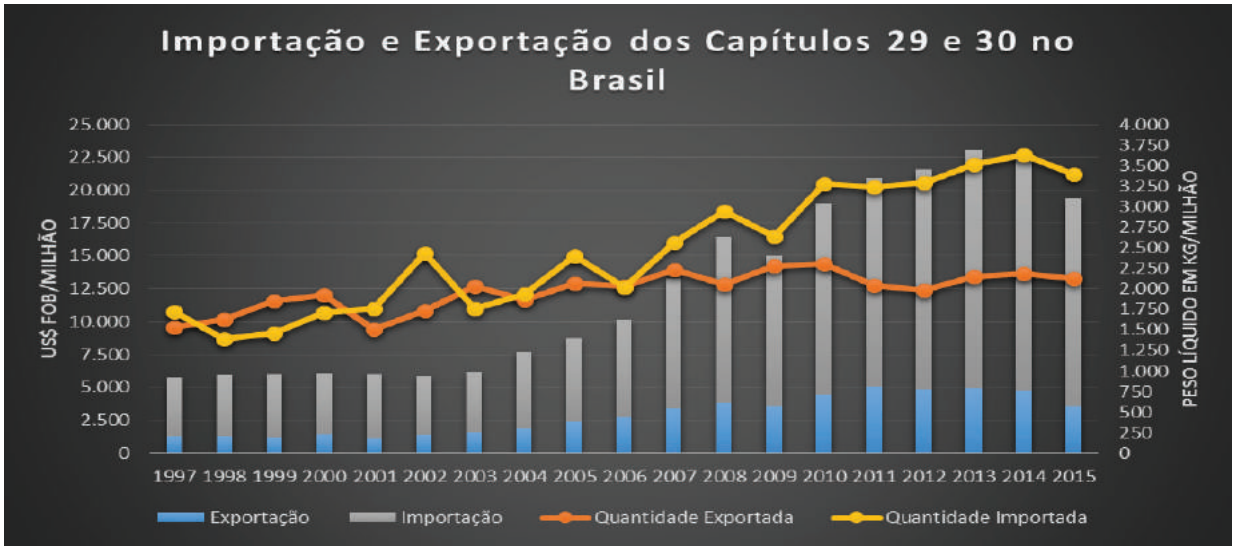
PRODUCT		
Acarbose	Acetohexamide	Albiglutide
Metformin	Canaglifozin	Dapagliflozin
Lina gliptin	Exenatide	Glibenclamide
Rosiglitazone	Glipizide	Insulin Aspartic
Insulin Detemir	Insulin Glargina	Insulin Glulisine
Bovine Insulin Isophane	Swine Insulin Zinc	NPH Insulin
Liraglutide	Mecasermin	Mecasermin Rinfabate
Sitagliptin	Miglitol	Nate glinide
Tolazamide	Lina gliptin	Sax gliptin
Alogliptin Benzoate	Pioglitazone	Simvastatin
Dulaglutide	Empagliflozin	Repaglinide
Gliclazide	Glimepiride	Regular
Biphasic Insulin	Insulin Degludeca	Pramlintide
Insulin Lispro	Insulin Aspartic Protamine	Insulin

Source: Created by the authors with data from RENAME (2016).

Note that the exports are insignificant in relation to Brazilian imports of API and antidiabetic drugs. This fact, as confirmed by Gadelha et al., aligns with the deficit of the Brazilian trade balance in the healthcare sector[26–28]. There are several nomenclature numbers for import and export in Brazil. They are identified by the Mercosur Common Nomenclature (NCM – Brazilian term). Chapter 29 of the NCM contains all API, and chapter 30 contains all medicines. These APIs and medicines were identified in the AliceWeb2 database.

In the NCM, each product must have its own number for customs purposes and for control by the Federal Revenue Service (RFB – Brazilian term). Although some drugs and medicines do not have NCM numbers yet, this fact did not affect the results of this study. Graph 1 shows the API trade balance.

Graph 1. API trade balance



Source: Created by the authors with MDIC, SECEX database ALICEweb (2016).

