

# Positive changes in the Latin American regulatory environment

## AUTHORS

**Mercedes Ponce de León**, Senior Manager, Regulatory Affairs, Argentina; **Claudia Arancibia**, Senior Manager, Regulatory Affairs, Chile; **Priscila Fagundes**, Associate Director, Regulatory Affairs, Brazil; **Joel Sachún**, Manager, Regulatory Affairs, Peru; **Christian Toro Lozano**, Manager, Regulatory Affairs, Colombia; **Ana Paulina Zamora**, Manager, Regulatory Affairs, Mexico; **Mariano Parma**, Senior Director, Clinical Management, LA; **Andrés Bayona**, Executive Director, Clinical Monitoring, LA Lead; all at PPD.

## KEYWORDS

*Latin America (LA); Argentina; Colombia; Mexico; Chile; Peru; Clinical trials; Assessment timelines; Regulatory framework; Research; Government; International Council for Harmonisation (ICH).*

## ABSTRACT

Latin American countries have been reviewing clinical research regulations, profiling a new horizon for clinical trial development in the region. It is expected that changes made by local governments will increase the contribution of Latin America to the global development of new therapeutic treatments. The increased alignment among countries in terms of processes and requirements, the reduction of regulatory approval timelines, the simplification of some importation processes and the increased understanding of specific country requirements, while maintaining patients' safety, are already leading to a greater number of clinical trials in the region. This article provides a review of the regulatory changes in Argentina, Brazil, Chile, Colombia, Mexico and Peru, as well as the impact noted since the legislative changes, based on bibliographic information and recent practical experience. It is expected to take time to alter the preconceptions of lengthy timelines and inconsistent requirements that have contributed to the decline of clinical research across Latin America. It is therefore important to continue to review trends and opportunities during clinical trial feasibility and country selection discussions for multinational trials. Assuming that the improved predictability and shorter regulatory review timelines continue, it is anticipated there will be a steady increase in clinical research across the region over the next two years.

A review of ClinicalTrials.gov analysed the number of clinical trials (all studies, Phases II–IV) registered in the period 2010–2018 and funded/sponsored by the industry and/or by the US National Institutes of Health (NIH) that would contribute data for the marketing application of a new drug. NIH studies were of particular interest in the region, given the prevalence data for Latin America (LA) for the infectious disease and vaccines arena. The total number of clinical trials within this scope have remained steady throughout the years, within the range of 3,300–3,600 studies per year since 2013.

North America and Europe were the leading regions, with 40% and 18% share, respectively, in the period from 2010 to 2018. Within LA, Mexico, Brazil and Argentina were the countries hosting most of the clinical trials, followed by Chile, Colombia and Peru. In total, LA contributed to 8% of the clinical trials funded by industry or NIH between 2010 and 2018. A deeper analysis per region shows that from 2010 through 2018 the US/Canada combined and Europe executed a steady number of clinical trials per year, at around 2,500 and 1,000, respectively, since 2013. However, LA showed a significant decrease in the number of clinical trials from 2010 until 2019 (see Figure 1).

Historical experience of long assessment timelines and poor predictability of regulatory review/opinion/approval outcomes, leading to increased cost, contributed to this reduction in LA clinical trial conduct. Additional hurdles for importation of medications and supplies have contributed to the reduction in positioning research within the region. Moreover, decisions for placing research at LA clinical sites have been impacted by a “domino effect”, starting with a perception of a “difficult” region to work with and predicted startup turnaround timelines being

