



REGULATORY SYSTEM STRENGTHENING IN THE AMERICAS

LESSONS LEARNED FROM THE NATIONAL
REGULATORY AUTHORITIES OF REGIONAL
REFERENCE

PAHO



Pan American
Health
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World Health
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REGIONAL OFFICE FOR THE
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Washington, D.C., 2022

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ISBN: 978-92-75-12520-5 (PDF)

ISBN: 978-92-75-12521-2 (Print)

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Suggested citation. Regulatory System Strengthening in the Americas. Lessons Learned from the National Regulatory Authorities of Regional Reference. Washington, D.C.: Pan American Health Organization; 2021. License: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at <http://iris.paho.org>.

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Corrigendum: citation number positions have been corrected on page 72, section 7.1, second paragraph.

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FOREWORD

We will only realize the twin goals of universal access to health and universal health coverage if we ensure access to safe, effective, and quality-assured medicines. Thus, as part of their national health systems, all countries in the Region of the Americas should strive for an effective and efficient regulatory system to regulate and oversee compliance with the highest quality standards for all medical products made available to their populations.

The Member States of the Pan American Health Organization (PAHO) have been at the forefront of regulatory systems strengthening. In 2010, they adopted Resolution CD50.R9, Strengthening National Regulatory Authorities for Medicines and Biologicals. This groundbreaking resolution, a first of its kind for the World Health Organization and its regions, called on Member States to strengthen their regulatory systems and create a regional approach for supporting countries to develop their capacities. It formally established regulatory systems as a public health priority. Moreover, it highlighted the need to build regulatory capacities to ensure that medicines and other health technologies are accessible, affordable, and compliant with internationally recognized standards of quality, safety, and efficacy. The resolution was predicated on benchmarking national regulatory capacities using a standardized tool. In the past decade, more than 75% of Member States have assessed their regulatory systems using standardized evaluation tools to help identify strengths, gaps, and opportunities for improvement. As a result, PAHO has recognized eight national regulatory authorities as regional reference authorities, a designation that attests to their functionality and ability in terms of regulatory and oversight capacities. Together, these eight national regulatory authorities of reference cover 82% of the population of the Americas.

It is now time to take stock of the progress made and examine the remaining priorities. This report represents a collaborative effort between the leading regulatory authorities of the Americas and PAHO. It highlights the significant progress the Region has made in strengthening regulatory systems in the past decade. In addition, it indicates opportunities for improvement and, importantly, for collaboration and cooperation among stakeholders and across countries to accelerate progress. This publication aims to provide a comprehensive overview that will stimulate fresh debate and promote new analyses, with the ultimate goal of helping to strengthen the regulatory authorities for medicines and other pharmaceutical products in the Americas.

While we were preparing the report, the COVID-19 pandemic was ravaging our Region and the globe. In this pandemic, the role of regulatory authorities as independent and science-based institutions has proved more critical than ever with the rapid deployment of clinical trials, the introduction of new and repurposed treatments, and now the development and use of new vaccines, many based on innovative and groundbreaking technological platforms. The pandemic has also intensified the need to reexamine the role of national and regional research and development and manufacturing capacities in enhancing national and sanitary security. In this context, we hope that the report will help clarify the role of national regulatory systems in fostering quality manufacturing in the Americas to serve people's needs in a post-COVID-19 era.

The eight national regulatory authorities of reference have contributed significantly to the development of this landscaping report. They have provided data, case studies, and experiences that can serve as a reference for other national regulatory authorities and the broader community of stakeholders in the Region to increase understanding of national regulatory remits and capacity, and help identify emerging markets and current and future challenges. I would like to thank them for their commitment to this report. I hope that this publication will represent a significant contribution to understanding the trends, challenges, and opportunities shaping the future of the Region's health systems, and provide an evidenced-based rationale to support decision-making across all the sectors involved.

Jarbas Barbosa da Silva Junior

Assistant Director

Pan American Health Organization

ACKNOWLEDGMENTS

This publication of the Pan American Health Organization (PAHO) Medicines and Health Technologies Unit was developed with the guidance and oversight of an Expert Committee, chaired by Jarbas Barbosa da Silva Junior, Assistant Director, PAHO. The committee members were selected based on their expertise and knowledge of issues related to regulatory systems, the regulated sector, and the impact of regulation on access to medicines. Thanks are due to Mikel Arriola, Antonio Britto Filho, Michelle Childs, Silvia Gold, Alberto Gutiérrez, Javier Guzmán, Catherine Parker, and Kenneth Shadlen for their insights, contribution, and guidance.

Special thanks are due to the Food and Drug Administration of the United States of America, which sponsored this publication as part of the 2018 workplan agreed by the working group of National Regulatory Authorities on Regional Reference. It also provided much appreciated technical and financial support.

For the contributions of technical experts from within the Latin American National Regulatory Authorities of Reference, special thanks are due to: the National Administration of Drugs, Foods and Medical Devices of Argentina; the National Health Surveillance Agency of Brazil; the Center for State Control of Drugs, Equipment and Medical Devices of Cuba; the Federal Commission for Protection against Sanitary Risk of Mexico; the Public Health Institute of Chile; and the National Food and Drug Surveillance Institute of Colombia. The valuable contribution to this document of the industry associations Asociación Latinoamericana de Industrias Farmacéuticas and Federación Latinoamericana de la Industria Farmacéutica is also gratefully acknowledged.

Analía Porrás, Chief, Medicines and Health Technologies Unit, PAHO, supervised the preparation of this publication. Charles Preston was in charge of the overall coordination of the project. Tatiana Andia, Ariel Arias, Alexandra Mata, María Luz Pombo, Analía Porrás, and Charles Preston constituted the core working group in charge of conceptualization, study design, and implementation. The technical input of the following PAHO technical officers from the Medicines and Health Technologies Unit contributed greatly to the conceptualization and development of the study: Francisco Caccavo, José Luis Castro, José Vicente Coto, Murilo Freitas, Alexandra Guta, Alexandre Lemgruber, Fernanda Lessa, José Daniel Peña, Tomás Pippo, and Edgard Rojas. In addition, the work and contributions of Dolores Cullen and Fabiana Jorge, who acted as consultants on this project, as well as the data and inputs from the contract research organization IQVIA are gratefully acknowledged. Finally, sincere thanks go to James Fitzgerald, Director, Department of Health Systems and Services, PAHO, for his insightful comments and support.

ABBREVIATIONS AND ACRONYMS

| | |
|-----------------|---|
| ADR | adverse drug reaction |
| ALALC | Latin American Free Trade Association |
| ANMAT | National Administration of Drugs, Foods and Medical Devices, Argentina |
| ANVISA | Brazilian Health Regulatory Agency |
| API | active pharmaceutical ingredient |
| BCS | Biopharmaceutics Classification System |
| CARICOM | Caribbean Community |
| CARPHA | Caribbean Public Health Agency |
| CECMED | Center for State Control of Drugs and Medical Devices, Cuba |
| COFEPRIS | Federal Commission for the Protection against Sanitary Risk, Mexico |
| CRO | clinical research organization |
| CRS | Caribbean Regulatory System |
| EMA | European Medicines Agency |
| FDA | Food and Drug Administration, United States of America |
| FPP | finished pharmaceutical product |
| GBT | WHO Global Benchmarking Tool |
| GCP | good clinical practice |
| GDP | gross domestic product |
| GMP | good manufacturing practices |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ICTRP | International Clinical Trial Registry Platform |
| IDP | institutional development plan |
| INN | International Nonproprietary Name |
| INVIMA | Colombia National Food and Drug Surveillance Institute |
| ISP | Public Health Institute of Chile |
| LMICs | low- and middle-income countries |
| MA | marketing authorization |
| MAH | marketing authorization holder |

| | |
|-----------------|--|
| MERCOSUR | Southern Common Market |
| MoH | ministry of health |
| MRA | mutual recognition agreement |
| NCE | new chemical entity |
| NRA | national regulatory authority |
| NRAr | national regulatory authorities of regional reference |
| PAHO | Pan American Health Organization |
| PANDRH | Pan American Network for Drug Regulatory Harmonization |
| PIC/S | Pharmaceutical Inspection Co-operation Scheme |
| PPP | public-private partnership |
| PV | pharmacovigilance |
| R&D | research and development |
| RBP | reference biological product |
| RTCAs | Central American Technical Regulations |
| SBP | similar biotherapeutic product |
| SF | substandard and falsified |
| SICA | Central American Integration System |
| SRA | stringent regulatory authority |
| UMC | Uppsala Monitoring Centre |
| WHA | World Health Assembly |
| WHO | World Health Organization |

EXECUTIVE SUMMARY

A central role of national regulatory systems is to promote and protect public health by overseeing the quality, safety, and efficacy of all health technologies in the market, including pharmaceuticals, vaccines, blood and blood products, and medical devices, among others. In order to accomplish that, systems need to make sure that the marketing authorization of products is based on sound science, that the intended benefits outweigh the risks, and that users receive proper and up-to-date information on product use. Some of the functions required to fulfill the system mandate include providing regulatory oversight for clinical studies during product development, reviewing and authorizing products for marketing, conducting safety surveillance and monitoring of products in the market, inspecting manufacturing practices, and effectively communicating with all stakeholders. Carrying out the oversight mission is becoming increasingly challenging because of rapid scientific changes, the increased diversity and complexity of products, and the current context of globalization of production and product supply chains. However, this may be also bringing opportunities in the form of greater regulatory cooperation and information sharing to gain efficiency.

Awareness of the critical role of national regulatory systems in public health and economic development is growing. Strengthening of the regulatory system has been a priority ever since the Pan American Network for Drug Regulatory Harmonization (PANDRH) was established in 1998, where PAHO Member States work together to support regulatory harmonization and convergence. They agreed to the development of a qualification system coordinated by PAHO in 2006, to help establish mechanisms for cooperation and recognition across national regulatory authorities (NRAs). Such an initiative paved the way to more formal commitments through the PAHO Directing Council Resolution CD50.R9 on Strengthening National Regulatory Authorities for Medicines and Biologicals in 2010. It called on Member States to evaluate and strengthen their own regulatory capabilities through external assessment and continuous improvement, and introduced the idea of using “regulatory authorities of regional reference” to benchmark and support other regulatory systems in the Region.

At a global level, regulatory system strengthening was also formally recognized as a public health priority in 2014 when the World Health Assembly (WHA) adopted the Resolution WHA 67.20. Like CD50.R9, WHA 67.20 calls on Member States to evaluate their regulatory systems and collect data that enable analysis and benchmarking for improvement. It also urges countries to network and collaborate as a way of pooling their regulatory capacities and strengthening any local production of quality-assured, safe, and effective medical products. In response to the growing interest in regulatory system strengthening, more countries are now looking to assess their systems using standardized evaluation tools that can help identify strengths and opportunities for improvement. A newly developed WHO Global Benchmarking Tool (GBT) reflects current thinking on the structure and functions of a competent national regulatory system, and is being piloted throughout the world.

This landscaping report was initiated as an activity of the group of national regulatory authorities of regional reference (NRAr) in 2018 to better understand the regulatory landscape of the Americas. It employs a data-driven approach that includes available data from PAHO NRA assessments and other relevant information. PAHO was asked to undertake the report because of its unique ability to work with all NRAs in the Region to gather and to analyze the information, with a specific request to:

- increase understanding of national regulatory remits and capacity in the Americas;
- raise awareness and appreciation of regional regulatory challenges;
- identify emerging markets and the regulatory issues these will bring; and

- highlight opportunities for evidence-based regulatory system strengthening based on lessons learned and best practice in the Region.

The analysis focused on processes and practices of NRAR in Latin America and the industries and markets they oversee, with less emphasis on the FDA and Health Canada because these systems are better understood. Information from other regulatory systems, including those from Central America and the Caribbean, is also included and discussed in the report.

The framework for the analysis presented in this report is based on PAHO/WHO's concept of a well-functioning regulatory system. Data were gathered and analyzed in separate chapters corresponding to essential functions—regulatory foundations; market authorization; inspections; clinical trials; pharmacovigilance and post-market surveillance—to understand current practices, identify key issues and present a series of recommendations for action. The report also includes a discussion on market outlook, biosimilars, and trade integration mechanisms in the Americas. The report would be incomplete without discussing the current and unprecedented public health emergency. Thus, a supplement is also included to describe salient regulatory emergency responses to the COVID-19 pandemic in the Americas. Key messages and recommendations from the analysis in those sections are summarized below.

NATIONAL REGULATORY SYSTEMS

A foundation of regulatory systems strengthening is the process by which regulatory systems undergo assessment and identification of strengths and opportunities for improvement via an institutional development plan (IDP). PAHO has assessed most NRAs in the Americas. Although information on legal and organizational frameworks shows that NRAs in the Region have significantly strengthened regulatory functions over the past decade, including that there are now eight NRAR as designated by PAHO, much more needs to be done to address regulatory capacity in smaller countries. In addition, cross-cutting elements such as budgets and staffing practices are challenging and threaten the sustainability and adequate performance of regulatory functions. For example, NRAR budgets have been stagnant or decreasing over the past few years. A welcome development is that NRAR are increasingly participating in global harmonization forums and this presents an opportunity for others to engage in this space.

RECOMMENDATIONS

- **Develop legal and organizational frameworks.** The limited or complete lack of legal and organizational frameworks for regulatory systems in a number of countries in the Americas today is worrisome. Since this increases the risk that their populations will not have access to safe, quality, and effective medicines, the development of such frameworks should be addressed and prioritized as soon as possible.
- **Prioritize resources for NRA assessment.** Resources are needed for PAHO/WHO and peer assessment teams to continue to spur regulatory system strengthening through the assessment and IDP processes.
- **Boost sustainability and efficiency.** Governments and NRAs must consider ways to increase sustainability and efficiencies of regulatory systems. Elements and strategies to secure adequate funding, autonomy, and institutional development should be assessed and properly addressed if needed.
- **Participate in harmonization initiatives.** NRAs should continue to increase their engagement in global harmonization activities and take up foundational guidelines adapted to their health system context.

MARKET OUTLOOK

There are large and growing pharmaceutical markets in Latin America, which is one of the fastest growing regions in the world. This fact will bring new challenges for regulators, in both the complexity and volume of products to be regulated, amid a recent financial environment of stagnating or declining budgets. Regulatory authorities will need to adopt more efficiencies and confront the challenges posed by industrial policies that will likely favor more local production of products ranging from generic medicines to biosimilars. There may be other strategic opportunities, such as expanding trade beyond the historical relationships and integration mechanisms to new subregions of the Americas.

RECOMMENDATIONS

- **Explore opportunities to expand trade.** Explore opportunities to expand trade among NRAR countries as well as with countries in other subregions in the Americas, including through the use of regulatory reliance.
- **Be ready for market changes.** Ensure that regulatory systems are prepared for market growth over the coming years, with strategies to manage influx and to maximize resources to ensure product safety, efficacy, and quality, including related to areas such as biotherapeutic and similar biotherapeutic products.
- **Improve understanding of generic market penetration.** Consider the need to develop mechanisms to understand and, if necessary, increase generic penetration in the Americas.

MARKETING AUTHORIZATION

Marketing authorization in Latin American (LA) NRAR is a complex area and one that poses a number of challenges for regulators, now and in the future. LA NRA tend to devote a significant share of staff resources to marketing authorization. However, growing markets will mean more associated life-cycle demands. Regarding marketing authorization standards, although LA NRAR have relatively similar quality, safety, and efficacy requirements for the authorization of new chemical entities, there seem to be important differences in regulation related to generics, especially around when to require bioequivalence. Resources are another important area, and this analysis shows that user fees to support LA NRA are very low in comparison with other international reference authorities, not only in absolute terms, but also when factoring in GDP. There are also opportunities to expand the use of reliance, including practices such as publishing information that can facilitate reliance.

RECOMMENDATIONS

- **Prioritize regulatory life-cycle management.** NRAR need to find ways to better handle and improve regulatory oversight using a holistic view of the entire life cycle of the authorization. Enablers for this should include, among others, considerations on how to better fund all regulatory activities, to increase and improve allocation of technical and human resources, and to adopt electronic tools to improve efficiencies.
- **Improve funding of regulatory activities.** The finding of significant differences in the manner NRAs are funded, and in the way regulatory user fees are allocated and managed, are worth highlighting. Because of the individual particularities of the different systems, NRAs and government bodies are asked to critically reassess the funding mechanisms in place including in relation to other reference authorities (e.g., ratios of user fees charged). The scope of this assessment must cover all the different regulatory functions required to support the development, authorization, and monitoring of medicines of good quality, safety, and efficacy for the population.

- **Improve bioequivalence harmonization.** Ensuring adequate regulatory oversight for generics in the Region requires that NRAs harmonize and adopt international requirements for bioequivalence and biowaivers to the greatest extent possible.
- **Implement procedures that enable use of reliance.** Although procedures that properly support the use of reliance are expected to significantly strengthen the market authorization regulatory function, they continue to be underutilized. The development of such procedures should be further prioritized by all NRAs in the Region.
- **Improve publicly available regulatory information.** Public access to marketing authorization and product related information from the NRA is crucial to support ongoing regional reliance efforts, and needs to be significantly improved by all authorities as part of good regulatory practices.

MARKETING AUTHORIZATION OF SIMILAR BIOTHERAPEUTIC PRODUCTS (SBPs)

The number of biologics and similar biotherapeutic products (SBP) in Latin American markets is growing rapidly, creating an important role for regulators. Differences in some key elements of SBP regulatory oversight like the implementation and use of regulatory standards, or the choice of the reference product for comparisons, are important opportunities for policy strengthening. Since some NRA countries are already producing SBPs, such differences would need to be tackled as soon as possible to avoid confusion and more difficulties with their regulatory oversight in the future. There is also an important role for pharmacovigilance and post-market surveillance of SBPs.

RECOMMENDATIONS

- **Develop and implement standards for SBP.** Establish, harmonize, and enforce appropriate manufacturing standards for SBPs and apply them equally to both international and domestically produced products.
- **Harmonize regulatory oversight.** Authorities need to continue efforts toward common regulatory approaches for SBPs, such as definitions, reference biotherapeutic products (RBPs), and interchangeability requirements.
- **Improve post-authorization surveillance.** Without common regulatory approaches for market authorization, the use of strong post-market requirements and oversight is even more critical and should be implemented as a standard practice for SBPs upon authorization.
- **Use reliance for SBPs.** Embrace and adopt reliance strategies for the regulatory oversight of SBPs where appropriate, including via use of the WHO collaborative procedure for accelerated registration of WHO-prequalified products.

GOOD MANUFACTURING PRACTICE (GMP) INSPECTIONS

Good manufacturing practices (GMP) are part of quality assurance activities aimed at making sure that medicines are consistently produced and that products meet quality standards appropriate to their intended use. GMP inspections in Latin America are shaped by the size and the structure of the regulatory authorities involved, the level of local manufacturing, and the extent of inter-institutional collaboration. Standards and approaches are relatively similar across NRAs; however, there are some differences including related to the conduct of active pharmaceutical ingredient (API) inspections and international inspections. The recent expansion of Pharmaceutical Inspection Cooperation Scheme (PIC/S) membership in the Region has helped countries adopt international standards and to establish a basis for securing trust in their GMP inspection certification. Reliance on GMP inspections conducted

by another authority is practiced, but it remains underused for increasing regulatory reach across foreign and domestic manufacturers and in considering risk-based approaches. Publication of inspectional information remains a critical issue as well, with NRAr making only a limited amount of information on their GMP inspections publicly available for use and/or reliance by other authorities.

RECOMMENDATIONS

- **Optimize inspection strategies.** GMP inspections are time-consuming and resource-intensive activities for both the authority and the manufacturer. NRAs should examine international inspection strategies to find an optimal mix of risk and efficiency, including relying on trusted authorities.
- **Leverage trusted GMP information.** Increase the use of trusted NRA material, including exchanging GMP information, such as certificates and inspection reports with NRAr, stringent regulatory authorities (SRAs), and PIC/S members.
- **Take advantage of available tools on GMP information.** Make better use of public databases, such as EudraGMDP and WHO prequalification databases, to check GMP status of individual manufacturing sites.
- **Improve regulatory transparency on inspections.** Make more inspection-related information publicly available on the NRA website and encourage manufacturers to authorize the sharing of inspection reports among NRAs.
- **Intensify API manufacturing oversight.** The absence of API requirements across countries in the Region needs to be addressed. NRAs must increase regulatory oversight of API manufacturing sites through diverse strategies including targeted increase of international inspections and/or reliance.

PHARMACOVIGILANCE (PV) AND POST-MARKET SURVEILLANCE (PMS)

Both pharmacovigilance (PV) and post-market surveillance (PMS) are activities needed to ensure that products on the market maintain an acceptable benefit-risk balance for the intended use after authorization. Although all NRAr have legal provisions for PV and PMS, no clear approaches have been implemented to support the performance of the required regulatory activities, with resources often fluctuating from one administration to the next. LA NRAr report adverse drug reactions to global monitoring systems at lower rates than other international reference authorities, but have made significant progress in reporting cases of substandard and falsified (SF) medicines. While there is room for improvement, some NRAr are using targeted or active PV to gain efficiencies in the detection and evaluation of medicines adverse reaction information, and their capacity to translate PV data into regulatory action is also increasing. The rise in illegal online sales of medicines and limited enforcement of advertising rules pose particular challenges to tackling SF products. Expanding the use of track and trace systems for PMS in the Region requires significant investment and technological upgrades across the supply chain.

RECOMMENDATIONS

- **Increase stability and allocate appropriate resources** (for example, funding, staff, training) to PV and PMS to ensure NRAs can respond to the growing number and complexity of products entering their health systems in a timely manner.
- **Strengthen coordination** with other programs and institutions to enable the active support and engagement of all stakeholders in PV and PMS activities.

- **Improve ADR management and assessment, including global reporting.** for example by using newer technologies.
- **Strengthen efforts to tackle SF products** by addressing existing gaps in regulation, training and dedicating regulatory staff to permanently monitor high-risk websites and social media, establishing links with law enforcement authorities, and creating awareness among users.
- **Strengthen efforts to translate PV and PMS information** into assessment and, where appropriate, regulatory action.
- **Establish national track and trace systems** that can contribute to international monitoring systems and support drug safety related actions in relation to SF quality reports.
- **Monitor one's own markets and boost efficiencies through reliance**, for example by sharing information with other NRAs and monitoring trusted sources for PV/PMS findings and news.

CLINICAL TRIALS

Clinical trials are the supporting pillar for the clinical development of medicines, and regulatory authorities play a critical role in their oversight. This requires good collaboration and coordination across different stakeholders in the regulatory system. All LA NRAs have a regulatory framework for clinical trials that is based on international guidelines, including approval by an ethics committee and good clinical practice inspections. However, many countries in the Region do not have legal frameworks for clinical trials, particularly smaller countries, despite the growing presence of clinical trials in the Region. All LA NRAs have procedures for considering local clinical trial results in marketing authorization processes, but only a few have procedures on compassionate use for participants after completion of the trial. Although all LA NRAs publish information about clinical trials in publicly available databases, such information may not be very useful in some cases because of a lack of standardization.

RECOMMENDATIONS

- **Review stakeholder roles and interactions.** Establish and reinforce intra- and inter-organizational links by clearly defining roles and responsibilities and developing procedures to ensure the smooth flow of regulatory information before, during, and after a clinical trial.
- **Develop or use tools to support handling of clinical trials regulatory information.** Implement the use of standard databases or registries that maintain relevant clinical trial information to enable adequate regulatory management, monitoring, and knowledge exchange across the Americas to support informed decision-making.
- **Broaden methods to assess regulatory efficiency.** Use multiple indicators to assess efficiency of clinical trials regulatory oversight which do not simply rely on trial approval rates and application review timelines and that include measurement of review quality.
- **Introduce extraordinary product access procedures for clinical trial participants.** Since many countries do not have or have not yet implemented them, consider the development of compassionate product use procedures for clinical trial participants once the study ends.
- **Develop clinical trials regulatory oversight where still missing.** Use foundational GBT indicators (Maturity Level 1 and 2) to implement clinical trials oversight in countries that currently have no relevant regulation in place.

- **Consider collaborative methods for clinical trials regulation.** Use models like AVAREF to potentially gain efficiencies in clinical trials oversight, particularly in smaller countries and in settings where there is a history of cooperation.

TRADE AND ECONOMIC INTEGRATION MECHANISMS

Trade integration mechanisms can play an important role in regulatory systems. Four key mechanisms in the Americas include CARICOM, SICA, MERCOSUR, and the Pacific Alliance, and their regulatory activities include subregional regulatory systems, reliance on GMP inspections, and information sharing. However, the success in fostering stronger regulatory practices is mixed. There is a focus on using these mechanisms for regulatory and public health strengthening in some settings, particularly in countries with smaller populations and markets (e.g., CARICOM), but challenges remain in terms of implementation, perhaps in part because economic development and trade considerations have not been part of the motivations. Alternatively, the MERCOSUR and Pacific Alliance mechanisms have had some regulatory successes but have struggled with implementation of more robust regulatory activities, in part because of varying regulatory standards among members.

RECOMMENDATIONS

- **Trade integration mechanisms can facilitate regulatory strengthening.** While there are significant challenges, there are also opportunities to improve and increase the number of regulatory activities within the Region’s integration mechanisms.
- **Provide sustained support and strong leadership to regulatory strengthening activities in trade integration mechanisms.** To become effective and significantly support further regulatory strengthening in the different subregions, these integration mechanisms need continued and strong political support and leadership.
- **Search actively for improved efficiencies.** Opportunities to increase efficiencies (e.g., implementing and/or improving the use of reliance, electronic platforms, promoting and funding training) should be identified and embraced within the Region’s integration mechanisms.
- **Analyze regulatory successes, best practices, and barriers in integration mechanisms and implement corrective actions.** Some mechanisms may need to address differing regulatory standards to further cement regulatory activities and reliance. Other mechanisms may need to add an economic development/trade rationale to further cement regulatory activities.

REGULATORY EMERGENCY RESPONSE TO THE COVID-19 PANDEMIC IN THE AMERICAS

Strengthening national and global capacities to detect, prepare for, and respond to epidemic and pandemic diseases were brought to the forefront of international concern by the emergence of severe acute respiratory syndrome (SARS), which in 2003 was the first “public health emergency” of the twenty-first century. Regulatory systems for medicines and other health technologies play an essential role in health systems, including public health emergencies. Yet in some countries, the regulatory system for medicines is not equipped to respond during public health emergencies and/or is not well integrated into the national emergency response. The ongoing COVID-19 pandemic has provided an opening to critically analyze the need and the value of these systems in emergencies, to assess their strengths, and to identify opportunities for improvement in the Americas. Some data from activities in the Pandemic Influenza Preparedness (PIP) framework suggest that there is room for improvement.

Data on information, challenges, lessons learned, and best practices shared at regular PAHO NRA emergency forums to discuss critical COVID-19 response topics during the last few months are presented. They show that LA NRAs have implemented emergency regulatory measures across a variety of domains and took many actions very early in the pandemic. The newly developed WHO Global Benchmarking Tool (GBT) offers an important framework to improve response to epidemics and pandemics by enabling understanding of the legal and organizational capacity of NRA emergency response capacity, and is discussed in this section.

RECOMMENDATIONS

- **NRAs should proactively consider implementing the use of the WHO GBT indicators** to develop regulations, policies, and procedures that facilitate strong regulatory emergency response.
- **NRAs should adopt the best practices and efficiencies noted** in this supplement for regulatory emergency response to the greatest extent possible.

INTRODUCTION

The Value of Strengthening National Regulatory Systems

Improving access to safe, effective, and quality medicines and other health technologies is a critical public health priority and a fundamental requisite for universal health. National regulatory systems play a key part in a country's health system by overseeing the safety, quality, and efficacy of all health technologies, including pharmaceuticals, vaccines, blood and blood products, and medical devices, among others. These systems are responsible for various functions, including for example, reviewing and authorizing products for legal sale, monitoring products in the market, inspecting manufacturing practices, laboratory testing, and regulating clinical trials. Their role is more important than ever in the context of globalization, where manufacturing and supply chains traverse continents but jurisdictions vary in their levels of oversight. National regulatory systems are also critical to combating other global health challenges, such as substandard and falsified products as well as antimicrobial resistance.

Regulatory systems affect economic activity too. They may influence whether a product can enter the market, the competition among different makers, and how quickly products can become available to patients and prescribers. These factors impact price and affordability, as well as the commercial performance of manufacturers, which in some countries are large contributors to national gross domestic product. Furthermore, the standards set by authorities in the regulatory systems, and the degree to which these are harmonized with other markets, can impact trade with other countries.

Awareness of the critical role of national regulatory systems in public health and economic development is growing. Countries in the Americas have a long record of prioritizing regulatory system strengthening. Ever since the Pan American Network for Drug Regulatory Harmonization (PANDRH) was established in 1998, Member States of the Pan American Health Organization (PAHO) have worked together to support regulatory harmonization and convergence. In 2006, they agreed to the development of a qualification system, coordinated by PAHO, to help establish mechanisms for cooperation and recognition across national regulatory authorities (NRAs). The initiative was the first of its kind and paved the way for more ground-breaking commitments through the PAHO Directing Council Resolution CD50.R9 on Strengthening National Regulatory Authorities for Medicines and Biologicals in 2010 (1). This resolution, which calls on Member States to evaluate and strengthen their regulatory capabilities through external assessment and continuous improvement, introduced the idea of using “regulatory systems of regional reference” to benchmark and support other regulatory systems in the Region (see Box 1).

Box 1. National regulatory authorities of regional reference

In the Americas, national regulatory authorities of regional reference (NRAR) refer to NRAs that have been assessed by PAHO and found to be competent and efficient in their performance of the health regulation functions needed to guarantee the safety, efficacy, and quality of medicines. This grouping meets regularly through in-person and virtual means to share strategic updates on challenges and/or important initiatives.

Each NRAR serves as a reference for other NRAs in the Region including to:

- support PAHO to strengthen other NRAs in the Region;
- be an example for best practices and other innovations in regulation;
- support reliance.

PAHO recognizes eight NRAR in the Americas:

1. National Administration of Drugs, Foods and Medical Devices (ANMAT), Argentina
2. Brazilian Health Regulatory Agency (ANVISA), Brazil
3. Center for State Control of Drugs and Medical Devices (CECMED), Cuba
4. Federal Commission for the Protection against Sanitary Risks (COFEPRIS), Mexico
5. Health Canada, Canada
6. Colombia National Food and Drug Surveillance Institute (INVIMA), Colombia
7. Public Health Institute of Chile (ISP), Chile
8. U.S. Food and Drug Administration (FDA), United States of America

Together, these NRAR cover 82% of the population in the Americas. These countries also represent some of the most active pharmaceutical markets in the Region, with extensive manufacturing and large consumption of medicines and other health technologies.

Regulatory system strengthening has remained one of PAHO's technical cooperation priorities over the past decade. The Organization continues to advocate for, and invest in, the development of robust, context-specific regulatory systems in the Region, increasing efficiencies through convergence, harmonization, and reliance wherever possible and appropriate.

At a global level, regulatory system strengthening was formally recognized as a public health priority in 2014 when the World Health Assembly (WHA) adopted Resolution WHA 67.20 (2). Like CD50.R9, WHA 67.20 calls on Member States to evaluate their regulatory systems and collect data that enable analysis and benchmarking for improvement. It also urges countries to network and collaborate as a way of pooling their regulatory capacities and strengthening any local production of quality-assured, safe, and effective medical products.

In response to the growing interest in regulatory system strengthening, more countries are looking to assess their systems using standard evaluation tools that can help identify strengths and opportunities for improvement. The new WHO Global Benchmarking Tool (GBT) (3) reflects current thinking on the structure and functions of a competent national regulatory system and is seeing unprecedented levels of country engagement. However,

analyses of regulatory systems, including using assessment data, remain scarce at the regional level. Such analyses are needed to appreciate the trends in regulatory system strengthening and are critical to understand the challenges faced by NRAs and identify opportunities for improvement.

About This Report

Purpose

This study is the result of conversations among NRAs to better understand the regulatory landscape of the Americas using a data-driven approach, including PAHO assessment data and other relevant information. A call for PAHO to undertake the study was made at an NRA meeting in 2018, with funding generously provided by the FDA, leveraging PAHO's unique ability to work with NRAs to gather and analyze the information, with a specific request to:

- increase understanding of national regulatory remits and capacity in the Americas;
- raise awareness and appreciation of regional regulatory challenges;
- identify emerging markets and the regulatory issues these will bring; and
- highlight opportunities for evidence-based regulatory system strengthening based on lessons learned and best practices in the Region.

Scope

In addressing the subject, the report focuses on the processes and practices of NRAs in Latin America and the industries and markets they oversee related to pharmaceutical regulation. The report places less emphasis on the FDA and Health Canada because these systems are better understood. Analyses of lesser-known Latin American NRAs could be particularly useful in informing other NRAs in the Region because of the many connections that bind them together, including trade relationships, geographical proximity, and cultural and linguistic ties. The report also includes information about NRAs from Central America and the Caribbean.

Methodology

The methodology of the report included literature reviews, analysis of PAHO data on regulatory assessment, desk reviews of NRA websites, and interviews with key stakeholders such as NRA officials and industry actors. An Expert Committee was convened to advise the themes and analyses in the report, while PAHO functioned as the secretariat. The Expert Committee included the following persons:

- Jarbas Barbosa da Silva Junior, PAHO Assistant Director (Chair)
- Mikel Arriola, former Federal Commissioner for the Protection Against Sanitary Risks (COFEPRIS)
- Antonio Britto, Executive President to the Brazilian Pharmaceutical Trade Association
- Michelle Childs, Head of Policy Advocacy at the Drugs for Neglected Diseases initiative (DNDi)
- Silvia Gold, President of Mundo Sano Foundation
- Alberto Gutiérrez, former director of FDA's Office of In Vitro Diagnostics and Radiological Health
- Javier Guzman, former Director General of the Colombian Food and Drug Surveillance Institute (INVIMA)
- Catherine Parker, former Director General of the Biologics and Genetic Therapies Directorate at the Health Products and Food Branch of Health Canada
- Kenneth C. Shadlen, Head of Department of International Development at the London School of Economics and Political Science (LSE)

To gather data for the report, the research team developed questionnaires for each chapter, to which NRAs provided responses either by telephone interview or through email exchanges. Once the data were processed, the information of interest was analyzed and tables and figures developed. Finally, the interpreted data were shared back to each NRA for validation.

Audience

The report is intended to be of interest and use to NRAs in the Region as well as a broader community of stakeholders, including:

- NRAs: to serve as a framework for best practice and strategic action;
- Ministries of health: to emphasize the role the NRA plays in promoting strong health systems and in achievement of Universal Health and the Sustainable Development Goals;
- Ministries of trade and finance: to raise awareness of the critical need to invest in regulatory systems to improve trade and economic development, including by creating more efficient and accountable climates for doing business; and
- Regional and global stakeholders, including development partners: to raise situational awareness of regulatory systems in the Americas and their role in supporting regional and global health systems.

Limitations

The report was difficult to compile for several reasons. NRA data are often confidential, fragmented across multiple systems and governmental bodies in the country, and difficult to access (especially where data have not been digitized). Different NRAs capture and maintain data differently, which makes it difficult to analyze and compare data across countries. The report identifies when there are such instances and adds a caveat on the data. An important outcome of this report may be to catalyze more harmonized collection of data on key regulatory metrics so that future comparisons and analyses can be easier and even more meaningful.

1. NATIONAL REGULATORY SYSTEMS: AN OVERVIEW

In brief

- This chapter provides an overview of regulatory system capacity in the Americas and focuses on how cross-cutting elements, such as budgets and staffing, differ across NRAR.
- Regulatory strengthening begins with a time- and resource-intensive assessment of strengths and weaknesses. For this, PAHO/WHO developed a tool that has evolved over the years into the WHO GBT today.
- PAHO has assessed most NRAs in the Americas, and the data show that NRAs in the Region have significantly strengthened regulatory functions over the past decade, but much more needs to be done to address regulatory capacity in smaller countries.
- Legal and organizational frameworks, and hierarchy in the health system, influence regulatory system functioning.
- Budgets are usually funded by a mix of government resources and user fees, but they have been flat or declining over the past five years.
- An increasing number of NRAR are joining global harmonization initiatives, although many authorities still do not participate.
- Information sharing is continuously improving among NRAR, and between NRAR and some NRAs in the Region, but in some subregions it remains low.
- Sustainability remains a critical issue for all NRAs in the Region.

1.1. A Framework for Assessing NRAs

National regulatory systems come in different shapes and sizes. In some countries, the oversight of medicines and other health technologies is delegated to a single national entity (an NRA); but in most cases, such regulatory oversight requires the involvement of many different government organizations along the product's life cycle. For example, a central authority may take charge of most regulatory issues while decentralized institutions are made responsible for specific functions, such as laboratory testing or ethical oversight of clinical trials.

Ideally, all entities involved in regulating medicines should be organized and integrated into a functional and well-coordinated system. Even if countries choose to use a combination of central and state authorities with different levels of jurisdiction, they are expected to work in an integrated and coherent way to ensure the safety, effectiveness, and quality of products at local and national levels, and even when these products cross borders.

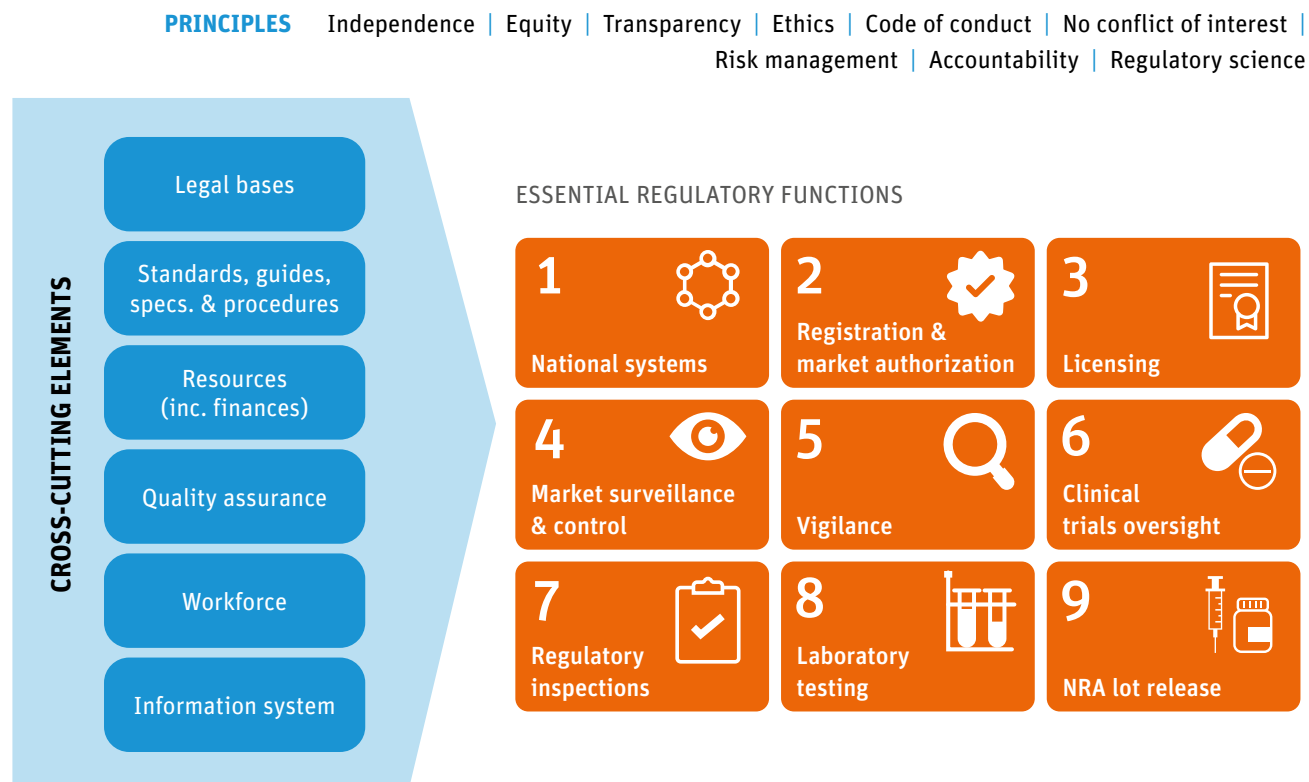
While there is no preferred model for organizing national regulatory systems, most experts agree that efficient and effective systems share some common characteristics. A 2012 report by the Institute of Medicine

identified five main attributes, saying that strong systems are: responsive, outcome-oriented, predictable, risk-proportionate, and independent (4).

PAHO has similarly defined the characteristics of a well-functioning regulatory system in a country with manufacturing and research and development (R&D) activities (see Figure 1.1). PAHO's framework includes a set of:

- Principles, including independence, equity, transparency, ethics, code of conduct, no conflict of interest, risk management, accountability, and regulatory science. These are considered universal to any regulatory system, regardless of size, scope, or context (5).
- Cross-cutting elements, including legal frameworks, resources, standards, quality assurance methods, and information systems. These elements exist in all countries studied, but vary in size and complexity with each regulatory system.
- Essential functions, including registration and market authorization, surveillance, vigilance, inspection, clinical trials oversight, and laboratory testing (see Table 1.1). These activities vary with the scope of the regulatory system and with the characteristics of the market it oversees.

Figure 1.1. The framework for a well-functioning national regulatory system



Source: Adapted from: Organización Panamericana de la Salud. Conceptos, estrategias y herramientas para una política farmacéutica nacional en las Américas. Washington, DC: OPS; 2016.

Table 1.1. The broad scope of each essential regulatory function

| Regulatory function | Scope |
|---|--|
| 1. NATIONAL REGULATORY SYSTEMS | <ul style="list-style-type: none"> • Legal frameworks • Level of centralization • Organizational framework and management • Institutions and infrastructure • Governance and transparency |
| 2. REGISTRATION AND MARKET AUTHORIZATION | <ul style="list-style-type: none"> • Product review and evaluation processes |
| 3. LICENSING | <ul style="list-style-type: none"> • Licensing of manufacturers, warehouses, and distributors |
| 4. MARKET SURVEILLANCE & CONTROL | <ul style="list-style-type: none"> • Import and export control • Regulation of substandard and falsified medicines |
| 5. VIGILANCE | <ul style="list-style-type: none"> • Data collection on medicine safety • Identification of adverse events and follow-up action • Monitoring quality of products in the market |
| 6. CLINICAL TRIALS OVERSIGHT | <ul style="list-style-type: none"> • Authorization and control of clinical trials for medicines |
| 7. REGULATORY INSPECTIONS | <ul style="list-style-type: none"> • Assessment of compliance with regulations, standards, and good practice (GxP) |
| 8. LABORATORY TESTING | <ul style="list-style-type: none"> • Quality control before and during commercialization |
| 9. LOT RELEASE | <ul style="list-style-type: none"> • Quality verification of vaccines and other biologicals • Consistency of production |

The description of well-functioning regulatory systems outlined in Figure 1.1 has formed the framework for PAHO’s assessments of national systems since 2007 (see Section 1.1.1). It also forms the framework for analysis presented in this report. Sections 1.2 and 1.3 below take an overarching view of national regulatory systems in the Americas, looking at some of the cross-cutting features and characteristics. The chapters that follow then take a deeper look at those essential regulatory functions that are considered the most informative to understand current practices, identifying key issues and presenting a series of recommendations for action for regulatory systems as a whole.

1.1.1. PAHO ASSESSMENTS AND THE WHO GLOBAL BENCHMARKING TOOL

Regulatory system strengthening begins with an assessment of the NRA across different regulatory domains. Although the outcome of the assessment is important, it is the process of identifying strengths and weaknesses, and developing a plan to address them, that is particularly valuable. PAHO’s tool for assessing NRAs, which is based on the framework described in Figure 1.1, reflects WHO recommendations for strengthening regulatory bodies and is implemented using a peer-reviewed, standardized method.

