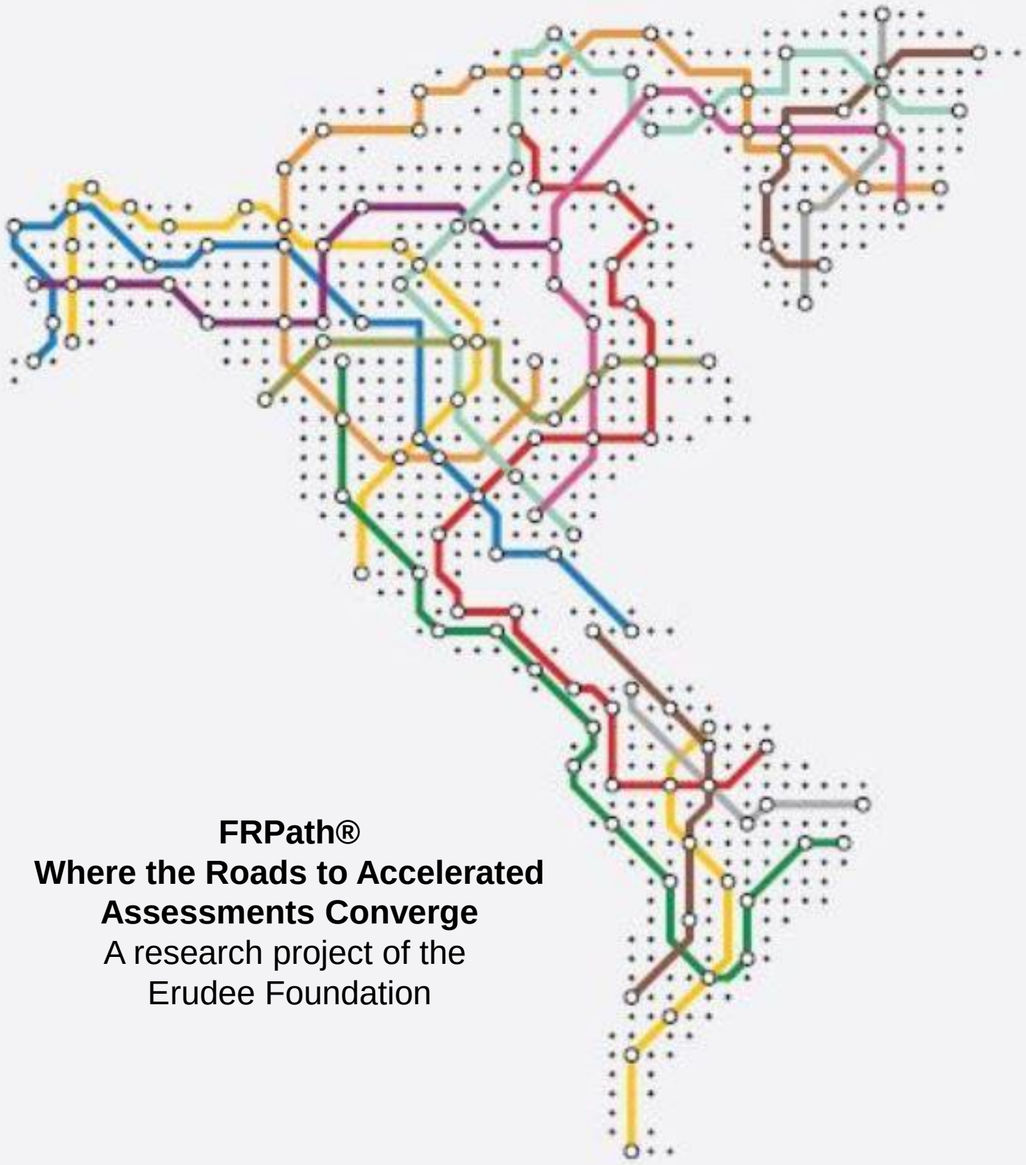

FRPath®
Where the Roads to Accelerated Assessments Converge
A research project of the
Erudee Foundation

The 2021

Annual FRPath® Yearbook

Executive Summary

Focus on Latin America

The 2021 Annual FRPath® Yearbook Executive Summary: Focus on Latin America, August 2021. ©The Erudee Foundation 2021.

This analysis was supported in part by an unrestricted educational grant from FIFARMA (Federación Latinoamericana de La Industria Farmacéutica).

About The Foundation and FRPath®

The mission of the Erudee Foundation (a 501c3 nonprofit) is to educate students in the health sciences and related fields and to inform the effective use of healthcare systems. It supports this mission through its unique scholarship program and innovative research projects. The FRPath Project (www.frpath.org) of the Erudee Foundation (www.erudee.org) is an educational research project designed to serve as a curated repository of key information about Facilitated Regulatory Pathways (FRPs). The FRPath project emerged through academic collaborations with Temple University (Philadelphia, PA USA) and Utrecht University (Utrecht, The Netherlands) to address the need to educate all stakeholders about FRPs. This project addresses the information needs of regulators, pharmaceutical companies, patients, procurers, payers, NGOs and other stakeholders with information about the evolving aspects of FRPs.

