

Research Article

Funding of clinical trials in Brazil for the development of new drugs: who are the sponsors?

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ABSTRACT

Background: A low rate of investment in science it is directly impacts the technological independence and capacity in health care costs. Knowledge of funding sources is critical to understand the problem and formulates hypotheses for future studies.

Methods: Two databases were used: the System for Control of Clinical Research (SCCR) from the Brazilian Health Surveillance Agency (Anvisa), and the International Clinical Trials Registry Platform (ICTRP).

Results: From 2009 to 2012, 77% of the clinical trials approved by Anvisa were sponsored by transnational pharmaceutical industry. On the other hand, the national pharmaceutical industry sponsored 8% of the trials over the same period. The most frequent sponsor of clinical trials involving drugs registered in the ICTRP from 2011 to 2012 was the transnational pharmaceutical industry (43%). Among the trials with national sponsors, are those involving neglected diseases such as chronic hepatitis C (ICD X B18.2), cutaneous leishmaniasis (ICD X B55.1) and yellow fever (ICD X A95), which were all sponsored by national governmental foundations. None of the active pharmaceutical ingredients studied by the transnational pharmaceutical industry or the transnational biopharmaceutical company were in the national list of essential medicines. On the other hand, 83% and 66.6% of the active pharmaceutical ingredients studied by national private universities and the international governmental agency, respectively, are in the national list of essential medicines.

Conclusions: The national pharmaceutical industry and government still invests little in Research and Development (R&D) activities, when compared with transnational industries. This affects directly its technological and innovation ability.

Keywords: Clinical trials, Sponsor, Research funding, Drugs

INTRODUCTION

The costs related to the development of new drugs are becoming increasingly higher. However, the number of novel molecules registered by the American regulatory agency (Food and Drug Administration-FDA) has decreased over the last years. Experts point out that the

current model of development and funding of research has been overcome. The world's economic crisis has influenced the costs related to the production and acquisition of active and non-active pharmaceutical ingredients, such as the excipients used in formulations.^{1,2}

Drug development begins with the characterization of potential molecular target, and is followed by

identification and synthesis of compounds that possibly act in these targets. It is then necessary to validate these targets by means of *in vitro* and pre-clinical studies and with the chemical and molecular characterization of the drug tested. Tests in humans begin with phase I clinical trials, which aim to evaluate the safety and tolerability of new drugs. Phase II trials assess the dose and the response to new drugs, and in phase III trials include a larger number of subjects to confirm the drug's efficacy and safety.^{1,2}

The current model of drug development does not focus on a broad characterization of the new molecule since the initial tests in *in vitro* and pre-clinical tests. Moreover, the initial phases of clinical trials are not designed to predict further problems related to safety that may lead to discontinuation of drug tests in more advanced phases. Because of this, few new drugs reach the market.^{1,2}

The pharmaceutical industry worldwide invests around 15% of the capital from its sales in activities related to research & development (R&D) of novel drugs. In the United States, there has been a reduction in the governmental budget for science and the government encourages the partnership between the university and the industry to stimulate innovations, the generation of jobs and the release of products with high therapeutic value. In Brazil, the Federal government has included the productive pharmaceutical chain as a priority target in its industrial politics.^{3,4}

The National Bank for Social Development (NBSD) has collaborated in the process of discussion, elaboration and execution of this politics and in the possibility to offer credit for the national chemical and pharmaceutical productive sector. This initiative is important since, according to the World Bank, investments in science & technology are directly related to a country's social and economic development in addition to its dependency upon foreign technology.³⁻⁵

The Support Funds for Scientific and Technological Development comprise an innovative mechanism to stimulate the strengthening of the national system of Science & Technology. Its resources originate from incident contributions from the billing from companies and/or from exploration of resources from the Union, portions from the taxes on industrialized products from certain sectors and from the Contribution of Intervention in the Economical Domain (CIED) incident upon values which remunerate the use or acquisition of technological knowledge/technology transfer from abroad.⁵

The aim of this study was to map the sponsors of clinical trials and to discuss the types of funding for the development of novel drugs in Brazil.

METHODS

Data were obtained from two databases: (i) the System for Control of Clinical Research (SCCR) from the Brazilian Health Surveillance Agency (Anvisa), between 2009 and 2012; (ii) the International Clinical Trials Registry Platform (ICTRP) from the World Health Organization, between 2011 and 2012.

