Protection of data package in Brazil: an incentive to innovation

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Protection of data package in Brazil: an incentive to innovation

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Introduction

In Brazil, there has been intense discussion on the importance of protecting data package for the research and development of new medicines. The subject has gained additional attention given the absence of a protection period in the country.

As we will see throughout the study, now published by Interfarma, most of the surveyed countries have an express protection period for the data package.

The definition and enforcement of a time period for data secrecy are not only a safeguard for those who invest in research and development of an innovative product but also an incentive to commercialize innovative medicines of proven quality, efficacy and safety – in other words, hope for countless patients waiting for a cure or improvement of their quality of life.

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Brazil is lacking a law guaranteeing a protection period for the data package as exists in other countries

Have you ever thought about how a new medicine is created? When you go to a pharmacy and ask for the medicine you require, you hardly realize how much work was necessary, for a little cartridge, containing a few tablets, to be made available to you. The development of research and the required tests are prerequisites in this process.

It is about this long and expensive process that we want to talk to you. Currently the process is common to all new pharmaceutical products – from a simple headache tablet to the most complex and potentially revolutionary medicine that is able to change the fate of millions of patients throughout history, such as antibiotics, vaccines, anesthetics, and contraceptives.

Today, thanks to the advancement of new technologies and scientific knowledge, research has gained an extraordinary dimension. New medicines are being developed not only to treat, but also aiming to cure chronic or degenerative diseases that have long affected humankind, such as Alzheimer's, Parkinson's, Obsessive-Compulsive Disorder – OCD, autism, rheumatoid arthritis – not to mention countless types of cancer.

The effort undertaken for this type of research is immeasurable. In order to understand the time and investment required in research and development, it is necessary to point out that even after the invention and formulation phases regarding a medicine for severe diseases are over, there are still around ten years of trial phases to come. On average every successful research that reaches people in the form of medicines costs 800 million dollars.

Therefore, as in any economic activity, those who believed and invested in an R&D project expect to see some return on their investment in order to offset and payback the effort made by companies, scientists, and researchers involved in the process. This legitimate and proven model is part of a virtuous circle that allows for the gains obtained to be reinvested in research and development of a new medicine.

Therefore, how do we get to a new medicine?

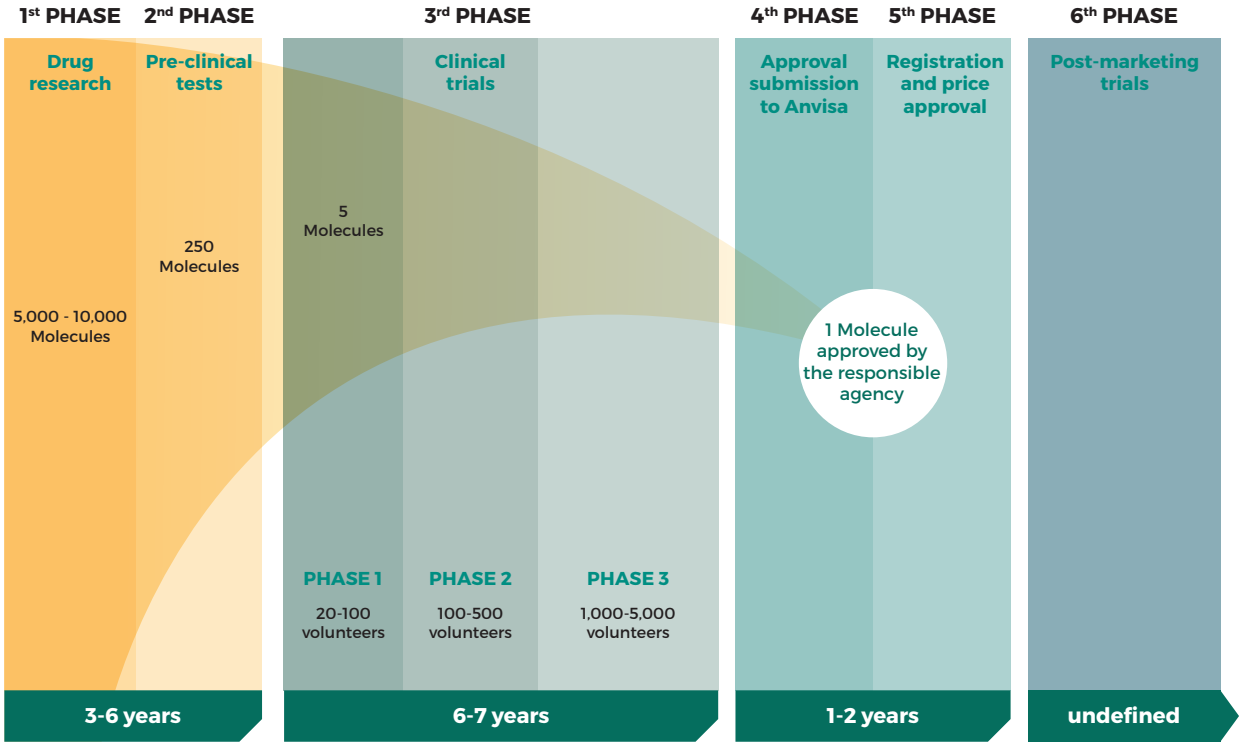
The creation of a reference medicine (the one that, whether patentable or not, is qualified as a benchmark of efficacy, safety and quality for the manufacturing and registration of generic and similar medicines) takes around ten to fifteen years, between the identification of the pharmacological target and the introduction in the marketplace. Six phases are identified, as illustrated in the graph below:

