An Insight into the Brazilian Clinical Trials Scenario

Located on the eastern coast of South America, Brazil is the fifth-largest country in the world in terms of area and population. With around 200 million inhabitants distributed among 26 states and a Federal District, it is a member of the BRIC group, representing the seventh-largest economy worldwide by GDP (gross domestic product). Presenting a mixed population, partly descended from the historical European immigration and slavery system, besides the original population of American Indians, Brazil presents a multi-ethnic population varying from Caucasians to people of black skin, mainly represented by phototypes III to V.

Technological research in Brazil is largely carried out in public universities and research institutes, with the majority of funding for basic research coming from various government agencies. With a highly-qualified professional class, Brazil represents an important region of interest for the whole pharmaceutical and cosmetic industry due to its potential market. However, local research is necessary mostly because of its unique characteristics and culture.

Brazil Clinical Trial Research History
The Brazilian regulatory legislation on medical research was put into place only about 20 years ago, and can be considered young compared to other parts of the globe. While the first international guidance on the ethics of medical research involving subjects, the Nuremberg Code, was defined in 1947 and adopted by developed countries since then in consequence of the horrors which occurred during the Second World War, in Brazil the first resolution focusing on this topic was published in 1988 by the National Council of Health (CNS - Resolução nº 1/88), framing only drug importation intended to be used in clinical trials. However, following the International Conference on Harmonization held in 1996, where chapter E6 defined several rules for ethical good clinical practices in clinical trials, the Brazilian authorities understood the need to better regulate studies occurring in the country. Because of this, in 1996 the resolution nº 196/96 from CNS was published, implementing instructions considering the ethical aspects of subjects enrolled in trials and complementing the resolution nº 1/88. At that time the Brazilian ethical committee system, CEP/CONEP, was created to perform a critical analysis, taking into consideration the subjects’ safety and protection. This resolution was reviewed and replaced in 2012 by the resolution nº 466/2012, applicable nowadays. Completing this recent legal structure for clinical trials, in 1998 another governmental publication (Portaria nº 9) from the National Sanitary Vigilance Secretary (SVS) was released to implement rules for clinical trial approval regarding the sanitary vigilance aspects of the drugs being tested. With an increasing demand for studies in Brazilian territory, medical community pressure to be part of the world’s medical research scene, and a great number of patients anxious for new treatments, it became clear that a dedicated agency was imperative to standardise all sanitary matters. Therefore, ANVISA (the National Sanitary Vigilance Agency) was created in 1999 and still performs all activities related to those demands, including sanitary aspects of clinical trial approvals.

Clinical Trial Legal Circuit Approval in Brazil
According to the local legislation, resolution nº 466/2012, and all complementary directives that describe ethical aspects of research involving human beings, all studies performed in Brazil must be initially evaluated and approved by the Brazilian ethical committee system. This system is structured in two levels: the National Research Ethical Committee (CONEP), which is one single organisation located in the capital of Brazil, Brasilia, and several local research ethical committees (CEP) all around the country. There are around 700 credentialed CEPs in the country, most of them concentrated in the South and Southeast of Brazil, the most developed areas of the country. Those committees are multidisciplinary, composed of doctors, psychologists, non-medical professionals, and at least one member of the community and user of the health system.

The CEP/CONEP system mission is to guarantee the rights and dignity of subjects enrolled in any research occurring in Brazilian territory. Besides that, the system contributes to the research quality and discussion of the research role and development within the community. The system also contributes to the appreciation of the research work, by recognising the ethical adequacy and importance of the investigation.