All clinical trials approved in Brazil are registered in the SCCR from the Anvisa. In this database the clinical trials involving drugs were selected.

The clinical trials selected from the ICTRP had the following features:

Intervention with active pharmaceutical ingredients;

Search for all types of sponsors;

Search for all recruitment status;

Intervention studies involving health products and observational studies were excluded.

The study population's age was classified according to National Institute of Health (NIH).⁶

The research project was evaluated by the Research Ethics Committee (REC) of the University of Brasilia and it was withdrawn because does not fall within the scope of evaluation research involving human beings. This REC understood that research does not involve the participation of human; it is research corresponds to collection of database. No authors had access to personal patient information.

RESULTS

Transnational pharmaceutical industries are the organizations that most frequently sponsor clinical trials with drugs, according to data from studies approved by the Anvisa from 2009 to 2012 (Figure 1). Over these for years, the frequency of studies sponsored by this type of organization was 81, 82, 75 and 72%, respectively. In contrast, the frequency of studies sponsored by the national pharmaceutical industry in the same period was 5, 8, 9 and 12%, respectively.

From 2009 to 2012, most (77.5%) of the clinical trials approved by Anvisa were sponsored by transnational pharmaceutical industry, followed by the national pharmaceutical industry (8.55), transnational biopharmaceutical companies (8%), international research centers (2.755), national governmental institution or foundation (2.255) and transnational biotechnology company (1%), as shown in Figure 1.

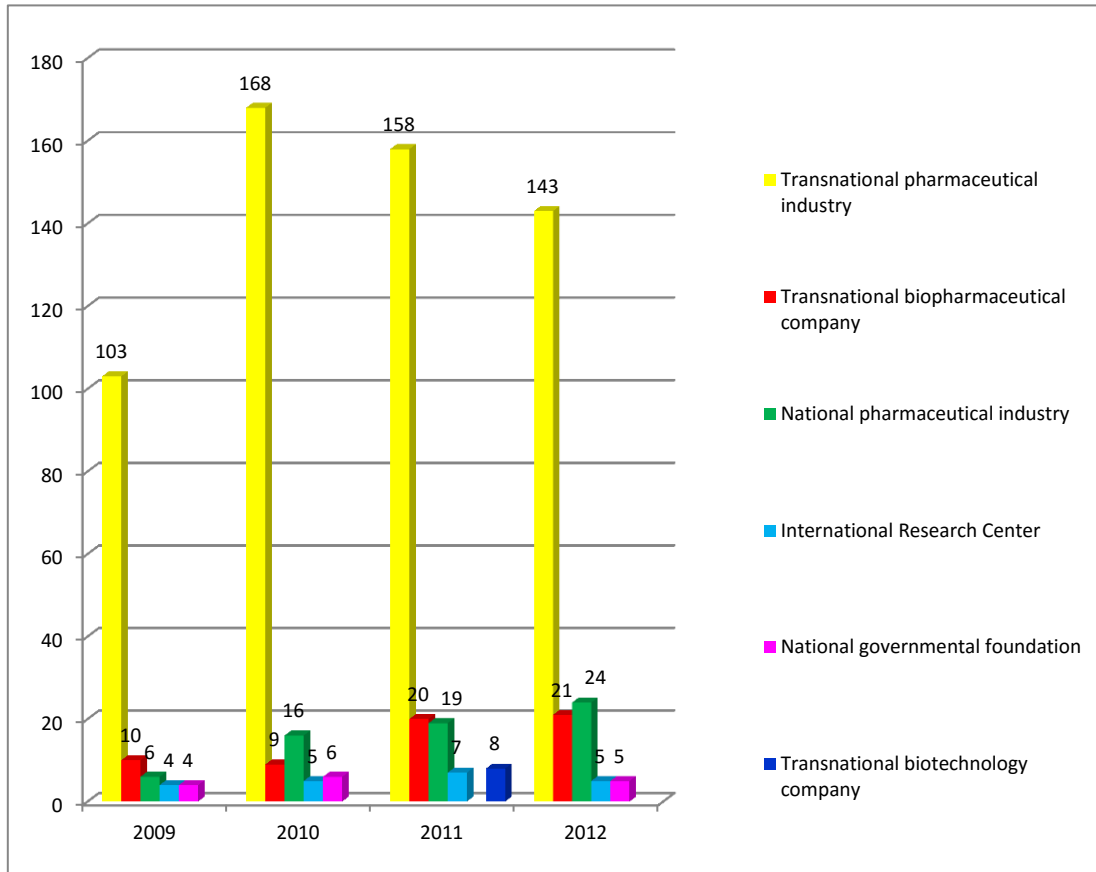


Figure 1: Number of clinical trials approved by Anvisa, according to the type of sponsor, from 2009 to 2012.