- **1ST PHASE:** identification of the pharmacological target and start of laboratory tests in order to analyze new compounds that are promising in terms of the fight against certain diseases. Approximately 90% of substances are already eliminated at this phase.
- **2ND PHASE:** pre-clinical toxicity tests on animals, *in vitro* and *in vivo*. These tests are essential to assess the safety and efficacy of a new drug, before tests on humans are initiated.
- **3RD PHASE:** tests on healthy humans are initiated (clinical phase I). These tests are intended to assess the drug's effect on the human body, the time it takes to start to be effective, how long it is effective on the organism, toxicity, among other factors. Subsequently tests are started with people who have the disease (clinical phases II and III). Here the efficacy to cure is assessed.
- **4TH AND 5TH PHASES:** approval and registration of the medicine to be commercialized; and price definition by regulatory authorities as is the case in Brazil.

- **6TH PHASE:** the medicine finally arrives at the pharmacy. At the same time, post-clinical or post-marketing trials are ongoing (phase IV) in order to broadly measure the therapeutic potential and adverse effects.

The body of data that includes the different types of information and the characterization and development of a medicine through the pre-clinical and clinical trials that prove its quality, efficacy and safety, has been given various names, such as data package, data or test body, test dossier, regulatory data, non-disclosed data, among others.

By simply analyzing the graph above, it is clear that the data package has a value in itself and therefore deserves to be protected. After all, its financial cost can be as high as 70% of the total amount necessary for the development of a new medicine.



Source: PhRMA

What happens with this data package?

The data package is mandatorily presented to the agency responsible for the registration and subsequent manufacturing authorization of medicines. In Brazil, this is the National Agency of Sanitary Surveillance – Anvisa.

It is important not to confuse this data package, which is submitted to Anvisa, with the data that is submitted to the National Institute of Industrial Property – INPI[1] in order to obtain the registration of a patent. In reality, every medicine needs an authorization by Anvisa to be marketed, while not every medicine that is marketed is protected by a patent. These two registrations are not to be confused. There is a patent whenever the medicine is an invention, i.e., different from everything that is already known. If it is not an invention, it will not be patented but will still require registration with Anvisa. In other words, the protection that is given to a granted patent for an innovative medicine is different from the protection owed to the data package submitted to Anvisa. Note the differences in the comparative table below:

1. The Brazilian Patent and Trademark Office.

	PATENTS	DATA PACKAGE
Law	Promulgation decree # 1,355, of 12/30/1994 (TRIPS Agreement), art. 27.3; Statute #9,279, of 05/14/1996 (LPI), art. 6 through 93.	Promulgation decree #1.355, of 12/30/1994 (TRIPS Agreement), art. 39.3; Statute #9.279, of 05/14/1996 (LPI), art. 195, XIV.
Nature	Industrial Property Law (under Intellectual Property Law).	Industrial Property Law (under Intellectual Property Law).
Object	Exclusivity on the medicine.	Exclusivity of the information relating to the safety and efficacy tests run by the holder.
Prohibits	Manufacturing, sale, import and export of a patented product or a product obtained directly from a patented process and/or the use of a patented process.	The commercialization approval of a competing product based on regulatory data gathered by the license holder.

