International Journal of Clinical Trials
da Silva RE et al. Int J Clin Trials. 2016 Feb;3(1):15-23
http://www.ijclinicaltrials.com
pISSN 2349-3240 | eISSN 2349-3259

DOI: http://dx.doi.org/10.18203/2349-3259.ijct20160474

Research Article

Pharmaceutical innovation and technological dependence: a study of the Brazilian scenario

Ricardo Eccard da Silva[1]*, Angélica Amorim Amato[2], Maria Rita Carvalho Garbi Novaes[3]

[1]Brazilian Health Surveillance Agency-Anvisa, Brazil
[2]Faculty of Health Sciences, University of Brasilia-UnB, Brazil
[3]Health Science Education and Research Foundation-Fepecs, Brazil

Received: 16 January 2016
Accepted: 30 January 2016

***Correspondence:**
Dr. Ricardo E. Silva,
E-mail: ricardo.eccard@gmail.com

ABSTRACT

Background: Among other factors, a country's pharmaceutical innovation and technological dependence is related to its ability to research and develop technology. Brazil imports pharmaceutical products and drugs, in order to meet the population's needs. The present work's objectives were to investigate whether the innovative drugs registered by the Brazilian Health Surveillance Agency (Anvisa) had been studied in the Brazilian population and, among those studied, to describe the profile of the clinical trials held.
Methods: Documental and descriptive study. The data were obtained from databases: i) Anvisa's Clinical Research Control System (SCPC) and ii) the Products and Services System in Health Surveillance (Datavisa).
Results: Among the drugs registered, the following were observed: 90 new molecules, of which 42% (38) had been studied in the Brazilian population; 24 new combinations of drugs, of which 33% (8) had been studied in the Brazilian population; 23 new biological drugs, of which 61% (14) had been studied in the Brazilian population; 80 new herbal drugs, of which 5% (4) had been studied in the Brazilian population. In the development of new synthetic molecules, 76% (29) had been studied in trials with foreign cooperation. For the new biological drugs, 86% had been studied in trials with foreign cooperation.
Conclusions: A large majority, therefore, of the studies of radical innovations (new molecules and new biological drugs) and incremental innovations (inclusion of new therapeutic indications) involve foreign cooperation, which shows foreign companies' capacity for innovation in contrast with those of Brazil.

Keywords: Innovation, Sponsor, New active pharmaceutical ingredients, Foreign cooperation

INTRODUCTION

The pharmaceutical industry is characterized as an oligopoly differentiated, based on the sciences, in which the competition in the market is grounded in the differentiation of the products.[1] Brazil's incipient capacity for innovation in the production of pharmaceutical ingredients has been reflected in the deficit in the balance of trade in ingredients and medicines since the first years of this millennium. Between 2005 and 2011, importations for the segments of the industry based in chemistry and technology went from US$ 1.7 billion to US$3.7 billion - a growth of 121% in six years.[2]

Innovation may be classified in three categories: revolutionary, radical and incremental. Revolutionary innovation is marked by conceptual advances, such as new scientific theories and principles, which form the basis for further research. For example, a new metabolic or biological pathway may be considered revolutionary. Radical innovation could be a new active pharmaceutical ingredient within a therapeutic class. Incremental

innovation, on the other hand, could be better described as the process of exploring and improving radical products, such as, for example, through investigating new therapeutic indications for an already-known active pharmaceutical ingredient.[3]

The universities have a fundamental role in generating knowledge. Cooperation between the business and academic sectors allows the development of products with a high aggregate value, as well as the improvement of processes. In one study undertaken in the United States, it was demonstrated that university research contributes to industrial projects being concluded, and assists in the implementation of new projects in the majority of companies.[4]

Considering that the knowledge of the capacity for innovation and clinical research is important for Brazil's competitiveness in the area of health, the objectives of the present work were to analyze whether the drugs registered by Brazilian Health Surveillance Agency-Anvisa had been studied in the Brazilian population, to classify the clinical trials in relation to the type of innovation studied (radical or incremental) and type of study (foreign cooperation or national), and to describe the characteristics of those clinical trials undertaken in Brazil.

METHODS

Documental and descriptive study. The data were obtained from databases: (i) the Anvisa Clinical Research Control System (SCPC); (ii) Products and Services System in Health Surveillance (Datavisa). All the clinical trials approved in Brazil are in Anvisa's SCPC.

