A CRITICAL ASSESSMENT OF BRAZIL’S
EMERGING PHARMACEUTICAL MARKET

Dissertação apresentada à Escola Brasileira de Administração Pública e de Empresas para obtenção do grau de Mestre

Jiibril Palmer
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Jiibril Palmer, MS

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JIIBRIL PALMER

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Dissertação apresentada ao Curso de Mestrado Profissional Executivo em Gestão Empresarial da Escola Brasileira de Administração Pública e de Empresas para obtenção do grau de Mestre em Administração.


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LIST OF SYMBOLS, ABBREVIATIONS, AND ACRONYMS

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<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
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<tbody>
<tr>
<td>ANVISA</td>
<td>National Health Surveillance Agency for Brazil</td>
</tr>
<tr>
<td>BRIC</td>
<td>Brazil, Russia, India and China</td>
</tr>
<tr>
<td>CEP</td>
<td>National Commission of Ethics in Research</td>
</tr>
<tr>
<td>CNS</td>
<td>National Research Council</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract Research Organization</td>
</tr>
<tr>
<td>CTA</td>
<td>Clinical Trial Application</td>
</tr>
<tr>
<td>CTP</td>
<td>Clinical Trial Protocol</td>
</tr>
<tr>
<td>DPA</td>
<td>Data Privacy Authorities</td>
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<tr>
<td>EC</td>
<td>Ethics Committee</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GDP</td>
<td>Gross Domestic Product</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practices</td>
</tr>
<tr>
<td>GSK</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>IB</td>
<td>Investigator’s Brochure</td>
</tr>
<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
</tr>
<tr>
<td>IMS</td>
<td>International Medical Services</td>
</tr>
<tr>
<td>INPI</td>
<td>National Institute of Industrial Property</td>
</tr>
<tr>
<td>IP</td>
<td>Intellectual Property</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>PAHO</td>
<td>Pan American Health Organization</td>
</tr>
<tr>
<td>PANDRH</td>
<td>Pan American Network for Drug Regulatory Harmonization</td>
</tr>
<tr>
<td>PhRMA</td>
<td>Pharmaceutical Research and Manufacturers Association of America</td>
</tr>
<tr>
<td>SUS</td>
<td>Sistema Unico da Saude, Universal Healthcare</td>
</tr>
<tr>
<td>US/USA</td>
<td>United States</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization.</td>
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<tr>
<td>WTO</td>
<td>World Trade Organization</td>
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</table>
ABSTRACT

Brazil has emerged as a leader in new sites selected for clinical trials, by offering a multitude of benefits to sponsors. Even though there are significant delays with regulatory timelines, it provides highly qualified investigators, low costs, a strong infrastructure, well-established ethical support, and high patient recruitment and adherence rates. However, in order to become a primary location for clinical trials, Brazil will have to streamline and improve regulatory processes and the current political and financial conditions. The study was conducted with consensus judgement and analysis of 15 experienced industry reviewers have provided informative descriptive data. The findings suggest areas in new clinical trial in which strategies for workflow and process development could improve efficiency of clinical development.
The benefits to performing clinical trials in BRIC countries are numerous. The pool of almost three billion patients in across major cities, leads to fast recruitment and economical trials. Increased spending in healthcare and research and development has led to a growing number of educated and trained health professionals. The pricing and demand should have multinational pharmaceutical companies lining up to expand into BRIC markets, but they are largely slowing. Increasingly complex regulatory guidelines, corruption, patent challenges, losses to generics, and import/export delays are clearing out multinational pharmaceutical companies looking for feasible sites. These challenges have left an overflow of available clinical sites with experienced investigators, state of the art diagnostic equipment, and good clinical practice (GCP) compliance. The regulatory bureaucracy is more complex in BRIC countries, as standards rise.

1 Clinical Trials in Brazil

Initiating clinical trials in Brazil saves an average cost of twenty to thirty percent for pharmaceutical companies as compared with western markets (29). Brazil’s national healthcare program is based on a tier system, with over twenty-five percent of the population opting to purchase private insurance for access to second and third tier of healthcare (18). This has resulted in a large patient population with reduced access to anything beyond the basic level of healthcare (18). Metropolitan areas like Sao Paulo and Rio de Janeiro provide concentrated patient populations of clinical opportunities and expertise. The doctor-patient relationship is strong and would aid in not only promoting participation in clinical trials, but retention as well. Brazil’s regulatory approval process for clinical trials is the most protracted in Latin America.

ANVISA, the national health surveillance agency for Brazil, operates much like the Food and Drug Administration (FDA) in the United States (US). Brazil’s regulatory environment is a complex and systematic process. First, the study protocol is sent for approval to each site’s ethics committee (CEP) as well as the coordinating site. Once approved by the coordinating site, it is sent to the national commission for ethics in research (CONEP) for final ethics approval. ANVISA has been
proactive in addressing some of the redundancies in the system and recently implemented a simplified process. A pharmaceutical company needs only to submit the protocol to the coordinating site’s CEP for ethics approval. Once approved by the coordinating site, the protocol is simply agreed to be implemented at the other sites and is sent to CEP for national approval. In addition, ANVISA has started to issue a special communique and import license to the coordinating site, which can then be implemented by each site upon approval by their ethics committee, all in an effort to decrease approval timelines. Recently, new measures were sought to reduce timelines even more, particularly for foreign managed trials. If the clinical research has been approved by the FDA, the European medicines agency (EMA), Japan’s Pharmaceutical and Medical Devices Agency, Australia’s Therapeutic Goods Administration, Health Canada, or the study has recruited patients in other countries, the simplified procedure can be used. Pharmaceutical companies can use this single step process and send the clinical research application directly to ANVISA and have it evaluated within ninety days.

Brazil’s peak came in 2011 when all of the top ten pharmaceutical companies were performing clinical trials in Brazil (24). Since then, clinical trials have steadily declined. Several multinational pharmaceutical companies have withdrawn from Brazil, allowing local companies to fill the gaps. Universities and government trials have steadily been increasing in Brazil since the departures began in 2011 (26). BRIC country powerhouse, Novartis, remains a key player in Brazil, along with Roche and AstraZeneca. Pfizer, Sanofi, and GlaxoSmithKline (GSK) have decreased their presence in Brazil.

2 Socio-Demographic and Economic Analysis

Brazil is the largest country in Latin America by population, by workforce, by geographic area, and by gross domestic product (GDP). A large majority of Brazil’s population lives in cities. Infant mortality rates have fallen and life expectancy has increased as access to adequate sanitation, healthcare and measures to alleviate poverty have improved. Brazil’s average life expectancy rate is likely to rise to match those seen in developed countries.
Brazil currently has a smaller percentage of over 65 year olds compared to Russia, India, China, and developed countries. However, by 2050, the proportion of the population over 65 years will be comparable to that projected for the US, Canada, and Australia, and will be higher than that projected for Russia, India and China. The increase in the population age reflects the improvement in healthcare and welfare of the people in Brazil. The growth of the elderly population facing many developed countries over the next couple of decades will occur later in Brazil.

The middle class in Brazil demographic has demanded access to affordable healthcare and quality medicine, representing an opportunity for medical insurance providers to provide affordable healthcare. A large income disparity exists with the more affluent able to afford high quality medical insurance and the less affluent only able to access minimal government healthcare provision.

Brazil is the fifth most populous country in the world and has the largest population in Latin America. Brazil’s population is expected to continue to grow, peaking at 220 million in 2040, according to the WHO. Brazil has the largest workforce in Latin America, an estimated 120 million workers, representing almost half of the total Latin American workforce. As life expectancy rates improve, with healthcare advances and falling birth rates, the over 65 demographic is set to grow generating a similar burden seen in western countries from an aging population. This will create an additional pressure on Brazil’s government, in terms of healthcare provisions.

Though, the life expectancy in Brazil has increased steadily, it still falls below that seen in the developed world, due to lower healthcare standards and the continued existence of malnutrition and a high proportion of morbidity and mortality from injuries. Brazil currently has a higher life expectancy than Russia, India and China. This is likely attributable to the country’s higher gross domestic product (GDP) per capita and higher per capita healthcare spending. There remains a large income divide and disparities in life expectancy, due to access to higher quality healthcare.
Healthcare System

Healthcare spending has increased in GDP terms, reflecting higher public expenditures. Due to deficiencies and limitations in the public healthcare system, one-fourth of Brazilians use the private system (18). Brazil’s recession is putting pressure on the government’s budget, including healthcare. According to current WHO statistics, healthcare spending rose to 8.5 percent of the GDP in 2016, as other sectors of the economy slumped, and as the government earmarked emergency funding to combat a public health crisis, the Zika virus. Due to the devaluation of the currency, there was a sharp drop in spending in 2016.

