Regulatory Convergence and Harmonisation Activities in Latin America

As demonstrated by numerous initiatives globally, cooperation and convergence activities among national regulatory authorities (NRAs) accelerates the drug development process, improves access to medicines and contributes greatly to public health. From region-specific programmes from organisations such as the Asia-Pacific Economic Cooperation (APEC) and the East African Community (EAC) to seminal initiatives such as the International Council for Harmonisation (ICH), these efforts enable regulators to share information and strategies to better face the challenges of working with an ever-evolving global biopharmaceutical industry. Regulatory convergence and harmonisation activities — and the common guidance documents they often produce — are particularly important in emerging regions, where many NRAs often lack the requisite infrastructure and resources needed to regulate medicines efficiently and effectively.

In Latin America, supporting regional cooperation initiatives to strengthen national regulatory capacities is a primary objective of the Pan American Network for Drug Regulatory Harmonization (PANDRH). Established in 1999 by the Pan American Health Organization (PAHO) and multiple NRAs in the region, PANDRH promotes the exchange of knowledge and information required for agencies to conduct essential regulatory functions effectively. In addition to providing a forum and a framework for NRAs to coordinate activities, the network also publishes technical documents to encourage implementation and adoption of common standards among member countries. Based on specific needs of the region, PANDRH has issued numerous technical documents since its inception, covering critical issues such as good laboratory practices, vaccines, counterfeit medicines and bioequivalence testing, among others.[1] Although adoption and implementation of standards vary widely across NRAs, the technical documents have nonetheless facilitated capacity-building and have helped to advance the development of regulatory networks within the region.[2,3]

Applying Common Standards

Progress toward improving the regulatory infrastructure in Latin America is evidenced most clearly in Brazil. Already the second largest pharmaceutical market among emerging countries (and seventh overall), pharmaceutical sales in Brazil are projected to reach $39–43 billion by 2023 – up from $31 billion in 2018.[4,5] To keep pace with this growth, the Brazilian Health Surveillance Agency (ANVISA) has implemented several programmes that will not only streamline regulatory requirements and improve access to medicines in Brazil but will also influence the manner in which NRAs throughout the region interact with industry sponsors significantly.

ANVISA is an active participant in several convergence and harmonisation initiatives and is the only ICH member from South America.[6] The ICH membership (achieved in 2016) provides the agency with valuable insight and perspective into global harmonisation efforts and progress toward common standards – knowledge that can then be shared with PANDRH members and other NRAs throughout Latin America to better coordinate their activities. ANVISA has subsequently adopted and implemented the ICH-established Common Technical Document (CTD) for dossier submissions and is working toward implementing the electronic version (eCTD) by 2023.

In addition to CTD, ANVISA has also implemented priority review, conditional approval and reliance pathways to help reduce redundancy and speed the development of treatments for neglected, rare, emerging, and re-emerging diseases. A regulation enacted in 2018 established eligibility criteria for the priority pathway and provided a framework for prioritising new drug registration, post-authorisation requests, and clinical research authorisations based on their relevance and import to public health.[7]

Also in 2018, ANVISA published a technical note regarding interchangeability between reference biologics and biosimilars.[8] The note emphasises that although the agency may determine a biosimilar product to be comparable in terms of quality, efficacy and safety, such designation does not imply interchangeability, and further maintains that policy and guidelines on substitution should be determined by the prescribing physicians and the Ministry of Health. Additionally, the directive prohibits multiple exchanges between products due to the difficulties in traceability and monitoring of use and suggests that pharmacovigilance and real-world data may elucidate new findings concerning interchangeability.

Although the WHO doesn't have a formal standard on the interchangeability of biotherapeutics – preferring instead to let national competent authorities define the issues and make determinations on substitution – ANVISA's procedure effectively delegates this complicated decision to physicians, which may increase the risk for conflicts of interest and potentially jeopardise patient safety.[9] In contrast, a position paper from three biopharmaceutical trade associations contends that pharmacy substitution of biotherapeutics should only occur when a product receives a formal interchangeability designation, is approved for all indications, and when physicians retain the option to dispense-as-written.[10] Additionally, the associations emphasise the need for relevant clinical evidence to justify switching decisions, as well as a robust pharmacovigilance system to monitor safety.