Between 2011 and the end of 2019, PAHO had coordinated and supported the assessment of NRAs in 27 out of 35 PAHO Member State countries (77%) in the Americas (see Table 1.2), including 20 in the past five years. In each case, the assessment categorized the system’s level of development and formed the basis of an institutional development plan (IDP) to guide improvements. IDPs are used to identify clear priorities for action based on the country’s regulatory gaps; help set attainable goals; and establish mechanisms for monitoring and evaluating progress against the assessment as a benchmark. IDPs are also beneficial because they provide a standardized framework for strengthening and can be used to facilitate coordination among development partners/interested parties.

The frequency of assessment is an important driver of improvement, but it is resource intensive. Some countries have not gone through the assessment process for many years, and there are still a few countries that have not gone through it at all. PAHO is currently transitioning to the GBT, which incorporates PAHO’s experience and uses the same conceptual framework. WHO is piloting the tool in multiple countries in the Americas, consolidating and standardizing the indicators of regulatory capacity across the different tools.

Table 1.2. PAHO assessments of NRAs in the Americas

| Member States | NRA assessed | Member States | NRA assessed |
|----------------------------------|--------------|------------------------------------|--------------|
| ANTIGUA AND BARBUDA | | GUYANA | ✓ |
| ARGENTINA | ✓ | HAITI | ✓ |
| BAHAMAS | ✓ | HONDURAS | ✓ |
| BARBADOS | ✓ | JAMAICA | ✓ |
| BELIZE | ✓ | MEXICO | ✓ |
| BOLIVIA (PLURINATIONAL STATE OF) | ✓ | NICARAGUA | |
| BRAZIL | ✓ | PANAMA | ✓ |
| CANADA | ✓ | PARAGUAY | ✓ |
| CHILE | ✓ | PERU | ✓ |
| COLOMBIA | ✓ | SAINT KITTS AND NEVIS | |
| COSTA RICA | ✓ | SAINT LUCIA | |
| CUBA | ✓ | SAINT VINCENT AND THE GRENADINES | |
| DOMINICA | | SURINAME | ✓ |
| DOMINICAN REPUBLIC | ✓ | TRINIDAD AND TOBAGO | ✓ |
| ECUADOR | ✓ | UNITED STATES OF AMERICA | ✓ |
| EL SALVADOR | ✓ | URUGUAY | |
| GRENADA | | VENEZUELA (BOLIVARIAN REPUBLIC OF) | ✓ |
| GUATEMALA | ✓ | | |

1.2. NRAs in the Americas: Structures and Resources

This section outlines some of the cross-cutting functions that characterize national regulatory systems in the Americas.

1.2.1. LEGAL BASES AND ORGANIZATIONAL FRAMEWORKS

The legal basis sets the foundation for regulating medicines and other health technologies. It should provide the oversight and enforcement power for a regulatory authority to effectively conduct its essential functions. Organizational frameworks are just as important as legal bases in providing the foundations for regulation. They can

take many different forms and tend to vary depending on historical context, underlying government arrangements, and the specific needs of different health systems and industrial sectors. The legal basis and organizational framework are critical determinants of an NRA's effectiveness and strength, and they can be used as a proxy for a country's regulatory capacity.

A look at publicly available data and the results of PAHO assessments over the past decade can help determine the strength of legal bases and organizational frameworks at the national level. Data reveal that 22 of the 35 PAHO Member States have at least some legal basis for a regulatory system (see Figure 1.2) (6).

Figure 1.2. Legal and organizational structures for regulating medicines in PAHO Member States

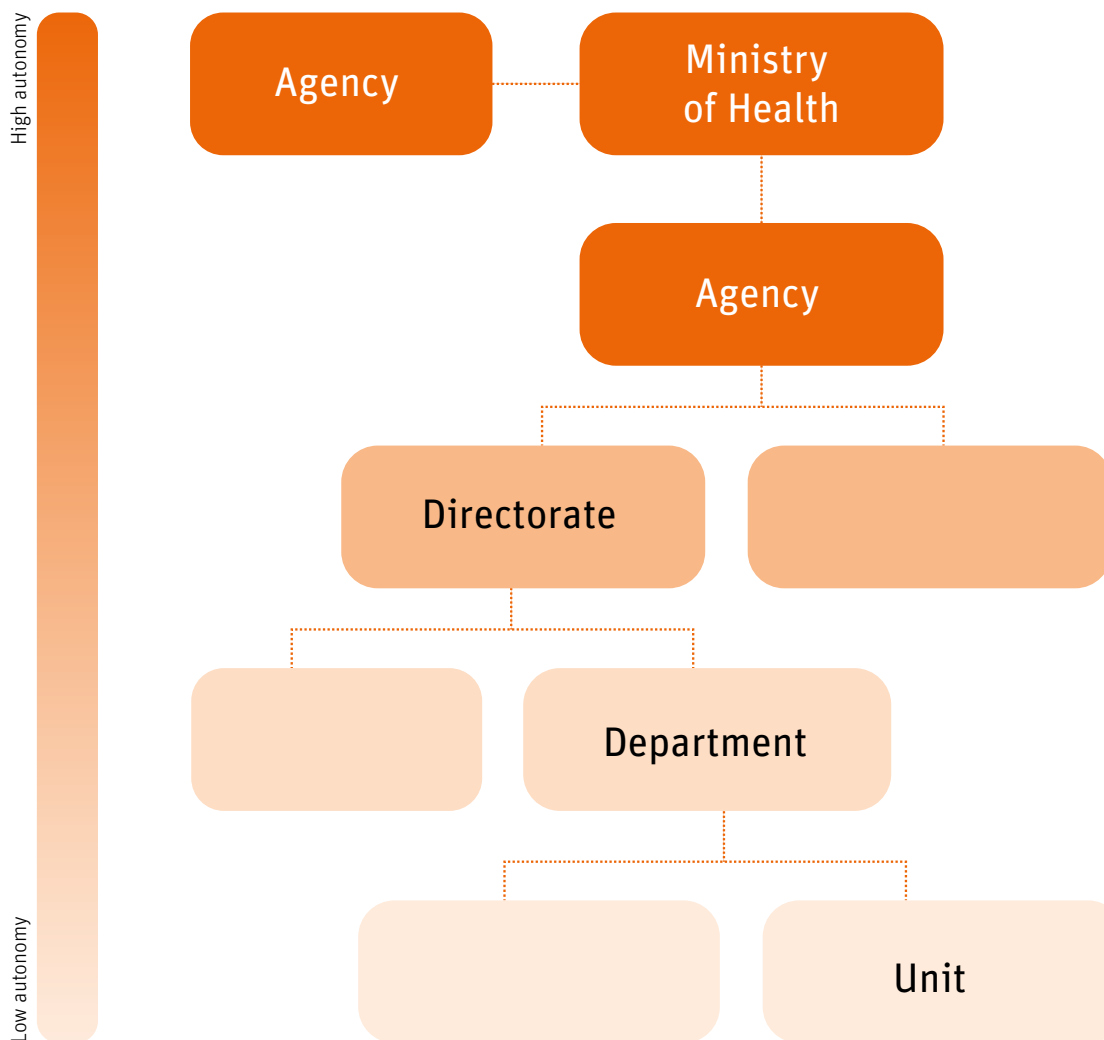


Note: In total there are 35 PAHO Member States, which represents 100%.

Eight countries (23%) have the most comprehensive legal bases and organizational frameworks for regulation and are home to NRAr; these are Argentina, Brazil, Canada, Chile, Colombia, Cuba, Mexico, and the United States of America. All these authorities are considered to have stronger oversight and enforcement mandates. Most of the countries with the greatest regulatory gaps lie in Central America and the Caribbean, although many of these are now involved in regulatory collaboration initiatives to address their needs for improvement (see Chapter 8).

In considering how the regulatory system is organized, the NRA's hierarchical position within and in relation to the national health authority (e.g., the ministry of health (MoH)) appears to be important (see Figure 1.3). The lower the position of the NRA in relation to the minister of health, the more burdensome processes become and the harder it is to fulfill regulatory functions effectively.

Figure 1.3. Potential degrees of separation between regulatory officials and ultimate decision-making bodies



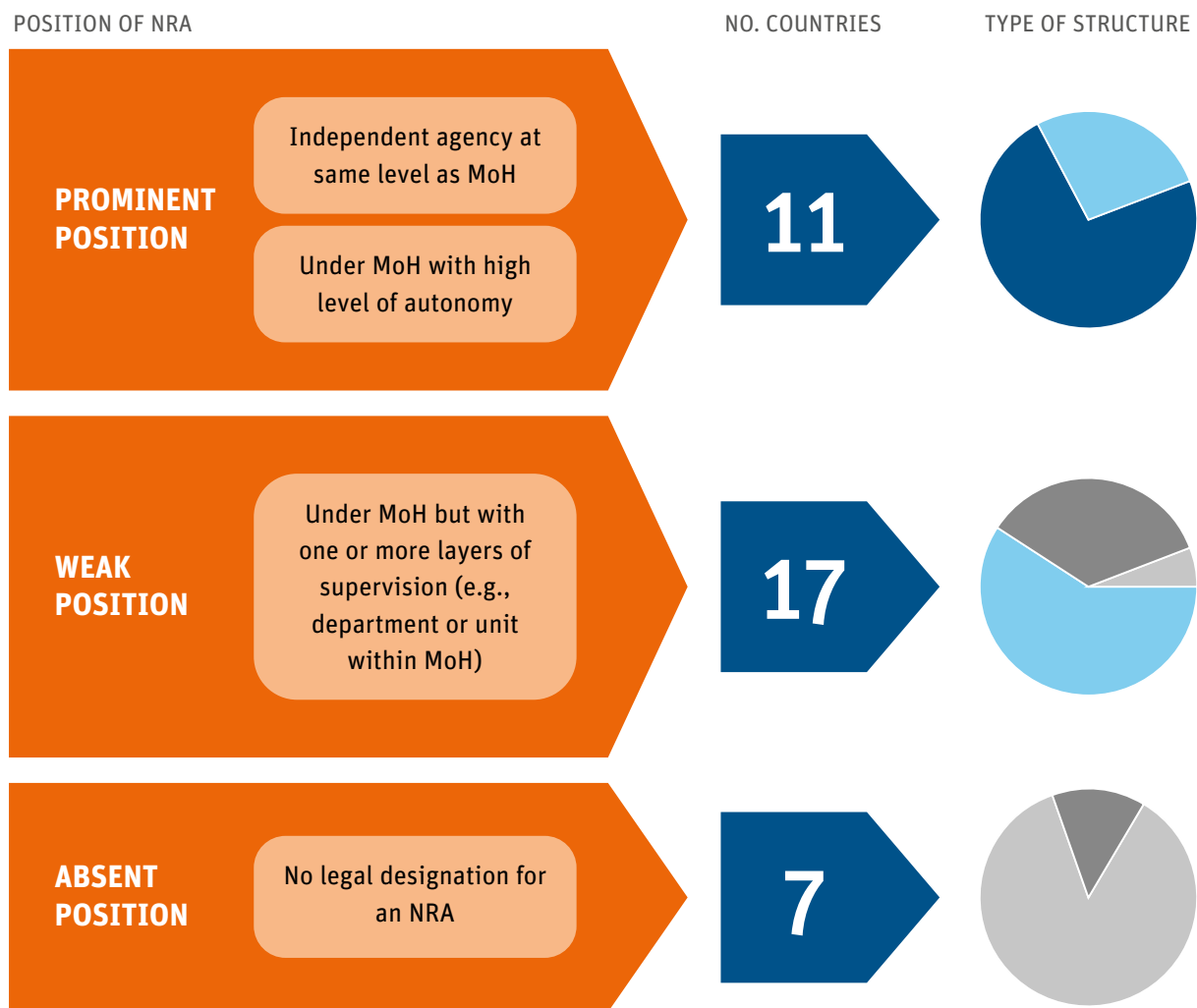
The most developed regulatory systems in the Region are marked by an NRA with a prominent position within the health system hierarchy (see Figure 1.4). For example, all NRAs are either standalone government agencies or enjoy a high degree of administrative, technical, and financial independence from the ministry of health and other government entities (see Box 2). This observation suggests that:

- countries that prioritize medicines regulation choose to create and nurture a high degree of technical and administrative independence for their regulatory authorities; and/or
- authorities with more administrative and technical independence are better equipped to fulfill regulatory functions well.

These points further suggest that changing the NRA’s position in the health system hierarchy could offer a route to regulatory system strengthening.

A quick summary overview of the NRA location within the government structure and the types of associated legal and organizational frameworks for countries in the Region is provided in Figure 1.4. Countries with NRAs that have a weaker or not clearly defined position within the MoH also have a less developed framework or no drug regulatory framework at all.

Figure 1.4. The position and capacity of NRAs within the health system hierarchy of PAHO Member States



KEY

MoH: ministry of health

- countries with most comprehensive legal and organizational framework (NRAs)
- countries with limited legal and organizational frameworks
- countries with foundational legal and organizational frameworks
- countries with no legal and/or organizational frameworks

Box 2. Position and structure of Latin American NRAR

ANMAT (Argentina)

ANMAT sits under the MoH with a high degree of technical, administrative, operational, and financial autonomy. It is a federal government entity that oversees all medical products at the national level and also coordinates and cooperates with provincial health authorities to ensure comprehensive and harmonized regulatory oversight at the local level.

ANVISA (Brazil)

ANVISA acts in coordination with, but independently from, the MoH. It has a high degree of technical, administrative, operational, and financial autonomy and coordinates regulatory oversight with state and municipal bodies. As a federal decentralized agency, ANVISA is headquartered in the capital, Brasília, and maintains a presence across the country, providing oversight in ports, airports, borders, and customs.

CECMED (Cuba)

CECMED is a centralized government agency that sits within the Ministry of Public Health, with a high degree of technical, administrative, and operational autonomy.

COFEPRIS (Mexico)

COFEPRIS is a deconcentrated government agency that sits within the MoH, with a high degree of technical, administrative, and operational autonomy, which coordinates with other regulatory bodies to ensure oversight of the market.

INVIMA (Colombia)

INVIMA is a centralized government agency that sits under the MoH, with full technical, administrative, operational, and financial autonomy. INVIMA is headquartered in the capital, Bogotá, and has a national presence to exercise the functions of inspection, surveillance, and sanitary control across the country, providing oversight in ports, airports, borders, and customs.

ISP (Chile)

ISP is a centralized government agency that sits within the MoH, with significant technical, administrative, and operational autonomy. It comprises a regulatory body (the Ministry of Public Health) and an executive body (the Public Health Institute, or ISP).

Stewardship and governance

Stewardship and governance are critical components of a regulatory system's organizational framework. Good governance requires credible and trustworthy institutions that are built on principles of transparency and accountability. The NRAR in the Americas all take a slightly different approach to governance (see Table 1.3) and their authorities are designated either with congressional oversight or directly by the executive branch. Their set-up reflects legal frameworks, standing within the national health system, and the constitutional underpinnings of the country.

There are differences in oversight and regulatory power depending on whether the country is federalist or unitary. For example, Chile, a unitary country, centralizes all regulatory functions while Brazil, which has a federalist constitution, shares regulatory responsibilities across central and state levels.

Table 1.3. Approaches to governance in NRAr

| NRAr | Highest authority | Selection process |
|--------------------------|--|--|
| ANMAT (ARGENTINA) | National administrator | <ul style="list-style-type: none"> Appointed by the Minister of Health |
| ANVISA (BRAZIL) | Director President of Board of Directors | <ul style="list-style-type: none"> Board is appointed by the executive (in agreement with the senate) for a five-year term. Director President is a member of the board chosen by the country's President. |
| CECMED (CUBA) | Director | <ul style="list-style-type: none"> Appointed by resolution of the Ministry of Public Health with the approval of the Presidents of the State and Minister Councils. |
| COFEPRIS (MEXICO) | Commissioner | <ul style="list-style-type: none"> Appointed by the President of the United Mexican States. |
| INVIMA (COLOMBIA) | Director | <ul style="list-style-type: none"> Appointed through presidential decree which is signed by the President and the Minister of Health. |
| ISP (CHILE) | Director | <ul style="list-style-type: none"> Chosen by the country's President from a list of candidates developed by ISP senior management. |

1.2.2. INSTITUTIONS AND INFRASTRUCTURE

While many countries delegate the regulatory oversight and enforcement of medicines and other health technologies to a single national entity or NRA, in most cases, this task involves more than one central player. Ideally, the different stakeholders involved in regulating medicines at different points along their life cycle should be organized and integrated into a functional, well-coordinated system. The coexistence of multiple players within the system allows, in many cases, for a high degree of specialization in specific functions. At the same time, it poses a coordination challenge in ensuring a systems approach along the product life cycle.

Functional systems can be organized in different ways and through different structures. Federalist countries may have a national centralized authority that coexists with provincial or state authorities with different levels of jurisdiction, but these are expected to work in an integrated and coherent way to ensure the safety, effectiveness, and quality of products at both state and national levels. Similarly, while the centralized authority may perform most of the regulatory functions, some specific ones, such as laboratory testing or ethical oversight of clinical trials, may be done by decentralized institutions.

In Latin American NRAr countries, the NRAr is the main, but not the only, institution involved in regulating medicines (see Table 1.4). In both Argentina and Brazil, the organization of the national regulatory system mirrors the country's constitutional organization, and provincial and state authorities retain regulatory functions. In Argentina, these authorities only have jurisdiction over products that are made and used in their own province; once a product crosses provincial lines for national or international commerce, it comes under the jurisdiction of ANMAT. In Brazil, state and municipal governments retain some oversight functions over locally produced medicines, such as GMP inspections, regardless of whether these go to local, national, or international markets.

Table 1.4. Organizations and institutions involved in regulating medicines in NRAr countries

| Country | Institutions | Regulatory functions | | | | | | | |
|------------------|---|----------------------|------------------------|-------------------------------------|------------------------|---------------------------|-------------|-------------|-----------------|
| | | Market authorization | Licensing ^a | Surveillance & control ^b | Vigilance ^c | Clinical trials oversight | Inspections | Lab testing | NRA lot release |
| ARGENTINA | ANMAT | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Instituto Nacional de Medicamentos | | | | | | | ✓ | ✓ |
| | Autoridades Provinciales | ✓ | ✓ | | | ✓ | ✓ | | |
| | Programa Ampliado de Inmunizaciones | | | | ✓ | | | | |
| BRAZIL | ANVISA | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| | Vigilância Sanitária local (Visa) | | ✓ | ✓ | | | ✓ | | |
| | Programa Nacional de Imunizações | | | | ✓ | | | | |
| | Conselho Nacional de Ética em Pesquisa | | | | | ✓ | | | |
| | Instituto Nacional de Controle de Qualidade em Saúde | | | | | | | ✓ | ✓ |
| CHILE | ISP | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Ministerio de Salud | | | | | ✓ | | | |
| | Programa Nacional de Inmunizaciones | | | | ✓ | | | | |
| | Secretarías Regionales Ministeriales de Salud | | | | | ✓ | | | |
| COLOMBIA | INVIMA | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Ministerio de Salud y Protección Social – Programa Ampliado de Inmunizaciones | | | | ✓ | | | | |
| | Entidades Territoriales de Salud | | | | ✓ | | ✓ | | |
| CUBA | CECMED | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Ministerio de Salud Pública | | | | | ✓ | | | |
| | Programa Nacional de Inmunizaciones | | | | ✓ | | | | |
| | Centro Nacional Coordinador de Ensayos Clínicos | | | | | ✓ | | | |
| | Comisión Nacional de Bioética | | | | | ✓ | | | |
| MEXICO | COFEPRIS | ✓ ^d | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Comisión Nacional de Bioética | | | | | ✓ | | | |
| | Comisión de Control Analítico y Ampliación de Cobertura | | | | | | | ✓ | |

Notes: All institution names are in the language of the country; ^a Licensing of pharmacies and wholesalers is decentralized to local health authorities; ^b Local health departments carry out surveillance and control through partnership agreements with NRAr; ^c Vigilance activities usually function through a network agreement involving authorities such as customs, police, and state-level health departments, among others; ^d In partnership with Authorized Third Party.

In all cases, NRAR have invested heavily in building a comprehensive system based on strong coordination and cooperation across institutions and functions. All have succeeded in achieving horizontal integration across the system. Maintaining this level of coordination, however, poses an ongoing challenge as institutions and their leaders change and evolve; it becomes particularly difficult during public health emergencies that require swift decisions and actions. Beyond NRAR, many regulatory systems in the Region have not achieved the necessary coordination to work effectively. The need for better integration through standard operational procedures and formal communication channels with relevant stakeholders is perhaps one of the most common observations made during PAHO-led evaluations of national authorities in the Region.

1.2.3. FINANCING

Levels of financing available to regulatory systems can have a large impact on how comprehensive and effective they are. Although vital to health systems, regulatory systems can be resource intensive. Adequate financing ensures they have enough resources, human and otherwise, to perform their duties.

Sources of funding

Latin American NRAR are funded through different mechanisms. NRAR charge regulatory user fees for market authorization, but also in some cases for other functions like inspections. Latin American NRAR have other sources of financing from their governments (see Table 1.5). These may include monies earned from fines related to enforcement actions (as in the case of ANVISA and INVIMA) or from revenue generated from assets like building rentals. Although there is debate over the appropriate mix of user fees in agency funding, some argue that it gives industry confidence that their payments are directly related to NRA performance on for example marketing authorization timelines. It is a good practice for user fees to be controlled by the NRA instead of going back to the government treasury; however, this is not typically an implemented practice in many NRAs throughout the Americas.

Table 1.5. Sources of financial resources for NRAR

| NRAR | Regulatory user fees charged | Selection process |
|-----------------------|------------------------------|---|
| ANMAT ^a | ✓ | • 100% user fees/other |
| ANVISA ^a | ✓ | • 50% user fees/other • 50% government |
| CECMED ^a | ✓ | • 36% user fees/other • 64% government |
| COFEPRIS ^b | ✓ | • 68% government • 32% user fees |
| INVIMA ^a | ✓ | • 100% user fees/other |
| ISP ^c | ✓ | • 54% user fees/other • 46% government |

Sources: ^a PAHO Country Survey conducted among NRAs in June 2019; ^b PAHO Country Survey conducted in September 2020. Data correspond to COFEPRIS 2019 budget; ^c Law No. 21.125 published in the official gazette of December 28, 2018 in accordance with the ruling No. 5735-18 of the Constitutional Court. Directorate of Budgets, Government of Chile.

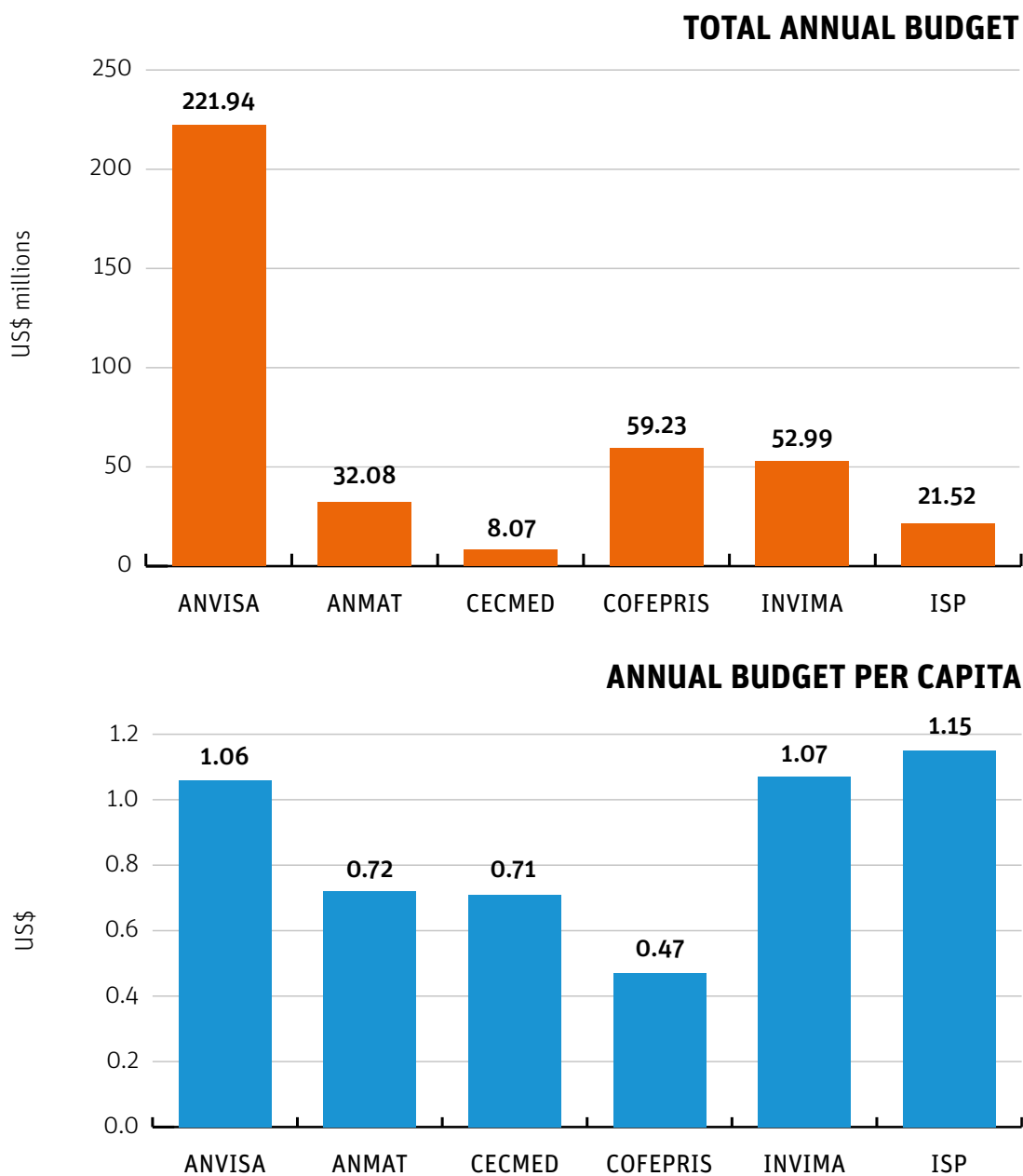
In general, Latin American NRAR user fees are relatively low compared with those charged by regulatory bodies in Canada, Europe, or the United States of America in absolute amount (7). These differences may reflect market size and the relative profit that industry expects to earn in a specific market; however, the ratio of fee size to country income status is also low compared with recognized agencies like the FDA (see Chapter 3: Marketing Authorization of Pharmaceutical Products, Figure 3.4). Lower fees hinder appropriate cost recovery and financial backing of the

NRAr. This is a particularly serious problem in subregions of the Americas with small populations and volumes of sale. In Caribbean countries, for example, user fees for marketing authorization range from US\$ 50–150 and this revenue often goes to the government rather than the NRA.

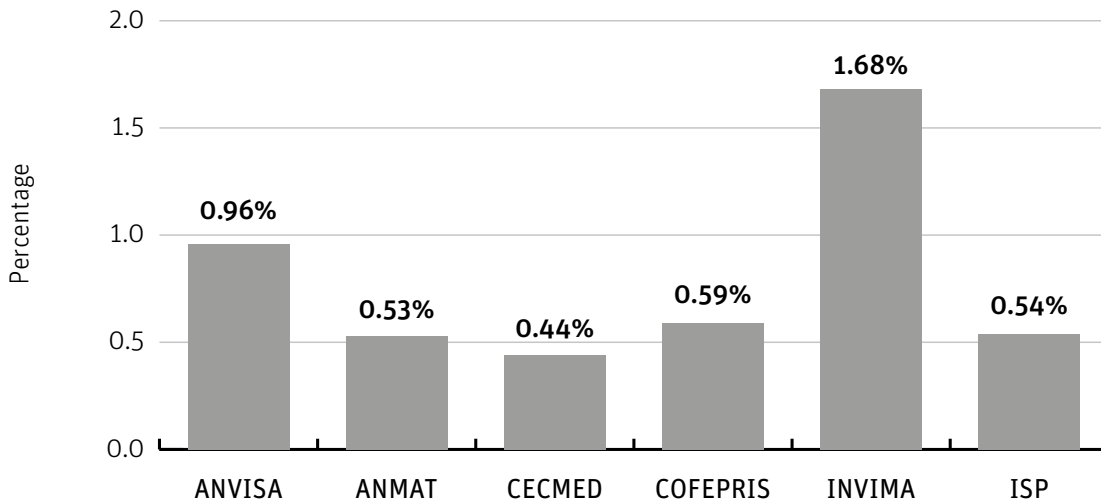
Annual budgets

In 2019, annual budgets across the NRAr ranged from nearly US\$ 222 million in Brazil to just over US\$ 8 million in Cuba. These differences reflect not only differences in resourcing but also differences in market size and population (see Figure 1.5). When standardized for budget per capita, ISP has the largest budget and COFEPRIS the smallest. The relationships are similar when looking at budget as a percentage of market value in dollars. In some cases, these numbers are only proxies for investment because they do not reflect funding for decentralized or state-led regulatory activities. As a reference for comparison, the 2019 fiscal year budget for the FDA was US\$ 5.7 billion, or US\$ 17.38 per capita.

Figure 1.5. Annual budgets for NRAr

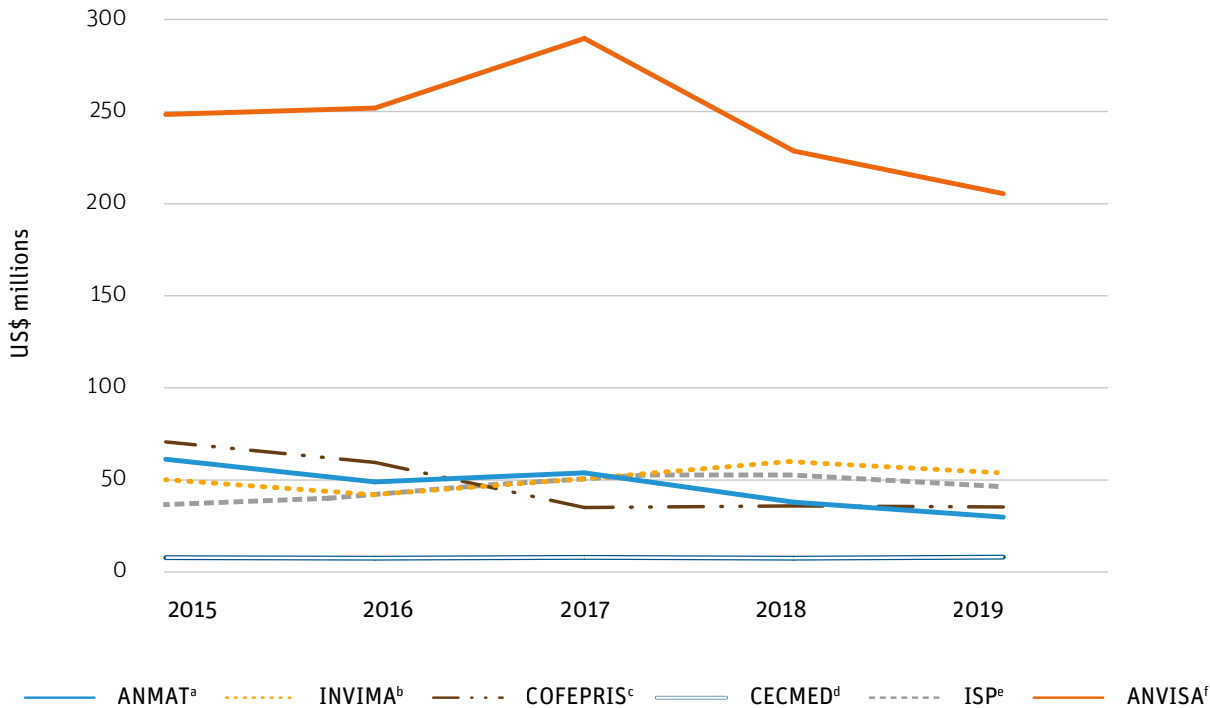


ANNUAL BUDGET AS % OF MARKET SIZE



The budgets for Latin American NRAR have remained relatively static over the past five years (see Figure 1.6), but the pharmaceutical markets in most of these countries have increased in both value and volume (see Chapter 2: Market Outlook). For example, even though Brazil's pharmaceutical market grew 12% in value and 8% in volume between 2015 and 2019 (8), ANVISA's budget fell. This highlights an important challenge for agencies to develop efficiencies as their responsibilities and volume of work increase with stagnant or decreasing funding.

Figure 1.6. NRAR budgets over time (2015–2019)



Note: Exchange rate history for each country was obtained using its central bank or the UN treasury website.

Sources: ^a Presupuesto abierto del Ministerio de Economía de Argentina [Internet]. Buenos Aires: Ministry of Finance; 2020. Quien gasta? Available from: <https://www.presupuestoabierto.gob.ar/sici/destacado-quien-gasta#>, cited 10 June 2020; ^b Ministerio de Hacienda y Crédito Público. República de Colombia: Decreto 2710 (December 26, 2014); Decreto 2170 (December 27, 2016); Decreto 2236 (December 27, 2017); Decreto 2467 (December 28, 2018); Ley 2008 (December 27, 2019); ^c Diario Oficial de la Gobernación, Secretaría de Gobernación, Estados Unidos Mexicanos. (Authorized budget calendar for fiscal years 2015 to 2019, cited 31 May 2020); ^d CECMED. Memoria de actividades 2018. Havana: CECMED; 2019. Available from: https://www.cecmecmed.cu/sites/default/files/adjuntos/reporte_anual/Memorias%20de%20actividad%20CECMED%202018.pdf, cited 10 June 2020; ^e Ministerio de Hacienda, Dirección de Presupuestos. República de Chile: Ley No 21.125 (Diario Oficial del 28 de diciembre de 2018); Ley No 21.053 (Diario Oficial del 27 de diciembre de 2017); Ley No 20.981 (Diario Oficial del 15 de diciembre de 2016); Ley No 20.882 (Diario Oficial del 5 de diciembre de 2015); Ley No 20.890 (Diario Oficial del 26 de diciembre de 2015); Ley No 20.798 (Diario Oficial del 6 de diciembre de 2014); ^f Quadro Detalhamento Da Execução Orçamentária Por Programa De Governo. In: Portal ANVISA [Internet]. Brasília: ANVISA; 2020 (portal accessed 1 June 2020).

1.2.4. HUMAN RESOURCES

Competent and sufficient human resources are critical for regulatory systems. The number of people working within Latin American NRAr varies from country to country, with ANVISA having the largest workforce and CECMED the smallest (see Table 1.6). It is important to note that in the case of Argentina and Brazil, the numbers only capture the workforce at the central agency and not at the state or provincial level. Other ways of looking at the staffing include counting the number of regulators per 1 million inhabitants, in which case ISP has the highest level of staffing and ANVISA the smallest. For comparison, there were 17,468 full-time equivalent staff at the FDA in 2018 (53 regulators per million inhabitants).

Table 1.6. Characteristics of the workforce within NRAr

| NRAr | Number of centralized workers (2019) ^a | Workforce structure | Number of regulators per 1 million inhabitants |
|-------------------|---|-------------------------------|--|
| ANMAT (ARGENTINA) | 1,074 | Centralized and decentralized | 24 |
| ANVISA (BRAZIL) | 1,769 | Centralized and decentralized | 8 |
| CECMED (CUBA) | 309 | Centralized | 27 |
| COFEPRIS (MEXICO) | 1,642 | Centralized | 13 |
| INVIMA (COLOMBIA) | 1,773 | Centralized | 36 |
| ISP (CHILE) | 842 | Centralized | 45 |

Note: ^a These data do not include people working within decentralized institutions in the case of Argentina and Brazil.

Staffing can impact the NRA’s ability to carry out regulatory functions. Agencies with fewer human resources may need to use other strategies to accomplish more with less; for example, relying on other authorities’ decisions or reducing administrative burdens through better use of electronic systems to receive, manage, and store data. Some small countries in the Americas have no dedicated staff and must consider how to prioritize the most critical regulatory functions (see Chapter 8: Trade and Economic Integration Mechanisms).

Another factor to consider when assessing the impact of staffing on regulatory oversight is the ratio between technical and administrative staff, their level of education, and the proportion of permanent versus temporary or contract workers. Data from the Region are difficult to compare because they are not recorded in the same way across systems. In general, too many administrative staff may come at the expense of scientific work, and too many temporary staff can harm continuity of mission and purpose and pose a threat to control of conflicts of interest. Because regulatory oversight is complex, it requires hands-on training, coaching, and time, in addition to the usual professional qualifications. Therefore, low retention and high staff turnover are generally considered to hinder regulatory performance, consistency, and predictability.

1.3. Efficiencies and Best Practices

Reliance

Reliance is a critical efficiency for regulatory systems (see Box 3). It can be used across a variety of different functions, including market authorization, inspections, and pharmacovigilance. It helps reduce workload so that resources can be prioritized elsewhere and is used by regulatory systems large and small. However, there are

challenges with implementation, such as sovereignty concerns, lack of sustained high-level political commitment to develop enabling legal and policy frameworks, and even competitiveness. To the latter point, reliance on another NRA decision can increase competition from importing companies and cause a perceived threat to local industries. The benefits seem to far outweigh the concerns, and this report will make a repeated case for more use of reliance by all NRAs in the Americas.

Box 3. What is regulatory reliance?

WHO defines regulatory reliance as “the act whereby the NRA in one jurisdiction may take into account and give significant weight to (i.e., 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.”¹

In this context, NRAs that use regulatory reliance leverage the work done by other NRAs to support their own decision-making. For example, an NRA may use the decision or information of a trusted NRA as the basis for its own regulatory decision.

In Latin America, the practice of regulatory reliance is encouraged by PAHO and PANDRH, which identifies five principles for practicing reliance: sovereignty, transparency, consistency, legal basis, and competency.²

Sources:

1. World Health Organization. Good regulatory practices: guidelines for national regulatory authorities for medical products. Geneva: WHO; 2016.
2. PANDRH. Regulatory reliance principles: concept note and recommendations. Washington, DC: Pan American Health Organization; 2018.

Harmonization

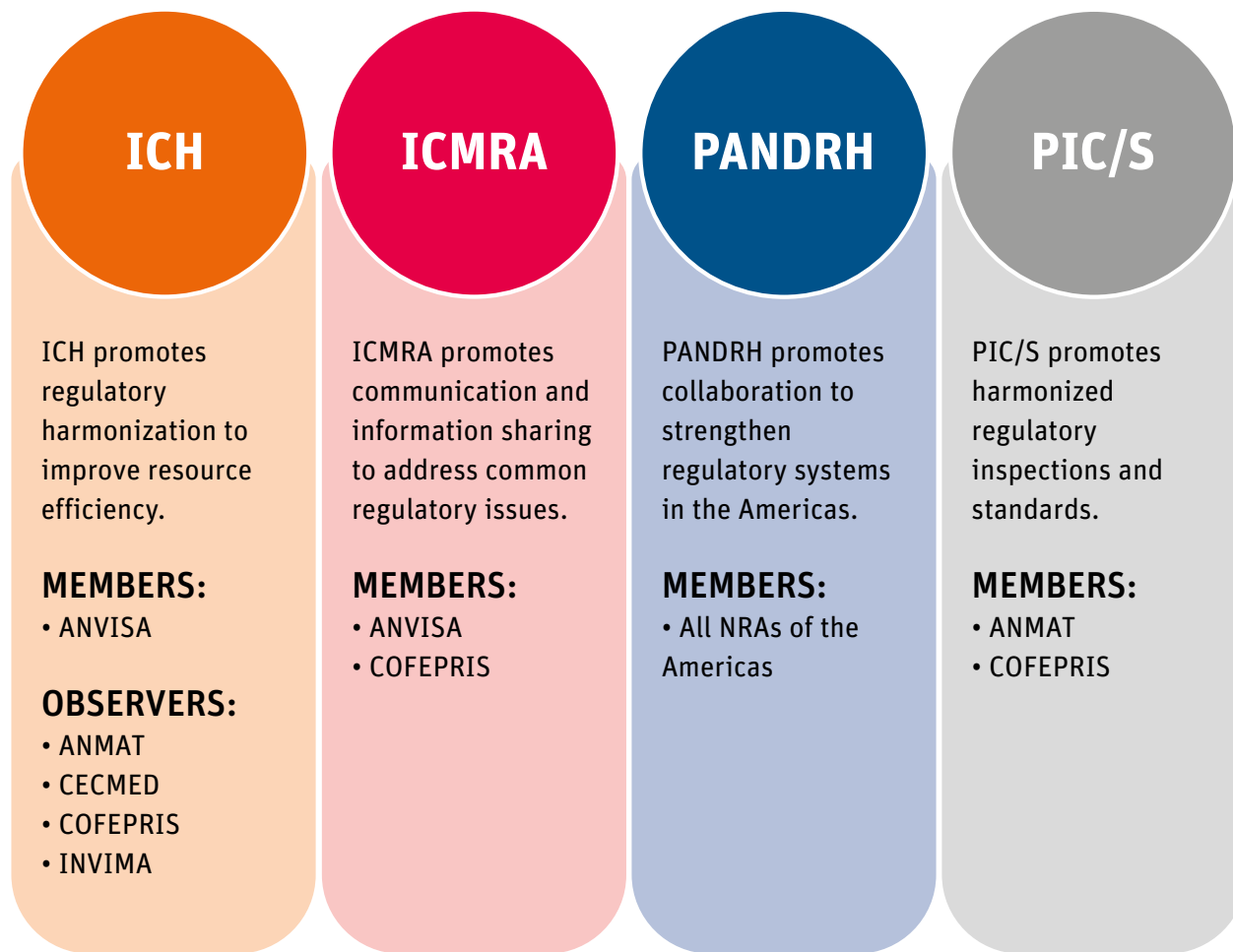
Participation in international harmonization and convergence initiatives can help to strengthen regulatory systems. It suggests that the NRA is willing to adopt and comply with established international standards and that it is open to collaborating with others. Moreover, the adoption of international standards usually translates into improvements for pharmaceutical companies that work in multiple markets, as they can then manufacture their products to a single common standard. It may also improve the reach of local manufacturers by facilitating export to other markets using the same standards.

In Latin America, all NRAs recognize the value of international harmonization and all participate in one or more harmonization initiatives within the Region and beyond (see Figure 1.7). All Latin American NRAs have a vital role in the Region’s oldest harmonization initiative, PANDRH, which focuses on providing a forum for exchanging information and best practices toward harmonizing regulatory requirements, including through membership in global harmonization initiatives. Brazil has made notable progress globally and is now a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Four more countries—Argentina, Colombia, Cuba, and Mexico—have recently been accepted as ICH observers.

Other forums are also relevant. The International Coalition of Medicines Regulatory Authorities (ICMRA) promotes communication and information sharing to address regulatory issues, and ANVISA and COFEPRIS are

both members. Another important forum is the Pharmaceutical Inspection Co-operation Scheme (PIC/S), which supports regulatory inspections by developing common standards in the field of good manufacturing practice and ensuring that those standards are implemented consistently across jurisdictions. Joining PIC/S requires a detailed assessment of the NRA's inspectorate, and both Argentina and Mexico have been able to gain membership. Despite these achievements, there are still only a few NRAs in the Region that participate in global harmonization networks, and more needs to be done to bring other agencies into these forums.

Figure 1.7. Latin American NRAr participation in international harmonization initiatives



Information sharing

Information sharing is foundational to regulatory success in an increasingly globalized world. All NRAr have bilateral or multilateral arrangements with other countries to share information and cooperate on a broad range of regulatory issues, but there are differences in the types of authorities they share information with (see Table 1.7). There is a high degree of information sharing with other NRAr, but less sharing with other stringent regulatory authorities (SRAs) or with authorities in Central America and the Caribbean. Information-sharing arrangements can be time-consuming and difficult to execute among many competing demands. They reflect the priority an NRA gives to information from other agencies, which can be based on trust or common products, be driven by risk, or by economic and trade interest between countries. Smaller authorities are less likely to have information-sharing arrangements, which can pose challenges for activities like reliance and post-market surveillance.

