



REGULATORY RELIANCE PRINCIPLES: CONCEPT NOTE AND RECOMMENDATIONS

Ninth Conference of the Pan
American Network for Drug
Regulatory Harmonization (PANDRH)



San Salvador,
24 to 26 October, 2018

PAHO

PANDRH Pan American Network for Drug Regulatory Harmonization



REGULATORY RELIANCE PRINCIPLES: CONCEPT NOTE AND RECOMMENDATIONS

**Ninth Conference of the Pan American Network for Drug Regulatory
Harmonization (PANDRH)**

San Salvador, 24 to 26 October, 2018

PAHO

PANDRH Pan American Network for Drug Regulatory Harmonization



Washington, D.C., 2019

REGULATORY RELIANCE PRINCIPLES:
CONCEPT NOTE AND RECOMMENDATIONS

Ninth Conference of the Pan American Network for Drug Regulatory
Harmonization (PANDRH)
(San Salvador, 24 to 26 October, 2018)

PAHO/HSS/19-003

© Pan American Health Organization 2019

All rights reserved. Publications of the Pan American Health Organization (PAHO) are available at www.paho.org. Requests for permission to reproduce or translate PAHO Publications should be addressed to the Publications Program through the website (www.paho.org/permissions).

Suggested citation. Pan American Health Organization. Regulatory Reliance Principles: Concept note and recommendations. Ninth Conference of the Pan American Network for Drug Regulatory Harmonization (PANDRH). (San Salvador, 24 to 26 October, 2018). Washington, D.C.: PAHO; 2019.

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

Publications of the Pan American Health Organization enjoy copyright protection in accordance with the provisions of Protocol 2 of the Universal Copyright Convention.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of PAHO concerning the status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by PAHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by PAHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall PAHO be liable for damages arising from its use.

CONTENTS

Acknowledgment	5
Acronyms	6
Summary	7
Background	7
Key concepts and definitions	8
Principles and critical elements to guide reliance activities	10
Reliance in practice	12
PANDRH recommendations	14

ACKNOWLEDGMENT

This document of the Pan American Network for the Drug Regulatory Harmonization (PANDRH) was coordinated by Analía Porrás, unit chief of the Medicines and Health Technologies unit of the Pan American Health Organization/World Health Organization (PAHO/WHO).

PAHO/WHO, as PANDRH's secretariat, thanks all PANRH members who contributed their technical knowledge during the discussion of this document in the framework of the Ninth PANDRH Conference. Special thanks are given to the collaboration of the National Regulatory Authorities of Brazil (ANVISA), Colombia (INVIMA), and Ecuador (ARCSA) and members of the Network who have voluntarily contributed with the technical revision of this work.

Likewise, the contribution of the following professionals of the Unit of Medicines and Health Technologies of PAHO/WHO that facilitated the execution and consolidation of the information, translation and edition of this work is acknowledged: Murilo Freitas, Fernanda Lessa, José Daniel Peña, María Luz Pombo, and Charles Preston.

ACRONYMS

CARICOM	Caribbean Community
CRS	Caribbean Regulatory System
EU	European Union
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
MDSAP	Medical Device Single Audit Program
NRA	National Regulatory Authority
PAHO	Pan American Health Organization
PANDRH	Pan American Network for Drug Regulatory Harmonization
PICs	Pharmaceutical Inspection Co-operation Schemes
WHO	World Health Organization

SUMMARY

The aim of this document is to outline key examples and principles for the practice of regulatory reliance. Its rationale is multifold: (a) it follows on previous discussions at the 2016 Conference of the Pan American Network for Drug Regulatory Harmonization (PANDRH)¹, and (b) it fulfills a recommendation by the Conference that requested PAHO to develop a concept paper on reliance for PANDRH stakeholders to consider for endorsement.

This concept paper builds on a presentation that was made at the 2016 Conference and integrates global thinking on the subject, including a recent document by the World Health Organization (WHO)².

The overarching goal is to ensure that PANDRH stakeholders continue to build understanding around reliance in ways that can better inform scenarios for its use.

