

Trends in the Regulatory Landscape for the Approval of New Medicines in Latin America

To address the complex challenges in the global regulatory environment and the growing demand for patient access to new medicines, regulatory agencies in Latin America are actively engaging in regulatory-strengthening and capacity- building initiatives, including the use of priority pathways, reliance on the prior reviews of trusted authorities and work sharing to facilitate better utilisation of resources.

This R&D Briefing focuses on the trends observed in 4 countries in Latin America region for 136 new active substances (NASs) approved from 2009 to 2017* (with subset analyses of various years). The briefing explores the changes over the decade and their reasons and suggest best practices for these agencies to maximise the value-added activities they can contribute to the medicines' review process.

*See page 6 for methodology

Briefing Highlights

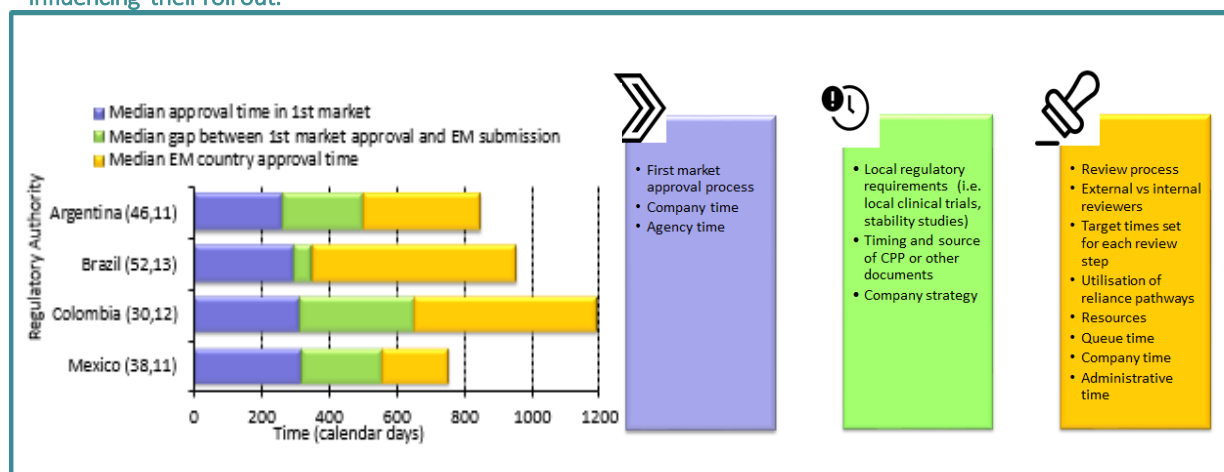
- Despite reforms undertaken by some LatAm agencies to streamline review processes, overall regulatory approval times increased over the past decade.
- In Brazil, average review times have declined recently due to ANVISA approaches to reduce backlogs.
- Variability in review times, especially in Brazil, Colombia and Mexico, results in a greater unpredictability regarding the access to medicines in Latin America.
- Use of the Equivalence Agreement route and Authorised Third Parties (ATP) resulted in a dramatic reduction in median review timing in Mexico.
- Reliance pathways are in place in Argentina, Brazil, Chile, Colombia, Cuba, Mexico and Peru and Brazil and Colombia conduct priority reviews.

Regulatory review processes and timelines

The time to regulatory approval of new active substance (NAS) in Latin America can be measured by three distinct time points:

1. **time of approval in the first market**, which generally is a first-wave market (USA or Europe);
2. **the submission gap** (time between first-market approval and submission to the particular authority);
3. **marketing authorisation (MA) time** (time between submission and approval, which includes company and agency time). (Figure 1). These time points are influenced by a number of factors, one of which is the regulatory landscape within different jurisdictions.

Figure 1: Overall median roll out time to select Latin American countries for NASs approved 2015-2017 and factors influencing their roll out.