	PATENTS	DATA PACKAGE
Purpose	Protect and stimulate inventions, revealing the knowledge.	Protect the scientific data relative to the safety and efficacy of the medicines and, by extension, preserve the consumer's right to have access to proven efficacious products.
Requirements	Art. 8, LPI: Novelty; Inventive Activity; Industrial Employment.	Art. 39.3, TRIPS: Novelty; and Considerable Effort.
Time frame	20 years counted as of the date of the deposit or 10 years counted as of the concession.	Veterinary medicines: 5 to 10 years; Human medicines: time not specifically regulated by the law in force.

The temporary protection of the data package is based on a unique legal framework, and it is not possible to reduce it to a supposedly inappropriate extension of the patents' expiration date. First, as mentioned, patent protection and data package protection are not to be confused, and therefore the latter cannot be considered a simple extension of the first. Second, both periods, run at the same time (when concurrent), entering the public domain at distinctive moments, due to their distinct duration. It is worth noting that there will often be data package protection only, as patent protection depends upon specific requirements of novelty, inventive activity and industrial employment – not always applicable to innovative medicines – whereas data package protection is a consumer and investment protection measure. Finally, because of the absence of a legally fixed timeline to protect data package, the effectivity of the due a *priori* protection will depend on an interpretive effort, making it difficult to obtain the expected financial return of the investment in the product, which in turn bears a direct influence on the business decision to invest in a new medicine.

When Anvisa is in possession of a data package, what are the agency's limits to use it?

Here is the explanation. As already mentioned, the reference medicine serves as a benchmark for the copy medicines, i.e., the generics and branded generics. This occurs because it undergoes long pre-clinical, clinical and post-clinical test schedules. However, for copy medicines, a simplified system was adopted to analyze and approve a registration, because these are only versions of the reference medicine. Through so-called 'registration by similarity', the copy and its reference are proven to be sufficiently similar to assume that the copy bears the same efficacy, safety and quality already proven in the reference medicine. Once the copy medicine has been proven equivalent to the reference medicine, the tests previously employed to prove the qualities of the reference are automatically extended to the similar, with no data survey required on the performance of the copy medicine itself.

ANVISA's understanding is that it is not reasonable to require the same tests for the copy medicine as those required for the reference, because this would be a waste of time and money, in addition to subjecting lives (animals and humans) to unnecessary risks. As a result, the entire burden falls to the holder of the reference medicine data package.

What kind of protection does Brazil provide to the data package?

In Brazil, medicine access policy is not harmonized with other policies and rights that are also based on constitutional safeguards, such as the incentive to technological innovation and scientific development.

There is no Brazilian law that expressly guarantees the protection period of the data package of reference medicines for human use, during which there is no registration of generics or branded generics, by means of similarity tests.

As already outlined in the comparative table of patent and data package, there are two legal provisions in Brazil that in effect guarantee the protection of data packages, namely:

- TRIPS Agreement art. 93 (which is one of the attachments of the Final Minute that incorporates the Results of the Uruguay Round of Multilateral Commercial Negotiations under GATT, enacted by the Decree no. 1.355/1994) – international norm that obligates the signatory countries to protect against unfair commercial use the results of tests or other non-disclosed data of pharmaceutical products, whose preparation had involved considerable effort and that had been submitted to the government agency as a condition to approve its commercialization. It also obligates countries to adopt measures to prevent that such data is disclosed, except in case of public interest or if sufficient protective measures are already in place intended to avoid unfair competition.
- Art. 195, XIV, of the Industrial Property Statute – LPI (Statute # 9,279/1996) – legal provision that provides for the unfair competition crime. The act lists as criminal conduct the disclosure, exploration and utilization of test results and other non-disclosed data, the preparation of which had involved considerable effort and that had been submitted to government agencies as a condition to approve the commercialization of products.

