REVIEW ARTICLE

Brazil is gaining its momentum in pharmaceutical development

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Abstract: Brazil is one of the world's largest economies and pharmaceutical markets, having the Brazilian government as an important purchaser. There are strong local companies that have grown sustainably after the introduction of generics and are investing in both incremental and radical innovation. However, research and development (R&D) expenditures are still modest; this could be explained by a combination of economic and political uncertainty in the past few years and a bureaucratic, complex regulatory framework. New regulations, efforts to reduce ethical and regulatory review timelines, and a Senate bill aimed to accomplish that goal should constitute the definitive regulatory landmark for boosting clinical research. In addition to government investments they have given a breath of relief in the market, as Brazil is trying to, once again, gain momentum as a "must-go" country for clinical development. Non-profit associations such as the Brazilian Society of Pharmaceutical Medicine (*Sociedade Brasileira de Medicina Farmacêutica*-SBMF), the Brazilian Association of CROs (*Associação Brasileira de Organizações Representativas de Pesquisa Clínica*-ABRACRO), the Brazilian Clinical Research Alliance (*Aliança Pesquisa Clínica Brasil*), amongst others, helped to give the impulse to trigger such changes. It is time to invest heavily in developing educational programs to address the growing need for clinical development scientists and physicians.

Keywords: clinical trials; Brazil; regulatory; SBMF; ABRACRO; Aliança Pesquisa Clínica Brasil

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1. Introduction

1.1 Brazilian Pharmaceutical Market and R&D

With a population of 206.1 million people and a total gross domestic product (GDP) of US$ 2.417 trillion, Brazil figures as one of the top 10 world's economies[1]. The pharmaceutical sector in Brazil is an important business; by 2020, the pharmaceutical market should increase at a rate of 7% to 10% annually, reaching the sum of BRL 107 billion. The institutional public market represents almost 23% of the total value[2]. Data on R&D investments in Brazil are limited; in 2009, local affiliates of global companies have received only US$ 140 million of the US$ 40 billion invested globally[3].

2. Regulatory and Ethical Framework for Clinical Trials in Brazil

2.1 The First Years

Historically, the approval process for clinical trials in Brazil has been complex, slow, and bureaucratic. The

first ethical landmark is the National Health Council (*Conselho Nacional de Saúde*-CNS) Resolution 196/96, under the guidance of the Helsinki Declaration. The ethical review system was established; institutional ethics committees were created all over the country under the supervision of a Central body, CONEP (National Ethics Commission, *Comissão Nacional de Ética em Pesquisa*), with the main purpose of regulating the system. CONEP should also deliberate over projects with foreign cooperation; by the time, in a newly created system and a country on the verge of globalization, the idea was to control and avoid "exploitation" of the studied participants in trials from multinational companies. ANVISA, the National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*) was created in 1999 and clinical trials started being evaluated by the agency. Trial initiation should only start after receiving both ethical and regulatory approvals. A formal appraisal system combined with a large pool of treatment-naïve patients, well-trained investigators, and strong academic research sites caught the attention of global pharmaceutical companies that made Brazil a destination for their clinical trials, especially on late phases. Over the years, the growing number of trials was not accompanied by changes in regulations and improved infrastructure of CONEP and ANVISA. In the first quarter of 2014, the average timeline for ANVISA's first review was around 200 days (Figure 1), with final approval obtained over a year, and on CONEP's side, first appraisal was received in approximately 180 days with total approval timelines reaching 250 days, on the same period (Figure 2). Considering that the process was sequential (coordinating EC appraisal/approval followed by CONEP's approval and further submission to ANVISA), we could expect a process of more than a year from submission to first-patient-in.

The lengthy and unpredictable review/approval timelines had a negative impact on the number of clinical trials. The new CNS Resolution 466/2012 and *Plataforma Brasil* were issued as a promise to expedite CONEP´s timelines and clarify CONEP's positioning on ethical requirements. Little changed from Resolution 196/96; data reported by ABRACRO members show a decrease in the number of clinical trials submitted for both ethical and regulatory approvals, from 80 in 2013 to 59 in 2015. The Brazilian participation to global clinical trials over the years remains around 2%[4]. A number of studies were closed prior to initiate recruitment. The lack of official metrics made it difficult to evaluate the impact on the loss of financial investments, as well as the number of patients that could potentially have participated in those trials.