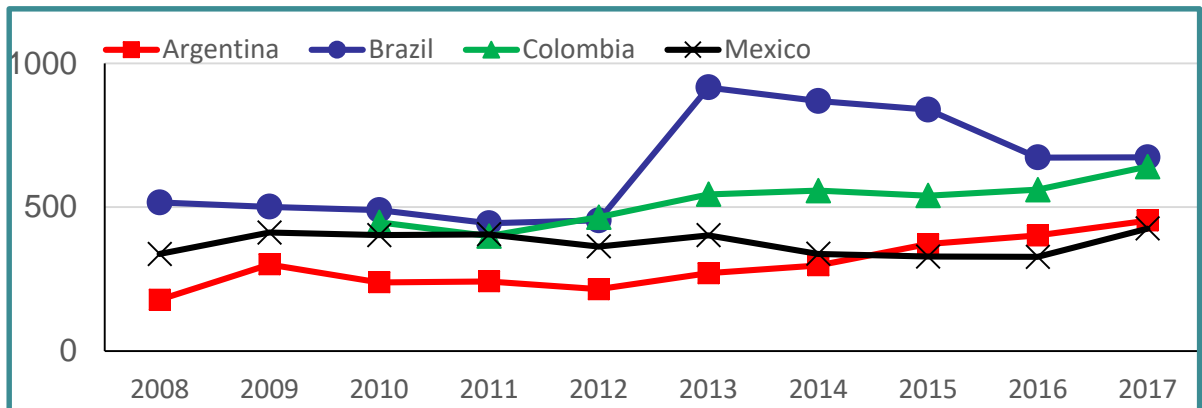


Trends and predictability in the review

Approval time trends over the last decade*

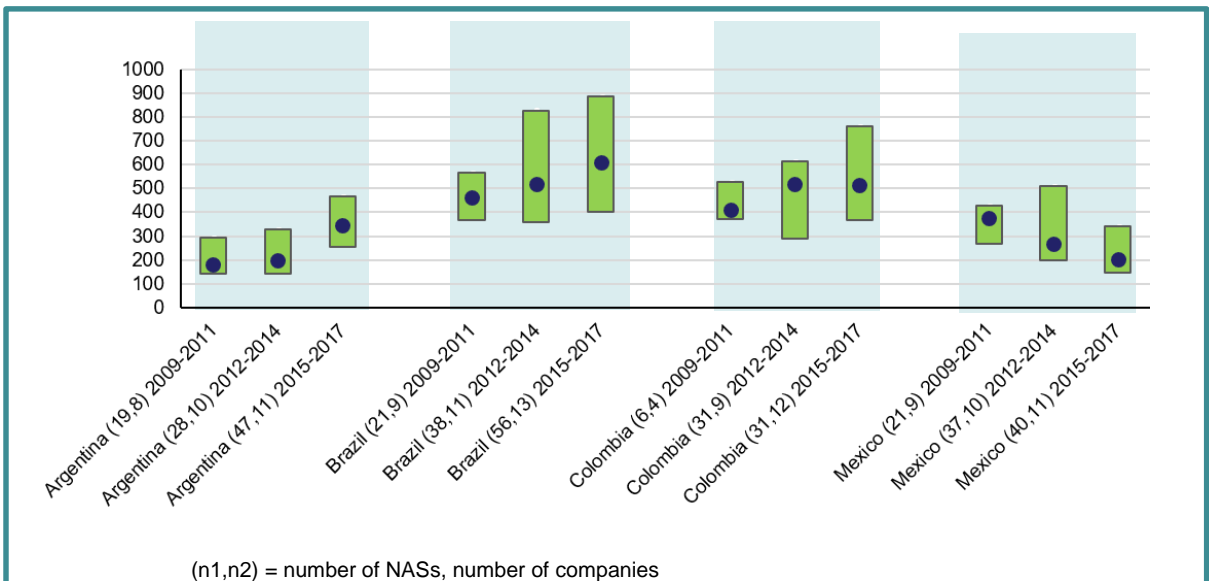
Despite the reforms undertaken by some LatAm agencies to streamline marketing authorisation review processes, overall regulatory approval times have increased over the past decade, as illustrated by the three-year moving average for NAS approval times in four key agencies (Figure 2). In Brazil (ANVISA), a sharp increase in approval time was observed approximately five years ago, due to the backlog of dossiers; however, review times have declined recently due to various ANVISA approaches to reduce this backlog. In 2012, Mexico (COFEPRIS) introduced Authorised Third Parties (ATPs), which provided fast-track review for dossiers pre-reviewed by approved external parties. However, while this effort temporarily decreased COFEPRIS review timing, reviews of the regulatory policy and processes are being undertaken by the new Mexican Government, which may result in change to the review times.