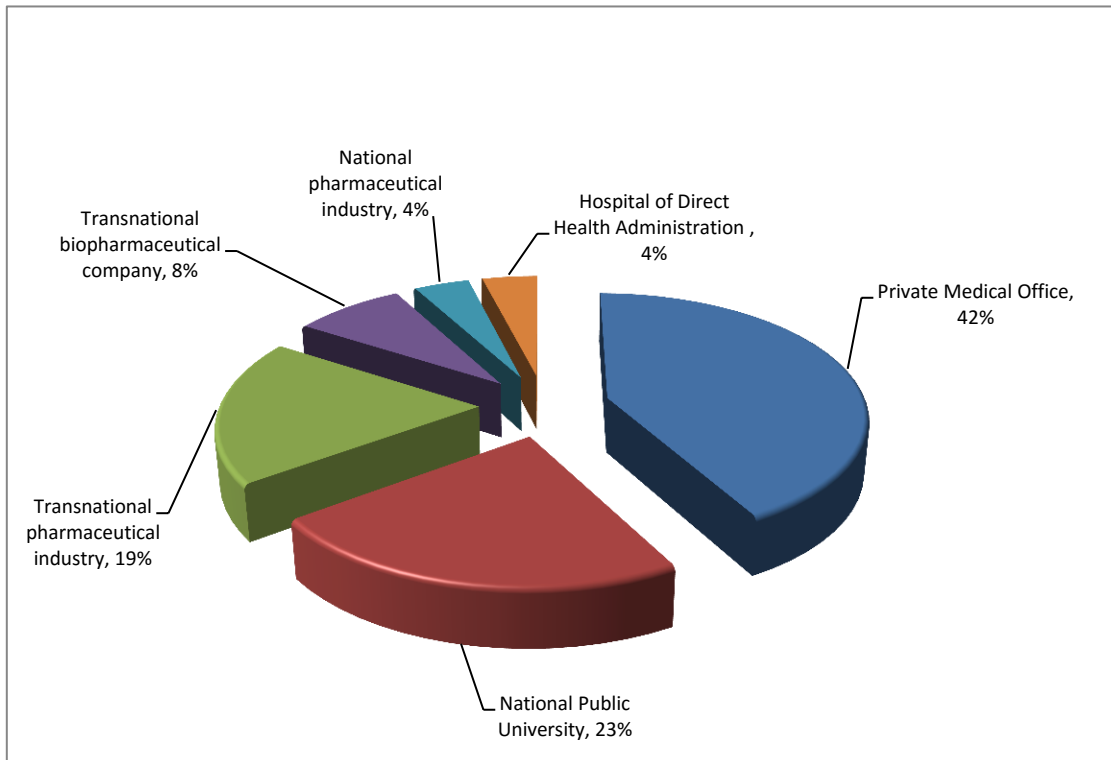


Figure 2: The most frequent types of phase I clinical trials sponsors in studies registered in ICTRP from the World Health Organization in 2011 and 2012.

The most frequent sponsors of clinical trials with drugs registered in the ICTRP in 2012 were the transnational pharmaceutical industry (43%), the national public university (14%) and the transnational biopharmaceutical company (11%).

The organizations that less frequently sponsor clinical trials registered in the ICTRP, totaling 1% of the trials, were the national governmental foundation, international research groups, clinics - beneficent entities without profitable purposes, private national hospitals, the international governmental agencies, national research groups and national entities without profitable purposes.

Private medical offices were the organizations that most frequently sponsored phase I clinical trials (%), as shown in Figure 2. The transnational pharmaceutical industry

sponsored more frequently phase II and phase III clinical trials. Phase IV trials were more frequently sponsored by the national public universities and the transnational pharmaceutical industry.