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Terms

CPP: Certificate of Pharmaceutical Product
FRP: Facilitated Regulatory Pathways are regulatory approaches used by ministries of health to reduce the burden of duplicative regulatory activities, helping to make the development and assessment of safe, effective, quality medicines more efficient and timelier. These may represent priority and other accelerated pathways along with pathways that work through reliance or recognition mechanisms, thereby promoting efficient access to important medicines worldwide.
PAHO: Pan-American Health Organization
Recognition: The routine acceptance of the regulatory decision of another regulator or other trusted institution. Recognition indicates that evidence of conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B.
Reliance: An act whereby a regulatory authority in one jurisdiction may take into account/give significant weight to work performed by another regulator or other trusted institution in reaching its own decision.

The FRPath® database represents one of the most comprehensive resources of academically curated FRP information, describing more than 130 FRPs from 64 countries and regional initiatives. It is based on publicly available, verifiable information. Readers are encouraged to access the system at www.frpath.org and to use the “Suggest an Edit” feature to provide their factual insights into FRPs from Latin America to help maintain this important resource.

Introduction

Facilitated Regulatory Pathways (FRPs) are regulatory approaches used by ministries of health to make the development and assessment of safe, effective, quality medicines more efficient and timelier.

The World Health Organization supports the implementation of reliance on other regulators' work in order to make the best use of available resources and expertise. This form of FRP enables leveraging the output of others whenever possible while placing a greater focus at the national level on value-added regulatory activities that cannot be undertaken by other authorities, such as in-country vigilance activities.

Latin American regulators have acknowledged the value and role of FRPs and reliance pathways, in particular. Although Good Reliance Practices have recently been promulgated, the FRP landscape in this region remains diverse and evolving.

In this report we used the FRPath® database to assess the characteristics of 27 FRPs from 15 countries in Latin America and a regional Caribbean initiative. The FRPath® data have been derived and curated from publicly available resources. While many agencies provide clear, transparent instructions and descriptions of their pathways, others offer few details, which limits the understanding of those pathways.

We have looked to identify common and best practices related to FRPs in Latin America. The adoption of best practices will encourage the efficient and effective use of regulatory resources and will facilitate the availability of important medicines to the Latin American public.

Introducción

Las Rutas/Vías Regulatorias Expeditas (VRE) son modalidades regulatorias utilizadas por los Ministerios de Salud para facilitar y hacer más oportuno y eficiente el desarrollo y la evaluación de medicamentos de calidad seguros y efectivos.

La Organización Mundial de la Salud respalda la implementación de mecanismos de "reliance" (confianza) en el trabajo desarrollado por otros reguladores con el objetivo de que las agencias aprovechen óptimamente sus recursos y conocimientos. La utilización de las VRE permiten aprovechar selectivamente los resultados de otras agencias y al mismo tiempo enfocarse en actividades que añaden valor a la agencia y que no pueden ser llevadas a cabo por otras autoridades; por ejemplo la vigilancia del mercado.

Los reguladores latinoamericanos valoran y reconocen y el papel de las VRE y en particular de las rutas de "reliance". Considerando que las Buenas Prácticas de Reliance se emitieron recientemente, la perspectiva de las VRE es diversa y continua en evolución.

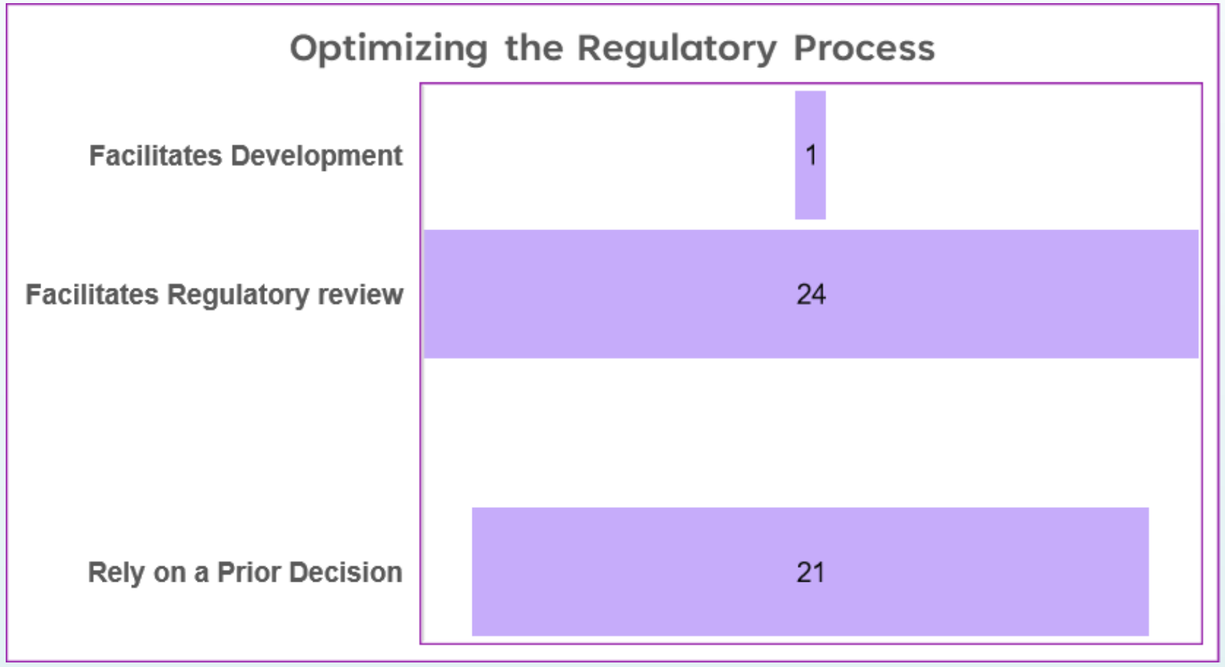
En la elaboración de este informe se utilizó la base de datos FRPath® para analizar las características de 27 VRE de 15 países de América Latina y la iniciativa de la región del Caribe CRS. La base de datos FRPath® se ha desarrollado a partir de fuentes de información disponibles públicamente. Muchas agencias ofrecen instrucciones y descripción clara y transparente de sus rutas expeditas (VRE). Sin embargo, algunas agencias dan muy pocos detalles de sus VRE, lo cual limita la comprensión de sus características.