BACKGROUND

Strengthening regulatory systems for medicines and other health technologies remains a critical priority for well-functioning health systems that want to achieve Universal Health. Regulatory systems can contribute to a country's social and economic development by supporting the medical products manufacturing sector. It is widely recognized, however, that regulatory systems can be very resource intensive. Establishing and sustaining mature regulatory systems is a high resourced enterprise that requires skilled human resources and large public investments among others. Moreover, the globalization of health technologies markets has pushed regulatory systems to act internationally to ensure the safety, quality and effectiveness of the products that are consumed locally. A seminal Institute of Medicine report stated that “the integrated global economy demands cooperation across borders... (so) that our food and medical products are safe and effective.”³ Thus, countries need to consider the merits of strategies to strengthen regulatory systems and that may help gain efficiencies and effectiveness.

While harmonization and convergence have been pursued for many years by international initiatives, the use of reliance is an emerging trend as a strategy to bring efficiencies to regulatory systems and of interest for regulatory systems strengthening. Thus, regulatory reliance merits an in-depth analysis that can shed light

1 VIII Conference of the Pan American Network for Drug Regulatory Harmonization (PANDRH): Recommendations and next steps. PAHO; 2016 Oct 21. Available from <https://www.paho.org/hq/dmdocuments/2016/viii-cpandrh-recommendations.pdf>

2 WHO Drug Information Vol. 30, No. 4, 2016. Collaboration, not competition: developing new reliance models. Available from: <http://apps.who.int/medicinedocs/documents/s23135en/s23135en.pdf>

3 Committee on Strengthening Core Elements of Regulatory Systems in Developing Countries; Board on Global Health; Board on Health Sciences Policy; Institute of Medicine; Riviere JE, Buckley GJ, editors. Ensuring Safe Foods and Medical Products Through Stronger Regulatory Systems Abroad. Washington (DC): National Academies Press (US); 2012 Apr 4. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK201164/> doi: 10.17226/13296

on the concept, the operational implications and implementation models. This document aims at presenting the overarching principles under which regulatory reliance should operate to ensure that it represents a positive tool for regulatory systems’ strengthening and has a positive impact on national health systems.

KEY CONCEPTS AND DEFINITIONS

For clarity in the discussion, it is important to define harmonization, convergence and reliance and other related terms. The following should not be considered formal definitions, but rather working definitions for the purpose of this document and for PANDRH-related activities.

In the context of regulation of medicines and other health technologies, harmonization “represents the development and adoption of the same standards or requirements. Harmonization may also be applied to procedures and practices, so they are the same across economies. Harmonization represents an important means for achieving regulatory convergence over time, as does the adoption of common procedures and practices.”⁴ It has also been defined as “the process by which technical guidelines are developed to be uniform across participating authorities.”⁵ Harmonization initiatives focus on working towards adopting common processes/standards. The International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) remains the most notable and influential international harmonization initiative and brings together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. In the ICH case, “harmonisation is achieved through the development of ICH Guidelines via a process of scientific consensus with regulatory and industry experts working side-by-side. Key to the success of this process is the commitment of the ICH regulators to implement the final Guidelines.”⁶ Undoubtedly, harmonization represents the strongest assurance that the same medical product receives the same regulatory consideration and oversight across different countries, a clear advantage to both industry and regulatory bodies that agree to cooperate. Similar standards and processes create predictable and consistent environments for companies, decreasing regulatory burden and speeding access to markets and access for patients. Yet, achieving regulatory harmonization is very laborious since this strategy relies in agreeing on a common standard that needs to work across countries with different legal frameworks and health systems.

4 Strategic Development Plan 2014–2020 of the Pan American Network for Drug Regulatory Harmonization (PANDRH). Washington, D.C. July 2014, PANDRH Series - Technical Document No. 14. Available from: <https://www.paho.org/hq/dmdocuments/2015/drug-harmonization-Strategic-Plan-PANDRH-04-20-2015.pdf>

5 Regulatory Harmonization and Convergence. U.S. Food & Drug Administration. Available from: <https://www.fda.gov/biologicsbloodvaccines/internationalactivities/ucm271079.htm>

6 Harmonisation for Better Health. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Available from <http://www.ich.org/about/mission.html>

