REGULATORY FOCUS

Brazil's Regulatory Environment Offers Positive Changes for Clinical Trials

By Priscila Fagundes, RPh, Patricia Dresel, RPh and Ana Elisa Miller, RPh

*This article summarizes recent changes in regulations and submission processes in Brazil's approach to conducting clinical trials that will speed the submissions processes and also help the country be more competitive in global clinical trials acquisition. The authors focus on changes affecting the main regulatory bodies involved in the review of clinical trials in Brazil—Agência Nacional de Vigilância Sanitária (*ANVISA*) and Comissão Nacional de Ética em Pesquisa (*CONEP*).*

Introduction

Brazil has been known as a country with relatively long regulatory timelines for evaluating clinical research. Those long timelines have adversely impacted the country's ability to participate in global clinical studies as other countries are able to obtain regulatory approvals more quickly than Brazil, so sites are able to start including subjects earlier as well. As a result, Brazil loses out in many multicenter international studies.

More frustrating is that the population in Brazil comprises some of the most desired characteristics for conducting clinical trials, such as genetic diversity, a large pool of potential volunteers and experienced researchers.{1} As a result, those who might be potential participants in these trials do not have the opportunity to receive new therapies that may improve their health, and Brazilian researchers lose opportunities to study innovative therapies. This reality is a profound loss for Brazil's population and its science professionals.

Recently, there has been mounting political pressure to improve regulatory timelines for evaluating clinical trials in Brazil in an effort to make the country more competitive when new trials are awarded. As a result, since 2015, Brazilian regulatory bodies have been taking action designed to improve the country's regulatory processes.

ANVISA—Dossiê de Desenvolvimento Clínico de Medicamento (Clinical Development Dossier of the Experimental Drug (DDCM))

In March 2015, Agência Nacional de Vigilância Sanitária (ANVISA), the Brazilian regulatory agency, published two resolutions, changing the submission process in Brazil. Resolutions RDC 09/2015 (for clinical trials with drugs){2} and RDC 10/2015 (for clinical trials with devices){3} initiated a process similar to the Investigational New Drug (IND) process of the US Food and Drug Administration (FDA). Instead of reviewing each clinical trial independently, as did the previous process, ANVISA reviews a dossier which is the *Clinical Development Dossier of the Experimental Drug (DDCM).* The DDCM includes detailed information about the overall development of the product, including efficacy and safety data, Chemistry, Manufacturing and Controls (CMC) information and clinical trials. This dossier must be submitted once for each experimental drug as clinical trials for the experimental drug conducted in Brazil are linked to this dossier. Subsequently, ANVISA reviews general information about the experimental drug once and then follows the development of the product. This new procedure may potentially reduce the length of timelines leading to registration of drug products.

Prior to the publication of these new resolutions, ANVISA held many meetings with local associations and institutions to better understand their concerns. When ANVISA published the final text in 2015, the agency had already considered the feedback received from local entities. This open communication facilitated the implementation of the resolutions by all involved parties and it was the first time ANVISA established firm timelines for its review. The agency established a deadline of 90 days for Phase 3 trials with synthetic drugs and for trials with devices and a timeline of 180 days for Phase 1 or 2 trials or with biologics.

Prior to RDC 09/2015 and RDC 10/2015, there were no official timelines. As a result, it could take up to eight months for the release of ANVISA's first opinion letter. Even this timeline could vary greatly. The two resolutions were an important improvement. To date, ANVISA is following the timelines established in RDC 09/2015 and RDC 10/2015 for the release of the first opinion letter. As a result, the implementation of timelines also has improved the overall predictability of the regulatory process in Brazil.

Priority Review

Brazil spent most of 2017 without an official procedure for prioritization requests related to new drug submissions. Previously, Resolution RDC 37/2014 governed the prioritization requests for analysis of marketing applications, changes in a marketing application and clinical trials submissions.{4} However, this resolution was revoked in March 2017. Since then, there have been no official process; prioritizations were being submitted as "exceptional requests" needing to be evaluated by ANVISA's director.