Hemos tratado de identificar las mejores y más comunes prácticas en relación a las VRE de América Latina. La adopción de mejores prácticas promueven el uso efectivo y eficiente de los recursos regulatorios y facilitan la disponibilidad de medicamentos importantes en América Latina.

The Latin American Landscape 2021: Fifteen Countries and One Regional Regulatory Initiative Offering 27 Unique FRPs

Region	Country	Agency	FRP Name
Central America Caribbean	Costa Rica	Ministerio de Salud	Mutual Recognition of Sanitary Registration of Medicines for Human Use
Central America Caribbean	Dominican Republic	DIGEMAPS	Simplified Procedure
Central America Caribbean	El Salvador	National Medicine Directorate (Dirección Nacional de Medicamentos- DNM)	Mutual Recognition Registration Process.
Central America Caribbean	Guatemala	Ministerio de Salud Pública y Asistencia Social (MSPAS)	Procedure for the recognition of sanitary registration of medicines.
Central America Caribbean	Honduras	Agencia de Regulación Sanitaria de Honduras (ARSA)	Mutual Recognition of Sanitary Registry of Medicines for Human Use.
Central America Caribbean	Panama	Ministry of Health	Abbreviated Pathway
Central America Caribbean	RRI (Regional Regulatory Initiative)	Caribbean Public Health Agency (CARPHA)	Verification Review of Medicines and Vaccines
Central America Caribbean	RRI (Regional Regulatory Initiative)	Caribbean Public Health Agency (CARPHA)	Verification Review for Biotherapeutic Product Applications
North America	Mexico	Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS)	Article 170
North America	Mexico	Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS)	Equivalence Agreement
North America	Mexico	Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS)	Recognition of MAs from Reference Authorities
South America	Argentina	Administración Nacional de Medicamentos, Alimentos y Tecnología Médica	Fast Track Proceedings: 'Article 3'
South America	Argentina	Administración Nacional de Medicamentos, Alimentos y Tecnología Médica	Fast Track Proceedings: 'Article 4'
South America	Brazil	Agência Nacional de Vigilância Sanitária (ANVISA)	ANVISA Priority Review
South America	Brazil	ANVISA	Biologics and Biosimilars Pathway
South America	Chile	InInstituto de Salud Pública (ISP CHILE)	Simplified Procedure (Procedimiento Simplificado de Registro)
South America	Chile	Instituto de Salud Pública (ISP CHILE)	Priority Review: Short Registration Procedure
South America	Chile	Instituto de Salud Pública (ISP CHILE)	Sanitary Registration of Orphan Medicines
South America	Chile	Instituto de Salud Pública (ISP CHILE)	Decree 54 Abbrv Reliance
South America	Colombia	stituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA)	INVIMA Abbreviated Procedure
South America	Colombia	Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA)	INVIMA Exceptional Circumstances
South America	Colombia	stituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA)	Emergency Use Authorization (ASUE)
South America	Ecuador	Agencia Nacional de Regulación, Control y Vigilancia Sanitaria (ARCSA)	Health Drug Registration for Homologation
South America	Peru	Dirección General de Medicamentos, Insumos y Drogas (DIGEMID)	Reliance Pathway
South America	Peru	National Authority of Pharmaceutical Products, Medical Devices and Sanitary Products (ANM)	Conditional Sanitary Registration of Medicines and Biological Products
South America	Suriname	Ministerie van Volksgezondheid (Ministry of Health)	TBD
South America	Uruguay	Ministerio de Salud Publica (MSP)	Expedited Procedure

How Do FRPs Help the Regulatory Process?