In the Datavisa system, the following data for registration of drugs approved by Anvisa were collected: (i) new molecule in Brazil, (ii) new combination of drugs in Brazil, (iii) new biological drug and (iv) new herbal drug. These registries are classified as radical innovation. Also collected were data on drugs with the inclusion of new therapeutic indication in Brazil approved by Anvisa. The drugs with new indications approved are classified as incremental innovation.

The registries of drugs selected were published in the Brazilian Official Journal of the Union (DOU) in the period between 01/01/2010 and 31/12/2012 with the status of "granted". For the drugs classified as radical and incremental innovation, the option of "reports" within Datavisa was accessed.

Subsequent to the obtaining of the data from the registry of drugs and inclusion of new indication, a retrospective analysis was undertaken in the SCPC in order to ascertain whether the drugs registered and those with the inclusion of new therapeutic indication in Brazil had been approved by Anvisa for undertaking clinical trials in Brazil.

RESULTS

In relation to the Anvisa data, Table 1 presents the new drugs approved between 2010 and 2012, considered as radical innovation, and the inclusions of new therapeutic indications in the same period, which were considered to be incremental innovations. These data indicate a reduction in the number of all types of registration of drugs by Anvisa in 2012 when compared with 2010. There were no inclusions of new therapeutic indication for new combination of drugs and herbal drugs. The number of inclusions of new therapeutic indications for synthetic drugs also reduced, while the number of inclusions of new indications for biological drugs was maintained.

Table 1: Number of new drugs registered, and inclusion of new indications approved by Anvisa between 2010 and 2012, according to type of drugs (Datavisa).

Registration of new drugs and inclusion of new therapeutic indications in Brazil	Year		
	2010	2011	2012
New molecules	29	39	22
New combination of synthetic drugs	9	10	5
New biological drugs	9	7	7
New herbal drugs	37	19	24
New therapeutic indications for synthetic drugs	20	23	10
New therapeutic indications for biological drugs	5	7	6
Total	109	105	74

Figure 1 shows the number of drugs registered as new, and drugs with inclusion of a new therapeutic indication, approved by Anvisa between 2010 and 2012, which were studied in the Brazilian population. These data show that the majority of the new molecules, the new combination of synthetic drug, and the new herbal drugs were not studied in Brazil.

Figure 2 shows the number of drugs (radical innovation) registered by Anvisa and which were not studied in the Brazilian population. Viral vaccines are between these drugs.

The synthetic drugs with inclusion of new therapeutic indication, which were not studied in the Brazilian population, classified by The Anatomical Therapeutic Chemical (ATC) Classification System: J05A direct acting antivirals; G02C other gynecological; G03A Hormonal Contraceptives for Systemic use. The biological drugs with inclusion of new therapeutic indication, which were not studied in the Brazilian

population, classified by ATC classification: B02B Vitamin K and others Hemostatics; H01A anterior pituitary lobe hormones and analogues.

Clinical trials with foreign corporation are the most prevalent among the clinical trials with drugs registered by Anvisa and which were studied in the Brazilian population (Figure 3).

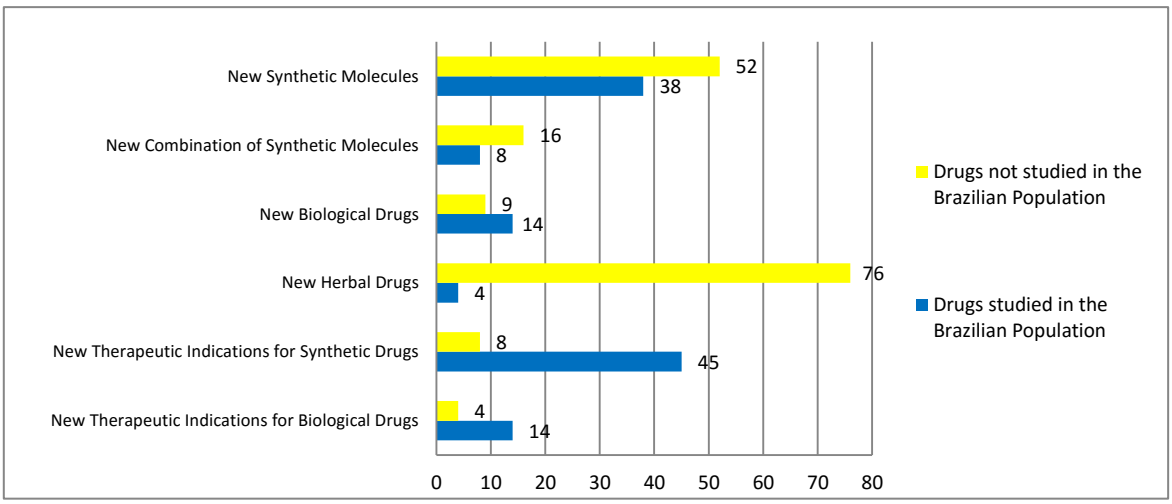

Figure 1: Number of drugs registered and inclusion of new indications approved by Anvisa in relation to the study of these drugs in the Brazilian population, by type of drug. (Data from Datavisa), 2010-2012.

