Review

Cooperation Agreements, Memorandums of Understanding, and Letters of Intent as Instruments to Facilitate the Implementation of Reliance in Latin America

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ABSTRACT

For more than a decade, the World Health Organization, Pan American Health Organization, Pan-American Network or Drug Regulatory Harmonization, and the International Conference of Drug Regulatory Authorities, have encouraged regulators to adopt reliance and recognition pathways to reduce duplication, improve efficiency and efficacy, and strengthen regulatory capabilities, in order to facilitate marketing authorization approval, thereby maintaining supply chain integrity. Several factors have limited the more widespread implementation of reliance pathways in Latin America, among which is having the appropriate legal tools in place between and among agencies. Key among these tools are the Memorandum of Understanding (MOU) and cooperation agreements. Herein we have reviewed the content and the characteristics of MOUs and cooperation agreements available on the official websites of the regulatory agencies of the region (we found 11 multilateral MOUs and 8 cooperation agreements published), signed by Latin American agencies and interregional organizations. In this commentary, common characteristics are identified and recommendations for further implementation are made to promote communication, information sharing, and trust, thereby supporting the broader use of reliance pathways in the region. (*Clin Ther.* 2022;44:1107–1128.)

Keywords: Agreement, Cooperation, Exchange, Recognition, Reliance.

INTRODUCTION

The Pan American Health Organization (PAHO) introduced the concept of reliance in 2016,[1] which was translated into Spanish as "*Utilización de Decisiones Regulatorias de Otras Jurisdicciones,*" endorsing it during the IX Conferencia Panamericana para la Armonización de la Reglamentación Farmacéutica. The primary goal of PAHO is that Latin American agencies adopt reliance and recognition pathways to reduce duplication, improve efficiency and efficacy, and strengthen regulatory capabilities, in order to facilitate marketing authorization approval, maintaining supply chain integrity. Reliance is not intended to limit an agency's sovereignty and decision-making for new product registrations and life cycle management.

In this same context, the PAHO report titled Strengthening the Regulatory System in the Americas, published in 2021,[2] mentioned that "Marketing authorization in Latin America is a complex area and one that poses certain challenges for regulators, now and in the future. National regulatory agencies (NRAs) tend to devote a significant share of staff resources to

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marketing authorization. However, growing markets will mean more associated life-cycle demands." To address this situation, PAHO, with the support of the Pan-American Network or Drug Regulatory Harmonization (PANDRH), focused on the implementation of reliance in several practical ways: prioritize regulatory life cycle management, implement procedures that enable use of reliance, search actively for improved efficiencies.

Reliance is defined as the act whereby the NRA in one jurisdiction may consider and give significant weight to (ie, totally or partially rely upon), evaluations performed by another NRA or trusted institution in reaching its own decision. The relying authority remains responsible and accountable for decisions taken, even when it relies on the decisions and information of others. It implies that the receiving authority uses this work according to its own scientific knowledge and regulatory procedures and retains its own regulatory responsibilities. Thus, NRAs that adopt regulatory reliance pathways leverage the work performed by other regulatory bodies to variable degrees.

The World Health Organization (WHO) promoted Good Reliance Practices in 2021,[3] with the main objective "of improving the effectiveness and efficiency of regulation of medical products. WHO noted that reliance allows NRAs to make the best use of resources, build expertise and capacity, increase the quality of their regulatory decisions, reduce duplication of effort and, ultimately, promote timely access to safe, effective and quality assured medical products,"[3] under the principle of respect of national and regional legal basis.

For WHO, "Reliance represents a 'smarter' form of regulatory oversight, based on constructive regional and international collaboration, that will facilitate and promote convergence and the use of common international standards and guidelines, resulting in more predictable, faster approval to improve access to quality-assured medical products for patients worldwide."[3]

Recently, in the context of the Covid-19 pandemic, the Community of Latin American and Caribbean States (CELAC) introduced the "Guidelines and Proposals for A Health Self-Sufficiency Plan for Latin America and the Caribbean." The first action proposal includes regulatory convergence and recognition, supported by regional mechanisms and subregional integration entities, such as the PANDRH and the Southern Common Market (MERCOSUR), and the Pacific Alliance, among others.[4]

Although there is an obvious interest in and recognition of the value of reliance pathways across Latin America, the main barrier for NRAs to implement reliance has been the limitations imposed by the legal framework of each country. Adjustment to these regulations might, therefore, be needed, which may be dependent on legislative changes, slowing the pace of implementing the regulatory changes. Recognizing this barrier, the WHO[3] explicitly addressed an approach to working within the context of national and regional laws: When regulations do not make explicit provision for the application of reliance, it may be adopted through interpretation of existing regulations, *if the legal framework does not explicitly preclude application of reliance approaches by the NRA*. Reliance can be implemented through policy change, as long as it is broadly consistent with national legislation. If the application of reliance is prohibited, revision of the legislation should be considered within a reasonable timeframe.[3] In this way, NRAs can evaluate the regulatory framework and seek the use of a reliance pathway, as long as there is nothing concrete that prohibits it.