Figure 3-1  Healthcare Spending

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</thead>
<tbody>
<tr>
<td>Life expectancy, average (years)</td>
<td>77.3</td>
<td>77.2</td>
<td>78.7</td>
<td>78.8</td>
<td>79.4</td>
<td>79.7</td>
<td>79.9</td>
<td>79.8</td>
<td>79.9</td>
<td>80.1</td>
</tr>
<tr>
<td>Life expectancy, male (years)</td>
<td>69.1</td>
<td>69.4</td>
<td>70.7</td>
<td>70.9</td>
<td>71.6</td>
<td>71.4</td>
<td>71.2</td>
<td>71.2</td>
<td>71.3</td>
<td>71.5</td>
</tr>
<tr>
<td>Life expectancy, female (years)</td>
<td>82.1</td>
<td>82.0</td>
<td>81.7</td>
<td>81.6</td>
<td>81.5</td>
<td>81.5</td>
<td>81.7</td>
<td>81.6</td>
<td>81.7</td>
<td>81.9</td>
</tr>
<tr>
<td>Infant mortality rate (per 1,000 live births)</td>
<td>21.2</td>
<td>20.5</td>
<td>19.8</td>
<td>19.2</td>
<td>18.6</td>
<td>18.0</td>
<td>17.5</td>
<td>16.9</td>
<td>16.4</td>
<td>15.9</td>
</tr>
<tr>
<td>Healthcare spending (R bn)</td>
<td>351.8</td>
<td>370.0</td>
<td>421.0</td>
<td>473.3</td>
<td>499.0</td>
<td>537.2</td>
<td>570.4</td>
<td>611.4</td>
<td>655.1</td>
<td>703.2</td>
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<tr>
<td>Healthcare spending (% of GDP)</td>
<td>8.1</td>
<td>8.3</td>
<td>8.5</td>
<td>8.3</td>
<td>8.4</td>
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</tr>
<tr>
<td>Healthcare spending (US$ bn)</td>
<td>112.2</td>
<td>103.1</td>
<td>109.0</td>
<td>111.1</td>
<td>112.9</td>
<td>114.7</td>
<td>116.7</td>
<td>118.9</td>
<td>121.4</td>
<td>126.0</td>
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<tr>
<td>Healthcare spending (US$ per head)</td>
<td>1,070</td>
<td>1,010</td>
<td>1,046</td>
<td>1,092</td>
<td>1,145</td>
<td>1,202</td>
<td>1,265</td>
<td>1,278</td>
<td>1,312</td>
<td>1,379</td>
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<td>Healthcare (consumer expenditure; US$ bn)</td>
<td>173.1</td>
<td>165.0</td>
<td>165.0</td>
<td>165.1</td>
<td>165.7</td>
<td>166.8</td>
<td>168.0</td>
<td>170.0</td>
<td>172.4</td>
<td>175.0</td>
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<td>Doctors (per 1,000 people)</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
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<td>Hospital beds (per 1,000 people)</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
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<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
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</tr>
</tbody>
</table>

* Actual, b Economist Intelligence Unit estimates. c Economist Intelligence Unit forecasts.

Source: Economist Intelligence Unit 2016

The Sistema Único da Saúde (SUS) was set up in 1988 with the aim of providing universal healthcare. It is funded through federal and local taxation as well as contributions from employers and employees. Brazil also relies on a substantial private health insurance industry. Efforts to improve the standard of public healthcare provision have been hindered by fiscal constraints. The
interim government has confirmed its intent to modernize the SUS by digitizing health records, among other measures.

3.1 Private Health Insurance

Private healthcare accounted for fifty-four percent of total healthcare spending in Brazil in 2014, according to the World Health Organization (WHO) data. Private insurance accounted for fifty percent of private spending, with out-of-pocket payments, mainly for pharmaceuticals, accounting for the rest. The poor state of healthcare service provision in the public sector has boosted the use of private healthcare by more affluent citizens, with coverage greater among the senior demographic. According to IMS, private health insurance plans covered 51 million people in 2014, a quarter of the population, making Brazil's insurance market the second largest by population in the world.

3.2 Healthcare Provision

According to the WHO, Brazil's doctor to patient ratio is low by regional standards, an estimated two doctors per 1,000 people in 2015. In the major urban centers, there is availability of doctors, including specialists. However, there is inequality in access in the public and private sectors, with most available doctors working in the private sector.

Figure 3-2 Beds to Doctors

Source: Economist Intelligence Unit 2016
3.3 Hospitals and Clinics

There were an estimated 2.5 hospital beds per 1,000 people in 2015, and their distribution and the quality of provision have been debated. SUS splits funding between public and private providers. Most inpatient services are privately operated and most outpatient services are publicly operated.

4 Pharmaceutical Market in Brazil

In 2012, Brazil ranked sixth in pharmaceutical spending (23). By 2017, International Medical Services (IMS) predicts that the country will grow to fourth, just behind Japan (16). Brazil is the largest pharmaceutical market in Latin America and the tenth largest in the world, accounting for around two percent of world demand. Brazil’s pharmaceutical sales were an estimated $25 billion in 2015 (30). Pharmaceutical sales have held up better than retail sales during the recession.

Figure 4-1 Drug Sales

<table>
<thead>
<tr>
<th>Year</th>
<th>2011a</th>
<th>2012b</th>
<th>2013b</th>
<th>2014b</th>
<th>2015b</th>
<th>2016c</th>
<th>2017c</th>
<th>2018c</th>
<th>2019c</th>
<th>2020c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sales (US$m)</td>
<td>34,816</td>
<td>33,174</td>
<td>33,001</td>
<td>32,631</td>
<td>25,475</td>
<td>25,575</td>
<td>26,225</td>
<td>27,582</td>
<td>26,677</td>
<td>32,662</td>
</tr>
</tbody>
</table>

Source: Economist Intelligence Unit, 2016.

4.1 Intellectual Property and Patent Review

From the perspective of the pharmaceutical industry, Brazil has been seen as one of the more problematic regions in which to enforce intellectual property (IP) rights. Brazil joined the Agreement on Trade Related Aspects of Intellectual Property Rights after it was introduced in 1995, which applies to all World Trade Organization members, and introduced IP law into the international trading system.
When a pharmaceutical patent is filed in Brazil, it is first analyzed by the National Institute of Industrial Property (INPI), before being submitted to ANVISA for separate analysis, and ultimately for a final decision. Since a new Industrial Property law was passed in 1996 in Brazil, a patent is valid for 20 years in Brazil and a utility model patent for 15 years from the filing date. However, because of the backlog of patent applications in Brazil, patents of invention are guaranteed for 10 years and utility model patents are valid for 7 years. However, there are no supplementary protection certificates or extensions available based on market approval delays in Brazil, which leads to significant litigation regarding the extension of patent term from 15 to 20 years of patents issued before the current IP statute was enacted (19).

The speed of patent review in Brazil is also problematic for companies seeking drug patents. At the time of writing, it takes 7 to 8 years to issue a pharmaceutical patent, with the delay arising from a shortage of patent examiners. The Patent and Trademark office of Brazil appears to be tackling this issue by increasing the number of examiners rather than by changing the law to offer patent term extensions, to compensate for time spent in regulatory review and the years lost while waiting for patents to be issued. The backlog of patent applications has occurred despite efforts to improve patent examining operations at the National Institute of Industrial Property (INPI). Pharmaceutical patents are generally approved within 2 years once they are reviewed with the majority of the delay attributed to the backlog. Historically, there has been little erosion of branded products post patent expiration.

4.2 Exclusivity

While Brazilian legislation provides data protection against unfair commercial use, it does not specify for how long, nor does it prevent regulators from using the data when approving generics or similar applications. The Pharmaceutical Research and Manufacturers Association of America (PhRMA) has also voiced concerns regarding this issue. It believes the Brazilian government fails to prohibit companies other than innovators from using test results and other data submitted by PhRMA member companies when approving marketing requests submitted by other companies. While it acknowledges that some positive steps have been taken to prevent inappropriate disclosure
of these data, it believes further efforts are needed to ensure that they are protected fully against non-reliance, as well as unauthorized disclosure and use (20).

The explanations that are most often used for allowing the use of data for generics approval is that this is done in the public interest, to minimize unnecessary clinical trials and that it is not for commercial purposes (20). It remains to be seen whether any future legal changes will prevent ANVISA from allowing generics approval based on originally published data.

4.3 Counterfeiting

Brazil is still seen by many as a country with inadequate intellectual property (IP) protection and weak enforcement of existing legislation. In practice, piracy is common and counterfeit drugs account for up to 10% of all drugs in circulation (12). Counterfeits are on the rise in Brazil, which many attribute to the weak foreign intellectual property laws and poor policing of the country’s domestic distribution chain and borders (12). There are several causes for concern and unresolved issues are having a negative effect on the pharmaceutical industry’s development.

Estimates suggest that 30% of the drugs sold in Brazil are not registered (12). According to the Brazilian Federal Police, 130 tons of non-registered and counterfeit medications were seized in 2008, mainly amphetamines, steroids, contraceptives and drugs for erectile dysfunction (12). From January to March 2009, ANVISA and the Ministry of Justice seized more than 170 tons of stolen, unregistered or falsified medicines (12). More worrying was the fact that the products were mainly found in accredited pharmacies run by owners who were involved. The culture of self-medication in Brazil and the sale of drugs without prescription are a common practice in Brazil. However, recent legislation was passed by the Senate to enforce the monitoring of medical products throughout their production, commercialization, distribution, and medical prescription, using electronic bar codes.

Despite the counterfeit drugs problem, Brazil is committed to making sure that isn’t used as an excuse to extend patent protections which would negatively impact the domestic generics business.
At a World Health Organization (WHO) Assembly in Geneva in May 2010, Brazil, along with India, argued that concerns about counterfeit drugs that are hijacked by pharmaceutical companies keen to protect their patents against legitimate generic competitors (25). Together with Latin American and African developing countries, the two nations urged the WHO to end its International Medical Products Anti-Counterfeiting Taskforce (Impact) partnership, which includes groups that represent the interests of pharmaceutical firms (12).

In addition, Brazil has been involved in a trade dispute with the World Trade Organization (WTO), after complaining that the EU violated international trade rules following its seizure of several shipments of generic drugs bound for Latin America and Africa, which the EU mistook for patent violation. Brazil is concerned that reinforcing intellectual property rights will lead to more, similar cases of legal generic drugs being wrongly treated as illegal counterfeits (12).

### 4.4 Importation

There are two ways in which foreign companies can import pharmaceuticals into Brazil via a local manufacturing unit or representative officer by appointing a local distributor that is authorized to import and distribute medical products. In both cases the product needs to be registered with ANVISA. For certain types of drugs, particularly controlled medicines, and import quotas exist.