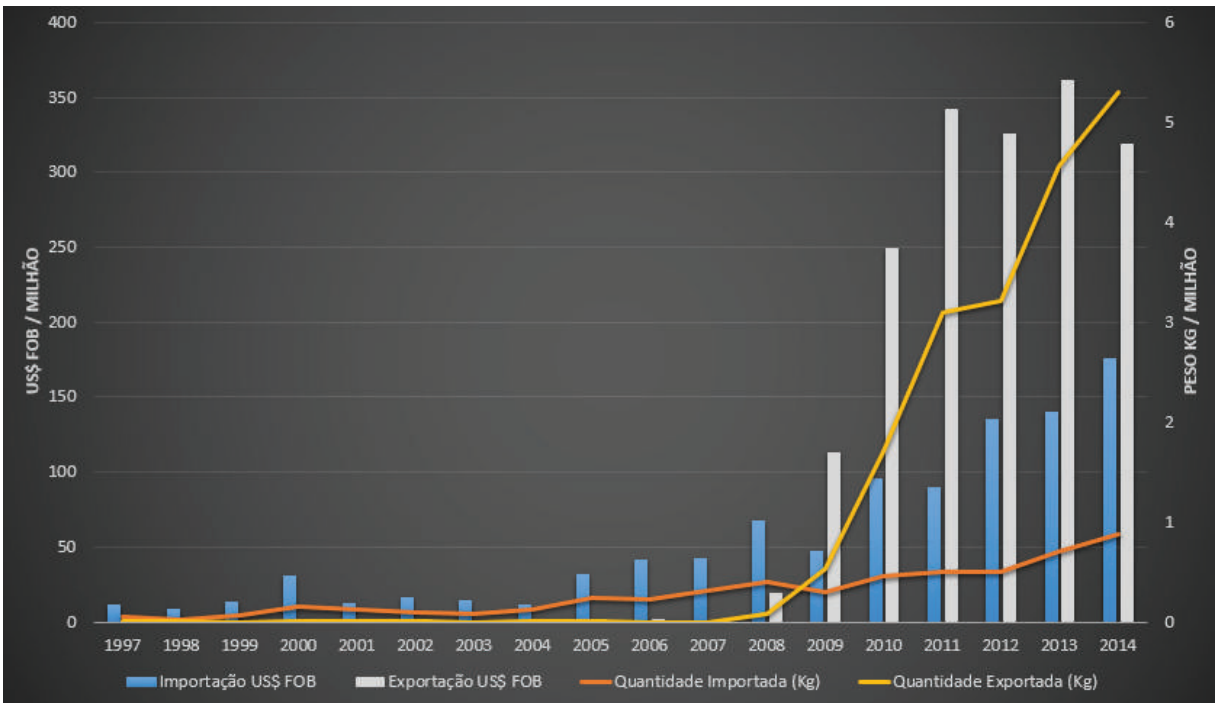
The expenditures on Brazilian imports of API between 1997 and 2015 amounted to approximately 185 Billion US dollars FOB[3]. To identify which drugs and medicines are part of the LFO Farmanguinhos portfolio and what their respective values in the trade balance are, the cut was made. It was observed that the value of API produced by this LFO corresponded to 6.21% of the total Brazilian trade balance in the analysed period, that is, approximately 11.5 Billion US dollars FOB (Figure 1).

In this scenario, it should be noted that 63.05% corresponded to imports of API (approximately 107 Billion US $ FOB), and 36.95% corresponded to imports of medicines (approximately 78 Billion US $ FOB). By this analysis, comparing the APIs present in the LFO Farmanguinhos Portfolio to the total API imported by Brazil, it can be observed that the API present in the LFO portfolio represent approximately 7.5 Billion US $ FOB, or 7,01% of the total imported into the country. In relation to medicines, the value was close to 4 Billion US $ FOB (5.13%). It can be concluded that approximately 11.5 Billion US $ FOB, or 12.14% of Brazilian imports, were related to products that are present in the LFO Farmanguinhos Portfolio. It should be noted that imports of API at this stage involve many public and private companies.

Concerning the number of antidiabetics present in the LFO Farmanguinhos portfolio, two products were identified: Insulin and Glibenclamide. Together (see graph 2), they represent approximately 990 Million US $ FOB (8.60%) of the total present in the LFO portfolio (11.5 Billion US $ FOB). Antidiabetic APIs represent approximately 476 Million US $ FOB (48.08%).