Regulatory convergence, “represents a voluntary process whereby regulatory requirements across economies become more uniform, or “aligned,” over time, as a result of the gradual adoption of internationally recognized technical guidance documents, standards, and scientific principles (harmonization), and common or similar practices and procedures. It does not represent the harmonization of laws and regulations, which is not necessary to allow for the alignment of technical requirements and for greater regulatory cooperation.”⁷ It involves instances where regulatory authorities work towards adopting processes and standards that align under the same scientific principles to yield similar outcomes but use context-specific processes that are not harmonized across systems. Convergence is generally gradual and focuses less on the adoption of identical pathways but more on achieving the same outcomes using similar—and not identical—regulatory requirements. PANDRH’s 2014-2020 strategic plan recognized the need to foster convergence amongst regional national regulatory authorities (NRA): Recognizing the “NRAs installed capacity at the regional level, and a shift toward a new regional paradigm that involves multiple integration mechanisms with different levels of participation by the countries and with different political, economic and strategic directions, it has become necessary to refocus PANDRH’s main mission towards the promotion of regional regulatory convergence.” It goes on to state that “regulatory convergence requires stepping up the cooperation between the countries and the NRAs for developing regulatory systems, sharing experiences and information on health regulatory processes, and designing training programs for the NRAs.” Thus, convergence is regarded as a mean to strengthening regulatory capacities and improving coherence across regulatory systems since consistency enables sharing of information and other collaborative approaches.

Lately, regulatory reliance has taken center stage in the discussions on how to improve regulatory capacities and efficiencies. According to WHO, reliance is, “the act whereby the NRA in one jurisdiction may consider 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.”⁸ Reliance implies “that the work done is shared by the trusted authority (e.g. through assessment or inspection reports), while the receiving authority uses this work according to its own scientific knowledge and regulatory procedures and retains its own regulatory responsibilities.”⁹ Thus, NRAs that adopt regulatory reliance pathways leverage the work performed by other regulatory bodies to a variable degree: an NRA may rely fully or partially on a process and/or decision of another entity and implies the use of regulatory decisions/information produced by another party (other NRA, third-party auditor, pre-qualifications, to name a few examples) as the basis for own regulatory decisions.

Regulatory reliance has been gaining popularity since it is regarded as a strategy for conserving resources by avoiding duplication and for improving allocation of resources where these are limited. Moreover, reliance

7 Strategic Development Plan 2014-2020 of the Pan American Network for Drug Regulatory Harmonization (PANDRH). Washington, D.C. July 2014, PANDRH Series - Technical Document No.14. Available from: <https://www.paho.org/hq/dmdocuments/2015/drug-harmonization-Strategic-Plan-PANDRH-04-20-2015.pdf>

8 World Health Organization. Good regulatory practices: 5 guidelines for national regulatory authorities for medical products. Oct 2016. Available from: http://www.who.int/medicines/areas/quality_safety/quality_assurance/GoodRegulatory_PracticesPublicConsult.pdf

9 WHO Drug Information Vol. 30, No. 4, 2016. Collaboration, not competition: developing new reliance models. Available from: <http://apps.who.int/medicinedocs/documents/s23135en/s23135en.pdf>

can help create more efficient regulatory authorities by focusing on priorities that can be done locally and leveraging what can be done by others or, in other occasions, distributing or sharing responsibilities amongst a group working together.

For this discussion, recognition is considered a form of reliance. WHO defines recognition as “the routine acceptance by the NRA in one jurisdiction of the regulatory decision of another NRA or other trusted institution. Recognition indicates that evidence of conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B. Recognition may be unilateral or multilateral and may be the subject of a mutual recognition agreement”. Recognition implies the acceptance of regulatory result/decision from another NRA based on a legal framework and can be mutual or unilateral. As stated by WHO “forms of cooperation such as mutual recognition agreements, which require establishment of a strong legal framework, are desirable and should be implemented whenever possible. However, they take a long time to set up, as the regulatory systems involved need to be mutually assessed and shown to be equivalent before implementation.”¹⁰ Alternatively, a country may choose to recognize the regulatory decision from another country unilaterally without reciprocity.

PRINCIPLES AND CRITICAL ELEMENTS TO GUIDE RELIANCE ACTIVITIES

When an NRA is confronted with the decision to adopt regulatory reliance practices, it should consider the alternatives in the context of the needs and characteristics of the national health system and regulatory system. Considering existing capacities, regulatory systems’ needs and how reliance can complement these capacities to drive efficiencies should be the basis for decision making on adopting reliance. Note that lack of resources or weaknesses should not be the exclusive drivers for reliance. Indeed, reliance should not be used only in limited resources settings; instead, reliance is a strategy that requires seeking a better use of resources. Moreover, reliance practices should not be limited to low capacity systems but should be considered as a good strategy to improve capacities in all a wide range of regulatory settings. In summary, while reliance may offer more clear advantages to developing regulatory systems, it is a strategy that should be considered for any regulatory body in search of efficiencies.

