Impact of Clinical Study Regulatory Approval Delays in Brazil

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As the largest country in Latin America, Brazil boasts impressive socioeconomic indicators, including an estimated population of 200 million in 2012 (rank: 5th worldwide),[1] a Gross Domestic Product (GDP) in excess of 2 trillion USD (rank: 7th),[2] and annual pharmaceutical market sales of nearly 28.5 billion USD (rank: 6th).[3]

In addition to a favorable and stable economic environment, strong culture, and regulatory compliance to good clinical practices by trained investigators and staff, Brazil's well-structured research sites have been attracting international investments over the past decade. Some of these investments are reflected in terms of the growth of international clinical studies conducted in the country from 16 Phase II and III industry-sponsored studies in 2002 to 103 in 2012.[4]

Following the Process

The regulatory process for implementing a clinical study in Brazil requires evaluation and approval of the proposed research by two entities within the Ministry of Health: an ethical approval by CONEP (*Comissão Nacional de Ética em Pesquisa* – National Ethics Committee) and a logistical approval by ANVISA (*Agência Nacional de Vigilância Sanitária* – National Agency of Health Surveillance). In fact, two ethics committees—an institutional ethics committee [IEC] at the local level and CONEP at the national level—approve the same documentation.

Considering multicenter studies, a coordinator site must be selected and the study protocol and related documents must first be approved by this site's local IEC, then forwarded to CONEP. Once granted final CONEP approval, all documentation must also be submitted to every single planned study site for obtaining approval from the local IECs.[5]

For ANVISA's logistics evaluation, the sponsor is responsible for providing a description of the study and related supplies (medication, lab kits, and equipment). After ANVISA approves the study, a license must be secured to start the supplies import process (see Figure 1 for a diagram of the study approval process in Brazil).

In many other countries, there is a single committee approval and, for instances where there is a national agency, it has the function of only supervising and supporting local ethics committees.[6]

Where to Go From Here?

Although a remarkable increase in the number of studies conducted in Brazil can be seen in recent years, initiating trials is a very challenging process, since timelines are unpredictable and considerably longer when compared to typical cases in other countries. Unfortunately, quite often international sponsors request the discontinuation of the approval process in Brazil once other countries have already finished their enrollment of patients.

However, there is hope for improvement: In January 2012, a new electronic submission process *(Plataforma Brasil)* was implemented in Brazil, intended to give greater security to the registration and monitoring of research. The rest of this paper aims to analyze Brazilian participation in international clinical trials, as well as to evaluate the impact of the regulatory process on performing clinical studies in Brazil.

Material and Methods

Brazil in the Context of BRIC Countries and Latin America

For the purpose of comparing participation in clinical trials, a total of six countries were selected:
- Four BRIC countries: Brazil, Russia, India, and China were chosen due to the similarity in their stages of economic development; and
- Two Latin American countries: Argentina and Mexico were chosen due to the similarity in political and cultural aspects within the region.

FIGURE 1: Study Approval Process in Brazil

Sponsor/CRO
Protocol package preparation:
- Protocol
- ICF
- Brochure
- Other study documents
- Sponsor's documents

Coordinator Site
Protocol package finalization:
- Investigator's and site's documents

Coordinator IEC
Expected approval time: 30-60 days
Ethical evaluation of the trial—Site level

CONEP
Expected approval time: 60 days (additional 60 days for response to raised issues)
Ethical evaluation of the trial—Country level

Other Sites' IECs
Expected approval time: 30-60 days
Ethical evaluation of the trial—Site level

ANVISA
Expected approval time: 90 days
Regulatory evaluation of the trial:
- Drug
- Supplies
- Involved sites

ANVISA Import License
Import Authorization for:
- Drug
- Supplies
- Involved sites

CRO: contract research organization; ICF: informed consent form; IEC: institutional ethics committee; CONEP: *Comissão Nacional de Ética em Pesquisa* – National Ethics Committee; ANVISA: *Agência Nacional de Vigilância Sanitária* – National Agency of Health Surveillance.

A basic economic index based on GDP with last available data from 2012 and on population (from 2013) was used as a reference to economic development, and was obtained from publicly accessible websites (http://data.worldbank.org/data-catalog/GDP-ranking-table and http://worldpopulation review.com). Details on numbers of studies were obtained from ClinicalTrials.gov.