All importers must register with the Secretariat of Foreign Trade (SECEX) to access the SISCOMEX computerized trade documentation system. The pharmaceutical product being imported must also be registered with ANVISA. Imports into Brazil amounted to approximately $5 billion, an increase of 21 percent increase since last year, mainly from the US, Germany, and Switzerland (30). All 450 tons of amoxicillin distributed on the Brazilian market every year are imported (30). In terms of exports, Brazilian products totaled more than $961 million in exports, a 29 percent increase (30). The main export markets are Venezuela, Argentina, and the US.

The devaluation of the Real in 2015-2016 has caused the pharmaceutical import bill to fall by 11 percent in 2015 and by another 30 percent in January-May 2016 year on year (30).
4.5 Pricing Regulations

Price controls are the responsibility of ANVISA, which operates mainly through the Câmara de Regulação do Mercado de Medicamentos (CMED). The CMED regulates prices and establishes regulatory guidelines for the entire pharmaceutical industry, including manufacturers, distributors and retailers. The prices of medicines that are already available on the market in Brazil are regulated by price freezes and increases implemented by the Brazilian government, under a price control mechanism which was introduced in 2000. Price control is regarded by the pharmaceutical industry as a major barrier to trade (15). The current system bases price adjustments on the general inflation rate in the preceding 12 months plus a variable component based upon the generic market share on a therapeutic class basis (15).

The compassionate use program, approved by ANVISA in August 2013, guarantees free orphan drug supply to those who have participated in a Phase III trial and benefitted from the drug. Because the patient population for a rare disease is limited, the pharmaceutical company’s Brazilian market for the respective orphan drug may be entirely comprised of its successful Phase III trial patients, negating any profit they may make in the country.

4.6 Reimbursement

In alignment with the World Health Organization’s (WHO) guidelines, Brazil established the National List of Essential Medicines (RENAME; Relação Nacional de Medicamentos Essenciais), which lists the available drugs that the government is prepared to fund through pharmaceutical assistance programs, on an outpatient basis. The drugs that appear on the RENAME list are selected based on criteria of effectiveness, safety and cost-effectiveness, and the lists are regularly updated (18).

Reimbursement in Brazil is limited to three programs. Although these medicines are available free of charge. Due to the limited nature of the program, access to pharmaceuticals is still fairly limited. Out-of-pocket payments account for a large proportion of pharmaceuticals sold in Brazil, around
80 percent (18). Additionally, access to medicines suffers from the same levels of inequality as the rest of the healthcare system, with the wealthiest 15 percent of the population accounting for half of all pharmaceutical sales. The government is responsible for purchasing 25 percent of all drugs sold in the country (18).

However, recently the government initiated public-private partnerships between government-run labs and private companies attempting to save money in government medicine purchases. Under the initiative, state-owned pharmaceutical companies will partner with private firms and produce drugs procured through the public health system. The initiative will develop generics of brands that have reached patent expiry. In addition, most private insurance organizations offer coverage only for pharmaceuticals dispensed in hospitals and patients have to pay out-of-pocket for drugs that are prescribed outpatient. Patients are forced to turn to the SUS for drugs in cases where access to medicines is inadequate. Multinational companies can be severely affected if Brazil decides to employ a more protectionist policy by favoring local manufacturers.

4.7 Leading Therapies
All therapy areas have experienced significant growth. This is attributed to the improving access to healthcare and pharmaceuticals among the population, as well as a growing middle class able to afford branded drugs.

4.8 Generics
Brazil has the largest generics industry in Latin America, aided by government policy aimed at extending the availability of medicines to less affluent patients. Under legislation introduced in 1999, purchases by the public healthcare system (SUS) must favor generics, even when prices are similar to branded drugs. According to data from IMS Health, generic drug sales reached $669 million from January to May of 2016, up 15 percent from last year. The increase in generic drug sales has outpaced that of branded drugs. Based on recent trends, many multinational companies are looking to penetrate the Brazilian markets and capitalize on its fast growth by gaining market access through acquisition of local generics players.
4.9 Technology

Over several decades, advances in medicine and research have helped healthcare providers improve the lives of patients. These medications treat a wide variety of disease states that have a significant impact on patients and their caregivers. Through the research and development of new therapies, patients now have more effective options to treat their diseases and live longer, healthier lives. Pharmaceutical companies are dedicated to bringing to market therapies that have the potential to change patient’s lives, through investment in innovation, and strong research and development programs.

Although technology is prevalent throughout the healthcare field, not all sites have implemented the most efficient clinical trial data capture systems. Online training and a global electronic data capture system can lead to greater GCP compliance and the ability to track clinical trial management in real time. Brazil should aim to harmonize these standards. Industry experts indicate that the future of data management is a central data capturing tool that is linked through a clinical trial management system. Additionally, it will enable companies and regulators to take electronic data capture snapshots and look at the performance per site in real time as well as increase transparency and communication across the industry.

Based on the research, there are fundamental issues in relation to traceability, validation, and control of data are new to electronic systems and are not unique to Brazil. Brazil could lead globally in this area, by establishing legislation, standards requirements, and guidance governing technologies and data in clinical trials, including GCP. A collaborative legislative effort with the pharmaceutical industry and patient advocates, would ensure that the collection, use, storage, or transfer of patients’ medical or personal data through the use of such technologies complies with all applicable data protection requirements, specifically, notice, consent, and transfer.

This conclusion is, however, subject to compliance with all applicable laws, regulations and guidance governing clinical trials, including all applicable Brazilian requirements, including Good
Clinical Practice and the Clinical Trial Data Guidelines. The applicable laws and regulations in Brazil do not treat technology enabled clinical trials separately from paper based trials. Consequently, the general principle that all data must be recorded truthfully, accurately, completely, timely and legally, applies equally to technology enabled clinical trials.

5 Regulatory Environment

Brazil is the fifth largest country worldwide and has the seventh largest economy with a population over 200 million. This makes Brazil very competitive in site selection for clinical research. Clinical research is a new endeavor for the Brazilians. In Brazil, several factors are advantageous for medical research, specifically clinical research, highly qualified investigators, economic growth, access to new technologies, information technology and data management infrastructure, access to large diverse patient populations, low operational costs, established regulatory system, and internationally harmonized regulations, all of which are in line with the greater demands and requirements of pharmaceutical drug development. However, Brazilian regulatory timelines are considerably longer than those found in other countries. This is due to two mandated ethical evaluations, one by the institution and the other national ethics review committee (CEP) and then one national methodological evaluation (ANVISA).
The Brazilian regulatory process is conducted in accordance with the International Conference on Harmonization (ICH), good clinical practice (GCP), and Pan American Health Organization (PAHO)/Pan American Network for Drug Regulatory Harmonization (PANDRH), and MERCOSUR. The first official Brazilian legislation regulating clinical research was Resolution CNS no. 01 in 1988 (8). However, it was only between 1996 and 1997 that the National Research Council (CNS) published important regulatory acts, particularly Resolution no. 196/96 and Resolution no. 251/97, to effectively recognize and regulate clinical research in Brazil (7). These regulations have been the basis for clinical trials in Brazil and directly address ethics and study management. In 1998, the Brazilian government published the 911/98 act, which described the documents and procedures required for the approval of clinical research. In 2004, the 911/98 act was updated by Resolution no. 219/04. This resolution is the reference for the structure of the study submission and must be presented to the ANVISA to obtain approval to receive the import license and special communique. These documents are the mainstay of approval documentation and mandated by ANVISA for the drug and device importation.

An important milestone in the development of Brazil’s regulatory process was the creation of ANVISA, which is equivalent to the Food and Drug Administration in the United States. It was established in 1999 to replace the Sanitary Surveillance Service, and linked to the ANVISA.
ANVISA oversees the development, manufacturing, and marketing of products and services that are designated for patients within its borders. Within ANVISA are the General Office of Drugs and the General Office of Research. Several divisions with these offices analyze and approve all clinical trials conducted in Brazil. Additionally, ANVISA analyzes and registers new drugs and/or devices, importation of supplies, and exportation of biological samples.

**Figure 5-2** Regulatory Timelines in Brazil

<table>
<thead>
<tr>
<th>Steps</th>
<th>Timelines</th>
<th>Cost (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documentation translation</td>
<td>2-3 weeks</td>
<td>$3,000-6,000</td>
</tr>
<tr>
<td>CEP approval</td>
<td>2-8 weeks</td>
<td>No fee -$1,200</td>
</tr>
<tr>
<td>CONEP approval</td>
<td>8-12 weeks</td>
<td>No fee</td>
</tr>
<tr>
<td>ANVISA approval – Special Communique</td>
<td>4-8 weeks</td>
<td>$6,000</td>
</tr>
<tr>
<td>ANVISA – License importation</td>
<td>2-4 weeks</td>
<td>No fee</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>18-35 weeks</td>
<td><strong>$9,000-14,200</strong></td>
</tr>
</tbody>
</table>

Brazil has emerged as a leader in new sites selected for clinical trials, by offering a multitude of benefits to pharmaceutical companies. The country has the largest population in Latin America and large numbers of patients with the major diseases of interest to the pharmaceutical industry. Furthermore, Brazil has highly qualified investigators, low costs, strong infrastructure, great patient recruitment, and high retention and adherence rates. Though there are significant delays with regulatory timelines, it has provided investigators and pharmaceutical company’s time to improve workflow and recruitment processes. This has enabled Brazil to become a leader in recruitment accruals completed ahead of schedule. However, in order to become a primary location for clinical trials, Brazil will have to overcome several policy challenges, by improving the clinical trial regulatory and approval process and increasing safety and monitoring protections. These
policy changes would address the challenges faced by the pharmaceutical industry and aid Brazil in being considered a primary selection site for clinical trials.