Recognizing the diversity of forms and settings in which reliance may be used by NRA, establishing the general and universal principles under which reliance should operate should help to guide and inform decision making by national regulatory authorities that are contemplating adopting reliance practices:

¹⁰ WHO Drug Information Vol. 30, No. 4, 2016. Collaboration, not competition: developing new reliance models. Available from: <http://apps.who.int/medicinedocs/documents/s23135en/s23135en.pdf>

Sovereignty: Reliance should be a sovereign decision. National authorities should decide if they want to use reliance, on whom they are going to rely and how.

Transparency: Reliance processes should be transparent regarding standards and processes. In addition, the basis/rationale for relying on a specific entity should be disclosed and understood by all parties.

Consistency: Reliance on a specific process/evaluation/ decision should be established for specific and well-defined category of products/ practices and should as well be predictable. Thus, it is expected that reliance shall be applied consistently for all products/practices in the same predetermined category.

Legal basis: Reliance should be coherent with national legal frameworks and supported by clear mandates/regulations that aim at the efficient implementation. Adoption of these legal frameworks should not detract from the efficiencies gained by reliance.

Competency: Reliance requires that national authorities build the necessary competencies for critical decision making for proper implementation. In most cases, they need to have a number of critical tools for implementation, whether information sharing arrangements or information platforms among others. Conversely, authorities being relied on should have and maintain competencies and performance in the given area and prove the use of internationally accepted standards. The competencies should be bench-marked by transparent processes that develop trust on the capacities of these reference authorities

Following these principles, reliance strategies can be tailored as needed to the needs of the national health and regulatory system. Under this framework, reliance can become a well-regarded practice that is based on clear understanding/knowledge of trusted source and that improves the efficiencies of the regulatory system rather than the mere outsourcing of regulatory processes. Furthermore, national regulatory authorities may choose to rely on others during special circumstances such as national health emergencies or as part of their routine regulatory oversight. Whatever the approach, the national authority needs to consider its own capacities and establish clear goals when adopting reliance. Moreover, it should determine political and technical feasibility and how to build and maintain trust of public and other stakeholders by communicating the advantages and any potential risks. While the national authorities need use reliance in a consistent manner, it should use caution on opening the door to entry of product to their markets that may not be of public health interest. Rather, reliance must promote the timely availability of products that can improve access to quality medicines and other health technologies according to the public health priorities of national health systems.

RELIANCE IN PRACTICE

Regulatory reliance can take many forms and encompasses a broad array of regulatory practices that can involve two or more regulatory bodies or authorized third parties. In addition, it can be limited to a discreet regulatory process or function or include the entire life cycle of a medical product.

There are many examples around the globe as well as in the Region of the Americas that illustrate current use of reliance and the diverse models in which NRA leverage the work done by others. In some cases, reliance is supported by harmonized processes or standards. As mentioned before, harmonization of requirements and regulatory processes is generally considered a very onerous process. Having harmonized requirements, however, facilitates the use of reliance between two or more regulatory authorities that leverage each other processes and/or decisions and eventually, enhance the efficiencies of the NRA involved. For example, harmonized standards act as facilitators of work sharing (regulatory authorities join forces in the field to perform processes) and other forms of reliance since identical standards guide regulatory processes. The European Union (EU) system is a clear example of international regulatory cooperation and its multiple regulatory pathways depend heavily on work sharing, recognition and other forms of reliance: “The various routes to medicines approval in the EU system are based on a single assessment system so that any assessment report from any of the agencies in the EU network can be used as a basis for reliance by other regulators.”¹¹ Arguably, a strong and common legal framework and harmonized regulatory standards shared among all EU countries are an intricate part and necessary for regulatory reliance.