Figure 2: 3-year moving average approval times for NASs approved 2008-2017.



Understanding process predictability

Figure 3: Median approval times for NASs in 3-year cohorts.

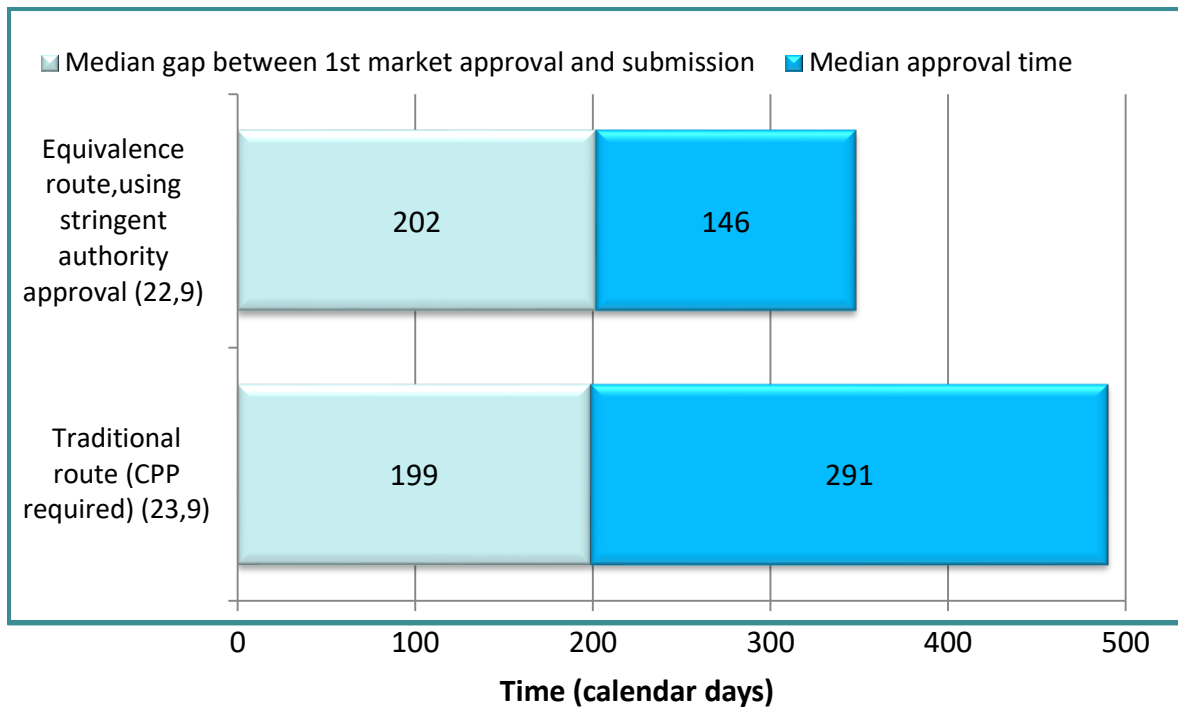


The median approval times and ranges (25th and 75th percentiles) for key LatAm countries by three-year range cohorts shows a consistent increase with the exception of Mexico; however, it is also important to note that these times include company and agency time. Timing variability is an indicator of an unpredictable process; the narrower the variability the more predictable the process. The wider variability shown here suggests inconsistencies in the review process and patients and healthcare professionals therefore are challenged to understand when new medicines may become available in their country. More narrow variability might be expected in Argentina because ANMAT conducts a simplified relatively consistent verification review process; however, even here, the variability has increased slightly. For Mexico, the variability has narrowed, which may be due to the shifting of assessment activities to ATPs.