Maintaining supply chain integrity has become a priority to guarantee the quality and tolerability of medicinal products. In this context, international regulatory cooperation is increasingly essential to ensure adequate supervision of complex supply chains, avoid duplication, and make the best use of limited resources, a goal for which reliance can play a role.[5]

As a result of these heterogeneous legal landscapes, Latin American countries have signed and maintained diplomatic and commercial instruments such as international free trade treaties, memorandums of understanding, and cooperation agreements,[6] with countries from other continents and interregional countries. In addition, they have integrated themselves into regional and subregional mechanisms to join forces by aiding in the mutual exchange of information, promoting cooperation and participation among the authorities involved. Their priorities include strengthening anticorruption, cross-border education and skills training, emergency preparedness, energy security, environmental protection, defense against pandemics, and infrastructure development, among others.

This approach is consistent with the recommendations from the International Conference of Drug Regulatory Authorities (ICDRA) held by the WHO in September 2021, in particular: "Plenary 4: Facilitated Registration of Medical Products Recommendations to Member States: Information exchange and data sharing are the bases for reliance-based regulatory activities and decision-making. Member states should seek to promote transparency and to conclude confidentiality agreements or equivalent to efficiently exchange actionable information, documents, and data on which regulation through reliance decisions can be informed. The development and implementation of information management systems (IMS), including the capacity to conduct virtual meetings, at the country, regional and continental level, aligned with international standards, is encouraged."[7]

We agree with recommendations from ICRDA, the WHO, and PAHO on the need to optimize the relationships between and among NRAs to facilitate information exchange, data sharing, and, ultimately, reliance through the implementation of legally binding agreements.

Therefore, following an assessment of the official websites of all of the regulatory agencies from Latin America, we conducted this review and analysis of key international legal instruments, found PDFs, including memorandums of understanding and cooperation agreements, signed between Latin American health authorities and authorities of other continents, as well as those in place between health authorities within the same region, along with the objectives, strategic plans, and treaties of three influential regional organizations (APEC, the Pacific Alliance, and MERCOSUR). We sought to identify the key characteristics to share information between agencies guaranteeing the confidentiality and offer recommendations that could serve as a basis for implementing the necessary steps in each country to introduce reliance pathways, thereby improving the availability of needed therapies in the region, allowing each country to respond quickly, safely, and efficiently to their specific regulatory needs.

INTERNATIONAL LEGAL TOOLS

Memorandum of Understanding Between National Regulatory Agencies

An MOU is a bilateral or multilateral agreement between agency-to-agency parties.[8] It expresses a convergence goal between the parties, indicating the intention to undertake a standard line of action. It is a slightly more formal alternative to a handshake agreement; they are voluntary and typically nonbinding. The intent of the parties, and position of the signatories, must be analyzed to decide whether an MOU is intended to be a legally binding document (eg, a treaty). An advantage of MOUs compared to other formal instruments is that, since obligations under international law can be avoided, many NRAs can implement MOUs without seeking approval from their central government.

We surveyed all regulatory websites of Latin American countries for MOUs between NRAs.

Table I provides the MOUs located on the official websites of the health authorities of countries in the region (National Health Surveillance Agency-Brazil ANVISA [Brazil], Federal Commission for Protection against Health Risks-México COFEPRIS [México], National Administration of Drugs, Food, and Medical Devices-Argentina ANMAT [Argentina], National Food and Drug Surveillance Institute-Colombia INVIMA [Colombia]; Public Health Institute-Chile ISP [Chile]) and from which we have the following observations.

Purposes: To (1) establish avenues of communication to facilitate the exchange of information relating to the regulation and conformity assessment of therapeutic products; (2) encourage the adoption of good regulatory practices, based on international regulatory convergence; and (3) encourage the development of collaborative activities between the participants.

Scopes: (1) The exchange of information about the regulation of therapeutic products by each participant, including policies, practices, standards, laboratory testing, premarket assessment, certificates, postmarket vigilance, market compliance, regulation of manufacturers, regulation of clinical trials and requirements for the regulation of therapeutic products; Good Manufacture and Practices; (2) information exchange mechanisms to evaluate health technologies with a focus on medicines and medical devices; and (3) exchanges of medicines, medical devices, foods regulations.

Title of the Signers: These are usually directors or legal representative of the NRA.

Confidentiality Clauses: The majority include confidentiality clauses, which is consistent with ICRDA recommendations to support reliance and recognition approaches to regulatory optimization.[7]

Table I. Memorandums of understanding signed between regulatory agencies (2012–2019).

Regulatory Agencies (Countries)	Purpose and Type of Products Involved	Scope	Signer	Valid Time Period	Include Confidential Agreement (Yes or No)
ANVISA-Brazil; BRICS (Brazil, Russia, India, China), 2019 (MOU between the BRICS health regulatory authorities; http://brics2019.itamaraty.gov.br/images/documentos/20191111_MoU_TIPAs_BRICS.pd; was accessed until Dec 2021)	To promote common solutions in the area of sanitary regulation; also to establish bases for a more structured dialogue and encourage the adoption of good regulatory practices, based on international regulatory convergence; **Type of products**: Product requires a sanitary authorization.	Fifth meeting of the BRICS health regulatory authorities, improving the transparency of the drug, vaccine and other health products markets universal coverage of vaccines and regulatory paths to favor trade in immunobiologics between countries; the local or global scarcity of health products and the necessary procedures for sanitary authorization for the use of products in these cases, through the rapid exchange of information or other alternatives	Brazil: Brazilian APEX Brazil's president; Russia: Ministry of Economic Development; China: Investment Promotion Agency of Ministry of Commerce of China; Trade Development Bureau of Ministry of Commerce of China; South Africa: Tisa's Head; INVETSA's Head; India: Invest India's Managing Director and CEO	Not defined	Yes