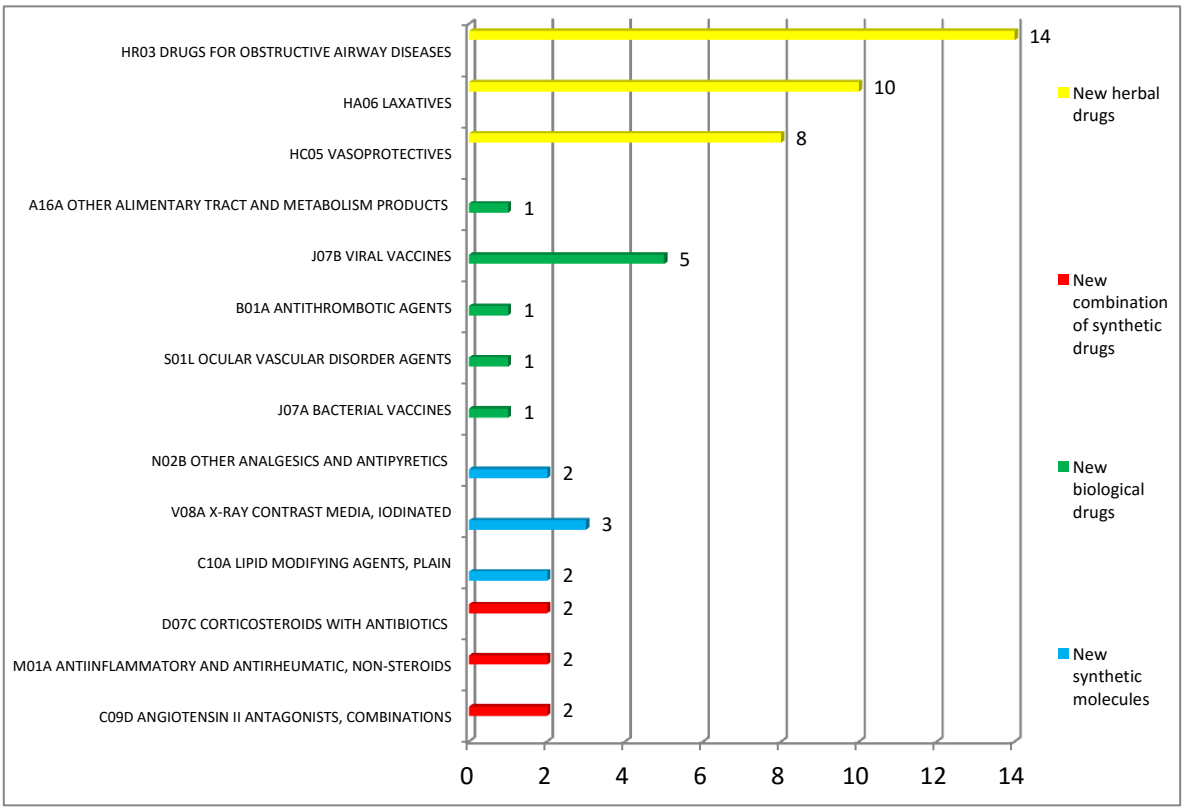

Figure 2: Number of drugs registered (radical innovation) by Anvisa and which were not studied in the Brazilian population, classified by type of registration and by Anatomical Therapeutic Chemical Code classification (Data from Datavisa), 2010 – 2012.