Resolution RDC 204/2017, published by ANVISA in December 2017, regulates criteria and procedures for priority review related to registration, post-registration, and clinical trial (DDCM and clinical trial application) submissions of drugs.{5}

For clinical trials, the following DDCMs are prioritized as:

1. new medicines with all stages of production carried out in Brazil
2. medicines that are part of the National Immunization Program
3. products that are part of the strategic product list (under the Unified Health System (SUS)) that are the object of a productive development partnership

The following clinical trial applications are prioritized as:

1. medicinal products used for neglected, emerging or re-emerging diseases and medical emergencies in public health or serious debilitating conditions in situations where there is no therapeutic alternative available
2. clinical trials conducted exclusively in the pediatric population
3. Phase 1 clinical trials conducted exclusively in the national territory of Brazil

For the DDCMs and clinical trial applications classified as priorities, ANVISA's first opinion letter is to be released up to 45 calendar days from the submission date. This timeline also applies for substantial changes and amendments.

Even for a Phase 3 trial with a synthetic drug (with 90 days as a standard timeline), ANVISA's timeline will be 50 percent shorter in cases where priority is granted.

Rare Diseases

In December 2017, ANVISA also published Resolution RDC 205/2017, regulating special procedures for clinical trials, registration and certification of Good Manufacturing Practices (GMPs) of drugs intended to treat, prevent or diagnose rare diseases.{6}

This step marks the first time ANVISA has developed a specific process for rare diseases submissions.

According to RDC 205/2017, a rare disease is classified as a disease affecting up to 65 people in every 100,000 inhabitants, as defined in the National Policy of Integral Attention to People with Rare Diseases. The prevalence should be based on national official data or, when not available, data published in technical-scientific documentation.

A drug for a rare disease must aim to treat, diagnose or prevent a rare disease, must be used for a serious and debilitating condition and must propose to change in a clinically significant way the course of the disease or to allow its remission.

RDC 205/2017 establishes a step-by-step process for submissions related to rare diseases. For DDCMs and Clinical Trial Applications (CTAs), the following steps are mandatory for dossiers from rare diseases:

1. pre-submission meeting with ANVISA
2. submission of the dossier (DDCM) and/or CTA
3. ANVISA analysis in no more than 30 calendar days
4. In the event ANVISA releases questions/requirements, the company must answer within 30 calendar days.
5. ANVISA's final review must be performed no more than 30 calendar days after submission of the responses.

For rare diseases, the timelines for ANVISA's first opinion letter are even shorter—30 days—as compared to 45 days for priority review.

Also, for rare diseases, another positive point is that ANVISA has established a 30-day timeline for the evaluation of the answers submitted by the companies. This timeline marks the first time the agency has established an official timeline for this step of the review process.

Both resolutions were published in December 2017 (RDC 204/2017 and RDC 205/2017) and became effective in late-February 2018, 60 days after publication. The determination of specific processes and timelines for rare diseases and prioritized reviews demonstrate ANVISA's continuing efforts to create predictable processes with established timelines. This has been an important change to Brazil's regulatory processes.

ANVISA Review in Parallel with Ethics Process

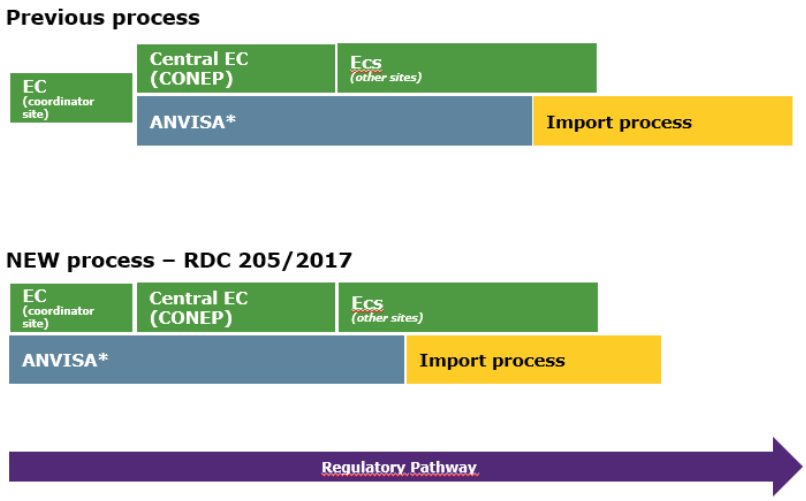
Resolution RDC 205/2017 established another important change for the regulatory process in Brazil by revoking some articles from RDC 09/2015 and eliminating the requirement of having an approval letter from the Local Ethics Committee (LEC) in the initial clinical trial application for experimental drugs as well as in the submission of protocol amendments.