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Table I. (*continued*)

Regulatory Agencies (Countries)	Purpose and Type of Products Involved	Scope	Signer	Valid Time Period	Include Confidential Agreement (Yes or No)
ANVISA-Brazil; Swissmedic-Switzerland, 2012 (MOU concerning cooperation in the regulation of therapeutic products; https://www.swissmedic.ch/swissmedic/en/home/about-us/international-collaboration/bilateral-collaboration-with-partner-authorities/agreements-on-information-exchange.html)	To promote an understanding between the Participants of each other's regulatory framework, requirements and processes; to facilitate the exchange of information and documentation relating to the regulation and conformity assessment of therapeutic products; to encourage the development of collaborative activities between the participants; and to enhance the ability of the participants in the provision of their services relating to or in connection with public health, to meet the needs of their respective population; **Type of products:** all types of therapeutic products regulated by the participants and permit meaningful collaboration between them.	Establish avenues of communication to facilitate the exchange of information about the regulation and conformity assessment of therapeutic products by each participant, including: policies, practices, standards, laboratory testing, premarket assessment, postmarket vigilance, market compliance, regulation of manufacturers, regulation of clinical trials and requirements for the regulation of therapeutic products; and undertake collaborative activities, including, where practical, the exchange of personnel	Switzerland: Swissmedic's representative; Brazil: ANVISA's representative; The digital public version no declares the signers positions	Not defined	Yes

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Table I. (*continued*)

Regulatory Agencies (Countries)	Purpose and Type of Products Involved	Scope	Signer	Valid Time Period	Include Confidential Agreement (Yes or No)
COFEPRIS México; AEMPS-Spain, October 2016 (MOU for regulatory cooperation; https://www.aemps.gob.es/informa/notasinformativas/laaemps/2016/ni-aemps_13-2016-aemps-cofepris/?lang=en)	To establish avenues of communication to facilitate the exchange of information about the regulation of therapeutic products by each participant, including policies, practices, standards, laboratory testing, pre-market assessment, certificates, postmarket vigilance, market compliance, regulation of manufacturers, and requirements for the regulation of therapeutic products; to foster the efficiency in processes related to medicines, included marketing authorization and GMP for allopathic, organic synthesis, biological and biotechnological products and active substances; to develop cooperation activities fostering experiences exchange related to tolerability and vigilance; **Type of products:** raw materials and pharmaceutical products, biological, biotechnological products and medical devices	Regulation of therapeutic products by each participant, including policies, practices, standards, laboratory testing, premarket assessment, certificates, postmarket vigilance, market compliance, regulation of manufacturers, and requirements for the regulation of therapeutic products; processes related to medicines, included marketing authorization and GMP for allopathic, organic synthesis, biological and biotechnological products and active substances; tolerability and vigilance	México: COFEPRIS' director; Spain: AEMPS' director	Not defined	It was not possible to confirm it

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Table I. (*continued*)

Regulatory Agencies (Countries)	Purpose and Type of Products Involved	Scope	Signer	Valid Time Period	Include Confidential Agreement (Yes or No)
COFEPRIS Mexico; ISP-Chile, September 2012 (MOU; https://www.ispch.cl/wp-content/uploads/2021/05/Convenio-Cofepris.pdf)	To promote the information and documentation exchange and collaboration; **Type of products**: medicine	To establish avenues of communication to facilitate the exchange of information about the regulation of therapeutic products by each participant, including policies, practices, standards, laboratory testing, premarket assessment, certificates, postmarket vigilance, market compliance, regulation of manufacturers, regulation of clinical trials and requirements for the regulation of therapeutic products; GMP	Mexico: COFEPRIS's legal representative; Chile: ISP's legal representative	Mutual decision or for initiative of one of them	Yes
INVIMA Colombia; AEPMS Spain, 2014 (MOU for regulatory cooperation https://www.invima.gov.co/documents/20143/347733/K-±MEMORANDO±DE±ENTENDIMIENTO±AEMPS±-±INVIMA.pdf/a23e214b-30ed-ca9f-9282-3db824717094; accessed until December 2021)	To promote an understanding between the participants of each other's regulatory framework, requirements and processes and reinforce the collaboration; to exchange of experts in evaluation of biological, biotechnological products, vaccines, and rare diseases products **Type of products**: all products regulated by both participants	To establish avenues of communication to facilitate the exchange of information about the regulation of therapeutic products by each participant, including policies, practices, standards, laboratory testing, premarket assessment, certificates, postmarket vigilance, market compliance, regulation of manufacturers, regulation of clinical trials and requirements for the regulation of therapeutic products; GMP	Colombia: INVIMA's director; Spain: AEMPS's director	Under mutual agreement	Yes

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Table I. (*continued*)