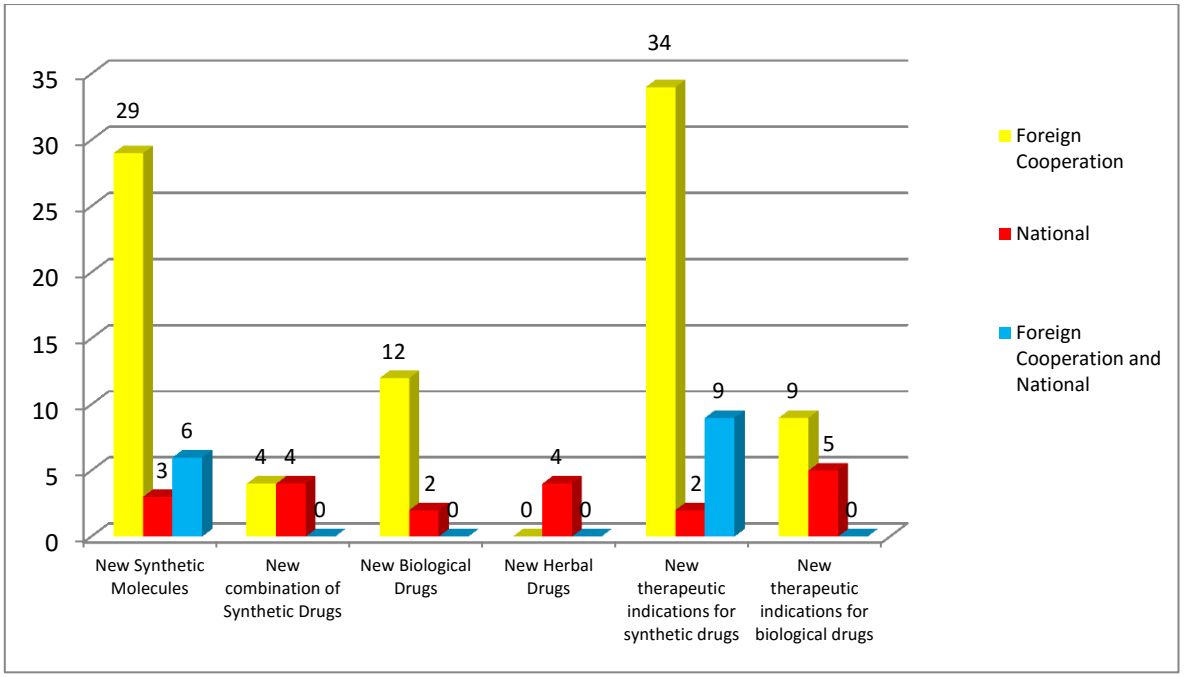

Figure 3: Number of drugs registered by Anvisa and which were studied in the Brazilian population, by type of study and registry of drug. (Data from Datavisa and SCPC), 2010 – 2012.