* Figures 2 and Figure 3 use different analysis and year-range data set; therefore, these should not be used for direct comparison. Figure 2 shows the approval time as a three-year moving average and figure 3 shows approval times in median and percentiles, using a three-year cohort.

Case study: Mexico – political will for change

Figure 4: Median time to roll out in Mexico for NASs approved 2013-2017 using facilitated regulatory pathways.



(n1,n2) = number of NASs, number of companies

Situation/Action

The Mexican government established an innovation policy relying on regulatory cooperation among different drug regulatory agencies in order to expedite the approval and entry of new medicines in Mexico. Several processes were introduced:

1. Equivalence Agreement for new drugs with prior approvals by the US FDA, Health Canada, TGA, Swissmedic or EMA.
2. To enhance internal efficiency and reduce review times, COFEPRIS appointed ATPs to conduct reviews that would inform COFEPRIS decisions.
3. To encourage local clinical research, Mexico developed an alternate route in which the Certificate of Pharmaceutical Product (CPP) requirement was waived if the dossier contained a report of a clinical study conducted in the Mexican population. This allowed sponsors to submit a dossier without prior approvals (for which a CPP would be required).

Impact

Figure 4 shows that by using the Equivalence Agreement route, there was a dramatic reduction in review timing, where the median time was halved compared with the route in which the CPP is required. Although not illustrated here, the creation of ATPs has resulted in reduction in review time by COFEPRIS.

It should be noted that a new government was elected in Mexico in December 2018. Under this administration, many of the existing regulatory policies are being reviewed and reassessed.

Facilitated regulatory pathways

Agencies in Latin America recognise that their review times are increasing and this is often due to lack of resources to keep up with an increasing workload. To address this issue, agencies are introducing various approaches to streamline their reviews and to efficiently use available resources. As regulators recognise that cooperation among agencies can result in the more efficient use of resources, new models of cooperation have emerged. Several countries and regions have developed or are developing formal and informal frameworks for cooperation and work sharing, helping agencies avoid duplicative work and provide added value to local jurisdictions.

Another cooperative approach to expedite review times is through the use of reliance pathways and as shown in table 1, LatAm agencies have introduced their use. In addition to national regulatory agencies, the Caribbean Regulatory System (CRS) is an example of a centralised process that benefits from reliance on prior decisions by references agencies. In the CRS, an abridged review is conducted by a centralised team of assessors and positive recommendations are then taken up by the individual constituent member states. Most maturing LatAm agencies have implemented some form of abbreviated, reliance mechanism. However as was seen in Figures 2 and 3, their efficiency remains less than optimal and opportunities exist to improve their outcomes in terms of timeliness and process predictability.

Table 1. Facilitated regulatory pathways in Latin American regulatory agencies.

	Verification route	Abridged route	Priority review
Argentina			
Brazil		(1)	
Chile			
Colombia		(2)	
Cuba	(3)		
Mexico			
Peru			

(1) Only biologics

(2) This assessment type has been legally approved, but has not been implemented.

(3) Used for selected applications

Glossary of definitions

Verification route: This model is used to reduce duplication of effort by agreeing that the importing country will allow certain products to be marketed locally once they have been authorised by one or more recognised reference agencies, elsewhere. The main responsibility of the agency in the importing country is to 'verify' that the product intended for local sale has been duly registered as declared in the application and that the product characteristics (formulation, composition) and the prescribing information (use, dosage, precautions) for local marketing conforms to that agreed in the reference authorisation(s).

Abridged route: This model also conserves resources by not re-assessing scientific supporting data that has been reviewed and accepted elsewhere but includes an 'abridged' independent review of the product in terms of its use under local conditions.

Priority review: Regulatory authorities speed the review of certain products to enable faster approval. The review time of an expedited review is substantially shorter than the review time of a standard review. A decision on which product to grant expedited review is normally based on its importance to public health aspects.

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Methodology

The data used for the analyses in this report have been derived from the CIRS Emerging Markets Regulatory Review Times Database, which tracks new medicines and line extensions in 18 emerging markets. The data used for this briefing include those for all new active substances approved between 2009-2017 in the 4 countries in the Latin America region that are included in the database.

Acknowledgements

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