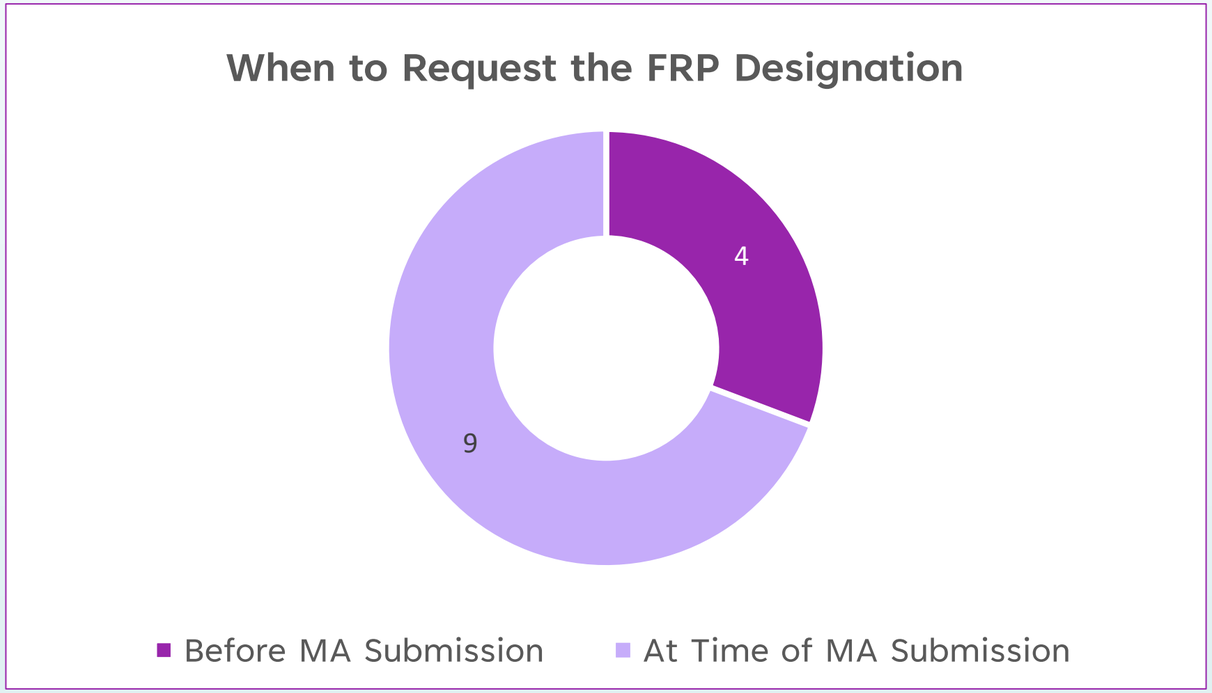
By relying on a prior decision from a recognized reference agency, an agency can contribute to the process while limiting duplicative efforts. Twenty-one pathways have the flexibility to rely on a prior decision as a form of reliance (see also Page 7). For those agencies where the information was specified, six agencies require the use of the decision of at least one reference agency, but in no case were more than two prior decisions required.

Facilitated Regulatory Pathways (FRPs) are regulatory pathways designed to accelerate submission, review and approval of medicines, by providing alternatives to standard regulatory review routes. FRPs may increase the communication and level of commitment between the developer and agency, can give a larger role to effects on surrogate end points, and may move the burden of evidence generation to the post-authorization phase. In general, FRPs emphasize particular approaches to accelerate the process: regulators working (early) with applicants to improve trial designs, surrogate and end point selection; facilitating the ability of regulators to make a decision based on an expedited assessment of preliminary clinical data or surrogate end points.

In this cohort of FRPs, as expected, the majority have been designed to facilitate the regulatory review process. While one pathway (INVIMA's Emergency Use Authorization) also helps companies during the development phase, as regulators evolve into partners of innovation, it can be expected to see the facilitation of development as a growing aspect of their role.

19 Latin American pathways offer the opportunity for the agency to interact with and provide guidance to the sponsor.

When is a Product Assigned an FRP?

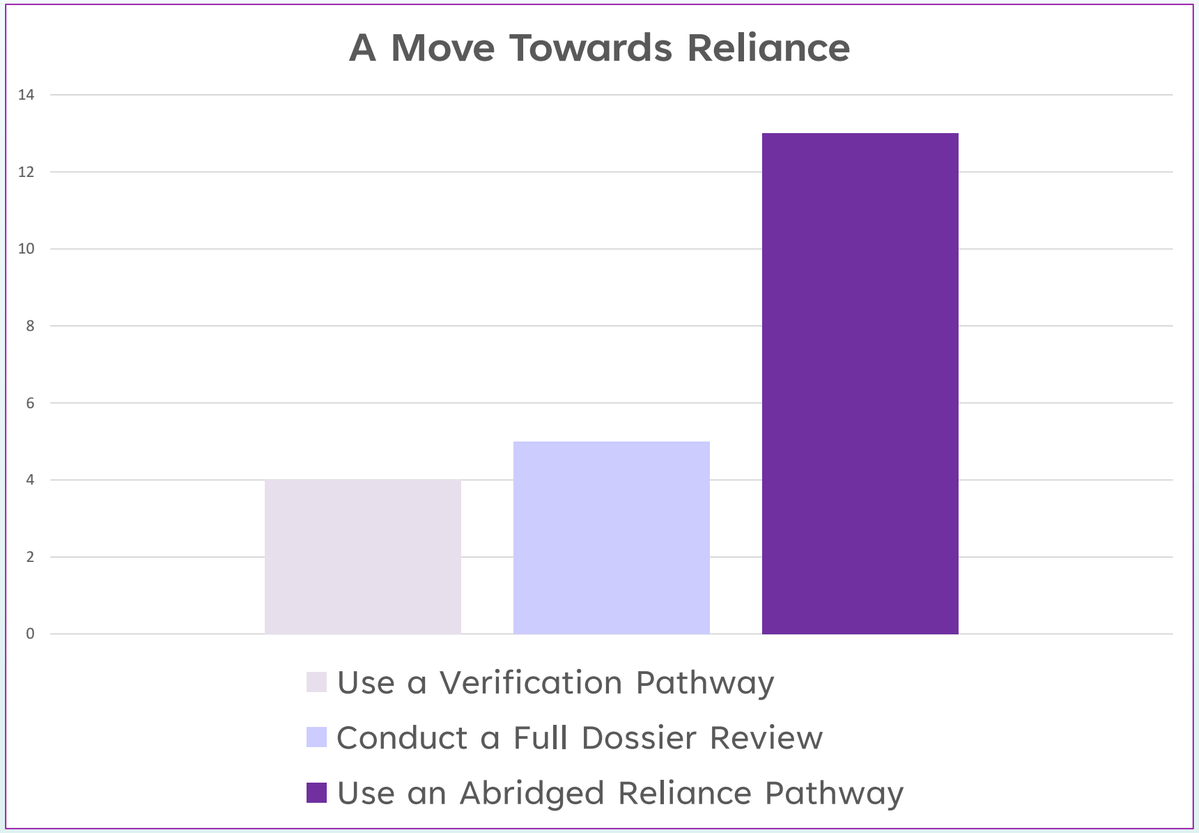


The decision to use an FRP can be complicated. Companies may need to prioritize personnel to support the potentially more rapid pace of the FRP, especially if a product is being submitted simultaneously to several agencies, each with their own FRP requirements and timelines.