Different associations started a movement to push

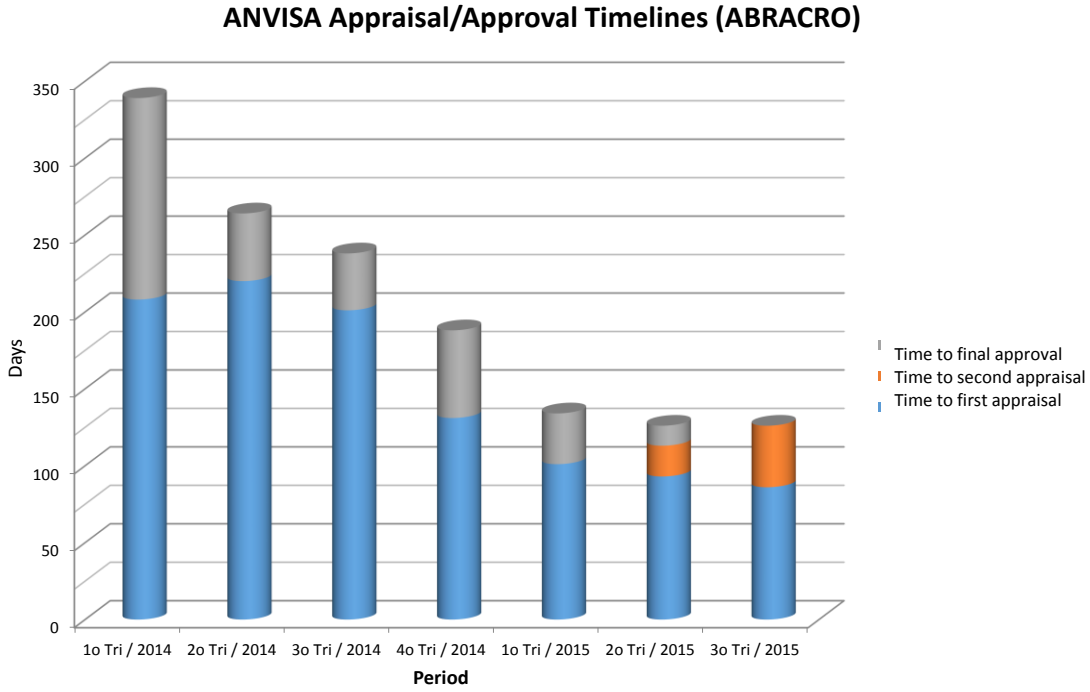

Figure 1. ANVISA appraisal and approval timelines as informed by ABRACRO member companies (internal survey). Time for CRO response to requirements was not included in the time to final approval.