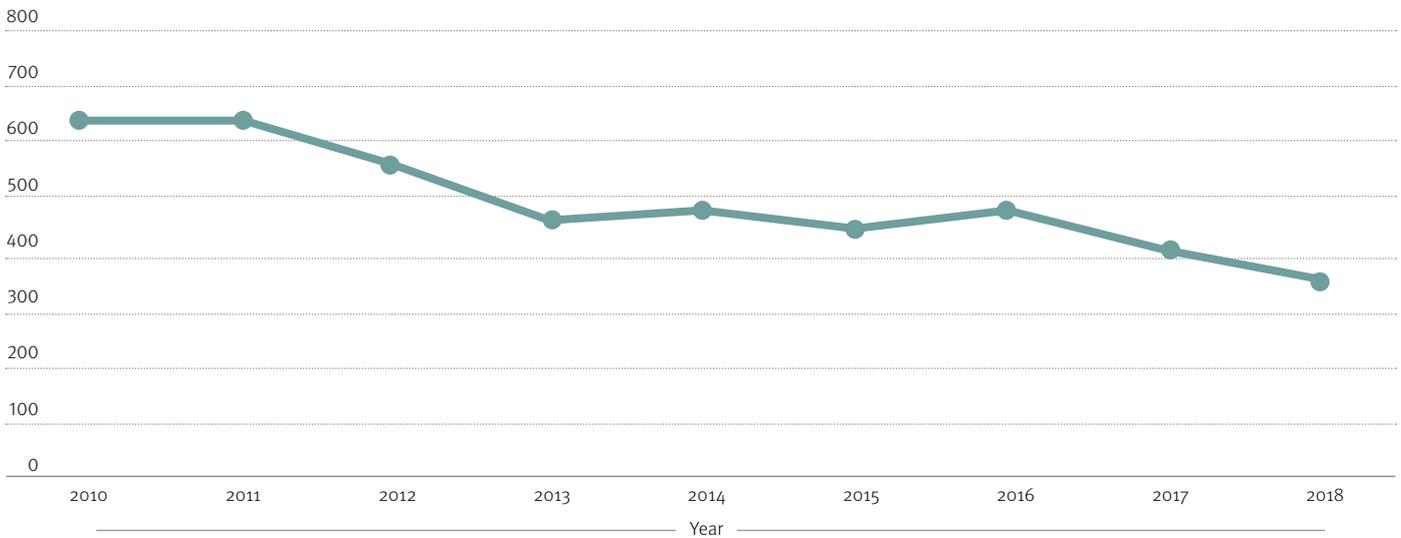
longer than the planned global recruitment targets. This is regrettable, given the wealth of tenure of the clinical research personnel with a footprint in the main LA countries, the vast experience at the site level and the health conditions landscape that continues to meet global clinical practice standards for R&D. As a result, clinical research decreased, patients were left without options and some sites were unable to sustain their infrastructure and had to close due to the subsequent economic impact.

Fortunately, governments, patients' associations, investigators, pharma companies and contract research organisations (CROs) have taken note of the effects of the decrease in activity and worked together to improve the landscape by applying different strategies and actions. Countries have been evolving and improving their predictability profile and therefore building trust in the processes for trial approval and importation. There are still several areas for improvement, but the foundations are solid. The robust regulations ensure compliance with clinical research standards (GxP) and favour data acceptability for global applications.

Evident changes promote an attractive scenario, offering the possibility for trial design (or even programme) discussions with regulators before submissions are performed and/or to follow expedited approval processes for some products such as orphan drugs. The LA clinical research community is making efforts to modernise and increase the efficiency standards of current regulatory processes in each country and align them with those from the US and EU. The proposed reforms, supported by their elected government officials, are showing positive effects on regulatory review timelines and importation processes, while securing patient safety and data quality at the highest levels.

FIGURE 1

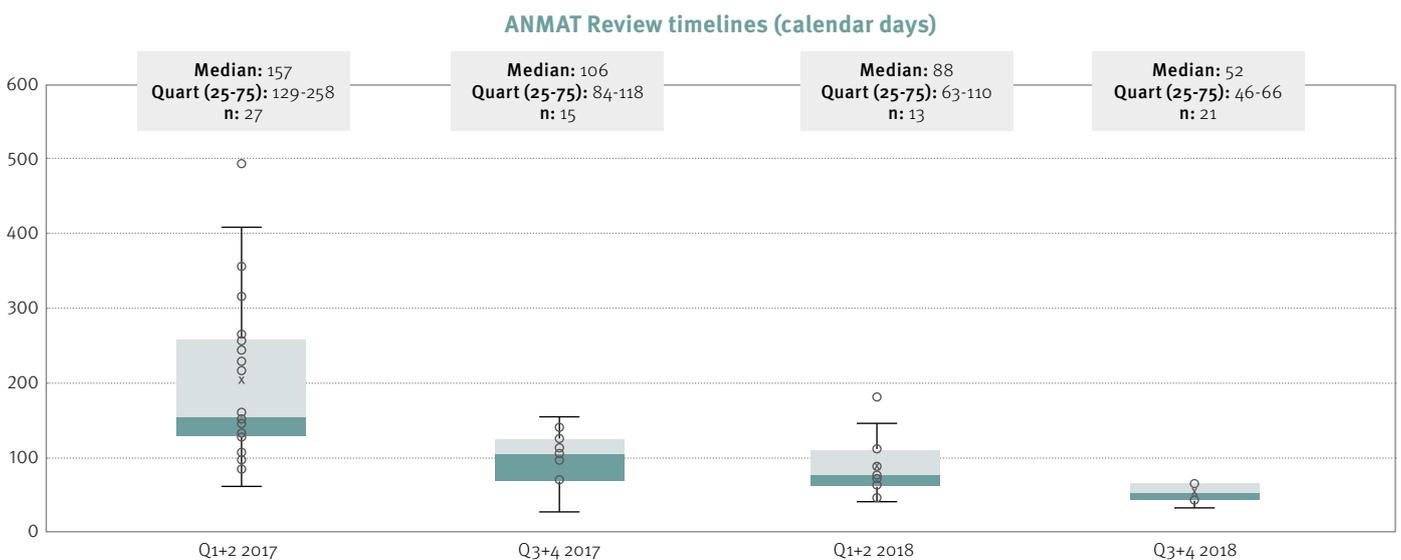
## LA's decrease in clinical trials from 2010 until 2018