5.1 ANVISA
ANVISA developed procedures for the approval of clinical trials with new medications and to grant permits for the importation of experimental drug. As part of this process, ANVISA requests CONEP to provide information demonstrating that the proposed study meets the ethical guidelines and to analyze the study protocol and the characteristics of the pharmaceutical company and institutions where the study will take place. If ANVISA is satisfied after reviewing these documents, it will release a special communique allowing the study to proceed and granting permission for the importation of the new medication for the implementation of the clinical trial.

The ANVISA is responsible for monitoring clinical trials, which is mandatory for the registration of generic medicines and other new medications. Resolution RDC No. 103/2003 requires these studies to take place in certified centers, and there is an inspection program to guarantee quality. More recently, Regulation RDC 34/2008 was approved and created a registry of study participants to prevent volunteers from simultaneously participating in several trials, being exposed to unnecessary risks, or potentially biased study results. Regulation RDC No 39 currently governs the approval process of ANVISA (3). It states that ANVISA must be informed of all adverse effects arising during the clinical trial, allows ANVISA to conduct inspections of the research centers with or without CONEP, and apply sanctions if infringements on good clinical practices (GCP) are found. ANVISA also regulates the Contract Research Organizations (CROs), which, through contracts with the pharmaceutical companies, facilitate the implementation of clinical trials in Brazil and are often responsible for all communications between the pharmaceutical company, ANVISA, and the principal investigator.

5.2 CEP/CONEP
The Institutional Ethics Committee is known in Brazil as CEP. CEP was created to review and monitor research involving humans. In accordance with the Common Rule and the ANVISA
regulations, CEP has responsibility for approving, requiring modification, or disapproving research. CEP also has the authority to suspend or terminate research for continued noncompliance with the general clinical practices (GCP), ANVISA regulations, or its own findings, determinations, and initial and continuing review procedures.

The ethical evaluation of research involving humans is performed through the CEP/CONEP structure, which is part of the National Health Council (CNS). The final approval of clinical trials of new pharmaceuticals and other health products, also involves ANVISA. Until recently, the CEPs of all the establishments where the study was to be conducted and the CONEP had to approve a project before ANVISA could authorize it and issue an importation license for the experimental drug or device to be tested in the trial. Both the CEPs and CONEP are agencies for the public good, they are multidisciplinary, function independently from the pharmaceutical company and the investigator, and they defend the interest and rights of the study participants. Committee members are volunteers who receive no compensation for their work on these committees, and are selected based on criteria of availability and commitment to ethical standards.

The CEPs are collegial bodies created by the institution they serve and are independent of the management of the institution, similar to the US Institutional Review Board (IRB). The CEPs are multidisciplinary, and must include specialists in health sciences, clinical sciences, statistics, and social and human sciences, with the restriction that members of the same professional category may not form more than half the committee. CEP members are elected for a three year term, half are elected by their colleagues, and one must represent the users of the institution.

The CEPs are responsible for the ethical review of all the projects taking place in their own institutions. CONEP examines projects approved by the CEPs that could pose an ethical risk and meet the requirements to be classified as special projects, such as research in genetics, human reproduction, international collaboration, biosafety, special demographics, and any project the CEP determines should be evaluated by CONEP. CONEP is also responsible for maintaining the registry, supporting the CEPs, proposing additional regulations, and providing technical
assistance. Both ANVISA and CONEP have the authority to make inspections of clinical trials and of the CEPs.

CONEP is part of the National Health Council (CNS) and receives logistical support from the Ministry of Health, but administratively it does not report to the Ministry and is independent in its decision making. CONEP consists of 15 members and 15 alternates chosen by the CNS and each serves for a period of four years. Six members are selected by lottery and nine based on their professional expertise. One member must represent healthcare workers, managers, and two members are the users of the National Health System (SUS). The CEP and CONEP coordinators are elected by the committee members.

CONEP may designate one or more Institutional Ethics Committee (CEPs) to review Brazil’s human patient research. Any designated CEP operates under the authority of Brazil’s CONEP when overseeing human patient research. A designated CEP’s primary responsibility is to ensure that the rights and welfare of patients are protected in human patient research. In doing so, the designated CEP must ensure that human patient research is conducted ethically and in compliance with regulations and ANVISA policies and procedures. The designated CEP fulfills these responsibilities by conducting prospective and continuing review of human patient research, including review of the protocol and proposals, the informed consent process, procedures used to enroll patients, as well as any adverse events or unanticipated problems reported to the CEP. Prospective review and approval of research or changes to previously approved research ensures that research is not initiated without CEP review and approval. In its communications to investigators, the CEP makes investigators aware of the requirement to submit changes for review and approval before initiation except where necessary to eliminate apparent immediate dangers to the patient.

No other Brazilian regulatory body may set aside or overrule a determination by a designated CEP to disapprove or require modifications in human patient research. The CEP will provide the investigator with a written statement of its reasons for disapproving or requiring modifications in
the proposed research and will give the investigator an opportunity to respond in person or in writing. CEP will carefully and fairly evaluate the investigator’s response in reaching its final ruling. There is no limit to the number of times a research project can be revised and resubmitted to the CEP for consideration. However, considerable cost can be incurred under these circumstances.

Clinical trials are submitted for evaluation through a portal called Plataforma Brazil. The information collected is directed to an ethical committee. All human patient research conducted in Brazil must be prospectively reviewed and approved by a CEP designated by Brazil’s CONEP. No human patient research may be initiated or continued in Brazil without prospective approval of a designated CEP. Any CEP designated by Brazil’s CONEP is empowered to take any action necessary to protect the rights and welfare of human patients in research conducted in Brazil. A designated CEP may suspend or terminate the enrollment and/or ongoing involvement of human patients in research as it determines necessary for the protection of those patients, especially in instances of serious or continuing noncompliance. The CEP has the authority to observe, monitor, and/or audit human patient research to whatever extent it considers necessary to protect human patients and assure compliance with applicable laws and regulations. In cases of serious or continuing noncompliance, the CEP may: disqualify an investigator from conducting a particular research project or research altogether; require education and training in the ethics and regulation of human patient research; or any other reasonable measure deemed appropriate to protect the rights and welfare of research patients.

5.3 Drug Approval and Regulatory Process
The regulatory system in Brazil is regarded by many as unpredictable. Many pharmaceutical companies have voiced complaints that the government in Brazil changes regulations too abruptly and too often. In addition, approval times are lengthy in Brazil, a problem that partly stems from the ongoing assessment of manufacturing plants to assessments of compliance with current Good
Manufacturing Practices (GMP) requirements, while the intellectual property (IP) environment is also considered weak, with slow patent reviews and conflicts between Brazilian agencies.

All pharmaceutical products registered in Brazil are grouped into one of three different categories. Generic drugs are those drugs which contain the same active substance in the same dose and pharmaceutical form, and are administered in the same way and with the same therapeutic dosage as reference drugs. Similar drugs are those drugs that contain the same active ingredient, the same concentration and pharmaceutical form, and are administered in the same way and with the same dosage and have the equivalent therapeutic result as the reference (branded) drug. Original drugs are usually innovative drugs which have scientifically proven effectiveness, safety, and quality. They are drugs that have been on the market for a long time and carry a well-known brand name. Most companies in Brazil produce generics and similars, as they have fewer resources, working capital, and qualified personnel. Most foreign pharmaceutical companies operating in Brazil manufacture more reference (branded) drugs.

5.4 Inspections
The cost of registering a drug depends on its category and the size of the company requesting it. To receive a visit from an ANVISA technician to obtain a “Certificate of Good Manufacturing Practice,” costs a company $18,500, regardless of its size. Inspections of plants by the authorities are becoming more common and are adding to the total approval time. Overall it now takes longer to receive approval for a drug than it did in the past in Brazil. There is no fast-track system, but ANVISA gives priority to less costly drugs and treatments for life-threatening and neglected diseases. Once a drug is approved, registration is only valid for 5 years.

6 OBJECTIVES
The purpose of this research is to analyze the potential pitfalls and delays in regulatory time lines for clinical research in Brazil. Apart of evaluation of legislative documents, this research provides the results from a survey carried out with the representatives of competent
authorities and research industry personnel, where they shared their opinions in conducting clinical studies in Brazil. Their experiences provide a glimpse of the market.

The objectives of the research is to

- Identify the reasons ANVISA and CEP/CONEP approval for new clinical research were delayed.
- Identify opportunities for optimization in the workflow of the regulatory process for approval.

### 6.1 METHODOLOGY

To attain the desired objective of the study, the following methods of data collection will be used:

- Describe the regulatory bodies in Brazil
- Describe the main regulatory procedures in clinical research in Brazil
- Compare regulatory requirements and procedures with other international regulatory bodies.
- Describe opinions of regulators and pharmaceutical personnel on existing regulation and improvements in Brazil.

### 6.2 Survey

The survey will collect the data from representatives of the competent authorities and research companies active in the Brazil. The survey will be accompanied by a letter, which explains the purpose of the study, the survey procedure, and confidentiality aspects of the survey. Both documents will be provided to the respondents in English and Portuguese. The surveys will be completed in-person, by email, or by telephone depending on the choice of the participant. To ensure the confidentiality of the survey, no personal names or names of the companies will be referenced in this study. The results of the survey will be presented based on the professional area
of respondents (defined either as “representative of a competent authority” or “industry representative”).

A survey has been developed to assess patterns of delay in clinical trial initiation through representatives of the ANVISA, other competent authorities, and research companies. The survey/survey will collect data from representatives of the competent authorities and research companies active in Brazil versus the United States. The survey was developed with the help of ANVISA, CEP/CONEP, and Novartis. The survey was accompanied by a letter, which explained the purpose of the survey, the survey procedure, and confidentiality aspects of the survey. Both documents will be provided to the respondents in English and Portuguese. The surveys can be completed in-person, by email, or by telephone depending on the choice of the participant. To ensure the confidentiality of the survey, no personal names or names of the companies will be referenced in this survey. The results of the survey will be presented based on the professional area of respondents (defined either as “representative of a competent authority” or “industry representative”).