Similarly, the use of an FRP, including reliance pathways, can place a strain on some regulatory agencies. Some FRPs require an assessment of the full dossier, albeit in a time frame shorter than a standard assessment timeline. Other pathways, while based on reliance, may require approaches to project management that may burden a maturing agency.

Therefore, it is important for both the pharmaceutical company and the agency to understand which products will be assessed using an FRP; the timing of this process is important. For agencies that provided this detail, the majority of their pathways confirmed the designation at the time of the marketing authorization submission. Four pathways provided input and confirmation of the FRP as part of the submission planning process, a practice we believe provides clarity and predictability to the FRP process.

Reliance: A Bridge to Regulatory Efficiency



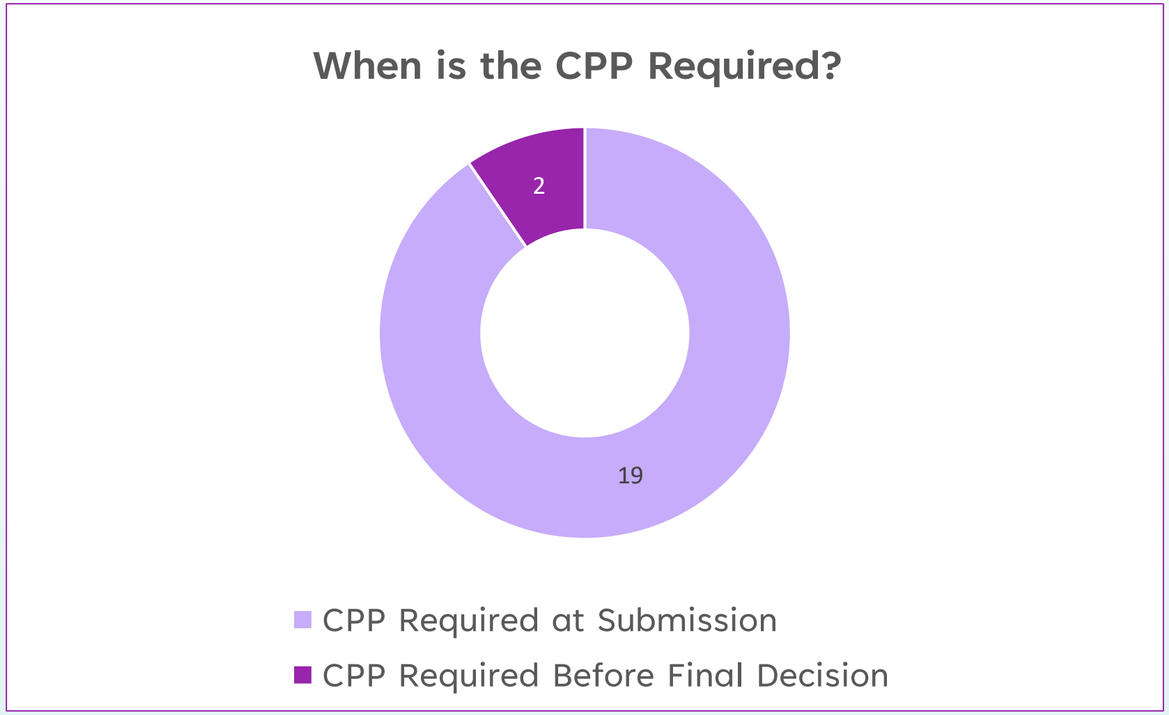
PAHO has noted that the use of reliance is an emerging trend as a strategy to bring efficiencies to regulatory systems and of interest for regulatory systems strengthening. We have seen that 21 LatAm FRP pathways rely on the prior decision of another agency (Page 5).

Of 22 pathways for which information was available, the majority (13) used a reliance pathway in which an abridged review of the dossier was used to facilitate the regulatory review. In these cases, the prior decisions informed the agency's decision. Four pathways can apply a verification approach, typically reserved for products that are identical in nature, indication and labelling.

FRPs that require the conduct of a full dossier review are typically associated with emergency use pathways, conditional approvals, or specific types of priority reviews (Chile, Colombia, Ecuador, Peru).

Latin American regulators have identified the opportunity to optimize their effectiveness and efficiency through the availability of reliance pathways. While the use of these pathways has not been implemented to its fullest potential, they offer the opportunity to accelerate patient access to innovative medicines.

How Can the Use of the CPP be Optimized?