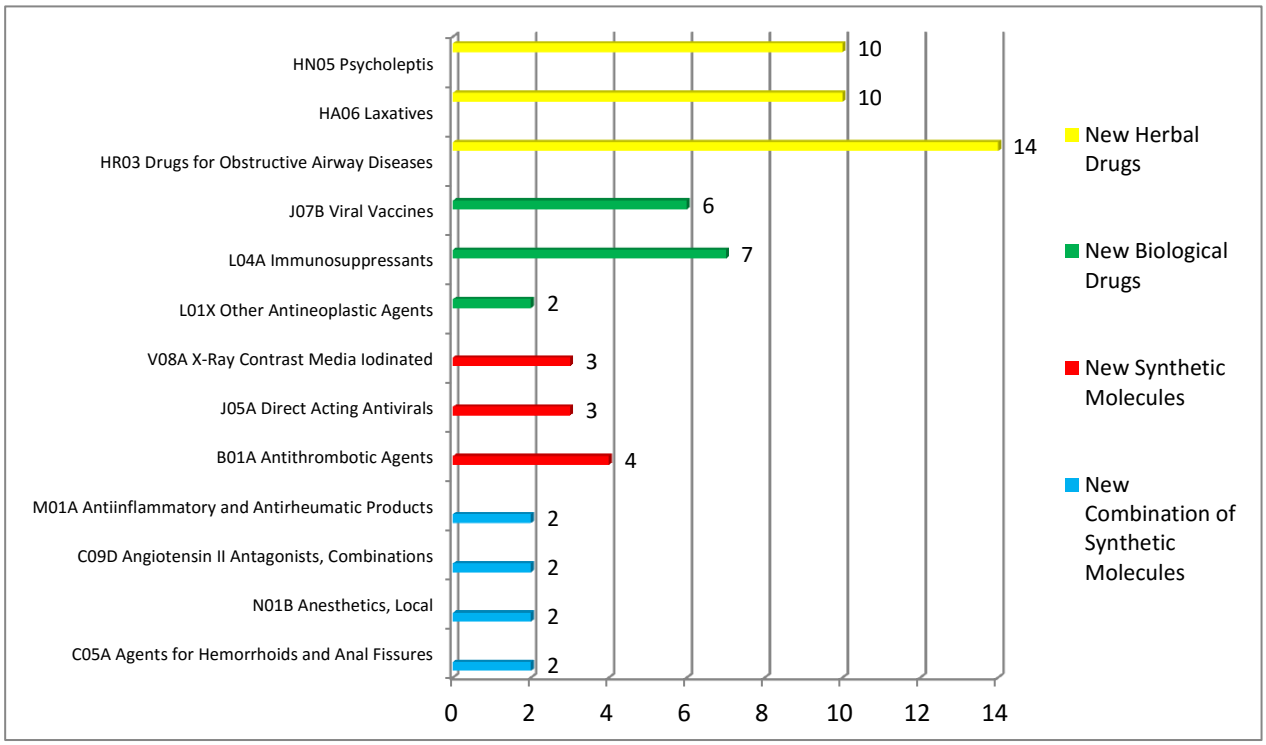

Figure 4: Number of drugs registered most (radical innovation), according to ATC classification. (Data from Datavisa), 2010 – 2012.

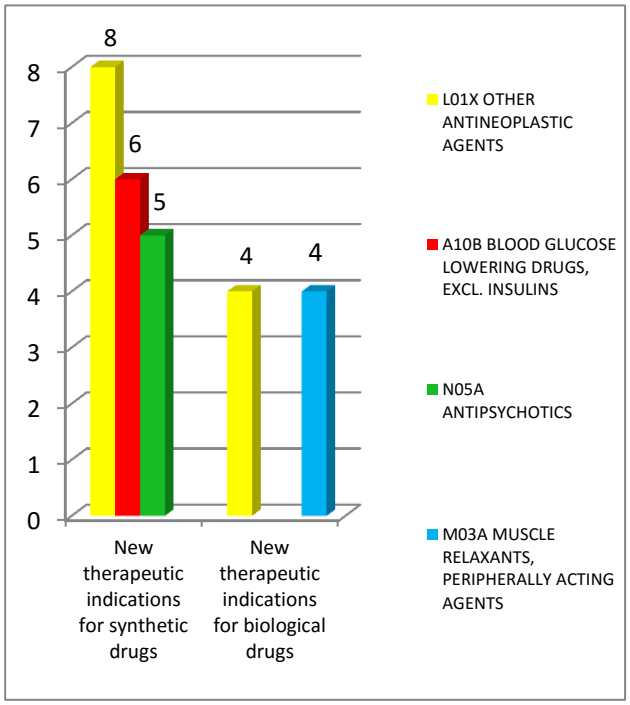

Figure 5: Number of drugs with inclusion of new therapeutic indication in Brazil (incremental innovation), according to ATC classification. (Data from Datavisa), 2010-2012.

Figure 4 shows that a large proportion of the new molecules registered are not indicated for the treatment of neoplasm. In contrast, as shown in Figure 5, the incremental innovations approved by Anvisa are antineoplastic drugs, whether synthetic or biological.

DISCUSSION

The results indicated a reduction in the number of all types of registration of drugs by Anvisa. In the United States the number of new drugs on the pharmaceutical market has reduced over recent years. The Food and Drug Administration (FDA) approved a mean of 22.6 new synthetic drugs and biological drugs per year between 2005 and 2009, below the 37.2 of the period 1995-1999. In 2013, the FDA approved 25 small molecules and 2 biological drugs. The submission of new molecular entities reduced, as in 2012 there were 50 submissions, and in 2013, there were 41.[5,6]

In the FDA there was also a reduction of registries of new molecular entities. This may have been due to the worldwide economic crisis, which affected various sectors of the economy, including the pharmaceutical. Another important factor is that the costs of developing a new molecule are increasingly higher.[7]

The registration of a new drug by Anvisa does not require that the clinical trials, which produce the scientific evidence for efficacy and safety, should necessarily be undertaken with the Brazilian population. These studies may be undertaken outside Brazil. What Anvisa evaluates, among other aspects, is the external validity, that is, the capacity for the generalization of the data to other populations.

In the development of new synthetic active pharmaceutical ingredients, the majority of these molecules have not been studied in the country. Research infrastructure is an important factor in the process of attracting clinical trials for a country. Differently, a large proportion of new biological drugs and drugs with inclusions of new therapeutic indications were studied in the Brazilian population. The transnational companies which dominate the biopharmaceutical and bio-technological market have great interest in Brazil, as the market for vaccines is promising in relation to the incorporation of these products by the public health system.[8,9] Although the large majority of these synthetic and biological drugs with inclusion of new therapeutic indication has been studied in Brazil, one important observation is that the new indications approved by Anvisa for these products are not the indications which were studied in the clinical trials authorized in Brazil with these drugs.