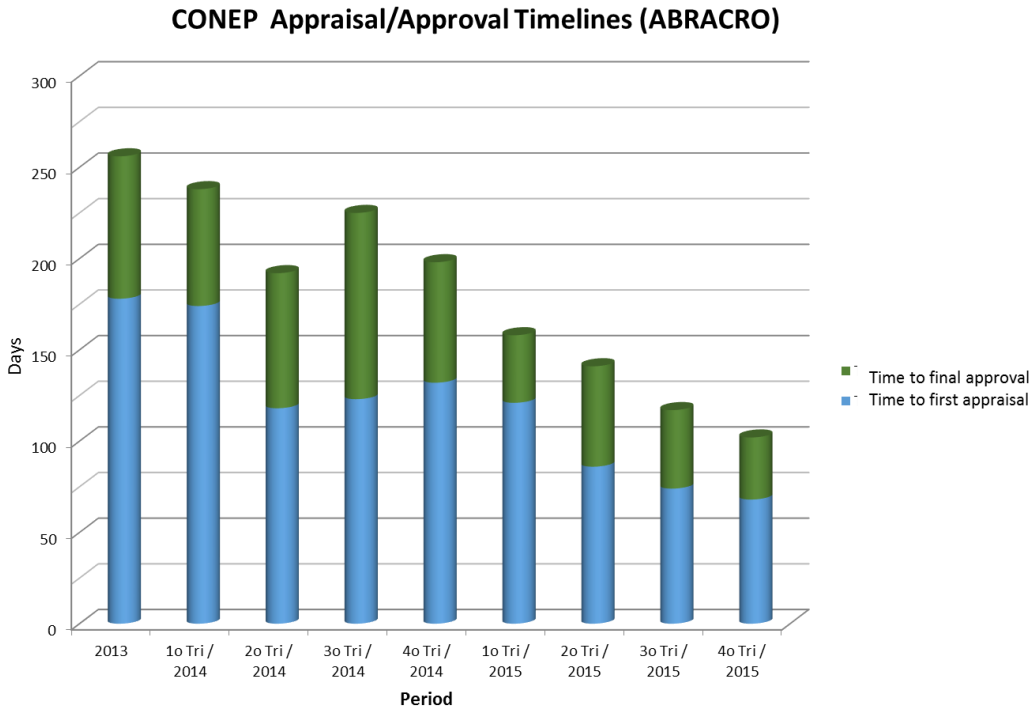

Figure 2. CONEP appraisal and approval timelines as informed by ABRACRO member companies (internal survey). Time for CRO response to requirements was not included in the time to final approval.

for a new, more efficient, and competitive scenario for clinical trials. *Aliança Pesquisa Clínica Brasil* was created in 2014 and discussions on the matter gained strength with the support of senators who embraced the idea of creating a definitive regulatory landmark for the country. PLS 200/2015 was issued in alignment with International Conference on Harmonization of Good Clinical Practice (ICH-GCP) guidelines. A lot of contributions were made by different players (investigators, academia, CONEP, ANVISA, and important Brazilian institutions) and the process is in its final stages of analysis at the Senate. Amongst its positive aspects, the definition of a 30-day period for ethical review and clear provisions for post-trial drug access, in alignment with international guidelines, were included in the text in order to maintain the rights of the participants involved in the studies.

3. The Current Scenario

The year 2015 started with a positive initiative from ANVISA; the new regulations for clinical trials of drugs and medical devices. RDC 09/2015 implemented the Dossier for Drug Clinical Development that must contain the entire plan for the drug development, as well as the trials that will be conducted in Brazil, with thorough details on good manufacturing practice (GMP). The definition of a timeline for the first review was defined as 90 days for phase III, international, multi-centric trials with small molecules. In case of no response from ANVISA or absence of further requirements, an importation document is issued and the study can be initiated, once all ethical approvals are obtained. Phase I and II study protocols, as well as those of biological products and products developed exclusively in Brazil, have a first review period of up to 180 days.

CONEP has also developed its infrastructure and made an effort to reduce the backlog of projects pending review. Timelines were reduced; in the third quarter of 2015, time for first appraisal was reduced to approximately 100 days and final CONEP approval was obtained in approximately 140 days, as reported by ABRACRO members.

4. Educational Efforts

Over the past 20 years approximately, many courses for training clinical research professionals have emerged. In 1999, a Post-Graduation Course on Pharmaceutical Medicine was started at the Federal University of São Paulo under the coordination of Dr. João Massud Filho. The program of the course was based on the syllabus of the Faculty of Pharmaceutical Med-

icine-London. In 2008, the course was granted accreditation by the International Association of Pharmaceutical Physicians (IFAPP). Since 2015, this course is given at the Research and Training Institute in Hospital S ́rio-Libanes (Syrian-Lebanese)-S ão Paulo.

There is a specific course on Clinical Research given at *Faculdade de Medicina da Santa Casa de S ão Paulo* and other small ongoing courses on clinical trials.

5. Perspectives

Biological products, in which, the national industry is investing heavily, seem to be the next big step in the country ́s clinical research and development. The number of clinical trials should increase heavily after the bureaucratic issues on regulatory/ethical requirements are solved. A growing need for qualified clinical development scientists and physicians is expected, and the professional organizations will play a significant role in qualifying those professionals in the following years.

Conflict of Interest and Funding

No conflict of interest has been reported by the authors and no funding is involved in this article.

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