Common Alternate Documents in Lieu of the CPP

Free Sale Certificate
Certificates of Bioequivalence
Certificates of Analysis
Notarized Health Registration Certificate
Certificate of Good Manufacturing Practices

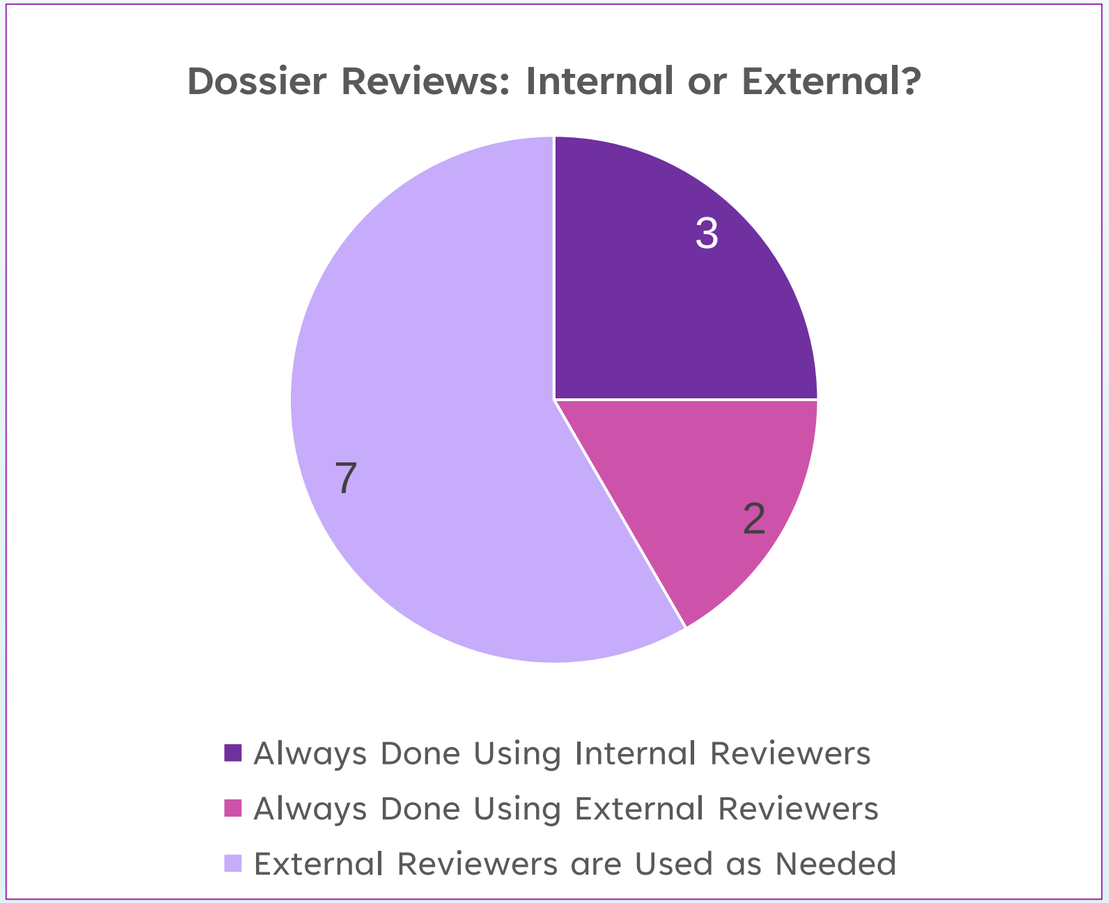
The rational use of the CPP promotes simplification and convergence of regulatory practices to enhance the globalization of the pharmaceutical market, regulatory environment, and product life cycle management. By relying on the previous thorough evaluation of the quality, safety, and efficacy of a product, regulators in maturing agencies can focus on added-value rather than duplicative assessment activities.

When the trade association SINDUSFARMA assessed the use of the CPP in Latin America in 2017, they observed that 22% (5/23) of agencies did not require approval in the Country of Origin (hence, the CPP) at the time of submission. The association recommended that harmonization of the rules and concepts on documents such as the CPP would make it simpler and faster to obtain a marketing authorization and decrease delays in the delivery of safe and effective medicines to patients. However, four years later, in 2021, we observed a similar divergence in the timing of the CPP, suggesting that there remains a significant opportunity to simplify and speed the way the CPP is used. To this end, moves towards the wider use of electronic CPPs, stimulated by the need for rapid authorizations during the COVID-19 pandemic, may play an important role in regulatory simplification in Latin America.