Regulatory Agencies (Countries)	Purpose and Type of Products Involved	Scope	Signer	Valid Time Period	Include Confidential Agreement (Yes or No)
INVIMA Colombia; ISP Chile, September 2013 (MOU https://www.invima.gov.co/documents/20143/347733/G_MEMORANDO±DE±ENTENDIMIENTO±INVIMA-ISP.PDF/a0944281-a79e-0106-4e37-e325b9713c0f accessed until December 2021)	To promote an understanding between the participants of each other's regulatory framework, requirements and processes and reinforce the collaboration and improve participants' capacities on public health **Type of products:** medicines, medical devices	The exchange of information about the regulation of therapeutic products by each participant, including policies, practices, standards, laboratory testing, premarket assessment, certificates, post-market vigilance, market compliance, regulation of manufacturers, regulation of clinical trials and requirements for the regulation of therapeutic products	Colombia: Invima's director; Chile: ISP's director	When one of participants decide to finish it or for mutual agree	Yes
INVIMA Colombia; DIGEMID-Perú, October 2015 (MOU; https://www.cancilleria.gov.co/sites/default/files/Normograma/docs/memorando_ms_invima_digemid.htm; accessed until December 2021)	To promote an understanding between the participants of each other's regulatory framework, requirements and processes; to facilitate the exchange of information and documentation relating to the regulation and conformity assessment of therapeutic products; biologics, medical devices, cosmetics; to encourage the development of collaborative activities between the participants **Type of products:** medical products and biologics	To establish avenues of communication to facilitate the exchange of information about the regulation of therapeutic products by each participant, certificates, postmarket vigilance, market compliance, regulation of manufacturers, GMP	Colombia: INVIMA's general director, Ministry of Health; Perú: DIGEMID's director, Ministry of Health	3 y and is automatically renewed	Yes

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Table I. (*continued*)

Regulatory Agencies (Countries)	Purpose and Type of Products Involved	Scope	Signer	Valid Time Period	Include Confidential Agreement (Yes or No)
INVIMA Colombia; ARCSA Ecuador, August 2015 (MOU https://www.invima.gov.co/documents/20143/347733/D-±MEMORANDO±DE±ENTENDIMIENTO±ARCSA±E±INVIMA.pdf/1077d9f3-96eb-d185-2122-7d34b02fbd7c accessed until December 2021)	To promote an understanding between the participants of each other's regulatory framework, requirements and processes and reinforce the collaboration **Type of products**: all products regulated by both participants	To establish avenues of communication to facilitate the exchange of information about the regulation of therapeutic products by each participant, including policies, practices, standards, laboratory testing, premarket assessment, certificates, postmarket vigilance, market compliance, regulation of manufacturers, regulation of clinical trials and requirements for the regulation of therapeutic products; GMP	Colombia: INVIMA's director; Ecuador: ARCSA's director	May be terminated at any time, by either; participant preferably by notice with 90 days in advance	Yes
INVIMA Colombia; DNM El Salvador, February 2016 (MOU https://www.invima.gov.co/documents/20143/347733/B_MEMORANDO±DE±ENTENDIMIENTO±ENTRE±DNM±E±INVIMA.pdf/93e043c3-81f7-7620-1d02-1aa5bca686c3 accessed until December 2021)	To ensure supply of products and collaboration between both countries **Type of products**: medicine, medical devices	The exchange of information about the regulation of therapeutic products by each participant, including policies, practices, standards, laboratory testing, premarket assessment, certificates, postmarket vigilance, market compliance, regulation of manufacturers, regulation of clinical trials and requirements for the regulation of therapeutic products; GMP	Colombia: INVIMA's director; El Salvador: DNM's legal representative	5 y (2016–2021); there is no evidence of its renewal	Yes

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Table I. (*continued*)

Regulatory Agencies (Countries)	Purpose and Type of Products Involved	Scope	Signer	Valid Time Period	Include Confidential Agreement (Yes or No)
INVIMA Colombia; ANMAT Argentina, February 2014 (MOU; https://www.invima.gov.co/documents/20143/347733/I-MEMORANDO+DE+ENTENDIMIENTO+ANMAT-INVIMA.pdf/c2eb0c73-e318-f18d-94c8-3506a75c22a3)	To promote information exchange to reinforce the NRA re-certification by WHO; to promote collaboration activities **Type of products**: all products regulated by both participants	Information exchange regard mechanisms to evaluate sanitary technologies focus on medicines and medical devices; exchanges of medicines, medical devices, foods regulations; any other cooperation way agreed between parts	Colombia: INVIMA's director; Argentina: ANMAT's national administrator	May be terminated at any time, by either participant	Yes
ISP Chile; AEMPS Spain, October 2018 (MOU; https://www.ispch.cl/wp-content/uploads/2021/05/CONVENIO-AEMPS.pdf)	To promote the information and documentation exchange and collaboration **Type of products**: products registered and submitted	The exchange of information about the regulation of therapeutic products by each participant, including policies, practices, standards, laboratory testing, premarket assessment, certificates, postmarket vigilance, market compliance, regulation of manufacturers, regulation of clinical trials and requirements for the regulation of therapeutic products	Chile: ISP's director; Spain: AEMPS' director	3 y (it is not clear whether was renewal)	Yes

For example, COFEPRIS established several pathways through the use of MOUs, including Article 170, its Equivalence Agreement, and the Recognition of Marketing Authorizations From Reference Authorities. These codified relationships with the Swiss Agency for Therapeutic Products (Swissmedic), European Commission, US Food and Drug Administration (FDA), Health Canada, Australian Therapeutic Goods Administration, and PAHO/WHO Reference Regulatory Agencies; prequalified by the WHO Prequalification Program for Medicines and Vaccines, and NRA members of the Pharmaceutical Inspection Cooperation Scheme.[9]

ANMAT has several signed MOUs, which are listed on its official website. However, given that the documents are not available for public review, their content is not listed in Table I.[10]

Cooperation Agreements Between Regulatory Agencies

This international tool is generally a legally binding agreement among two or more autonomous bodies or communities to collaborate on matters of their competence.[11] There is a general tendency to apply the term *agreement* to restricted bilateral or multilateral treaties. Cooperation agreements are instruments of technical or administrative nature signed by representatives of government departments, but which do not require ministerial-level confirmation. The most common agreements deal with economic, cultural, scientific, and technical cooperation issues. Especially in international economic law, the term *agreement* is also used as a title for broad multilateral agreements (for example, commodity agreements).[12] Every agreement has two fundamental elements: mutuality and commitment.

