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E. STRENGTHENING NATIONAL REGULATORY AUTHORITIES FOR MEDICINES AND BIOLOGICALS: PROGRESS REPORT

Background

1. In 2010, the 50th Directing Council of the Pan American Health Organization (PAHO) adopted Resolution CD50.R9, Strengthening National Regulatory Authorities for Medicines and Biologicals *(1)*. The resolution urged Member States to, among other things, strengthen and evaluate their regulatory capabilities with respect to the functions characteristic of a regulatory and oversight agency for medicines and biologicals through an examination of the performance of these essential functions. It requested the Pan American Sanitary Bureau (PASB or the Bureau) to support the development of a system for the qualification of national regulatory authorities and their designation as regulatory authorities of regional reference. The resolution further urged Member States to use the results of the qualification activity and the designation of regulatory authorities of regional reference to strengthen their performance in terms of the steering role of the health authority.

2. The 67th World Health Assembly in 2014 recognized this and similar regional initiatives in Document A67/32, Regulatory System Strengthening *(2)* and through the adoption of Resolution WHA 67.20, Regulatory System Strengthening for Medical Products *(3)*. This Resolution, which established the strengthening of regulatory systems as a global public health priority, urges Member States of the World Health Organization (WHO) to promote international cooperation for information sharing and to engage in global, regional, and subregional networks of national regulatory authorities (NRAs). This progress report summarizes the key achievements in this area over the past decade in the Region of the Americas and the challenges that remain to be addressed.

Analysis of Progress Achieved

3. Countries in the Region have prioritized the strengthening of their regulatory systems for medicines and other health technologies as a public health need, as regulatory capacity remains a critical component of well-functioning health systems. In addition, regulatory systems can contribute to a country's development by supporting the

manufacturing sector. PAHO promotes the development of context-specific national regulatory systems that can serve the needs of the national health system and that seek efficiencies through regulatory convergence, harmonization, and reliance, when possible and appropriate.

4. As of December 2019, PAHO has coordinated and supported assessments of national regulatory systems in 29 countries, using a standardized indicator-based tool. The results of these assessments are used to support the preparation of institutional development plans (IDPs) to guide improvements in national regulatory capacities. IDPs identify clear priorities based on the most urgent needs and help set attainable goals based on gap analysis and context. The assessments also inform the periodic monitoring and evaluation of IDPs with respect to their implementation and progress. The results of the evaluations are available to participating regulatory bodies and are shared through the Regional Platform on Access and Innovation for Health Technologies (PRAIS), an online collaborative platform.

5. While the aim of the technical cooperation program is to strengthen national regulatory systems, with particular attention to the less mature systems in the Region, the evaluations have also helped identify those authorities that perform at a higher level and can be designated as reference authorities, according to the criteria established by Document CD50/20, Rev. 1, Strengthening national regulatory authorities for medicines and biologicals *(4)*. As of 2019, PAHO has recognized eight national regulatory authorities of regional reference (NRAr): the National Administration of Drugs, Foods and Medical Devices (ANMAT) of Argentina; the National Health Surveillance Agency (ANVISA) of Brazil; the Center for State Control of Drugs, Equipment and Medical Devices (CECMED) of Cuba; the Federal Commission for Protection against Health Risks (COFEPRIS) of Mexico; Health Canada; the Public Health Institute (ISP) of Chile; the National Food and Drug Surveillance Institute (INVIMA) of Colombia; and the United States Food and Drug Administration. These NRArs represent eight of 35 countries in the Americas (23%), and because these eight countries are among the most populous, these reference authorities cover 82% of the population of the Americas. These countries also represent some of the most active pharmaceutical markets in the Region, and PAHO has defined quality criteria indicating that the products registered and commercialized in NRArs can be a trusted source of products for the PAHO Regional Revolving Fund for Strategic Public Health Supplies and the PAHO Revolving Fund for Access to Vaccines. In addition, the NRArs have fulfilled their commitment to actively support efforts to strengthen the regulatory systems of countries with lesser capacities. Framed by the IDPs, bilateral cooperation between the NRArs and other countries has served to multiply capacities beyond the direct support of PAHO, taking advantage of best practices in each reference authority.