Outside bilateral or multilateral information-sharing agreements, there are other ways to share information, including through regulatory networks of focal points. Smaller authorities use these less-formal channels as well as publicly

available information from advanced authorities. Hence, all NRA, but in particular these smaller authorities, would benefit from more transparency of information from advanced authorities (see Chapter 3: Marketing Authorization of Pharmaceutical Products, Table 3.4 and Chapter 5: Good Manufacturing Practice Inspections, Table 5.3).

Table 1.7. Major regulatory confidentiality and information-sharing arrangements across NRAr

| NRA | NRAr | SRA | South America | Central America | Caribbean | India/China | Other |
|---------------|------|-----|---------------|-----------------|-----------|-------------|-------|
| ANMAT | ✓ | | ✓ | | | ✓ | ✓ |
| ANVISA | ✓ | ✓ | ✓ | | | ✓ | ✓ |
| CECMED | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ |
| COFEPRIS | ✓ | | ✓ | ✓ | ✓ | | |
| INVIMA | ✓ | | ✓ | | | | |
| ISP | ✓ | | ✓ | | | | |
| TOTALS | 100% | 17% | 100% | 34% | 34% | 50% | 50% |

Recommendations for Action

- **Develop legal and organizational frameworks.** The limited or complete lack of legal and organizational frameworks for regulatory systems in a number of countries in the Americas today is worrisome. As this increases the risk that their populations will not have access to safe, quality, and effective medicines, the development of such frameworks should be addressed and prioritized as soon as possible.
- **Prioritize resources for NRA assessment.** Resources are needed for PAHO/WHO and peer assessment teams to continue to spur regulatory system strengthening through the periodic evaluation of IDP processes and their modification if needed.
- **Boost sustainability and efficiency.** Governments and NRAs must consider ways to increase sustainability and efficiencies of regulatory systems. Elements and strategies to secure adequate funding, autonomy, and efficiencies such as reliance should be assessed and properly addressed if needed.
- **Participate in harmonization initiatives.** NRAs should continue to increase their engagement in global harmonization activities and take up foundational guidelines adapted to their health system context.
- **Revisit the landscape of regulatory systems in the Americas on a periodic basis.** Stakeholders should prioritize this landscape to include key metrics that can be harmonized to facilitate better analysis and understanding across NRAs and drive performance improvement.

2. MARKET OUTLOOK

In brief

- There are large and growing pharmaceutical markets in Latin America, which is one of the fastest growing regions in the world.
- Biotherapeutics make up an increasingly costly segment of the market and will continue to do so in the future.
- Although data are difficult to interpret because of differing definitions, there appear to be opportunities for cost savings through more generic penetration of markets.
- NRAs have an important role to play in creating an enabling environment for generic medicines, such as through more efficient review processes and timelines, and this in turn fosters competition that can lower prices.
- There is significant local production in NRAr countries, especially Argentina, Brazil, and Cuba.
- Trading patterns tend to be shaped by geographical proximity and integration mechanisms, with high levels of trade within Latin America and to a lesser extent Central America.
- Raising regulatory standards can positively affect export prospects; for example, in the case of Mexico becoming an NRAr and increasing its exports to Central America via reliance.
- There is no major export base to markets like Canada or the United States of America, though a number of strategic shortage products are manufactured in Latin American NRAr.
- NRAr rely heavily on imports of raw and finished products, often from China and India.
- Local production is increasingly seen as a way of addressing pharmaceutical budgets, as well as reducing dependence on foreign sources.
- Argentina, Brazil, Cuba, and Mexico manufacture similar biotherapeutic products (also known as biosimilars) but there is not significant export of these.
- While there is increased interest in local manufacturing, there also appear to be important challenges and opportunities in relation to regulatory oversight and uptake of generics and similar biotherapeutic products. Assuring the quality of locally made products, especially in new areas such as biologics and similar biotherapeutic products, remains a regulatory challenge.

2.1. Market Trends in the Region

An analysis of market dynamics is important to understand the forces that shape medicines regulations. In Latin America, as everywhere else, these dynamics are marked by changes in demand and supply. On the demand side, there are three key trends across the Region:

- Increasing prosperity. Several countries are experiencing rising levels of gross domestic product (GDP) that is increasing prosperity and changing lifestyles, prompting a transition in epidemiology toward noncommunicable, rather than infectious, diseases (9).
- Aging populations. Many societies are growing older and will require more health care (10).
- Broadening health coverage. Health systems are increasingly covering more people, which adds to demand and budgetary pressures (11).

On the supply side, Latin American economies are historically and culturally tied together through multiple integration mechanisms and trade agreements in globalized supply chains. Innovation is spurring an array of new, more complex and significantly more expensive products that is driving an increasing dependency on imports. A few governments are pursuing industrial policies that support local production to reduce the otherwise growing deficit in the trade balance of pharmaceuticals.

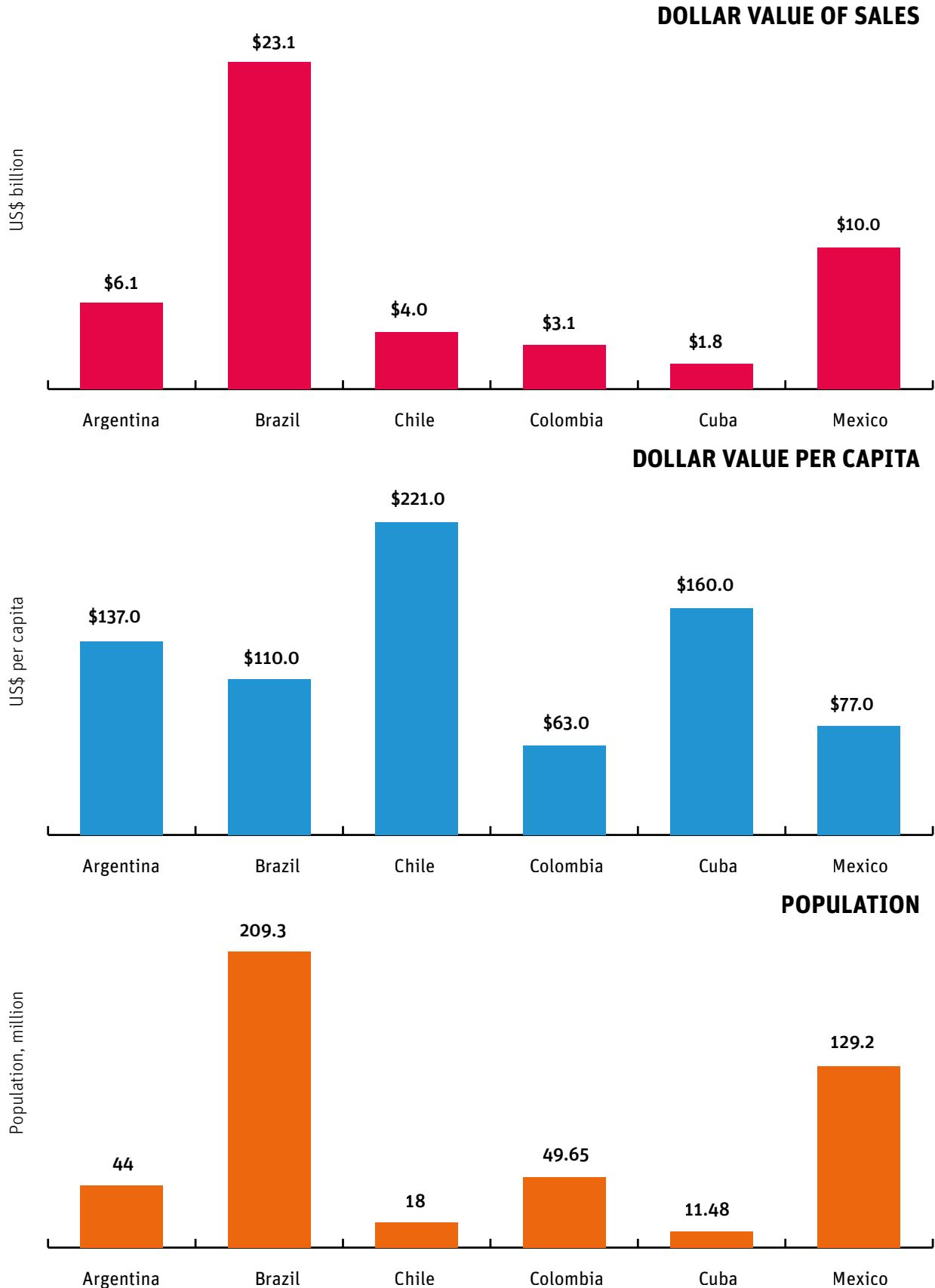
2.1.1. MARKET SIZE

There are some important metrics for characterizing pharmaceutical markets, including:

- population size indicates the number of potential customers; and
- dollar value of sales or volume of units sold are different ways to discuss the level of business activity in the market.

By any of these measures, NRAR country markets vary. Cuba is the smallest market when measured by population size and dollar value of sales, while Brazil is the largest (see Figure 2.1). The Brazilian pharmaceutical market is the sixth largest in the world, behind the United States of America (US\$ 340 billion), Japan (US\$ 94 billion), China (US\$ 87 billion), Germany (US\$ 46 billion), and France (US\$ 37 billion) (12). Mexico is the second largest regional market in terms of both population and dollar value of sales (see Figure 2.1). Both Brazil and Mexico are among the 10 most populous countries of the world; together their pharmaceutical markets are twice as big as all the other NRAR markets put together. Market value per capita, however, reveals a different picture. Per capita assessments are important because they give a measure of how lucrative a market may be. By this, Chile, Cuba, and Argentina are the three biggest NRAR markets (see Figure 2.1). The United States of America, for comparison, has a per capita market value of US\$ 1,044 (13).

Figure 2.1. NRAr market size by dollar value of sales, dollar value per capita, and population



Source: Adapted from: IQVIA. Pharmaceutical Market Landscape in Latin America. Washington, DC: IQVIA; 2019.

2.1.2. MARKET GROWTH

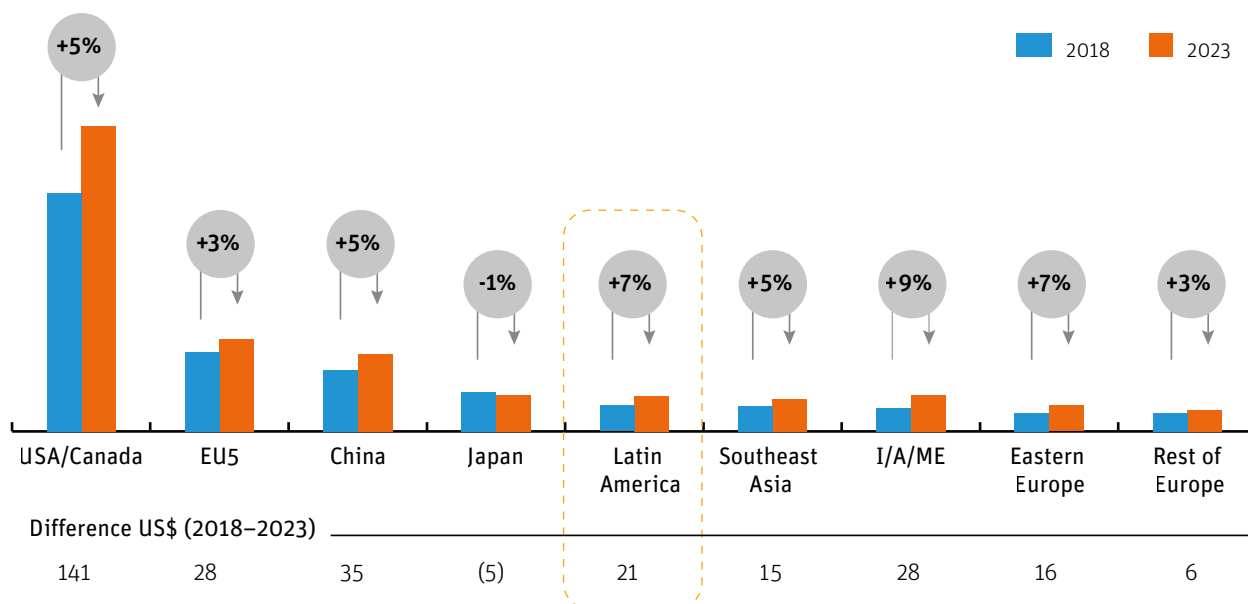
Analysis by data science company IQVIA predicts the global pharmaceuticals market will grow 3%–6% from 2018 to 2022. Within this global trend, individual countries and regions will experience variable growth rates. The fastest growth is expected to occur in the so-called “pharmerging” markets of low- and middle-income countries (LMICs) where pharmaceutical use is growing fast. These markets, which include both Brazil and Mexico, are predicted to grow 6%–9% between 2018 and 2022, compared with 0%–3% in high-income countries and 2%–5% in the rest of the world (14).

Driven in part by these two fast-growing markets, the collective Latin American NRAR pharmaceuticals market is predicted to grow 7% by 2023. This makes it the second-fastest growing regional market of the world (see Figure 2.2).

Figure 2.2. Predicted growth rates of regional pharmaceutical markets (US\$ 2018–2023)

Total market in values

Thousands of millions US\$; CAGR (%) 2018–2023



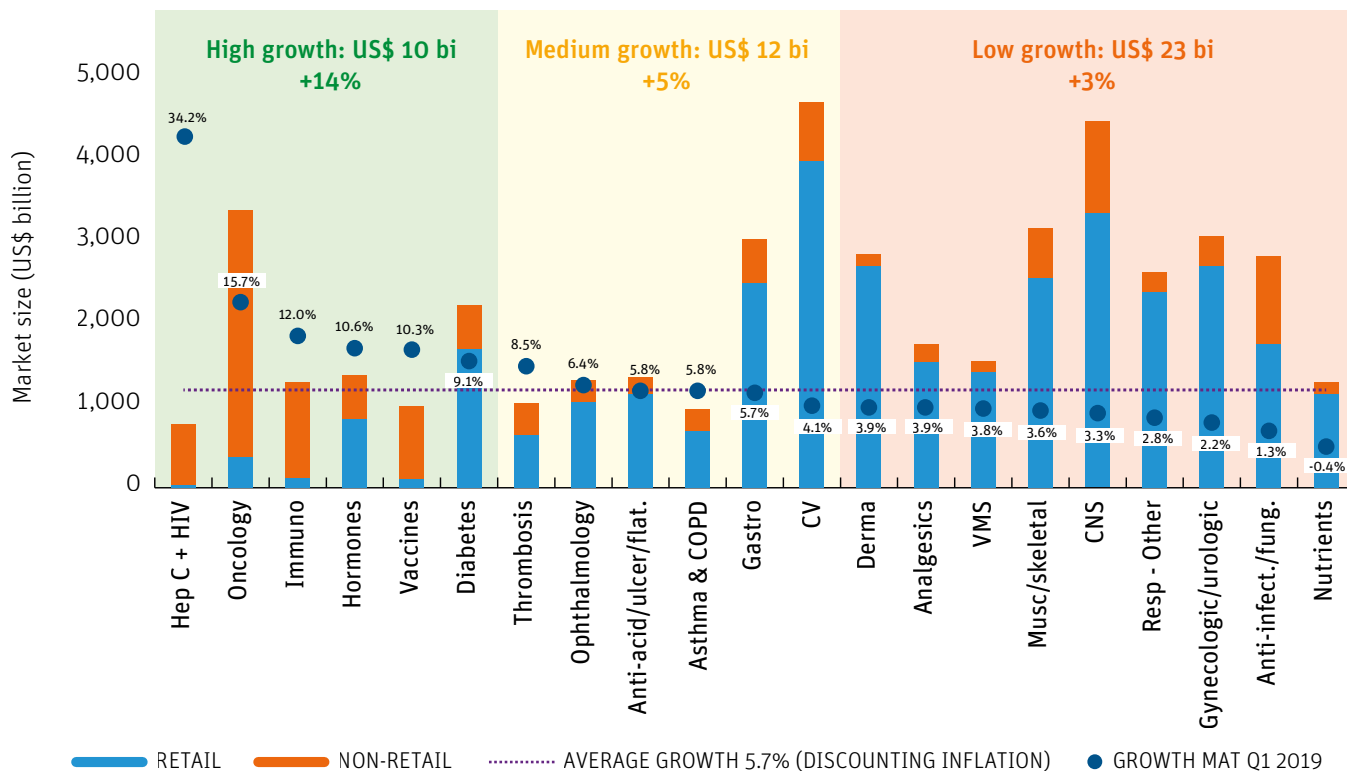
Notes: EU5: European Union Five (France, Germany, Italy, Spain, United Kingdom); Latin America: Argentina, Brazil, Chile, Colombia, Mexico, and Peru; Southeast Asia: Australia, Democratic People’s Republic of Korea, Indonesia, Malaysia, Philippines, Singapore, Taiwan, Thailand, and Viet Nam; I/A/ME (India, Africa, and the Middle East): Algeria, Bangladesh, Egypt, Kazakhstan, India, Nigeria, Pakistan, South Africa, and United Arab Emirates; Eastern Europe: Czech Republic, Hungary, Poland, Romania, Russian Federation, Slovakia, and Turkey; Rest of Europe: Belgium, Denmark, Finland, Greece, Netherlands, Portugal, Sweden, and Switzerland.

Sources: IQVIA Market Prognosis Issue March 2019, ex-man price. MIDAS, ex-manufacturer price, do not include rebate and discount. Have audited and not audited data. Brazilian. Market Price List non-institutional and institutional markets in second level of price. Growth in constant US\$, except Argentina (because of the high inflation rate).

The growth dynamics of different therapeutic areas in Latin America can be divided into high, medium, and low (see Figure 2.3). The fastest-growing areas include hepatitis C and HIV, oncology, and immunotherapy. Many of the new products in these areas will be expensive biologics that are paid for in the non-retail space and so will increasingly strain government budgets. In the United States of America, biologics’ share of pharmaceutical spending has already increased from 13% to 27% between 2006 and 2016 (15). Across the therapeutic areas of

medium and low growth, most products are bought in the retail setting, meaning that different payers, including patients spending out of pocket, will be more affected.

Figure 2.3. Growth dynamics of different therapeutic areas in Latin America



Notes: Latin American Pharmaceutical Market (US\$ billion) – audited market.

Countries surveyed: Argentina, Brazil, Chile, Colombia, Ecuador, Mexico, and Peru.

Sources: Retail Market MIDAS MAT Q1 2019 with Brazil @ price PPP; NRC Brazil MAT Q1 2019 @ 2nd price level; SISMED Colombia MA T Q1 2019; Mexico NRC+GSdT MAT Mar-19 @ ex-mnf price level; NRC Ecuador MAT Q1 2019; NRC market in other countries estimated (ARG, C.A., CHL, PER). Growths calculated in constant US\$ exchange rates. Exchange rates: ARG 38.87; BRA 3.77; CHL 667; COL 3135; ECU 1.00; MEX 19.21; PER 3.32.

Market size and growth in the pharmaceutical sector are heavily influenced by macroeconomic factors. The devaluation of a currency or exchange rate can have a significant impact on the dollar value of a market. It can also make it more difficult to import active pharmaceutical ingredients (APIs) or finished pharmaceutical products (FPPs), especially those based on more advanced (and expensive) technologies, including biologics.

2.1.3. THE RISING COST OF BIOLOGICS

Data consolidated for this report show that while biologics currently make up a small proportion of NRAr markets in market by volume (ranging from 1% in Colombia to 6% in Argentina), they are expected to significantly increase their share of the market over the next five years.

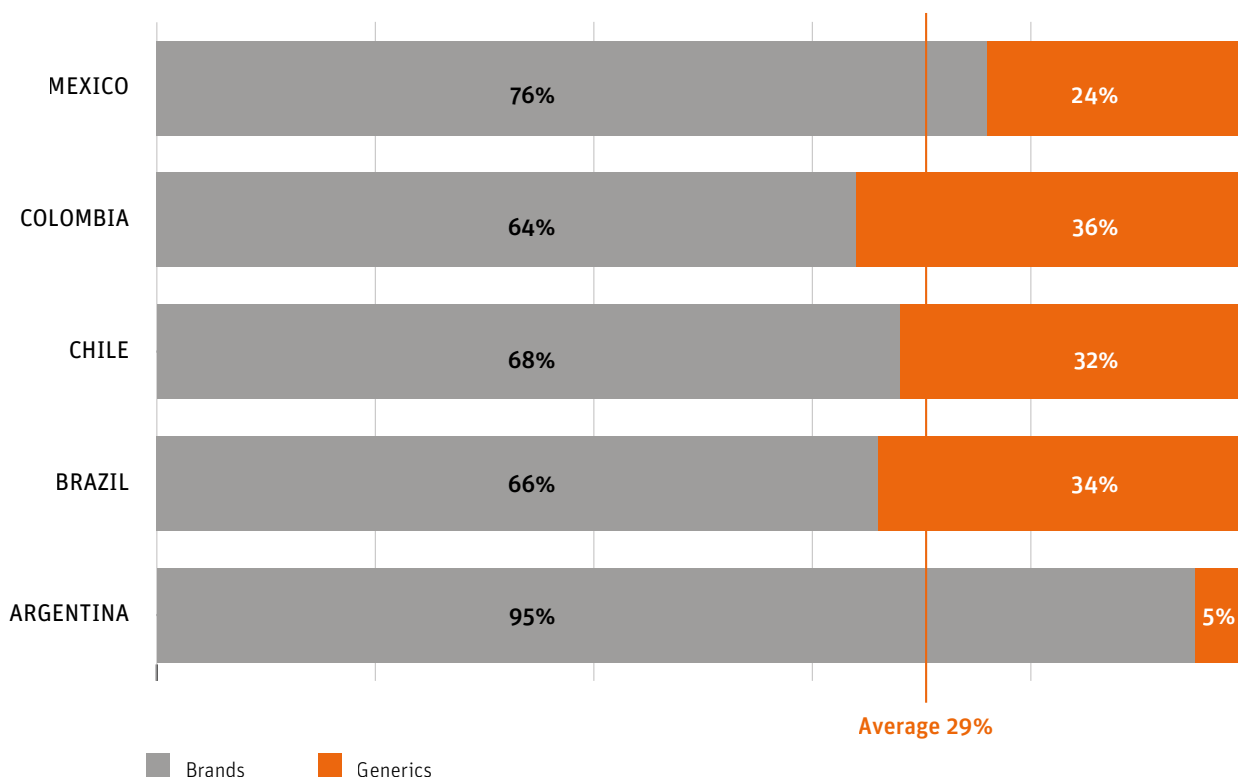
Experience from other countries and regions where biologics are already prevalent suggests that this predicted rise will cause significant financial pressures for payers of medicines, including patients, insurers, and governments. A steady rise in levels of prescribed biologics in the United States of America, for example, is already causing these

medicines to represent a disproportionate amount of total expenditures. In 2018, biologics were less than 2% of prescriptions in the United States of America, yet represented nearly 37% of net drug spending (16). The cost of biologics is likely to be burdensome for Latin American countries that could increasingly depend on imports of these medicines.

2.1.4. MARKET PENETRATION OF GENERICS

Beyond size and growth, the penetration of generic medicines in pharmaceutical markets indicates opportunities for improving efficiencies and reducing costs without compromising quality of care. Generic competition can foster lower prices of medicines for patients and governments, but in Latin American NRAr countries, generic medicines appear to make up less than a third of the pharmaceuticals market (see Figure 2.4). At 5%, Argentina seems to have the lowest penetration of generics. However, this requires closer interpretation because the “generics” category in Figure 2.4 includes products that are prescribed and marketed under their INN with no visible brand; it does not include branded generics. Yet in Argentina, around 97% of all generics are branded and as such, would feature in the “brands” category.¹ This may underestimate the penetration of generic products in the country (although the branded generics’ effect can be to raise price because of factors such as brand loyalty) (17–19). Other Latin American NRAr countries may also have a substantial segment of their markets that are “similar” (see Section 3.2.2).

Figure 2.4. Generics penetration by country in Latin American NRAr (Pack units; MAT June 2019)



Source: Data provided by IQVIA, Retail Market MIDAS MAT Q2 2019.

¹ Data from the National Chamber of Pharmaceutical Laboratories (CILFA) provided for this report.

The relatively low levels of generic penetration in NRAR markets compared with other markets (penetration is 90% of market share by volume in the United States of America, for example) (20) suggest that there are still opportunities to increase uptake of safe, quality, and effective generic products. NRAs have a part to play in realizing the potential of generics to foster competition and reduce prices by creating an enabling environment for the marketing authorization of these products. This may require a number of different policy initiatives, and for example, the FDA has said they are working to remove barriers to generic drug market entry through improving the efficiency and timelines of the generic drug development, review, and approval process, and closing loopholes that may allow brand-name drug companies to delay generic competition (21).

Ensuring that countries have access to innovative and generic medicines is a delicate balance. In Latin America, some governments have a range of mechanisms that affect this balance (see Table 2.1). These include:

- Data exclusivity protection, which provides exclusive rights over safety and efficacy data used in registration. As long as data exclusivity lasts, generic manufacturers have to repeat any clinical trials and other relevant tests and submit their own data to gain marketing authorization.
- Patent term extensions, which extend the timeframe of the original patent to compensate for any time lags caused by the original authorization process.
- Patent linkage, which prevents marketing authorization of a generic medicine until the original product’s patent has expired.

All the mechanisms mentioned above pose barriers or delays to market entry for generics and some countries with NRAR (including Argentina, Brazil, and Cuba) do not have them. Conversely, the “Bolar”-type exemption can be used by all Latin American countries with NRAR to facilitate access to generic medicines by allowing manufacturers to conduct research and development activities to obtain the required regulatory approvals while the patent is still in effect (see Table 2.1) (22).

Table 2.1. Mechanisms to delay and accelerate the entry of generics into NRAR markets

| | Data exclusivity* | Patent term extensions | Patent linkage | “Bolar”-type exemptions** |
|------------------|-------------------|------------------------|----------------|---------------------------|
| ARGENTINA | × | × | × | ✓ |
| BRAZIL | × | × | × ^a | ✓ |
| CHILE | ✓ (5 years) | ✓ | ✓ ^b | ✓ |
| COLOMBIA | ✓ (5 years) | Optional | Optional | ✓ |
| CUBA | × | × | × | ✓ |
| MEXICO | ✓ (5-6 years) | ✓ | ✓ | ✓ ^c |

Notes: ^a Brazil has a prior consent procedure (not linked with the marketing authorization) through which ANVISA is, in some circumstances, involved in evaluating patent applications; ^b There is a difference of opinion as to whether the legislation implies patent linkage in Chile; ^c Ley Federal de Protección a la Propiedad Industrial, art.57 fracción II.

Sources: * World Health Organization; World Intellectual Property Organization; World Trade Organization. Promoting access to medical technologies and innovation: Intersections between public health, intellectual property and trade. Geneva: WHO, WIPO, WTO; 2013.

** National legislation.

2.2. Trade and Local Production

Several NRAR country markets have significant domestic industries for pharmaceuticals, with around two-thirds of units sold in Argentina, Brazil, and Cuba made locally (23–25). However, these three countries import most of their APIs from overseas, in large part from China. They also import significant levels of FPPs, especially from India. Chile, Colombia, and Mexico rely heavily on imported supplies of APIs and FPPs from China and India as well. With regard to similar biotherapeutic products, Argentina and Brazil have the greatest number of manufacturing facilities with 14 each, but Cuba and Mexico produce some too.

NRAR countries also export pharmaceutical products. Mexico and Brazil were the countries with the highest value of exported products in 2018 (US\$ 1,540 million and US\$ 1,187 million, respectively); however, the combined value of their export market is a fraction of the value of the world's largest pharmaceutical exporter, Germany (US\$ 62 billion). Still, they have a significant impact at the regional level. Argentina, Colombia, and Chile's values are US\$ 721 million, US\$ 351 million, and US\$ 169 million, respectively.

The trading patterns of NRAR countries are shaped by geographical proximity and trade integration mechanisms (see Chapter 8: Trade and Economic Integration Mechanisms). For example, many exports from Argentina and Brazil go to other members of MERCOSUR, while Chile, Colombia, and Mexico tend to export to their fellow members in the Pacific Alliance (see Figure 2.5). Within Latin America:

- Argentina's exports to Brazil, Chile, Paraguay, and Uruguay make up 40% of the country's pharmaceutical exports.
- Brazil exports mostly to Latin America, the Middle East, and some European markets, according to information provided by industry stakeholders for this report.
- Chile has only recently started exporting pharmaceuticals, but major destinations already include Bolivia (Plurinational State of), Ecuador, Paraguay, and Peru.
- Colombia sends more than 60% of its exports of human and veterinary pharmaceutical products to Ecuador, Panama, Peru, and Venezuela (Bolivarian Republic of).
- Cuba exports to many countries, including the Dominican Republic, Ecuador, and El Salvador in the Americas.
- Mexico sends around 65% of its pharmaceutical exports to Brazil, Colombia, Ecuador, Panama, and the United States of America.

Figure 2.5. Major Latin American destinations for exports from NRAr countries



Several NRAr countries trade with members of the Central American Integration System (SICA), facilitated by their status as NRAr. For example, El Salvador and Guatemala have both established reliance mechanisms to recognize and use marketing authorization decisions of NRAr, making import of medicines from these countries much more efficient. COFEPRIS estimates that Mexican exports have grown by about 40% since COFEPRIS became an NRAr in 2012, in part due to trade with Central American countries (26).

There is less interaction between Latin American NRAr countries and the Caribbean or North American markets. In the Caribbean, an unpublished PAHO analysis of sources of medicines among government procurers in Barbados, the Organization of Eastern Caribbean States, and Trinidad and Tobago shows that less than 2% of products come from companies with headquarters in Central America or South America. This lack of integration despite geographical proximity may in part be due to language barriers: producing English labels and packaging is potentially too costly given the small markets and volumes of sale within each Caribbean country. This may change with the increasing attractiveness of pooled market mechanisms in the subregion like the Caribbean Community’s Caribbean Regulatory System (see Chapter 8: Trade and Economic Integration Mechanisms).

There is also limited integration of Latin American NRAr markets with the United States of America. Data from 2018–2019 show that the FDA conducted just 30 drug quality inspections across all Latin American NRAr (20 in Mexico and 5 each in Argentina and Brazil), compared with 77 inspections in Canada alone during the same time period (27). This may be a result of business factors, such as language differences in packaging, as well as strategic decisions of Latin American NRAr governments to focus industrial policies on production for domestic and regional consumption.

Tackling supply shortages

NRAr countries produce a wide range of medicines that are identified as having supply shortages in the United States of America (28). Table 2.2 looks at shortage products registered in example NRAr markets by what seem to be local manufacturers. Sourcing products from the Americas could be a strategic option for countries that have concerns about the security of supply chains and too much dependence on certain markets (29). However, shortages of APIs would affect Latin American NRAr manufacturing given their dependence on foreign sources, so a more detailed analysis of what medicines are available is warranted.

Table 2.2. Medicines with FDA-listed shortages that are locally produced in three NRAr countries

| Medicine (generic name or active ingredient) | Local production | | |
|---|------------------|--------|--------|
| | Argentina | Brazil | Mexico |
| Asparaginase Erwinia chrysanthemi | n/a | ✓ | |
| Calcium chloride injection, USP | | ✓ | |
| Cefepime injection | ✓ | ✓ | |
| Cefotaxime sodium injection | ✓ | ✓ | ✓ |
| Dexrazoxane injection | n/a | ✓ | |
| Diphenhydramine injection | ✓ | ✓ | |
| Dobutamine hydrochloride injection | ✓ | ✓ | ✓ |
| Leucovorin calcium lyophilized powder for injection | ✓ | | n/a |
| Lidocaine hydrochloride injection | n/a | | ✓ |
| Lidocaine hydrochloride injection with epinephrine | n/a | ✓ | |
| Nystatin oral suspension | ✓ | ✓ | ✓ |
| Peritoneal dialysis solutions | n/a | n/a | ✓ |
| Piperacillin and tazobactam injection | ✓ | ✓ | ✓ |
| Potassium acetate injection, USP | ✓ | | n/a |
| Sodium bicarbonate injection, USP | ✓ | ✓ | ✓ |

Notes: The list of medicines included in this table was selected from FDA’s website and the database for shortage drugs for key therapeutic areas of pediatric and cancer medicines, <https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>, cited 17 December 2019. The analysis examined electronic registration databases for the selected countries and if a local company had a registered product for the generic name, this was counted as local production. Limitations include the possibility of intermediary companies for non-local firms being counted as local firms.

n/a: no search results available

2.2.1. DRIVERS OF LOCAL PRODUCTION AND THE NEED TO ENSURE QUALITY

Latin America's heavy dependence on China and India for APIs and FPPs poses potential risks to the quality of pharmaceuticals (30). China is the leading global producer and exporter of APIs by volume, manufacturing more than 2,000 of them (31). Meanwhile, India makes up 70% of the world market share of generic medicines and 50% of vaccines. But regulatory oversight is limited in those countries and several well-resourced regulatory authorities have flagged significant and repeated problems with manufacturing sites in the past. For example, around half of the warning letters that the FDA sent to manufacturers in 2018 and 2019 went to facilities in China and India (31).

The concerns with Chinese and Indian manufacturers are one reason why some Latin American governments are looking to increase local production. Another driver is cost, in part because the need for costly biologic products is growing and there is limited penetration of generic medicines. Whatever the reason behind boosting local production, there may be significant risks to quality if it is not regulated well; increasing local production requires enhanced regulatory capacity to carry out the comprehensive suite of WHO recommended functions, including domestic regulatory inspections.

Considering that multiple Latin American NRAr countries are moving toward more domestic production, it should be noted that interviews with local industry representatives flagged concerns about economic conditions and policies that may inhibit growth in the area, such as unfavorable exchange rates, inflation, interest rates, and tax pressures. Industry interviewees stressed that governments could do more to control and/or modify these and other factors.

Recommendations for Action

- **Be ready for market changes.** Ensure that regulatory systems are prepared for market growth over the coming years, with strategies to manage influx and to maximize resources to ensure product safety, efficacy, and quality, including related to areas such as biotherapeutic and similar biotherapeutic products.
- **Strengthen the role of the regulatory authority in facilitating market entry of generic medicines.** Develop mechanisms to improve efficiencies in the review and timelines of generic medicines.
- **Explore opportunities to expand trade.** Consider the possibility to increase exchanges with NRAr countries or with countries in other subregions in the Americas, including through the use of regulatory reliance and harmonizing to international standards.

3. MARKETING AUTHORIZATION OF PHARMACEUTICAL PRODUCTS

In brief

- Latin American NRAR tend to devote a significant share of staff resources to marketing authorization; however, life cycle regulatory oversight for products entering or already in the market is not as well resourced.
- Latin American NRAR have similar quality, safety, and efficacy requirements for new chemical entities.
- Some differences remain in the requirements for generic products, especially when it comes to bioequivalence and biowaivers.
- Industry reports review timelines that are sometimes twice as long as international reference authorities.
- Latin American NRARs' user fees are much smaller than those charged by other reference authorities.
- While many regulatory authorities in the Americas rely on the market approvals of NRAR, Latin American NRAR do not tend to rely on others for this function.
- NRAR only make public a minimal proportion of their information that could enable reliance by other NRAs.

3.1. NRA Foundations for Authorizing Pharmaceutical Products

A marketing authorization is an official document issued by the competent regulatory authority to allow the marketing or free distribution of a product after it has been evaluated for quality, safety, and efficacy. Countries may also call it “marketing approval,” “registration,” or “licensing,” and it is one of the essential regulatory functions performed by any NRA (see Figure 3.1).

3.1.1. LEGAL AND ORGANIZATIONAL FRAMEWORKS

All Latin American NRAR have legal frameworks that require a product to gain marketing authorization before it can be legally sold in their markets, with the precise requirements and pathways available differing according to product type. Generally, authorization applications are made for two broad types of products (32):

- New products. These cover applications for any product containing new chemical entities (NCEs) or biological APIs, including new routes of administration, new strengths, new indications, and new fixed-dose combinations.
- Generics. These cover applications for multisource pharmaceutical products; in some countries, this may include new marketing authorization holders and new dosage forms.

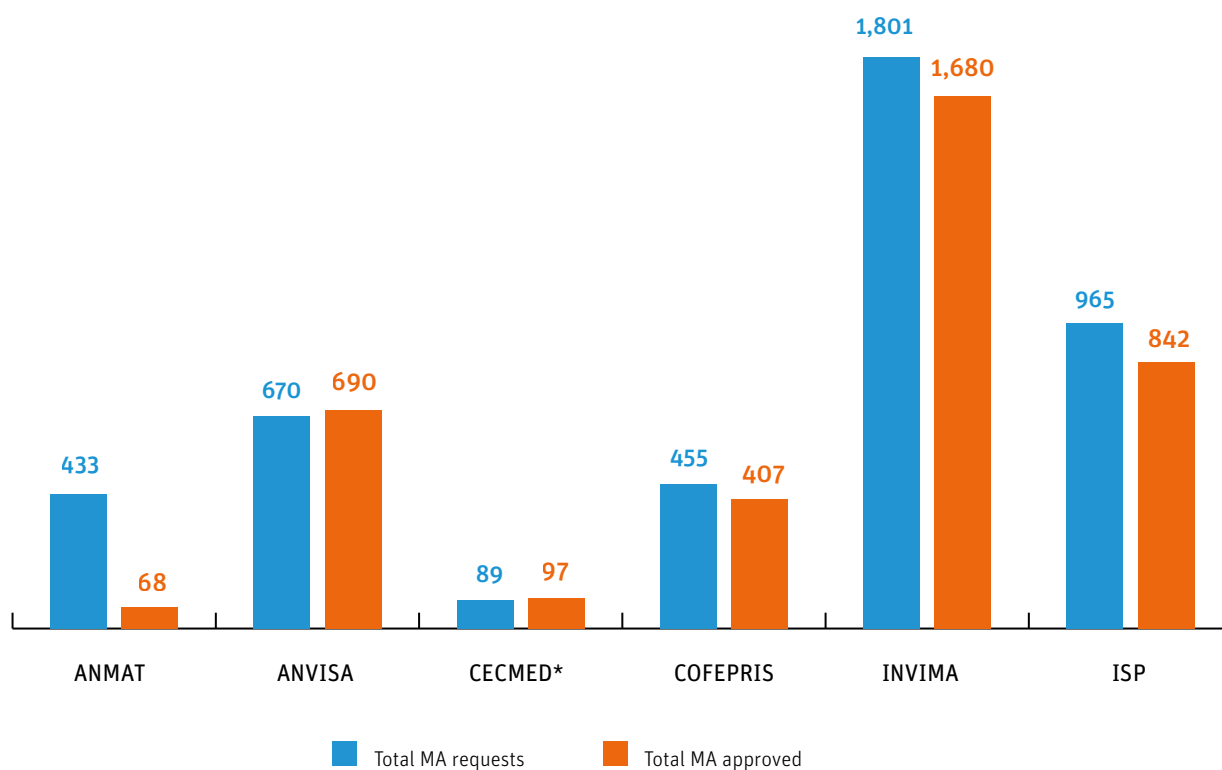
Both new and generic product marketing authorization holders may need to apply to renew their authorization throughout the product life cycle for:

- Variations. These cover applications for any change to an existing marketing authorization, for example reformulations, revisions of shelf-life, or changes in the manufacturing sites.
- Renewals. These cover applications to renew existing marketing authorizations after they expire (all Latin American NRAR have limits to their market authorizations).

3.1.2. HUMAN RESOURCES AND FINANCING

The human and financial resources needed to support marketing authorization depend in part on the number of marketing applications received for processing. Marketing authorization is a complex and time-consuming activity that can involve multiple people (for example, physicians, pharmacologists, toxicologists, statisticians, and pharmacists) to work with the applicant to review documentation, seek clarifications, evaluate data, and enable a decision. Each authorized product also requires continued life-cycle management, including renewed authorization for variations and renewals where applicable. Although the data are imperfect because authorities may document their applications in slightly different ways, figures from 2018 suggest that in most cases, Latin American NRAR receive and process hundreds of applications each year (Figure 3.1).

Figure 3.1. Marketing authorization applications submitted to and approved by NRAR in 2018



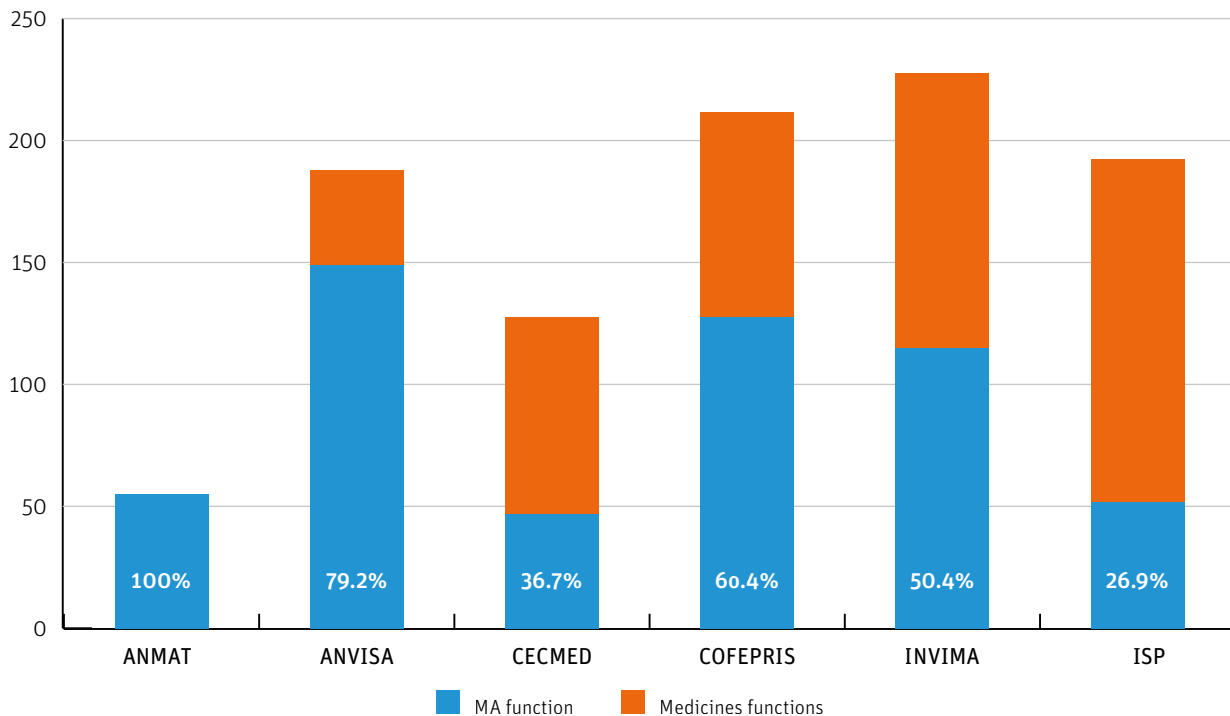
Notes: Although informative, these data should be interpreted with care because the timing of the application does not necessarily correspond with that of the decision (for example, ANVISA received applications in one year and approved them the next). In addition, authorities track applications differently and data combine all applications for new, generic, and biotherapeutic products.

Sources: Data collected by PAHO using the following methodology: Each LA NRAR identified a focal point for this report. PAHO developed an instrument with the data requested, the instrument was filled by the LA NRAR focal point, followed by a phone interview/email communication to validate the data included in the report. Two rounds of data validation were performed. The investigation and analysis were conducted from March 2019 to October 2020.

* CECMED. Memoria de actividades 2018. Cuba: CECMED; 2019. Available from: https://www.cecmecmed.cu/sites/default/files/adjuntos/reporte_anual/Memorias%20de%20actividad%20CECMED%202018.pdf, cited 26 June 2020.

Marketing authorization processes and performance are regularly scrutinized by external stakeholders such as lawmakers, industry, and patient groups; and marketing authorization may also be a significant money-earner through user fees. As such, it tends to get a greater share of the NRA’s resources, often at the expense of other important regulatory functions that are necessary to manage authorization throughout the product life cycle, including inspections, pharmacovigilance, and post-marketing surveillance and enforcement. Across many NRAr, marketing authorization staff make up 50% or more of all staff devoted to medicines regulation (see Figure 3.2).