We surveyed all regulatory websites of Latin American countries for Cooperation Agreements Between NRAs. Table II provides the Cooperation Agreements found.

We assessed crucial characteristics, such as the document purpose, scope, types of products involved, the signatories' position, whether it includes a confidentiality clause, and the duration (time period) of the validity of the document. We observed the following key characteristics.

Purposes: To (1) share certain specific scientific and technical information and documents (collectively "information") related to ensuring the tolerability, efficacy and quality of medical/medicinal products for human and veterinary use, authorized or under review, with regard to medical/medicinal products; (2) facilitate the exchange of information and documentation relating to the regulation and conformity assessment of therapeutic products; and (3) encourage the development of collaborative activities between the participants.

Scopes: (1) Activities related to the regulation of medical/medicinal products for tolerability, efficacy and quality, such as licensing and approvals, authorization of clinical trials, audits of manufacturers and conformity assessment bodies; and (2) information contained in marketing authorization application and applications to vary a marketing authorization.

Title of the Signers: These documents must be signed by persons with the appropriate authority, typically Directors or a legal representative of the regulatory agencies.

Confidentiality Clauses: The majority include confidentiality clauses.

In 2021, ANVISA and the European Medicines Agency (EMA) signed a cooperation agreement with the purpose of sharing certain specific scientific and technical information and documents regarding activities related to the regulation of medical/medicinal products for tolerability, efficacy, and quality, such as licensing and approvals, authorization of clinical trials, audits of manufacturers and conformity assessment bodies, product labelling, and the development of policies and guidance, activities related to compliance monitoring, such as the collection, monitoring, and analysis of adverse reactions or incident data, as well as benefit–risk assessments, and policy development to regulate.[13] In March 2022, ANVISA and the US FDA signed a Declaration of Cooperation to maintain and strengthen their collaboration mechanisms. This supersedes the previous declaration to continue cooperation in the areas of health regulation, maintaining the exchange of technical information and exploring new opportunities for partnerships.

In the cases of both the MOUs and cooperation agreements, their goal is to establish avenues of communication to facilitate the exchange of information, including conformity assessment of therapeutic products; they also make it clear that the shared information must be protected while respecting confidentiality, and seek to improve the efficiency of processes and capabilities, activities that all align with the purpose of reliance.

Table II. Cooperation agreements signed between regulatory agencies (2012–2021).

Regulatory Agencies (Countries)	Purpose and Type of Products Involved	Scope	Signer	Expiration Date	Include Confidential Agreement (Yes or No)
ANVISA (BZ)-EMA (EU), 2021 (working arrangement between DG SANTE/EMA and ANVISA for the exchange of nonpublic information on medical/medicinal products; https://www.ema.europa.eu/en/documents/other/working-arrangement-between-ema-directorate-general-health-food-tolerability-dg-sante-brazilian-health/medicinal-products_en.pdf)	To share certain specific scientific and technical information and documents (collectively "information") related to ensuring the tolerability, efficacy and quality of medical/medicinal products for human and veterinary use, authorized or under review both in Brazil and in the Union, exclusively for use in the performance of their respective duties with regard to medical/medicinal products, as well as for the protection of public health. **Type of products:** medicines for human use, including vaccines and pharmaceutical ingredients, and medical devices; include veterinary only for EMA	Activities related to the regulation of medical/medicinal products for tolerability, efficacy and quality, such as licensing, and approvals, authorization of clinical trials, audits of manufacturers and conformity assessment bodies, product labelling, and the Development of policies and guidance; activities related to compliance monitoring such as the collection, monitoring and analysis of adverse reactions or incident data as well as benefit–risk assessments, and policy development to regulate marketed medical/medicinal products, and compliance and enforcement activities with regard to medical/medicinal products, such as inspections, compliance verification, recalls, investigations and enforcement measures and risk assessment	Europe: EC's director-general; EMA's executive director; Brazil: ANVISA's director-president	It is not defined a specific timeline	Yes

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Table II. (*continued*)

Regulatory Agencies (Countries)	Purpose and Type of Products Involved	Scope	Signer	Expiration Date	Include Confidential Agreement (Yes or No)
ANVISA-Brazil- Denmark,* 2020 (project: Strategic Sector Cooperation 2020–2023; https://um.dk/~/media/um/danida-en/ssc%20brazil%20health%20phase%20ii.pdf?la=en)	The joint objective is to inspire improved regulation and agile case handling, supporting (eg, revision of administrative procedures, guidelines, policies and cross-disciplinary thinking; the main objective of the SSC Phase 2 is to support ANVISA in the implementation of the new strategic plan running from 2020–2023 with a special focus on improved and more agile case handling **Type of products**: a Diagnostic Related Groups (DRG) System and Digital Transformation Regulation of pharmaceuticals (biologics, vaccines, and biosimilars included) and medical devices	ANVISA has limited capacity to respond to an increased demand for pharmaceuticals. This has given rise to a substantial backlog on handling applications for authorization of pharmaceuticals, posing long waiting times for approval of medicines and hence barriers for better and faster access to new and innovative pharmaceuticals for the population. PILLAR II is a continued cooperation between the Brazilian Health Surveillance Agency (ANVISA) and the Danish Medicines Agency (DKMA) aiming at supporting more efficient, faster and transparent approval processes of pharmaceuticals and Brazil's something new—medical devices.	Brazil: Ministry of Health; Denmark: Ministry of Health	2023	