Source: Based on ClinicalTrials.gov

FIGURE 2

## Evolution of regulatory review timelines per semester in Argentina during 2017 and 2018



Source: www.anmat.gov.ar; CAOIC (Data refers to the first approval)

Despite lacking a common review process, all countries in the region, without exceptions, follow International Council for Harmonisation good clinical practice (ICH GCP) guidelines. More frequently, agencies are validating and agreeing common processes under the oversight of the Pan American Health Organization (PAHO). It is critical to have access to local expertise and knowledge to leverage the positive changes and similarities, while understanding the diverse approaches each country require.

These actions are already showing positive results: when comparing 2018 versus 2017, median regulatory review timelines for the first approval have already decreased 10–25% for PPD across the region. In Brazil, CONEP (Brazilian Central Ethics Committee) reviews remain stable and within the expected 90 days. For Phase I–II trials/biologic investigational products, there is a 10% reduction for 2018 versus 2017 ANVISA (Brazil's regulatory agency) timelines. This overall decline is mainly due to the projects that were prioritised or classified as rare diseases.

The following sections provide an overview of the impact of the regulatory changes on these six LA countries.

### Argentina

Argentina's drug regulatory agency, the Clinical Trial Department at the National Administration of Drugs, Food and Medical Technology (ANMAT), issued a new regulation in March 2017.<sup>1,2</sup> The preamble stresses the importance of generating clinical trial data with high quality and in a timely manner to support the approval of new medicines to prevent and treat diseases. This supports the collaborative activities started earlier by industry players like CROs, as well as global and Argentinian pharma and biotech companies. The major changes were:

- Electronic submissions through a dedicated platform for trials. Faster review process and daily interaction between regulatory authorities and applicant. It is also an integral platform that stores all the

information of the investigational product development in the country.

- Studies being conducted in countries such as Austria, Belgium, Brazil, Canada, Cuba, Denmark, France, Germany, Israel, Italy, Japan, Mexico, the Netherlands, Spain, Sweden, Switzerland, the UK and the US are to be reviewed and approved within 55 working days. Proof of study conduct in one of these countries needs to be included in the submission. If a study is not being conducted in any of these countries, then the approval timelines are 70 working days.
- Simplified review process for Phase I studies. With the aim of developing Phase I studies in the country, the current regulation permits a pre-submission meeting to discuss protocol design. Sites with capabilities for performing Phase I trials are prequalified and registered as preapproved by ANMAT.

The Chamber of CROs (CAOIC) is actively monitoring and tracking the impact on regulatory timelines. The data show a significant reduction in assessment time when comparing submissions done per semester in 2017 and 2018. Overall timelines have decreased by 41% with a median of 52 working days for the studies submitted as of December 2018 (see Figure 2).<sup>3</sup>

## Peru

The Peruvian government published a new clinical trial regulation in June 2017.<sup>4,5</sup> The aim was to improve the protection, rights, safety and welfare of research subjects (including minors). Furthermore, it simplified some of the processes, for example, eliminating the need for annual renewals, and removing the need for a good manufacturing practice (GMP) certificate for the comparator medication, which can be replaced by a manufacturer/authorisation statement with information about the manufacturer and the manufacturer's licence. The current regulation demonstrates the vision of the Peruvian competent authority to strengthen and promote clinical research in Peru, as it considers that clinical research conducted in the country provides access to new information and technology and generates new employment opportunities.