3 US$ FOB means “free on board” – Price excluding customs duties.

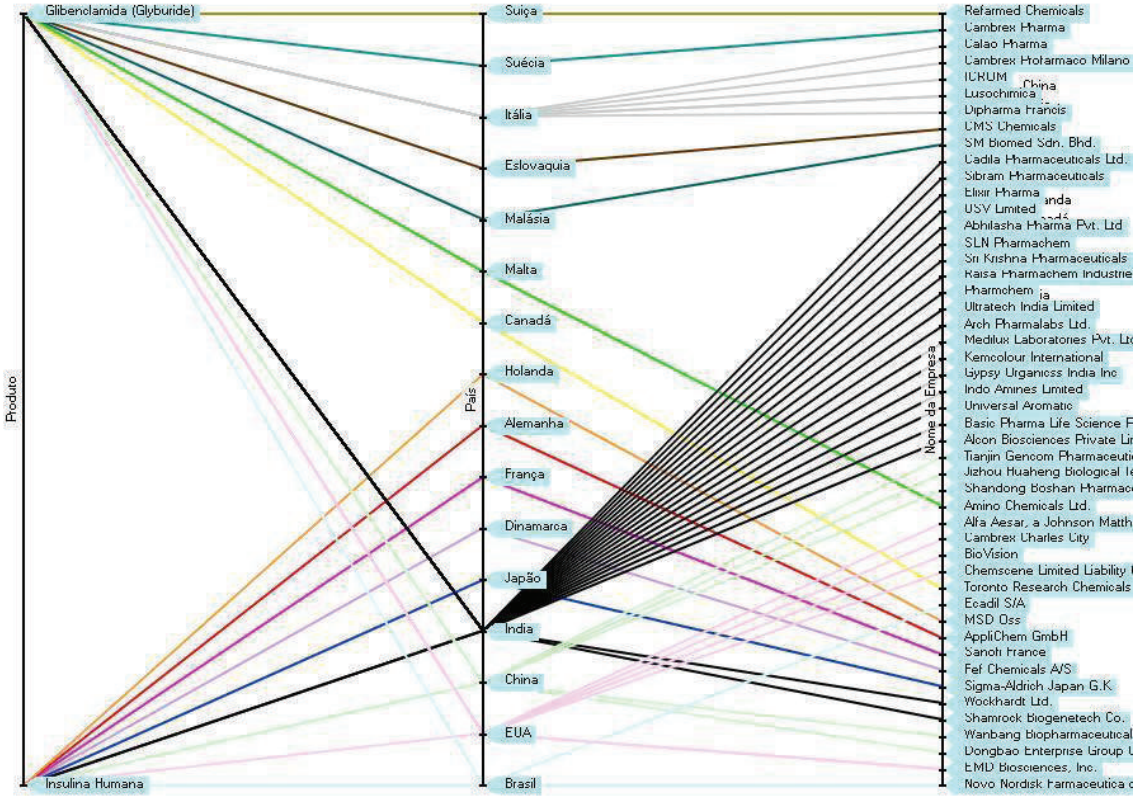
Graph 2. Trade balance of antidiabetics found in the LFO Portfolio



Source: Created by the authors with MDIC, SECEX database ALICEweb (2016).

Considering the data extracted from the AliceWeb database and the Directory of World Chemical Producers (DWCP), it was observed that the possible suppliers of APIs imported and present in the Farmanguinhos portfolio come from India, the USA, Italy, and China, among others. It is important to highlight the potential supplier because the AliceWeb system provides information regarding the "exporting" country, and the existence of API producers in that country was verified in the DWCP database. Figure 1 shows the origin of the country that supplied glibenclamide or insulin to Brazil and the producing company.

Figure 1. Countries exporting Glibenclamide and Insulin to Brazil and potential suppliers.

