Phytomedicines: Legislation And Market in Brazil

Fitomedicamentos: Legislação e Mercado no Brasil

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ABSTRACT

Brazil has nearly a third of the world flora represented in ten biomes with an exuberant biodiversity, however, very little has been done to transform this potential into competitive advantage in the market for herbal medicines and medicinal plants. The use of plant species in the treatment of various diseases can ensure the diffusion of new technologies and the development of the consumer market as well as social inclusion and reduction of economic inequalities. This study aims to review the regulatory aspects of the registration of herbalmedicines and medicinal plants in Brazil, as well as the global market situation and national levels in this segment. We conducted the survey and analysis of publications related to the issue to know the reality of the herbal medicines industry, research and governmental actions for the development and integration of herbal medicines in the country. In short, this review discusses the regulatory aspects required to register a new herbal medicine in Brazil, also addressing the global pharmaceutical industry involved in this and how our country is within this context

Keywords: phytotherapeutic drugs; plants medicinal; products registration; health care; coordination and monitoring

RESUMO

O Brasil tem quase um terço da flora mundial representado em dez biomas com uma biodiversidade exuberante, no entanto, muito pouco tem sido feito para transformar esse potencial em vantagem competitiva no mercado de medicamentos fitoterápicos e plantas medicinais. O uso de espécies de plantas no tratamento de várias doenças pode assegurar a difusão de novas tecnologias e o desenvolvimento do mercado consumidor, bem como inclusão social e redução das desigualdades econômicas. Este estudo tem como objetivo revisar os aspectos regulamentares de registo de herbalmedicines e plantas medicinais no Brasil, bem como a situação global do mercado e níveis nacionais neste segmento. Foi realizado o levantamento e análise de publicações relacionadas com a questão de saber a realidade da indústria de medicamentos fitoterápicos, pesquisas e ações governamentais para o desenvolvimento e integração de ervas medicinais no país. Em suma, esta revisão aborda os aspectos regulamentares necessários para registrar um novo medicamento à base de plantas no Brasil, abordando também a indústria farmacêutica global envolvido neste e como nosso país é dentro deste contexto

Palavras-chave: medicamentos fitoterápicos; plantas medicinais; registro de produtos; cuidados de saúde; coordenação e acompanhamento.

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Introduction

The use of plants in the treatment of various diseases is a practice used since our ancestors especially in times of absence of more advanced pharmaceuticals, practice as old as human civilization (Rates, 2001).

This practice represents the accumulation of knowledge about the action of plants by various ethnic groups, being an integral part of all cultural backgrounds. In addition this practice forming for centuries the basic therapy and the first and/or unique feature of much of the therapeutic population (Coelho-Ferreira, 2000; Pasa *et al.*, 2005).

After the industrial revolution and World War II, the emergence of the first antibiotics and the discovery of active compounds against disease-causing agents contributed to great progress in controlling various diseases. For years scientific research has been involved in search for new molecules capable of controlling and / or combat disease causing agents. Thus the use of more potent drugs was a common practice in human and veterinary medicine (Camurça-Vasconcelos *et al.*, 2005).

However, although molecular engineering have advanced obtaining resources that can be used for diagnostics and pharmaceutical industry have large arsenal against several diseases, treatment of the disease remains a serious problem in many countries (Camurça-Vasconcelos *et al.*, 2005).

The difficult access to most of the world population to synthetic drugs, because the high cost, lack of product availability in some rural areas or far from markets, the risk of environmental pollution, as well as the development of resistance by microorganisms led to return to the study of plants with medicinal properties (Hammond *et al.*, 1997).

Brazil, a country with recognized biodiversity, presents a social diversity that involves many people and communities with visions, knowledge and own cultural practices, intrinsically related to their territories and natural resources as an integral part of socio-cultural and economic reproduction. In this sense, it is essential to promote the recovery, recognition and appreciation of traditional and popular use of herbal medicines and medicinal plants in ensuring provide health care through plants as a treatment method based on the results of surveys of flora especially native with quality assurance and qualified in employment insurance (Eldin & Dunford, 2001; Yunes *et al.*, 2001; Rodrigues *et al.*, 2006).