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Table II. (*continued*)

Regulatory Agencies (Countries)	Purpose and Type of Products Involved	Scope	Signer	Expiration Date	Include Confidential Agreement (Yes or No)
ANVISA-Brazil; Agence Nationale de sécurité du médicament et des produits de santé de la République Francaise, December 2019 (agreement for collaboration on information exchange between The Agéncia Nacional de Vigiláncia Sanitária of Republica Federativa do Brasil and The Angence Nationale de sécurité du médicamnt et des produits de santé de la Républiqie Francaise; https://www.gov.br/anvisa/pt-br/acessoainformacao/institucional/relacoes-internacionais/cooperacao/arquivos/Acordo%20de%20Colaboracao%20entre%20Anvisa%20e%20ANSM)	To establish a framework for the exchange of information between the sides. **Type of products**: medicine, including raw materials for pharmaceutical use, biological products (blood, tissues and cells) medical devices and cosmetics products.	To exchange of information about the regulation of therapeutic products by each side, including policies, practices, standards, laboratory testing, pre-market assessment, post-market vigilance, market compliance, regulation of manufacturer, regulation of clinical trials and requirements for the regulation of therapeutic products.	It is not defined the signers' job position.	It is not defined. It may be terminated by each side upon 2 months' notice	Yes

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Table II. (*continued*)

Regulatory Agencies (Countries)	Purpose and Type of Products Involved	Scope	Signer	Expiration Date	Include Confidential Agreement (Yes or No)
ANVISA Brazil-Health Sciences Authority of Singapore (HAS), 2016 (exchange of information and specific knowledge; https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2016/anvisa-firma-parceria-regulatoria-com-agencia-de-cingapura)	To exchange information and knowledge **Type of products:** regulatory activities in the areas of medicines and health products	Post-authorization data of pharmacovigilance data held by one participant witch raises tolerability concerns about a product manufactured or distributed in the territory of the other country. Info Quality defect or product recalls in relation medical products o medical devices; info contained in marketing authorization application and applications to vary a marketing authorization; info contained in reports on inspections done by one of participant.	Brazil: ANVISA's director-president; Singapore: HSA's executive director	It is not defined	Yes

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Table II. (*continued*)

Regulatory Agencies (Countries)	Purpose and Type of Products Involved	Scope	Signer	Expiration Date	Include Confidential Agreement (Yes or No)
ANVISA Brazil-Swissmedic, 2012 (Memorandum of Understanding concerning cooperation in the regulation of therapeutic products; https://www.swissmedic.ch/swissmedic/en/home/about-us/international-collaboration/bilateral-collaboration-with-partner-authorities/agreements-on-information-exchange.html)	To promote an understanding between the participants of each other's regulatory framework, requirements and processes; to facilitate the exchange of information and documentation relating to the regulation and conformity assessment of therapeutic products; to encourage the development of collaborative activities between the Participants; and to enhance the ability of the Participants in the provision of their services relating to or in connection with public health, to meet the needs of their respective population **Type of products:** all types of therapeutic products regulated by the participants and permit meaningful collaboration between them	To establish avenues of communication to facilitate the exchange of information about the regulation and conformity assessment of therapeutic products by each participant, including: policies, practices, standards, laboratory testing, premarket assessment, postmarket vigilance, market compliance, regulation of manufacturers, regulation of clinical trials and requirements for the regulation of therapeutic products; and undertake collaborative activities, including, where practical, the exchange of personnel	Brazil: ANVISA's director; Switzerland: representative of the Swiss Agency for Therapeutic Products (Swissmedic)	It is not defined	Yes

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Table II. (*continued*)

Regulatory Agencies (Countries)	Purpose and Type of Products Involved	Scope	Signer	Expiration Date	Include Confidential Agreement (Yes or No)
ANVISA Brazil; US FDA, December 2021 (declaration of cooperation between the US FDA and the National Health Surveillance Agency of Brazil in relation to cooperation to expand activities of mutual interest; https://www.fda.gov/international-programs/cooperative-arrangements/fda-brazil-statement-cooperation-enhance-activities-mutual-interest)	This Statement of Cooperation (SOC) is intended to strengthen existing structures and develop new opportunities for cooperative engagement in regulatory and scientific matters and public health protection that are related to the products the participants regulate **Type of products:** all products regulated by both participants, as well as efforts and activities under their mandate	This work is intended to facilitate the effective exchange of information, develop new or strengthen existing cooperative efforts/initiatives, and coordinate, when appropriate, with stakeholder groups relevant to product regulation within their respective countries	Brazil: ANVISA's director; US: FDA's associate commissioner; Office of Global Policy and Strategy	5 years	Yes

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Table II. (*continued*)