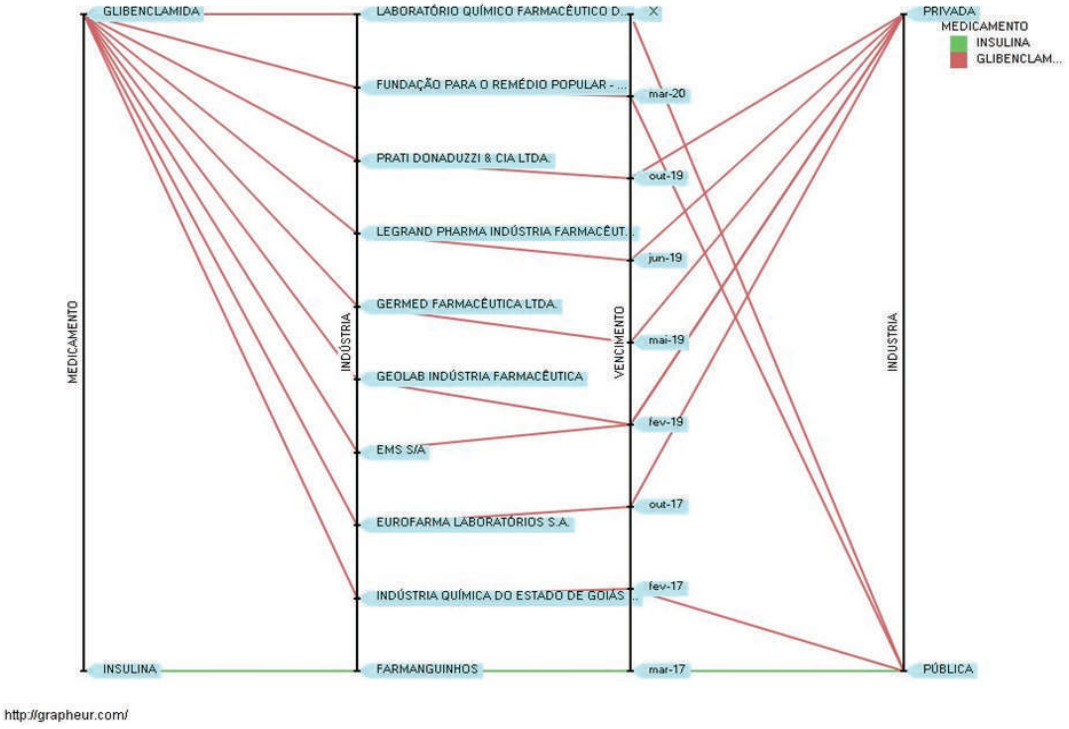


Source: Created by the authors using Grapheur® software with DWCP and AliceWeb2 database (2016).

According to the DWCP, there are 2 national producers: Novo Nordisk Farmacêutica do Brasil

Ltda. and Ecadil S/A. Similarly, according to ANVISA, it was possible to identify 7 companies that have registries of antidiabetic medicines in Brazil, whether public or private, with registrations that are valid until 2020 (Figure 2). In LFO, we highlight the Farmanguinhos, Foundation for Popular Medicine (FURP – Brazilian term) and the Chemical Industry of the State of Goiás (IQUEGO – Brazilian term), which have records for insulin production until 2017 and glibenclamide production until the year 2020.

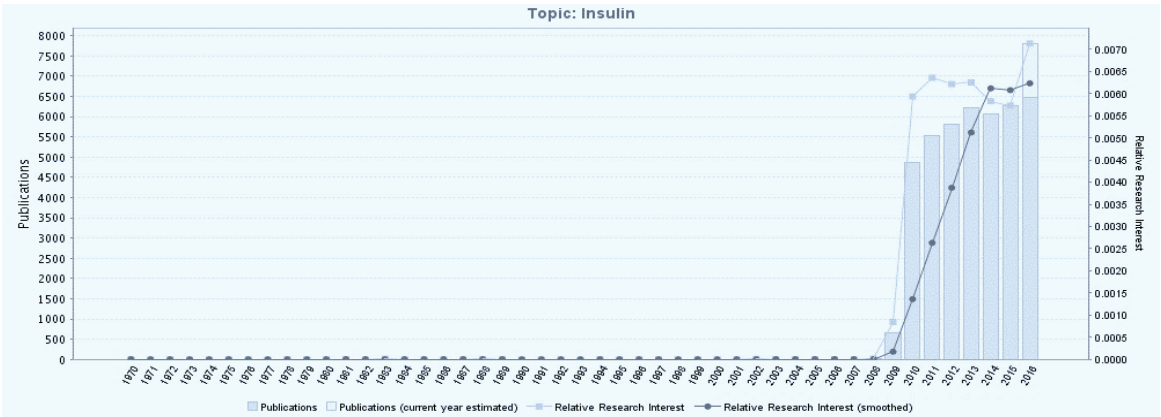
Figure 2 Companies with licenses to market Insulin and Glibenclamide.