The nation has made a considerable investment in research training and deployment of laboratories for analysis of medicinal plants with continued encouragement in the study of pharmacological properties, mostly trying to prove the validity of the popular use of medicinal plants and represented in leading international publications in the area of plants in Latin America (Calixto & Siqueira Junior, 2008). The idea that presided over these studies was to use natural products as affordable option to conventional therapy. Although many plants are being used and marketed for therapeutic purposes, the vast majority do not have scientific data proving its effectiveness and its spectrum drug in humans, as well as quality assurance in production and, consequently, marketing (Ferreira *et al.*, 1998; Calixto & Siqueira Junior, 2008). Thus, this study aims to present aspects of the legislation for registration of herbal medicines and the market for medicinal plants and herbal medicines, focusing on government actions that encourage the inclusion of herbal medicines in health care in Brazil, aiming to aid researchers companies and managers for consideration and decision on the subject, registration and regulation of herbal medicines.

Materials and Methods

An electronic search was conducted between the months of July 2011 and February 2012, in SciELO databases, Biological Abstracts, Chemical Abstracts, Medline, Lilacs, SciELO and Web of Science using the descriptors in health science (DeCs): "phytomedicines"; "products registration" and "market of herbalmedicines". Was excluded articles that did not deepened information about the relationship between registration and marketing of herbal medicine, and those who were outside the survey period (2000-2011), and those who were not fully obtained, even after sending the message to main author. It was adopted as a criterion for inclusion, articles whose main theme approached the themes of the registration of herbal medicines and herbal pharmaceutical market related. The choice of items was performed by an independent auditor.

Results and Discussion

Phytomedicines in Brazil: what laws govern them and how to register them?

Herbal medicinal product is obtained by employing solely active vegetable raw materials. It is characterized by knowledge of the effectiveness and risks of their use, as well as the reproducibility and consistency of its quality (Brazil. RDC ANVISA-MS N°. 14/10).

In Brazil, the National Health Surveillance Agency (ANVISA), a federal agency, government agency of the Ministry of Health, has a role to regulate all medicines, including herbal medicines, and monitor the industries producing drugs in order to protect and promote health of the population, control of production, release for consumption (record) and monitoring of medicines and may withdraw them from the market if their use presents risk to the population (Rodrigues *et al.*, 2006).

The role of ANVISA is fundamental in ensuring the quality of medicines, establishing requirements for registration and marketing, avoiding ineffective products, dangerous and shoddy made available to the population, which poses risks and dangers (Carvalho *et al.*, 2008).

A visit to the site of ANVISA (http://www.anvisa.gov.br) represents the most accessible source for information about the registration of medicines, offering several tools to query, being free and easy access.

The need of the market organization of plant, given the great expansion of this sector, encouraged by international assignments, especially the World Health Organisation (WHO) from the 70's, the recognition of biological and cultural diversity of Brazil, as well as the need for conservation and sustainable use of natural resources and preservation of folk wisdom, with the recognition of national scientific and technological capacity, resulted in the adoption of various measures and regulatory actions established by the Federal Government, especially by ANVISA, with landmark in the 80's the Program for Natural Products Research (PPPN), implemented by the Central Drug (CEME), aiming at the restructuring of phytotherapy in Brazil, demanding academic research, industry and the public health, activeness and shared development of studies scientists that prove the safety and efficacy, permitting, in the country, production, recording and marketing of vegetable products with quality, within the time limit set by law.

It appears that, after the publication of Resolution of the executive board (RDC) N°. 17, February 2000 (Carvalho *et al.*, 2008), the pharmaceutical industry have developed new standards for registration of herbal medicines; demanding market National adaptation to the new rules, to ensure the quality, efficacy and safety of these drugs. In March 2004, this resolution was revoked by the publication of RDC N°. 48/04 (Carvalho *et al.*, 2007) and later by the RDC N°. 14/10 (Da Costa Alves *et al.*, 2008), presenting some conceptual changes in an attempt to fit the standards of other drugs ANVISA, but the criteria for registration for herbal medicine has not changed much between these regulatory mandates.