1. How accessible is medical care to the average Brazilian patient?
2. How regulated are clinical trials in Brazil, as compared with western countries?
3. What is the climate of clinical research in Brazil?
4. How do timelines in Brazil compare with other markets?
5. What have you noticed as being a common issue in the approval process?
6. What is the most time consuming part of the approval process?
7. What would you change about the approval process?
8. What experience do HAs/ Health Technology Authorities have with digital technologies in clinical trials?

6.3 ANALYSIS OF THE RESULTS
These interviews have been conducted with the representatives of competent authorities and industry representatives. None of the respondents were able to provide statistical data on the
number of approved studies per year. Below we will summarize the most common responses obtained during the survey:

Question: How accessible is medical care to the average Brazilian patient?
   1. Not very accessible, although basic services are provided under the universal healthcare system SUS
   2. Accessible for more affluent patients
   3. Getting better

Question: How regulated are clinical trials in Brazil, as compared with western countries?
   1. Equally regulated
   2. More regulation
   3. Bureaucratic hurdles
   4. Redundant ethics committees

Question: What is the climate of clinical trial research in Brazil?
   1. Positive
   2. The regulatory agencies of Brazil are being proactive and addressing timelines via newly initiated processes.
   3. Growing
   4. The regulatory agencies understand that they have an opportunity to make a significant impact on the market.

Question: How do timelines in Brazil compare with other markets?
1. Much longer timelines, however fee schedule makes Brazil more attractive to a pharmaceutical company, who could save 20-30 percent by conducting clinical trials in Brazil. Additionally, the economic issues affecting the Brazilian Real have made the fee schedule even more attractive.

Question: What have you noticed as being a common issue in the approval process?

  1. Study design
  2. Safety
  3. Ethics approval
  4. Clinical study does not meet GCP standards or requirements of legislation.
  5. Poor quality of the informed consent form that lacks proper communication of risks and benefits, use of terms and vocabulary understandable for local communities, consideration of cultural perceptions of nature, cause and treatment of certain diseases.
  6. Importation
  7. Continued care post clinical trial participation
  8. Health insurance provisions for study participants do not meet regulatory requirements.

Question: What is the most time consuming part of the approval process?

  1. Redundancies of Ethics committee approval
  2. Importation of study drug

Question: What would you change about the approval process?

  1. Redundancy in the approval process
  2. Fee schedule
3. Allowing exceptions and expedited approvals
4. Requirements to the study sites.
5. Requirements to provision of health insurance for study participants.
6. Regulatory approval times.
7. Quality of inspections of study sites and their frequency.
8. A strong enforcement mechanism.

Question: What experience do HAs/ Health Technology Authorities have with digital technologies (including e-signature) in clinical trials?

1. None
2. Recently, implemented Platforma, a digital technology that is used to submit Clinical Trial Application for the approval process.

6.4 Interviewees

1. Clinical Study Manager for multinational pharmaceutical company in Brazil
2. Head of Development for multinational pharmaceutical company in China
3. Global Program Regulatory Manager for multinational pharmaceutical company in the USA
4. Patient Associate Relationship Consultant for multinational pharmaceutical company in Brazil
5. Principal Product Development Engineer for a multinational pharmaceutical company in the USA
6. Principal Development Engineer for multinational pharmaceutical company in the USA
7. Digital Development Lead for multinational pharmaceutical company in the USA
8. Director of Digital Development for a multinational pharmaceutical company in the USA

9. Developer for a multinational pharmaceutical company in the USA

10. Director of Disruptive Technologies for multinational pharmaceutical company in the USA

11. Assistant Director of Digital Development for multinational pharmaceutical company in the USA

12. Senior Clinical Manager for multinational pharmaceutical company in the USA

13. Director of Digital Medicine for multinational pharmaceutical company in the USA

14. Former Regulatory Manager for USA drug regulatory body

15. Managing Director of a private clinical research organization (CRO) in Brazil

7 CONCLUSIONS AND RECOMMENDATIONS

It is clear that pharmaceutical companies have been hesitant in initiating large scale, global trials in BRIC countries as of late, believing the risks outweigh the benefits. With this pull back, however, greater opportunity arises with widely accessible sites and available investigators, untapped patient pools and therapeutic areas, and a generous cost savings, if the pharmaceutical company can navigate the delays in Brazil’s regulations. Despite the attractiveness of fast recruitment and cost-effective trials, there are many issues unique to BRIC markets that can delay trials and drive costs upwards: local needs, regulatory hurdles, customs problems, manufacturing quality, GCP (Good Clinical Practice) and GCLP (Good Clinical Laboratory Practice) standards, high turnover rate of CROs, and a disconnection of data between sites and pharmaceutical companies and/or CROs are all obstacles that need to be addressed (15). Successful pharmaceutical companies are able to traverse the delays and red tape by maintaining local units and/or partnering with CROs, as well as working with local consultants.
One thing is for sure, the BRIC clinical trial climate is changing. While some pharmaceutical companies are beginning to explore other emerging markets, there are others who have decided to stay and invest in BRIC. Those that believe that despite the rapidly changing regulatory requirements, corruption, and patent protection losses, BRIC countries remain cost-effective and timely, if a pharmaceutical company can navigate the red tape. By increasing a local presence in these countries and building a strong relationship with regulatory bodies, local sites and investigators, and the community, it is possible to reap the benefits of fast recruitment and quality data that these markets afford. These recommendations suggest Brazil focus and streamline processes, to create a more integrated healthcare system with a robust pharmaceutical industry and world class healthcare supporting them. These recommendations could positively affect efficiency and help Brazil maintain its focus on innovation and growth, and be in a stronger position to manage future expansion. The sharp decline in the value of the Real could make mergers and acquisitions activity attractive to foreign investors going forward.

Clinical trials are economical in Brazil because the salaries and grants to investigators and assistants are lower than those of staff in higher salaried countries and because the majority of the clinical trials are conducted in the medical facilities of the SUS. Thereby SUS is seemingly subsidizing research, because mechanisms do not exist to separate the direct and indirect costs associated with a clinical trial, including staff time given to patient recruitment and to other processes specifically related to the clinical trial. More clinical trials of new medications are carried out in Brazil than in any other Latin American country. According to Clinicaltrials.gov, 1,397 clinical trials had been registered thus far in 2016.

Conducting clinical trials in Brazil offers several advantages to the pharmaceutical industry:

- The availability of patients with different patterns of disease.
- People with few resources to purchase needed medications who are willing to participate in clinical trials.
- An ethnically varied and young population
- A high proportion of drug naive, potential patients.
Large, well-equipped medical centers

Trained, multilingual personnel, wanting to participate in clinical trials.

Brazil’s location allows clinical trials of medications for seasonal health problems

To ensure a high retention rate for clinical trials, participants receive special services that are unavailable under the Brazilian National Health System (SUS), such as transportation to the research center, reimbursement for meals, and additional health examinations. The ease of recruitment compensates for the time required for regulatory approval of a clinical trial through the CEP-CONEP system.

Close alignment with the pharmaceutical industry and medical teams is essential to success. By operating as a collaborative healthcare system, Brazil will secure its future as a world class pharmaceutical market and will be in a better position to lead the industry and contribute to innovations that will make a real difference in patients’ lives in Brazil and around the world. A more collaborative approach to clinical trial development and working with pharmaceutical companies as a united enterprise, will allow growth and the ability to share and connect more easily across functions. The goal is to have more clinical trials in development and to get drugs to the marketplace faster. It will also strengthen collaboration and accelerate best-practice sharing and harmonization across multiple functional areas. Some recommendations include:

- Speed the approval process for clinical trials by permitting parallel evaluations by CEP/CONEP and ANVISA. The parallel system would allow ANVISA to approve the importation of experimental medications when the first Committee for Research Ethics (CEP) approves a multicenter clinical trial, without waiting for CONEP’s approval.

- An enforcement mechanism must be established.

- Incorporating strategies to permit the correction of errors.

- Integrate ANVISA and CEP/CONEP, accelerate best practice sharing, increase harmonization, and increase efficiency.
- Technological recommendations would bring together data management, provide coordination and standardization across digital technologies, trial management, and align interactions and presence with external partners, regulators, and physicians.

Brazil has emerged as a leader in new sites selected for clinical trials, by offering a multitude of benefits to pharmaceutical companies. However, in order to become a primary location for clinical trials, Brazil will have to overcome several policy challenges, by improving the clinical trial regulatory and approval process and increasing safety and monitoring. These are important steps towards strengthening Brazil’s ability to innovate with the speed and the excellence needed to provide new advancements for patients around the world. Further cementing Brazil’s contribution to future innovation and ultimately bring new treatment options to all patients in need through a legacy of transforming medicine, bending the curve of life, and being a leader in medical innovation.

Brazil has the opportunity to reimagine the future of drug development, but it must continue to work together with the industry and embrace change, while maintaining focus on technology to ensure it continues to deliver for patients and build a collaborative culture. To keep pace with the external trends and rapidly evolving innovation that are shaping the pharmaceutical industry, Brazil should be willing to collaborate across international regulatory agencies and pharmaceutical companies. This would allow Brazil to identify synergies across both regulatory functions of ANVISA and CEP/CONEP, to further harmonize, and increase resources for innovation. By continuing to focus on new technologies, Brazil will ensure it remains at the cutting edge of pharmaceutical development.
A Critical Assessment of Brazil's Emerging Pharmaceutical Market
Thesis
Jiibril Palmer, MS
APPENDIX I: CONEP

MINISTERIO DA SAUDE Conselho Nacional de Saude

Oficio Circular Nº. 062/2011/CONEP/CNS/MS

Brasilia, 19 de julho de 2011.