Source: Created by the authors using Grapheur® software with the ANVISA database (2015).

Regarding scientific research in the field of antidiabetics, 15728 publications were identified, including publications on insulin and Glibenclamide. The scientific advances of these studies can be demonstrated through scientific publications, as shown in graphs 3 and 4. The researchers aim to improve the health of the population with new molecules, new means of treatment, and improving adherence to treatment, among other methods. For insulin, we identified indexed publications from 2009 and each following year until 2016, with an average of 6,000 publications per year (graph 3).

Graph 3. Scientific publications related to Insulin.

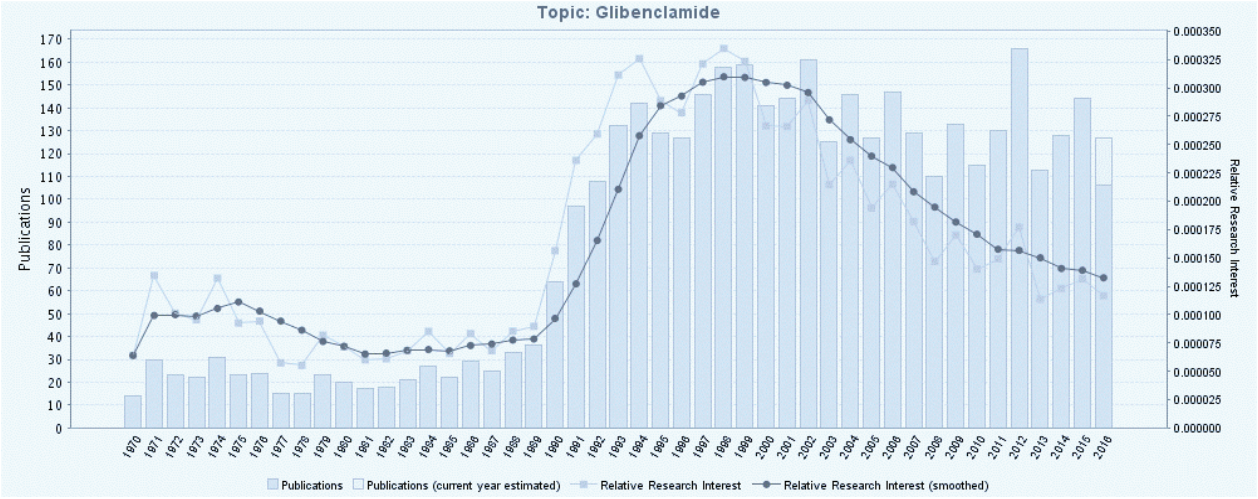


Source: Gopubmed database, September 2016.

For glibenclamide, the scenario is much more disparate; because it is an oral antidiabetic drug,

the searches conducted include older studies. Graph 4 shows that between the 1970s and 1980s, the number of scientific publications was constant (approximately 25 a year), but from the 1980s onward, the number of publications grew by more than 700% and remained at that level until 2016.

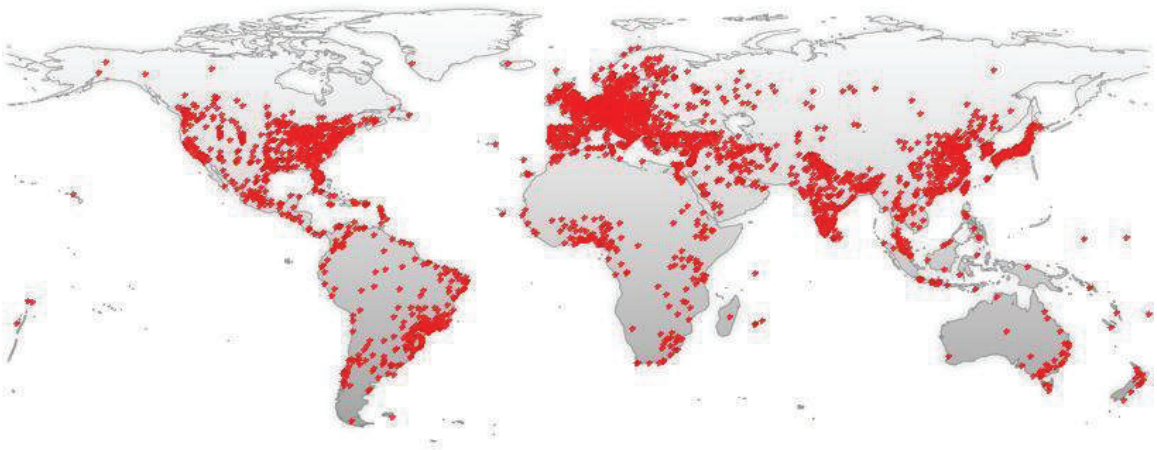
Graph 4. Scientific publications related to Glibenclamide.