According to data from the National Institute of Health of Peru (INS) and the General Office of Research and Technology Transfer (OGITT), 402 clinical trials were approved in the country between 2014 and 2018. Although there was a reduction in the number of submissions between 2013 and 2017 (from 92 to 41), the trend reverted in 2018 due to an increase in submissions compared with the previous year from 41 to 56. It is also important to note that the number of unauthorised clinical trials has been decreasing in the past five years, with none in 2017 and 2018.<sup>5</sup>

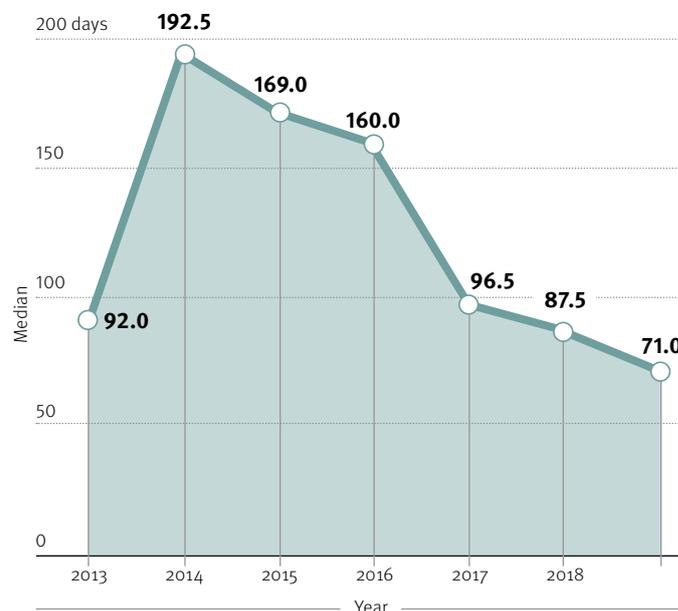
In addition, INS is working to improve the efficiency of its regulatory processes, which is evidenced by a decrease in the approval timelines of clinical trials. Although the agency does not release data on the median of all the evaluations carried out per year, experiences in Peru indicate a significant drop in approval timelines since 2016, as shown in Figure 3.

## Brazil

A public audience organised by the Brazilian Senate in March 2014 began an open discussion about Brazil's role in clinical research. Since then, several positive changes have been observed. New ANVISA regulations for the submission of clinical trials was introduced in March 2015.<sup>6,7</sup> The review process is similar to the US FDA investigational new drug (IND) process. ANVISA now reviews the entire development of the experimental products instead of each clinical trial individually. Review timelines are established and adhered to, which leads to increased predictability. Rare diseases have a mandatory pre-submission meeting to discuss the clinical programme, expectations and anticipated recommendations.

FIGURE 3

## Evolution of regulatory review timelines per year in Peru 2013–2018



Source: PPD's Peru operations (Data refers to the first approval)

Furthermore, ANVISA was accepted as an ICH member in November 2016, with the expectation that procedures and requirements in Brazil will now be aligned with international standards.

In 2017, ANVISA published new regulations for priority review and rare diseases and established shorter review timelines.<sup>8,9</sup> Prioritisation can be requested, for example, for projects that evaluate a medicinal product used for: neglected, emerging or re-emerging disease; clinical trials conducted exclusively in the paediatric population; and Phase I clinical trials conducted exclusively in Brazil. Rare disease resolution is applicable for diseases affecting up to 65 people in every 100,000 inhabitants.

As standard, Phase III studies with synthetic experimental drugs are evaluated within 90 days, while prioritised dossiers and clinical trials are evaluated within 45 calendar days, and rare diseases within 30 calendar days. Ethics and regulatory process reviews are in parallel (previously sequentially). Regulations assume 75 days for initial analysis (30 days to respond in case of queries) plus 45 days for CONEP's review of any answer, so the total timeline expected is now 150 days (in case of one round of questions). Based on experience, review timelines for CONEP (Brazil's Central Ethics Committee) have improved considerably. The first opinion letter from CONEP is being received within 45 days on average (and sometimes within 30 days) versus five months in the past. Average timelines for the final approval can be expected in around 90 days, which is 60% less time when compared to 2014.

All clinical trials with foreign sponsorship must be reviewed by CONEP. Criteria for the accreditation (certification) of local ethics committees (ECs) were published in 2016<sup>10</sup> and are a voluntary procedure. Not all ECs will need to go through the process. ECs that volunteer to participate in the accreditation process will undergo a training period in which CONEP will closely follow up on ECs' 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. CONEP will no longer centralise the review process. Currently, the resolution is still in its

implementation phase, but this new resolution represents an initial step for decentralisation of the ethical review process in Brazil and a potential optimisation of cycle times.