For registration of herbal medicines, the domestic industry should follow the provisions of Law N° 6.360 of September 1973 regulated by Decree N° 79.094 of January 1977, in response to particular provisions, and the determinations that regulate medicines, among which stands out Resolution RDC ANVISA-MS 96/08 which deals with advertising, publicity, information and other practices whose purpose is the dissemination and commercial promotion of medicines, as well as Resolution RDC ANVISA-MS N° 17/2010 which provides for the Good Manufacturing Practices and Drug Administration revokes Resolution RDC ANVISA-MS N° 210/03 (Table 1).

It is worth noting four (04) regulations provide specific criteria for herbal medicines: Resolution - RE Nº 88/04 which determines the publication of the "List of references for evaluation of safety and efficacy of Herbal Medicines", which divides the selected references hierarchically according to the relevance of the studies presented, the Resolution - RE Nº 89, which publishes the "List of simplified registration for registration of herbal medicines", which have records facilitated by not having to establish criteria for safety and therapeutic efficacy due to the widespread recognition in the scientific community; Resolution - RE Nº 90/04 with the "Guide for the studies of pre-clinical toxicity," which aims to specify standard methods for studies of preclinical toxicology and Resolution - RE Nº 91/04 consisting of a "Guide to making changes, additions, cancellation notices and post-registration", which aims to classify changes and additions to the stage of post-registration of medicines and establish documentation and testing required by ANVISA (table 1).

ANVISA recognizes, within those herbal medicines with the greatest number of scientific studies, the "List of simplified registration of herbal medicines" containing 34 (thirty four), the majority of

exotic species, allowed to obtain the simplified registration by industry (Carvalho *et al.*, 2008), there is no need to validate the therapeutic indications and safety of use.

If the herbal medicine does not incorporate the "List of simplified registration of herbal medicines" to obtain registration and renewal, the company must petition with ANVISA a dossier with technical and administrative product information according to specific regulations. During the analysis of a registration process, there are the main aspects related to the production process, quality control, safety and efficacy trials, the company's legal data, labeling and package leaflet (Carvalho *et al.*, 2007).

Thus, based on the prevailing regulatory mandates, pharmaceutical companies must follow three different paths. The first option, that being the most costly is the least used by the industry, consists in carrying out safety tests (toxicology, preclinical and clinical) and treatment efficacy (pre-clinical pharmacology and clinical) of the drug (Carvalho *et al.*, 2008).

The second option allows the pharmaceutical industry to use the presentation of the plant drug monographs present in the formulation of the drug, attesting on these studies. These must be submitted to ANVISA, which assesses the seriousness of the work through a scoring scale of reference. Thus, for the pharmaceutical laboratory to prove the safety and efficacy of herbal medicine through the presentation of studies described in these works, the product must be at least six points, awarded according to the scale scores of references. In this case, much of the work refers to textbooks that include international studies conducted mainly with plants originating from European countries (Silva *et al.*, 2006).

The third option, the industry must present a ethnopharmacological and technoscientific survey or documentation to evaluate the indication of use, consistency with proposals regarding the therapeutic indications, no toxic hazard to the user and proven safe to use for a period of not less than 20 years (Toledo *et al.*, 2003).

Thus, on one hand the law can strengthen the criteria for safety and efficacy of herbal medicines registered in Brazil, it also favors a way to incorporate in the national pharmaceutical market, considered exotic plants, since most of the literature reference does not include clinical studies of the flora of plants used in folk medicine. Moreover, the results of clinical safety and efficacy accepted by law for the registration of these herbal medicines were obtained in studies of population of different ethnic and epidemiological profile of the Brazilian, questioning the need for caution in transposing these results to our population (Ribeiro *et al.*, 2005).