ClinicalTrials.gov is a web-based registry maintained by the U.S. National Library of Medicine and updated by the sponsors or principal investigators of the clinical studies listed in its database. This registry includes general information about medical studies in human volunteers in 185 countries.[7] It was first made available to the public in February 2000, and its registration requirements were further expanded in 2007, under the Food and Drug Administration Amendment Act of 2007, Section 801. Data from 2007 onward were more reliable for this comparison.

The search comprised the allocation of industry-sponsored Phase II–III clinical studies to the six countries mentioned above in the calendar year of 2012 compared to the calendar year of 2007. No significant variations, either for increases or decreases, were noted in the years of 2008, 2009, 2010, or 2011 that could cause any bias to this analysis.

Overview of Regulatory Approval Process in Brazil
Forty-six industry-sponsored studies allocated to Brazil with available long-term submission data and started between June 2007 and June 2013 were selected for this analysis: 28 (61%) were successfully approved and 18 (39%) were discontinued during the process due to the delay in approval and conclusion of patient enrollment by other countries that were allocated to the same studies.

For the 28 approved studies, information about ethics (from the applicable IECs and CONEP) and National Agency (ANVISA) approval times has been collected. Also, data on the first patient screened in Brazil were compared to first patient screened in the overall study. Brazilian local timelines were also compared before and after *Plataforma Brasil.*

Statistical Analysis
Statistical analysis was performed for studies allocated to Brazil before and after *Plataforma Brasil* by an independent non-paired t-test of means. The level of statistical significance was set at $p < 0.05$.

TABLE 1: Comparison of Study Allocation in 2012 vs. 2007

Country	GDP (rank)*	Estimated Population (rank)**	Number of Studies***			Trial Density	
			2007	2012	2012 x 2007	2007	2012
Brazil	2,252,664 (7th)	200,674,130 (5th)	120	106	-11.7%	0.60	0.53
Russia	2,014,776 (8th)	142,572,794 (9th)	205	229	11.7%	1.44	1.61
India	1,841,717 (10th)	1,210,193,422 (2nd)	161	73	-54.7%	0.13	0.06
China	8,358,363 (2nd)	1,384,694,199 (1st)	90	136	51.1%	0.06	0.10
Mexico	1,177,956 (14th)	122,730,392 (11th)	134	136	1.5%	1.09	1.11
Argentina	470,533 (26th)	41,499,700 (32nd)	142	135	-4.9%	3.42	3.25

GDP: Gross Domestic Product.
* Data presented in millions of U.S. dollars for 2012, available at http://databank.worldbank.org/data/download/GDP.pdf
** Data estimated for 2013, except for India (2011), available at http://worldpopulationreview.com/countries/
*** Data from http://clinicaltrials.gov (Phase II–III and industry-sponsored), total of 3,292 studies (2007) and 2,777 studies (2012)

Results

Brazil in the Context of BRIC Countries and Latin America
According to data available at ClinicalTrials.gov, a total of 2,777 Phase II–III industry-sponsored studies were conducted worldwide in 2012, for a reduction of 15% compared to 2007 (n = 3,292). For BRIC countries, despite the fact that overall variation was almost null, there was a striking difference between the increases in Russia (11.7%) and China (51.1%) when compared to reductions in Brazil (-11.7%) and India (-54.7%). Argentina (135 studies) and Mexico (136 studies) have maintained their participation, conducting around 30% more clinical studies than Brazil in 2012 (see Table 1). In fact, Brazil has a significantly lower trial density (number of studies divided by estimated population in millions) during the same period.

Overview of Regulatory Approval Process in Brazil
Regulatory approval timeline data were considered only for the 28 approved studies. On average, it takes 46 days to obtain the local IEC's approval (range from seven to 248 days) in Brazil. There is a substantial increase in timelines when approvals at CONEP (average 175 days; range 62 to 362 days) and ANVISA (average 168 days; range nine to 328 days) are considered, adding a regulatory approval of at least six months.

Compared to other countries, this timeline forces Brazil to start recruiting patients on a first patient/first visit (FPFV) basis 11 months (328±120 days) later than other countries (see Table 2). All other evaluated countries were estimated to be ready for FPFV in less than 30 weeks after receiving documentation (internal data).