Regulating Advanced Therapies

Biosimilars are only one of many types of new medical products presenting challenges for NRAs in Latin America. Cell- and gene-based therapies and other advanced therapy medicinal products (ATMPs) require effective regulatory environments and more specialised expertise than is often available to regulators in emerging regions. Recognising the limitations of many Latin American NRAs to regulate and monitor the safety of ATMPs, PANDRH made several recommendations to regulators at its 2018 conference in El Salvador, primarily encouraging NRAs to adopt ATMP-specific guidelines and apply international standards for approving these therapies and regulating the facilities in which they are created.[11] Specific recommendations include establishing a manufacturing

licensure process to affirm compliance with standard practices (e.g., GMP, CLP and GCP), requiring clinical trial authorisation and monitoring, maintaining an adverse event detection system, and developing a registry of patients who have been treated with an ATMP. To be sure, the amount of resources and technical expertise required to effectively regulate advanced therapies is daunting – even for NRAs in Europe and the United States. For Latin American NRAs, ATMPs present significant challenges yet they also provide an opportunity to adopt, implement and strengthen existing reliance pathways to help facilitate and harmonise regulatory activities in the region.

Reliance pathways can be particularly useful in emerging regions as they enable resource-constrained NRAs to make use of shared information yet retain their autonomous decision-making responsibilities.[12] Recent global examples include reliance on pre-marketing assessment reports for quality, safety and efficacy, as well as GMP compliance inspections conducted by other authorities.[13] For NRAs struggling to address the challenging aspects of ATMPs, reliance upon pre-clinical and clinical data from a stringent regulatory authority (SRA) may be a more practical, less burdensome approach than lengthy and costly capacity development. These arrangements can be unilateral or bilateral, and may also be a prelude to more formalised forms of cooperation such as mutual recognition agreements.[14] Reliance pathways for some specific regulatory elements are already in use by NRAs in Argentina, Costa Rica, Ecuador, El Salvador and Panama, and more can be reasonably expected as PANDRH's efforts to encourage adoption and implementation of common, internationally accepted standards envisions a regulatory paradigm based on the concepts of reliance, work-sharing and international collaboration.[15,16]

Harmonising Capacities

With limited resources and a global biopharmaceutical industry that is increasingly complex, national regulatory authorities in Latin America face significant challenges in their efforts to regulate the safe and effective use of medical products. Internationally accepted guidelines – from ICH, WHO and PANDRH – may help strengthen regulatory capacities and regional cooperation, but consistent application of such standards remains elusive. The CTD,

for example, is only partially accepted in Latin America with only Brazil and Mexico having fully adopted and implemented their use. Argentina's regulatory authority, ANMAT, recently announced plans to implement the CTD as one of its priority initiatives for 2019, but no other NRAs in the region have established CTD implementation plans.[17]

Greater harmonisation of requirements in Latin America may be achieved in the coming years, however, as more NRAs participate in global convergence activities. ICH Observers from the region now include Mexico (COFEPRIS, since 2016), Colombia (INVIMA, since 2017) and Cuba (CECMED, since 2017), and it is hoped that these NRAs will influence regulatory coordination by adopting and implementing common global standards. In addition, PANDRH recognises that a shortage of human capital with appropriate competencies limits the effectiveness of many NRAs, and has consequently developed a curriculum for regulatory professionals in the region that incorporates recommendations from WHO and other government leaders in regulatory science.

Cooperative regulatory efforts will ultimately be fruitful over time, but harmonisation and convergence initiatives must also include the strengthening of national regulatory capacities to allow for the incorporation and deployment of common standards throughout the region. In doing so, NRAs can potentially decrease the time-to-market for new therapies, reduce uncertainty for biopharmaceutical sponsors, and increase patient access to much-needed medical treatments.