Figure 3.2. Number of staff devoted to marketing authorization in NRAr medicines units



Source: Data collected by PAHO using the following methodology: Each LA NRAr identified a focal point for this report. PAHO developed an instrument with the data requested, the instrument was filled by the LA NRAr focal point, followed by a phone interview/email communication to validate the data included in the report. Two rounds of data validation were performed. The investigation and analysis were conducted from March 2019 to October 2020.

3.2. Marketing Authorization in Practice

3.2.1. NEW CHEMICAL ENTITY REQUIREMENTS

In general, the quality, safety, and efficacy requirements for new chemical entities (NCEs) are similar across Latin American NRAr. They include requirements for product manufacturing and characterization, as well as requirements for stability and clinical trials.² Latin American NRAr also have requirements to ensure companies provide post-market surveillance data. For example, companies may need to include a risk management plan in their applications to establish how they will do pharmacovigilance and post-authorization effectiveness and safety studies. While all NRAr have similarly rigorous requirements, only Brazil and Cuba require marketing applications to be organized and presented using the ICH common technical document structure.

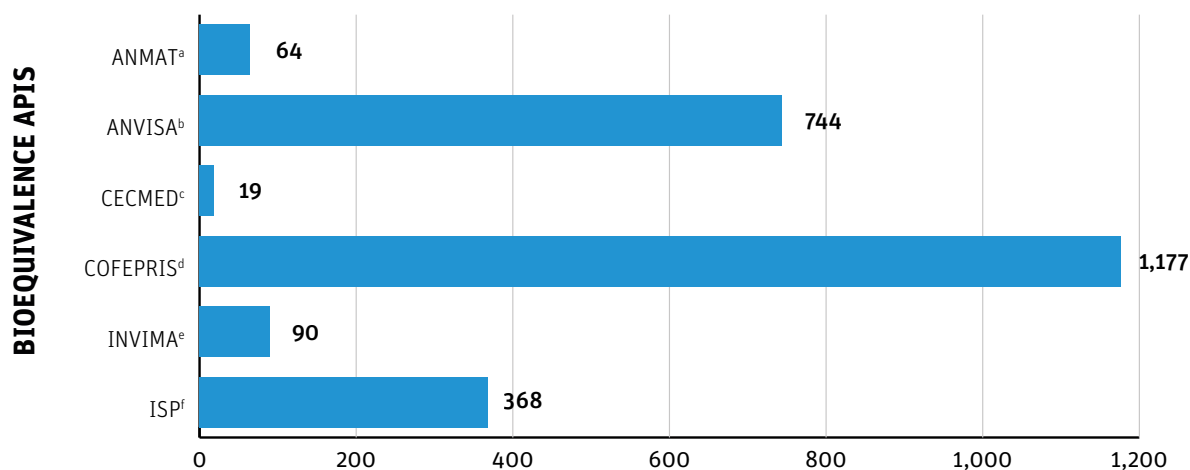
² Requirements cover studies and reports for Phase I–III trials and include requirements for pharmacokinetics, pharmacodynamics, and toxicology studies (to quantify parameters such as dose toxicity, genotoxicity, carcinotoxicity, reproductive and developmental toxicity, among others).

3.2.2. GENERICS REQUIREMENTS

Requirements for generics differ across NRAR. Even the definition of a generic product varies. In Brazil and Mexico, the term “generic” is reserved for products that are off-patent, are marketed using the International Non-proprietary Name (INN), and have been shown to be interchangeable with the reference product (that is, they are bioequivalent³) (32). In other countries, including Argentina, Chile, Colombia, and Cuba, the term “generic” refers to off-patent products using the INN irrespective of whether they are proven to be bioequivalent or not. Additionally, there are other multisource pharmaceutical products that are neither the reference product nor the original patent holder but are marketed using a brand name rather than the INN. In some countries, like Brazil, such products are called “similar”; in other countries they are colloquially called “copies” or “branded generics.”

Another area where requirements for market approval differ across NRAR is bioequivalence. Most Latin American NRAR maintain their own lists of APIs that must demonstrate bioequivalence (33). The number of APIs included in each list varies significantly, from just 19 in Cuba to more than 1,000 in Mexico (see Figure 3.3). WHO has issued guidance on the different methods that can be used to establish equivalence, including pharmacokinetic, pharmacodynamic, clinical trials, and in vitro tests, depending on the characteristics of the API and finished product (34, 35).

Figure 3.3. Number of APIs that must demonstrate bioequivalence



Notes: Lists of APIs published in NRAR official websites were extracted and analyzed after eliminating any duplicates to ensure comparable data. COFEPRIS list includes APIs alone and in combination.

Sources: ^a ANMAT [Internet]. Biodisponibilidad y bioequivalencia. Buenos Aires: ANMAT; 2020. Available from: http://www.anmat.gov.ar/medicamentos/Biodisponibilidad_Bioequivalencia.asp, cited 3 March 2020; ^b ANVISA [Internet]. Regularização de Produtos - Bioequivalência e Biodisponibilidade. Brasília: ANVISA; 2020. Available from: <http://portal.anvisa.gov.br/registros-e-autorizacoes/medicamentos/medicamentos/medicamentos-de-referencia/lista>, cited 3 March 2020; ANVISA [Internet]. Regularização de produtos - Medicamentos. Brasília: ANVISA; 2020. Available from: <http://portal.anvisa.gov.br/registros-e-autorizacoes/medicamentos/medicamentos-de-referencia/lista>, cited 3 March 2020; ^c CECMED. Requerimientos para estudios de biodisponibilidad y bioequivalencia. Havana: Ministry of Health; 2020. Available from: https://www.cecmec.cu/sites/default/files/adjuntos/Reglamentacion/reg.18-07_requerimientos_para_el_estudio_de_biodisponibilidad_y_bioequivalencia.pdf, cited 3 March 2020; ^d COFEPRIS [Internet]. Documentos informativos de medicamentos. Mexico City: COFEPRIS; 2020. Available from: <https://www.gob.mx/cofepris/documentos/documentos-informativos-de-medicamentos>, cited 3 March 2020; ^e INVIMA. Listado de medicamentos para los cuales es exigible la presentación de estudios de bioequivalencia (BE) con sus respectivos productos de referencia. Bogotá: INVIMA; 2016. Available from: <https://www.invima.gov.co/documents/20143/453029/listado+de+moléculas+para+la+exigencia+de+estudio.pdf/5fde1192-521f-d508-8596-07117967e8db?t=1540932334856>, cited 3 March 2020; INVIMA. Sistema de clasificación biofarmacéutica para los principios activos que deben presentar estudios de bioequivalencia de acuerdo con el anexo técnico 2 de la resolución 1124 de 2016. Bogotá: INVIMA; 2016. Available from: https://www.invima.gov.co/documents/20143/1310540/BCS_principios-activos-que-deben-presentar-estudios-de-bioequivalencia_anexo-tecnico-2-resolucion-1124v2feb-2018.pdf, cited 3 March 2020. <https://www.invima.gov.co/es/web/guest/biologicos-y-de-sintesis-quimica>; ^f ISP. Productos de referencia: exigencia a producto de liberación convencional. Santiago: ISP; 2018. Available from: http://www.ispch.cl/sites/default/files/referentes_liberacion_convencional.pdf, cited 3 March 2020; ISP. Productos de referencia: exigencia a product de liberación modificada. Santiago: ISP; 2018. Available from: http://www.ispch.cl/sites/default/files/referentes_liberacion_modificada.pdf, cited 3 March 2020.

³ Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailabilities, in terms of peak (C_{max} and T_{max}) and total exposure (area under the curve) after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same. Manufacturers of generic products are usually required to prove that their products are bioequivalent to the innovator product. For most orally administered APIs, WHO recommends that bioequivalence be proven through in vivo studies. But in some cases (for example, for highly soluble and permeable APIs), NRAs can decide to grant a biowaiver. APIs with a biowaiver do not require in vivo studies, which can be time consuming and expensive, to establish their bioequivalence but can use in vitro methods instead.

Latin American NRAr report that their bioequivalence lists are developed based on a set of health risk criteria that take into account key characteristics of the molecule (such as narrow therapeutic index) as well as epidemiological characteristics of the country (36). Chile's ISP takes a slightly broader approach to defining its bioequivalence list, looking beyond the level of risk to include, for example: whether the product is included in public health programs; whether it is important for public health expenditure; and whether the reference product is available, among other things. The precise number of APIs included in the bioequivalence list changes over time in response to new knowledge and evolving selection criteria. Sometimes the addition of a new API to a bioequivalence list also has implications for generic products that are already on the market. Each NRAr has a transitional strategy that informs their approach to dealing with these cases.

In some cases, bioequivalence is not needed. Latin American NRAr grant biowaivers based on the Biopharmaceutics Classification System (BCS), which classifies APIs into four groups according to their solubility and permeability (37). WHO recommends that APIs with high solubility and high permeability (BCS Class I) should be evaluated for biowaiver eligibility. APIs that are highly soluble but poorly permeable (BCS Class III) are also eligible if they are rapidly dissolving. WHO's grouping of APIs according to BCS is updated every year, and over the past decade the solubility and permeability criteria have been relaxed without substantially increasing the risk to public health or the individual patient. Most NRAr follow WHO recommendations and waive in vivo studies for BCS Class I and Class III products. Brazil is the exception, only waiving in vivo studies for a specific list of products. It is also important to note that the ICH M9 Biopharmaceutics Classification System-based Biowaivers Guideline was agreed in November 2019 and is now being implemented worldwide (38). This development is expected to bring significant improvement and harmonization to biowaivers around the globe.

The differences in how and when bioequivalence requirements were introduced in the Americas have led to significant cross-country variation in the number of finished products containing listed APIs that have demonstrated bioequivalence. In 2019, the total number of bioequivalence-certified products varied; for example, from 126 in Colombia to more than 5,500 in Brazil. According to WHO, APIs belonging to BCS Classes II and IV should always demonstrate bioequivalence via in vivo study. Data gathered for this report, however, showed that some products in these classes were not required to have bioequivalence in Argentina, Colombia, or Cuba.

3.2.3. VARIATIONS AND RENEWAL REQUIREMENTS

Regulators must be able to oversee changes to products over time, such as those to labeling, or changes in manufacturing sites. These are called "variations," and all NRAr provide guidance on how and when manufacturers should address them in their marketing authorization.⁴ Variations can be a significant burden on time and even the largest and most resourced authorities can incur large backlogs when processing them.

Latin American NRAr countries also have policies related to renewing marketing authorizations after a fixed period of time. In most cases, this period is five years and stands in significant contrast to other regulators like the FDA and Health Canada who issue marketing authorizations indefinitely. In most cases, marketing authorization holders (MAHs) must submit their renewal requests at least three months before their marketing authorization is due to expire. The marketing authorization is automatically extended while the NRAr evaluates the request. Some NRAr, like INVIMA, grant automatic renewals with abbreviated review under certain circumstances (specifically, for products that have a valid good manufacturing practices certificate and have maintained the validity of the

⁴ Type I variations (also known as "do and tell") include administrative and minor changes that do not require previous approval by the NRA. Type II variations are major changes that require NRA approval before they can be implemented (32).

information and the characteristics approved during the period of the marketing authorization) (39). There are pros and cons to renewals. Some countries use them to charge an additional fee and update their knowledge on the product, but it can be another resource burden. In 2018, Latin American NRAr approved between 636 and 1,651 renewal requests.

3.2.4. REVIEW TIMES

It is in the public interest for pharmaceutical products to be made available as quickly as possible, provided there has been an appropriate review of safety, quality, and efficacy (32). At the FDA and European Medicines Agency, the median review time of applications for new therapeutic agents between 2011 and 2015 was 306 (~10 months) and 383 days (~12 months), respectively (40). In Latin America, available information suggests that the average review time for new drugs is comparable for some NRAr but significantly longer for others (see Table 3.1). Generic drug review timelines are becoming faster; for example, the FDA is working toward 10-month or shorter review time from submission (41).

Table 3.1. Average review times for pharmaceutical products across NRAr

| NRAr | Review timeframes (months) set in regulations ^a | Review timeframes (months) reported by: | |
|----------|---|---|--|
| | | Industry ^b | Centre for Innovation in Regulatory Science ^c |
| ANMAT | 4 ^d | 18–24 | 12 |
| ANVISA | 4 (for prioritization requests) 12 (for ordinary requests) | 18–24 | 12 |
| CECMED | 9 ^e | N/A | N/A |
| COFEPRIS | 3 ^f | 12–24 ^g | 7 |
| INVIMA | 6 | 12 | 18 |
| ISP | 6 ^e | 12 | N/A |

Notes and sources: ^a Country laws and regulations consulted in June 2020: Argentina: Disposición 3554/2002 http://www.anmat.gov.ar/webanmat/Legislacion/Medicamentos/Disposicion_3554-02.pdf; Brazil: Law 13.411/2016 <http://antigo.anvisa.gov.br/en/drugs>; Chile: Decreto 3 Aprueba Reglamento del Sistema Nacional de Control de los Productos Farmacéuticos de Uso Humano <https://www.leychile.cl/Navegar?idNorma=1026879#registro0>; Colombia: Decreto 19 de 2012 <http://www.suin-juriscol.gov.co/viewDocument.asp?id=1004430> & Decreto 677 de 1995 https://www.invima.gov.co/documents/20143/453029/decreto_677_1995.pdf; Cuba: Resolución Ministerial No.31 <http://legislacion.sld.cu/index.php?P=DownloadFile&Id=522>; Mexico: Reglamento de insumos para la salud <http://www.ordenjuridico.gob.mx/Documentos/Federal/pdf/wo88318.pdf>; ^b Interviews with pharmaceutical industry stakeholders, 2017; ^c Adapted from: Patel P, McAuslane N, Liberti L. R&D Briefing 71: Trends in the Regulatory Landscape for the Approval of New Medicines in Latin America. London: Centre for Innovation in Regulatory Science (CIRS); 2019; ^d This period does not consider the verification of the manufacturing site, which by regulation can last 60 days; ^e This period does not consider the admissibility of submission request, which the regulation mentions can last 10 days; ^f Only applies to new molecules and biologics. For molecules already registered in Mexico or a reference authority the timeframes may vary from 40 to 60 days, and with the use of an authorized third party, the law mentions 20 days; ^g Lower timeframes due to use of authorized third parties.

In almost all cases, the application review timeframes reported by industry are significantly longer than those stated in the regulations or those reported by CIRS. Such findings strongly suggest that NRAr could still find more ways to gain efficiencies. Stakeholders interviewed for this report identify multiple reasons for the observed lag in market authorization, including, among other things: fast-growing pharmaceutical markets that are increasing the volume of marketing authorization applications and workload; and the need to process authorization variations and renewals, which limits the resources available for processing new applications.

That said, understanding the differences in review times or authorization rates is complex. Application requirements vary and requests may not be submitted for marketing approval in all relevant countries, or they may be submitted

at different times. Simple numerical comparisons of approval rates and timelines do not take into account things like type and complexity of the evidence filed to support efficacy, safety, or quality of the product.

Using approval rates and timelines as a proxy for NRA efficiency can also be hazardous. While the timely authorization of products may be critical to allow access to much-needed products, failure to provide proper regulatory oversight may ultimately carry inherent risks for the intended group of the population if they are exposed to products that do not show the claimed positive beneficial effects, or that show higher than expected frequency of negative adverse effects. For this reason, assessment of NRA efficiency should be extended beyond timelines to include measurement of regulatory review quality.

3.2.5. USER FEES

In addition to meeting standard safety, quality, and efficacy criteria, all marketing authorizations in Latin American NRAs require payment of a user fee. In part this is to recover the costs of the regulatory work needed to review the products (for example, some authorities wrap on-site inspections into the fees) as well as to add predictable and accountable timelines for these processes. There are various types of fees including for different product types. User fees for new products are higher than those for generic medicines because there is more work involved in processing them. Table 3.2 compares fees charged by NRAs for new products, generic products, and renewals. These data are an underrepresentation of actual fees charged because there are often other ancillary fees to be paid, but they offer a good approximation. United States of America user fees are included for comparison.

Table 3.2. User fees (for new products and generic drugs) across NRAs

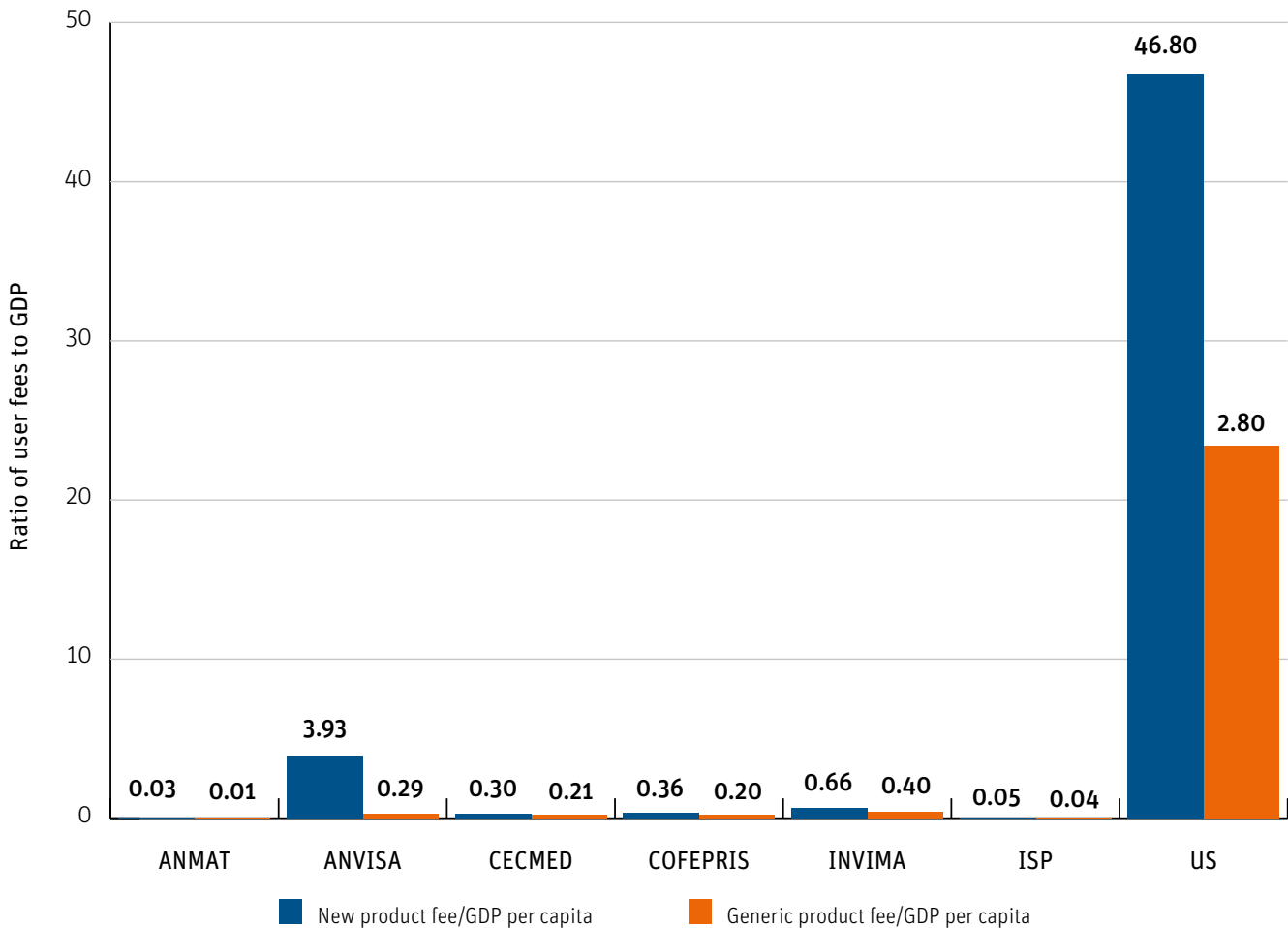
| NRA ^a | New product fee (US\$) | Generic product fee (US\$) | Renewal product fee (US\$) |
|-----------------------|------------------------|----------------------------|----------------------------|
| ANMAT ^a | 645.08 | 253.72 | 187.70 |
| ANVISA ^b | 58,709.00 | 4,357.50 | 26,106.00 |
| CECMED ^c | 2,620.00 | 1,850.00 | 980.00 |
| COFEPRIS ^d | 7,428.90 | 4,154.72 | 4,344.00 |
| INVIMA ^e | 9,773.14 | 6,004.62 | 6,129.00 |
| ISP ^f | 1,359.40 | 1,049.62 | 407.00 |
| U.S. | 2,942,965.00 | 176,237.00 | Not applicable |

Sources: ^a ANMAT [Internet]. Buenos Aires: ANMAT; 2019. Aranceles vigentes de los trámites ante ANMAT. Available from: <https://www.argentina.gob.ar/anmat/regulados/aranceles>, cited 20 June 2020; ^b Ministério da Fazenda. Diário oficial da união. Brasília: Ministério da Fazenda; 2015. Available from: <http://www.fazenda.gov.br/acesso-a-informacao/institucional/legislacao/portarias-interministeriais/2015/arquivos/portaria-interministerial-no-701-de-31-de-agosto-de-2015-1-1.pdf>, cited 2 March 2020; ^c CECMED. Reglamento para la aplicación de la lista oficial de precios de los servicios científico técnicos del CECMED. Havana: Ministry of Health; 2017. Available from: <https://www.cecmec.cu/ultimas-regulaciones/reglamento-aplicacion-lista-oficial-precios-servicios-cientifico-tecnicos>, cited 24 April 2020; ^d COFEPRIS. Comisión Federal para la Protección contra Riesgos Sanitarios. Mexico City: COFEPRIS; 2019. Available from: <https://www.gob.mx/cms/uploads/attachment/file/424938/TarifasDePago2019.pdf>, cited 2 March 2020; ^e INVIMA [Internet]. Bogotá: INVIMA; 2019. Tarifas. Available from: <https://www.invima.gov.co/web/guest/tarifas>, cited 2 March 2020; ^f ISP [Internet]. Santiago: ISP; 2019. Registro sanitario de productos farmacéuticos. Available from: http://www.ispch.cl/anamed_/registros, cited 2 March 2020.

An important consideration for Latin American NRAs is whether their user fees are in line with reference authorities around the world, including with similar markets. This can be assessed by looking at the ratio of user fees to market size or GDP, or GDP per capita of the country (7). The ratio of user fees to GDP per capita across NRAs varies and depends on whether the fees are for new products or generic ones, but in all cases they are significantly smaller

than United States of America figures (see Figure 3.4). This has important implications: in a time of stagnating or decreasing budgets and broader economic concerns, NRAr may want to re-examine their fees and align them more closely with the ratios of fees charged by other authorities.

Figure 3.4. Ratio of user fees to GDP per capita for new and generic products across NRAr



3.3. Best Practices and Efficiencies in Marketing Authorization

3.3.1. PRE-SCREENING, OUTSOURCING, AND PRE-TESTING

Some authorities, including COFEPRIS and ISP, have developed pre-screening processes to verify that the dossier is complete before starting on marketing authorization. In ISP, this pre-screening is done in-house. In COFEPRIS, since 2012, pre-screening is done by “authorized third parties” that are bound to conduct their activities under the same principles as NRA officials (that is, they must be technically sound and financially solvent with no conflict of interest). Beyond pre-screening, COFEPRIS also uses authorized third parties to carry out laboratory tests, comparability tests, and interchangeability tests (42). According to two interviewees for this report, the use of authorized third parties has been a key factor in relieving the pressure of marketing approval requests, although the approach does carry some risk, including lessening NRA control over the process.

Some countries in the Americas require product testing as part of the marketing authorization application. This poses an additional burden and in small countries where resources are already scarce, and laboratory capacity limited, it can

significantly delay the application and compromise timely access to medicines. Such testing is unnecessary unless there is evidence to suggest that good manufacturing practices have not been followed. Shifting emphasis away from this kind of work could enable countries to reallocate resources to other areas, such as risk-based post-market surveillance testing.

3.3.2. PARALLEL EVALUATIONS

Most NRAr use parallel evaluations of the quality, pharmacological, clinical, and legal components of marketing authorization as a way of expediting the process. The exception is ANMAT, which evaluates each component consecutively: at any point, if the product fails one of the evaluations it cannot go through the next stage. In the case of Colombia, parallel evaluations are followed by analysis conducted by an expert committee that not only makes recommendations on marketing authorizations but also on any relevant clinical trial approvals.

3.3.3. JOINT EVALUATIONS/COLLABORATIVE REVIEWS

Joint evaluations and collaborative reviews are another way to add efficiencies to the marketing authorization processes. Such approaches are particularly common in economic communities, such as in Africa (43), where regulators gather on a periodic basis to review dossiers. Information and judgments from these sessions can then be used to expedite official marketing authorization decisions in respective countries. In the Americas, Central American regulators have adopted this approach for the review of generic medicines (see Chapter 8: Trade and Economic Integration Mechanisms). INVIMA, ISP, COFEPRIS, and CECMED started “Ateneos” in 2018, which is a cooperation program to exchange scientific information on similar biotherapeutic product evaluations (see Chapter 4: Marketing Authorization of Similar Biotherapeutic Products). It is informal and non-binding, but can pave the way for more collaboration in the future, including through reliance, because it increases information sharing and builds trust among NRAs.

An additional program that uses collaborative reviews is called the “WHO Collaborative Procedure.” This program does not bring regulators together to review products, but rather shares WHO’s reviews of prequalified products, including confidential information such as inspection and assessment reports, or facilitates the sharing of information on products approved by reference authorities with participating regulatory authorities that leverage the information to expedite their own marketing authorization decisions of these products. The countries of the Caribbean Community are the only ones that participate in this program in the Americas, according to the list of participating authorities on the WHO website (44).

3.3.4. ELECTRONIC SUBMISSIONS

Most Latin American NRAr use electronic submissions as a way of reducing paperwork and improving processing times. COFEPRIS is the only one that does not have an electronic submission system. However, across all Latin American NRAr there is significant room to expand the use of digital platforms to support marketing application handling and review processes.

Use of electronic submissions is not widespread in subregions like the Caribbean. PAHO recommends adopting electronic systems for marketing authorization, including for registered products, even if this simply means using commonly available digital spreadsheets (45). The Organization further suggests that some of the dossier submission requirements, such as physical samples, could be waived in favor of electronic samples of the authorized packaging. In smaller countries, acquiring physical samples can cause delays and because storage is often inadequate or inappropriate, samples cannot be used for post-market checks later. A better approach could be to request physical samples upon need.

3.3.5. PRIORITIZED RESOURCES FOR REGULATION OF PRODUCTS WITH GREATER PUBLIC HEALTH RELEVANCE

Some regulatory authorities prioritize the marketing authorization review and processing of products that have important public health relevance. For example, “priority review” occurs where there is evidence of increased effectiveness, a substantially reduced treatment limiting drug reaction, an increase in compliance, and/or new evidence of safety and effectiveness in a subpopulation (46). “Breakthrough therapy” is a designation to expedite development and review of products and receive organizational commitment from senior managers, when there is promising evidence of substantial improvement over available therapy for a serious clinical condition (47).

Another way of prioritizing can be to look at which products are being commercialized. In resource-limited NRAs, handling products that are not eventually commercialized is particularly inefficient, taking up valuable resources without providing any health benefit to local populations. To discourage this practice, some NRAs, like INVIMA, have introduced legal provisions that allow a marketing authorization to be revoked if the product is not commercialized. Other authorities like ANMAT and ISP issue marketing authorizations on the condition that companies meet specific deadlines for first batch release.

3.3.6. REGULATORY RELIANCE

Regulatory reliance is another way NRAs can gain efficiency in marketing application review. NRAs use reliance to improve the efficiency of their marketing authorization in various ways, including accelerated approvals for specific products or circumstances, which can be categorized into two main types:

- **Verification approval:** when the NRA from the importing country allows a product to be marketed locally after verifying that it has been authorized, in the same form, by one or more recognized reference authorities.
- **Abridged approval:** when the NRA conducts an abridged independent review that does not typically include assessing any scientific supporting data that has already been reviewed and accepted by one or more recognized reference authorities.

All Latin American NRAs acknowledge the potential value of regulatory reliance in reducing the workload and speeding up the processing time of marketing approval decisions. Its implementation among NRAs is, however, variable and has gradations. Only two out of six NRAs practice the most direct form of reliance, verification: ANMAT conducts a verification review of products approved by SRA, in which a Certificate of Pharmaceutical Product is the most important document; and CECMED conducts a verification review to check if the product is approved by an NRA, SRA, or WHO. Other NRAs’ accelerated approval involves a longer, but abridged, review (see Table 3.3).

Table 3.3. Accelerated marketing approval pathways of NRAs

| NRA | Verification route | Abridged route |
|----------|--------------------|----------------|
| ANMAT | ✓ | |
| ANVISA | | ✓ ^a |
| CECMED | ✓ | ✓ ^b |
| COFEPRIS | | ✓ ^c |
| INVIMA | | ✓ |
| ISP | | ✓ ^d |

Notes: ^a Only for biologics; ^b For products that have been authorized by PAHO NRA, Australia, Japan, New Zealand, Sweden, Switzerland, or EMA; ^c For products registered by EMA, FDA, Australia, and WHO Prequalification; ^d For products that have been registered in FDA or EMA. ISP is currently modifying the regulation of medicines to include issuance of approval or refusal resolution for marketing authorization requests of medicines that have been registered in an SRA or NRA, within a period not exceeding three months if amendments or clarifications are not required.

Source: Patel P, McAuslane N, Liberti L. R&D Briefing 71: Trends in the Regulatory Landscape for the Approval of New Medicines in Latin America. London: Centre for Innovation in Regulatory Science; 2019.

Another way in which some NRAr use reliance is through exemptions or temporary marketing authorizations under special conditions. Most notably, many Latin American countries tend to waive market authorization requirements for any vaccine, pharmaceutical, or other product that is procured through the PAHO Strategic Fund or Revolving Fund.

NRAr: trusted sources for reliance

NRAr are widely relied upon for marketing authorization by a diverse group of NRAs across the Americas. This means that their practices not only impact access to medicines in their own countries but also influence market authorization across the Region as a whole. In 2017, INVIMA and PAHO conducted a survey to explore the reliance practices and needs of 11 non-reference NRAs in the Americas⁵ (48). The results indicate that 73% of participating NRAs have legal provisions to formally rely on marketing approvals from NRAr; although all report informally relying on NRAr by using the publicly available information on their websites. Countries in Central America, including Dominican Republic, El Salvador, and Guatemala, rely on NRAr individually; while countries in the Caribbean Community (CARICOM) rely on NRAr collectively, through the Caribbean Regulatory System (49).

Without confidentiality agreements, which can be time-consuming to negotiate and are rarely established between large and small authorities, reliance depends on reviewing the publicly available information that is published on NRAr websites. A lot of the information NRAs need to support their market approval decisions is, however, either absent or difficult to find, especially for generic products (see Table 3.4). The limited availability of this information is a major barrier to using reliance to speed up marketing approval in the Americas. More transparency of information would also address the problem of companies selling different versions of the same product to different markets, with lower-tier products (for example, those with lower quality API or those from lower-cost manufacturing sites) going to less lucrative markets or markets where there are fewer regulatory controls (50). The WHO Prequalification website publishes much more of this information and is a good model.

Table 3.4. Publicly available information on marketing authorizations of generics in NRAr

| | ANMAT ^a | ANVISA ^a | CECMED ^a | COFEPRIS ^a | FDA ^{b*} | Health Canada ^{c*} | ISP ^{a*} | INVIMA ^a | WHO FPP PQ ^d |
|---|--------------------|---------------------|---------------------|-----------------------|-------------------|-----------------------------|-------------------|---------------------|-------------------------|
| Searchable electronic MA database | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Qualitative/quantitative formula | | | | | | | | | |
| Summary of product characteristics | | | | | | | | ✓ | ✓ |
| Authorized packaging | | | | | | | | | ✓ |
| Manufacturing site address | | | | ✓ | | | | ✓ | ✓ |
| Totals | 20% | 20% | 20% | 40% | 20% | 20% | 20% | 60% | 80% |

Note: * FDA and Health Canada make more information available for new products, including SMPC and product monograph.

Sources: ^a Data collected by PAHO using the following methodology: Each LA NRAr identified a focal point for this report. PAHO developed an instrument with the data requested, the instrument was filled by the LA NRAr focal point, followed by a phone interview/email communication to validate the data included in the report. Two rounds of data validation were performed. The investigation and analysis were conducted from March 2019 to October 2020; ^b U.S. Food and Drug Administration [Internet]. Silver Spring: FDA; 2020. Drug approvals and databases. Available from: <https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases>, cited 3 March 2020; ^c Government of Canada, Health Canada [Internet]. Ontario: Health Canada; 2020. Drugs and health products. Available from: <https://www.canada.ca/en/health-canada/services/drugs-health-products.html>, cited 3 March 2020; ^d World Health Organization [Internet]. Geneva: WHO; 2020. Medicines/Finished Pharmaceutical Products. Available from: <https://extranet.who.int/prequal/content/prequalified-lists/medicines>, cited 3 March 2020.

⁵ The survey included 11 countries: Belize, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Paraguay, Peru, and Uruguay. All except Guatemala, Nicaragua, and Uruguay reported having legislation to rely on marketing approvals from NRAr.

Recommendations for Action

- **Prioritize regulatory life-cycle management.** NRAs should consider ways to improve regulatory oversight using a holistic view of the life cycle of the authorization, including pre- and post-market stages. Enablers for this should include, among others, considerations on how to better fund all regulatory activities, to increase and improve allocation of technical and human resources, and to improve efficiencies, such as through reliance, risk-based approaches, electronic tools, and other approaches.
- **Improve bioequivalence harmonization.** Ensuring adequate regulatory oversight for generics in the Region requires that NRAs harmonize and adopt international requirements for bioequivalence and biowaivers to the greatest extent possible.
- **Increase efficiencies in the prioritization of products with public health impact.** Consider implementation of policies and programs related to this area, such as priority review and/or revoking marketing authorizations when products are not commercialized.
- **Implement procedures that enable use of joint/collaborative reviews and reliance.** Although procedures that support the use of reliance can strengthen the market authorization regulatory function, they continue to be underutilized. Similarly, the use of joint/collaborative review mechanisms to bolster review capacity and to support reliance should be considered. All NRAs in the Region should continue to prioritize the development of legal frameworks and processes to operationalize these mechanisms.
- **Improve publicly available regulatory information.** Public access to marketing authorization and product related information from the NRA is crucial to support ongoing regional reliance efforts, and needs to be significantly improved by all authorities as part of good regulatory practices.
- **Improve funding of regulatory activities.** The finding of significant differences in the manner NRAs are funded, and in the way regulatory user fees are allocated and managed, is worth highlighting. Because of the individual particularities of the different systems, NRAs and government bodies should consider reassessing the funding mechanisms in place, including in relation to other reference authorities (e.g., ratios of user fees charged). The scope of this assessment must cover all the different regulatory functions required to support the development, authorization, and monitoring of medicines of good quality, safety, and efficacy for the population.

4. MARKETING AUTHORIZATION OF SIMILAR BIOTHERAPEUTIC PRODUCTS

In brief

- Biotherapeutics are an increasing driver of healthcare cost, and several NRAr governments are pursuing local production strategies, including for similar biotherapeutic products (SBPs).
- Some Latin American NRAr countries are producing SBPs.
- However, there are differences in some key elements of SBP regulatory oversight, like the implementation and use of regulatory standards, or the choice of the reference product for comparisons.
- SBPs require strong post-marketing strategies to ensure their long-term safety, but pharmacovigilance of these products is still incipient.
- There are reliance programs for SBPs, including through WHO prequalification.

4.1. NRA Foundations for Regulating SBPs

WHO defines biotherapeutic products as biological medicinal products developed and prepared using genetically engineered bacteria, yeast, fungi, cells, or even whole animals and plants (51). The development of these products—including, for example, insulin, erythropoietin, and a number of monoclonal antibodies used in cancer treatments—has significantly contributed to the treatment and control of many life-threatening diseases. However, they are generally expensive to produce and their cost can be prohibitive, especially in LMICs. These high costs have increased the attention on SBPs, which are designed to be “similar” to an already-licensed originator biotherapeutic (reference product), and have the potential to render biotherapeutics more affordable and accessible.

The regulatory work required to evaluate and license SBPs is, however, challenging. NRAs cannot simply use the established approach for small-molecule generics because SBPs are biological substances made up of relatively larger and more complex molecules that are significantly more difficult to characterize. It is broadly acknowledged that an SBP cannot be regarded as a generic of a marketed biological medicine because natural variability and more complex manufacturing do not allow exact replication at the molecular level (52, 53). The clinical performance of SBPs is also believed to be highly dependent on the manufacturing processes used, which means they require clinical studies to establish their safety and efficacy (54).

Countries in Latin America are increasingly interested in and/or manufacturing SBPs. In 2019, there were four NRAr countries with local manufacturing capacity for SBPs: Argentina, Brazil, Cuba, and Mexico.⁶ The governments of Argentina, Brazil, and Cuba have actively prioritized and supported the local manufacturing of SBPs through a variety of mechanisms; while most of the SBP manufacturing in Mexico is driven by private companies, with little promotion by the government. In all cases, there is potential for tensions to arise between initiatives to increase domestic production and the need to ensure appropriate regulation.

⁶ Venezuela (Bolivarian Republic of) also has local manufacturing capacity for biotherapeutics, but it was not evaluated for this report because it is not an NRAr country.

4.1.1. LEGAL AND ORGANIZATIONAL FRAMEWORKS

The regulatory landscape of biotherapeutics and SBPs in Latin America has changed dramatically in the past decade. In 2009, a PAHO survey of 17 countries found that marketing approval requirements for biotherapeutics were consistently underdeveloped, often undistinguishable from requirements for other biological products (such as vaccines and blood derivatives). In some cases, requirements for biotherapeutics and SBPs were even the same as those for pharmaceuticals (55). In contrast, in 2019, many Latin American countries (with the exception of some in the Caribbean) either introduced or drafted a specific regulatory framework for SBPs⁷ (56).

In general, regulatory frameworks for SBPs are relatively new and there is a burgeoning literature on how SBP regulatory frameworks in Latin America have been developed, as well as the extent to which they follow international standards. However, there are no published studies that evaluate the implementation processes or material impacts of different regulations. Even though some Latin American countries have had regulatory frameworks for SBPs for more than a decade, the number of SBPs that have been approved in the Region remains low.

4.2. Regulating SBPs in Practice

Specific regulatory requirements for SBPs are broadly similar across NRAR countries. Allowing for some variation to account for local contexts (57), they follow WHO guidelines and focus on demonstrating that there is no clinically meaningful difference in safety, quality, and effectiveness between the SBP and the already-licensed reference biotherapeutic product (RBP). As recommended by WHO, this is generally achieved by generating and evaluating comparative data in a stepwise fashion, starting with detailed analytical studies and then moving to animal studies and then clinical studies (54). At the end of each comparability exercise, the decision to progress to the next drug development step is taken based on whether any relevant differences between the SBP and RBP have been found. Some NRAR, including ANVISA in Brazil and INVIMA in Colombia, offer fast-track pathways for SBP approval:

- In Brazil, SBP applications can be submitted to the traditional stepwise comparative pathway or to an “individual development pathway,” which requires complete, but not comparative, quality data, and which has the potential for a reduced number of non-clinical and clinical studies (58).
- In Colombia, SBP applications can similarly be submitted to the traditional stepwise comparative pathway or to an abbreviated comparability pathway. The abbreviated pathway can be used when there is information from another country where the SBP has been accepted with studies demonstrating a similarity with the RBP’s active principle (59); additionally, the API must be considered widely known, of low complexity, and exhaustively characterized.

Despite the similarities in approval requirements across NRAR in manufacturing countries, there are some important differences, especially in the definitions and the nomenclature used for SBPs. For example, SBPs are called “known multisource biological products” in Cuba but are known as “biocomparables” in Mexico. More significantly, NRAR countries also differ in their requirements for RBPs. RBPs are central to the approval of SBPs because they provide the basis for establishing safety, quality, and effectiveness through comparison. International guidelines recommend that the RBP be licensed with full quality, safety, and efficacy data in the given country. This means that SBPs cannot be used as the reference product. In Mexico, COFEPRIS offers a special approval pathway for companies to use an SBP as a reference product in specific cases. In Colombia, INVIMA similarly allows the use of an SBP as the RBP if that SBP has already been approved based on a full dossier in a reference authority country.⁸

⁷ In 2016, Garcia and Araujo found that only Bolivia (Plurinational State of) and Ecuador lacked a regulatory framework for biotherapeutic products; on checking, we find in 2019 that both countries have now issued regulatory guidelines for these products.

⁸ The reference authority countries used by INVIMA include Australia, Canada, Japan, United States of America, as well as the European Union.

Several key RBPs and SBPs have been approved by Latin American NRAR and are available to patients and prescribers (see Table 4.1). In most cases, both the RBP and SBP for each class of product are authorized. However, there are some cases where an NRAR has authorized an SBP even though the RBP is not authorized.

Table 4.1. Reference and similar biotherapeutic products approved by Latin American NRAR

| Medicine | Biosimilar (reference in italics) | Argentina | Brazil | Chile | Colombia | Cuba | Mexico |
|--------------------|---------------------------------------|-----------|----------------|-------|----------|------|--------|
| INFLIXIMAB | <i>Remicade (Janssen)</i> | ✓ | ✓ | ✓ | ✓ | | ✓ |
| | Remsima (Celltrion Inc.) | ✓ | ✓ | ✓ | ✓ | | ✓ |
| FILGRASTIM | <i>Neupogen (Amgen)</i> | | ✓ ^a | ✓ | ✓ | | ✓ |
| | Zarzio (Sandoz) | | ✓ | ✓ | ✓ | | ✓ |
| | Others (locally produced or imported) | ✓ | ✓ | ✓ | ✓ | ✓ | |
| RITUXIMAB | <i>Mabthera (Genentech/Roche)</i> | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Novex (MABxience – Elea) | ✓ | | | | | ✓ |
| | Vivaxxia (MABxience – Libbs) | ✓ | ✓ | | | | ✓ |
| | Others (locally produced or imported) | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| TRASTUZUMAB | <i>Herceptin (Genentech/Roche)</i> | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Zedora (Libbs) | | ✓ | | | | |
| | Others (locally produced or imported) | | ✓ | ✓ | ✓ | ✓ | |

Notes: Market presence of products was identified through the existence of a marketing authorization in February 2019 for ANMAT and COFEPRIS, and in October 2020 for ANVISA, CECMED, INVIMA, and ISP through searches in their databases; ^a Registered as Granulokine in Brazil.

4.2.1. POST-MARKET SURVEILLANCE

In the past few years, Latin American NRAs have begun working on pharmacovigilance of SBPs. However, the lack of uniform requirements for product naming poses a significant if well-recognized challenge to the regulatory oversight and post-market surveillance of SBPs.

Acknowledging the complexities of these products, and the fact that they can be considered similar but not identical to RBPs, all Latin American NRAR (like most regulatory agencies elsewhere) require the manufacturer to submit a risk-management plan setting out plans for pharmacovigilance as part of their application for marketing authorization.

4.2.2. ACCESS TO INFORMATION

Stakeholders interviewed for this report highlighted a lack of transparency in approval information as a key challenge to improving trust and uptake of SBPs. They reported problems in accessing information from Latin American NRAR about approval pathways for SBPs and in accessing summaries of product characteristics for authorized RBPs and SBPs. ANVISA and CECMED are the only Latin American NRAR that currently publish a complete summary of product characteristics for each authorized biotherapeutic—reference or similar.