Source: Gopubmed database, September 2016.

Regarding the location of the research centres where these publications originated, it can be seen from the map in figure 3 that the TOP 10 countries for publications on glibenclamide are the United States (897), Japan (393), the United Kingdom (220), Germany (207), China (203), India (172), Canada (144), Italy (134), France (122) and Brazil (116). For insulin, the TOP 10 countries are the United States (28,514), Japan (6,851), the United Kingdom (6,882), China (5,868), Germany (4,717), Italy (4,460), Canada (3,899), France (3,705), Australia (2,834) and Spain (2,577).

Figure 3. Origins of articles published on diabetes.



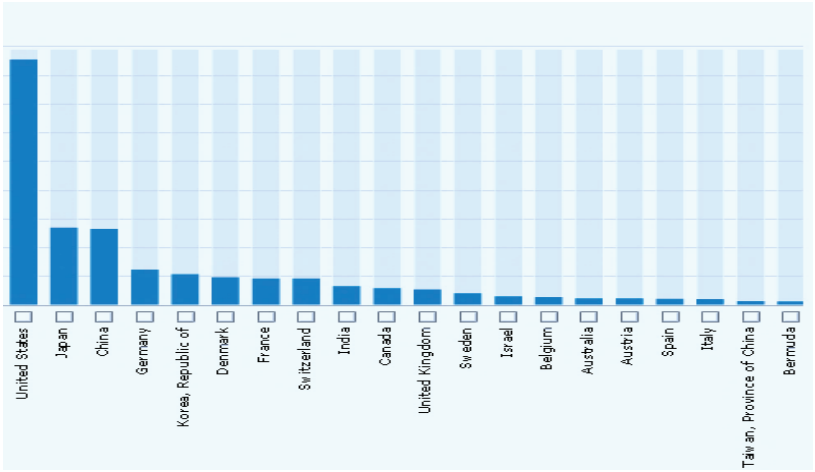
Source: Gopubmed database, September 2016.

Concerning the technological scenario, patents are one of the best indicators of technological

innovation [29–31]. According to the National Institute of Intellectual Property (INPI)[22], every patent filed receives a priority date from the day of deposit, and the applicant has a period of 12 months to make other deposits in other countries to protect its invention or utility model, as the well-known "PCT" Cooperation Treaty[32]. Intellectual Protections are usually for 20 years for inventions and 15 years for utility model technologies. Thus, after the term of protection granted by the State, the technology enters the public domain and generates opportunities for the generic production of the technology and the development of incremental innovations[33].

Graph 5 shows the trends for patents deposited in patent offices in the world corresponding to the antidiabetic group, with 38 for glibenclamide and 4,532 for other antidiabetics, for a total of 4,570 patents. It is worth noting that some of the patents counted were from 2017. That 99% of the deposits are for insulin may be explained by the fact that glibenclamide is a drug whose patent is already under public domain, but it is noteworthy that there are evolutionary studies with this drug. Notably, the TOP 10 countries with publications in scientific journals concerning antidiabetics are the same countries that deposit patents.