REFERENCES

1. Pan-American Health Organization (April 2014). Strategic Development Plan 2014–2020 of the Pan American Network for Drug Regulatory Harmonisation (PANDRH). Available at: https://www.paho.org/hq/dmdocuments/2015/drug-harmonisation-Strategic-Plan-PANDRH-04-20-2015.pdf. Accessed: April 11, 2019
2. Pombo ML, Porrás A, Saidon PC, Cascio SM. Regulatory convergence and harmonization: barriers to effective use and adoption of common standards. Rev Panam Salud Publica. 2016 May;39(5):217-225. PubMed PMID: 27706409
3. Forum on Drug Discovery, Development, and Translation; Board on Health Sciences Policy; Institute of Medicine (IOM); Weisfeld V, Lustig TA, editors. Washington (DC): National Academies Press (US); 2013 Oct 24.
4. Barbosa da Silva, J. Regulatory Advances in Drug Regulation Accelerated Pathways of Approval. Presented at the DIA 2018 Global Annual Meeting. Available at: http://portal.anvisa.gov.br/documents/219201/219401/ANVISA+JB+DIA+2018+Annual+Meeting+INGL%C3%8AS/4bea5429-ef3c-4b6a-9bb3-324896228c9e. Accessed: April 11, 2019
5. The IQVIA Institute for Human Data Science (January 2019). The Global Use of Medicine in 2019 and Outlook to 2023. Available at: https://www.iqvia.com/institute/reports/the-global-use-of-medicine-in-2019-and-outlook-to-2023. Accessed: April 11, 2019
6. Huynh-Ba, K. & Beumer Sassi, A. ANVISA: an introduction to a new regulatory agency with many challenges. AAPS Open. 2018; 4(9). DOI: 10.1186/s41120-018-0029-x
7. Cerqueira, D. Regional and Global Regulatory Priority Updates. Presented at the DIA 2019 Latin America Regulatory Conference; February 2019.
8. Agência Nacional de Vigilância Sanitária (ANVISA), Gerência de Avaliação de Produtos Biológicos (GPBIO) (October 2018). Clarification No. 003/2017/GPBIO/GGMED/ANVISA – REVISED. Exchange and replacement of registered products by means of development by comparability ("biosimilars") and the biological product comparator. Available at: http://portal.anvisa.gov.br/documents/33836/4095801/Nota+de+esclarecimento+003+de+2017+-+Medicamentos+Biol%C3%B3gicos/0774f2d7-5c83-45b7-832d-37efdf21790c (in Portuguese). Accessed: April 11, 2019
9. de Assis MR, Pinto V. Strengths and weaknesses of the Brazilian regulation on biosimilars: A critical view of the regulatory requirements for biosimilars in Brazil. Ther Adv Musculoskelet Dis. 2018 Oct 31;10(12):253-259. doi: 10.1177/1759720X18809683. eCollection 2018 Dec. Review. PMID: 30515251.
10. European Biopharmaceutical Enterprises (EBE), European Federation of Pharmaceutical Industries and Associations (EFPIA), International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). (February 2017). Considerations for physicians on switching decisions regarding biosimilars. Available at: https://www.ebe-biopharma.eu/wp-content/uploads/2017/04/considerations-for-switching-decisions_biosimilars-and-rbps-final-branded-1.pdf. Accessed: April 11, 2019
11. Porrás A. Challenges in the regulation of cell therapy products: Regional situation and recommendations endorsed by the IX Pan American Network for Drug Regulatory Harmonisation Conference (CPANDRH). Presented at the DIA 2019 Latin America Regulatory Conference; February 2019.
12. Luigetti, R. Collaboration, not competition: developing new reliance models. WHO Drug Information. 2016;30(4):556-568. Available at: https://www.who.int/medicines/publications/druginformation/WHO-DI_30-4_RegCollaboration.pdf Accessed: April 11, 2019
13. World Health Organization (2016). Good regulatory practices: guidelines for national regulatory authorities for medical products. Working document QAS/16.686. Available at: https://www.who.int/medicines/areas/quality_safety/quality_assurance/GoodRegulatory_PracticesPublicConsult.pdf. Accessed: April 11, 2019
14. Liberti. Globally Applicable Facilitated Regulatory Pathways to Improve Equitable Access to Medicines (2017). ISBN 978-94-6182-806-4. Available at: https://www.offpage.nl/ebooks/2017_lliberti/ Accessed: April 11, 2019.
15. European Federation of Pharmaceutical Industries and Associations (2017). White paper on reliance and expedited registration pathways in emerging markets. 23/11/2017. Available at: https://www.efpia.eu/media/288592/white-paper-on-reliance-and-expedited-registration-pathways-in-emerging-markets.docx. Accessed: April 11, 2019
16. Brady, P. Regulatory Cooperation and Reliance. Presented at the DIA 2019 Latin America Regulatory Conference; February 2019
17. Aprea, P. ANMAT Regulatory Initiatives and Priorities for 2019. Presented at the DIA 2019 Latin America Regulatory Conference; February 2019

Adam Istas

Adam Istas is a science writer with the Drug Information Association (DIA) in Washington, DC. A long-time advisor and contributor to the DIA, he has 20 years of experience in healthcare communications. Previous roles include directing thought leadership initiatives at Quintiles (now IQVIA) and managing a disease-specific clinical trials registry and educational website at Washington University School of Medicine in St Louis.

Email: adistas@gmail.com