4.2.3. INTERCHANGEABILITY AND EXTRAPOLATION

With no global consensus, there is an active debate on how to treat interchangeability and handle extrapolation of indications. Establishing interchangeability between the SBP and its RBP needs substantial clinical data beyond what is normally required for initial product licensing. A recent review of SBP use in selected European countries and the United States of America shows that in some European countries the interchanging of RBPs and SBPs during treatment is not recommended, while in others it is left to the discretion of the prescribing physician (60). In the United States of America, some SBPs (called follow-on biologics) can provide the required evidence to be authorized as interchangeable. In Canada, authorization of an SBP is not a declaration of equivalence and it is up to each province to decide whether the product can be used interchangeably with the RBP. In Latin America, none of the NRAR have any specific recommendations on interchangeability.

Given the absence of a common global regulatory approach to using extrapolation for SBPs, all Latin American NRAR allow for the extrapolation of data to other clinical indications on a case-by-case basis, and only if similar efficacy and safety have been demonstrated. In Brazil, extrapolation is only allowed for products approved through the comparability pathway and not for those approved through the individual development pathway.

4.3. Best Practices and Efficiencies in Regulating SBPs

The complexities of regulating SBPs offer an important opportunity to use reliance strategies for robust oversight. Combining reliance on a more trusted authority with sound national pharmacovigilance and post-market surveillance could prove an excellent route to gathering the needed evidence to support knowledge and development in this field. In 2017, WHO launched a pilot project for prequalifying SBPs so that these products can become eligible for procurement by United Nations agencies (61). Countries can access important confidential information that enables them to rely on WHO prequalification of these products if they participate in WHO's collaborative procedure for accelerated registration (44). The Caribbean Public Health Agency's Caribbean Regulatory System participates in the WHO collaborative procedures for SBPs. It has also developed approval criteria outside of collaborative procedure, requiring that the SBP must be approved and commercialized (with accompanying post-market surveillance) in select reference authority markets.

Recommendations for Action

- **Develop and implement standards for SBP.** Establish, harmonize, and enforce appropriate manufacturing standards for SBPs and apply them equally to both international and domestically produced products.
- **Harmonize regulatory oversight.** Authorities need to continue efforts toward common regulatory approaches for SBPs, such as definitions, RBPs, and interchangeability requirements.
- **Improve post-authorization surveillance.** Without common regulatory approaches for market authorization, the use of strong post-market requirements and oversight is even more critical and should be implemented as a standard practice for SBPs upon authorization.
- **Use reliance for SBPs.** Embrace and adopt reliance strategies for the regulatory oversight of SBPs where appropriate, including via use of the WHO collaborative procedure for accelerated registration of WHO-prequalified products.

5. GOOD MANUFACTURING PRACTICE INSPECTIONS

In brief

- Good manufacturing practice (GMP) inspections in Latin America are shaped by a variety of factors including the organization, human, and financial resources of regulatory authorities involved, the level of local manufacturing present, and the extent of interinstitutional collaboration.
- All Latin American NRAR conduct domestic inspections, but some do not conduct international inspections.
- NRAR use pre- and post-market inspection strategies and follow similar procedures in doing this; however, many do not conduct pre-market inspections of API facilities.
- Reliance for GMP inspections is a common but underused strategy among Latin American NRAR.
- The recent expansion of PIC/S in the Region has helped countries adopt international standards and establish a basis for securing trust in their GMP inspection certification.
- Transparency remains a critical issue, with NRAR making very little information on their GMP inspections publicly available for use by other authorities.

5.1. NRA Foundations for Good Manufacturing Practice Inspections

GMPs describe the minimum standards that pharmaceutical manufacturers must meet in their production processes. These practices serve to manage and minimize the risks inherent to pharmaceutical manufacturing in order to ensure the quality, safety, and efficacy of products (62). Adhering to GMPs ensures that medicines are consistently produced and controlled according to quality standards appropriate for the intended use and as required by relevant marketing authorization and product specifications (63).

Ensuring that manufacturers follow GMP is a key role for NRAs. This is achieved through inspection and licensing activities. Well-functioning NRAs have a legal mandate to fulfill this role: they are empowered to carry out on-site inspections and to issue, suspend, or withdraw establishment licenses, including authorizations or certifications for the activities performed by these establishments.

GMP inspections are required at all stages and sites of the manufacturing process if they are to assure the quality of a finished product. This means NRAs also need to provide oversight of supply chains, which are increasingly global (4). For example, a typical supply chain begins with the manufacture of the API, which is then shipped to one or more other sites for use in intermediate products before again being transferred to produce the finished product. In many cases, this movement of products crosses regulatory jurisdictions and often takes place in countries with less developed regulatory systems (64). Regularly inspecting all the different manufacturing sites involved in such supply chains is logistically challenging and resource intensive. As such, NRAs are increasingly adopting strategies, such as reliance, that can improve efficiencies, spare resources, and avoid duplication of efforts (see Section 5.4) (31).

5.1.1. LEGAL AND ORGANIZATIONAL FRAMEWORKS

In general, the scope of GMP inspections is set by the NRA doing the inspection. While some countries develop their own requirements for GMP, the great majority rely on internationally accepted recommendations and standards. These vary in detail, but tend to cover the same 12 basic components (see Figure 5.1).

Figure 5.1. Twelve common components of GMP standards



WHO guidelines have driven standards for GMP inspections over many decades, with more than 100 countries across the world incorporating them into their national medicines laws (65). These guidelines cover the 12 basic components highlighted in Figure 5.1. They define measures for production and quality control and describe general measures to define, validate, review, and document manufacturing processes, and to check the suitability of personnel, premises, and materials. WHO guidelines also include the legal components required to cover responsibilities for distribution, contract manufacturing, and complaints and product recalls.

5.1.2. THE ROLE OF PIC/S

A growing number of countries are joining PIC/S in a push to develop, implement, and maintain a set of harmonized GMP standards across jurisdictions (66). Joining the initiative involves a detailed assessment of the NRA's inspectorate. PIC/S standards include the 12 common components of GMP. They closely mirror WHO guidelines, reflect changing scientific and industrial technology, and comply with stringent manufacturing or health requirements, including for new areas like biologics. In addition to defining GMP standards, PIC/S also works to train GMP inspectors and to facilitate discussion and knowledge-exchange in specialized areas. Four countries in

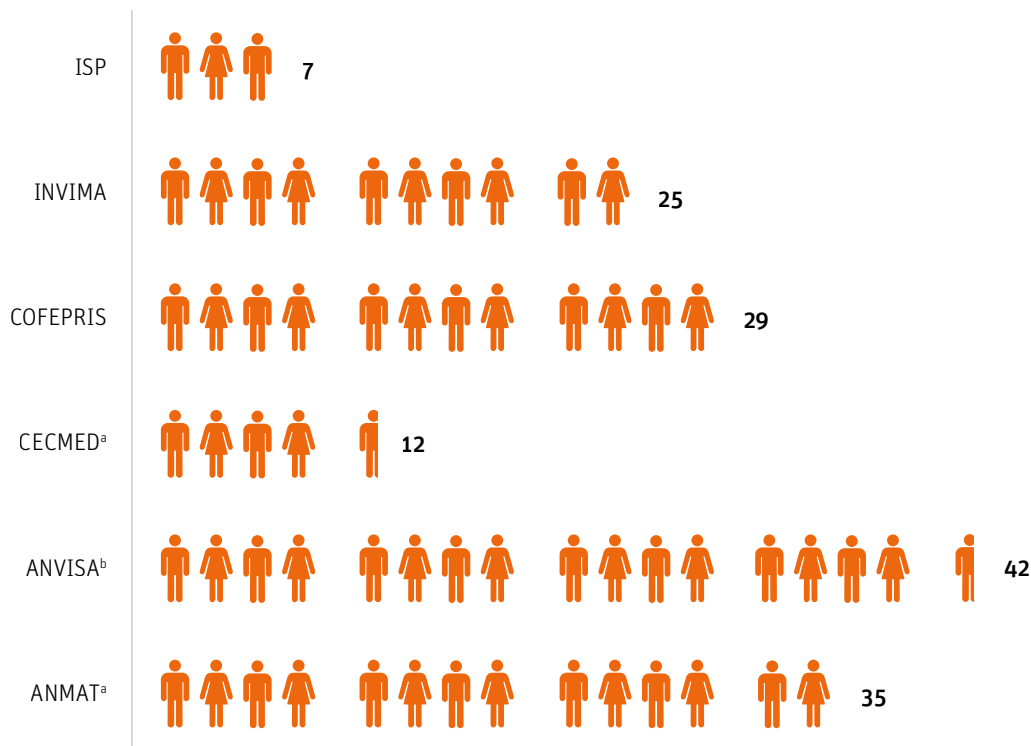
the Americas are currently PIC/S members: Argentina, Canada, Mexico, and the United States of America. Brazil is applying for membership.

5.1.3. STAFFING AND RESOURCE REQUIREMENTS

The number of qualified inspectors available in the NRA can indicate the scope and reach of its GMP activities, for example, the extent to which an NRA can oversee different types of manufacturing (e.g., API or FPP); it also plays a role in the frequency of inspections and whether or not the NRA can inspect foreign manufacturing facilities, among other things. In Latin America, the size of NRAr inspectorates varies from country to country (see Figure 5.2). Brazil has the largest inspectorate for pharmaceutical products and Chile the smallest.

The levels of qualification among inspectorate staff vary across NRAr. Inspectors are typically required to hold, at a minimum, a university degree in a relevant field, such as pharmacy, industrial engineering, chemistry, microbiology, toxicology, or biochemistry. However, levels of education in NRAr inspectorates can often be higher. For example, in ANMAT, around a quarter of all inspectors have postgraduate qualifications.⁹

Figure 5.2. Number of GMP inspectors for pharmaceutical products in NRAr in 2019



Notes: Data include number of inspectors qualified for pharmaceutical products of chemical synthesis and biologics; inspectorates may have more staff for other types of inspections.

^a ANMAT and CECMED figures reflect the number of GMP inspectors overseeing facility compliance only; they do not include the authority’s general inspectors that oversee product-related compliance; ^b Only centralized inspectors at ANVISA level are considered. In the National Sanitary Surveillance System (ANVISA and local surveillance) there are 105 inspectors of medicines and/or pharmaceutical supplies. Of these, 42 are centralized ANVISA inspectors. The classification as an inspector of drugs and/or pharmaceutical supplies was established in the Qualification and Training Program for Inspectors of Drug Manufacturing Establishments.

Source: Data collected by PAHO using the following methodology: Each LA NRAr identified a focal point for this report. PAHO developed an instrument with the data requested, the instrument was filled by the LA NRAr focal point, followed by a phone interview/email communication to validate the data included in the report. Two rounds of data validation were performed. The investigation and analysis were conducted from March 2019 to October 2020.

⁹ Internal data provided by ANMAT during June 2019 meeting presentation.

5.2. GMP Inspection in Practice

GMP inspection practices are broadly similar across Latin American NRAr. All have:¹⁰

- **Regulatory frameworks** based on international guidelines and standards, including WHO and PIC/S (see Table 5.1).
- **GMP requirements** for the 12 common components of GMP.
- **Standard procedures** to guide the activities that must be performed before, during, and after each inspection.
- **Non-compliance management systems** that categorize non-compliance by severity and enable a corrective plan of action to be developed.

All NRAr have adopted a risk-based strategy of inspection that prioritizes manufacturing sites by the estimated risk these may pose to patients and product quality. This means that NRAr target their resources in terms of timing and frequency of inspections. In all cases, NRAr carry out both pre- and post-market inspections to ensure quality, efficacy, and safety throughout the product life cycle.

Table 5.1. International guidelines providing the basis for NRAr regulatory framework

| COUNTRY | INTERNATIONAL GMP STANDARD CITED IN REGULATION | |
|------------------|---|---|
| | Organization | Document |
| ARGENTINA | <ul style="list-style-type: none"> • WHO • MERCOSUR • PIC/S | <ul style="list-style-type: none"> • TRS No. 908, 2003. 37th Report • Res 15/2009 |
| BRAZIL | <ul style="list-style-type: none"> • WHO • MERCOSUR • PIC/S IN PROCESS | <ul style="list-style-type: none"> • TRS No. 908, 2003. 37th Report • Res 15/2009 • PIC/S GMP Guide and Annexes |
| CHILE | <ul style="list-style-type: none"> • WHO | <ul style="list-style-type: none"> • TRS No. 908, 2003. 37th Report, Annex 4 • TRS No. 834, 1993. 33rd Report, Annex 3 (Biological Products) • TRS No. 961, 2011. 45th Report, Annex 6 (Sterile Products) |
| COLOMBIA | <ul style="list-style-type: none"> • WHO | <ul style="list-style-type: none"> • TRS No. 908, 2003. 37th Report • TRS No. 957, 2010. 44th Report, Annex 1 (Quality Control Laboratories) • TRS No. 834, 1993. 33rd Report, Annex 3 (Biological Products) • TRS No. 961, 2011. 45th Report, Annex 6 (Sterile Products) |
| CUBA | <ul style="list-style-type: none"> • WHO | <ul style="list-style-type: none"> • TRS 961, 2011. 45th Report |
| MEXICO | <ul style="list-style-type: none"> • WHO • PIC/S | <ul style="list-style-type: none"> • TRS No. 908, 2003. 37th Report |

Source: Data collected by PAHO using the following methodology: Each LA NRAr identified a focal point for this report. PAHO developed an instrument with the data requested, the instrument was filled by the LA NRAr focal point, followed by a phone interview/email communication to validate the data included in the report. Two rounds of data validation were performed. The investigation and analysis were conducted from March 2019 to October 2020.

¹⁰ Data collected by PAHO using the following methodology: Each LA NRAr identified a focal point for this report. PAHO developed an instrument with the data requested, the instrument was filled by the LA NRAr focal point, followed by a phone interview/email communication to validate the data included in the report. Two rounds of data validation were performed. The investigation and analysis were conducted from March 2019 to October 2020.

5.2.1. PRE-MARKET INSPECTIONS

Pre-market inspections cover those made before a product first enters the market. NRAr requirements for pre-market inspections vary depending on whether the product is an API or FPP.

APIs

Many Latin American NRAr do not require API manufacturing GMP documentation for marketing authorization, even though it is recommended by ICH guidelines and WHO prequalification programs. ANVISA and INVIMA require GMP documentation for some, but not all, APIs (67). COFEPRIS is the only Latin American NRAr that requires GMP documentation for all APIs.

FPPs

All NRAr require a GMP certificate for FPPs as part of marketing authorization. They may carry out inspections to that end, or they may accept the results of another authority's inspection through an arrangement for reliance. In the case of federal countries such as Argentina and Brazil, the state or municipal authorities may also carry out inspections (see Box 4).

Box 4. Multi-tier inspections in federal countries

Federal countries often use multi-tier inspections to issue GMP certificates.

In Argentina, ANMAT is responsible for certifying domestic manufacturing sites when the product is authorized for national markets or for export. If the product will only be used within a particular province, it is the local inspectorate that issues the GMP certificate. A national harmonization and capacity-building program, ANMAT Federal, ensures that the requirements are standardized across jurisdictions and that local inspectorates have the skills they need to carry out effective inspections.

In Brazil, inspections are carried out at the federal, state, and municipal levels.¹ At the federal level, ANVISA is responsible for international inspections of API and FPP. ANVISA can delegate the power to inspect medicine manufacturing sites to local health authorities. State and municipal health authorities that meet ANVISA's minimum criteria and have GMP regulations harmonized with PIC/S are eligible to inspect manufacturing sites and issue site licenses and GMP certificates for APIs and FPPs, except for medicinal gases. ANVISA remains responsible for national inspections where states or municipalities cannot meet the criteria and for those places lacking local resources. ANVISA audits the quality management system of these local health authorities every three years.

Sources: 1. Geyer ARC, Sousa VD, Silveira D. Inspeções de boas práticas de fabricação de medicamentos: Resultados e não conformidades encontradas. Brasília: ANVISA; 2015. Available from: <https://sindusfarma.org.br/arquivos/Andrea-Apresentacao.pdf>, cited 9 February 2020.

5.2.2. POST-MARKET INSPECTIONS

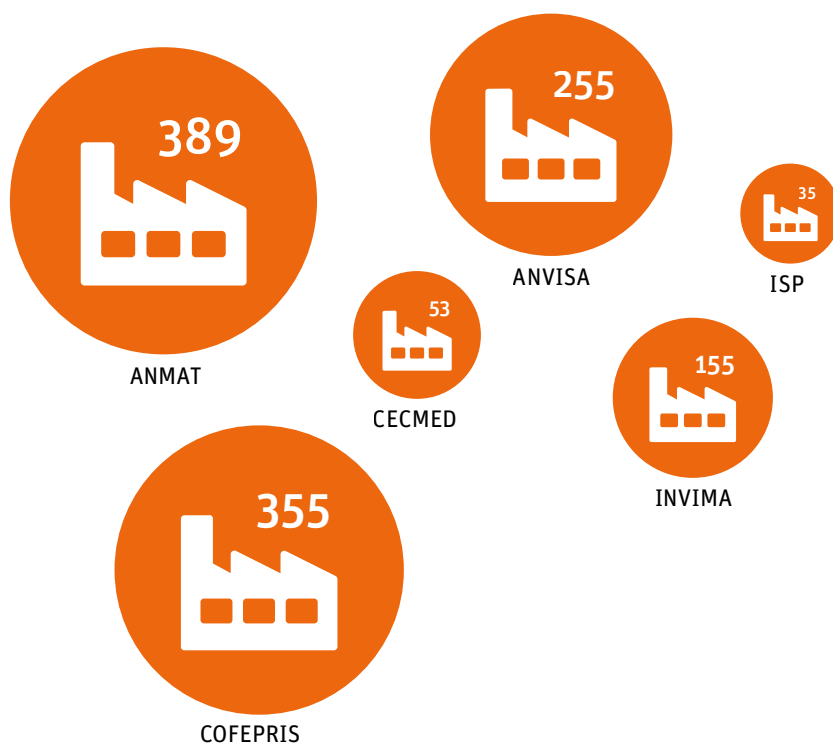
Post-market inspections of manufacturing sites include all those made once a product is on the market and in use. In Latin American NRAr, post-market inspections are carried out using a risk-based approach that identifies triggers for inspections:

- A number of changes can prompt an inspection. Such changes include, for example, a modification to the manufacturing site or line of production, an addition of new products or group of products to a marketing authorization application, the use of a new API, a change in dosage form, or the termination or reactivation of operations. Manufacturers are required to give the NRAr advance warning of the changes being introduced.
- Alerts or product market failures are grounds for “for-cause” inspections in NRAr.
- Expiry of the GMP certificate also triggers inspection in NRAr. GMP validity periods vary across the six NRAr, with certificates being issued for anything between one and three years. The shorter the validity period, the more likely it is to ensure GMP compliance; but short-lived certificates are also resource-intensive, requiring more frequent inspections.

Licensing establishments

The number of licensed manufacturing facilities varies across NRAr (see Figure 5.3). These data can seemingly point to the scope of the inspectorate’s responsibilities because each licensed establishment should ideally be inspected on a regular basis. But such interpretation should be made with care. Depending on the country’s rules, the number of licensed facilities may not include all those that are overseas. Neither does the number necessarily provide a good indication of domestic manufacturing capacity. It does not differentiate between facilities that are owned by domestic companies and those owned by multinational ones; nor does it distinguish facilities that produce one product from those with multiple lines of products. This is perhaps why the number of facilities in Cuba is low even though the country is known to have a large domestic pharmaceutical industry: much of its production of biological products is consolidated at licensed facilities. For reference purposes, there are far fewer licensed facilities in Latin American countries than in either Canada (752) or the United States of America (1,823).

Figure 5.3. Number of manufacturing facilities for medicines and biologics licensed by NRAr



Note: Data include finished pharmaceutical products and APIs of chemical synthesis and biologics.

Source: Data collected by PAHO using the following methodology: Each LA NRAr identified a focal point for this report. PAHO developed an instrument with the data requested, the instrument was filled by the LA NRAr focal point, followed by a phone interview/email communication to validate the data included in the report. Two rounds of data validation were performed. The investigation and analysis were conducted from March 2019 to October 2020.

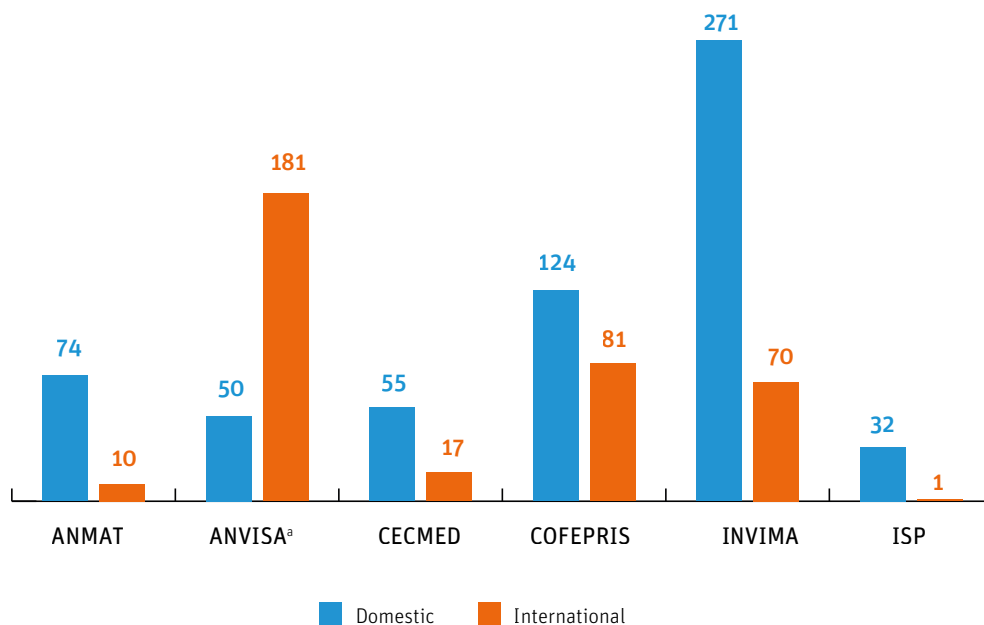
5.3. International Inspections

The global nature of pharmaceutical supply chains makes international inspections an increasingly important issue for NRAs in the Americas. Each NRAr takes its own approach to inspecting international manufacturers:

- ANMAT reserves the right to carry out international inspections and decides which establishments to inspect, and when, based on a risk assessment that includes information from the exchange of inspection records with other PIC/S and MERCOSUR members.
- ANVISA is responsible for doing all international inspections itself, but it designs its inspection strategy based on reliance agreements with some MERCOSUR countries and Cuba.
- CECMED recognizes GMP documentation of FPPs when granted by an SRA; otherwise, it does the international inspection itself.
- COFEPRIS does all international inspections itself.
- INVIMA recognizes GMP documentation of FPPs when granted by an SRA or by a health authority that is part of the Interinstitutional Cooperation Agreement within the Pacific Alliance; otherwise, it does the international inspection itself.
- ISP does not conduct international inspections for marketing authorization of imported products, and accepts GMP documentation of FPPs issued by the NRA in the country of origin.

The number of international inspections for medicines carried out by Latin American NRAr varies from country to country; it is usually smaller than the number of domestic inspections because countries typically prioritize in-country action (see Figure 5.4). In Brazil, the low number of domestic inspections for ANVISA is explained by the fact that it delegates many of these responsibilities to state and municipal authorities. Direct comparisons between number of inspections per country without considerations on things like the actual number of products or of manufacturers to be evaluated, or the information available to the authorities, could be misleading. That said, data from 2018 suggest that ANVISA carries out the highest number of international inspections of the NRAr (although it still does fewer than the United States of America, which did 713 inspections in 2018) (68).

Figure 5.4. NRAr domestic and international inspections for medicines in 2018



Notes: These data do not include inspections carried out by state or municipal authorities.

^a ANVISA's domestic inspection accounts only for GMP certification purposes and does not cover monitoring and investigational inspections.

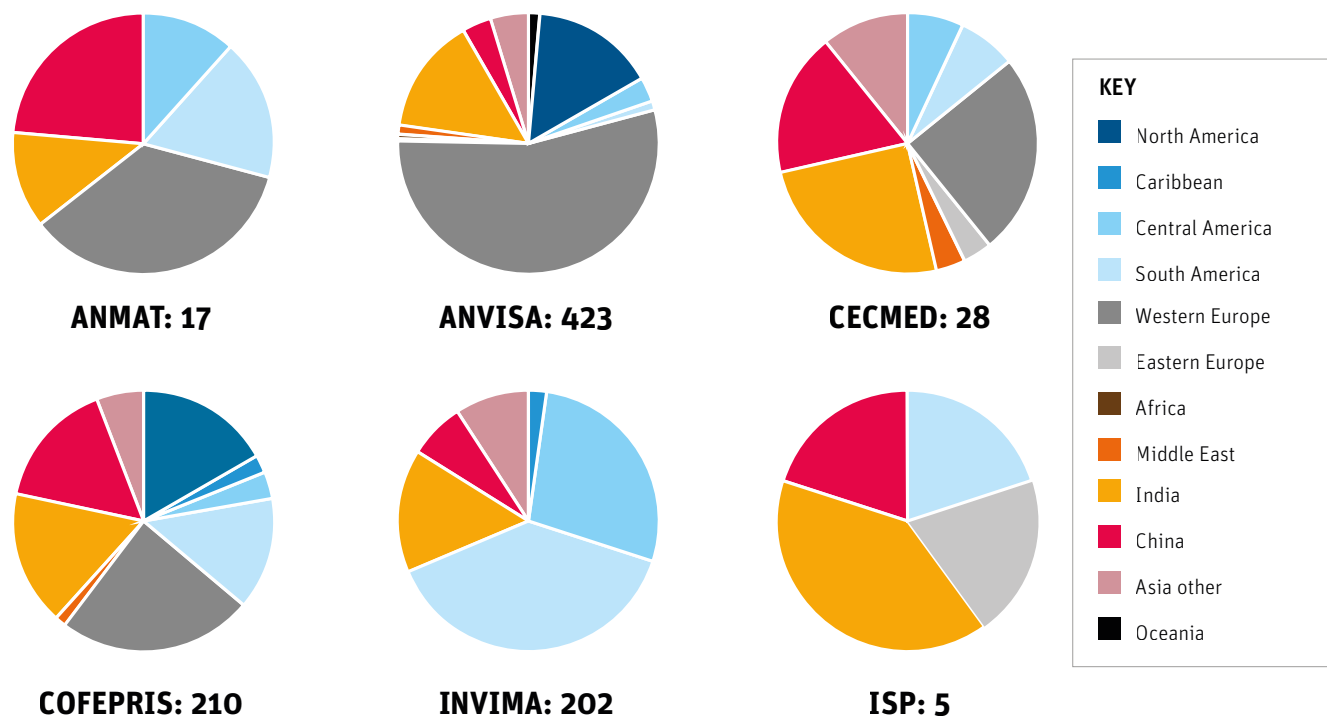
Source: Data collected by PAHO using the following methodology: Each LA NRAr identified a focal point for this report. PAHO developed an instrument with the data requested, the instrument was filled by the LA NRAr focal point, followed by a phone interview/email communication to validate the data included in the report. Two rounds of data validation were performed. The investigation and analysis were conducted from March 2019 to October 2020.

There are important strategic considerations to be made in setting the size and scope of international inspection programs, including whether to have them at all. The ability to conduct international inspections gives an NRA more hands-on oversight of the global supply chain, which may be especially useful when risk is high. But international inspections are resource-intensive and may be difficult to justify when risk is low.

Agencies looking to understand these issues may wish to examine their international inspections footprint. Data from 2017–2019 show that a large proportion of international inspections by some NRAs are done in Western Europe (see Figure 5.5), which is home to highly competent regulatory authorities. Conducting inspections there seems counter-intuitive. The motives for this are unclear but interviewees suggested that one reason may be because products are sometimes manufactured for export only and as such are not necessarily regulated with the same standards (69). There may be other non-risk-related reasons for the high number of inspections in Western Europe (4).

Latin American NRAs do fewer inspections in North America than Western Europe, which is also a highly regulated environment that is home to export-only practices. It is unclear why there is this discrepancy. There are also relatively few inspections in South America. This perhaps reflects a lower perception of risk due to closer integration through mechanisms such as MERCOSUR, or a higher level of reliance, or both; or other factors. Interestingly, less than a quarter of all international inspections are done in China or India even though both countries have documented gaps in regulatory capacities.

Figure 5.5. Regional breakdown of NRA international inspections for medicines, 2017–2019



Source: Data collected by PAHO using the following methodology: Each LA NRA identified a focal point for this report. PAHO developed an instrument with the data requested, the instrument was filled by the LA NRA focal point, followed by a phone interview/email communication to validate the data included in the report. Two rounds of data validation were performed. The investigation and analysis were conducted from March 2019 to October 2020.

5.4. Best Practices and Efficiencies in Inspections

5.4.1. RELIANCE

As regulators grow to appreciate the value of reliance, it is increasingly applied to the field of GMP inspections. Reliance strategies for GMP inspections can take many forms, from recognizing GMP decisions and certificates in pre-market settings (see Box 5) to using inspection reports to inform surveillance in post-market contexts. Regulatory harmonization and standard-setting bodies recognize the value of reliance too. For example, recent PIC/S guidance outlines a process for desktop assessment that can confirm acceptable GMP without the need for on-site inspections. Reliance can play a vital part in strengthening GMP inspections by:

- reducing the resource burden of carrying out inspections;
- extending an NRA's reach in overseeing global supply chains; and
- increasing access to medicines, such as through reduced processing timelines and reduced prices from lower transaction costs.

Box 5. Reliance to reduce on-site inspections

In Canada, reliance is used to reduce the need for international on-site GMP through “paper assessments.” In 2015–2016, Health Canada did 1,541 GMP paper assessments of foreign establishments involved in manufacturing, packaging, and testing drugs, but only 16 of these were on site.

The Health Canada reliance program combines two strategies:

- 1. Mutual recognition agreements (MRAs).** Health Canada establishes MRAs with other regulatory authorities around the world and uses these to exchange GMP certificates rather than carry out a full paper review or on-site inspection. The MRAs allow for the exchange of certificates of GMP compliance and a batch certificate of conformity instead of conducting on-site inspections.
- 2. Trusted partners.** For non-MRA countries, Health Canada reviews inspection reports of trusted regulatory partners to verify that international sites comply with GMP.

Only if there is no MRA in place and no inspection reports available from trusted partners (or if an importer requests it) does Health Canada consider doing an international on-site inspection.

Source: Government of Canada/Health Canada [Internet]. Ottawa: Health Canada; 2019. Inspectorate Program annual inspection summary report 2015–2016. Available from: <https://www.canada.ca/en/health-canada/services/drugs-health-products/reports-publications/compliance-enforcement/inspectorate-program-annual-inspection-summary-report-2015-2016.html>, cited 24 June 2020.

Among Latin American NRAs, the use of reliance for GMP inspection is common. Different authorities use different frameworks for their reliance activities, according to their historical and socioeconomic ties and technical needs. All NRAs have reliance instruments linked to one or more other NRAs (see Table 5.2).

Table 5.2. Pre- and post-market reliance mechanisms used by NRAr for medicines

| NRAr | NRA RELIED ON | PRE-MARKET/POST-MARKET RELIANCE |
|-----------------------------|---|--|
| ANMAT | Brazil, Paraguay, and Uruguay through MERCOSUR, PIC/S | Decisions on which sites are inspected, and when, are based on a risk assessment that considers information from inspection records exchanged with NRA relied on. |
| ANVISA | Argentina and Uruguay through MERCOSUR; Cuba; PIC/S | Decisions on whether to inspect are based on a risk assessment, considering the manufacturer facility risk, changes of scope and facilities, product related information (PQR), enforcement and surveillance activities, and international context (PIC/S partners information). |
| CECMED | NRAr, SRA | Recognition of GMP certificates for FPPs issued by NRA relied on. |
| COFEPRIS^a | Argentina and Colombia (through Pacific Alliance); specific SRAs (Australia, Canada, United States of America, Japan, Korea, United Kingdom, Switzerland and EMA) | Exchange of inspection reports to inform decisions (exceptions are sterile and high-risk medicines). Recognition of the CPP as a document equivalent to the GMP issued by COFEPRIS. |
| INVIMA | Canada, European Union, Japan, United States of America, WHO/PAHO; Pacific Alliance members (Mexico, Chile) | Recognition of GMP certificates for FPPs and for APIs of biological products issued by NRA relied on; post-market inspections approach informed by agreements with Pacific Alliance members. |
| ISP | NRA | Recognition of GMP certificates for FPPs in marketing authorization application from the NRA of country of origin; post-market inspections approach informed by agreements with NRAr in the Pacific Alliance. |

Sources: Data collected by PAHO using the following methodology: Each LA NRAr identified a focal point for this report. PAHO developed an instrument with the data requested, the instrument was filled by the LA NRAr focal point, followed by a phone interview/email communication to validate the data included in the report. Two rounds of data validation were performed. The investigation and analysis were conducted from March 2019 to October 2020.

^a COFEPRIS. Guía sobre la aplicación de criterios que se deben observar para la evaluación de la certificación de buenas prácticas de fabricación de fármacos, medicamentos, dispositivos médicos y almacenes de acondicionamiento primario que acompañen a las solicitudes de modificaciones, prórrogas y registros sanitarios [Internet]. Mexico: COFEPRIS, March 2020. Available from: https://www.gob.mx/cms/uploads/attachment/file/539408/Guia_sobre_la_aplicacion_de_criterios_Certificacion_de_Buenas_Practicas_de_Fabricacion_ver_06_de_marzo_de_2020.pdf, cited 6 July 2020.

Although reliance is common among Latin American NRAr, the data suggest some opportunities for further strengthening. For example, most reliance mechanisms in NRAr cover FPPs, but API oversight is also very important. The API industry is mostly located in China and India, with an increasingly consolidated number of producers integrated in many supply chains. Using reliance on trusted authorities with the capacity to inspect these facilities offers a clear opportunity to gain regulatory efficiencies in overseeing APIs manufactured beyond national borders.

Stronger reliance could also be achieved by deepening the number of SRA, NRAr, and PIC/S members that participate in reliance initiatives. NRAr appear to rely on a few of these authorities, but not all members.

A third option for reliance, not currently used by any Latin American NRAr, is third-party reliance. The benefits of third-party reliance have been well demonstrated by the Medical Device Single Audit Program (70), which was created in 2012 by the NRAs of Australia, Brazil, Canada, Japan, and the United States of America to enable the global auditing and monitoring of medical device manufacturers. ANMAT recently joined as an affiliate member.

5.4.2. PUBLIC ACCESS TO INFORMATION

While there is information sharing among NRAr, confidential exchange between NRAr and other NRAs in the Region is rather limited. This not only poses problems for market authorization (see Chapter 3: Marketing Authorization of Pharmaceutical Products), it is also a challenge for inspections and related data that can inform post-market surveillance. Many smaller NRAs have no option but to use publicly available information if they want to carry out reliance.

According to legal provisions of each country, some NRAs make significant amounts of GMP information publicly available. For example, European Union authorities publish all their GMP certificates in an online database called EudraGMDP (71), and this provides a useful reference for checking the GMP status of individual manufacturing sites. WHO’s Prequalification program for medicines also publishes the addresses of approved manufacturing sites and the inspection reports for FPPs (44). But the level of GMP inspection information that is publicly available through NRAr websites in the Americas remains limited and varies according to country legal provisions (Table 5.3). Only a few NRAr publish addresses of approved sites, lists of non-compliant sites, GMP certificates, or inspection reports, which constitute critical information to support reliance.

Table 5.3. GMP inspection information available on NRAr websites

| Information available on NRAr website | ANMAT | ANVISA | CECMED | COFEPRIS | FDA | Health Canada | INVIMA | ISP |
|--|----------------|--------|--------|----------|-----|---------------|--------|-----|
| APPROVED MANUFACTURING SITE ADDRESS OF THE API | ✓ | | | ✓ | | | | |
| APPROVED MANUFACTURING SITE ADDRESS OF THE FPP | ✓ | | | ✓ | | | ✓ | |
| NON-COMPLIANT SITES | ✓ | | | | ✓ | ✓ | ✓ | |
| GMP CERTIFICATES | | ✓ | | | | | | |
| INSPECTION REPORTS | ✓ ^a | | | | | | | |
| TOTAL | 80% | 20% | 0% | 40% | 20% | 20% | 40% | 0% |

Note: ^a Includes data and conclusions, not the complete inspection reports.

Source: Data collected by PAHO using the following methodology: Each LA NRAr identified a focal point for this report. PAHO developed an instrument with the data requested, the instrument was filled by the LA NRAr focal point, followed by a phone interview/email communication to validate the data included in the report. Two rounds of data validation were performed. The investigation and analysis were conducted from March 2019 to October 2020.

Recommendations for Action

- **Optimize inspection strategies.** GMP inspections are time-consuming and resource-intensive activities for both the authority and the manufacturer. NRAs need to examine international inspection strategies to find an optimal mix of risk and efficiency, including relying on trusted authorities.
- **Leverage trusted GMP information.** Increase the use of trusted NRA material, including exchanging GMP information such as certificates and inspection reports with NRAr, SRAs, and PIC/S members.
- **Intensify API manufacturing oversight.** The absence of API requirements across countries in the Region needs to be addressed. NRAs must increase regulatory oversight of API manufacturing sites through diverse strategies including targeted increase of international inspections and/or reliance.
- **Take advantage of available tools on GMP information.** Make better use of public databases, such as EudraGMDP and WHO prequalification databases, to check GMP status of individual manufacturing sites.
- **Improve regulatory transparency on inspections.** Make more inspection-related information publicly available on the NRA website and encourage manufacturers to authorize the sharing of inspection reports among NRAs.

6. PHARMACOVIGILANCE AND POST-MARKET SURVEILLANCE

In brief

- All NRAR have legal provisions for pharmacovigilance (PV) and post-market surveillance (PMS), but the resources allocated to these are limited compared with pre-marketing.
- Some NRAR use targeted or active PV to gain efficiencies in detecting and evaluating adverse reactions related to specific medicines or diseases.
- NRAR capacities to translate PV data into regulatory action are increasing but there are still opportunities for improvement.
- Expanding the use of track and trace systems for PMS in the Region will require significant investment and technological upgrades across the supply chain.
- NRAR report adverse drug reactions to global monitoring systems at a low rate, but have made progress in reporting adverse events and substandard and falsified products.
- The rise in illegal online sales of medicines and limited enforcement of advertising rules pose particular challenges to tackling substandard and falsified products.

6.1. NRA Foundations for PV and PMS

PV and PMS are core responsibilities of NRAs. These functions help to ensure that there are systems in place to ensure the quality, safety, and efficacy of medicines by monitoring and, where appropriate, responding to adverse events or substandard and falsified (SF) products in the market. In practice, PV and PMS are usually divided according to the definitions below, but the activities in both overlap and are highly complementary:

- **PV**, as defined by WHO, encompasses the science and activities related to detecting, assessing, understanding, and preventing adverse events or any other medicine-related problems. For NRAs, this includes establishing a national PV system that can enable and ensure the reporting and investigation of adverse drug reactions (ADRs), followed by corrective actions. In this sense, PV focuses on safety and risk management.
- **PMS** refers to the collection of information on the quality, safety, or performance of medical products once they are in the market. For NRAs, PMS comprises several activities, including ongoing market authorization (for example, for changes or renewals), regular inspections of manufacturers, wholesalers, distributors, and retailers, and control of promotional activities. It also involves the regular sampling and surveying of both regulated and unregulated supply chains to identify SF products (see Box 6) (72). In this sense, PMS focuses on a product's quality and how it impacts effectiveness (or lack thereof).

Box 6. SF medical products

The growing number of SF medical products found in health systems all over the world poses an unacceptable risk to public health. While it is difficult to quantify the impact of SF medical products, experts agree that they can endanger patient health and safety, undermine confidence in health professionals, products, and systems, create distrust about the effectiveness of vaccines and medicines, and may contribute to the development of antimicrobial resistance.¹

WHO defines substandard medical products as those that are authorized but fail to meet their quality standards or specifications, or both. They result from poor manufacturing, shipping, or storage conditions, or from sales beyond the expiration date. By contrast, falsified medical products are those that deliberately or fraudulently misrepresent their identity, composition, or source.

Recent studies suggest that between 10.5% and 13.5% of all medicines sampled in LMICs are substandard or falsified.^{2,3} Few of these studies, however, include data from Latin America.⁴

Sources:

1. World Health Organization. WHO Global Surveillance and Monitoring System for substandard and falsified medical products. Geneva: WHO; 2017. Available from: <https://www.who.int/medicines/regulation/ssffc/publications/gsms-report-sf/en/>, cited 12 February 2020.
2. World Health Organization. A study on the public health and socioeconomic impact of substandard and falsified medical products. Geneva: WHO; 2017.
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6.1.1. LEGAL AND ORGANIZATIONAL FRAMEWORKS FOR PV

The value of well-organized PV systems is increasingly recognized among Latin American NRAr. These authorities have made progress in introducing legal provisions for PV systems, including developing the information systems and human resources capacity needed to implement them.

Data collected by PAHO for this report show that legal provisions for PV of medicines including vaccines exist in all Latin American NRAr countries. In each case, the NRAr is legally required to establish a reporting and monitoring system to collect adverse event data using standardized terminology, and to use this information to take regulatory action where appropriate. In the case of serious adverse effects associated with vaccines, all NRAr countries have established procedures or norms for coordinating their investigation and subsequent action with the national immunization programs, which is often perceived as a challenge in non-NRAr countries throughout the Americas. Additionally, all Latin American NRAr have legal provisions that require marketing authorization holders (MAHs) to have a PV system in place to monitor the safety of their products and to report adverse event data and other PV-related information to the NRA. In all cases, the NRAs have the authority to inspect the MAH.

6.2. PV in Practice

PV involves the collection, detection, assessment, and acting on information associated with the occurrence of noxious and unintended reactions to medicines in the market. Safety-related information can come from a variety

of sources, including spontaneous reports by patients, healthcare professionals, and other stakeholders; research findings from pre-clinical, clinical, or post-marketing studies; or safety update reports gathered and submitted by MAHs as part of their legal requirements.

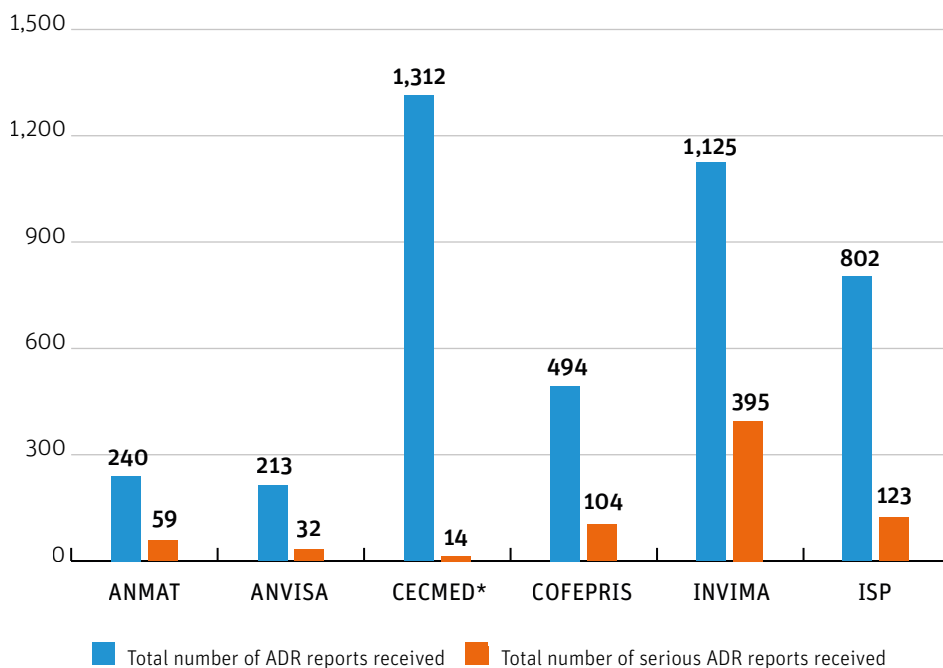
Latin American NRAr use different approaches to PV, including advanced strategies for gathering and assessing ADRs, such as targeted and active surveillance. Some NRAr have established programs to intensively monitor specific medicines with safety concerns; for example, clozapine and isotretinoin. NRAr also have procedures for systematically collecting and evaluating safety information reports through collaborative projects with public health programs for vaccines, tuberculosis, and malaria, for example. Between 2015 and 2017, ANMAT, INVIMA, and ISP took part in a proof-of-concept project, as part of a global protocol, that used sentinel hospitals to confirm the magnitude of association of measles, mumps, and rubella vaccines with idiopathic thrombocytopenic purpura and aseptic meningitis.