6. Countries that possess the legal and organizational elements for comprehensive regulatory systems but have not reached NRAr status account for 16% of the population in the Region. This leaves 2% of the population in countries that have few or none of the legal and organizational foundations for regulatory systems. While this is a small percentage, it

represents 18 million people, predominantly in the small states of the Caribbean, living in countries with inadequate or no regulatory systems.

7. Since 2016, countries in the Caribbean Community (CARICOM) have been implementing regionalization through the Caribbean Regulatory System (CRS). Managed by the Caribbean Public Health Agency (CARPHA) with technical support from the Bureau, CRS offers a single-entry portal for market authorization to the 17 million people of CARICOM. This regionalization strategy increases market size, reduces fragmentation of standards, and offers a chance for small states working together to achieve appropriate oversight of products circulating within the Caribbean Community, something that would not have been possible for states acting individually. Six of the registering countries in CARICOM (Belize, Guyana, Haiti, Jamaica, Suriname, and Trinidad and Tobago) are participating in the CRS registration and post-marketing system. The CRS uses efficiencies such as reliance, information sharing, work sharing, and digitization strategies to help small state systems do more with less. Using reliance on NRArs and other trusted authorities, it has recommended over 80 medicines to Member States since it became operational in 2017, with a growing number of companies submitting products for review each year. It has also supported the submission of hundreds of reports to its regional reporting platform, VigiCarib,[1] on adverse events and substandard and counterfeit medicines. The CARPHA Medicines Quality Control and Surveillance Lab (MQCSD) has adopted a risk-based, post-market surveillance strategy that tests products on the market, with bidirectional information sharing between MQCSD and CRS/VigiCarib. PAHO has issued and published a series of policy recommendations for improving regulatory capacities within the small-states context, adopted by the IX Conference of the Pan American Network for Drug Regulatory Harmonization (PANDRH) in 2018 *(5)*.

8. Recently, Central American national regulatory authorities have come together to develop a regional approach to the regulation of medicines. Toward this end, they have launched the Central American Regulatory Mechanism with the support of the Bureau and the World Bank. This initiative relies on a multi-country approach to accelerate market entry and improve availability of quality medicines while ensuring efficiencies and best use of resources in the subregion. Countries jointly assess and evaluate the dossiers of the products for issuing marketing authorization and conduct post-marketing surveillance of strategic products.

9. It is widely recognized that regulatory systems can be highly resource intensive. Establishing and sustaining mature regulatory systems requires skilled human resources and large public investments, among other inputs. Countries therefore need to formulate strategies to strengthen regulatory systems, considering national policy objectives and characteristics of pharmaceutical markets while at the same time ensuring efficiencies and effectiveness. Regulatory reliance has been gaining popularity in the most developed

[1] VigiCarib is an electronic reporting system for the CARICOM region where stakeholders such as patients, providers, industry and governments can report adverse events and substandard and falsified medicines via the VigiCarib webpage. CRS staff then work with implicated governments to share information and take any needed regulatory action.

regulatory systems since it is regarded as a strategy to improve regulatory decision making and oversight in an efficient and effective way. Reliance helps conserve resources by avoiding duplication and improves allocation of resources where these are limited. With the support of the Bureau, the 2018 PANDRH conference adopted Regulatory Reliance Principles: Concept Note and Recommendations *(6)* to guide Member States and outline key examples and principles for the practice of regulatory reliance.