In summary, government and regulatory authorities are committed to improving the country's regulatory review process and timelines.

## Chile

The regulatory environment in Chile remains stable, with no major changes in the past few years. Currently, Chile is the LA country with the most predictability in terms of regulatory timelines. It is not typical to receive queries from the Chilean regulatory agency, Instituto de Salud Pública de Chile (ISP), while median assessment timelines are within 28–30 days. ISP typically takes four to six weeks to grant the initial study approval. The Secretaria Regional Ministerial de Salud (SEREMI) oversees the EC accreditation process. Only accredited ECs can review and approve clinical trials in Chile (voluntary process issued in 2016).<sup>11</sup> Several sites can use the same accredited EC for the revision of a study and, therefore, one EC approval is sufficient for all sites, making the process more efficient.

The Chamber of CROs (ACROCHI), along with other local organisations, is working with the government to enforce the regulation which was submitted for public consultancy in 2017. Due to administrative steps and ongoing discussions, any decision in this regard is unlikely to happen imminently. However, clinical trial execution in Chile is maintained with business as usual, with no constraints.

## Colombia

The Colombian regulatory agency, National Institute for the Surveillance of Drugs and Food of Colombia (INVIMA), published updated guidelines in 2016,<sup>12</sup> changing the agency's structure and creating a dedicated clinical research group aimed at developing guidelines related to clinical research and the evaluation of clinical trials.

Guidelines were updated again in 2018<sup>12</sup> to provide consistency in the review of protocol amendments, new sites, new investigators, ICFs and stability studies. Pre-submission meetings to discuss questions that might be raised during the review process are possible. Timelines for the initial review of protocols are expected within 60 calendar days.

INVIMA was accepted as an ICH member in November 2017, so in the future the expectation is that procedures and requirements will be aligned with international standards. In summary, INVIMA expects to improve its processes to support and stimulate national and transnational investments in research and development, in addition to fostering the development of products.

## Mexico

The regulatory environment and clinical research development in Mexico is stable, as part of the vision of the governmental regulatory agency "Comision Federal para la Proteccion contra Riesgos Sanitarios" (COFEPRIS). COFEPRIS is actively proposing initiatives to enhance internal efficiency, while clear guidelines have been developed and published to improve the regulatory process.

COFEPRIS established the Unidades Habilitadas de Apoyo al Pre Dictamen (habilitated units to support the preapproval, known as UHAP). UHAPs were created based on the signature of the "Bases of collaboration for the evaluation of research protocols for human health"<sup>13</sup> between COFEPRIS and the Coordinating Commission of National Institutes of Health and High Specialty Hospitals (CCINSHAE), with the purpose of assisting in the evaluation and preapproval of clinical trials, while adhering to the legal dispositions in force and being aligned to the process of evaluation of COFEPRIS. UHAPs are COFEPRIS' authorised third

parties for clinical trial preapproval. They provide an optional process that reduces COFEPRIS review timelines from 90 days to 30 days. Currently the CCINSHAE coordinates nine UHAPs established in different institutions. UHAP submission is made after EC approval is obtained, but prior to COFEPRIS submission. Timeline for UHAP preapproval is 30 working days. After UHAP preapproval is obtained, COFEPRIS review is expedited to 30 working days, which reduces RA revision to approximately 60 days. Some UHAPs accept that more than one site is included in the initial clinical trial application (CTA), so instead of submitting a single site in the first CTA to COFEPRIS, the initial CTA can be submitted with several sites included.

Therefore, depending on the regulatory authority's timelines trends and study timelines, the process with preapproval from UHAP can be considered. Local expertise is key to leveraging this opportunity and gaining the potential faster review process.

## Conclusion

Governments, health authorities and industry leaders across LA are working to improve the regulatory framework to support clinical trial research and increase predictability, which consequently will increase regional contributions to the development of new, safe and effective therapeutic treatments to patients worldwide. Data collated over the past few years provide reassurance that the changes being applied locally in each country are having a positive effect on the approval process. With shorter timelines and clearer processes for importation, sponsors will recognise the advantages of including LA in clinical research programmes. This is clearly an evolving environment.

Data continue to show that regulatory review timelines may not be a major obstacle in the startup process of clinical trials. The new regulatory climate, propelled by improved regulatory timelines in Argentina and the reopening of clinical trials for paediatric patients in Peru, in addition to the ongoing evaluation and review in the regulatory arena in Brazil, Mexico, Colombia and Chile, will not only enhance a better environment for clinical trials in the region, but also will provide tangible opportunities for scientific and health development in LA. ■

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