6.2.1. NATIONAL ADR REPORTING

In Latin America, the level of ADR reporting to the NRAr varies (see Figure 6.1). All NRAr countries exceed the standard population-based reporting ratio of 200, as defined by the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC) (73). Some NRAr receive multiples of this number. On average, 20% of all ADR reports to NRAr are serious. But there is important variation across individual NRAr, with some having less than 1% serious ADR reports while others have up to 38% (see Figure 6.1).

There are many reasons why spontaneous reporting systems may be low, and under-reporting is a well-known limitation of these systems worldwide. Nevertheless, ADR reporting to the NRA is generally regarded as an indicator of a PV system’s development. Higher levels of reporting are thought to reflect significantly higher awareness and participation by all stakeholders in the system, including patients, healthcare providers, MAHs, and government bodies. In this regard, following local ADR reporting trends is important to monitor the development of national systems in the Region.

Figure 6.1. Annual ADR reports per million inhabitants for NRAr



Notes: The corresponding years of the data per country are: Argentina 2016; Colombia 2017; Brazil, Chile, Cuba, Mexico 2018.

* It should be noted that Cuba uses a different definition for serious ADR.

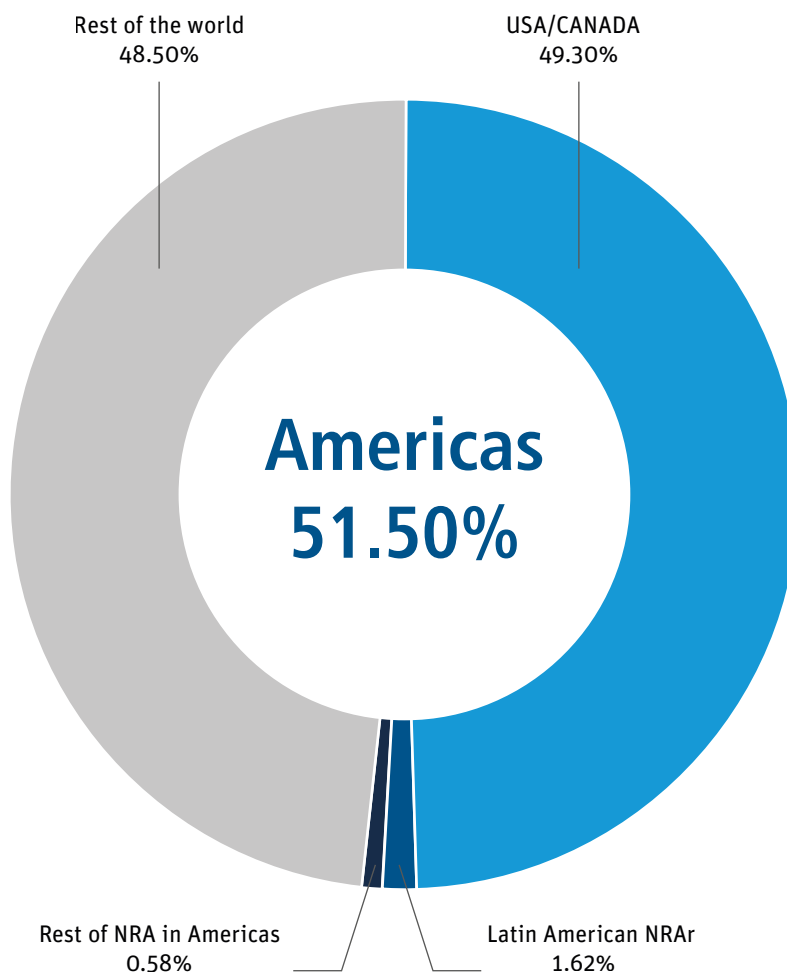
Source: Data collected by PAHO using the following methodology: Each LA NRAr identified a focal point for this report. PAHO developed an instrument with the data requested, the instrument was filled by the LA NRAr focal point, followed by a phone interview/email communication to validate the data included in the report. Two rounds of data validation were performed. The investigation and analysis were conducted from March 2019 to October 2020.

6.2.2. GLOBAL ADR REPORTING

Sending ADR reports to global databases is important to ensure that signs of previously unknown safety problems are identified and information about them is shared so that individual countries can take appropriate action to protect patients. Good PV practice dictates that countries should share their ADR reports globally, and countries do this by uploading them to the UMC-hosted database VigiBase, which is part of the WHO Programme for International Drug Monitoring (PIDM) (74, 75).

Although around half of all the reports in VigiBase come from the Americas, Latin American countries represent less than 5%, and the proportion of those without NRAR is even less (see Figure 6.2). The fact that ANVISA submits a significantly higher number of reports than other NRAR, and that some NRAR did not submit any reports during 2019, shows that many NRAR have no mechanism to ensure continued reporting to VigiBase (see Figure 6.3).

Figure 6.2. Proportion of ADR reports to UMC by the Americas

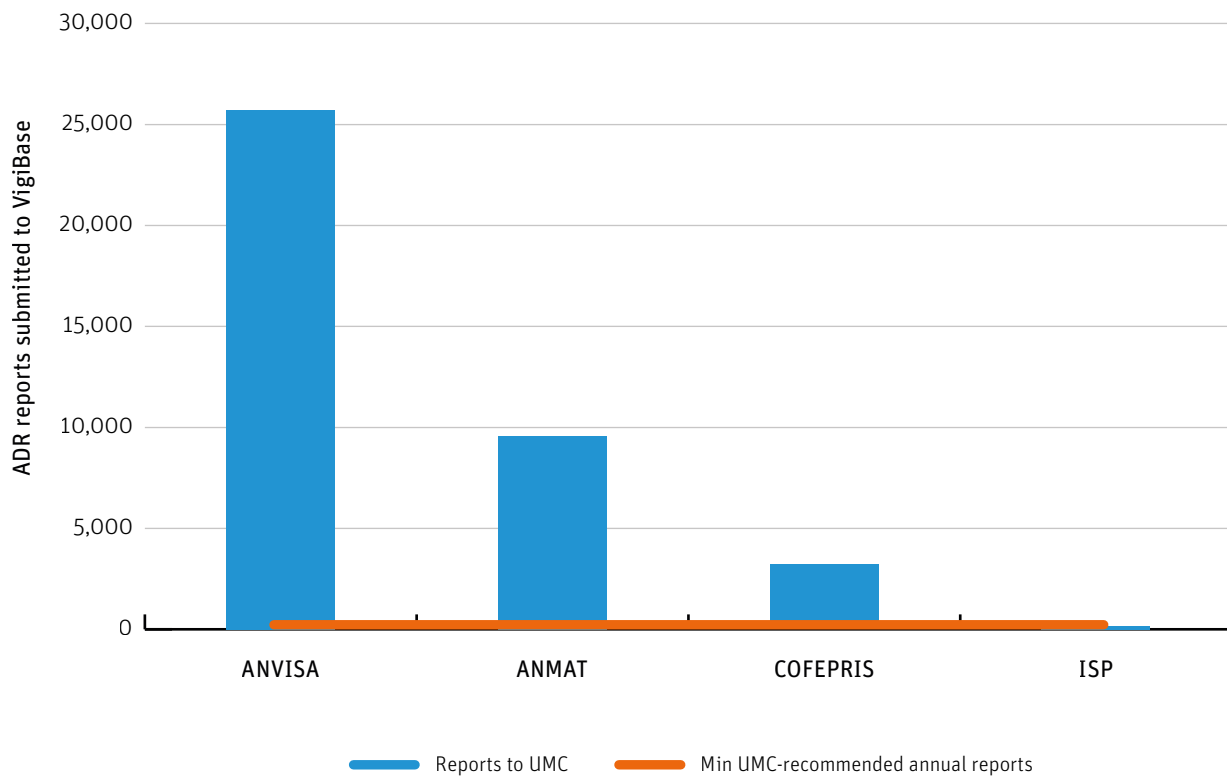


Notes: Latin American NRAr: Argentina, Brazil, Chile, Colombia, Cuba, and Mexico.

Rest of NRA in the Americas: only those with more than 500 reports; i.e., Barbados, Costa Rica, Ecuador, El Salvador, Jamaica, Panama, Peru, Uruguay, and Venezuela (Bolivarian Republic of).

Source: Uppsala Monitoring Centre [Internet]. Uppsala: UMC; 2020. VigiLyze. Available from: <https://www.who-umc.org/vigibase/vigilyze>, cited 17 June 2020.

Figure 6.3. Number of ADR reports submitted to the WHO VigiBase by Latin American NRAr in 2019



Note: CECMED and INVIMA did not report to UMC during the period consulted.

Source: Uppsala Monitoring Centre [Internet]. Uppsala: UMC; 2020. VigiLyze. Available from: <https://www.who-umc.org/vigibase/vigilyze>, cited 17 June 2020.

According to stakeholders interviewed for this report, an important reason behind the differences in reporting is a lack of compatibility between national software and VigiBase. Without compatible software, ADR reports can only be uploaded to the database by manually entering data to VigiFlow, the case report management system developed by UMC to ensure data are stored, processed, and shared in a standard format. Manual uploading is resource-intensive and limits the number of reports that can be shared. ANVISA introduced new software (VigiMed) that is fully compatible with VigiBase in 2018. In doing so, it has strengthened its capacity for global ADR reporting, with the total number of ADR reports shared with UMC rising from 1,752 in 2017 to more than 25,000 in 2019.¹¹

6.2.3. REGULATORY ACTION

The translation of data into regulatory actions is a critical component of the PV oversight function. All six Latin American NRAr have procedures for analyzing and detecting drug safety signals (see Table 6.1). There is, however, limited information on the way signals are handled, assessed, and acted upon once a safety risk is confirmed. Data gathered for this report only indicate whether NRAr have taken specific actions, rather than how often they take them. These data show that most NRAr use PV-related data to issue safety notices or enforce modifications to market authorizations; and some NRAr have also used PV-related information as the basis for significant regulatory measures, including canceling, restricting, or suspending market authorization.

¹¹ Data collected by PAHO using the following methodology: Each LA NRAr identified a focal point for this report. PAHO developed an instrument with the data requested, the instrument was filled by the LA NRAr focal point, followed by a phone interview/email communication to validate the data included in the report. Two rounds of data validation were performed. The investigation and analysis were conducted from March 2019 to October 2020.

Table 6.1. PV actions in Latin American NRAr

| | ANMAT | ANVISA | CECMED | COFEPRIS | INVIMA | ISP |
|---|-------|--------|--------|----------|--------|-----|
| SAFETY INFORMATION COLLECTED USED FOR DECISION-MAKING ABOUT MA^a | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| SAFETY NOTICES ISSUED | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| MODIFICATIONS TO MA ENFORCED^b | | ✓ | | ✓ | ✓ | ✓ |
| MA TEMPORARILY SUSPENDED^c | | | | | | ✓ |
| MA CANCELED^d | | ✓ | ✓ | ✓ | | |
| CONDUCTED PV INSPECTIONS^e | ✓ | ✓ | ✓ | | ✓ | ✓ |
| PARTICIPATED IN REGIONAL PV INITIATIVES | ✓ | ✓ | | | ✓ | |

Notes: ^a MA: marketing authorization; ^b Periods consulted: ANMAT, ANVISA, COFEPRIS, and INVIMA (2014–2016); CECMED and ISP (2014–2018); ^c Periods consulted: ANMAT, COFEPRIS, and INVIMA (2014–2016); ANVISA (2017–2018); CECMED (2014–2018); ISP (2016–2018); ^d Periods consulted: ANMAT, ANVISA, COFEPRIS, and INVIMA (2014–2016); CECMED (2014–2018); ISP (2016–2018); ^e Periods consulted: ANMAT (2014); ANVISA (2018); CECMED (2016–2018); COFEPRIS (N/A); INVIMA (2017–2018); ISP (2018).

Source: Data collected by PAHO using the following methodology: Each LA NRAr identified a focal point for this report. PAHO developed an instrument with the data requested, the instrument was filled by the LA NRAr focal point, followed by a phone interview/email communication to validate the data included in the report. Two rounds of data validation were performed. The investigation and analysis were conducted from March 2019 to October 2020.

The data indicate that all NRAr have procedures to support PV regulatory action. But the scarcity of evidence available to document which implementation and strategies are used, and when, suggests that this is an area that needs further development. At a global level, both PV and pharmacoepidemiology are growing and evolving fast, and all NRAr in the Region, including Latin American NRAr, have much to gain from investing in them. Failing to invest in this fast-growing area could have important consequences for the Region’s capacity to keep up to date and to ensure adequate monitoring of the safety and use of medicines on its markets.

6.3. Legal and Organizational Frameworks for PMS

Just as the frameworks for PV in Latin America have improved, so too have the capacities for PMS. All Latin American NRAr countries currently have legislation that allows them to:

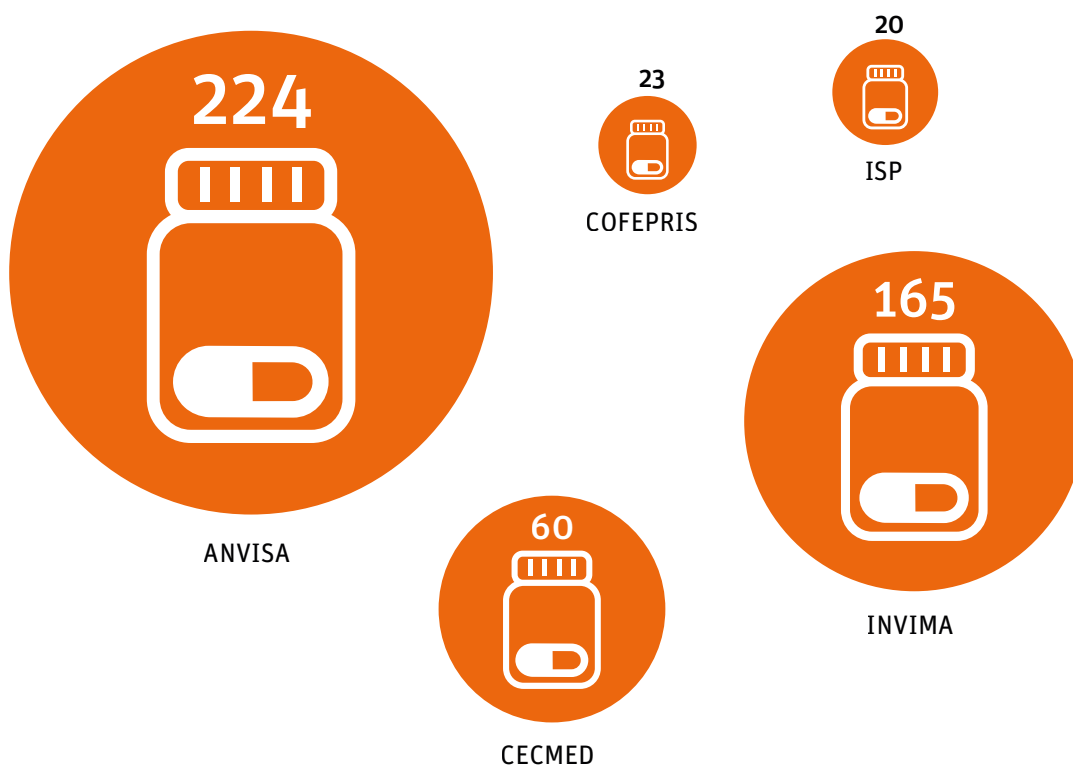
- suspend, restrict, or impede the manufacture, import, export, distribution, sale, and/or use of medicines;
- request the recall of pharmaceutical products when they infringe the regulations in place; and
- require importers, exporters, wholesalers, and distributors to comply with good storage and distribution practices to get their license or authorization.

All Latin American NRAr also have agreements in place with the customs authority or other national enforcement authority to control imported and exported products and respond to incidents of SF medicines.

6.3.1. PMS IN PRACTICE

All Latin American NRAr have a PMS strategy that is supported by laboratory testing, although their testing approaches and the annual number of products per API monitored for quality control varies from 20 to 224 (see Figure 6.4). According to NRAr officials and stakeholders interviewed for this report, the variation in sampling and monitoring, as well as the limited number of related actions, may be explained by a lack of resources and frequent fluctuation in funding.

Figure 6.4. Number of products (per active pharmaceutical ingredient) monitored by NRAr quality control programs (2018 or 2019)



Note: Data not available for ANMAT.

Source: Data collected by PAHO using the following methodology: Each LA NRAr identified a focal point for this report. PAHO developed an instrument with the data requested, the instrument was filled by the LA NRAr focal point, followed by a phone interview/email communication to validate the data included in the report. Two rounds of data validation were performed. The investigation and analysis were conducted from March 2019 to October 2020.

Although product testing is an important activity in post-market surveillance, the maintenance of adequate testing facilities may not be affordable to a number of NRAs in the Americas. A few strategies have been used to enable the performance of such activity, including the establishment of subregional laboratories (e.g., CARPHA in the Caribbean region) and contracting out to private laboratories. Some of the challenges of these approaches include costs and coordination, limited reliability, and risk of inconsistent access to testing. Limiting laboratory testing efforts to products with a higher risk to public health if substandard or falsified (e.g., those that are purchased in higher volumes, have narrow therapeutic indices, and/or are from manufacturers with known compliance issues) is an efficiency that is being recommended for regulatory authorities known as risk-based post-market surveillance (76), and is already in use by some authorities such as CARPHA. NRA use of new detection technologies can be a helpful complement to post-market surveillance work; for example, by rapidly screening products at borders (77). In addition, the publishing of product testing results can alert the public to companies that are selling problematic products and act as a deterrent to non-compliance.

6.3.2. TRACK AND TRACE SYSTEMS

Traceability, or track and trace systems, are used to identify the origin and various stages of production and distribution of individual medical products. They enable NRAs to establish where a given product is within the supply chain. Such systems can be useful and efficient tools in the fight against the falsification and illicit use and distribution of medical products, and many countries around the world are adopting traceability regulations to this end.

In Latin America, all NRAs require some form of registration system in the distribution chain to ensure traceability of batches and to facilitate an effective system for product recalls if necessary. ANMAT in Argentina has the most developed mechanism, with a full national traceability system in place for nearly a decade (see Box 7). In Brazil, ANVISA has also made significant progress in developing a traceability system over the past five years and is now ready to launch a pilot program to test it.

According to the stakeholders interviewed for this report, one of the main barriers to implementing track and trace systems is the high cost of upgrading existing technologies and the subsequent investments that would be required throughout the supply chain. There can also be challenges in terms of governance (for example, establishing who will finance it or who owns the data) and technology; for example, finding ink that meets security standards, working out how to serialize primary and secondary packaging, and ensuring that the tracking technology cannot be falsified.

Box 7. ANMAT's National Medicines Traceability System

ANMAT officially created the National Medicines Traceability System in 2011. It was the culmination of significant groundwork laid after an incident involving falsified vials of Factor VIII. From the very beginning of ANMAT's efforts to develop traceability measures, it aimed for real-time control of all transactions involving medicines, facilitating the verification of their origin, and registering the history of their location and movement along the distribution chain.

ANMAT started by defining which "logistical events" to capture in the system: quarantines and batch releases, transfer to the next stage of the supply chain, receipt from the previous stage, dispensing to patients, damage to the product or code, and theft or loss of the product. A unique code would be used to track each product along the supply chain from the manufacturer to the final user, and would be deactivated in the case of some events like loss or theft to prevent the product from re-entering the legal chain.

Essential requirements were defined for labeling and packaging; for example, every medicine must carry a Global Trade Item Number and unique serial number in a way that complies with GS1 standards, is readable by the human eye, and is tamper-proof.

ANMAT's track and trace system has progressively incorporated products in the Argentinian market. At first, the focus was on medicines that had previously been adulterated or falsified, were expensive to buy, or had any other potential for abuse. Later, other therapeutic categories were added, including oncologicals, antiretrovirals, antibiotics, and antidepressants. By 2012, ANMAT's track and trace regulation required all newly registered products to comply with the system.

6.3.3. ACTIVITIES TO COUNTER SUBSTANDARD AND FALSIFIED PRODUCTS

As global supply chains become more complex, the opportunities for mistakes, bad practice, and unethical activity increase. In Latin America, the growth of e-commerce and illegal online providers poses a particular risk because online sales are often unregistered, and SF products are marketed by unlicensed distributors outside the legal supply chain (78). Tackling the problem requires NRAs to address existing gaps in regulation, to train dedicated staff, to permanently monitor high-risk websites and social media, and to establish links with law enforcement authorities (see Box 8). Building awareness among users, who often choose to buy their medicines online because they are cheaper and easier to get, is also important (79).

Box 8. Tackling illegal online sales

Latin American NRAs are adopting diverse strategies to tackle illegal online sales and stop the flow of SF medical products in their countries. These include:

- **Online monitoring.** Some NRAs regularly monitor e-commerce platforms and social networks such as Facebook and Instagram.
- **Curbing illegal online advertising.** In 2018–2019, for example, INVIMA and COFEPRIS took down 780 and 1,002 illegal online advertisements, respectively, of products that infringed regulations. Furthermore, ANMAT, INVIMA, and COFEPRIS have all signed agreements with some of the most important stakeholders in online sales, including e-commerce platforms such as MercadoLibre.com, to take down illegal advertisements as and when they occur.
- **Bans on internet advertising.** In Argentina, the internet is formally prohibited as a mechanism for direct sales of medicines to the public.
- **Licensed sales.** ANVISA has developed specific regulations so that only licensed Brazil-based pharmacies with a full-time pharmacist can sell prescription medicines online (following a valid request). Each licensed internet pharmacy must publish its ANVISA authorization number on its website.
- **Global anti-crime operations.** In 2018, 19 countries in the Region^a participated in INTERPOL's Operation Pangea XI, an international effort to disrupt the online sale of falsified products and raise awareness of the risks associated with products bought from unregulated websites. The operation resulted in the seizure of US\$ 14 million worth of medicines and 859 arrests worldwide.^b

Note: ^a Antigua and Barbuda, Argentina, Belize, Bolivia (Plurinational State of), Canada, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Mexico, Nicaragua, Paraguay, Peru, United States of America, and Uruguay.

^b INTERPOL. Illicit online pharmaceuticals: 500 tonnes seized in global operation. In: INTERPOL [Internet]. Lyon: INTERPOL; 2018. News and events. Available from: <https://www.interpol.int/News-and-Events/News/2018/Illicit-online-pharmaceuticals-500-tonnes-seized-in-global-operation>, cited 12 February 2020.

Global reporting offers another way to tackle SF products. Just as sharing ADR reports with the PIDM can help protect global patient health and safety, so too can the reporting of SF cases within the country to the NRA and then to WHO. The WHO Global Surveillance and Monitoring System (GSMS) for SF medical products (80) was

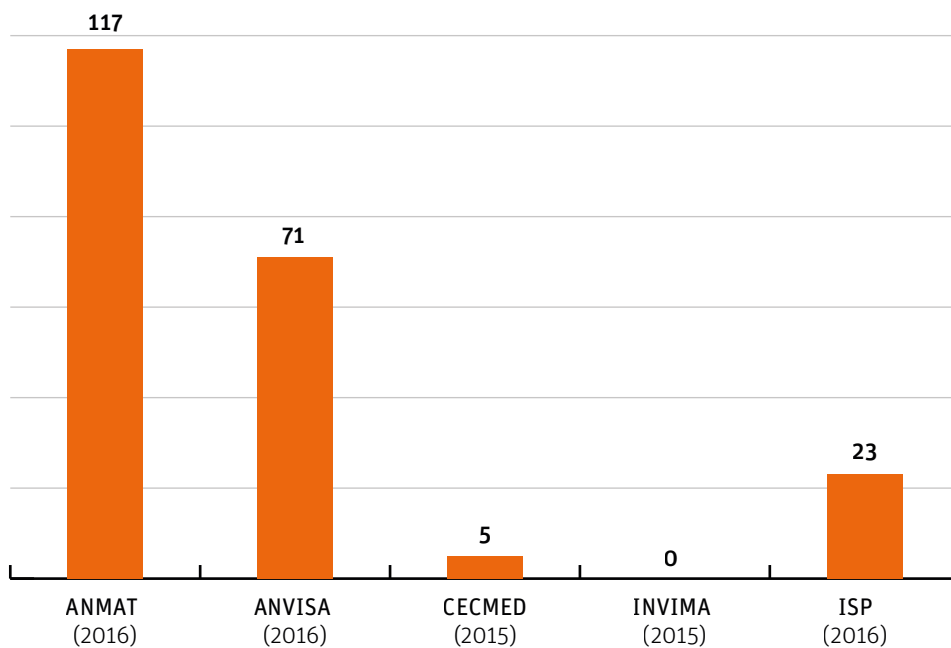
launched in 2013 and is part of the operational plan of the WHO Member State Mechanism on SF products, which is a WHO-convened policy forum for governments to address SF issues (81). The GSMS enables NRA focal points to report suspected SF products to a centralized database managed by WHO. Looking at all reports entered for a given product helps to quantify the scope of the SF problem. Focal points can also search the database for similar incidents reported by other governments, which can help to identify which companies are making the SF products. The WHO team that manages the database regularly publishes technical guidance; for example, on how to contact manufacturers about suspected SF products. The team also responds to emergency reports (with technical advice or laboratory support) and issues global product safety alerts where appropriate.

Across Latin America, NRAs regularly report SF products to the GSMS. Out of 196 alerts shared through the regional network of focal points in 2016–2019, 180 originated in, or concerned, countries in the Americas. In total, there were 112 alerts of substandard products and 84 alerts of falsified products. All NRAs have issued and shared alerts through GSMS over the past few years; CECMED, INVIMA, and ISP also reported withdrawing medical products from the market as a result of quality problems in the last registered year.¹²

6.3.4. GOOD DISTRIBUTION PRACTICES

Good distribution practices are another critical element of PMS. They ensure that products are stored and distributed in good conditions after they have left the manufacturing plant toward their intended destination. Good distribution practice inspections of pharmacies, warehouses, and other facilities are important to ensure a product’s quality is maintained during its life cycle. Data collected for this report show a seemingly large difference in good distribution practice monitoring across NRAs countries (see Figure 6.5). But these data should be interpreted with care because they do not necessarily account for local context; nor do they reflect the extent to which non-NRA organizations are performing inspections. The differences may be even more stark in smaller countries, where staffing limitations to conduct inspections (often in tropical weather) can pose particular problems for the quality of medicines.

Figure 6.5. Number of annual good distribution practice inspections by NRA, 2015–2016



Note: No data available for COFEPRIS.

¹² ISP and CECMED reported data from 2018; INVIMA reported data from 2015–2016.

6.3.5. PROMOTION AND ADVERTISING

Rules that control promotional, marketing, and advertising activities of medical products can be useful in preventing the communication of false or misleading information to health professionals, populations at risk, the public, or any other stakeholder. In Latin America, the 2013 PANDRH Ethical Criteria for Medicine Promotion, Advertisement, and Publicity serves as a framework for developing and implementing such rules (82). It includes a set of 24 general principles that countries should follow to ensure medicines promotion, advertisement, and publicity are mainly aimed at benefitting users and society and not third parties.

All six Latin American NRAr countries have legal provisions to control promotion and advertising of medicines. In particular, these:

- only allow prescription medicines to be promoted and advertised to prescribers;
- prohibit the use of incentives for prescribers and dispensers as promotion strategies; and
- include guidelines or regulations on promoting and advertising over-the-counter medicines.

Since 2015, all six NRAr have had a system or strategy to enforce these rules, including the imposition of sanctions on rule-breakers. However, as sanctions are rarely used, with no evidence that they have been implemented in practice, their usefulness could be questioned.

6.4. The Role of PANDRH in PV and PMS in the Americas

In Latin America, NRAs have substantially advanced the development of PV and PMS systems in the past decade through PANDRH. Between 2008 and 2010, for example, PANDRH's pharmacovigilance working group developed a set of good PV practices for the Americas. PANDRH's guidance has been widely adopted in the Region, with 68% of countries surveyed in 2016 reporting use of the document to develop national PV requirements. This represents a higher rate of use than any other technical document across seven areas of regulatory work.

Since 2017, one of PANDRH's core activities has been the establishment of two networks of focal points throughout the Americas to exchange PV and SF information and conduct collaborative projects. For example, NRAs in Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Mexico, Paraguay, and Peru have all participated in joint evaluations of PV documents, such as risk management plans and periodic safety update reports. These evaluations are prioritized to focus on strategic products with gaps in their safety profile, as well as biologicals and molecules with specific critical risks. PMS activities facilitated by the PANDRH focal points include rapid dissemination of product safety alerts and investigations into clusters of cases in the Region.

6.5. Best Practices and Efficiencies in PV/PMS Systems

Reliance and information sharing with reference authorities can be used to strengthen PV/PMS systems. In the Americas, NRAs are well connected to NRAr and each other through the PAHO PV and PMS network groups, but there are also other sources of useful information. WHO, for example, publishes a regular newsletter on PV signals, and reference authorities around the world frequently publish information and findings related to PV and PMS actions. There is, however, no substitute for PV and PMS of one's own market, as there may be unique PV interactions in a local population that cannot be found elsewhere, or product failures of locally manufactured products that are not sold in other markets. Because it is so critical for all NRAs to monitor their own markets, PAHO recommends that even the smallest authorities (such as those in the Caribbean and Central America where PV systems are the most limited) prioritize PV and PMS and use tools and initiatives like the PIDM and GSMS to bolster their approaches (6).

Electronic systems and flexible reporting through, for example, voice messages or phone apps, can also increase efficiencies.

Recommendations for Action

- **Increase stability and allocate appropriate resources** (for example, funding, staff, training) to PV and PMS to ensure NRAs can respond in a timely manner to the growing number and complexity of products entering their health systems.
- **Improve ADR and SF case management, global reporting, and use of information for regulatory action.** These efforts should include facilitating and improving reporting to the NRA through public, provider, industry, and other stakeholder networks. It is also important to maintain dedicated staff who can be assigned to analyzing and processing reports, sharing and searching regional, global, or other relevant databases, conducting specialized assessments to consider the need for regulatory action, and communicating relevant findings to the public.
- **Strengthen efforts to tackle illegal online sales** by addressing existing gaps in regulation, training and dedicating regulatory staff to permanently monitor high-risk websites and social media, establishing links with law enforcement authorities, and creating awareness among users.
- **Establish national track and trace systems in NRAs** that can contribute to international monitoring systems and support drug safety related actions in relation to SF quality reports.
- **Boost efficiencies to conduct PV and PMS.** This can be done by enhancing the sharing of information with other NRAs, adopting risk-based post-market surveillance strategies, and continued and well-structured monitoring of trusted sources of PV/PMS information.

7. CLINICAL TRIALS

In brief

- The number of clinical trials in the Americas is increasing, including in countries that may have more limited regulatory frameworks.
- All Latin American NRAs have a regulatory framework for clinical trials oversight that is based on international guidelines, including approval by an ethics committee and good clinical practice inspections.
- However, many other NRAs in the Region do not have any legal frameworks for clinical trials.
- Clinical trial oversight in Latin American NRA countries requires collaboration and coordination across different stakeholders in the regulatory system.
- Although all Latin American NRAs publish information about clinical trials in publicly available databases, sometimes such information may not be very useful because of a lack of standardization.
- All Latin American NRAs have procedures for considering local clinical trial results in marketing authorization processes, and a few have procedures for compassionate use for participants after completion of the trial.
- More can potentially be done to boost clinical trials regulation through efficiencies like collaborative reviews, particularly in smaller NRAs.

7.1. NRA Foundations for Regulating Clinical Trials

NRAs have a major role to play in overseeing clinical trials. They must ensure that the trial design meets scientifically sound objectives and standards; they must protect the safety and rights of trial participants; and they must prevent any potential fraud and misuse of trial data (3).

High-income countries host most clinical trials, but the global share of trials in LMICs, including those in Latin America, is growing fast (83). The increased penetration of clinical trials in LMICs is being driven by factors such as a surge in the number and sample size of research protocols; a growing interest in emerging markets; efforts to reduce the cost of research and development; uptake of international good clinical practices (GCP) in regulations; and the lower costs of the trials in LMICs (84, 85).

7.1.1. LEGAL AND ORGANIZATIONAL FRAMEWORKS

All Latin American NRAs have legal provisions to provide regulatory oversight for clinical trials. Such provisions are rooted in the widely implemented GCP guidelines established by the ICH (86). They include legal provisions for:

- **Trial approval.** Clinical trial sponsors must get approval from the NRA to start a clinical trial and for any changes to the study protocol thereafter. All clinical trials must also be reviewed and approved by a research ethics committee (REC).

- **Ongoing trial oversight.** All relevant institutions involved in the conduct of a trial must comply with GCP guidelines, including proper monitoring and management of participants' risks. All Latin American NRAr are legally empowered to inspect, suspend, or stop clinical trials as they deem necessary.

In most countries, clinical trial oversight is a collaborative exercise, implemented by multiple stakeholders across a country's regulatory system, including but not necessarily limited to the NRA and the REC. To be effective and efficient in their joint task, these stakeholders need clear roles and responsibilities. They also need good channels of communication that enable the smooth exchange of information. Considering how NRAs and RECs need to work and interact, it is particularly important to ensure that all relevant study documents and material are carefully assessed, and that studies are conducted in line with trial approval. Each Latin American NRAr works with one or more other organizations to authorize and oversee clinical trials (Annex 1), and all must coordinate activities with these organizations to ensure proper oversight and reporting.

Even though NRAr have major requisites for clinical trials regulation, the legal and organizational frameworks to provide regulatory oversight and ensure adherence to GCP in clinical trials are limited or still lacking in several other NRAs in the Americas (see Section 7.2). This potentially increases risks for clinical trial participants, and the development of robust legal and organizational frameworks should be viewed as a priority in those countries.

7.1.2. REGULATION OF CLINICAL TRIALS

At all stages of a clinical trial, proper procedures and documentation are essential to support GCP compliance and data integrity (87). NRAr split regulatory documentation requirements into three general steps to carry out their regulatory oversight activities: 1) pre-trial (for trial approval), 2) in-trial (for monitoring purposes), and 3) post-trial evaluation. These are further discussed below.

Before the trial

The requirements for authorization of clinical trials are similar across Latin American NRAr. At this stage, they require documentation to be provided by the trial's sponsor (usually through a clinical research organization, CRO). Requirements may include:

- **Investigator's brochure**, documenting all relevant clinical and nonclinical information about the product being studied (the "investigational product").
- **Signed protocol and sample case report form (CRF)**, documenting investigator and sponsor agreement on these.
- **Certificates of analysis of investigational products shipped**, documenting the identity, purity, and strength of all products that will be used in the trial.
- **GCP certification**, in order to be able to conduct the trial in a GCP certified center.

Latin American NRAr have indicated that they have the authority to approve or reject clinical trial applications. Data gathered for this report were somewhat limited in identifying the processes, actual functioning, and extent of the review recommendations provided by different stakeholders involved in the assessment of the clinical trial applications (see Annex 1). However, the information gathered suggests that the NRA's role and responsibilities during the assessment (for example, on investigational product quality, protocol study design, study conduct and risk management, data analysis, ethical considerations) are not clearly defined and point to a potential opportunity for NRA strengthening. These data gaps provoke questions about the role of RECs in the Region, such as: Do they issue recommendations beyond ethical considerations? What is their training and composition? How are they overseen? What is their scope and authority?

During the trial

The second stage of documentation is used to provide oversight when the clinical trial is active and running. During this stage, all Latin American NRAs require additional documentation if there are any changes to the original trial information, including changes to the protocol or case report form, the informed consent form, or the researchers involved. Certificates of analysis are also required for all new batches of investigational products.

Since safety of trial participants is paramount, monitoring and notification of clinical trial adverse reactions must be conducted and reported to the sponsor and, when applicable, to the RECs and/or the NRA, to allow further analysis and action. All Latin American NRAs have clinical trial requirements and procedures for the recording and reporting of ADRs. They all also conduct on-site GCP inspections when deemed necessary and document their inspection findings in monitoring visit reports. The number of inspections conducted each year varies across countries, from 2 or 3 in Brazil to 12 in Chile, although the data for this report are limited in suggesting reasons for this difference.

The finding that all NRAs perform GCP inspections as part of their role in monitoring clinical trial conduct is important. It is possible that those inspections are closely related to their overall monitoring activities on clinical trials. But, considering that many clinical trials in the Region are done in countries without a strong regulatory presence or legal framework for clinical trial oversight, the overall degree of GCP compliance for trials done in the Region remains uncertain.

Given the diverse and complex number of elements involved in conducting clinical trials, comparisons about the frequency of annual NRA inspections require in-depth and careful analysis beyond the scope of this report. Such analysis could focus on the elements more frequently addressed, as well as topics that are rarely looked at during inspections. Are matters related to product quality, risk management, and ethical conduct equally represented? How do they compare with inspections in other regions?

Similarly, more research is required to better understand the roles of different stakeholders in clinical trials in Latin America. This should include, for example, examining the role of RECs in trial monitoring, and investigating how these committees interact with the NRA and other stakeholders.

After the trial

The third stage of documentation happens after the clinical trial is finished. At this stage, requirements vary across the NRAs. ANVISA, INVIMA, and ISP all require investigators to produce a final notification to document completion of the trial, and a clinical study report to document trial results and their interpretation. Both documents must be submitted to both the REC and the NRA. They also require investigators to submit evidence documenting the destruction of any unused investigational product. In addition, ISP also requires a complete subject identification code list, so that the authority can easily identify everyone that participated in the trial in case any follow-up is needed.

The request for notification of trial completion and for evidence documenting the destruction of unused investigational product are well-accepted practices worldwide and should be followed by all NRAs. But the use and value of requiring complete clinical study reports once the trial is complete and beyond market authorization is not completely understood. NRAs may never look at them if the study is never used to support a given product market application, and there will be no regulatory decision attached to it. Study reports that do become part of a product application must be included with all the other study reports in the application.

7.1.3. REGULATING CLINICAL TRIALS IN PRACTICE

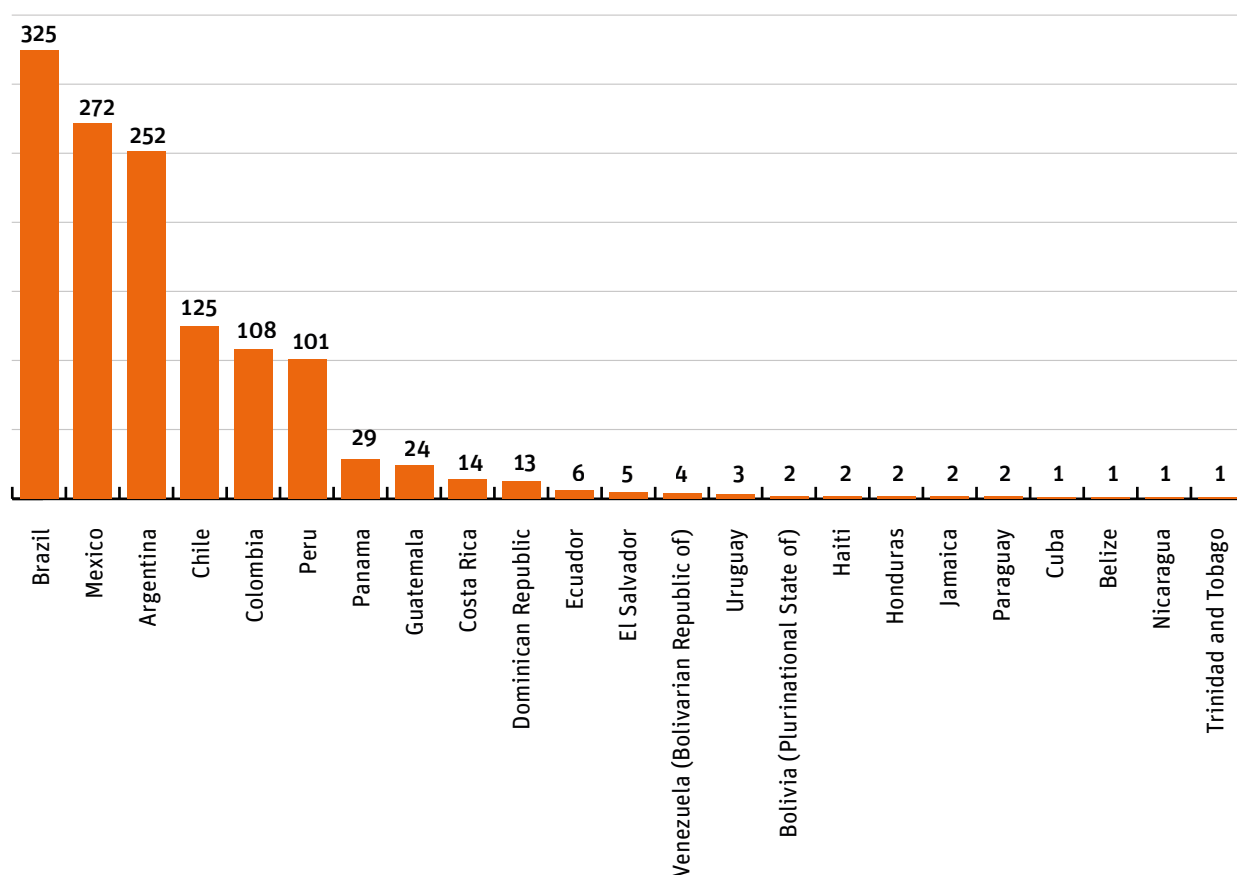
Active trials

The continued strengthening of regulatory frameworks in Latin America makes the Region an attractive option for clinical research, with an increasing number of clinical trials held there each year. Between 2005 and 2012 the total number of clinical trials held in Latin America grew by 12% (88). Data from 2018 show that Latin American NRAR countries host the largest absolute number of clinical trials in the Region, but other countries in the Region host a proportionally significant number of trials relative to the size of their population (see Figure 7.1). Such observation requires more attention and analysis, especially given that PAHO’s evaluations of NRAs reveal limited clinical trials regulatory functions in many countries of the Region. Eleven out of 35 countries (31%), which are mostly the smaller population states in Central America and the Caribbean, do not have any clinical trial legal provisions at all.