In other words, an LEC approval letter was removed from the list of documents required for the submissions of any clinical trials with experimental drugs, making the ANVISA process independent from the ethical process in Brazil (LEC/CONEP—National Ethics Committee) with parallel reviews of both.

Since 27 February 2018 when RDC 205/2017 became effective, ANVISA submissions have been performed without an Local Ethics Committee (LEC) approval letter, a change with the potential to reduce the regulatory process period in Brazil by at least one month. Also, by anticipating ANVISA review, the import processes will start sooner, as ANVISA approval is required for importing the products into the country.

Figure 1 indicates the previous process (ANVISA submission after LEC approval) and the new process already in effect.

Figure 1. Regulatory Process in Brazil



**To illustrate the order of the regulatory submissions, a standard dossier was selected for ANVISA's timelines (example: a synthetic drug and Phase 3 study, which represent the majority of the submissions in Brazil). It is important to highlight that ANVISA timelines depend on the classification of the experimental drug (example: synthetic or biologic), the phase of the clinical trial, the type of disease (rare disease or not) and whether the dossier can be prioritized.*

Comissão Nacional de Ética em Pesquisa (CONEP)

CONEP was created in 1996 to implement the norms and directives regulating research with human participants. It's part of the National Health Council (CNS) and has a consultative, deliberative, normative and educational function, acting in conjunction with a network of ECs established in the institutions where research is carried out.

Under Resolution CNS 466/2012, CONEP also reviews projects such as research involving human genetics, such as the shipment of human genetics overseas or any other human biological material for obtaining genetic material, storage of biological material or human genetic data abroad, human reproduction research and research with coordination and/or sponsorship originated outside Brazil, except those with the Brazilian Government co-sponsorship.{7}

According to data presented by CONEP in the Opening Meeting *from "Municipal Clinical Research Dissemination Week,"* conducted 12 March 2018 in São Paulo, Brazil, the areas reviewed by CONEP represent only two percent of all projects submitted to ECs in Brazil. {8} That is not considered a high percentage considering the total research conducted in the country. However, as CONEP reviews all clinical trials with foreign sponsorship, CONEP timelines have a direct impact on international studies conducted in Brazil.

Shorter Cycle Times

The cycle timelines for CONEP have accelerated considerably in recent years due to an intensive effort from CONEP. According to data presented by CONEP on 12 March 2018, the average timelines in 2013 for CONEP's first opinion letter (approval or questions) was around 107.5 days. In 2017, this average was down to 27 days, a reduction of more than 70 percent.

Although it is still common to receive at least one round of questions from CONEP, average timelines for the final approval also have been reduced. Even when questions are received from CONEP, the final opinion letter can be expected to have turnaround times around 60 percent lower as compared to the time required in prior years.

Frequently Asked Questions

Resolutions published by the National Health Council determine the rules and guidelines for conducting clinical trials with human subjects in Brazil. Despite these resolutions, it is common to receive questions from CONEP after their review of submitted documents as the resolutions are not always specific and detailed enough to indicate exactly what CONEP expects to receive in the documentation.

In 2015, in an effort to provide more details about the requirements and avoid questions, CONEP published a manual entitled "Orientation Manual: Frequent Questions In Clinical Research Protocols."{9}

The purpose of this manual is intended to assist researchers and sponsors in preparing and submitting protocols and to reduce the number of questions raised by CONEP. The intent is also to accelerate the review process by ECs and CONEP. This manual also provides details about the most common questions corresponding to the main ethical issues CONEP has indicated in its opinion letters.