Assunto: Documentos necessarios para Inclusao de Centro; Exclusao de Centro; Alteracao de Centro Coordenador e de Pesquisador; Transferencia de Local de Estudo; Alteracao de Investigador; Cancelamento;Suspensao e Encerramento do Estudo

Senhor (a) Coordenador (a),

1. Segue, em anexo, a lista de documentos necessarios para Inclusao de Centro; Exclusao de Centro; Alteracao de Centro Coordenador e de Pesquisador; Transferencia de Local de Estudo; Alteracao de Investigador; Cancelamento; Suspensao e Encerramento do Estudo, para analise da Comissao Nacional de Etica em Pesquisa (CONEP).

2. Conforme preconiza a Resolucao CNS 346 (item 5), apenas o CEP do primeiro centro se encarregara das notificaes a CONEP.

Atenciosamente,

GLEISSE DE CASTRO DE OLIVEIRA
SECRETARIA EXECUTIVA SUBSTITuta DO
CONSELHO NACIONAL DE SAUDE
INCLUSAO DE CENTRO:

Documentos:

a. Justificativa da inclusao do novo centro participante;
b. Encaminhar o(s) names da(s) Instituto;ao(6es)/Cidade/Estado e o Comite de Etica que acompanhar a pesquisa no novo centro/Cidade/Estado;
c. Encaminhar o(s) nome(s) do(s) pesquisador(es) que seni(ao) responsavél (eis) pelo estudo em cada novo centro de pesquisa;
d. Curricula do(s) novo(s) pesquisador(es) (preferencialmente o curricula inscrito na Plataforma Lattes).

EXCLUSAO DE CENTRO

Documentos:

a. Justificativa da exclusao do centro participante;
b. Relatorio detalhado das etapas da pesquisa ocorridas no centro que sera excluido quando estava em andamento devidamente assinado pelo pesquisador responsável pelo centro de estudo;
c. Relatorio detalhado em relacao aos sujeitos de pesquisa, incluindo informac;ao(s) sobre o impacto da transferencia para outros locais de estudo e/ou informac;ao(s) sobre o deslocamento e demais informac;ao(s) sobre o sujeito de pesquisa.

ALTERACAO DE CENTRO COORDENADOR

Documentos:

a. Justificativa da alterac;ao do centro coordenador, emitido pelo pesquisador principal do antigo centro coordenador;
b. Relatorio detalhado do andamento da pesquisa assinado pelo pesquisador (antigo), principalmente em relacao aos sujeitos de pesquisa, incluindo informac;ao(s) sobre o impacto da transferencia para outros locais de estudo, tais como o deslocamento para os sujeitos de pesquisa, etc., e se houve ou nao prejuiz;o (e especifica-lo(s) para o(s) sujeito(s) de pesquisa com a alterac;ao do Centro Coordenador);
c. Envio de informac;ao(s) sobre alterac;ao(s) nas formas de recrutamento (caso ocorra) e sobre os sujeitos de pesquisa (principalmente se serao pacientes do SUS e ou/ particulares) e informar sobre qual a instituc;ao assume as responsabilidades inerentes â”Instituc;ao de Pesquisa”;
d. Declaração assinada do responsavél pelo Centro de Pesquisa concordando com o desenvolvimento do estudo e informando sabre a existencia de infra-estrutura disponAfvel para a realizac;ao da pesquisa, bem como para o oferecimento da garantia de assistencia integral aos sujeitos de pesquisa diante de complicac;ao(s) e danos decorrentes da pesquisa. Quando essa assistencia for garantida por instituc;io parceira, deve-se apresentar documento explicitando o convenio ou outras relac;ao(s) envolvendo pessoas juridicas, assinado pela Diretoria Tecnica da mesma;

Esplanada dos Ministerios, Bloco “G” – Edificio Anexo, Ala “B” – 1º andar, Sala 104 – 70058-900 – Brasilia, DF
Telefones: (061) 3226-8803/3225-6672-Fax: (061) 3315-2414/3315-2472-e-mail: cns@saude.gov.br
e. Informação sobre o vínculo do pesquisador com o novo Centro de Pesquisa;
f. emissão de uma nova Folha de Rosto contendo as informações retificadas e as assinaturas dos respectivos responsáveis pelo novo Centro.
g. Parecer do CEP Responsável pelo acompanhamento da pesquisa no centro em questão aprovando a transferência do local de estudo e especificar sobre as repercussões desta troca sobre a execução do referido protocolo;
h. Curriculum vitae do novo pesquisador.

TRANSFERÊNCIA DE LOCAL DE ESTUDO
Documentos:
a. Envio de informações sobre alterações nas formas de recrutamento e sobre os sujeitos de pesquisa (principalmente se serão pacientes do SUS e ou/ particulares) e informações sobre qual instituição assume as responsabilidades inerentes à "Instituição de Pesquisa";
b. Declaração assinada do responsável pelo Centro de Pesquisa concordando com o desenvolvimento do estudo e informando sobre a existência de infra-estrutura disponível para a realização da pesquisa, bem como para o oferecimento da garantia de assistência integral aos sujeitos de pesquisa diante de complicações e danos decorrentes da pesquisa. Quando essa assistência for garantida por instituição parceira, deve-se apresentar documento explicitando o convenio ou outras relações envolvendo pessoas jurídicas, assinado pela Diretoria Técnica da mesma;
c. Avaliação da repercussão da troca sobre o valor do ressarcimento dos custos com deslocamento para os sujeitos da pesquisa;
d. Informação sobre o vínculo do pesquisador como novo Centro de Pesquisa;
e. emissão de uma nova Folha de Rosto contendo as informações retificadas e as assinaturas dos respectivos responsáveis pelo novo Centro.
f. Parecer do CEP Responsável pelo acompanhamento da pesquisa no centro em questão aprovando a transferência do local de estudo.

ALTERAÇÃO DO INVESTIGADOR DO CENTRO COORDENADOR E/OU CENTRO(S) PARTICIPANTES
Documentos:
a. Justificativa da solicitação da troca de investigador principal emitida pelo(a) pesquisador(a) anterior;
b. Folha de Rosto contendo o nome e os demais dados do novo(a) Investigador;
c. Curriculum vitae do(a) novo(a) investigador(a);
d. Parecer consubstanciado do CEP sobre as repercussões desta troca sobre a execução do referido protocolo;
e. Relatório do andamento da pesquisa emitido pelo(a) pesquisador(a) anterior.
ENCERRAMENTO DO ESTUDO
Definição: Quando é finalizado após o cumprimento das etapas previstas.

Documentos:
a. O Roteiro para Elaboração de Relatório Final de Estudos Clínicos Unicentricos e Multicentricos encontra-se no link:

SUSPENSÃO DO ESTUDO
Definição: Quando a interrupção se dá em pesquisa em andamento.

Documentos:
a. O Roteiro para Elaboração do Relatório de Suspensão de Estudos Clínicos Unicentricos e Multicentricos encontra-se no link:

CANCELAMENTO DO ESTUDO
Definição: Quando a interrupção se der antes do início do recrutamento dos sujeitos da pesquisa ou da efetiva coleta de dados.

Documentos:
a. Registro CONEP
b. Título do projeto
c. Razões do cancelamento

Analise do CEP sobre as razões do cancelamento
APPENDIX II: Open Letter

Open Letter to the representatives of regulatory authorities and research organizations, active in clinical research

Dear Ladies and Gentlemen,

There is a growing tendency for international research companies to choose Emerging Markets such as Latin America, Eastern Europe, and Asia as a place to carry out clinical research. Emerging countries offer different regulatory and logistic provisions and being familiar with them helps research industry to understand advantages of each particular country and improve strategic planning. For national regulatory authorities it is important to ensure a clear Clinical Trial Application submission and evaluation system and thorough supervision of the conduct of a trial.

The purpose of our survey is to identify opinions of representatives of regulatory authorities and research organizations about regulatory systems in Brazil. This study is performed within the framework of Corporate International Masters program course at and Georgetown University.

Main goals of the study:

- To describe CTA approval and review process in Brazil
- To compare regulatory requirements and procedures with the US system
- To provide opinions of regulators and pharmaceutical companies, operating in Brazil, on practical aspects of clinical trial conduct.

To answer these research questions I have developed a survey that focuses on two main aspects: first, on the experience of regulatory authorities and research industry gathered in Brazil and second, on their assessment of existing regulatory systems. The survey can be conducted either by phone or by email.

Based on the results of the survey, practical recommendations for carrying out clinical trials in Brazil and on strengthening cooperation between regulatory authorities and the pharmaceutical industry can be made.

I invite you to participate in this survey and look forward to your collaboration.

Sincerely,

Jiibril Palmer

Confidentiality and Ethical aspects
This survey is completely voluntary. If you agree to proceed, you may choose to stop completing the survey or answering the questions during phone interview at any time. If you do not wish to answer a certain question please feel free to do so.

This survey is anonymous. Your answers will be seen only by me. I am interested in personal opinions and experiences. By the submission of this thesis, the results will show only research country and professional area of respondents, defined either as “regulatory authority” or “research industry” will be indicated.

Results of the survey will be published in the master thesis for the Corporate International Master’s program at the Brazilian School of Public and Business Administration of Fundacao Getulio Vargas.

Survey procedure
You may answer survey questions either by phone or by email.
Phone survey: interview will be conducted on day and time specified by respondent. A phone call will be given on phone number provided by respondent, language: English or Portuguese.
E-survey: electronic version of the survey will be sent to respondents by the email, language: English or Portuguese.

We have tried to develop a survey as comprehensive as possible. However, we would be very grateful for any additional comments you may want to provide to any of the questions.

It will take about 15 minutes for you to fill up the survey. Your input is very valuable for me and I would greatly appreciate your taking time to answer these questions.