10. To encourage efficiencies, the Bureau has supported development of the Regulatory Exchange Platform–secure (REPs), a virtual platform that facilitates the exchange of non-public regulatory information to foster cooperation and reliance. REPs comprises two modules. The first, Regulatory Information Secure Exchange (RISE) module enables Member States to exchange non-public regulatory information, such as Good Manufacturing Practices inspection reports, thereby strengthening regulatory systems through a collaborative process. Argentina, Brazil, Canada, Chile, Colombia, El Salvador, Mexico, and the United States of America have signed memorandums of understanding with the Bureau to use this tool, and Argentina and Brazil began actively sharing reports in 2019, as a pilot initiative. The second, module dedicated to Medical Device Single Audit Program (MDSAP) initiative created in 2012 by the NRAs of Australia (Therapeutic Goods Administration), Brazil (ANVISA), Canada (Health Canada), Japan (Ministry of Health, Labor and Welfare/Pharmaceuticals and Medical Devices Agency), and the United States of America (US Food and Drug Administration). Through this program, audit organizations recognized by MDSAP members perform a single regulatory audit of the quality management system of a medical device manufacturer. In 2019, MDSAP launched the category of affiliated members, which extends MDSAP benefits to other regulatory authorities. The ANMAT of Argentina is the first NRA of the Region to be recognized in the affiliate category. From October 2018 to February 2020, the REPs-MDSAP module has facilitated the exchange of 3,585 audit reports and oversight of 5,064 manufacturing facilities.

11. The Region of the Americas has played an active role in supporting regional and global regulatory initiatives. The participation of regulatory authorities of the Americas played a major role in the adoption of a global benchmarking tool (GBT) that can be used to assess countries' regulatory capacities across all WHO regions, using a single standard. Results from GBT evaluations will form the basis, together with performance evaluations, for designation by WHO of a new category of reference authorities: WHO-Listed Authorities (WLA). The WLA designation should provide guidance in identifying the NRAs that countries can rely on and cooperate with. It will replace the previous designation of Stringent Regulatory Authority (SRA) for prequalification of medical products.

12. In the past decade, the Bureau has supported the organization of three PANDRH conferences to assist countries in the development of a new working model for the network based on project-driven collaborations rather than development of guidelines. Moreover, as PANDRH secretariat, the Bureau is now an observer at the International Medical Device Regulators Forum (IMDRF) and International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), as well as a member of the

International Pharmaceutical Regulators Program (IPRP) forum. The Bureau has actively disseminated regional achievements in relevant regulatory forums such as the International Coalition of Medicines Regulatory Authorities (ICMRA), International Conference of Drug Regulatory Authorities (ICDRA), Drug Information Association (DIA), and Asia-Pacific Economic Cooperation (APEC), among others. The Organization has also supported participation by Member States in these harmonization and convergence initiatives.

13. The experience over this last decade shows that the adoption of standardized, transparent and peer-based evaluation of regulatory systems coupled to the adoption of IDPs has proven to be a successful approach to improving regulatory systems 'capacities regardless of their initial maturity level. The strategies and overall design of the regulatory system, however, need to be coherent with local context and national health system. Not all countries need to develop complex regulatory systems since many can use innovative approaches to accomplish the essential functions relying on information from trusted regulatory authorities, regionalization and work sharing.

Action Necessary to Improve the Situation

14. While the Region's regulatory capacities have improved significantly over the past decade, continuing efforts are needed. There are several national health authorities that have yet to prioritize the strengthening of their regulatory bodies. Regulatory system strengthening takes time and commitment, and it should therefore be adopted as a state policy and sustained over time. NRAs should adopt plans for continuous improvement so as to maintain their status and confront the increasing demands of more complex health technologies and a globalized supply chain. Countries that are still in the process of achieving functional status should invest resources and renew their political commitment to the process.

15. While Resolution CD50.R9 concentrated on pharmaceuticals and biologicals, regulatory systems face challenges associated with other health technologies such as medical devices, advanced cell therapeutic products *(7)*, combination technologies, and personalized medical products, among others. These new and growing technologies require immediate action and cooperation to ensure timely access to new treatments that can save lives. At the same time, it is critical to ensure that they enter the health system with appropriate oversight of effectiveness, quality, and safety that can ensure the best health outcomes, and that health systems invest in products that have proven added value to the population.

Action by the Directing Council

16. Considering the extraordinary and unprecedented circumstances presented by the COVID-19 pandemic, and in accordance with Resolution CE166.R7, this report will be published for information purposes only, and will not be discussed by the Directing Council.

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