Another problem of the criteria used by the Brazilian legislation on herbal medicines with respect to the devaluation of popular practice, since most of the plants traditionally used by the population has not yet been evaluated in terms of toxicological and pharmacological, which would make it prohibitive registration as herbal medicine (Ribeiro *et al.*, 2005).

Thus, it becomes necessary to amend existing legislation in order to take advantage of the therapeutic arsenal consists of empirical knowledge of many different peoples and communities in Brazil, a situation that should stimulate and encourage institutions to promote the studies needed to confirm the efficacy and safety of these plants.

It appears that Brazil has legislation for registration of medicinal plants and herbal medicines, recognized worldwide as highly demanding in order to guarantee quality of such products. But in light of the foregoing, it is a question: with so strict legislation, the Brazilian population has access the quality of these products as a treatment option? Not yet, given the finding of gaps, especially given the wide availability of drugs recorded as plant food, but marketed and used as medicines, as well as the lack of inter-and multidisciplinary studies of plant species used as medicines and therefore the lack of monographs in official compendia, and also the lack of incentives in research, development and innovation of herbal medicines of native plant species and broad therapeutic use in popular practice.

Market for herbal medicines: the global and national perspective

The latest figures show that overall growth of the pharmaceutical market in 2009 was around 4.5 to 5.5% over the previous year, indicating that sales in the pharmaceutical market exceeded US$ 820 billion in 2009, reflecting expectations (Bradfield & El-Sayed, 2009).

Table 02 shows the eleven largest companies in 2009, especially Pfizer (after the acquisition of Wyeth U.S.) and Merck (after purchase of the U.S. Schering-Plough), responsible for approximately 15% of pharmaceutical sales.

This growth observed is due to mergers and acquisitions of large companies, encouraging investment in Research and Development (R&D) of new drugs and release of the market, making it even harder to enter this market in countries like Brazil. According to Figueiredo (2005), the competitiveness of the chemical-pharmaceutical industry in Brazil is practically nil in the case of patented products. The scaling of R&D makes even more remote possibility of reversing this situation in a foreseeable time horizon.

In the pharmaceutical market, the space for the development of drugs of plant origin has been taken recently in the world since the turbulence that the pharmaceutical industry has experienced in recent years, partly due to the nature, based on technology and rapid growth, and Furthermore, due to various pressures that are suffering, especially from the cost control state. Industry executives estimate that for a laboratory must remain competitive to invest in research and development, at least US$ 2.0 billion/ year(Villas Bôas & Gadelha, 2007).

Analysis of the international pharmaceuticals derived from plants, demonstrates a significant increase in sales in the countries of Europe and the United States of America, from the beginning of the 90s, with annual growth rates between 10-20% in most countries , moving US$ 14 billion annually and employing an average of one hundred thousand people (Bradfield & El-Sayed, 2009).

In Europe, by a movement led by Germany itself, this new class of drugs has been incorporated by the health system, supported by the evidence on medicines quality, efficacy and safety. The major distinction of rational phytotherapy has become, therefore, their comparison on an equal footing with therapies that utilize drugs synthesized. Although the documentation of the effectiveness of products through appropriate pharmacological investigations, identified in papers themselves, there are numerous products whose efficacy has not been tested in the same way, and its use is classified as traditional therapy (Villas Bôas & Gadelha, 2007).

Germany, representing the largest market in this segment since 2001, owns 39% of the European market, having only twenty (20) endemic species (own region), compared with 25.000 Brazilian species, representing the largest research center worldwide in herbal medicines; worth mentioning the inclusion of phytotherapy in the compulsory curriculum in medical schools, 70% being prescribed by doctors (compared to only 3% in Brazil), contributing to the representativeness of the country in this segment (Rates, 2001a).