Table 1 shows the diseases studied in clinical trials registered in ICTRP, according to the type of sponsor. Type 2 diabetes was the most frequently studied disease in clinical trials sponsored by the transnational pharmaceutical industry, corresponding to 39% of the studies. Malignant lung neoplasms also stand out as the most frequently studied disease in clinical trials sponsored by the transnational biotechnology company, corresponding to 9% of the studies. Among the studies with national sponsors are those involving neglected diseases, such as chronic hepatitis C (B18.2), cutaneous leishmaniasis (B55.1) and yellow fever (A95), which were sponsored by the national governmental foundation.

Table 1: Types of diseases most frequently studied in clinical trials registered in the ICTRP, according to the type of sponsor, in 2011 and 2012.

Type of sponsors - ICTRP 2011 and 2012	Most frequently studied disease (classified according to the ICD)	Number of studies	Percentage (%)
Transnational pharmaceutical industry	Type 2 diabetes (E11)	18	39
Transnational biopharmaceutical company	N39.0 Urinary tract infection, site not specified	3	21
	Acute hepatitis C (B17.1)	3	
	Peritonitis (K65)	3	
Transnational biotechnology company	Malignant neoplasm of bronchus and lung (C34)	4	9
National governmental foundation	Chronic hepatitis C (B18.2)	1	8
	Cutaneous leishmaniasis (B55.1)	1	
	<i>Plasmodium vivax</i> malaria (B51)	1	
	Yellow fever (A95)	1	
National public university	Chagas' disease (chronic) with heart involvement (B57.2)	3	7
International research group	Human immunodeficiency virus disease resulting in other conditions (B23)	2	4
National pharmaceutical industry	N95.1 Menopausal female climacteric states	2	4
Hospital / beneficent nonprofit entity	I21 Acute myocardial infarction	2	4
National research group	C90.0 Multiple myeloma	1	2
National private hospital	I25.1 Atherosclerotic heart disease	1	2

The most prevalent types of sponsors in clinical trials registered in the ICTRP from the World Health Organization involving exclusively newborns (up to 1 month of age), in 2011 and 2012, were the transnational pharmaceutical industry (53%), the transnational biopharmaceutical company (27%), the transnational biotechnology company (7%), the national public university (7%) and the investigator-sponsor (7%). The transnational pharmaceutical industry and the transnational biopharmaceutical company were the organizations that conducted most of the studies with newborns (aged up to 1 month), infants (aged from 1 to 23 months), children (aged from 6 to 12 years) and

elderly (aged over 65 years). Data from studies involving children are presented in Figure 3.

In 2011, the organizations that most frequently sponsored studies exclusively involving children were the transnational pharmaceutical industry (56%), the transnational biopharmaceutical company (9%), the national pharmaceutical industry (7%) and the national public university (7%). In 2012, these data were: the transnational pharmaceutical industry (55%), the transnational biopharmaceutical company (16%), the national pharmaceutical industry (3%) and the national public university (10%).