TABLE 2: Approval Timelines of Studies Successfully Implemented in Brazil

	Total	IEC	CONEP	ANVISA	FPFV
Average (days)	378	46	175	168	328
Median (days)	358	35	159	144	303
Standard Deviation (days)	96	46	83	87	120
Minimum–Maximum (days)	256–587	7–248	62–362	9–328	170–609

IEC: Institutional Ethics Committee; CONEP: *Comissão Nacional de Ética em Pesquisa* – National Ethics Committee; ANVISA: *Agência Nacional de Vigilância Sanitária* – National Agency of Health Surveillance; FPFV: first patient/first visit.

TABLE 3: Approval Timelines for Canceled* Studies in Brazil

	Total	IEC	CONEP	ANVISA
Mean (days)	296	47	204	215
Median(days)	299	39	201	225
Standard Deviation (days)	88	46	55	91
Minimum–Maximum (days)	161–497	0–209	133–293	77–359

IEC: Institutional Ethics Committee; CONEP: *Comissão Nacional de Ética em Pesquisa* – National Ethics Committee; ANVISA: *Agência Nacional de Vigilância Sanitária* – National Agency of Health Surveillance; FPFV: first patient/first visit.

* Canceled means study has been given up before approval by the required entities

For the 18 canceled studies (see Table 3), timelines are much longer and could not be correctly assessed. It took 10 months (296±88 days) from the first local IEC submission until the sponsor's final decision to give up the study in Brazil.

Based on the growth observed during the same period in BRIC countries (2007 vs. 2012; see Table 1), which are regarded as being in the same stage of economic development, Brazil could have conducted 40 more studies (106 actual vs. 146 projected) within the increment of studies allocated to China, Russia, and India (see Table 4).

Regulatory Approval Process after Plataforma Brasil

Twenty-eight initiated studies were compared regarding approval timelines before and after the *Plataforma Brasil* new submission process; 24 studies were submitted before its launch and four after. Regulatory timelines before and after *Plataforma Brasil* are shown in Table 5. There was a tendency for increasing regulatory timelines of 1.3 month (38 days) at CONEP (169 vs. 208 days; $p = 0.40$) and a significant increase of almost four months at ANVISA (151 vs. 266 days; $p = 0.01$), which means a total regulatory impact of 166 days (354 vs. 520; $p = 0.00045$), on average.

Discussion

According to the International Federation of Pharmaceutical Manufacturers & Associations, the introduction of a new drug is a long process that often takes from 10 to 15 years. From each five screened compounds from a total of 5,000 to

TABLE 4: Number of Estimated Studies that Could be Conducted in Brazil Based on BRIC Countries and Latin American Data (2012 vs. 2007)

Region	Average # Studies	**Δ Brazil
BRIC	146 *	40
Latin America	136	30

* Brazil was not included in the calculation, only the average between Russia (229), China (136), and India (73) for BRIC; and Argentina (135) and Mexico (136) for Latin America.

** Δ Brazil was calculated based on the difference between the average number of studies performed in BRIC and Latin American countries, and the number of studies effectively conducted in Brazil (106) during the same period.

10,000 entering clinical trial phases, only one is approved.[8,9] In addition, it is estimated that only two out of 10 marketed drugs generate revenues that exceed research and development costs.[10] Therefore, pharmaceutical companies must have in place efficient mechanisms of managing this high-risk drug development process.[11]

More specifically for the process of clinical trials, study allocation is an essential step, and ethics review of research is vital to protect the rights and safety of subjects.[5,12,13] However, in practice, the current process in Brazil is not only time consuming, it also deprives too much of the Brazilian population in general and too many researchers in particular from participating in innovative clinical trials.

As early as 2008, an independent report developed by the clinical research community had already stressed structural and operational problems that prevented Brazil from achieving good results in clinical research. At that time, some measures, like complete decentralization of the IEC-CONEP system for multicenter studies with foreign participation, adoption of a single system of questioning for a research project, and tacit approval as well as elimination of the requirement for presentation of foreign approval documents, were proposed to improve the system,[6] but none of them were implemented.

The Ministry of Health in Brazil requires a double ethical approval by the local IEC and CONEP for Phase I–III studies or for any clinical studies that have foreign co-participation. This is one of the steps that cause the most delays in the regulatory evaluation process. This legislation is not in harmony with other countries from Latin America and the world, which require only one step in ethical evaluation. Efforts are being directed to implement a change to the current situation of double ethical evaluation in Brazil.