None of these provisions solves the problem in its entirety. First, the Art. 195, XIV sets out a punishment for conduct that has already taken place, while the intended protection by the international norm is of preventive nature, i.e., under Brazilian law there is only punishment for the inappropriate use of data, but no prevention against such use. Also, without a fixed protection period, there is only legal uncertainty about the protection period, **and not the lack of protection**. Finally, the international norm mentions 'unfair commercial use', which is a much broader concept than the 'unfair competition' in the Brazilian law.

In 2000, when the final report of the CPI (Parliamentary Investigation Committee) of medicines was concluded, the Committee recommended that the Executive amend article 195, item XIV aiming to correct the permanent protection that falls on the data package, and establish a defined period in this respect.

However, what is most astonishing about the Brazilian legislature's approach on this matter, is that the above changes where previously implemented for **veterinary products, fertilizers and agrochemicals** only, which already have a specific legal norm to regulate the protection of the data package that have been submitted to regulatory bodies for marketing approval. Statute # 10.603/2002, under art. 3, prevents the use by the competent authorities of the respective data confided to them, over an established protection period (5 or 10 years), varying according to the innovation level incorporated to the product, i.e., giving a longer protection period for radical inventions (new molecules) and shorter periods for incremental innovations (improvement of known molecules).

It is noteworthy that the abovementioned law resulted from the conversion of the Provisory Measure no. 69/2002, which had also expressly provided for the protection of the data package relative to **human pharmaceutical products** for a determined period of time. However, the relevant provisions were excluded from the final text, because it was understood that it was only urgent to adopt the rule for **veterinary products, fertilizers, and agrochemicals** by provisory measure[2]. This position was taken by the government due to a defeat suffered by Brazil in an arbitration initiated by Argentina before the MERCOSUL Administration Secretary, as a response to a commercial barrier

2. Under the Brazilian Constitution, for the government to issue a Provisory Measure, there are two necessary requirements: relevance and urgency.

imposed by our country on Argentinian similar phytosanitary products). As a result, the government felt compelled to adapt and regulate the data package protection of agricultural and livestock products as soon as possible.

Therefore, to this day there is a lack of regulation regarding the period of protection for data package of human pharmaceutical products, although the marketing approval of all mentioned products (human and agricultural and livestock) is granted in a similar fashion.

How is this protection provided in other countries?

The protection provided to data package of human use medicines is no novelty around the world. On the contrary, it is common in most member countries of the World Trade Organization – WTO.

In most countries the protection is given directly (*a priori*) with a previously established period, during which the authority responsible for granting sanitary registrations does not even accept registration requests for generic medicines, or where they do, these are only granted after a certain period of time.

See the comparative table below:

COUNTRY(IES)	PROTECTION PERIOD
European	10 – 11 years (Formula 8+2+1)
United States of America	5 – 12 years
Switzerland	10 years
Japan	8 years
China	6 years
Canada	8 years (Formula 6+2+½)
Chile, Colombia, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Peru, Dominican Republic and Venezuela	5 years
Australia	5 years
Argentina, Bolivia and Brazil	Non-specified period *(a posteriori)*
India	No protection (under analysis, 5 years).

The **European Union** adopts a timeline system of 8+2+1 (years). Under this formula, during the eight years counted from the grant of the sanitary registration of an innovative medicine, the competent authority does not even accept registration requests for any other generic medicines (even if authorized by the innovative registration holder). After this period, requests are accepted but the commercialization (if authorized) can only commence ten years after the approval of the innovative medicine registration, i.e., the exclusivity of commercialization is ensured for a minimum period of 10 years (in total). If a new therapeutic indication is added to the medicine registration, the exclusivity period is extended for one further year.

In the **United States** the system is more complex, because it is intertwined with the patent law, thus producing several variations. However, the minimum period of protection is five years and can get as long as twelve years in some cases.

Switzerland adopts a simple protection system of 10 years counted from the registration of the innovative medicine, but allows others to use the data for their own registration requests with the product holder's authorization.