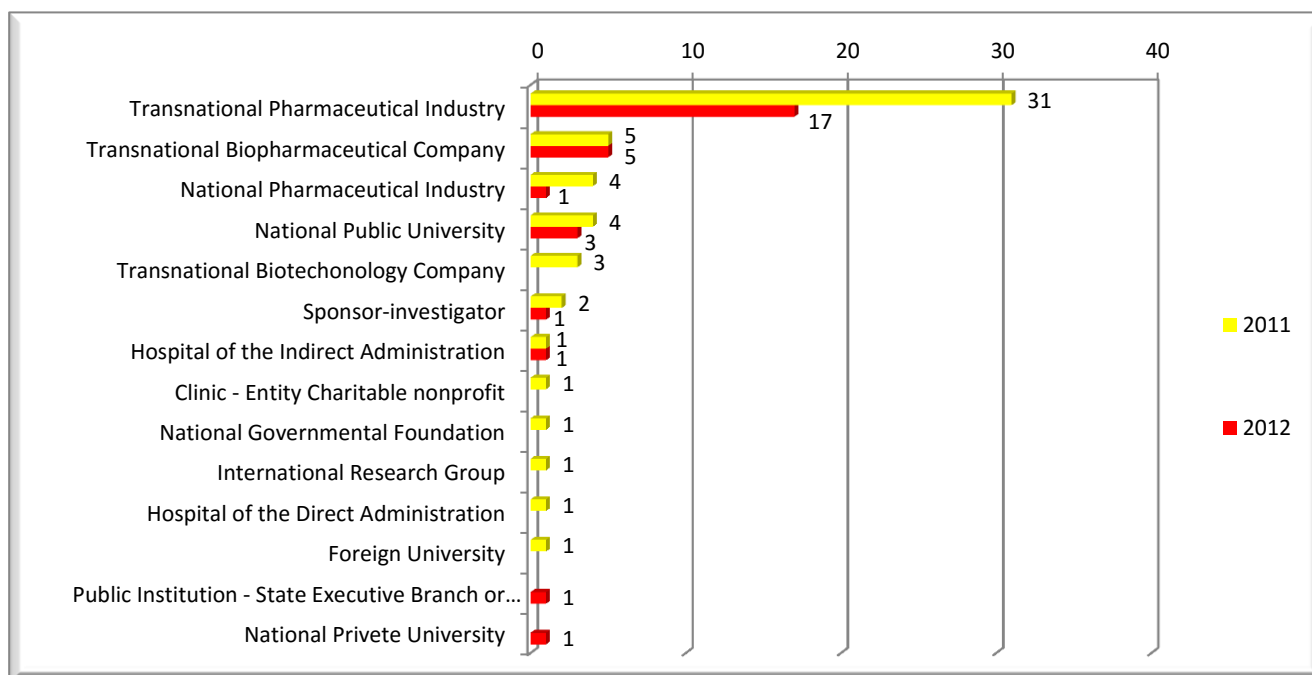


Figure 3: Most prevalent types of clinical trials registered in the ICTRP from the World Health Organization, exclusively with children (6 to 12 years old, 2011 and 2012).

Table 2: Active pharmaceutical ingredients most frequently studied in clinical trials registered in the ICTRP, according to the type of sponsor, in 2011 and 2012.

Type of sponsor	Pharmaceutical ingredients	Number of studies	Percentage (%)
Transnational pharmaceutical industry	Tofacitinib	8	30
	Trastuzumab	4	
	Pertuzumab	4	
Transnational biopharmaceutical company	Ceftazidime	3	12
	AMG 145 (evolucumab)	3	
Biotechnology transnational company	Denosumab	2	12
	Recombinant activated factor VII	2	
	Lebrikizumab	2	
National private university	Azithromycin	1	12
	Botulinum Toxin	1	
	Carbamazepine	1	
	Ketoprophen	1	
	<i>Paullinia cupana</i>	1	
National pharmaceutical industry	Lidocaine	1	
	Ibuprophen	3	6
International government agency	Isoniazid and rifapentine	1	6
	Lopinavir and ritonavir	1	
	Quadrivalent human papillomavirus virus	1	
National philanthropic entity	<i>Capsicum frutescens</i>	1	6
	<i>Hibiscus sabdariffa</i> and <i>Centella asiatica</i> dye	1	
	<i>Maytenus ilicifolia</i>	1	
Foreign university	Alteplase	1	6
	Mebendazole	1	
	Riphampicin	1	
National government foundation	Meglumine	2	4
National research group	Dexamethasone	1	4
	Thalidomide	1	
International research group	Lopinavir and ritonavir	1	2

Regarding the clinical trials approved by Anvisa from 2009 to 2012, around 7% of the studies corresponded exclusively to the population aged 12 or less. The population aged 65 or more corresponded to 2% of the studies.

The most frequently studied active pharmaceutical ingredients in clinical trials registered in the ICTRP are correct, according to the Anatomic, Therapeutic and Chemical (ATC) classification were: 58% are not classified in ATC classification, 15% classified as other antineoplastic agents (L01X) and 11% as immunosuppressants (L04A). The most frequently studied active pharmaceutical ingredients in clinical trials registered in the ICTRO, in 2011 and 2012, according to the type of sponsor, are shown in Table 2. Among the three most frequently studied drugs by the transnational pharmaceutical industry, two are monoclonal antibodies. Ibuprofen was the most frequently studied drug by the national pharmaceutical industry, corresponding to 6% of the studies registered in the ICTRP, and plant extracts were most frequently studied by the philanthropic national entities, also corresponding to 6% of the studies registered in the ICTRP.