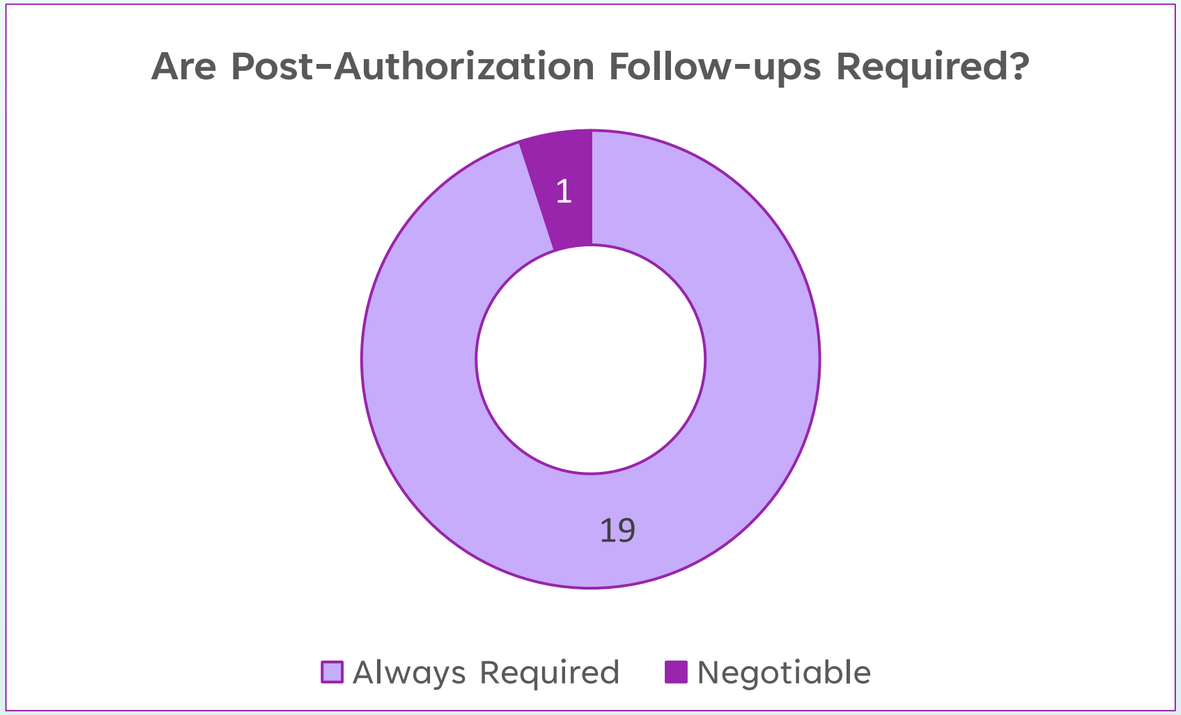
External Reviewers: a Double-Edged Sword

Even the most well-resourced and mature agencies can be faced with situations in which having independent input into the decision-making process from specialist advisors can add an additional level of expertise, vision and confidence to the agency's regulatory decision. External specialists can serve as reviewers or independent advisors to the dossier assessment process.

In our analysis of Latin American FRPs, where such details were presented, we observed a large degree of regulatory flexibility in the way that external resources are used to support the agency decision-making process. While two pathways (Chile) relied on external reviewers, seven other pathways (from Argentina, Colombia, Costa Rica, Mexico) used external reviewers on a flexible basis. Three pathways (from the CARICOM system and Dominican Republic) use internal staff reviewers only. Using external specialists can assist a resource-constrained agency in its timely assessments, while strengthening their internal expertise by learning from the experience of those advisors. However, if the specialists are not held to timelines or to standardized assessment practices, the process can be delayed, limiting the potential benefits of the use of external specialists.



