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Establishing a regulatory value chain model: An innovative approach to strengthening medicines regulatory systems in resource-constrained settings

Harinder Singh Chahal,[1] *Farrah Kashfipour,*[2] *Matt Susko,*[2] *Neelam Sekhri Feachem,*[2] *and Colin Boyle*[2]

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ABSTRACT *Medicines Regulatory Authorities (MRAs) are an essential part of national health systems and are charged with protecting and promoting public health through regulation of medicines. However, MRAs in resource-constrained settings often struggle to provide effective oversight of market entry and use of health commodities. This paper proposes a regulatory value chain model (RVCM) that policymakers and regulators can use as a conceptual framework to guide investments aimed at strengthening regulatory systems. The RVCM incorporates nine core functions of MRAs into five modules: (i) clear guidelines and requirements; (ii) control of clinical trials; (iii) market authorization of medical products; (iv) pre-market quality control; and (v) post-market activities. Application of the RVCM allows national stakeholders to identify and prioritize investments according to where they can add the most value to the regulatory process. Depending on the economy, capacity, and needs of a country, some functions can be elevated to a regional or supranational level, while others can be maintained at the national level. In contrast to a "one size fits all" approach to regulation in which each country manages the full regulatory process at the national level, the RVCM encourages leveraging the expertise and capabilities of other MRAs where shared processes strengthen regulation. This value chain approach provides a framework for policymakers to maximize investment impact while striving to reach the goal of safe, affordable, and rapidly accessible medicines for all.*

Key words Pharmaceutical preparations; standards; international cooperation; legislation, pharmacy; quality assurance, health care; medicines; Americas.

Countries with limited financial, human, and technical resources often struggle to provide effective oversight of the market entry and use of health commodities. As the number and classes of medical products available for human use continue to grow, so do the challenges. Inadequate regulatory oversight of medicines has led to growing concerns over the rise of antimicrobial resistance and the proliferation of falsified and substandard medicines (FSM), which has led to calls for more responsive and effective regulatory capacities at all levels (1, 2).

Well-functioning Medicines Regulatory Authorities (MRAs) can help address these challenges. MRAs are an integral part of health systems and are a crucial means to protect and promote public health. Unfortunately, MRAs receive less funding than many other components of health systems and tend to draw significant attention from the public and policymakers only after something has gone

[1] Department of Clinical Pharmacy, University of California, San Francisco, California, United States of America. Send correspondence to Harinder Chahal, email: Harinder.Chahal@ucsf.edu; or Colin Boyle, email: Colin.Boyle@ucsf.edu

[2] Global Health Sciences, University of California, San Francisco, California, United States.

wrong (1, 3, 4). Ideally, MRAs should be able to employ a comprehensive, rapid, and scientific review process to ensure the safety and quality of medicines from the point of a product's approval throughout its lifecycle. Nevertheless, many MRAs in resource-constrained settings are not able to execute core regulatory functions, such as quality control testing and post-market surveillance, at a level consistent with their mandates (5, 6). Limited political, financial, and infrastructure commitments can result in under-resourced and inadequately trained regulators (3).

Many countries in the Region of the Americas face substantial challenges to medicine regulation and access. A 2014 analysis of 25 countries in the Region (6) found that a significant number did not have the capacity or legal authorities to carry out many basic functions of regulatory agencies: almost one-half (48%) did not have the authority to regulate clinical trials and up to 80% lacked the legal provisions to communicate characteristics of registered drugs to the public. Furthermore, the impact of rare diseases compounds the challenges of regulation and access faced by countries in the Region. Compared to countries in other regions, those in South and Central America have only recently enacted legislation to improve access to medicines for rare diseases (7, 8). The laws and regulations vary widely among the countries, with differing requirements, definitions of orphan diseases, approval pathways, and review timelines (8, 9). Regulatory review times also vary greatly, ranging from months to years, presumably due to limited resources (7). The lack of harmonized requirements across Latin America and the Caribbean creates a regulatory challenge that decreases the efficiency and access to necessary medicines (7–9).

A number of organizational and operational innovations, such as regional harmonization initiatives, have attempted to strengthen regulatory capacities, but a dearth of data, knowledge, and focus continues to plague many systems (10). To overcome these challenges, a new approach to the regulation of medicines is needed.

The following paper proposes applying a regulatory value chain model (RVCM) as a conceptual framework that policymakers and regulators can use to think strategically about how best to invest in strengthening regulatory systems (11). The model gives stakeholders a stepwise framework to consider alternative models and strategically allocate resources across the full range of regulatory activities.

CHALLENGES TO IMPLEMENTING CORE REGULATORY FUNCTIONS

A primary goal of an MRA is to ensure that health products are safe, effective, and meet quality standards. However, the role of MRAs extends well beyond that mandate. To express the reach and complexity of the role, an iron triangle of health systems adapted to MRAs was designed (Figure 1). It suggests that MRAs have three key objectives: (i) to improve population health, (ii) to ensure equitable access for all, and (iii) to provide value that enhances the overall health system. Ensuring timeliness of product availability for patient use (the center of the triangle) is essential to achieving the three objectives. All MRAs, and particularly those in low-resource settings, face challenges when securing the human and financial resources needed to adequately address all the requirements and manage any potential trade-offs.