Regulatory Agencies (Countries)	Purpose and Type of Products Involved	Scope	Signer	Expiration Date	Include Confidential Agreement (Yes or No)
COFEPRIS-Mexico-Swissmedic, European Commission, US FDA, Health Canada, Medicines Australia, Reference Agencies PAHO/WHO; prequalification vaccine WHO program regulatory agencies member of pharmaceutical inspection cooperation, January 28, 2020 (recognition agreement of the registration requirements as equivalents; https://www.dof.gob.mx/nota_detalle.php?codigo=5585043&fecha=28/01/2020)	To reduce timeline of approval and guarantee the supply of therapies **Type of products**: medicines and medical devices.	Marketing authorization; renewal of marketing authorization; postapproval change	N/A, it is a local regulation	It is not defined; it is a regulation	N/A; it is a local regulation

(*continued on next page*)

Table II. (*continued*)

Regulatory Agencies (Countries)	Purpose and Type of Products Involved	Scope	Signer	Expiration Date	Include Confidential Agreement (Yes or No)
ISP Chile-INVIMA Colombia-COFEPRIS-México_DIGEMID-Perú (APEC-July 2013; cooperation agreement https://www.invima.gov.co/documents/20143/347733/H-ACUERDO±INTERINSTITUCIONAL±DE±COOP±AP.pdf/59f9a349-14bb-22d2-8c34-e49b63eea296 accessed until December 2021)	To stablish bases to facilitate the Marketing authorization of small molecules and GMP between countries members **Type of products**: small molecules and GMP	The exchange of information about the regulation of therapeutic products by each participant, including policies, practices, standards, laboratory testing, pre-market assessment, certificates, postmarket vigilance, market compliance, regulation of manufacturers, regulation of clinical trials and requirements for the regulation of therapeutic products; GMP	Chile: Ministers of Health; Perú: Minister of Health; Colombia: Invima's Head; México-Cofepris' Head	Unlimited	Yes
ANMAT Argentina- ISP Chile, October 2018 (cooperation agreement; https://www.ispch.cl/wp-content/uploads/2021/05/Resoluci%C3%B3n-convenio-ANMAT-Firmado-2018.pdf)	To reinforce the cooperation relationship to facilitate the exchange of information about the regulation of therapeutic products by each Participant and mutual understanding, creating specific technical cooperation projects **Type of products:** all products regulated by both participants, as well as efforts and activities under their mandate	The regulation of therapeutic products by each participant, including policies, practices, standards, laboratory testing, premarket assessment, certificates, postmarket vigilance, market compliance, regulation of clinical studies, and requirements for the regulation of therapeutic products	ANMAT-National Administrator; ISP-Director	3 years; automatic renewal	Yes

*ANVISA-Denmark collaboration project PILLAR II Benefits: ANVISA will further strengthen their regulatory capacity and deepen the knowledge of relevant Danish/European regulation and procedures. PILLAR II will focus on supporting training and introducing suggestions of optimized processes related to complex regulatory areas, in order for ANVISA to further strengthen the handling of pharmaceuticals and medical devices. For instance, each catalog could consist of a suggestion to provide for a change to:• an existing procedure/ implementation of a new procedure;• new or altered legislation/guideline/approach;• altered cross-disciplinary approaches; or• education of staff; or• other initiatives that may support a positive change that strives for optimization

INTERREGIONAL INTEGRATION ORGANIZATIONS

Three interregional integration organizations that connect the Latin American region, among each other and third parties outside regional borders, are the Pacific Alliance, the Asia-Pacific Economic Cooperation (APEC), and MERCOSUR.

Pacific Alliance

The Pacific Alliance is an initiative of regional integration comprising Chile, Colombia, Mexico, and Peru, officially established in 2011. One of its objectives is to build in a participatory and consensual way and area of deep integration to move progressively toward the free mobility of goods, services, resources, and people.[14] A working group focused on cooperation was formally established through the MOU on the Pacific Cooperation Platform, signed by the Foreign Ministers of the four countries. The goal of this working group is to promote cooperation among the member countries and with third parties, in the areas of environment and climate change; innovation, science, and technology; social development; as well as others that the countries establish by common agreement. It is within the context of this MOU that there exists the possibility of developing a conversation around the shared use of regulatory reliance among these countries.

Asia-Pacific Economic Cooperation

APEC is the main forum to promote economic growth, technical and financial cooperation, trade facilitation and liberalization, and investment across the Asia-Pacific region. APEC is made up of 21 economies, of which 3 are Latin American (italics):

Australia, Brunei Darussalam, Canada, *Chile,* China, Hong Kong, Indonesia, Japan, Korea, Malaysia, *Mexico,* New Zealand, Papua New Guinea, *Peru,* Philippines, Russia, Singapore, Taipei-China, Thailand, United States, and Vietnam.

Ones of its objective is encouraging and facilitating collaboration between health and other sectors and other APEC fora and international health bodies. Although APEC is not a treaty or binding agreement, the decisions made within APEC are by consensus and commitments assumed voluntarily, as its mission establishes that "Our initiatives turn policy goals into concrete results and agreements into tangible benefits."[15] Furthermore, the Strategic Plan 2016–2020[16] aligns with the Healthy Asia Pacific 2020 initiative, including the associated roadmap, which aims to promote people's health and well-being throughout the whole life-course by using a collaborative approach to promote health security, growth, and development in the Asia-Pacific region consistent with the WHO Sustainable Development Goals. Through the initiatives of the Health Working Group, the Life Sciences Innovation Forum (LSIF), and the Regulatory Harmonization Steering Committee, APEC has sought to train NRAs on the topic of reliance to best understand the role that reliance can play among these economies.