For questions and comments please email: jp1544@georgetown.edu
APPENDIX III: Survey
1. Question: How accessible is medical care to the average Brazilian patient?
   Answer:

2. Question: How regulated are clinical trials in Brazil, as compared with other markets?
   Answer:

3. Question: What is the climate of clinical trial research in Brazil?
   Answer:

4. Question: How do timelines in Brazil compare with other markets?
   Answer:

5. Question: What is the current timeline for starting a study in Brazil?
   Answer:

6. Question: What have you noticed as being a common issue in the approval process?
   Answer:

7. Question: What is the most time consuming part of the approval process?
   Answer:
8. Question: What would you change the approval process?
   Answer:

9. Question: What experience do HAs/ Health Technology Authorities have with digital technologies (including e-signature) in clinical trials?
   Answer:

APPENDIX IV: Open Letter in Portuguese
Carta aberta aos representantes das autoridades e organismos de investigação regulamentar, ativa em pesquisa clínica
Senhoras e senhores,

Há uma tendência crescente para as empresas internacionais de pesquisa para escolher mercados emergentes como a América Latina, Europa Oriental e Ásia como um lugar para realizar a pesquisa clínica. Países emergentes oferecem diferentes disposições regulamentares e logísticas e estar familiarizado com eles ajuda a indústria a pesquisa para entender as vantagens de cada país em particular e melhorar o planejamento estratégico. Para as autoridades reguladoras nacionais é importante para garantir um sistema de clínica clara de teste de aplicativos apresentação e avaliação e supervisão completa da realização de um ensaio.

O objetivo de nossa pesquisa é identificar opiniões dos representantes das autoridades reguladoras e organizações de pesquisa sobre sistemas reguladores no Brasil. Este estudo é realizado no âmbito do Mestrado Internacional de Empresa claro programa em e Georgetown University.

Os objetivos principais do estudo:
• Descrever a aprovação CTA e do processo de avaliação no Brasil
• Para comparar os requisitos e procedimentos de regulamentação com o sistema dos EUA
• Para fornecer opiniões dos reguladores e as empresas farmacêuticas, que opera no Brasil, sobre aspectos práticos de conduta ensaio clínico.

Para responder a estas questões de investigação que tenho desenvolvido um questionário que se concentra em dois aspectos principais: em primeiro lugar, sobre a experiência das autoridades reguladoras e da indústria de pesquisa reunidos no Brasil e em segundo lugar, na sua avaliação de sistemas de regulamentação existentes. A pesquisa pode ser realizada por telefone ou por e-mail.

Com base nos resultados da pesquisa, recomendações práticas para a realização de ensaios clínicos no Brasil e no reforço da cooperação entre as autoridades reguladoras e da indústria farmacêutica podem ser feitas.

Convido você a participar desta pesquisa e aguardamos a sua colaboração.

Atenciosamente,
Jiibril Palmer

Confidencialidade e Aspectos éticos
Esta pesquisa é totalmente voluntária. Se você concorda em continuar, você pode optar por deixar de completar o questionário ou responder as perguntas durante a entrevista por telefone.
a qualquer momento. Se você não quiser responder a uma determinada pergunta, por favor sintase livre para fazê-lo.

Este inquérito é anónimo. Suas respostas serão vistas apenas por mim. Estou interessado em opiniões e experiências pessoais. Com a apresentação desta tese, os resultados vão mostrar único país área de pesquisa e profissional dos entrevistados, definida quer como “autoridade reguladora” ou “indústria de pesquisa” será indicado.

Os resultados do estudo serão publicados na tese de mestrado para o programa de Mestrado Internacional das Sociedades da Escola Brasileira de Administração Pública e de Empresas da Fundação Getúlio Vargas.

procedimento de inquérito

Você pode responder a perguntas da pesquisa por telefone ou por e-mail.

Telefone pesquisa: entrevista será realizada no dia e hora especificada pelo entrevistado. Um telefonema será dado no número de telefone fornecido pelo entrevistado, idioma: Inglês ou Português.

E-pesquisa: versão eletrônica do questionário será enviado aos participantes pelo email, idioma: Inglês ou Português.

Temos tentado desenvolver um questionário mais abrangente possível. No entanto, ficaríamos muito gratos por quaisquer comentários adicionais que você pode querer fornecer a qualquer uma das perguntas.

Vai demorar cerca de 15 minutos para você preencher o questionário. A sua opinião é muito valiosa para mim e eu gostaria muito de seu tempo a tomar para responder a estas perguntas.

Para perguntas e comentários e-mail, por favor: jp1544@georgetown.edu
APPENDIX V: Survey in Portuguese

1. Pergunta: Como acessível é cuidado médico ao paciente média brasileira?
   Responda:

2. Pergunta: Como regulamentado estão ensaios clínicos no Brasil, em comparação com os países ocidentais?
   Responda:

3. Pergunta: Qual é o clima de pesquisa clínica no Brasil?
   Responda:

4. Pergunta: Como cronogramas e tabelas de honorários no Brasil comparar com o FDA?
   Responda:

5. Pergunta: Qual é o cronograma atual para iniciar um estudo no Brasil?
   Responda:
6. Pergunta: O que você tem notado como sendo um problema comum no processo de aprovação?
Responda:

7. Pergunta: Qual é a parte mais demorada do processo de aprovação?
Responda:

8. Pergunta: O que você mudaria o processo de aprovação?
Responda:

9. Pergunta: Qual a experiência que foi / Autoridades Tecnologia de saúde têm com as tecnologias digitais (incluindo e-assinatura) em ensaios clínicos?
Responda:
APPENDIX VI: Sponsor Declaration

STATEMENT FORM
National Health Surveillance Agency
Researches, Clinical Trials, New Drugs and Biologics Management - GFHIN
Coordination of Research and Clinical Trials - CEP/CIC
Sponsor Declaration

1. Sponsor’s name:
   
2. Sponsor’s address:
   
3. Name of Product or Product Study:
   
4. Indications:
   - Medication: Yes ☐ No ☐ International ☐ National ☐
   - Top of the planned survey in Brazil: ___________________ (month/year)
   - Planned start of the survey: ___________________ (month/year)
   - Termination of the research provided in the World: ___________________ (month/year)
   - Duration of Study:
     - Duration of Treatment: ___________________ (month/year)
     - Registry number:
     - Medicines approved in the World: Yes ☐ No ☐
     - Countries where the drug is approved: ___________________
     - Date of first approval: ___________________ (month/year)
     - Trade Names in places of Approval: ___________________

5. Information on all sites:
   
<table>
<thead>
<tr>
<th>Institution</th>
<th>CNES</th>
<th>Status CEP</th>
<th>Subjects in the site</th>
<th>Investigator</th>
<th>CEP</th>
</tr>
</thead>
</table>

6. Title and code of the Research (include date and version):

7. Research with the participation of ORPC (Outstanding Research Organizations): Yes ☐ No ☐ (If yes, attach contract and letter of delegation)
   
<table>
<thead>
<tr>
<th>Name, Address and Telephone of ORPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responsible person:</td>
</tr>
</tbody>
</table>

8. Responsibilities
   - The sponsor, through its legal representative, declares to be responsible in Brazil for the conduct of the clinical trial on medicines, in accordance with the approved protocol.
   - To provide full and free assistance to trial subjects regarding the occurrence of adverse events arising from the use of medicines investigated or procedures used in accordance with the approved Clinical Protocol.
   - To distribute the drugs in research only to research institutions authorized to participate in this clinical research.
   - At the end of the study, account the products imported and not used, giving its proper destination, whether its destruction in the national territory other than returned to the origin, keeping the regular records of the procedures adopted.
   - To disseminate the results of the clinical trial, after the conclusion of that with proper analysis of the data, including statistical analysis when appropriate, even if the results are favorable or not.
   - To ensure that the drug under investigation is produced according to Good Manufacturing Practice.

9. Signature of Sponsor or Responsible Authorized
   
   Date / /
APPENDIX VII: Importation Licensing

ANNEX III
Request Form for Authorization of IMPORTATION LICENSING

<table>
<thead>
<tr>
<th>National Health Surveillance Agency Researches, Clinical Trials, New Drugs and Biologics Management Request Form for Authorization of Importation Licensing (LII)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial Data</strong></td>
</tr>
<tr>
<td>Data visa exp file number:</td>
</tr>
<tr>
<td>Clinical Protocol Code:</td>
</tr>
<tr>
<td>Approval Document Number:</td>
</tr>
<tr>
<td>Data from Interested:</td>
</tr>
<tr>
<td>Company Name:</td>
</tr>
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<tr>
<td>Telephone number:</td>
</tr>
<tr>
<td>Fax number:</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Number of the L.I.</strong></th>
<th>Request:</th>
<th>Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permits for single import?</td>
<td>Yes ☐ No ☐</td>
<td></td>
</tr>
<tr>
<td>Licensing of import replacement?</td>
<td>Yes ☐ No ☐</td>
<td></td>
</tr>
</tbody>
</table>

| **Planned number of subjects to the trial** |
| In the World: | In Brazil: |

| Calculation of Rational, qualitative and quantitative of products to use in the study in Brazil: |

| Importation for | Clinical Trial | |

Information on the imported products:
List of pharmaceutical used:
APPENDIX VII: Importation Licensing continued