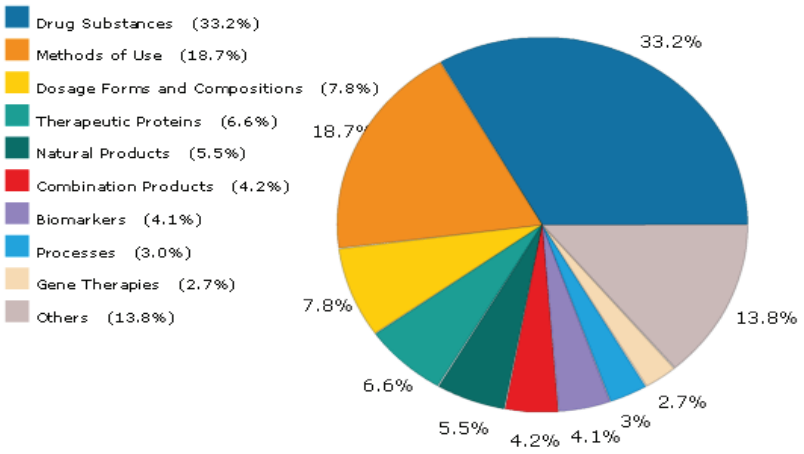
Graph 5. Countries depositing patents for insulin and glibenclamide.



Source: *Thomson Reuters Integrity*, October 2016.

It should be noted that the USA is the largest depositor of patents for glibenclamide and insulin, with a total of 1709 deposits. Graph 6 shows the types of patents made for antidiabetics, such as the creation of new drugs, methods of use and dosages and compositions. Together, the 3 types represent approximately 60% of the total.

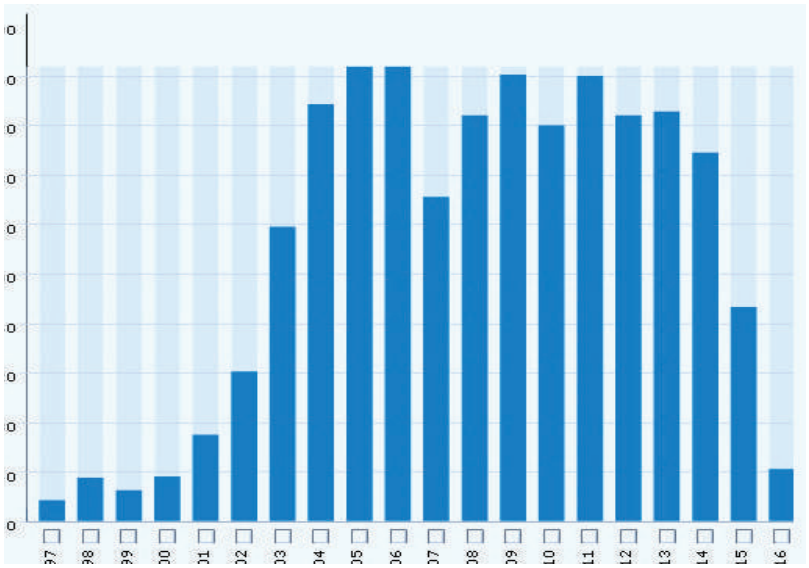
Graph 6. Kinds of patents deposited for insulin and glibenclamide.



Source: *Thomson Reuters Integrity*, October 2016

For insulin patents alone, it is noted that until the turn of the millennium, deposits were very simple, with increases in 2002 and 2003. Over the next ten years, from 2004 to 2014, there were approximately 330 deposits/year, with a record 386 deposited in 2006 (graph 7).

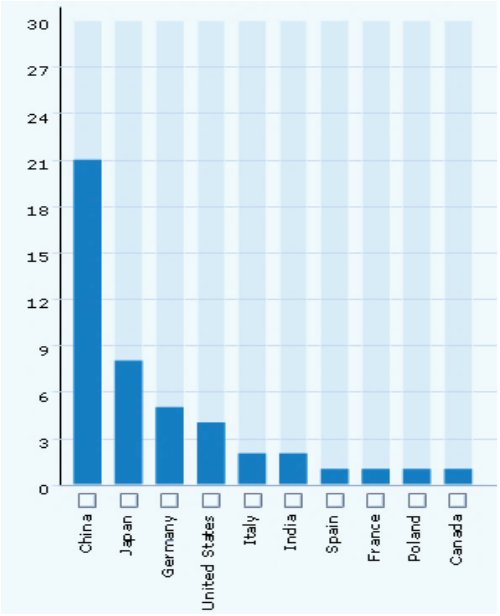
Graph 7. Priority date of the insulin patents.