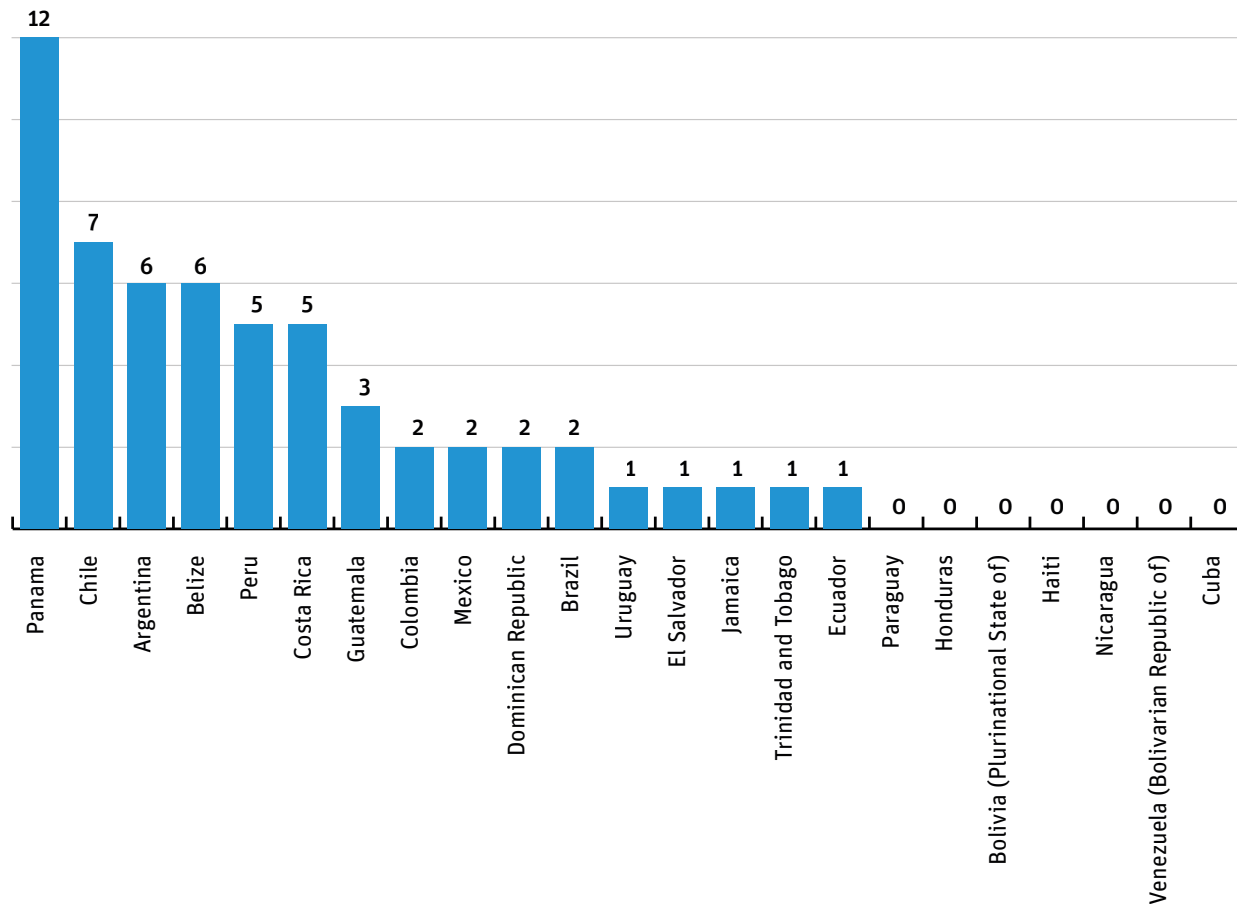
These trends underscore the importance of continuing to develop and strengthen clinical trial oversight, not only among the Latin American NRAR countries, but across all countries in the Region. The GBT outlines a number of foundational indicators that countries can implement to strengthen clinical trial oversight (3).

Figure 7.1. Active clinical trials in Latin America

a) Number of clinical trials with drug interventions



b) Number of clinical trials with drug interventions per 1 million inhabitants



Source: ClinicalTrials.gov data and World Bank Population data for 2018 (cited 26 November 2019).

Across all countries, most of the trials conducted in the Region are sponsored by multinational pharmaceutical companies. Data collected for this report indicate that just 1%–7% of trials authorized in Latin American NRAr countries were sponsored by national entities. This reflects general trends in the literature worldwide showing that the share of international industry-sponsored trials is significantly higher than that of national sponsored ones (89).

7.1.4. APPROVAL RATES AND TIMELINES

Approval rates by Latin American NRAr for clinical trial applications vary but are in general high, with only a few rejections or withdrawals (see Table 7.1). Application review times also differ but take more than 30 days on average (see Table 7.1).

Table 7.1. Overview of clinical trial approval rates, timelines, and relevant resources in NRAr

| | | ANMAT | ANVISA | CECMED | COFEPRIS | INVIMA | ISP |
|--|-----------------|------------------|--------------------|---------------------|--------------------|--------------------|------------------|
| No. CROs present | | 15 | 28 | 1 | 37 | 26 | 20 |
| CT APPROVAL REQUESTS | 2018 | 158 | 173 | 6 ^a | 804 | 90 | 86 |
| | 2019 | 164 | 221 | 3 ^a | 767 | 85 | 72 |
| CTS NOT RUN IN THE PAST YEAR | Rejections | 3 | 10 | 1 ^a | 38 | 1 | 0 |
| | Withdrawals | - | - | - | 5 | 6 | 2 |
| Approval processing times* | | 50–70 | 80–160 | 90–165 ^b | 90 | 90–120 | 45 |
| NO. STAFF DOING CT OVERSIGHT ACTIVITIES | Permanent staff | 1 | 18 | 5 ^c | 15 | 6 | - |
| | Contract staff | 21 | - | - | 3 | 5 | 5 |
| Trials per staff | | 7.3 | 11.8 | - | 43.6 | 7.9 | 15.8 |
| Total CTs in registry | | 708 ^d | 1,668 ^e | 74 ^a | 3,475 ^f | 1,345 ^g | 697 ^h |

Notes: * real NRA + CRO working days; CT: clinical trial.

Sources: Data collected by PAHO using the following methodology: Each LA NRAr identified a focal point for this report. PAHO developed an instrument with the data requested, the instrument was filled by the LA NRAr focal point, followed by a phone interview/email communication to validate the data included in the report. Two rounds of data validation were performed. The investigation and analysis were conducted from March 2019 to October 2020; ^a CECMED. Memoria de actividades 2018. CECMED: Cuba; 2019. Available from: https://www.cecmecmed.cu/sites/default/files/adjuntos/reporte_anual/Memorias%20de%20actividad%20CECMED%202018.pdf, cited 7 July 2020; ^b República de Cuba. Regulation No. 21-08. Requisitos para la autorización y modificación de ensayos clínicos. Available from: https://www.cecmecmed.cu/sites/default/files/adjuntos/Reglamentacion/Reg_21-08.pdf, cited 7 July 2020; ^c Data available correspond to year 2015; Sources of data and year per Latin American NRAr: ^d ANMAT: Data provided for this report during the interview, timeframe provided included from July 2012 to October 2019; ^e ANVISA: Official Website CT query timeframe 2009–2020. Available from: <http://portal.anvisa.gov.br/consulta-de-ensaios-clinicos-autorizados>, cited 8 July 2020. Data were treated to eliminate duplicates; ^f COFEPRIS: Official Website CT query timeframe 2013–2018. Available from: <http://siipris03.cofepris.gob.mx/Resoluciones/Consultas/ConWebRegEnsayosClinicos.asp>, cited 20 July 2020; ^g INVIMA: Data provided for this report during the interview is updated to 14 November 2020; ^h ISP: Official website CT database timeframe 2006–2011. List of Resolutions for the Importation and Use of Medicines without Health Registration for the Purposes of Scientific Research. Available from <http://www.ispch.cl/ensayos-clinicos>, cited 20 July 2020.

Understanding the nature of different approval rates and timelines is complex. Application requirements vary and applications for the same study may not be submitted for approval in all countries, or may be submitted at different times. Moreover, simple numerical comparisons of approval rates and timelines do not take into account things like type and complexity of the study design, quality of the product and the application itself, complex ethical related issues, or quality of assessment.

Using approval rates and timelines as a proxy for NRA efficiency can also be risky. While the timely authorization of clinical trials may be critical to developing and accessing new beneficial products, if they are not properly regulated, clinical trials ultimately carry inherent risks for participants and eventually for the whole population. For this reason, assessment of NRA efficiency should be extended beyond timelines to include measurement of quality.

The efforts of some NRAr exploring different mechanisms for shortening the time it takes to approve and authorize clinical trials are worth highlighting (see Box 9). But the impact of newly introduced changes in the overall performance of this important regulatory function will need to be assessed in the future.

Box 9. Speeding up approval in Brazil

Since 2015, ANVISA has introduced a series of measures to speed up its approval timelines for clinical trials. These include:¹

- **Consolidated application.** In 2015, resolutions RDC 09/2015 and RDC 10/2015 consolidated all the documentation required for clinical trial approval into a single dossier, the Clinical Development Dossier of the Experimental Drug.
- **Priority review.** In 2017, resolutions RDC 204/2017 and RDC 205/2017 enabled expedited review for clinical trial applications classified as priorities (these include, for example, clinical trials for new medicines that will be fully produced in Brazil, are part of the National Immunization Program or Strategic Product List, target neglected or rare diseases, or are for pediatric patients). Priority reviews receive a first opinion letter within 30–45 days (compared with the standard 90–180 days).
- **Known protocols.** Clinical trials protocols that have been previously approved by ANVISA are also given an expedited review that is twice as fast as the standard review. In these cases, ANVISA also holds regular meetings with the sponsor or CRO to discuss potential problems with protocols so that these can be speedily addressed.
- **Parallel processes.** Resolution 205/2017 enabled ANVISA reviews of clinical trial applications to be done in parallel with (rather than after) ethics reviews.
- **Decentralized ethics review.** Before 2016, all ethics reviews were done by the national ethics committee, CONEP, which caused a bottleneck in approval timelines. In 2016, resolution CNS 506/2016 enabled CONEP to accredit local ethics committees and ease the central bottleneck by distributing applications to them for review and approval.

Source: 1. Fagundes P, Dresel P, Miller AE. Brazil's regulatory environment offers positive changes for clinical trials. Regulatory Focus. Rockville, Maryland: The Regulatory Affairs Professionals Society; 2018. Available from: <https://ppdicomcontenteus.azureedge.net/uploads/2018/06/2018-June-Regulatory-Focus-Brazil.pdf>, cited 14 February 2020.

7.2. Best Practices and Efficiencies in Clinical Trial Oversight

7.2.1. OVERSIGHT COORDINATION

Clinical trial oversight is a function of multiple stakeholders within a regulatory system. Making sure that it works effectively and efficiently requires strong collaboration and coordination between all those involved. At a national level, adequate regulatory oversight requires both intra- and inter-organizational coordination. All Latin American NRAR claim to have strong coordination within their own organizations, and GCP inspectors report support and good intra-organizational cooperation for their activities.

All Latin American NRAR have established inter-organizational links to the bodies that accredit and supervise ethics committees in their countries and have joint oversight processes and timelines. In some countries, including Chile and Colombia, RECs are certified and supervised by the MoH. In others, like Brazil, local RECs are supervised by the national ethics committee (CONEP), which in turn is part of the national health council (CNS). It should be mentioned, however, that there are reports questioning the coordination and actual performance of ethical related oversight for clinical trials in the Region, including Latin American NRAR countries (90).

At a global level, exchanges and coordination seem to be rather limited. It is not clear if the Latin American NRAr have a mechanism for actively exchanging clinical trial related information with each other or with NRAr from other jurisdictions, either before or during the trial. All Latin American NRAr say they rely on information posted on ClinicalTrials.gov or other regulatory registries when analyzing new applications, or for GCP inspection related purposes.

7.2.2. REGISTRATION AND PUBLICATION OF CLINICAL TRIAL RESULTS

WHO advises each country to develop its own national registry for clinical trials, but since 2009 WHO has also brought data from these national registries together through the International Clinical Trial Registry Platform (ICTRP). All data in the ICTRP must meet WHO standards for clinical trial registration, which include criteria for: content, quality and validity, accessibility, unambiguous identification, technical capacity, and administration and governance. ANVISA and CECMED both have a national clinical trial registry that meets all the WHO criteria and as such are designated primary registries (91). All other Latin American NRAr also maintain a public database containing information about the clinical trials that have been approved in their country, although the type of information they provide differs (see Table 7.2). Some national databases omit crucial information for participants, such as the targeted medical condition or disease, or the study start and end dates. Many stakeholders report that the databases are not easy to use or understand.

Better standardizing the information that each NRAr makes public would be a useful step to strengthening clinical trial oversight in Latin America. Although not guaranteed, the implementation and use of better and common database standards could help NRAr manage and monitor clinical trials, lead to more transparent results, and enable knowledge exchange among stakeholders across countries in the Region. All countries are encouraged to carefully consider the possibility of implementing the WHO ICTRP as an alternative or complementary option to hosting a national clinical trial registry.

Table 7.2. Information captured in NRAr public databases for clinical trials

| | ANMAT | ANVISA ^a | COFEPRIS | INVIMA | ISP |
|---|-------|---------------------|----------|--------|-----|
| CLINICAL TRIAL STATUS | ✓ | ✓ | ✓ | ✓ | |
| CONTROL NUMBER | ✓ | ✓ | ✓ | | |
| DISEASE | ✓ | ✓ | | | ✓ |
| MEDICATION NAME | ✓ | ✓ | ✓ | ✓ | ✓ |
| MEDICAL CONDITION | ✓ | ✓ | ✓ | | ✓ |
| POPULATION UNDER STUDY (GENDER, AGE) | ✓ | | ✓ | ✓ | |
| PROTOCOL NUMBER | ✓ | ✓ | ✓ | ✓ | ✓ |
| PROTOCOL TITLE | ✓ | ✓ | ✓ | ✓ | ✓ |
| RESULTS OF CLINICAL TRIAL | ✓ | | ✓ | | |
| SPONSOR NAME | ✓ | | ✓ | ✓ | ✓ |
| STUDY START DATE | ✓ | | ✓ | | ✓ |
| STUDY END DATE | | | | | ✓ |

Notes: Data for CECMED not received. ^a Information verified using ANVISA's database of authorized clinical trials, available from: http://www7.anvisa.gov.br/Datavisa/Consulta_Comunicados/Resultado_Comunicados_Detalhe.asp.

Beyond databases and registries, some NRAr also publish reports summarizing trends in clinical trial activity. ANVISA, for example, produces annual reports about clinical trials in Brazil, listing approved and rejected trials, identifying key characteristics of authorized trials, and summarizing the results of GCP inspections. These kinds of reports are useful in providing NRAs and other stakeholders with a clear picture of the current focus areas in clinical research and can support horizon scanning for future marketing approval requests. ANVISA's 2017 and 2018 annual reports clearly show that the most researched medical conditions in clinical trials in Brazil are oncology—especially breast and colon cancer—diabetes, and increasingly, orphan diseases such as Crohn's disease (92, 93).

Making the results of clinical trials, both positive and negative, publicly available is considered good practice because it supports informed decision-making by patients, practitioners, and policymakers. A trial registry is broadly acknowledged to be the most useful platform for publishing clinical trial information.

7.2.3. ACCESS TO MEDICINES

International ethical guidelines for clinical research suggest that any intervention or product developed through clinical trials in low-resource settings should be made reasonably available as soon as possible to the population or community where those trials were carried out (94). A 2015 study of post-trial availability and affordability in Latin America found that 20 months after the FDA had approved the commercialization of 33 products in the United States of America, only eight (25%) had been registered and commercialized in all the Latin American countries where they were tested (95). There is growing concern among researchers, public health advocates, and ministries of health in Latin America that products in the Region remain inaccessible to local populations once the clinical trial is over. Reasons for that are multiple and may include regulatory, non-regulatory, or a mix of both types of considerations. As clinical trials are normally part of a well-structured plan for the clinical development of a given product, the marketing and broad access to the product once the trial is completed will necessarily depend on the results and the totality of evidence gathered to support its regulatory approval.

NRAr officials interviewed for this report identified two mechanisms for improving the accessibility of investigational products after a clinical trial is finished. First is building intra-NRA links between the GCP team and the marketing authorization team to help speed up registration processes. All NRAr report having mechanisms to ensure information about any clinical trial conducted in the country is incorporated into marketing authorization processes. For example, in INVIMA and ISP, a member of the GCP team has a permanent seat in the marketing approval committee.

While this type of mechanism can be seen as supporting work for the marketing authorization related function, the inclusion of views related to local clinical trial experiences could also be seen as removing some degree of independence during the marketing authorization assessment; some commentators go as far as to recommend a complete separation of these two regulatory assessment functions. Regardless, evidence gathered from locally conducted trials in the Region is most probably very limited in the context of the whole product development plan and represents only a minimal part of the evidence submitted for marketing authorization.

The second mechanism mentioned by interviewees is regulating for the continued access of participants to the investigational product immediately after the clinical trial ends. NRAr regulations for this kind of compassionate use vary significantly:

- In Chile, regulation for compassionate use is still under development and so remains voluntary. It requires treatment to be continued after the trial has finished, with costs covered by the sponsor. How long such post-trial treatment continues is determined by the principal investigator, depending on the therapeutic utility of the product (96).
- In Brazil, ANVISA has regulated for compassionate use that is guaranteed by the sponsor if there is perceived benefit to the trial participant and according to the treating physician. Procedures related to rare diseases are managed by the Conselho Nacional de Saúde, and sponsors are responsible for five years of treatment (97, 98).
- Other countries, like Colombia, have no provisions related to compassionate use, although are in the process of establishing them.

This second mechanism refers to a separate topic on medication access. It refers to access to products that patients and healthcare providers believe could be of benefit to individual trial participants once the trial is finished. Such product use occurs outside the needed and comprehensive regulatory assessment for marketing and access of the product to the entire population. The development of provisions that allow special access of products to trial participants immediately after a trial ends is valuable but must be tailored to the relevant legal frameworks in the individual countries, including those in medical and pharmacy practice.

In all cases, it is expected that the pharmaceutical industry, as well as the healthcare community, government authorities, and the population, can significantly benefit from the conduct of clinical trials; and that NRAs could play a larger role in ensuring that the knowledge and products developed through these trials have a positive impact across Latin America.

7.2.4. REGIONAL COLLABORATION ON CLINICAL TRIALS REVIEW

There are additional efficiencies to potentially be gained in clinical trials regulation by working together. The African Vaccines Regulatory Forum (AVAREF) (99) is an example of this. African NRAs and ethics committees assess clinical trials applications at the continental level, and the work helps to facilitate faster processing of these trials at the national level. Such models may be a way of boosting clinical trials regulatory capacity in the Americas, particularly for smaller countries that already work together in regional integration mechanisms, such as in CARICOM and Central America.

Recommendations for Action

- **Review stakeholder roles and interactions.** Establish and reinforce intra- and inter-organizational links by clearly defining roles and responsibilities and developing procedures to ensure the smooth flow of regulatory information before, during, and after a clinical trial.
- **Develop and use tools to support handling of clinical trials regulatory information.** Implement the use of standard databases or registries that maintain relevant clinical trial information to enable adequate regulatory management, monitoring, and open knowledge exchange, and support informed decision-making by patients, healthcare professionals, researchers, etc.
- **Broaden methods to assess regulatory efficiency.** Use multiple indicators to assess efficiency of clinical trials regulatory oversight that do not simply rely on trial approval rates and application review timelines and which include measurement of review quality.

- **Introduce extraordinary product access procedures for clinical trial participants.** Since many countries do not have or have not yet implemented them, consider the development of compassionate product use procedures for clinical trial participants once the study ends.
- **Strengthen clinical trials oversight in NRAs with limited capacity.** Use foundational GBT indicators (Maturity Level 1 and 2) to implement clinical trials oversight in countries that currently have no relevant regulation in place.
- **Consider collaborative methods for clinical trials regulation.** Use models like AVAREF to potentially gain efficiencies in clinical trials oversight, particularly in smaller countries and in settings where there is a history of cooperation.

8. TRADE AND ECONOMIC INTEGRATION MECHANISMS

In brief

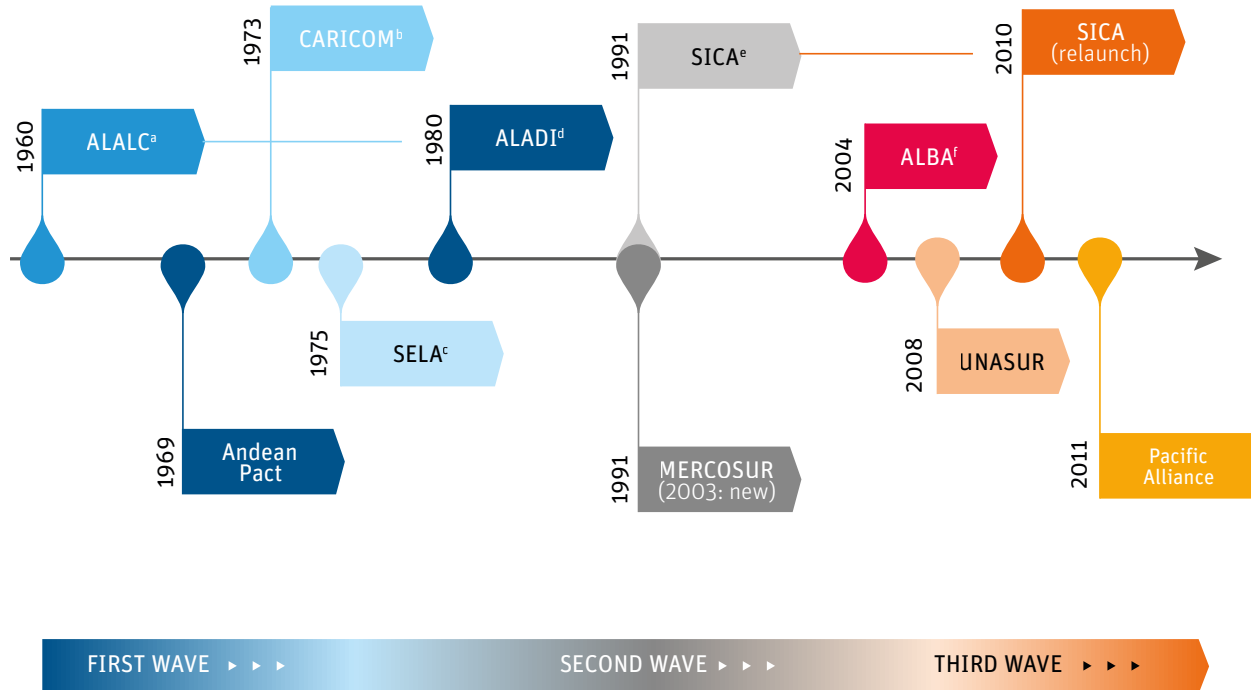
- Four key trade integration mechanisms in the Americas—CARICOM, SICA, MERCOSUR, and the Pacific Alliance—have different activities in medicines regulation.
- The regulatory activities include cooperation groups, regional centers, joint decision-making, and information sharing within the mechanisms.
- Regulatory capacities vary across and within the different mechanisms, but all four mechanisms use reliance to varying degrees as a way of improving efficiencies.
- There is a focus on using these mechanisms for regulatory and public health strengthening in some settings, particularly in countries with smaller populations and markets (e.g., CARICOM and SICA), but challenges remain in terms of implementation, perhaps in part because economic development and trade considerations have not been part of the discussions.
- Alternatively, the MERCOSUR and Pacific Alliance mechanisms have had some regulatory successes, in part because of their grounding in economic and trade rationale, but have struggled with implementation of more robust regulatory activities, in part because of varying regulatory standards among members.

Regulation, trade, and economic development in the Americas are closely interwoven and strongly shaped by the Region's economic and trade integration mechanisms. Economic and trade integration can boost the efficiency of pharmaceutical importation and exportation by pooling markets and creating a similar or unified set of rules. Integration tends to raise regulatory standards toward those highest in the group.

Trade integration in Latin America dates back more than six decades, with three well-defined “waves” of integration since the mid-20th century (see Figure 8.1):

- **First wave.** Before the 1980s debt crisis, trade integration focused on replacing foreign imports with regional production through intra-regional trade integration in the manufacturing sector and high tariffs on trade for countries outside the bloc (100). Examples from this wave include the Latin American Free Trade Association and the Latin American and the Caribbean Economic System.
- **Second wave.** In the 1990s, trade integration shifted to focus on helping Latin American countries adjust to and participate in the new global trade regime. Exemplified by the Southern Common Market (MERCOSUR) and the Andean Community, the new approach eliminated trade barriers beyond the manufacturing sector, with no differential treatment for countries outside the bloc.
- **Third wave.** At the turn of the century, amid changing political contexts within the Region, another approach to trade integration emerged. This approach is marked by two types of agreements: those that remain committed to free trade (for example, the Pacific Alliance), and those that instead focus on political, social, and productive integration (for example, the “new” MERCOSUR and the Bolivarian Alliance for the Peoples of Our America).

Figure 8.1. Major trade integration mechanisms established in Latin America since 1960



Notes:

^a ALALC: Latin American Free Trade Association; ^b CARICOM: Caribbean Community; ^c SELA: Latin American and the Caribbean Economic System; ^d ALADI: Latin American Integration Association; ^e SICA: Central American Integration System; ^f ALBA: Bolivarian Alliance for the Peoples of Our America.

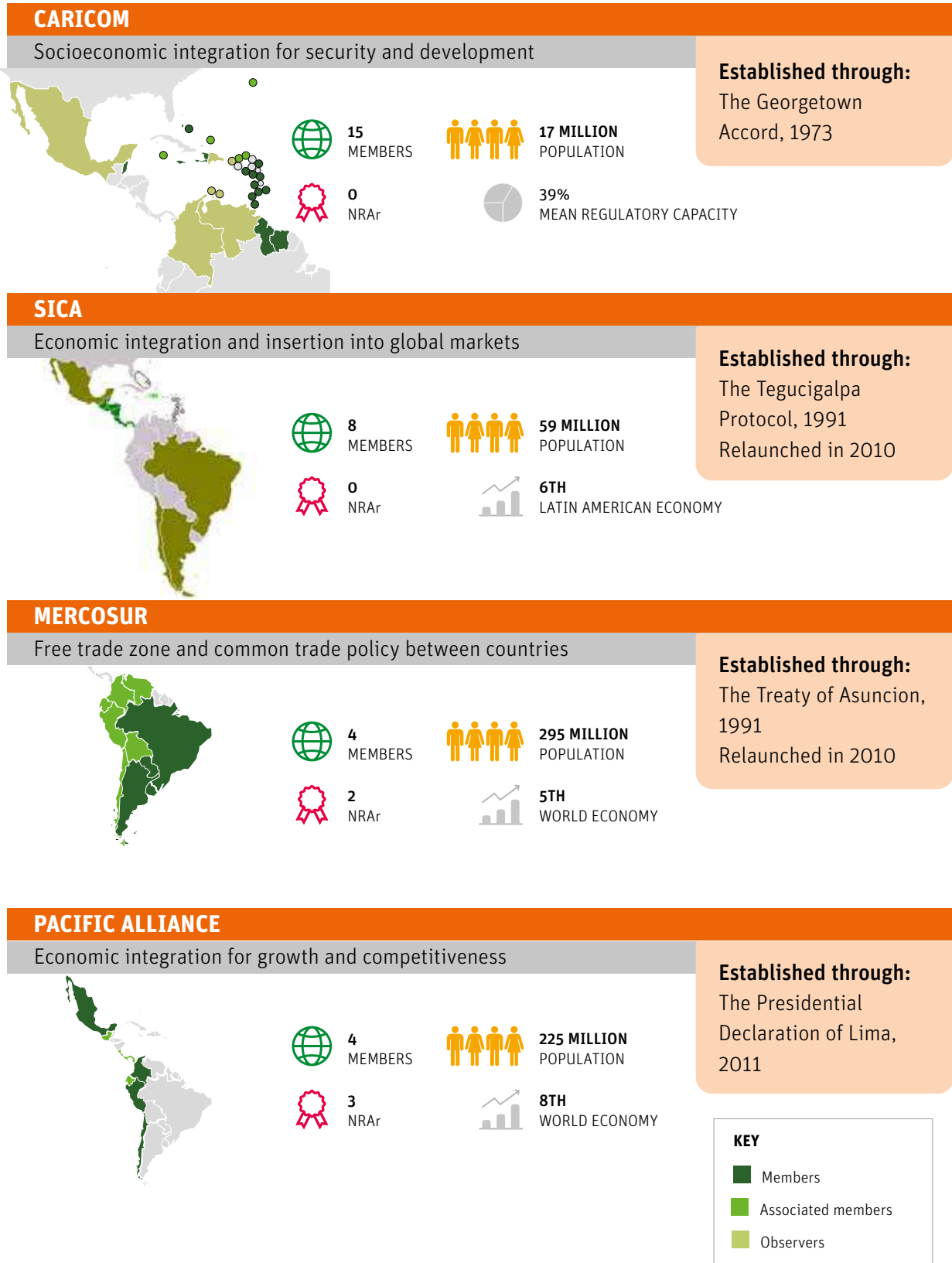
8.1. Regulation in Trade and Economic Integration Mechanisms

While the focus of trade integration in the Americas has evolved over time, most of the major mechanisms that exist in the Region include a regulatory component. These regulatory components attempt to improve the quality, safety, and efficacy of the products in the market, and/or facilitate trade and boost access to markets and/or exports. In general, the scope of these components covers several strategic economic and development areas. Four mechanisms in particular include a component for pharmaceutical regulation among their activities:

- the Caribbean Community (CARICOM);
- the Central American Integration System (SICA);
- the Southern Common Market (MERCOSUR); and
- the Pacific Alliance.

CARICOM, MERCOSUR, and SICA are long-standing treaties that started as communities to enhance trade (first within the Region and later with the rest of the world) and have recently been relaunched for deeper integration across social, productive, and regulatory policies. The Pacific Alliance was formally established in 2011 and seeks to achieve the free movement of goods, services, resources, and people in the Asia-Pacific region. Each integration mechanism has its own specific members, scope, and objectives (see Figure 8.2). These affect the nature of the regulatory activities carried out by each mechanism. For example, in MERCOSUR, which has evolved to support trade and economic development, the regulatory activities are shaped to deliver those objectives. By contrast, in CARICOM, which seeks deeper socioeconomic integration, regulatory activities cut across social and productive policies and also attempt to address public health concerns related to the limited capacity of small state regulatory systems to assure access to affordable and quality medicines.

Figure 8.2. Basic characteristics of four key trade integration mechanisms in Latin America



When it comes to pharmaceuticals, the four integration mechanisms do different regulatory activities, including sharing GMP inspection reports, harmonizing processes for market authorizations, jointly purchasing medicines, and establishing joint systems for reporting of adverse events and SF products (see Table 8.1).

Table 8.1. Pharmaceutical regulatory cooperation within key trade integration mechanisms

| MECHANISM | ACHIEVEMENTS IN REGULATORY COOPERATION |
|---------------------------------------|--|
| MERCOSUR^{a-d} | <ul style="list-style-type: none"> • Sharing of GMP inspections • Training and capacity-building activities for inspectors • Structural Convergence Fund (FOCEM) to finance various projects, including regulatory knowledge-sharing and technology transfer, to reduce asymmetries in the bloc |
| PACIFIC ALLIANCE^{e,f} | <ul style="list-style-type: none"> • Interinstitutional Agreement of Cooperation to facilitate the processes of marketing authorizations • GMP reliance project for inspection reports and marketing authorization of generics |
| SICA^g | <ul style="list-style-type: none"> • Central American Technical Regulations (RTCA) to harmonize requirements for marketing authorizations, labeling, stability studies, and quality aspects • Harmonized list for the joint purchase of medicines for critical diseases • Regional reporting system for AEs |
| CARICOM^{h,i} | <ul style="list-style-type: none"> • The Caribbean Public Health Agency/Caribbean Regulatory System • Reliance mechanism for marketing authorization • Regional reporting system for AEs and SF • Regional drug-testing laboratory (Medicines Quality Control and Surveillance Department [MQCSD]) |

Sources: ^a Sarti I. Integración regional y participación social: logros y desafíos en la institucionalidad de un Mercosur ampliado. *Revista Latinoamericana de Estudios del Trabajo*. 2017;23-24:7-17; ^b Protocolo de Ushuaia sobre Compromiso Democrático en el MERCOSUR, la República de Bolivia y la República de Chile. 1998; ^c Declaración Política del MERCOSUR, Bolivia y Chile como Zona de Paz. 1998; ^d Protocolo de Olivos. MERCOSUR. 2002; ^e Cartilla Alianza del Pacífico. 2017; ^f Ortiz Morales C. La Alianza del Pacífico como actor regional: Factores de éxito para la cohesión regional hacia la proyección internacional. *Desafíos*. 2017;29(1):49-77; ^g SICA [Internet]. El Salvador: SICA; 2020. Algunos logros de SICA. Available from: www.sica.int/iniciativas/inicio, cited 7 February 2020; ^h Jones WP. The Caribbean Community (CARICOM): Origins, Achievements, The Future. Kingston: Economic Development; 2003. Available from: <https://econwpa.ub.uni-muenchen.de/econ-wp/dev/papers/0411/04110006.pdf>, cited 7 February 2020.; ⁱ CARICOM [Internet]. Guyana: CARICOM; 2020. Key Community Milestones and Achievements. Available from: <https://caricom.org/about-caricom/who-we-are/key-community-milestones-achievements/#paginate-1>, cited 7 February 2020.

8.2. Integration for Regulatory System Strengthening

Using trade and economic integration mechanisms is increasingly a strategy of choice for public health focused regulatory system strengthening around the world, including within the economic communities of Africa (101). A key rationale is that regulatory systems are too resource intensive for individual countries, especially the smallest ones, to build and maintain their own NRA. Rather, states can achieve effective regulatory oversight by working together, adopting and sharing efficiencies, and very importantly, pooling markets. Research has found that there is a direct association between population size and regulatory capacity, and between GDP and regulatory capacity (6). The smaller the population size or GDP, the lower the level of regulatory capacity, regardless of income level—likely because of limited human and financial resources, among other factors. Population and market size also affect the degree to which industry is attracted to a market and willing to comply with its rules.

All of this makes the NRAs and ministries of health in the smaller countries of the Americas particularly vulnerable to limited regulation, but they are also uniquely positioned to work together. Both PAHO and WHO work within trade and integration mechanisms in the Caribbean (CARICOM) and Central America (SICA) for regulatory strengthening and, along with other key stakeholders, have helped to establish and operationalize regulatory activities in these blocs (see Sections 8.2.1 and 8.2.2).

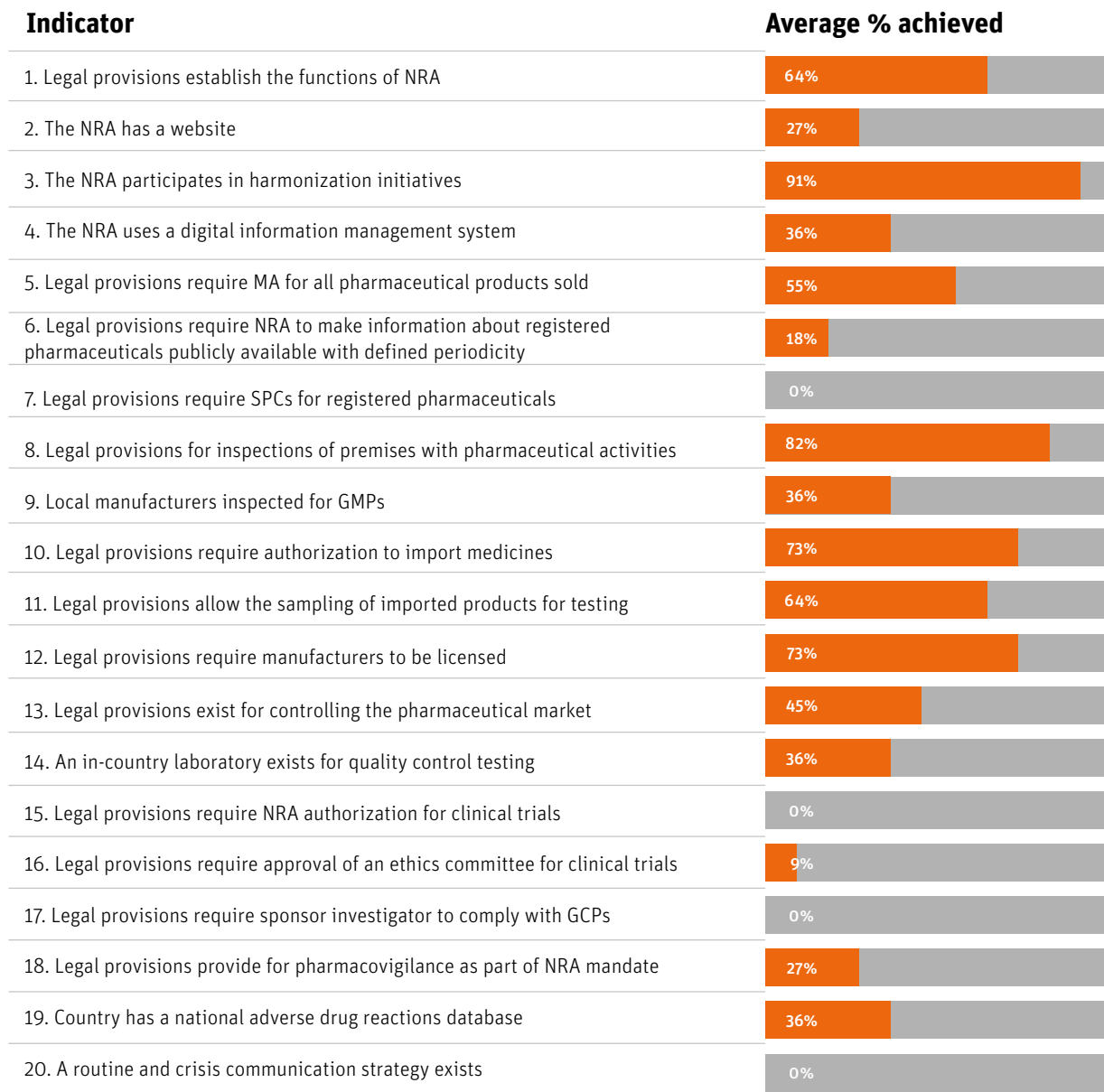
8.2.1. CARICOM

Established in 1973, CARICOM is the oldest of the trade integration mechanisms with a pharmaceutical regulatory component. It is built on four pillars of cooperation: economic integration; foreign policy coordination; human and

social development; and security (102). It includes 20 governments and 17 million people in the Caribbean. With few exceptions, CARICOM members tend to have relatively small populations and markets; they are also fairly homogenous in terms of absolute level of development, language, and culture.

Although many country members are considered high or middle income, the bloc is marked by limited regulatory capacities, with members facing chronic challenges in overseeing medicines and other health technologies. A PAHO analysis from 2016 showed that 11 members of CARICOM had implemented just 39% of the 20 basic indicators of regulatory capacity, compared with 90% or more implemented by all other subregions of the Americas (103). These countries were found to have particularly limited capacity in essential regulatory functions like marketing authorization, pharmacovigilance, and post-market surveillance (see Figure 8.3).

Figure 8.3. Average regulatory capacity achieved by CARICOM members across 20 basic indicators



Source: Preston C, Chahal HS, Porrás A, Cargill L, Hinds M, Olowokure B, et al. Regionalization as an approach to regulatory systems strengthening: a case study in CARICOM member states. *Revista Panamericana de Salud Pública*. 2016;39(5):262–8.

CARICOM strategies for regulatory success

CARICOM has historically performed some regulatory activities (for example, its regional drug testing laboratory was established as early as 1976) and Member States have talked about using a regional approach to regulation for many years. Such an approach was officially enshrined in the Caribbean Pharmaceutical Policy in 2011, and was operationalized and endorsed by CARICOM ministers of health as the Caribbean Regulatory System (CRS) in 2014 (104). The CRS started operations in 2017 as a regulatory unit within the Caribbean Public Health Agency (CARPHA), the CARICOM regional public health agency. The working strategy was, and still is, to pool resources and markets together, with a single set of standards, to create a voluntary system that augments countries' abilities to perform key regulatory functions, guided by an appointed board of advisors from CARICOM Member States, called the Technical Advisory Committee on Pharmaceutical Policy, or TECHPHARM.

The CRS currently performs the two regulatory functions that PAHO recommends should be prioritized above all others in small states: marketing authorization and PV/PMS, and it leverages efficiencies to perform them in the context of limited resources (45). For example, it uses time- and space-saving electronic systems to handle documents. It also uses reliance to recommend essential medicines (including vaccines) for marketing authorization: products that have been approved by PAHO-designated NRAs, the European Union, or the United Kingdom, and that are prequalified by WHO, are recommended for approval by CARPHA Member States. The process is designed to reduce the staff and time requirements for applications that a trusted regulatory authority has already examined and approved. In these cases, the CRS review focuses on verifying that the product in the application is the same as the one that was already approved by the reference authority. This is particularly important given the known practices of sending export-only or lower-tiered versions of products to less regulated or less lucrative markets (50, 69). By pooling resources through the CRS and relying on trusted authorities' decisions, CARICOM's process aims to expedite marketing authorization within the bloc. The process takes roughly 4–8 weeks within the CRS and, if a favorable recommendation is made, Member States are asked to decide on marketing authorization within 60 days.

To support post-market surveillance, the CRS created and maintains a regional reporting system through which health providers, industry, and the public can submit reports on both adverse events and SF products through an electronic portal, called "VigiCarib" (105). These reports are analyzed by CRS staff, who follow up with the reporters and work with country governments as appropriate. The CRS also copies these reports to global databases, which increases the level of representation of ADRs and SF products from CARICOM countries.

Implementation challenges

Despite over 100 products recommended and more than 300 reports of ADRs and SF products received by July of 2020, the CRS continues to face challenges, including limited integration into Caribbean health systems. The new system took time to generate a pool of recommended medicines that was large enough for governments to use effectively, and some countries have not yet changed their regulatory approval processes or national procurement strategies to take these medicines up. Turnover in senior health positions across governments has meant that the leadership to drive change has not been constant. Another challenge is that the CRS does not currently review products that are not approved in a reference authority. This leaves a significant proportion of the products that are regulated by Caribbean countries in limbo, including those that are locally or regionally manufactured. Countries also require foreign companies to identify a local importer before they can get market authorization. So, even after CRS issues a recommendation, bottlenecks in establishing business relationships at the local level can pose challenges to implementing CRS decisions. In many cases, companies have failed to meet the importer criteria; it is not clear why this is, although it may simply be a byproduct of the fewer business incentives to move aggressively in small markets.

A final challenge for CRS is that it has not yet linked its work to a broader trade and economic development rationale that can be appreciated beyond the health sector, including articulating the benefits of a more predictable and transparent business climate for pharmaceuticals.

8.2.2. SICA

Established in 1991, SICA is the economic and political organization of Central America, covering eight countries that are home to more than 59 million people who share broadly similar levels of development, language, and culture (106). It is the sixth largest economy of Latin America and represents a subregion whose governments have a solid history of establishing integration mechanisms to tackle common challenges (107, 108). Like in CARICOM, SICA Member States have to grapple with relatively small markets and limited resources for regulatory system strengthening. The bloc is marked by important asymmetries in the medicines available in each country. There are more than 18,000 commercialized pharmaceutical products in Central America, but only 2,202 of them are available in all of the countries.

In 2010, a relaunch of the regional integration process confirmed SICA's commitment to achieving five common development goals: democratic stability; disaster risk management and climate change; social inclusion; economic integration; and institutional capacity building (109). Within this framework, Central American governments have implemented a set of regional public policy initiatives, some of which have had significant socioeconomic impact (108). For example, by using a harmonized list to jointly purchase medicines for critical diseases, governments decreased drug acquisition costs across SICA by approximately 40% between 2012 and 2013 (110).