Japan applies a period of eight years called "reevaluation period", during which additional data is collected about the new pharmaceutical product until it is considered well established in the marketplace. During this period, registration requests for other medicines with the same active substance are not examined, and this therefore also amounts to an exclusivity period in respect of the regulatory data. In case it is deemed necessary, the competent authority can extend the reevaluation period, also resulting in an extension of the exclusivity period of the regulatory data. Although this measure benefits the reference medicine holder, its actual purpose is consumer protection, as the extension occurs only if there is not enough safety and efficacy data about a given medicine to so that it can be more broadly distributed among the population with generics.

China ensures an exclusivity period for the data package of six years and it allows for the registration of medicines with the same active substance in cases where the applicant runs all tests again. This conduct however is not allowed in most countries for ethical reasons, because the repetition

of all tests poses an excessive risk to the health of volunteers (humans) and subjects animals to unnecessary suffering.

The system adopted in **Canada** is very similar to the European system described above. However, in Canada the formula is 6+2+½. The additional half-year protection period applies only to pediatric medicines.

Several South-American countries, such as **Chile**, **Colombia**, **Peru** and **Venezuela**, in addition to **Mexico** and countries from **Central America**, protect regulatory data in their laws. These countries adopt a simple protection system for a period of five years counting from the grant of sanitary registration for an innovative medicine.

This is also the system adopted in **Australia**.

To this day, **India** does not recognize the exclusivity right of regulatory data, but a potential period of three to five years is in discussion. The resistance to adopting regulatory data protection is because India is one of the largest manufacturers of generic medicines. However, India is facing huge problems due to the poor quality of its medicines. According to information from the *Central Drug Standard Control Organisation* – CDSCO, it is estimated that at least 25% of the Indian medicines are below quality standards accepted worldwide.

Among the countries, that (like **Brazil**) adopt a protection system only against unfair competition, without an established period *(a posteriori)*, the examples of **Argentina** and **Bolivia** stand out.

Still in the international context, the fact that the data protection regime has not prevented the entrance of generic products in respective domestic markets is noteworthy. In fact, analyzing some of the world's main pharmaceutical markets it is easy to find **false** the syllogism stating that data package protection prevents a broader access of the population to medicines. This is shown in the graph below, which demonstrates that it is possible to have the appropriate protection of innovation peacefully side-by-side with the positioning of generic medicines in the marketplace.

In the US, for example, where the data package protection is ensured for 5 to 12 years, 80% of the medicines sold are generic and only 20% are reference medicines.

Share of Generics in the pharmaceutical market in other countries

COUNTRY	Protection DPE	% IN UNITS
USA*	5 – 12 years	80
Germany*	10-11 years (Formula 8+2+1)	66
United Kingdom*	10-11 years (Formula 8+2+1)	60
Canada*	8 years (Formula 6+2+½)	45
France*	10-11 years (Formula 8+2+1)	42
Chile**	5 years	44
Colombia**	5 years	57
Peru**	5 years	38
Brazil*	---	28
Argentina**	---	11

(*) Source: IMS Health, Dec 11.

(**) Source: Kaplan WA, Wirtz VJ, Stephens P (2013) The Market Dynamics of Generic Medicines in the Private Sector of 19 Low and Middle Income Countries between 2001 and 2011.

What is Brazil losing when ignoring the protection of the data package?

Brazil incurs substantial losses by choosing not to adopt the temporary protection of the data package:

- The Brazilian consumers lose, because they are denied faster access to state-of-the-art, safer, and more efficacious medicines;
- The Brazilian researcher loses;
- The innovation agenda in Brazil loses;
- Brazil loses the ability to attract national and international productive investments;
- The country's image abroad is damaged.

For patients to **have fast access to state-of-the-art medicines**, manufactured by the national and international industry, it is key that these medicines have a reasonable level of protection.

Let us look deeper at the situation in Brazil: during the 25 years when the country restricted protection to innovation in the pharmaceutical field (1971-1996), there were almost no products introduced to the market that would effectively contribute to increasing the therapeutic arsenal available in the country, leaving patients with the only option of importing products through the Humanitarian Transport Service of Medicines from Abroad, administered by the now extinct VARIG® Airlines. However, after 1996, Brazil (like other countries) started to be more receptive to innovation, resulting in the gradual increase of investments by companies in new, more efficacious and safer products, directly benefitting the pharmaceutical market and in particular the population.