Biodiversity and cultural diversity of Brazil, associated with socioeconomic differences in the vast extent of territory, having recognized the unequal distribution of resources to health, with a concentration of specialist services in large urban areas, favoring a small portion of the population, unfeasible and / or hindering access to public health services by the majority, favored for the use of medicinal plants were preserved, contributing significantly to the current moment of rise of the use of plants and products for the Brazilian population, with a proven increase availability and marketing of such products in the domestic market (Junior *et al.*, 2005; Packer & Luz, 2007; Agra *et al.*, 2008).

The comparative market analysis of products derived from plants internationally and nationally, shows that in Brazil, from the decade of 90, there was also a significant increase in sales (Assad, 2010).

In Brazil, production of herbal medicines predominantly in south and southeast, the herbal medicines market generates an annual average volume of US$ 400 million and sales have increased 12% per year, while synthetic drugs have annual growth of 5 % (Scariot & Pereira, 2011)

Evaluation study of the structure of the market of herbal medicines in the context of the Brazilian pharmaceutical industry, said 103 (one hundred and three) laboratories in the herbal segment, selling 367 (three hundred sixty-seven) drugs in 53 therapeutic classes predominated antihypertensives, antiulcer, antispasmodic and anticholinergic. This study shows also that among the 103 (one hundred and three) laboratories herbal, only 5 holds 52.3% of sales in this segment, representing large corporations, which keeps monopoly, with significant operations in the area of sales and widely distributed in class, thus creating barriers to entry in national companies.

Currently, among the herbal-registered for marketing in ANVISA, predominantly obtained from Aesculushippocastanum L., Arnica montana L., Cynarascolymus L., Ginkgo biloba L., Panax ginseng C. A. Mey., Passifloraincarnata L., Peumusboldus Molina, Sennaalexandrina Mill. andValerianaofficinalis L., a species representing the cast list of the Simplified Registration of Herbal Medicines of Ministry of Health (SVS-MS) in Resolution N°. 89/04), therefore easier to record, without the need for validation studies (Carvalho *et al.*, 2007)

The specific requirements of the laws of herbal medicines with strict regulatory mandates for registration of associations of plant species, provoked a change in the market for herbal medicines, going to dominate the record monodrogas (Neto *et al.*, 2006; De Freitas, 2007).

In the analysis of the domestic herbal studies indicate that, despite representing a promising market, there are serious barriers such as investment fledgling R & D; lack of partnerships between universities and companies, lack of studies with native plant species and therapeutic use popular, lack of standardization of herbal studies, the difficulty of interaction and inter and multidisciplinary, and also the barrier arising from the institutional norms and criteria for production and marketing (Simões & Schenkel, 2002; Klein *et al.*, 2010).

In the context of the expansive development of so called new biological entities (NBE), the development of medicinal plants is presented as a strong niche market, representing an alternative for some companies as a new paradigm, able to keep them within the current global market. The production of new drugs of plant origin is therefore a demand of the international pharmaceuticals industry, despite the issues related to access, intellectual property and distribution of social benefits advise caution to investors awaiting policies to ensure contracts and the appointment of new procedures.

Brazil has nearly a third of the world flora represented in ten biomes with an exuberant biodiversity. However, very little has been done to transform this potential into competitive advantage in product patents, especially considering the development as a means of social inclusion, protection and maintenance of these ecosystems. The development carried out from the modern view of national systems of innovation, local development and in the case, from each biome represents a concrete and viable alternative to come up with new products, new methodologies, performing in terms of global competitive advantage our natural resources, promoting a major technological leap in the production of drugs, breaking the vicious cycle of competing paradigms using the same technological development of drugs produced in countries where biodiversity can not compare to Brazil. We take for granted the evidence that biodiversity is a source of competitiveness of the country, lacking, however, the formulation and implementation of a policy to ensure sector organization (Villas Bôas & Gadelha, 2007).