Local EC Accreditation

The review of projects performed by CONEP for some specific areas is considered a "centralization" of the ethical review in Brazil. This centralization has been criticized as CONEP reviews used to be the "bottleneck" impeding the start of clinical trials in Brazil.

An initial step toward decentralizing ethical review in Brazil was the publication of Resolution CNS 506/2016, which established the criteria for the accreditation (certification) of local ECs.{10}

The accreditation will be a voluntary procedure as not all ECs will need to go through this process. The accreditation process will involve a training period in which CONEP will closely follow the EC's activities and opinion letters to verify if they are aligned with CONEP's procedures. After this period, CONEP will distribute the projects among the accredited local ECs, which will be able to review and approve all types of clinical trials. As a result, CONEP will no longer centralize the review.

Although published in March 2016, the resolution is still in its implementation phase and many steps are yet pending. At minimum, the publication of this new resolution demonstrates a potential for optimizing the process and cycle times.

Conclusion

This review of recent regulatory actions and resolutions demonstrate how Brazilian regulatory bodies are optimizing processes and establishing shorter timelines for the review of clinical research. Prior to 2015, startup timelines in Brazil were commonly longer than one year. Currently, by virtue of the changes and new resolutions described in this article, startup timelines may be less than six months, depending on the type of submission. With these changes, and considering the closer communication between the associations/institutions and regulatory bodies, it is possible that Brazil can now play a greater role in international clinical research.

References

1. The Improvement of the Clinical Research Regulatory Scenario in Brazil. 1 September 2016. ABRACRO website. http://abracro.org.br/en/news/443-the-improvement-of-the-clinical-research-regulatory-scenario-in-brazil. Accessed 14 June 2018.
2. Resolution RDC 09/2015 (for Clinical Trials with Drugs). 3 March 2015. http://portal.anvisa.gov.br/documents/10181/3503972/RDC_09_2015_COMP.pdf/e26e9a44-9cf4-4b30-95bc-feb39e1bacc6. Accessed 22 June 2018.
3. Resolution RDC 10/2015 (for Clinical Trials with Devices). 3 March 2015. http://portal.anvisa.gov.br/documents/10181/3503972/%281%29RDC_10_2015_.pdf/0437d155-8bf8-4a8d-8e94-10ec1203a8b1. Accessed 22 June 2018.
4. Resolution RDC 37/2014. 18 June 2014. http://portal.anvisa.gov.br/documents/10181/3250283/%282%29RDC_37_2014_COMP.pdf/542a755a-96e3-47eb-b9f5-bda2c30e256d. Accessed 22 June 2018.
5. Resolution RDC 204/2017. 28 December 2017. http://portal.anvisa.gov.br/documents/10181/2718376/RDC_204_2017_.pdf/b2d4ae64-2d91-44e9-ad67-b883c752c094. Accessed 22 June 2018.
6. Resolution RDC 205/2017. 29 December 2017. http://portal.anvisa.gov.br/documents/10181/2718376/RDC_205_2017_.pdf/996fc46e-216b-44ab-b8c8-2778151b786e. Accessed 22 June 2018.
7. Resolution CNS 466/2012. 12 December 2012. http://conselho.saude.gov.br/resolucoes/2012/466_english.pdf. Accessed 22 June 2018.
8. Municipal Clinical Research Dissemination Week. CONEP Opening Meeting. 12 March 2018, São Paulo, Brazil.
9. Orientation Manual: Frequent Questions In Clinical Research Protocols. http://conselho.saude.gov.br/Web_comissoes/conep/aquivos/documentos/MANUAL_ORIENTACAO_PENDENCIAS_FREQUENTES_PROTOCOLOS_PESQUISA_CLINICA_V1.pdf. Accessed 14 June 2018.

10. Resolution CNS 506/2016. 3 February 2016. http://conselho.saude.gov.br/resolucoes/2016/Reso_506.pdf. Accessed 22 June 2018.

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