In relation to the new herbal drugs, 95% were not studied in the Brazilian population. This may be related to the possibility for evidencing the efficacy and safety of an herbal drug from the time of use of the product in the population or market, and the data from the literature based on popular use.

According to resolution N. 292/1999[10] of the Brazilian National Health Council, studies coordinated from outside Brazil, or undertaken with foreign participation, are considered to be those which involve, in their promotion and/or undertaking, the following aspects: (i) collaboration of foreign private individuals or legal entities, whether public or private; (ii) the sending and/or receiving of biological materials originating from human beings; (iii) the sending and/or receiving of data and information collected for aggregation in the results of the study; and (iv) international multicentric studies.

These results indicate that both in radical innovations (new synthetic molecule in Brazil or new biological drug) and in incremental innovations (inclusion of new therapeutic indication in Brazil for a synthetic or biological drug), foreign participation is significant in the development of drugs. A large proportion of the innovations in the pharmaceutical area, therefore, are undertaken by international organizations. The innovations in this area which originate from Brazilian organizations remain incipient.

The Brazilian pharmaceutical retail market reached US$ 26 billion in 2011. Between 2003 and 2011, it presented significant growth, of over 20%, with the participation of Brazilian laboratories in the Brazilian market rising from 32.5% to over 50%. On the other side, the Brazilian

sector invests 4.9% of its earnings in innovative activities. However, speaking more strictly, referent to internal Research and Development (R&D) activities, this percentage is 1.4%. Among the major global companies, investment in R&D is superior to 17% of all sales. This scenario is reflected in the disparity between the participation of the Brazilian pharmaceutical market worldwide which is approximately 2.5% and its participation in the total of investments in clinical research, which is below 0.4%.[11]

In the most recent worldwide ranking referent to innovation in various areas, Brazil appears in 68th position. In the previous ranking, Brazil was in 50th position. The 2010 edition of the Global Innovation Index states that Brazil's social inequality, lack of infrastructure, and weakness of the system for protecting intellectual property are factors which strongly influence the country's ability for innovation.[12]

The FDA observed that, in the period of 2012, in 41% of the registries of drugs, the sponsors were emerging, that is, were companies which received the first approval of their drugs.[13] In relation to the companies to which Anvisa awarded registries of drugs between 2010 and 2012, the majority were transnational, regardless of the type of registration. These results reveal that the registries of drugs referent to radical and incremental innovations are dominated by transnational companies. The situation of biological drugs is highlighted, as in the three years evaluated, the registration of new biological drugs was only granted to transnational companies.

The exception was the herbal drugs market, which, in practice, was restricted to the Brazilian industry. Brazil's biodiversity may be a factor explaining Brazilian companies' interest in seeking new drugs based on research into native plants. In addition to this, transnational companies' lack of interest in developing herbal drugs may be due to the lack of specific rules for patents on medicinal plants, which-as they are living beings-cannot be patented. Brazilian legislation also considers the whole or part of living beings and biological materials found in nature, as well as their materials in isolation, not to be inventions. Only standardized formulations with established purposes obtained from plants can be patented.[14]

The investment in research in 2013 by the Brazilian Ministry of Health was R$248.7 million, which represented an increase of seven times in relation to the investment in research made in 2011. In the United States, the investments made in health research by the National Institutes of Health (NIH) and the industry was $88.8 billion. On the other hand, this investment in itself is not sufficient to support a country's progress. The new technologies in health bring benefits, but also many costs.[15,16]

The majority of the synthetic drugs with the inclusion of a new therapeutic indication in Brazil were studied in the Brazilian population. However, in the studies with these drugs, the clinical indications studied did not correspond to the new therapeutic indications approved by Anvisa. In the period 2010-2012, 40 new therapeutic indications approved by Anvisa were not studied in Brazil, and only 13 new indications approved by Anvisa were studied in Brazil. This shows that these drugs with new therapeutic indications approved by Anvisa are being studied in Brazil, but not for the indications for which they are being approved. One explanation is that the clinical indications which were studied in Brazil had not yet been submitted for evaluation by Anvisa. Another possibility is that some clinical indications studied in Brazil have not been successful during their clinical development, either for reasons of safety or efficacy. In relation to the biological drugs with the inclusion of new therapeutic indication in Brazil approved by Anvisa in the period 2010-2012, 12 new indications approved were not studied in Brazil, and 6 new indications were studied. The reasons for not undertaking studies with the new therapeutic indications approved by Anvisa can be similar to those for the synthetic drugs.