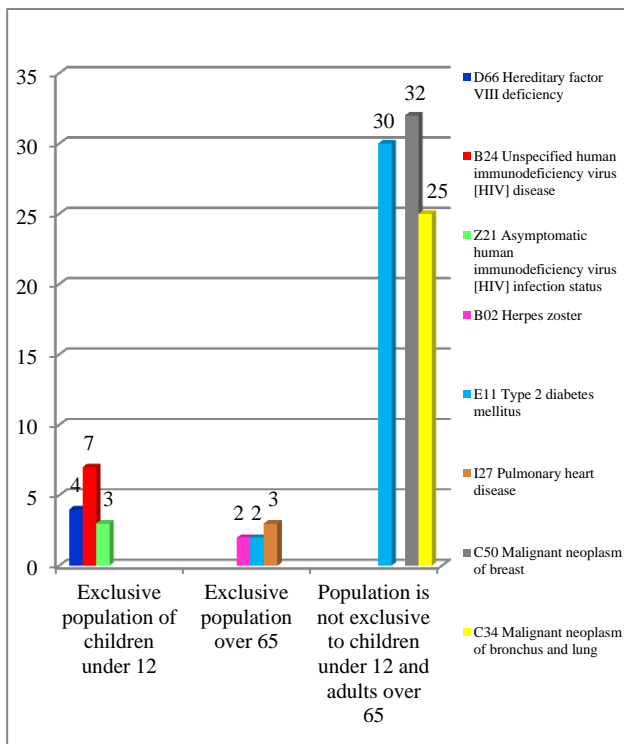


Figure 4: Frequency distribution of the most commonly studied diseases in clinical trials with foreign cooperation, approved by the Anvisa, according to the age of the population studied, from 2009 to 2012. Diseases were classified according to the International Classification of Diseases.

The frequency of the diseases most frequently studied in clinical trials involving foreign cooperation, according to the age of the population studied, is shown in Figure 4. In

the population involving exclusively subjects aged 12 or less, the most commonly studied diseases were unspecified human immunodeficiency virus disease (B24; 27%) and hereditary factor VIII deficiency (D66, 15%).

In the population aged 65 years or more, the most frequently studied diseases were the cardiopulmonary ones (42%). In the population not exclusively aged 12 years or less or 65 years or more, the most commonly studied diseases in the trials with foreign cooperation were breast malignant neoplasms (15%), type 2 diabetes (14%) and lung malignant neoplasms (12%).

In national clinical trials, the diseases studied in the population aged 12 years or younger were allergic diseases, leukemia, meningococcal meningitis (one study each). In the population aged 65 years or more, there was only one study registered, involving degenerative macular disease. The most frequently studied diseases in national trials in the population not exclusive of 12 years of age or less and of 65 years of age or more were varicose vein disease (13%) and asthma (17%).

DISCUSSION

The most frequent sponsors of clinical trials with drugs registered in the ICTRP in 2011 and 2012 were the transnational pharmaceutical industry, the national public university and the transnational biopharmaceutical company. It is common that international sponsors do not have a branch in Brazil and select a university to be the coordinating center of the study in the country. The university is then a representative of the sponsor in Brazil and, when the study is registered in the electronic basis of registration, the university is described as the sponsor of the study. The information that the public national university is among the 3 organizations that most frequently sponsor clinical trials in Brazil may therefore not be reliable.

Private medical offices were the organizations that most frequently sponsored phase I clinical trials (%). This is because Private medical office carry out bioequivalence studies to investigate pharmacokinetic variables in healthy volunteers, and these studies are classified as phase I clinical trials in the ICTRP.

Among the studies with national sponsors are those involving neglected diseases, such as chronic hepatitis C (B18.2), cutaneous leishmaniasis (B55.1) and yellow fever (A95), which were sponsored by the national governmental foundation. The national public university studied Chagas' heart disease. Neglected diseases, which are common in poor or developing countries, still arise little interest from the transnational pharmaceutical companies. Although research involving these diseases is a high priority for Brazil, they do not result in financial return to companies.⁷ However, regarding the transnational biopharmaceutical company, the most

frequently studies diseases were infectious and contagious diseases. These diseases still have a worldwide market for the development of novel active pharmaceutical ingredients, mostly antibiotics.