Through studies conducted by the Ministry of Health was able to describe and evaluate the market structure and the main variables of conduct of companies in the herbal medicines in the current context of the Brazilian pharmaceutical industry. It is noteworthy that of all drugs marketed in 2003, 226 were characterized as isolated drug and 172 as associations of plant-based medicines. In 2006, the situation changes and 238 classified as drugs are marketed together isolated drug to 129 combinations. Expressive and expected drop of 25% of all drug combinations sold in the period, whereas the current legislation favors the records isolated drug (Macedo & Gemal, 2009).

In terms of size, the segment of Brazilian herbal earned during the period november 2003 to october 2006 US$ 122 billion from the sale of pharmaceutical units. The total number of companies producing herbal medicines determined by the survey was 103 for the year 2006. Of this total 4.85%, or five companies held 52.3% of the revenues of the segment and seven companies, or 6.85% of total companies in the sector traded 50.7% of total presentations of herbal medicines . The laboratory is the most representative AltanaPharma, the German capital, followed by the laboratories Farmasa and Marjan. The remaining 83 laboratories shared the remaining 15.3% of sales, which thus indicates the possibility of concentrated markets by company, the segment of herbal medicines in the country (Nogueira *et al.*, 2010).

In fact, brazilian biodiversity has provided several very important substances as medicines. An example is pilocarpine, extracted from the leaves of trees of the genus Pilocarpus, native to the neotropics and very common in the Atlantic forest. This material was used for decades by Merck for the preparation of medicament indicated for the treatment of glaucoma. Pilocarpine is also used to relieve the "dry mouth" (xerostomia), side effect of radiotherapy for cancer because it stimulates the secretion of saliva and this property was already known to the Amerindians - the name "jaborandi" means "plant that makes drool ". Another important contribution of Brazilian medicinal flora is the d-tubocurarine. This substance makes up the "curare," preparation made with Chondrodendrontomentosum (Menispermaceae), native to the amazon and used as a poison by the peoples of that region. In 1940, the d-tubocurarine (Intocostrin ®) was introduced in anesthesiology because of its relaxing effect of skeletal muscle (Nogueira *et al.*, 2010).

The animal kingdom has also provided important bioactive natural products. The brazilian pit viper venom pit *Bothrops viper*, for example, is the source of a major discoveries in the field of natural products in recent decades. From it was developed captopril, a drug widely used to control hypertension. All the chemical and pharmaceutical research has been done in Brazil, but the international industry and

holds patent rights to market the product. The benefits of these discoveries for humanity are incalculable, but Brazil can not receive any economic return for them (Rates, 2001b).

New technologies have been introduced in the innovation of medicines in general, which led to an increase of the enterprises in the biotechnology sector. This fact, along with the turmoil that has occurred with the big pharmaceutical companies, as we saw earlier, opens opportunities for the entry of new players in the industry. Countries with biodiversity such as Brazil, tend to benefit from this situation. Natural products have traditionally been an important source for medicines. Although organic chemistry through the synthesis has succeeded in producing many bioactive compounds and combinatorial techniques have expanded the number of compounds available for testing, it still remains relatively high number of natural products and derivatives of the drugs sold worldwide. Interest in this source has increased again as expected lower the cost of research and development (Villas Bôas & Gadelha, 2007).

It is necessary to direct the reconstruction of the production structure in order to facilitate a broad articulation of the interests and priorities of national, regional and local level, in order to promote the positive synergies mobilizing agents and partners to ensure survivability, competitiveness and innovation to the institutions and companies engaged in this process.

In addition, policies should ensure the dissemination of new technologies, equipment, systems, logistics and organizational formats, and developing consumer market, contributing to the reduction of economic and social inequalities, social inclusion of excluded groups. Course is structured on this basis, the development will be giving their contribution to the formulation of new scientific and industrial policies, as well as giving examples of structures aimed at promoting sustainable development, definition of new strategies and challenges.