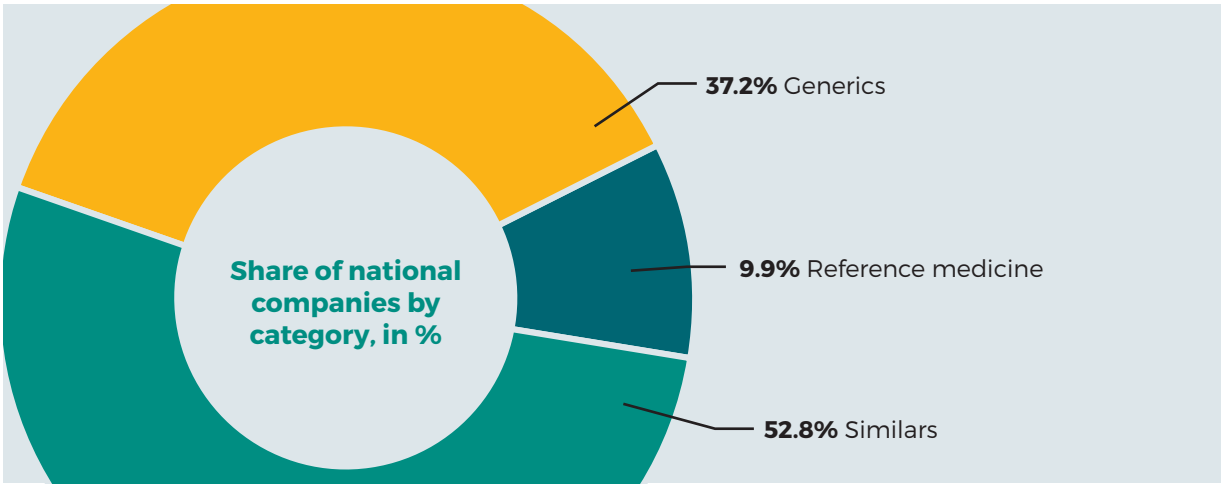
A good example is Cristália Laboratory, a Brazilian pharmaceutical company with 100% national capital, and the only company to perform the entire cycle of a medicine on national territory, from the conception of a molecule to the final product. Currently, as announced on their website, Cristália is Latin America's largest manufacturer of anesthetics, in addition to being the largest manufacturer of two of the most used muscle relaxants in Brazil and all the narcotic analgesics available in the Brazilian marketplace. Cristalia is the holder of 76 patents. Of these, Helleva®, a medicine to treat erectile dysfunction stands out. The Helleva® project resulted in an accumulated body of competencies for the laboratory, both in the research technical aspects, including manufacturing and development, and phase I, II and III clinical trials, consisting of the data package submitted to ANVISA. The project enabled and stimulated the company to work on other innovations.

Another good example is the Aché Laboratory, also a 100% Brazilian company that invests in research and development, especially phytomedicines, all developed from standardized extracts of Brazilian plants. Among these, is Acheflan®, the first medicine totally researched and developed in Brazil, which is an anti-inflammatory drug for the treatment of chronic tendinitis and muscle pain. The research of the medicine was carried out in partnership with four Brazilian universities (UFESC, UNIFESP, PUC/Campinas and UNICAMP) and made a very large step forward with the discovery of the active substance responsible for the inti-inflammatory action in the early stages of the tests with animals, revolutionizing everything that occurred thereafter. An international patent request

was filed (PCT), which, after completion of international processing, started its national phase in Europe, Austria, Brazil, Canada, Japan, Mexico and United States. The European Patent Office has already granted the patent, while the analysis is still pending in other countries. In Brazil, in addition to the patent request, the data package containing all required information was submitted to ANVISA.