The development of novel medications for the pediatric population is still not a priority for the pharmaceutical industry or other research institutions. Data from the adult population should not be generalized to children and teenagers. The number of medications approved by the Food and Drug Administration (FDA) over the last five years for the pediatric population was 28, with maintenance of a mean of 5 medications approved per year, and this is still a small number.^{8,9}

Chronic diseases such as type 2 diabetes and malignant neoplasms, frequently studied in the population aged 65 or more, are diseases related to lifestyle, but also to the process of aging. Although the interest in research involving rare diseases has increased, this interest is still considered small by the public and private organizations. In the United States, the main front lines of research involving this type of disease comes from donations of certain drugs to the university and the NIH, which received an investment of 3.6 billion dollars for research in this area. The pharmaceutical industries that invest in research involving these diseases are few. However, according to experts, there are new pharmaceutical companies entering this market, which is currently expanding. This is because although they involve rare diseases, the prices of drugs that are marketed outweigh the restricted market. Moreover, in the United States and Europe, an advantage of investing in this sector is the regulatory incentives, with a simplification of the process for approval of these drugs. There are also fiscal incentives for the conduction of clinical trials involving these diseases.¹⁰

The international governmental agencies receive drug donations from the pharmaceutical industries to conduct multicenter international clinical trials. The clinical indications for the drugs studied by these agencies were tuberculosis, human immunodeficiency syndrome and papillomavirus infection.

None of the active pharmaceutical ingredients studied by the transnational pharmaceutical industry and by the transnational biopharmaceutical company are in the national list of essential medicines. This list refers to medicines that the Brazilian population must have a broad access, since they are very important in public health. In contrast, most of the active pharmaceutical ingredients studied by the national private university and the international governmental agency are in the national list of essential medications (83 and 66.6%, respectively). Therefore, the international governmental agency is studying ingredients of interest for public health in Brazil.

Ibuprofen was investigated by the national pharmaceutical industry for muscle pain and tendinitis. On a general perspective, data described in Table 2 point that foreign sponsors develop new active pharmaceutical ingredients, whereas national clinical trials study molecules already registered and for indications already registered in their label, but not for new indications.

These are studies for regulatory adequacy, that is, studies with more robust outcomes when compared with those previously published.

According to the data from the ministry of Health in 2009, the most common causes of hospitalization of individuals aged 5 to 9 years are, in a descending order, those related to pregnancy, labor and puerperium, mental and behavioral disturbances, diseases of the circulatory system and neoplasms.¹¹ Therefore, the diseases studied in the trials approved by Anvisa do not correspond to the most frequent causes of hospitalization in a certain age range, because the most commonly studied diseases were unspecified human immunodeficiency virus disease and hereditary factor VIII deficiency.

Clinical trials with foreign cooperation involve diseases associated with higher mortality, such as neoplastic diseases, whereas national trials investigate diseases associated with lower mortality, such as varicose vein disease. This may be related both to technological development capacity as the market issues. More serious and complex diseases may require more sophisticated medicines that require more investment in research. To invest more in research and innovation, the organization also seeks the recovery of investment in the most promising research areas such as cancer, which are a major cause of death worldwide.

In the United States, the government, specifically the NIH, sponsors almost half of all biomedical research. The financial support from the government is strongly directed towards basic scientific research. It is suggested that American researchers have a greater interest for basic research that for research directed to the development of new drugs because of the support provided by the government.¹²

The Ministry of Health from Brazil has supported clinical research in the country by stimulating competitiveness and innovation in the health industrial complex. From 2002 to 2009, it had invested 140 million reals (Brazilian currency unit) in 368 research projects. Among them, the majority of sponsored projects involved basic research. The higher investments were directed towards clinical trials (44 million) and research infrastructure (37 million).^{13,14}

In the Brazilian scenario, research funding by the government occurs in different ways. The *Inova Saúde* (Innovates Health) program is part of the *Plano Inova Empresas* (Innovates Companies Plan), which involves

other productive chains and will offer 32.9 billion reais in credit modalities. The Inova Empresas has already received of more than 1.9 thousand funding requests from companies, which totalize 56.2 billion reais. Biopharmaceuticals, pharmaceuticals and medicines are among the priority lines of the program.¹⁵

In the context of stimulation of technological development in Brazil, the Ministry of Health develops the politics of Partnerships for Productive Development (*Parcerias para o Desenvolvimento Produtivo*, PDP), which involves technology transfer from public and private laboratories to the national production of strategic products for health system. The partnership enables medicines purchase at a lower price, since the government acquires a great amount of products with a progressive reduction in their price over the years. The number of biological products nationally produced will rise from 14 to 26 with the partnerships.¹⁶