Conclusion:

The scientific literature on herbal shows that, in recent years, a large and growing global interest in herbal medicines has occurred, both in developed and developing countries. Market growth has attracted much botanical interest from pharmaceutical companies, which in turn invest in pre-clinical studies and clinical in order to participate the amount involved in sales of herbal. It is clear that in Brazil there was an improvement in the processes of regulation and harmonization of legislation that addresses the phytomedicines, and the general trend is to use the experience of other countries regulations, together with scientific data and traditional knowledge (monographs), to ensure a product effective and safe for the population.

Table 01. Legislation for registration of herbal second determinations of the National Health Surveillance Agency (ANVISA), Brazil

Legislation	**Scope**
Law Nº 6.360/73	Provides for the health surveillance which are subject to the drugs, drugs, pharmaceutical raw materials and related products, cosmetics, disinfectants and other products, and other measures
Decree Nº 79.094/77	Regulates Law No. 6.360 of September 23, 1976, to submit health monitoring system medicines, pharmaceutical ingredients, drug related, cosmetics, hygiene products, disinfectants and other
RDC N° 14/10	sets forth the minimum requirements for records of herbal medicines
RDC Nº 17/2010	Provides for the Good Manufacturing Practice for Medicinal
RDC Nº 96/08	Provides for advertising, marketing, information and other practices whose purpose is the dissemination and commercial promotion of medicines
ANVISA-MS Nº 88/04	List of references for evaluation of safety and efficacy of herbal medicines
ANVISA-MS Nº 89/04	List of records for simplified registration of herbal
ANVISA-MS Nº 90/04	Guide to the studies of pre-clinical toxicity
ANVISA-MS N° 91/04	Guide to making changes, additions, notifications and cancellations post-registration
RDC ANVISA-MS Nº 47/09	Establishes rules for development, harmonization, updating, publishing and provision of drug leaflets for patients and health professionals
RDC ANVISA-MS Nº 71/09	Establishes rules for the labeling of medicines
RE ANVISA-MS Nº 01/05	Guide for Conducting Stability Studies
RDC ANVISA-MS Nº 138/03	Provides for the environment in the category of selling drugs
RDC ANVISA-MS Nº 04/09	Provides for the rules of pharmacovigilance to holders of record of human medicines
ANVISA-MS Nº 899/03	Guide for validation of analytical and bioanalytical methods
ANVISA-MS Nº 249/05	Determines all establishments manufacturers of intermediates and active pharmaceutical ingredients, compliance with the guidelines set forth in the Technical Regulation of Good Manufacturing Practice for Intermediates and Active Pharmaceutical Ingredients
Normative Instruction Nº 05/08	Determine the publishing of the "List of Herbal Medicines Registration Simplified."
Normative Instruction Nº 05/10	List of References for Security, Evaluation of Efficacy of Herbal Medicines
RDC ANVISA-MS N° 39/08	Approves the regulations for the conduct of clinical research, updated regulations for preparation of the dossier to obtain a special announcement to conduct clinical research on drugs and health products and other measures
RDC CNS-MS Nº 196/96	Adopting guidelines and rules for research involving human
RDC CNS- MS Nº 251/97	Approves the guidelines for research involving human beings in the thematic areas of research with new drugs, medicines, vaccines and diagnostic tests

Source: prepared by author

TABLE 2: The largest pharmaceutical companies in sales worldwide, 2009

	Company	Sales (US$ billion)
1	Pfizer (Estados Unidos)	75,0
2	Merck (Estados Unidos)	47,0
3	Roche (Suíça)*	43,1
4	Novartis (Suíça)	41,46
5	Sanofi-Aventis (França)	34,9
6	GlaxoSmithKline (Grã-Bretanha)	33,6
7	AstraZeneca (Grã-Bretanha)	31,6
8	Abbott (Estados Unidos)	29,5
9	Johnson & Johnson (Estados Unidos)**	24,6
10	Bristol-Myers Squibb (Estados Unidos)	20,6
11	Eli Lilly (Estados Unidos)	20,4

Source: IMS Health Market Prognosis, March 2011

* If successful association with the American subsidiary Genentech.

** only for pharmaceutical activities, the whole group is worth 63.7 billion dollars.

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