In light of the above, once the data package is submitted to the public officers for the necessary registration, is it still possible to claim the data obtained with such enormous effort and difficulties not to be protected? Would it not be more stimulating for the Brazilian researcher or the Brazilian pharmaceutical industry if a general rule was in place to ensure the temporary exclusivity of the data package, both as a measure to protect their investment and (mainly) to preserve the consumer's best interest? Can the lack of a legal rule truly be considered as anything other than an obstruction to the research of new medicines in Brazil?

As seen in the graph below, despite all the described problems, 9.9% of the Brazilian pharmaceutical industry was working in R&D in 2014. Would it not be reasonable to admit that this percentage would be much higher if there was an effective legal provision for the temporary protection of tests?



Source: Grupo FarmaBrasil (Folha de S. Paulo)

With the invasion of the Brazilian market by low-price Asian products, with which it is impossible to compete, the **country's innovation agenda** has no other alternative than to foster the manufacturing of innovative and reference medicines that yield genuinely Brazilian knowledge and innovation, particularly in the areas where the country and its industries have a natural vocation, for instance the fight against tropical diseases. It is noteworthy that just manufacturing versions of reference medicines cannot be understood as an innovation agenda, as the copy brings no new knowledge.

Therefore, the greatest losses for Brazil, at least the most evident, are the reduced ability for Brazil to attract national and international investments in innovation, in addition to the negative impact on the national industry's competitiveness, mainly due to the requirement of efficacy and safety tests internationally required by the regulatory authorities.

In regard to **foreign investments in Brazil**, the World Bank carries out a study called *Doing Business*. A report is released annually and the study is currently in its 13th edition (2016). The report investigates regulations that improve or restrict the business environment in 189 countries, from Afghanistan to Zimbabwe, surveying ten different areas. Brazil is currently ranked in 116th position.

The **country's image abroad** is also affected. In April 2014 the British magazine *The Economist* published a report titled "The 50-year snooze", where it analyzed the lack of productivity in Brazil, highlighting that the Brazilian workforce contributes only 40% to the GDP, a percentage lower than other emerging countries (in India it is 67% and in China it is as high as 91%). Among the causes of this low rate, the article highlights precisely the small investment in innovation and the low production of patents. The report concludes that the combination of these factors results in an environment where backwardness and low efficiency strive.

At last there are international studies that prove the contribution of *IP-intensive industrial sector* - of which the pharmaceutical sector is a fair representative –to the levels of employment and prosperity in a country. In the European Union, for example, a study of September/2013, produced by the

Office for Harmonization in the Internal Market (OHIM) and titled *"IP-intensive industries: contribution to economic performance and employment in the EU"*, concluded that these industries are responsible for one in every five jobs and for almost 40% of the European GDP. In the US, a study of 2012 called "*IP and the US Economy: Industries in Focus*" showed that IP holders have generated 19% of the national jobs and were responsible for 35% of the US GDP.

In conclusion, Brazil incurs substantial losses due to low levels of protection to Intellectual Property overall and the data package in particular.

How to overcome the problem?

The legal regime for protection of the data package can be a double-impact weapon: it serves as an incentive to innovation by Brazilian scientists and, at the same time, stimulates the introduction of medicines with proven efficacy and safety in Brazil, thus reducing the room for poor quality medicines.

Adopting the simplified model already in place in most of our neighboring countries in Latin American is the least we can do to improve the situation. The protection period issue warrants better discussion since, as we have seen, the data of veterinary and agrochemical products is subject to a five to ten year protection period.

It is also important to highlight that the data package protection will have no impact on the manufacturer's price because the maximum prices (for every medicine) are regulated by the CMED (Chamber of Medicines), which is connected to the regulatory agency, ANVISA. This position will not change by adopting a system that establishes a *priori* exclusivity legal period for the data package.

It is therefore urgent to adopt a mechanism that gives the human use reference medicine the same protection already provided to veterinary medicines and agricultural products, fixing an exclusivity period during which it cannot be used by the competent authorities to favor third parties, without the appropriate authorization by the holder. As a result, unfair commercial use can be avoided, in compliance with the TRIPS Agreement signed by Brazil. In the meantime, it is key to at least extend the regime that is already in place for the agriculture and livestock sector to the human sector, as a way of mitigating the inexplicable imbalance between them.

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