The Brazilian studies mentioned in the present analysis covered different areas of treatment, but if we consider that the country starts recruiting patients on average 311 days after other countries, it means that many more patients could have participated in clinical studies performed in Brazil. In fact, Christie et al. has evaluated the impact of delays in approval process in oncologic studies in

TABLE 5: Comparison of Studies Initiated before (n = 24) and after (n = 4) *Plataforma Brasil*

	Total Timeline		IEC		CONEP		ANVISA	
	Before	After	Before	After	Before	After	Before	After
Mean (days)	354	520	46	46	169	208	151	266
Median (days)	361	523	35	41	173	208	139	293
Standard Deviation (days)	79	58	49	35	83	82	78	80
Minimum (days)	271	449	7	11	62	128	9	149
Maximum (days)	564	587	248	91	362	287	292	328

IEC: Institutional Ethics Committee; CONEP: *Comissão Nacional de Ética em Pesquisa* – National Ethics Committee; ANVISA: *Agência Nacional de Vigilância Sanitária* – National Agency of Health Surveillance.

Australia, and concluded that they have an effect on the survival of cancer patients. The survival rate from all types of cancer in Australia is improving at a rate of just more than 1% per year. A delay of two months in this improvement represents approximately 60 avoidable cancer deaths. Although not all trials save lives, each patient for whom entry into a trial is prevented because of these delays has therefore lost a significant opportunity to have access to state-of-the-art drugs and newer therapeutic approaches.[14]

In addition, 39% of studies were canceled due to the impractical timelines observed either at CONEP, ANVISA, or both, emphasizing the inefficiency of the country in terms of competitiveness in the clinical research environment. None of these studies was "purely" placebo-controlled. The sponsor had committed to provide assistance and study medication to patients on a post-trial basis, which adds inconsistent requirements to already unpredictable timelines, making for an increasingly challenging environment in which to conduct international industry-sponsored studies in Brazil. Nevertheless, in those studies for which Brazilian investigators obtained regulatory approvals in a timely manner, researchers delivered outstanding performances, enrolling a significant number of patients.[15–17]

Recent evaluation shows that there is still a gap, even after implementation of *Plataforma Brasil,* the new electronic submission tool; there was a significant increase in regulatory timelines, mainly at ANVISA. Furthermore, according to ABRACRO *(Associação Brasileira das Organizações Representativas de Pesquisa Clínica* – Brazilian Association of Contracted Research Organizations), of the 85 protocols recently submitted (January 2013 to March 2014) to CONEP and ANVISA, which would benefit around 4,971 patients and many clinical investigators, only 12 (14%) were already approved by both entities. Further, during the same period, CONEP was able to evaluate 30% more studies than ANVISA.[18] This recent analysis reflects an ongoing process of adaptation to the new electronic tool, which may improve over the time.

As a consequence, sponsor management teams are now accepting and committing only to participating in projects with a large number of patients and longer recruitment periods while planning studies in Brazil, rendering the country a noncompetitive environment in terms of clinical research scenarios. In fact, this impact can already be seen, based on the analysis of the number of studies that could potentially be conducted by the country when compared to the performance observed in some BRIC and Latin American countries.

Finally, there are some important points to be considered regarding how clinical research is conducted with and/or affects the people of Brazil:

- The results of trials conducted in high-income countries may not always be applicable to the Brazilian population.
- Local investigators must have the opportunity to contribute to the design of clinical trials that they are going to conduct.
- In addition to financial losses that certainly occur to the country, there is also a loss of "image," since Brazil is becoming an increasingly difficult country in which to work.
- The proposed changes already noted in 2008[6] still figure as the main contributors to promote a change in the current clinical research scenario in Brazil.
- Several actions from civil associations such as the National Investigator Society, patient-focused disease societies, and the Pharmaceutical Doctors Society, which recently created the Clinical Research Alliance Brazil, are important initiatives to expedite the regulatory process in the country.[6]

Conclusion

Brazil has a huge potential for conducting clinical trials; sponsor, investigators, and authorities should work together for developing an easy, efficient, and predictable approval process. Despite all the difficulties, Brazilian investigators are most often top recruiters of the trials they conduct. This regulatory environment must be improved; otherwise, it will not result in tangible patient, society, and medical benefits.

In addition to a favorable and stable economic environment, strong culture, and regulatory compliance to good clinical practices by trained investigators and staff, Brazil's well-structured research sites have been attracting international investments over the past decade.

Although a remarkable increase in the number of studies conducted in Brazil can be seen in recent years, initiating trials is a very challenging process, since timelines are unpredictable and considerably longer when compared to typical cases in other countries.

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