Source: *Thomson Reuters Integrity*, October 2016.

The glibenclamide corresponds to 0.74% of the total, with 46 patents. In the TOP 10, China is the largest deposit holder, with 21 patents (45.65% of the total), followed by Japan, Germany, the USA, Italy, India, Spain, France, Poland and Canada (graph 8).

Graph 8. Countries that hold glibenclamide patents.

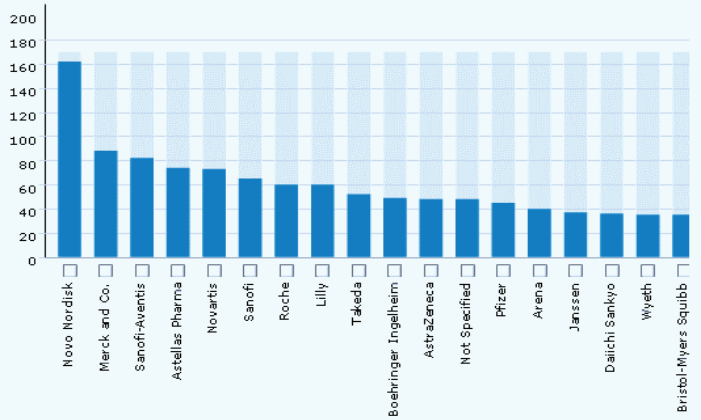


Source: *Thomson Reuters Integrity*, October 2016

When analysing the types of deposits made for glibenclamide, it is observed that the patent holders use glibenclamide in combination with other drugs, which corroborates the already mentioned fact that this drug, when formulated alone, is already in the public domain. The protected forms in the deposits are: methods of use (21.7%), pharmaceutical combination (19.5%), compositions and dosage forms (15.2%), drug substances (13%), natural products, 6%), processes (6.5%), synthesis intermediates (6.5%), kits (2.1%), targets (2.1%) and others (4.3%). The deposits remained constant between 2000 and 2015.

The main depositors of insulin and glibenclamide technologies can be seen in graph 9. The main innovative company in the area of antidiabetics is Novo Nordisk, with 162 patents, followed by Merck with 88 and Sanofi-Aventis with 82 patents. The TOP 10 deposit holders are the US, China, Canada, the Republic of Korea, Japan, Mexico, Russia, Denmark, Germany, and the United Kingdom.

Graph 9. Top patent holders for insulin and glibenclamide.



Source: *Thomson Reuters Integrity*, October 2016

CONCLUSIONS

The pharmaceutical industry continues to reassert itself with one of the most intense R & D & I initiatives, with investments of approximately 20% of sales, which is already more than US $ 1 trillion per year.

The global diabetes mellitus crisis is notorious, with over 400 million people affected and projections to reach almost 650 million by the year 2040. In Brazil, the estimate will be an increase on the order of 65% of the currently existing cases.

Through its public health policies, the Government, acting through the Economic Industrial Health Complex, uses the Public Laboratories as one of the pillars to assist SUS with the production of pharmaceuticals, including antidiabetics. Farmanguinhos has registered 2 antidiabetic products (insulin and glibenclamide), and 90% of these active pharmaceutical ingredients are imported.

The market scenario for antidiabetics in Brazil is substantial, and for API alone, glibenclamide and insulin account for approximately US $ 480 million FOB. The stratification of Brazilian trade balance products is performed by the NCM; however, although a minority, not all drugs have a defined NCM, and some are included among its chemical groups. Thus, the Government must provide for the creation of NCM in a dynamic way to obtain better statistical and financial control of particular molecules.

The scientific trends in antidiabetics were observed; there are more than 15 thousand articles in the area, and the USA is the leading producer of research. In the technological area, patents were verified; the leadership is again maintained by the USA, followed by China, Japan and Germany, when glibenclamide insulin is dissociated.

Brazil depends on the import of antidiabetic drugs from countries such as the USA, Italy, China, and India. Regarding the production of drugs in Brazil, there is a greater number of private laboratory registrations in ANVISA than in the LFO. With the entry of some patents into the public domain starting in 2017, opportunities for new entrants, such as incremental and generic research, will be available.

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