The drugs for treatment of cancer and orphan indications dominated the registration by the Food and Drug Administration (FDA) which approved 8 drugs against cancer and 9 new orphan molecular entities between 2011 and 2013 (33% of the total). Moreover, it approved 8 medications against cancer in 2013 (30%), 2012 (33%) and 2011 (27%). 6 of the approvals for drugs against cancer were also orphan indications. Other therapeutic areas in which a higher number of drugs was approved include endocrine and metabolic therapies (2 approvals for type II diabetes mellitus and one for dyslipidemia), antivirals (2 approvals for Hepatitis C and one for HIV) and products for medical imaging (3 approvals).[6]

The most-studied drugs in Brazil, according to data from Anvisa's SCPC, in the period 2009-2012 were 10 other antineoplastic agents (L01X); 9 immunosuppressants (L04A); and 7 without ATC classification. Comparing the drugs most frequently registered in Anvisa with those most frequently studied, according to the approval of clinical trials by Anvisa, the immunosuppressants are among the new most-registered biological drugs, and also among those most studied. Many new active pharmaceutical ingredients in development are not yet placed in the ATC classification.

The drugs placed in the class of monoclonal antibodies are being developed mainly to be options for treatment of cancer and rheumatic and inflammatory diseases. In the registering of new biological drugs, these correspond to the monoclonal antibodies (22% in 2010; 43% in 2011; 57% in 2012). Radiocontrast agents were prevalent in the registries of Anvisa and the FDA. Among the antivirals registered by Anvisa, one is for treatment of HIV, and 2

for Hepatitis C, which is identical to what occurred in the FDA.

According to data from Anvisa's Management Economic Evaluation of New Technologies (GERAE), the therapeutic classes which present the greatest number of new molecules in which the purchase order prices were analyzed by GERAE in the period 2004 – 2011, in decreasing order, were 12% anti-neoplastics (L01), 5.91% drugs used in the treatment of diabetes (A10), antibacterials, systemic antifungals (J01 and J02), 5.91% anticonvulsants, antipsychotics and antidepressants (N03, N05 and N06). These new products are placed in categories I and II of Resolution N. 2 of 2004 of the Technical Chamber of Medicines. Category I refers to those molecules which are the object of a patent in Brazil and bring some benefits of treatment in relation to the therapies already used for the same therapeutic indication. Category II are new products which are not placed in category I.[17]

Various drugs approved by the FDA were not classified as scientific innovations with clinical importance and commercial potential. All of these innovative drugs were registered by transnational companies which have already been active in the pharmaceutical market for many years and already have a tradition of registering new drugs.[6]

In Anvisa, only 3.24% of new products registered in the period 2004 – 2011 were the object of patents in Brazil and brought some benefits in the treatment in relation to the medications already registered for the same therapeutic indication.[17] As a result, it is necessary to reflect that a new drug, which may be considered a type of innovation, may not bring direct benefits either to the population or to the health system, in relation to those already available on the market.

The development of new drugs is closely intertwined with the patent system. The researching and development of drugs requires substantial technical knowledge and investment. The combination of market exclusivity and income from patents drives private investment in innovation, which contributes to the development of new drugs. However, this system also has important implications for public health. For example, when patented products are prescribed, their high costs can reduce patients' compliance with treatment regimes. The costs of brand name drugs contribute to the increase of expenses related to healthcare and can reduce the use of clinically-necessary drugs among patients. It is necessary to balance the incentives for investments in research and development with guarantees that the products will be available to the patients at a reasonable cost.[5]

The reduced concession of intellectual property rights in relation to patent applications filed by Brazilian universities is due to the lack of an executive body capable of administering the policies for protection of intellectual property, licensing and technology sales, in the forms of these which exist in the North-American universities. The creation of nuclei of technological innovation within the Institutes of Science and Technology (which includes the universities) was a requirement of the Innovation Law 10,973 of December 2004, regulated by Decree 5,563, of October 2005. These nuclei must be responsible for managing their innovation policy, for evaluating their research activities, and for monitoring the process of transformation of creation into technological innovation, as well as for promoting partnerships between university and companies.[18]

In the inclusions of new therapeutic indication approved by Anvisa, both for synthetic and biological drugs, a large proportion of inclusions are conceded to transnational companies. The purely national companies are a minority in this process. Furthermore, the majority of new indications are studied in trials involving foreign cooperation. Therefore, considering that the radical and incremental innovations in the pharmaceutical sector are undertaken by international organizations, the national institutions, whether industrial or based in universities or other centers of research, mainly invest in the development of copies (generic medications or similar), after the patents of innovative products have expired. The development of generic and similar drugs is also important for Brazil, and makes it possible to meet some public health needs, as it reduces the prices of the drugs and broadens the population's access. However, these needs also require the use of innovative products, which may have therapeutic advantages which make a difference in the treatment of the patients.