<table>
<thead>
<tr>
<th>Product to import data</th>
<th>Comment/Additional Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active principle or placebo</td>
<td></td>
</tr>
<tr>
<td>Trade name</td>
<td></td>
</tr>
<tr>
<td>Presentation</td>
<td></td>
</tr>
<tr>
<td>Route of administration</td>
<td></td>
</tr>
<tr>
<td>Daily Dose</td>
<td></td>
</tr>
<tr>
<td>Unit / Day</td>
<td></td>
</tr>
<tr>
<td>Total amount needed for the study as the document specified in existing legislation. Amount requested in this L.I.</td>
<td></td>
</tr>
<tr>
<td>Batch number (required):</td>
<td></td>
</tr>
<tr>
<td>Proforms INVOICE: (optional):</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Batch authorized by</th>
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</thead>
<tbody>
<tr>
<td></td>
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<table>
<thead>
<tr>
<th>Batches</th>
<th>Unit (tablet, ...)</th>
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<tbody>
<tr>
<td>Number</td>
<td></td>
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</tr>
<tr>
<td>Number</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quantity needed until the end of the study (Balance)</th>
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</thead>
<tbody>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

### Equipment or product para a assisão

<table>
<thead>
<tr>
<th>Datos do produto a importar</th>
<th>Comentário/Observação</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product data to be imported</td>
<td></td>
</tr>
<tr>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>Trade name</td>
<td></td>
</tr>
<tr>
<td>Model</td>
<td></td>
</tr>
<tr>
<td>Manufacturer</td>
<td></td>
</tr>
<tr>
<td>Total quantity for the study document as specified in the legislation. Amount requested in this L.I.</td>
<td></td>
</tr>
<tr>
<td>Batch number (required):</td>
<td></td>
</tr>
<tr>
<td>INVOICE: (optional):</td>
<td></td>
</tr>
<tr>
<td>Comment / Note</td>
<td></td>
</tr>
<tr>
<td>Amount requested in this L.I.</td>
<td></td>
</tr>
<tr>
<td>Batch number (required):</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX VII: Importation Licensing continued

TABLE Q1
Filling:
If importation of medicines fill one table Q1 per pharmaceutical form:

Identification of the product:
Batch number:
Manufacturer Name:
Address:
City, Country:
Category:
(i) Food
(ii) Cosmetics
(iii) Medicines
(iv) Medical devices
(v) Finished product (i) semi-prepared (ii) Bulk (iv) Raw material
Place of Importation:
(i) Marketing/Manufacture
(ii) Research
(iii) Studies to register in MS
(iv) Free Sample of Medical Device
(v) Donations
(vi) Other
Quantity (specify the international metric unit):
Physical state / pharmaceutical form
Conservation conditions:
Manufacture Date:
Shelf life:

TABLE Q1
Filling:
In the case of medicines should fill one per pharmaceutical form:

Fill in the spaces below for each substance or ingredient:
Repeat as many fields as are the substances / ingredients:

1. Substance (IC50, D50, CAS, INCI):
2. Trade name:
3. Synonyms:
4. Function in the formulation:
5. Active principle

Transmissible Spongiform Encephalopathies
Is there any raw material that may be obtained from animal tissues or fluids? Yes ( ) No ( )
APPENDIX VII: Importation Licensing continued

5. Family classification:
   - bovine
   - goat
   - pig
   - sheep
   - other: plant

6. Tissue/fluids and category as Annexes of the RDC No. 305/02.

7. Name of supplier:

8. Country (supplier):

9. Country (origin of the tissue/cell):
   - yes
   - no

Q1 and documentation provided in the table Q3 of the RDC 660/97?
   - yes
   - no

Click the yes option also when there is change in manufacturer or supplier of raw material.

Controlled drug?
   - yes
   - no

Portaria 344/98, List

Conditions for storage and transport

Statement of responsibility

I assume, civil and criminally, full responsibility for the accuracy of the information presented here (including to the recipient imported), the destruction of goods not used in the study, or to ensure the return to the source and distribute the goods in question only to centers that have the appropriate regulatory approvals.

Company/Institution:

Date:

Signature: CNPJ:

Responsible Name: CPF:

This field is for exclusive use of the health authority.
APPENDIX VIII: Clinical Trial Application

ANNEX IV

CLINICAL TRIAL APPLICATION FORM 1 (FFPI)

National Health Surveillance Agency
Clinical Research
Clinical Trial Application Form 1 (FFPI)

(For use of the government body)

<p>| | | |</p>
<table>
<thead>
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</thead>
<tbody>
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Company Data

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<td>Number of Authorization/Register</td>
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<tr>
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<td>Manufacturer</td>
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<td>6</td>
<td>Number of Authorization/Register</td>
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Data Product

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<td>Therapeutic class / category</td>
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<td>8</td>
<td>Characteristics of the study</td>
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<td>Controlled Studies</td>
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<td>9b</td>
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<td>9c</td>
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<td>9d</td>
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Population under study:

- Age of 12
- More than 65 years
- Infants
- Women of childbearing age (only)
- Patients with special needs
- Not applicable

The study is:

- Strictly National
- Foreign Cooperation

Is there exclusive use of placebos in the study? ( ) Yes ( ) No

Clinical indication to research

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<td>No. of forms</td>
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APPENDIX VIII: Clinical Trial Application continued

ANNEX Y
CLINICAL TRIAL APPLICATION FORM 2 (FPP2)

<table>
<thead>
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<th>Document Identification</th>
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<td>(For use of the government body)</td>
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| 01 | Number of file (Process #) | 02 | Request (Day/Month/Year) |
| 03 | Subject of Petition (codes and description) | 04 | Fact Generator (date/period) |
| 05 | Title of Clinical Protocol | 06 | No. of the Protocol (version and date) |
| 07 | Stage Research (I, II, III, IV) |

**Company Data**

| 08 | Name / Official name | 09 | CNPJ |
| 10 | City / Town | 11 | State/District |
| 12 | Country |

**Manufacturer Data**

| 13 | Manufacturer | 14 | Number of Authorization / Register |
| 15 | City / Town | 16 | State/District |
| 17 | Country |

**Applicant Data**

| 18 | Name | 19 | CNPJ / CPF |
| 20 | City / Town | 21 | State/District |
| 22 | Country |

**Data of Presentation**

| 23 | Registration number (if any) | 24 | Shelf life (in months) |
| 25 | Presentation of the Product | 26 | Number of the formula |
APPENDIX VIII: Clinical Trial Application continued

<table>
<thead>
<tr>
<th>27</th>
<th>Route of Administration</th>
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<th>Physical state / Pharmaceutical form</th>
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<td>29</td>
<td>Restriction of Use</td>
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<td>Conservation Conditions</td>
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<tr>
<td>30</td>
<td>Controlled Drug</td>
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</tbody>
</table>

**Statement of Responsibility**

We assure civil and criminal, full responsibility of the information provided here (including a description of the components of the formula and Presentations attached), as well as the quality of the product (s) (s) to be used in the research being presented, including the appropriate cases, their sterility and/or pyrogen-free.

_________________________  ___________________________
Legal Responsible          Responsible
Pharmacist                  (Signature and Stemp)

(Stemp)                    (Signature and Stemp)
APPENDIX IX: Presenation of Study Form
ANNEX VI
PRESENTATION OF STUDY FORM

PRESENTATION OF STUDY FORM

Trial Information

| COMPANY | FAX: |
|--------------------------------|
| TITLE OF THE TRIAL |
| PROTOCOL CODE or Number | VERSION/DATE |
| NUMBER OF SUBJECTS TO THE TRIAL | WORLD: BRAZIL: |
| CEP (FIRST SITE) |

Informations about the Research Sites

| INSTITUTION | PRINCIPAL INVESTIGATOR |
|--------------------------------|
| Name | CNES* | Status of approval by the CEP | Planned number of subjects per site | Name | Insurance Registration Number (CPF) |

* Establishment of National Register of Health - CNES: available in http://cnes.datasus.gov.br/Lista_15_Name.asp?VTipo=0

Name of Legal Responsible
Signature of Legal Responsible
APPENDIX IX: Presentation of Study Form continued

“Any change concerning the above estimate should be reported to ANVISA in an application for importation license (LI) and notified to the study approved.”

__________________________  __________________________
Name of Legal Responsible    Signature Legal Responsible
APPENDIX X: Statement of Responsibility

<table>
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<tr>
<th>Statement of Responsibility and Commitment of the Investigator</th>
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<tr>
<td>National Health Surveillance Agency</td>
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<tr>
<td>Research, Clinical Trials, New Drugs and Biologics Management</td>
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<tr>
<td>CNES</td>
</tr>
<tr>
<td>Coordination of Research and Clinical Trials - CEPEC</td>
</tr>
</tbody>
</table>

1. Investigator's Name and address:  
   Name ____________________________
   Address ____________________________

2. Name and address of the institution where the research will be developed:  
   National Register of Establishment of Health Services (CNES).

3. Name and Address Services (Laboratory of Clinical Chemistry, radiological, etc.), which will be used in the trial:

4. Name and Address of Institutional Review Board responsible for the assessment of trial:

5. Name of Sub-Investigators who will participate in the trial:

6. Title and Code of the trial that will be conducted by the Investigator (include date and session):

7. Responsibilities:
   - I agree to conduct the trial according to the clinical protocol, with the Good Clinical Practices, with the Good Laboratory Practices and with Resolution 190/96.
   - I agree to implement changes in the protocol after notifying the sponsor and the Research Ethics Committee, except changes necessary to protect the safety, rights and welfare of trial subjects.
   - I agree to inform the sponsor of the study and the Institutional Review Board (CEP) about the serious adverse events that will occur during the development of the research.
   - I have read and understood the information contained in the investigator's brochure, including the potential risks and side effects of drugs under study.
   - I agree to start the clinical trial only after obtaining the necessary ethical approvals (CEP) and regulatory approval (ANVISA).
   - I assume, civil and criminally, the veracity of the information presented herein.

8. Investigator's Signature:
   Date ____________________________

Note: The search can be initiated only after the approval and issuance of ethics (CF).
BIBLIOGRAPHY


10 Claux D (2009) Record numbers of new generics to enter the Brazilian generics market in 2009. Global Insight, January 28


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