Southern Common Market

The founding member states of MERCOSUR and co-signers to the Asunción Treaty are Argentina, Brazil, Paraguay, and Uruguay. Other associate states are Bolivia, Chile, Colombia, Ecuador, Guyana, Peru, Suriname. Its main objective is creating a common market coordinated by macroeconomic and sectoral policies between state parties. These encompass support for foreign trade, agriculture, industry, fiscal, monetary, exchange and capital, services, customs, transport, and communications; ensure adequate conditions of competition between state-parties, as well as their commitment to harmonize their legislation to achieve the strengthening of the integration process.[17]

In 1995, the European Union and its member states signed a multilateral cooperation agreement on one side, and MERCOSUR and its member states, on the other, which was ratified and updated during 2019. The scope of this agreement "covers trade and economic matters, cooperation regarding integration and other fields of mutual interest in order to bring about closer relations between the parties and their respective institutions."[18] Although the treaty signed between MERCOSUR and the European Union focuses more on the trade of certain items, it clarifies that it includes all sectors, with access to drugs being a sensitive factor and a priority for its member states.

With these structures in place, APEC, the Pacific Alliance, and MERCOSUR have mechanisms that seek cooperation between their countries to ease processes by reducing bureaucracy facilitating the introduction of novel aligned approaches. It is within this framework that reliance could find a home.

DISCUSSION AND RECOMMENDATIONS

The results of our review of the content of MOUs and cooperation agreements available and listed in the

Tables I and II show that through these instruments NRAs can establish communication channels to enable cooperation between the co-signing organizations, because the scope and purpose of these agreements involve sharing of technical and scientific information between the parties, especially as it relates to regulation and conformity assessment of therapeutic products. Furthermore, these approaches define the confidentiality framework, as recently recommended by the ICDRA participating authorities,[7] and this recommendation made during the Extraordinary (Virtual) ICDRA allows inferring that these instruments have not been used to implement reliance.

While we observed important differences across jurisdictions in the content and scope of these documents, there also were important consistencies in their approaches. We therefore recommend that best practices for the design and implementation of MOUs and cooperation agreements be developed, which would include templates for each document that could be readily adopted by an agency. PAHO or PANDRH could promote such an initiative. Similarly, the three Latin American countries that are members of APEC (Mexico, Chile, Peru) together with the MERCOSUR members could rely on exchanging guidelines established in both organizations to further their understanding of each other's process, an important step in building trust among Latin American NRAs. Trust is the basis upon which reliance is built. Furthermore, information sharing with the US FDA through APEC can only strengthen this learning experience.

Of importance is that the directors and/or legal representatives of the NRAs establish either MOUs or cooperation agreements. Because both share some characteristics (eg, confidentiality clauses), an agency can opt for the most expeditious process, thereby facilitating communication and information sharing. They could be considered a prompt and effective way to implement reliance mechanisms, applying the principles of the WHO Good Reliance Practices.[3]

While our focus has been on reliance pathways, several agencies in Latin America have implemented recognition pathways (defined as the routine acceptance by the NRA in one jurisdiction of the regulatory decision of another NRA or other trusted institution). It may be the subject of a mutual recognition agreement. *Recognition* implies the acceptance of regulatory result/decision from another NRA based on a legal framework and can be mutual or unilateral.[3] In this sense, the implementation of cooperation agreements as the legal basis for the signatory countries could open a path for the country that wishes to apply either reliance or recognition as a mechanism of convergence and regulatory streamlining.

For the above reasons, we recommend that Latin American health agencies consider evaluating their involvement in MOUs and cooperation agreements to promote the path of regulatory convergence through the implementation of reliance and recognition mechanisms, especially as these apply to products for treating unmet medical needs, life-threatening conditions, and rare diseases. Moreover, establishing these agreements provides opportunities for (1) optimizing access to groundbreaking treatments, advanced therapies, pioneering methods of innovation, scientific development, and research and (2) guaranteeing the availability of new treatments and supply continuity.

We believe that the observations presented in this review provide regulators and the industry with views on key documents that underpin reliance processes and that we have provided a pathway for what is needed to help optimize the timely availability of important medicinal products. We encourage regulatory agencies to publish their formal MOUs and cooperation agreements and information related to their use, as a best regulatory practice to share with agency staff, the industry, trade associations, and other agencies.

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AUTHOR CONTRIBUTIONS

All of the authors designed the study, analyzed the data, and wrote the manuscript. The study was conceived of, executed, and written during the course of the authors' daily jobs.

CONFLICTS OF INTEREST

Heraclio Rodríguez and María Lucia De Lucia are Sanofi employees and may hold shares and/or stock options in the company. Sanofi was not involved in the design of the study; in the collection, analysis, or interpretation of the data; in writing the manuscript; or in the decision to submit the manuscript for publication. All of the authors hold positions within the pharmaceutical industry or academia, but they have not received any grant, honoraria, or other

compensation to author the manuscript. The views expressed in this research paper are the independent views of the authors and should not be understood or quoted as being made on behalf of or reflecting the position of their respective companies or any other affiliation. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

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