A more recent example is the Medical Device Single Audit Program (MDSAP)¹² created in 2012. MDSAP is a groundbreaking and innovative use of regulatory reliance. MDSAP recognizes “Auditing Organizations to conduct a single regulatory audit of a medical device manufacturer that satisfies the relevant requirements of the regulatory authorities participating in the program.” The auditing organizations execute their functions based on harmonized processes and standards among participating NRAs: the harmonized standards enable and leverage these third parties to inform decisions of NRAs.

Harmonization is not a prerequisite for reliance, however. National regulatory authorities may leverage the decision of a trusted source to feed own process or decision without sharing common standards. In this case, trust is the critical element since the reliance is based on the confidence that the regulatory outcome is based on strong regulatory processes and standards and thus, trustworthy. Consequently, initiatives that improve trust among regulatory authorities have been a way to foster reliance. Benchmarking of national regulatory systems in the Americas and with similar standardized benchmarking tools such as the WHO/Global Benchmarking Tool¹³ or the evaluation of inspection capacities done by the Pharmaceutical Inspection

11 WHO Drug Information Vol. 30, No. 4, 2016. Collaboration, not competition: developing new reliance models. Available from: <http://apps.who.int/medicinedocs/documents/s23135en/s23135en.pdf>

12 Medical device single audit program (MDSAP). Available from: <http://www.imdrf.org/workitems/wi-mdsap.asp>

13 WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems. Available from: http://www.who.int/medicines/regulation/benchmarking_tool/en/

Co-operation Scheme (PICs)¹⁴ have increased trust among participating NRAs and are behind a number of reliance strategies. Globally, benchmarking national regulatory authorities have allowed WHO and other UN agencies to improve efficiencies and access to essential medical products such as vaccines since it has been used for the purpose of Prequalification of public health supplies.

The Caribbean Regulatory System (CRS)¹⁵ is an example of a non-harmonized reliance program. Many small states in the Caribbean Community (CARICOM) lack the resources and capacity to conduct full medicines regulation on their own, and so use the CRS as a regional reliance mechanism to more efficiently accomplish the marketing authorization function. Specifically, the CRS uses trusted authorities including PAHO NRAs,¹⁶ the European Union, and WHO prequalification to inform the products it recommends for marketing authorization in the region. To be eligible, a product must be approved in one of these trusted authorities before it can be reviewed by the CRS. If this condition is met, the CRS then does a verification review to determine whether the product is the same as that approved by the trusted authority. After a recommendation is made, CARICOM Member States are requested to make a marketing authorization decision within 60 calendar days. The intent is to make this decision-making process easier for countries (including through mitigation of the time, people, and technical capacity needed to make the decision) and thus speed access to markets industry and access to medicines by patients.

The above-mentioned examples represent a series of good practices where regulatory reliance has resulted in efficiencies and improvement for regulatory capacities. Moreover, although the practices may seem very divergent, they all follow the underlying principles mentioned in the previous section.

14 Pharmaceutical Inspection Co-operation Scheme. Available from: <https://www.picscheme.org/>

15 The Caribbean Regulatory System (CRS). Available from: <http://carpha.org/what-we-do/laboratory-services-and-networks/crs>

16 System for Evaluation of the National Regulatory Authorities for Medicines. Available from: https://www.paho.org/hq/index.php?option=com_content&view=article&id=1615:2009-sistema-evaluacion-autoridades-reguladoras-nacionales-medicamentos&Itemid=1179&lang=en

PANDRH RECOMMENDATIONS

The recommendations of the Pan American Network for Drug Regulatory Harmonization are: (a) to adopt the phrase “use of regulatory decisions of other jurisdictions” to describe reliance; (b) to share the concept note on regulatory reliance principles with Member States to ensure that it helps decision making to improve their regulatory efficiencies; (c) to consider following the principles proposed in this document when applying and adopting regulatory reliance strategies for processes, products and/or practices; (d) to recommend the inclusion of reliance-related provisions and language in legal documents, where appropriate, for registry, inspection, laboratory testing, etc.; (e) to encourage Member States to use reliance to increase efficiencies and in particular, states with limited resources which are seeking fast improvements in regulatory capacities; and (f) to request that PAHO and its Member States monitor and evaluate the impact of regulatory reliance across the Region.

PAHO

PANDRH Pan American Network for Drug Regulatory Harmonization



Pan American
Health
Organization



World Health
Organization
ORGANIZATION OF THE AMERICAS