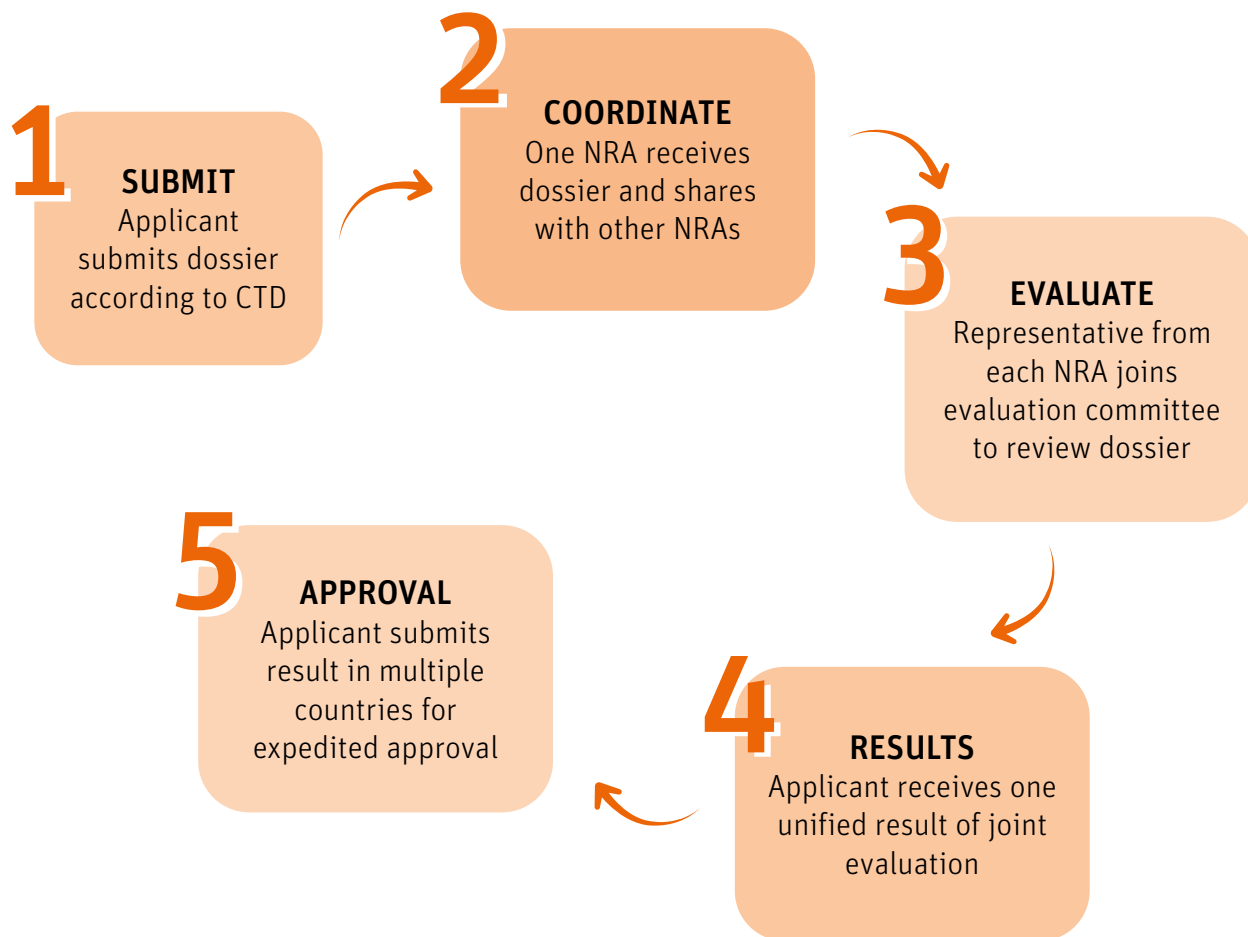
SICA strategies for success

Like CARICOM, SICA's approach to strengthening pharmaceutical regulation emphasizes joint action to harmonize systems, reduce costs, and improve efficiencies. In particular, through two of its technical secretariats—the Council of Economic Integration Ministers and the Council of Health Ministers—SICA members work together to develop the Central American Technical Regulations (RTCAs) that harmonize requirements for marketing approval, labeling, stability data, and quality standards for pharmaceutical products. Today, there are nine RTCAs in force for medicines for human use. These are being actively used in Costa Rica, El Salvador, Guatemala, Honduras, and Nicaragua, although they are implemented differently from country to country.

The differences in how RTCAs are implemented means countries do not necessarily use the same criteria for evaluating a dossier for marketing approval. This poses problems for manufacturers that want to submit products to multiple SICA members. To address this challenge, and to build on the collaborative action created by the RTCAs, PAHO worked with SICA ministers of health to develop a strategy for unifying evaluation criteria to make registration across the Region less burdensome for manufacturers and more efficient for countries. The result of their efforts is the Joint Evaluation Mechanism, which was launched in October 2019 (111). The mechanism is based on a document of common technical requirements that cover all the evaluation requirements in each SICA country,¹³ and countries work together to jointly evaluate the submitted dossier and provide a single result that can be submitted to all countries for expedited approval (see Figure 8.4).

¹³ The specific requirements of this document can be found in the Central American Technical Regulation of Pharmaceutical Products, Medicines for Human Use, Marketing Authorization Requirements (RTCA 11.03.59:11). These requirements are specific to Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama.

Figure 8.4. Steps for implementing the Joint Evaluation Mechanism in SICA



Implementation challenges

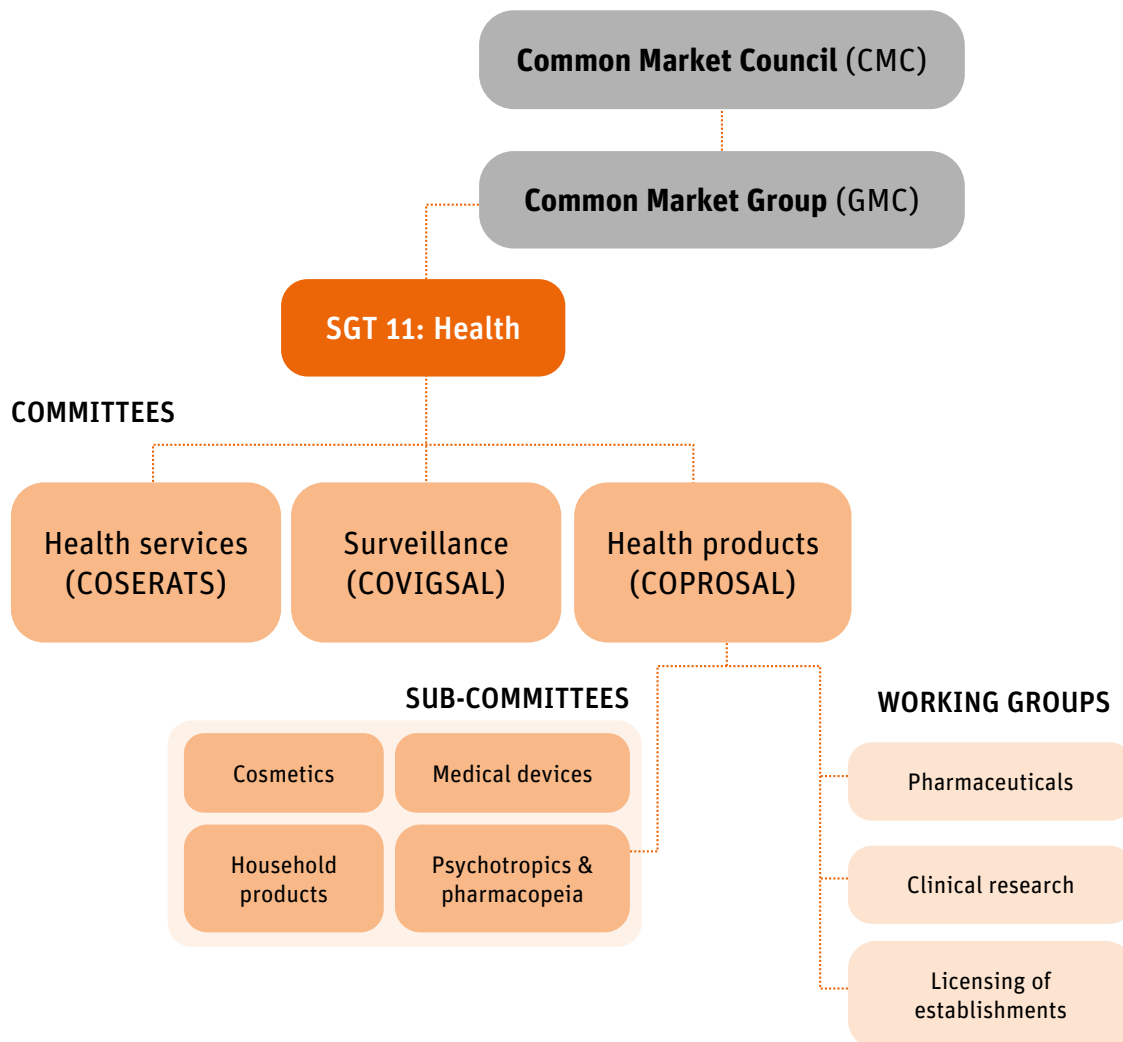
The promise of the Joint Evaluation Mechanism is that it will give manufacturers and importers a single and unified evaluation with accelerated timelines for accessing regional markets. It will also afford NRAs the opportunity to build technical expertise and reduce inter-country asymmetries in registration, while accelerating access to critical medicines evaluated by the mechanism. Yet there are challenges too, including those frequently encountered in regional initiatives around sovereignty and varying needs and capacities of member countries. Stakeholders require a significant amount of sensitization to adopt new processes and ways of doing things, and there remains the need for sustained and predictable leadership to drive implementation across governments. Other issues may have to be addressed as well. For example, the scope of the Joint Evaluation Mechanism does not currently extend to products beyond pharmaceuticals, and the mechanism does not currently incorporate the use of reliance. Lessons learned from other regional integration mechanisms can be incorporated, such as the value of improving access to publicly available information about the mechanism, including procedures, fees, timelines, and participating countries (e.g., via website), as has been done in the CARICOM mechanism.

8.2.3. MERCOSUR

Established in 1991, MERCOSUR is a regional integration mechanism with four member countries: Argentina, Brazil, Paraguay, and Uruguay. These countries vary significantly in terms of size, market, and industrial development, but together they are home to more than 295 million people and make up the fifth largest economy of the world (112). The bloc identifies international cooperation as a priority at all operating levels and supports cooperation in several areas of development, including health, education, environment, gender, and trade.

MERCOSUR has a long history of aligning its regulatory systems to improve operational efficiencies and effectiveness. Since 1996, the bloc has included a subgroup (Subgroup 11, SGT 11) that is in charge of harmonizing national health regulations and increasing the compatibility of health systems across member countries. The subgroup manages three areas of work: health products, surveillance, and health services. It does this through a combination of committees, sub-committees, and working groups (see Figure 8.5). The committee for health products (COPROSAL) is very active, issuing more than 140 resolutions over the past decade. According to interviewees from Paraguay and Uruguay, COPROSAL’s work is particularly valuable in securing political commitment to develop new regulations. NRAs in these two countries lack administrative autonomy and depend on the MoH to issue new norms. In this context, COPROSAL resolutions offer a high-level vehicle for getting new regulations onto the agenda of MoH decisionmakers.

Figure 8.5. Groups and committees responsible for health in MERCOSUR, including harmonization



MERCOSUR successes and challenges

MERCOSUR's activities in regulation include sharing and relying on GMP certificates issued by member NRAs.¹⁴ ANMAT exchanges information with its subregional neighbors and decides which sites to inspect using a risk assessment approach that includes information from their inspection reports. ANVISA exchanges information with Argentina and Uruguay and likewise decides whether to inspect sites based on inspection reports and desk reviews. Experts interviewed for this report said that MERCOSUR's results in this area have been supported by good lines of communication between member NRAs and the development of GMP inspector capacity through knowledge-exchange and joint training.

While the exchange of GMP certificates is acknowledged to have been a MERCOSUR success story, several implementation challenges remain. These include a growing gap in GMP standards between Argentina and Brazil and other members. This makes it increasingly difficult to find the equivalence needed to rely on each other's certificates. It is possible that the gap may widen even more following the recent acceptance of Argentina into PIC/S. Another challenge is training, and while joint training of inspectors has been implemented, training continues to be a resource-intensive activity that is not always adequately financed.

8.2.4. PACIFIC ALLIANCE

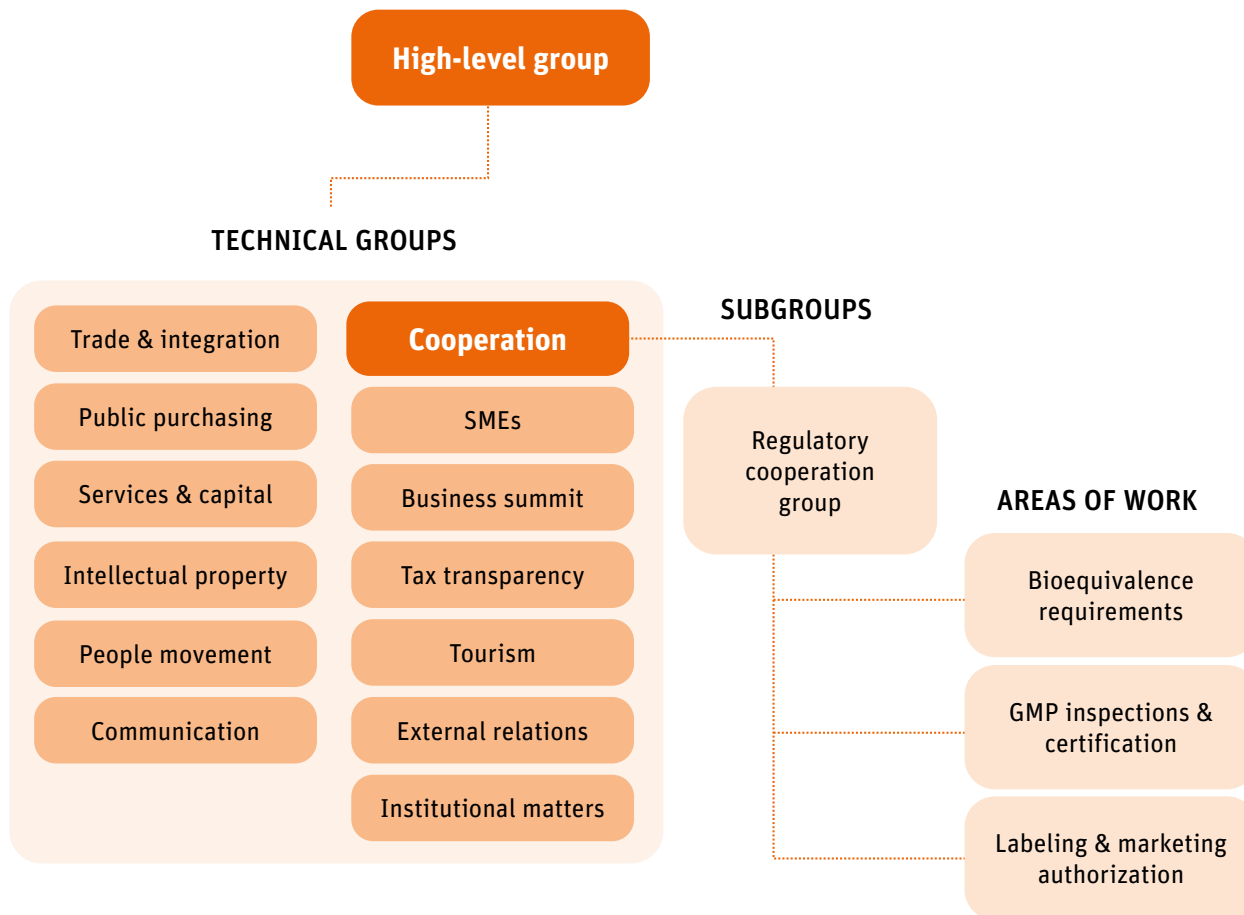
Established in 2011, the Pacific Alliance comprises four members: Chile, Colombia, Mexico, and Peru. These countries vary in terms of size, market, and industrial development, but together they represent more than 225 million people and are the eighth largest economy in the world (113). The Pacific Alliance covers 38% of Latin America's GDP and 50% of the Region's total trade. The bloc promotes free trade and aims to drive economic growth, development, and competitiveness by forging strong economic ties with the Asia-Pacific region and making better use of existing bilateral agreements. Like MERCOSUR, the Pacific Alliance is home to countries with very different regulatory capacities and standards for pharmaceuticals.

Pacific Alliance successes and challenges

The Pacific Alliance's approach to pharmaceutical regulation is marked by joint decision-making. A regulatory cooperation subgroup, managed by the technical working group on cooperation and made up by regulatory staff from all four member countries, was responsible for setting the current agenda on pharmaceutical regulation (see Figure 8.6).

¹⁴ Shared GMP inspection criteria are implemented through GMC Resolution No. 20/17, which contemplates common procedures for inspections of manufacturers. Likewise, GMC Resolution No. 22/17 contemplates the Common Procedures for Inspections in Pharmaceutical Establishments and Minimum Content of Inspection Acts in the area of medicines.

Figure 8.6. Entities of the Pacific Alliance responsible for regulatory issues



The subgroup selected which issues to work on by consensus, based on what was seen to represent the biggest barriers to trade and what was most likely to illustrate the value of regulatory cooperation. The business sector had a leading role in the negotiations (and later in implementing pilot projects). In the end, the subgroup identified two priority areas of work: bioequivalence requirements for generic products, and GMP certification and inspections. Pilot projects to implement reliance in each of these areas were established.

Interviewees for this report agree that the pilot project on GMP reliance was a success. NRAs signed an inter-institutional agreement not only to rely on partners’ GMP inspection records but also to establish equivalences across national standards. They began by comparing how things were done in each country and identifying where and how standards and procedures overlapped. Then they implemented reliance as and where appropriate, starting with GMP certification renewals and gradually expanding to include new GMP inspections. During the project, INVIMA granted 20 GMP certificates to Mexican manufacturing facilities based on COFEPRIS inspection records. COFEPRIS did the same for 18 Colombian manufacturing facilities inspected by INVIMA. The pilot project on bioequivalence was not as successful and ultimately was unable to overcome the differences in national regulations that exist within the alliance.

Despite the success of the GMP reliance pilot project, the project has faced several challenges, including limited participation and variable standards. The four member countries remain willing to cooperate, but their continued differences in regulatory capacity and GMP standards pose a significant hurdle to harmonization. Similarly, differences in national regulations have been identified as barriers to reliance in the bioequivalence requirements

within the alliance. Some countries require bioequivalence for all products; others require it only for specific, high-risk products. This context has raised concerns from some manufacturers, who became worried the cooperation initiative would increase the requirements placed on them and were reluctant to participate.

Recommendations for Action

- **Trade integration mechanisms can facilitate regulatory strengthening.** While there are significant challenges, there are also opportunities to improve and increase the number of regulatory activities within the Region's integration mechanisms.
- **Provide sustained support and strong leadership to regulatory strengthening activities in trade integration mechanisms.** To become effective and significantly support further regulatory strengthening in the different regions and subregions, these integration mechanisms need continued and strong political support and leadership.
- **Improve efficiencies.** Opportunities to increase efficiencies (e.g., implementing and/or improving the use of reliance, electronic platforms, promoting and funding training) should be identified and embraced within the Region's integration mechanisms.
- **Analyze regulatory successes, best practices, and barriers in integration mechanisms and implement corrective actions.** Some mechanisms may need to address differing regulatory standards to further cement regulatory activities and reliance. Other mechanisms may need to add an economic development/trade rationale to further cement regulatory activities.

POSTSCRIPT

9. REGULATORY EMERGENCY RESPONSE TO THE COVID-19 PANDEMIC IN THE AMERICAS

9.1. Foundations of NRA Involvement in Emergencies

PAHO started this regulatory landscape report before the start of the coronavirus disease 2019 (COVID-19) pandemic, and it was planned to address regulatory-related topics under ordinary circumstances. The report would be incomplete, however, if it did not address measures taken during the current and unprecedented public health emergency. Thus, this section supplements the original report and describes salient regulatory emergency responses to the COVID-19 pandemic in the Americas.

Regulatory systems for medicines and other health technologies play an essential role in health systems, including public health emergencies. Yet in some countries, the regulatory system for medicines is not equipped to respond during public health emergencies and/or is not well integrated into the national emergency response. The ongoing COVID-19 pandemic has provided an opening to critically analyze the need and the value of these systems in emergencies, to assess their strengths, and to identify opportunities for improvement in the Americas.

9.1.1. LEGAL AND ORGANIZATIONAL FRAMEWORKS

Strengthening national and global capacities to detect, prepare for, and respond to epidemic and pandemic diseases has been a topic of at least nine World Health Assembly resolutions since the founding of WHO (114). Those topics were brought to the forefront of international concern by the emergence of severe acute respiratory syndrome (SARS), which in 2003 was the first “public health emergency” of the 21st century. It led to significant revisions of the International Health Regulations (IHR) that were first adopted as an international treaty among all WHO Members in 1969. Importantly, recent revisions included State Party obligations to develop certain minimum core public health capacities. Another WHO Member State-led process was also spurred by the growing concern of a possible influenza A (H5N1) pandemic. The high cost of needed vaccines and their anticipated limited supply were cause for great concern by developing countries that queried why they should share viruses with a system that provided nothing in return. The process culminated in the adoption of the Pandemic Influenza Preparedness (PIP) Framework. For these two WHO initiatives, preparedness was considered both the driver and the desired outcome.

Although the PIP framework was developed as a unique tool to promote global action to prepare for pandemic influenza, a number of its elements would be also applicable to similar situations, like the current COVID-19 pandemic. The complex multisectoral “path” under the PIP framework starts at the time of the detection of a new influenza virus and culminates with the protection of the global community. Regulatory capacity-building is one of the four groups of activities selected as priorities for implementation of the PIP framework. Indeed, in a pandemic,

a specific vaccine or new treatment will have to be developed and rapidly produced to vaccinate or treat people against the new pathogen. Such a vaccine or treatment, like all medicines, will have to be assessed for quality, safety, and efficacy and approved for use. However, the regulatory assessment process during a pandemic will need to be expedited, as countries receiving those products are responsible for the safety of their citizens and must make very quick decisions.

Some regional data on legal and organizational frameworks related with NRA involvement in emergencies in the Americas can be obtained from PIP-related activities to date. In the PIP 2018 annual report, WHO referred to a survey of countries on key areas of implementation (115). The survey found that globally, 88% of countries (92/104) had a national pandemic influenza plan, though only 40% (42/104) had tested their plans through simulation exercises in the past five years. In the Americas, 94% (15/16) of countries said that they had a national pandemic influenza plan but only 31% (5/16) had tested it recently. Self-assessed scores on systems capacity such as surveillance, investigation, and assessment and health services and clinical management were in the 60%–70% range. However, preventing illness in the community through pharmaceutical and nonpharmaceutical interventions received a relatively lower score at 51.5%. Within that category, some scores were even lower. In fact, only 19% (19/104) of the countries would consider using the WHO Collaborative Procedure for registration of a prequalified vaccine, and just 26% (27/104) would consider using a generic emergency pathway for a drug or biologic. This is important, as these may be critical pathways for ensuring access to COVID-19 vaccines to the population. Thirty-nine countries (38%) globally, and 6/16 in the Americas, mentioned that they did not have a plan to ensure the availability of essential medicines, medical supplies and devices during an influenza pandemic. However, 37 of these countries intended to develop a plan, of which 26 countries (25%; regional range 0%–54%) anticipate a need for technical assistance. Of the 65 countries with a plan to ensure the availability of essential medicines, medical supplies and devices during an influenza pandemic, 55 (84%) had a plan that addresses the roles and responsibilities of the NRA for medicines and health products. The above data clearly suggest that there is room for improvement.

The newly developed WHO Global Benchmarking Tool (GBT) offers an important framework to improve response to epidemics and pandemics by enabling understanding of the legal and organizational capacity of NRA emergency response capacity. The comprehensive set of GBT indicators covering market authorization, inspections, pharmacovigilance, and other product regulatory oversight functions includes indicators that are specifically related to activities in situations of emergencies throughout the entire instrument. Although GBT assessment data from specific countries are not yet available, the indicators themselves are helpful in showing what should be in place, and can be used as a reference for countries going forward. With its implementation and as the GBT becomes increasingly administered in the Americas, it will begin to generate the data needed to understand which of these policies and processes are in place, and which may need further strengthening. Table 9.1 shows the emergency-related capacities and references the specific indicator and the maturity level (ML), with ML1 being the most foundational capacity and ML4 the most advanced.

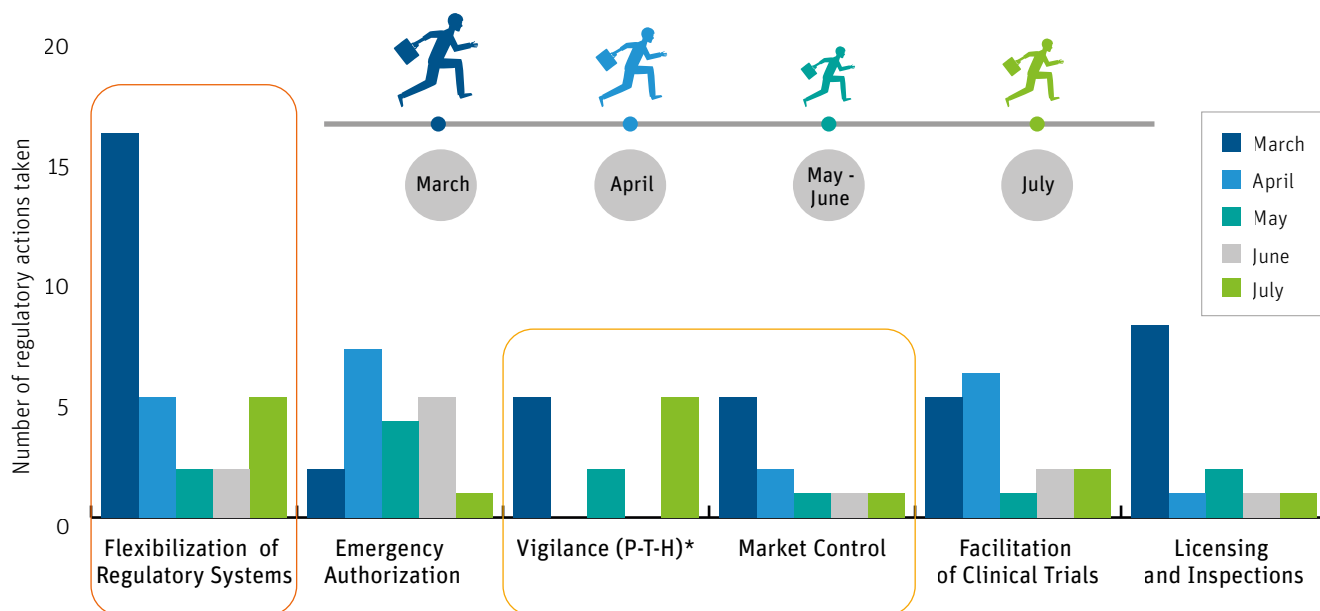
Table 9.1. Emergency-related indicators in WHO GBT

| |
|---|
| <ul style="list-style-type: none"> • Are there written criteria to explain circumstances and procedures for how regulatory activities should be conducted in an emergency? (GBT indicator RS4.05, ML3) |
| <ul style="list-style-type: none"> • Are there legal provisions to cover circumstances under which the routine market authorization procedures may not be followed in an emergency (e.g., is there an Emergency Use Authorization procedure or equivalent)? (GBT indicator MA1.06, ML1) |
| <ul style="list-style-type: none"> • Are there legal provisions or regulations that define regulatory requirements and procedures to approve the use of donations of medical products? (GBT indicator MA01.07, ML1) |
| <ul style="list-style-type: none"> • Are there legal provisions or regulations related to circumstances in which the routine clinical trials regulation procedures may not be followed in an emergency? (GBT indicator CTO1.05, ML2) |
| <ul style="list-style-type: none"> • Are there legal provisions and regulations that allow the NRA to require manufacturers and/or MAHs to conduct specific studies on product safety and effectiveness under specific conditions (e.g., public health emergency)? (GBT indicator VLO1.04 , ML2) |
| <ul style="list-style-type: none"> • Are there well-documented procedures and implemented mechanisms to ensure the involvement, coordination, and communication among all stakeholders relevant to vigilance activities (e.g., AEFI surveillance by EPI and NRAs)? (GBT indicator VLO2.02, ML3) |

9.2. NRA Emergency Response in Practice – Initial Actions

This section is based on information, challenges, lessons learned, and best practices shared at the regular PAHO NRA emergency forum to discuss critical COVID-19 response topics that started in March 2020. The section is also informed by press releases and other communications made by individual NRAs during the pandemic, which were collated by PAHO. These data show that Latin American NRAs implemented emergency regulatory measures across a variety of domains and took many actions very early in the pandemic (see Figure 9.1). These actions align with three key areas that are discussed below.

Figure 9.1. Latin American NRA regulatory trends overview from March to July 2020



Notes: * P-T-H: Pharmacovigilance, technovigilance, and hemovigilance. The figure shows the areas in which regulatory actions are categorized. Each bar represents a month and despite the fact that regulatory actions are usually sustained over time, this helps to visualize where efforts are concentrated. Most of the regulatory actions focus on the relaxation of regulatory requirements. Areas such as market surveillance and control are those that have had less prominence. It can also be observed that most of the regulatory actions were taken in March and that in July there is an increase in the measures related to surveillance.

Source: Analysis performed using the regulatory actions shared by NRAs with PAHO through a common repository established during the emergency in the Regional Platform on Access and Innovation for Health Technologies (PRAIS).

9.2.1. IDENTIFICATION OF ESSENTIAL HEALTH PRODUCTS TO MANAGE THE COVID-19 PANDEMIC

All Latin American NRAr have made available on their websites lists of the products needed for COVID-19, including medicines (e.g., antibiotics, corticoids), personal protective equipment (PPE), and medical devices (e.g., mechanical ventilators). Doing this provided an important focus to efforts.

9.2.2. FLEXIBILITY OF REGULATORY REQUIREMENTS

To help ensure availability of the listed essential products, Latin American NRAr have prioritized evaluation and approval processes using flexible mechanisms including implementation of Emergency Use Authorizations (EUA) and/or Compassionate Use Authorizations. Some examples of this are the authorization of compassionate use of chloroquine in critically ill COVID-19 patients by ANVISA (116); and the emergency use authorization by CECMED of Jusvinza (CIGB 258), an immunomodulatory synthetic peptide for hyper-inflammation in COVID-19 patients (117).

Another measure was implemented by INVIMA with the extension of procedures for products considered “vitales no disponibles” (vital but unavailable) to include other products, particularly medical devices. This type of essential health product does not have to go through the regular marketing authorization process in case of emergency, provided there is already enough information on quality, safety, and efficacy, which usually comes from evaluation and approval elsewhere. Other Latin American NRAr have extended renewals and validity of authorizations, certificates, and licenses for products and/or manufacturers, importers, and distributors. The majority of exemptions and abbreviated procedures were related to PPE and diagnostic products. Measures included exemptions in compliance with labeling and insert of packages, or with the verification of documents, as well as acceptance of incomplete applications (e.g., with pending laboratory analysis documents). Other authorities like CECMED and COFEPRIS have prioritized import procedures as well.

Latin American NRAr also increased flexibility around physical documentation requirements. They established virtual communication channels to expedite submissions and, for example, both ANMAT and INVIMA enabled remote processing platforms, which allowed INVIMA to reduce procedures to import COVID-19 products from six days to one business day.

9.2.3. MARKET CONTROL TO AVOID RISKS OF SHORTAGES AND PROMOTE RATIONAL USE

ANVISA and ANMAT urged companies to report any identified risk of shortage from the listed essential products. Other requirements involved increasing the manufacturing and distribution capacity of these products and providing timely reports on the quantity of traded goods and their recipients. In some cases, and to prevent shortages, companies were also mandated to request authorization from the NRAr prior to export of essential COVID-19 related products. Several authorities, like ANVISA and ISP, also modified the sales conditions of selected medicines in pharmacies, like hydroxychloroquine and antibiotics such as azithromycin, requiring medical prescriptions to dispense these products in order to avoid stockouts that could affect patients in need of the treatment for other medical conditions. All of these measures have been accompanied by a call to promote the rational use of medicines, PPE, and other medicines and health technologies.

9.3. NRA Emergency Response in Practice by Key Regulatory Function

Actions continued to be taken throughout the pandemic, when by August 2020, Latin America had become the region with more COVID-19 confirmed cases than anywhere else in the world (118). The following is a summary by key topic categories.

9.3.1. PHARMACOVIGILANCE, TECHNOVIGILANCE, AND HEMOVIGILANCE

Latin American NRAs took important actions related to PV and market control. Examples include the publication of guidelines for adverse event reporting in relation to plasma transfusions by ANVISA; the development of guidelines for the monitoring of adverse events in patients with COVID-19 under treatment with chloroquine or hydroxychloroquine by ISP; the establishment of active surveillance activities for medicines and medical devices targeted for the treatment, prevention, and diagnosis of COVID-19 by CECMED; and the provision of safety information to the population on tocilizumab and chlorine dioxide by COFEPRIS. It is important to mention that, together with the measures related to “vitales no disponibles” taken by INVIMA, there was a call to strengthen vigilance activities, requiring importers to provide pertinent information regarding the traceability of products, and to report any adverse events according to the country’s pharmacovigilance, technovigilance, and reagents surveillance programs.

9.3.2. CLINICAL TRIALS

Prioritization of clinical trials related procedures was a common trend among regulatory authorities in the Region and aimed to accelerate the approval of investigation protocols. Examples of clinical trial regulatory actions include the creation of an Evaluation Committee for Clinical Studies, Registration, and Post-Registration of Medicines that analyzes requests in 72 hours by ANVISA; and a similar action by INVIMA where investigation protocols are to be evaluated in only five business days. Such actions came together with the publication of guidelines and technical communications to orient sponsors and researchers regarding the requirements for clinical trials related to COVID-19, like the issuance of special provisions for participation in clinical studies for institutions in the country that are not certified in good clinical practices (GCP) by INVIMA. One important measure by ISP relates to access during lockdown to research facilities and/or to treatment of study subjects. The guideline developed includes the following: 1) facilitating patient access to study centers by allowing sponsors to pay for transportation; 2) allowing additional treatment supplies when needed due to mobility restriction; 3) ensuring the delivery of treatments through transport services and coordination with pharmacies and drug stores near patients’ homes; 4) referral of study patients to other centers where the same study is being carried out and which are located in more accessible areas; and 5) assisting patients via remote monitoring or directly in their homes.

9.3.3. LICENSING AND REGULATORY INSPECTIONS

NRAs have increasingly used reliance for the GMP inspection function during the COVID-19 pandemic. For instance, INVIMA decided to recognize and validate the inspection reports granting GMP issued by PIC/S agencies in processes related to marketing authorizations, renewals, modifications, and associated procedures of medicines required for the emergency. ANVISA decided to temporarily accept the use of information from foreign regulatory authorities that participate in the MDSAP (Medical Device Single Audit Program), to replace the inspections carried out by the agency. ANVISA and INVIMA have established guidelines and requirements for virtual inspections while onsite international inspections cannot be performed. ANMAT has also started to conduct virtual inspections.

9.4. Challenges

Some of the challenges noted by several NRAs in the Americas, including the Latin American NRA, cut across multiple domains. The demand of switching to 24/7 operations during the pandemic was noted as difficult to sustain, especially when staff are required to be physically present in the building. This has required having a sound employee health plan and a clear strategy to ensure everyone is safe and taking proper precautions. Communications was also identified as very important issue. Many NRAs believe that it is very useful to learn from what the others are doing; however, information sharing between authorities is not always as strong as it could be. PAHO has set up platforms for the publishing of information related to regulatory actions such as the PRAIS website and also hosts the RISE platform for confidential information exchange, but countries stated there is also a need for more bilateral information sharing with memorandums of understanding. The need to identify and tackle false information was also mentioned. As an example, to handle this problem, INVIMA has put in place an immediate response group, which monitors social networks for false information and seeks to provide accurate information to the public on health alerts, negative side effects, and access issues.

9.5. Best Practices and Efficiencies

The ongoing experience with COVID-19 highlights a number of potential best practices and efficiencies for regulatory action during emergencies, even though COVID-19 is unique in terms of its pervasiveness and duration of threat. These best practices and efficiencies appear to include the following:

- **Flexibility in regulations and processes.** Numerous NRA actions point to the need to be flexible in emergencies, including by having up-to-date policies and procedures, such as emergency use authorization and extension of certifications and periods of validity, etc.
- **Virtual strategies.** NRAs have taken advantage of modern modes of communication such as through use of virtual documentation and the conduct of work in virtual formats.
- **Faster timelines.** Faster timelines for regulatory processes are important, and examples include expedited review of clinical trial applications.
- **Prioritized resources for emergency efforts.** Latin American NRA have focused their efforts on 24/7 operations, including prioritization of regulation of emergency-related products.
- **Learning and information sharing.** Agencies continue to learn much from what other agencies are doing, including through information exchange.
- **Communications.** Enhanced communication with stakeholders is an essential aspect of emergency response. This includes communication with the public to provide accurate and up-to-date information, with the industry to understand new developments or potential shortages, with academia to identify much-needed expertise, and with local or international government representatives to coordinate emergency actions.
- **Reduction of duplication of efforts.** The increased use of reliance to respond to the ongoing COVID-19 pandemic is worth carefully considering to increase regulatory efficiency, such as in GMP inspections.

Recommendations

- NRAs should proactively consider the use of the WHO GBT indicators to develop regulations, policies, and procedures that facilitate strong regulatory emergency response.
- NRAs should adopt the best practices and efficiencies noted in this supplement for regulatory emergency response to the greatest extent possible.

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ANNEX 1. ENTITIES RESPONSIBLE FOR THE OVERSIGHT OF CLINICAL TRIALS IN LATIN AMERICAN NRAR

Overview of the entities involved in the authorization and oversight of clinical trials, and their roles in six Latin American markets

| Country | Organization | Role |
|-----------|--|---|
| ARGENTINA | ANMAT – DEM Dirección de Evaluación de Medicamentos | <ul style="list-style-type: none"> - Evaluate the protocol and clinical trial information to issue a recommendation to the National Director of ANMAT to authorize or reject the clinical studies. - GCP inspections. <p>(The evaluation of the documentation of clinical trials is carried out in the Clinical Trials Service, Directorate of Evaluation and Registration of Medicines (DERM), National Institute of Medicines (INAME), ANMAT. This Service has an Evaluation Area, a Security Area, and an Inspection Area.)</p> <ul style="list-style-type: none"> - Receive adverse events reports (for those medicines that are not being commercialized, would only notify ANMAT's PV system). |
| | IEC (Investigation Ethics Committee – Comité de Ética en Investigación, CEI) | <ul style="list-style-type: none"> - Review and issue an approval document for the clinical trial; this is a requirement that has to be submitted to ANMAT to receive the final approval to start the trial. - Report of adverse events. |
| | ANMAT Federal – Provincial authorities | <ul style="list-style-type: none"> - NRA articulates with the different jurisdictions the activities related to oversight, authorization of health establishments, and approval of ethics committees. These activities are the responsibility of the provincial authorities who will create an entity to perform them. |
| BRAZIL | ANVISA – CONEP (Clinical Research Coordination on Medicines and Biological Products) | <ul style="list-style-type: none"> - Review and approval of clinical trial applications for registered and unregistered drugs. |
| | CEP (Local ethics committees) / CONEP (National ethics committee) | <ul style="list-style-type: none"> - Authorization and supervision of ethics committees. |
| CHILE | ISP – ANAMED | <ul style="list-style-type: none"> - It is the responsibility of ISP to authorize the use of medicines with or without a sanitary record, for the purpose of scientific research and clinical trials after a favorable report from the responsible scientific ethics committee. - GCP inspections. - Serious adverse events reporting and evaluation. |
| | SEREMI (Regional Ministry of Health Secretariats) | <ul style="list-style-type: none"> - Accreditation of scientific ethics committees (or CEC in Spanish). - CEC supervision. |
| | CEC (Scientific ethics committees) | <ul style="list-style-type: none"> - Evaluate the protocols or projects of biomedical scientific research that are submitted for consideration and make an approval report. |

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| COLOMBIA | INVIMA | <ul style="list-style-type: none"> - Research Projects Registry - Project approval - GCP inspections |
| | GIC (Group of Clinic Investigation) | <ul style="list-style-type: none"> - Evaluate the protocol and clinical trial information to issue a recommendation to Directorate of Medicines and Biological Products (DMPB) to authorize or reject the clinical studies. - Scientific ethics committees oversight. |
| | CEI (Institutional ethics committees) | <ul style="list-style-type: none"> - Evaluate the research project, the informed consent form, known information about the drug (including reports of unexpected adverse events), and all publicity planned to get potential participants. |
| CUBA | CECMED | <ul style="list-style-type: none"> - Competent authority to authorize the start and modification of clinical trials, for which the presentation of the trial approval opinion by the CEI is a mandatory requirement. - Responsible for conducting inspection to verify compliance with the GCP of authorized clinical trials. - Certification of sites and clinical establishments, with experience in conducting studies, in which the revision of the CEI with documented evidence of structure, adequate performance and experience in clinical trials is included as a mandatory requirement. |
| | MINSAP | <ul style="list-style-type: none"> - The commission of the Directorate of Science and Technological Innovation of MINSAP has the functions of methodologically directing, controlling, and advising the CEI. |
| | CENCEC | <ul style="list-style-type: none"> - The National Clinical Trials Coordinating Center (CENCEC) prepares the CEI in the process of certification of sites and services. This process consists of the diagnostic evaluation of compliance with committee responsibilities, practical theoretical training of members, and implementation of documentary requirements or other actions to ensure their proper functioning. |
| | CEI (Ethics committees) | <ul style="list-style-type: none"> - Evaluate and issue the approval opinion report for the clinical trials. |
| | COFEPRIS | <ul style="list-style-type: none"> - Regulatory authority responsible for approving all clinical studies. - Authorized to monitor and verify approved clinical studies to be conducted in Mexico. |
| MEXICO | CAS (Sanitary Authorization Commission – Comisión de Autorización Sanitaria) | <ul style="list-style-type: none"> - One of COFEPRIS administrative units and central to the research protocol authorization process. - Responsible for issuing, extending, or revoking clinical research authorizations. |
| | UHAP (Enabled Pre-Assessment Support Unit – Unidad Habilitada de Apoyo al Predictamen) | <ul style="list-style-type: none"> - Performs pre-assessment evaluation of the clinical protocols, required before the submission in NRA. |

CONBIOÉTICA (National Bioethics Commission – Comisión Nacional de Bioética)

- Decentralized entity of the Secretariat of Health.
- Has technical and operational autonomy in defining and establishing national bioethics policies in medical care and health research.
- Responsible for promoting the organization and operation of research ethics committees (RECs) and hospital bioethics committees (comités hospitalarios de bioética – CHBs) in public and private health institutions.
- Establish and disseminate criteria to support development of REC activities.
- Provide committee member training support.
- REC, BC, CHB must be registered in CONBIOÉTICA (registration valid for 3 years).

REC (Research ethics committees) & BC (Biosafety committees)

- Must assess and approve the research protocol at the beginning of the project and periodically throughout the project's duration.
- RECs and BCs' (when applicable) favorable decision is then submitted to COFEPRIS as part of the application to get the protocol authorization.

Sources:

PAHO assessments.

<https://clinregs.niaid.nih.gov/>

Data collected by PAHO using the following methodology: Each LA NRAR identified a focal point for this report. PAHO developed an instrument with the data requested, the instrument was filled by the LA NRAR focal point, followed by a phone interview/email communication to validate the data included in the report. Two rounds of data validation were performed. The investigation and analysis were conducted from March 2019 to October 2020.

Improving access to safe, effective, and quality medicines and other health technologies is a critical public health priority and a fundamental requisite for universal health. National regulatory systems play a key part in a country's health system by overseeing the safety, quality, and efficacy of all health technologies, including pharmaceuticals, vaccines, blood and blood products, and medical devices, among others.

The aim of this document is to better understand the regulatory landscape of the Americas, with an emphasis on Latin American National Regulatory Authorities of Reference. This report presents data and analysis corresponding to essential regulatory functions and systems foundations to understand current practices, identify critical issues, and present a series of recommendations for action. The report also includes an overview of the market outlook and economic integration mechanisms in the Americas and their influence on regulatory policy and pharmaceutical trade. In addition, the report includes a supplement to describe salient regulatory emergency responses to the COVID-19 pandemic in the Americas.

Through this report, the Pan American Health Organization aims to increase the understanding of national regulatory remits and capacity in the Americas, raise awareness and appreciation of the regional regulatory progress and challenges, identify the regulatory issues emerging markets will bring, and highlight opportunities for evidence-based regulatory system strengthening.



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