Before starting a trial it is necessary to send a dossier to the ethical committee system, containing the study protocol, informed consent form, investigational product safety declaration and previous test results, among other documents, such as the study centre infrastructure declaration, principal investigator agreement to follow good clinical practices, Helsinki declaration, etc. The dossier is submitted for evaluation through an online platform called “Plataforma Brasil” (Figure 1) and directed to the institute’s ethical committee. If the researcher requesting the evaluation is not linked to any institution presenting to an ethical committee, the national ethical committee (CONEP) will designate one to judge the project. The local ethical committee (CEP) will then perform the evaluation and release a report giving its opinion, pending or approved. The local CEP can however redirect the project to CONEP for a second opinion if they believe not to have the conditions to evaluate the project or if it represents one of the specific topics called “special thematic areas” defined in resolution 466/2012. There is a precise list defining those topics, such as stem
cell projects, foreign participation, human genetics, biosafety, research involving Indian population, etc.

All communication between the research centre, the principal investigator and the ethical committee system must be done through the online platform and any close contact must be avoided to allow a perfectly impartial evaluation of the project, always keeping in mind the safety and best conditions for the subjects involved in the trial.

In parallel with the ethical request, in some cases, such as studies with pharmaceutical new drugs or new drug indications and medical devices, it is also necessary to have Sanitary Vigilance approval to use those drugs / devices in clinical trial subjects. This request must be made to ANVISA, who will authorise the study conduct and drug/device importation if necessary. In summary, clinical trials in Brazil cannot begin without those two approvals: CEP/CONEP and ANVISA (when applicable). Figure 2 presents a schematic illustration of this system.

New Directions for Regulatory Framework
This entire regulatory pathway for clinical trials in Brazil has two paradoxical aspects. On the one hand, it is a very well-established structure recognised worldwide for its reliability and seriousness, that truly takes into consideration all international ethical standards. On the other hand, unfortunately even if the theory and design of the system is consistent, its applicability doesn’t correspond to the scientific and market demands. With very bureaucratic steps and a very heterogeneous quality of CEPs project evaluation, this legal approval requirement route has become a real nightmare for all researchers. Even if, theoretically, the timeframe for a study approval evaluated by the ANVISA and CEP/CONEP system should not exceed 90 days (three months), in reality it can take up to 360 days (12 months). Therefore, for the pharmaceutical and cosmetic industries working in a global context with extremely tight deadlines, the Brazilian regulatory framework is really a business brake. This scenario makes the scientific world demotivating for most Brazilian researchers, and reduces private R&D investments into the country, despite its extraordinary potential.

Struggling in this reality a new law project (PL n° 200/2015) has been released this year (2015) with the
intent of reformulating this compressed regulatory skeleton. Even if this project has divided the community into two opposite sides, it demonstrates the dissatisfaction of at least some of the concerned users and a need for improvement that may arrive in the very near future.

Cosmetic Research in Brazil

Regarding cosmetic clinical research, the regulatory pathway is a little easier than in the pharmaceutical field, as ANVISA approval is not necessary. Besides that, most of the trials do not fit into the “special thematic areas” and study projects need only to be evaluated by the local ethical committee (CEP). A guide to cosmetic safety evaluation (Figure 3) has been distributed by ANVISA in 2012 in order to give a direction to cosmetic producers regarding the minimum legal requirements asked by this agency to provide the product registration and release the product onto the market. The study protocols are, then, based on this guide and international standards. Even if the cosmetics research legal framework looks simpler, those steps are always an extra time and cost that needs to be considered in the studies’ budgets and schedules, and are not necessarily required in other countries where cosmetic science may be even simpler. One of the big difficulties encountered in all this scenario is the very heterogeneous demands and reports provided by those CEPs. In consequence of which, many projects may be delayed, affecting the whole chain of product availability on the market due to a very immature and bureaucratic system.

To outline those problems, many CROs and research institutes have adapted their service to standardise their projects, as well as train the CEP members on the cosmetic science to facilitate the approvals, always keeping the ethical principles as a major concern. Besides that, the new law project is really a hope for improvement on the regulatory framework to be put in place in the year 2015.

Even with those extra steps, Brazil remains a very interesting country to perform clinical trials due to its recruitment potential, highly-qualified professionals, and local market demands.

References

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