Learning From Post-Authorization Experiences

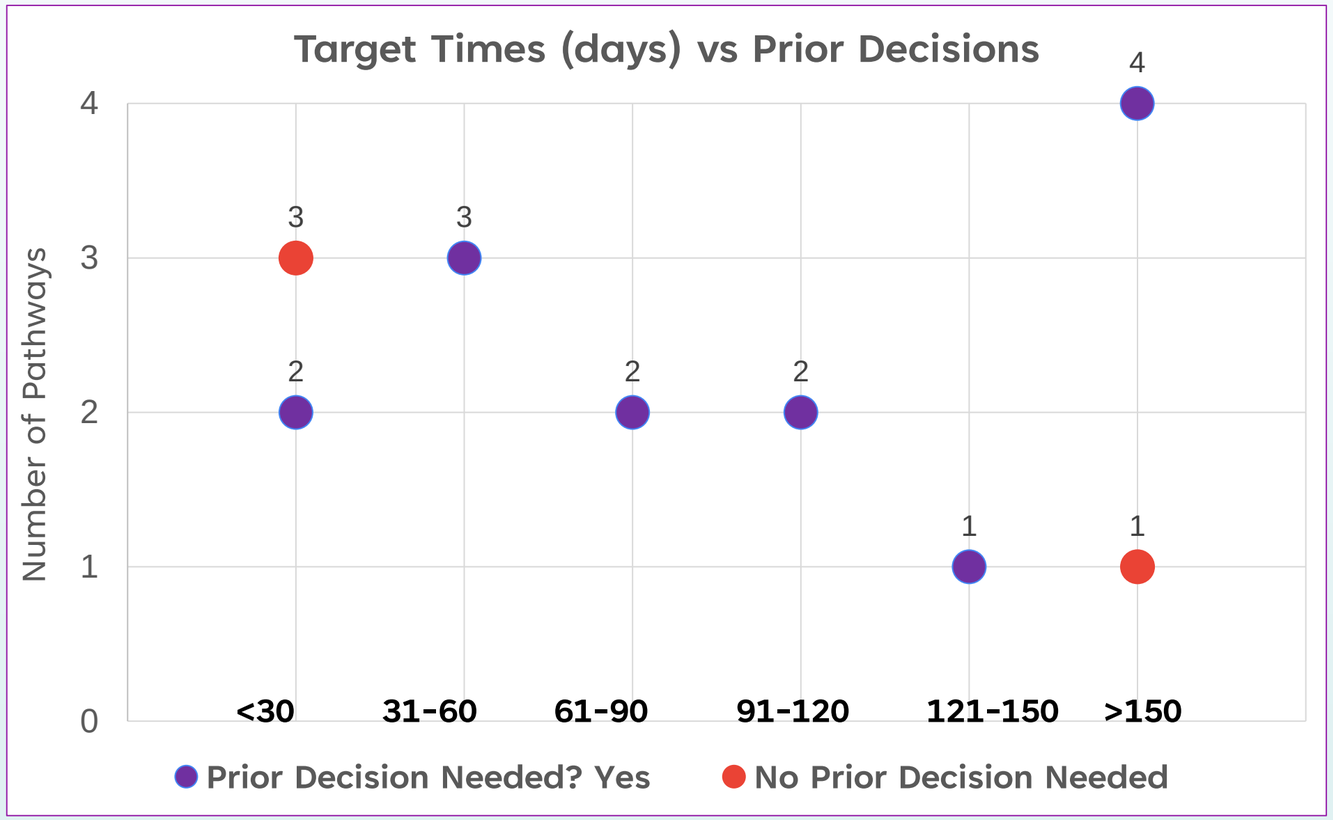


Facilitated Regulatory Pathways can improve regulatory efficiencies, at times shortening authorization timelines for important medicines. Often these accelerated pathways are applied to products used to address an unmet medical need (e.g. oncology, genetic diseases). These products may have previously benefitted from an FRP in a reference country (e.g. FDA Priority Review or Accelerated Approval or EMA Accelerated Assessment or Conditional Marketing Authorization), and in these cases the clinical experience with the product continues to develop.

Consequently, every FRP in Latin America for which a post-authorization process was described in our analysis requires some form of post-authorization follow-up. These vary by jurisdiction and could encompass enhanced safety surveillance, special studies in the local population or reporting of specific international safety experiences.

PAHO has noted that the sparse descriptions of which implementation strategies are used suggests that this is an area that needs further development. Because post-authorization safety monitoring is rapidly evolving, all NRAs in the region have much to gain from investing in these systems to ensure adequate monitoring of the safe use of authorized medicines, including those approved through an FRP.

Does the Use of Prior Decisions Shorten Target Assessment Times?



Publishing target times for both agency and company activities during the regulatory assessment process provides process predictability and transparency to all stakeholders. Meeting target assessment times is the goal of every regulatory agency, but in practice can be difficult to achieve.

We assessed the agency target times as published in the public domain for 18 FRPs in Latin America to determine the extent to which relying on a prior decision by a reference agency might be related to the stated agency target time.

Target times ranged from less than 30 days to greater than 150 days (5 FRPs from Argentina, Chile and Mexico). Most FRPs had agency target times of 90 days or less, which is a justifiable timespan for an accelerated or reliance review.

However, while two FRP pathways that required a prior decision had the shortest target times. three pathways that do not need the prior decision also have very short target times (<30 days). While the association of a short timeline and a prior decision is expected, this analysis suggests that rapid decisions can be made efficiently even in the absence of a prior decision.

Resources of Interest

Doerr P et al: Reliance: a smarter way of regulating medical products - The IPRP survey, Expert Review of Clinical Pharmacology, 2021;14:2, 173-177, https://www.tandfonline.com/doi/pdf/10.1080/17512433.2021.1865798?needAccess=true

Duran CE et al: Regulatory reliance to approve new medicinal products in Latin American and Caribbean countries. Rev Panam Salud Publica 2021:45:1-10. https://iris.paho.org/bitstream/handle/10665.2/53563/v45e102021.pdf?sequence=1&isAllowed=y

PAHO: Regulatory System Strengthening in the Americas. Lessons Learned from the National Regulatory Authorities of Regional Reference (2021). https://iris.paho.org/handle/10665.2/53793

Good reliance practices in regulatory decision-making: high-level principles and recommendations. (2020). https://www.who.int/medicines/areas/quality_safety/quality_assurance/QAS20_851_good_reliance_practices.pdf?ua=1

Wood A, Cuff P (eds): Regulating Medicines in a Globalized World: The Need for Increased Reliance Among Regulators (2020). https://www.nap.edu/catalog/25594/regulating-medicines-in-a-globalized-world-the-need-for-increased

Padua A et al: Registration pathways to accelerate regulatory assessment of innovative medicines in Latin America. Journal of Public Health Policy. 2020;41:481–495. https://pubmed.ncbi.nlm.nih.gov/32879437/

WHO: Good reliance practices in regulatory decision-making for medical products: high-level principles and considerations (draft). (2020). https://www.who.int/medicines/areas/quality_safety/quality_assurance/QAS20_851_Rev_1_Good_Reliance_Practices.pdf?ua=1

PAHO: Reliance for Emergency Use Authorization of Medicines and Other Health Technologies in a Pandemic (e.g. COVID-19) (2020). https://iris.paho.org/handle/10665.2/52027

Patel P et al: R&D Briefing 71: Trends in the Regulatory Landscape for the Approval of New Medicines in Latin America. Centre for Innovation in Regulatory Science. London, UK (2019). https://cirsci.org/wp-content/uploads/2020/02/CIRS-RD-Briefing-71-Trends-in-the-regulatory-landscape-Latin-America.pdf

Regulatory Reliance Principles: Concept note and recommendations. Ninth Conference of the Pan American Network for Drug Regulatory Harmonization (PANDRH) . San Salvador. October, 2018 (2019). https://iris.paho.org/bitstream/handle/10665.2/51549/PAHOHSS19003_eng.pdf?sequence=1&isAllowed=y

WHO: Proposal for revision of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce (April 2018). https://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/qas_certif_scheme_2011.pdf

SINDUSFARMA Working Group Regulatory Latam. Nº 1 | November / Novembro 2017. https://sindusfarma.org.br/**cadastro/public/uploads/legislacao/Boletim_DAR_Regulatory_Latam_05dez17.pdf?__cf_chl_jschl_tk__=pmd_c014117288d07c75e7965c44290250a9ca214884-1627475239-0-gqNtZGzNAnijcnBszQuO**