The Brazilian health industries' lack of ability to invest in innovation has guided governmental investment in healthcare for the population towards importation, passing on particular benefits to countries outside Brazil and placing at risk the continuity of the social policies, due to the growing deficits in the balance of trade. This deficit is thought to have been of US$2.9 billion in 2004, for the health sector as a whole, of which US$1.7 billion were related to active pharmaceutical ingredients and medicines.[20]

The Brazilian government, observing the need to strengthen the pharmaceutical industry, selected this sector as strategic within its industrial policy. The action of the National Development Bank (BNDES) was inserted in this context, through the launch of the Support Program for the Development of the Healthcare Industrial Complex (PROFARMA), which had specific lines of financing available for levering the growth of the Brazilian pharmaceutical industry in the activities of production, research, development and innovation.[19]

The Brazilian Ministry of Health has supported the clinical research sector in the country, aiming to encourage competitiveness and innovation in the healthcare industrial complex. In the period 2002-2009, R$140 million were invested in 368 projects. The largest

number of projects financed was in basic research, with 118 projects. The biggest investments were directed towards clinical trials (44 million) and research infrastructure (37 million).[21,22]

In developing new drugs, the main actors involved work separately. Academia is essentially focused on the basic research. The pharmaceutical industry is focused on the applied investigation and development. The government, on the other hand, is involved in the supervision and regulation of the research activities. In the United States, there are initiatives established so as to improve the clinical trials process. The Clinical Trials Transformation Initiative (CTTI) was created in 2007 between the Food and Drug Administration (FDA) and Duke University as a public-private partnership aiming to identify practices which increase the quality and efficiency of the clinical trials.[23]

The Brazilian State has taken certain steps to ensure the sustainability of the health policy, and to reduce the commercial deficit. The new Public Procurement Law (Law 12,349/2010) alters Law 8,666/93, and establishes a differentiated margin of preference in public procurement for products produced or developed in Brazil.[19] An important legal milestone was a publication of Law 13,243 of January 2016. It establishes incentives for scientific and technological research and innovation to achieve national technological autonomy.[24]

CONCLUSION

The Anvisa data referent to the registering of new drugs, the inclusion of new therapeutic indications, and the types (foreign cooperation and Brazilian) of clinical trials held in Brazil showed that foreign institutions have capacity for radical and incremental innovation in the pharmaceutical area.

The data from registration of drugs by Anvisa indicate a reduction in the number of all types of registration of drugs in 2012, when compared to 2010. The number of inclusions of new therapeutic indications for synthetic drugs also reduced, and the number of inclusions of new indications of biological drugs was maintained.

The majority of the new molecules, the new combination of synthetic drugs and the new herbal drugs were not studied in Brazil. The few studies undertaken with herbal drugs were undertaken in Brazil. Therefore, this market of development of herbal drugs belongs almost exclusively to Brazilian industries.

A large proportion of the new biological drugs were studied in the Brazilian population. One hypothesis is that Brazil is entering the route of development of new biological drugs. The majority of synthetic and biological drugs with the inclusion of new therapeutic indication in Brazil were studied in the Brazilian population. In studies with these drugs, however, the clinical indications studied did not correspond to the new therapeutic indications approved by Anvisa. This shows that these drugs with new therapeutic indications approved by Anvisa are being studied in Brazil, but not for the indications which are being approved.

The classes of drugs studied most (SCPC), according to the ATC, were (L01X) Other Antineoplastic Agents and (L04A) Immunosuppressants. On the other hand, those most registered were (HR03) Drugs for obstructive airway diseases; (HA06) Laxative and (HN05) Psycholeptics. It follows that there is no consonance between the drugs which are being studied most and those which are being registered most in Brazil.

The medicines produced in Brazil need to be competitive in relation to foreign products regarding the demand for purchasing of pharmaceutical ingredients and medicines by the Brazilian Ministry of Health. The establishing of priorities for health research and investment in the development of innovations must take into account the epidemiological profile and the health needs of the regions. What is most important is that innovation in the area of health, in addition to improving peoples' lives, should broaden the population's access to new therapeutic options.

ACKNOWLEDGMENTS

The authors thank the Brazilian Health Surveillance Agency (Anvisa) (Brasília, DF, Brazil).

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: da Silva RE, Amato AA, Novaes MRCG. Pharmaceutical innovation and technological dependence: a study of the Brazilian scenario. Int J Clin Trials 2016;3(1):15-23.