The technology transfer contracts in Brazil occur mainly for biological products, especially vaccines. With these contracts, it is possible to acquire technology for the development of known products. Technology transfer has commercial goals for the company that will transfer technology. The companies with higher aversion to risk and with smaller propensity to invest in research and development use this strategy. Technological learning will depend upon the existence of previous knowledge and of the nature of technology that will be transferred. The technology transfer strategy may aggregate technological competence, as opposed to the strategy of simply importing products, which does not aggregate technological knowledge.¹⁶

The *Modelo Hélice Tripla* (Triple Helix Model) proposes a dynamic relationship between the government, science conducted at the university and technology developed in companies. Only by means of an interaction between the government, university and companies it is possible to develop an innovation system that is sustainable and durable, in a knowledge-based economy. This model considers that, besides multiple interactions, each component of the system should perform tasks that were previously to the other two, with the formation of networks between the various institutional spheres. The cooperation process between university and companies presupposes a variety of interactions, aiming the growth of knowledge basis of both participants, in a process of transfer and transformation of products and services.¹⁷

The reduction in governmental budgets for science has forced universities to seek other funding sources. The inventions sponsored by private corporations do not have limited applications, directed only to business interests, but they result in as much as social benefits as those sponsored by public institutions.¹⁸

The *Programa de Estímulo à Interação Universidade-Empresa para Apoio à Inovação* (Program for

Stimulation of University-Company Interaction for the Support of Innovation) was created by the Law number 10.168 from 29 December 2000 and has as its main aim the stimulation of Brazilian technological development, by means of scientific and technological research programs that intensify the cooperation between higher education institutions and research centers with the productive sector, therefore contributing to accelerate the process of technological innovation in the country.¹⁹

In the framework of recovery of national investments in science it should be pointed that in Brazil the production of science is essentially restricted to public universities and some research institutes. Despite the magnitude of its budget, the University of São Paulo (USP) does not have resources to directly fund research. USP's financial contribution should be understood as the physical conditions, libraries, computer network and communication services and, especially, the salaries of researchers and of the support staff. The direct financial input to research products is restricted to the limited ingredients from the university's dean office.⁵

The role of the *Fundos de Apoio ao Desenvolvimento Científico e Tecnológico* (Funds for Supporting Scientific and Technological Development) is very important for the advance of science and one of its basic premises is to support the development and the consolidation of partnerships between universities, research centers and the productive sector, aiming to induce the increase in private investments in science and technology. However, the regional impact of state investment in science and technology varies in the country. The scenario of different ingredients for science and technology funding also affects the social and economic indicators, which may in turn reinforce inequalities.⁵

Investment in research is an important aspect in the process of innovation in health. However, besides from the investments, it is important to analyze the processes of innovations in health in the view of public politics. There is still little interaction between public politics and research. The consonance between the funding of research defined in the national agenda of health priorities and the industrial politics priorities for the development of new medicines must be considered a goal to be reached, because the process of innovation is still viewed through the industrial logic and not through the health politics logic.²⁰

The amount of expenses with R&D relative to the gross national product in Brazil, Russia and China is significantly lower than the global mean, representing less than half of the percentage of the world's expense. The expenses with this activity by Brazilian pharmaceutical industries are around 0.83% of their sales revenue. On the other hand, transnational pharmaceutical industries invest around 15% of their sales revenue in R&D activities. In the health sector, the research funding agencies direct 25 to 30% of their budget to health.^{21,22}

CONCLUSIONS

Overall, clinical trials involving foreign cooperation investigated high-mortality diseases, such as neoplasms. National trials investigated lower-mortality diseases, such as varicose vein disease and asthma. Research involving neglected diseases, which were the least studied ones in clinical trials approved by the Anvisa, are being sponsored by the national governmental agency and the national public university.

There is a large investment in research for the development of new medicines by the transnational pharmaceutical industry, the active pharmaceutical ingredients that are being developed are not always match health needs from the Brazilian.

Brazil and other developing countries still invest little in R&D activities, since transnational pharmaceutical industries can allocate a significant fraction of their revenue in research. This affects directly its technological and innovation ability and increases its competition power. The national pharmaceutical industry still invests little in R&D activities, but our findings suggests that it sponsors more clinical trials in Brazil than other institutions, such as governmental organizations and transnational biotechnology industries.

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Ethical approval: Not required

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