The Institute of Medicine (IOM) has identified nine functions that are vital to achieving the three key objectives of MRAs delineated above (Table 1) (3, 12). Unfortunately, many countries in the Region of the Americas have not been consistent in effectively implementing these core functions (6). An analysis by the Pan American Health Organization (PAHO) found that, on average, only 69% of basic MRA functions have been implemented across the 25 countries assessed (6). Furthermore, the PAHO analysis indicates that deficiencies exist in countries at all income levels in the Region (6). As a consequence, the vast majority of people are left without the protections afforded by an effective regulatory authority (1, 3, 6, 12).

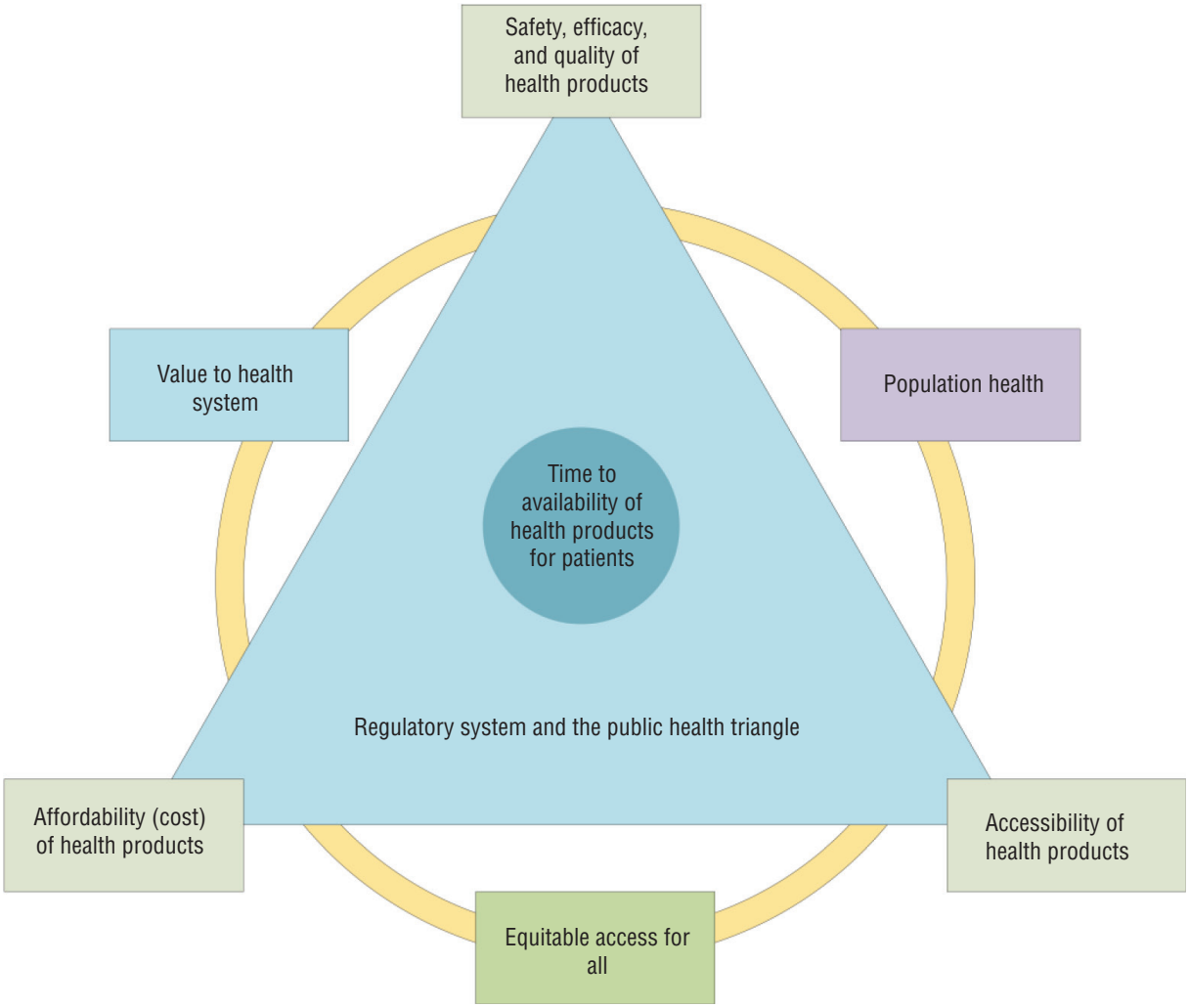
APPLYING THE VALUE CHAIN CONCEPT TO MRAs

A value chain is a concept drawn from organizational analysis and business management that is increasingly being applied to the health sector (6, 13). A value chain provides a systems framework in which production, processing, and sale of a given product are operated and analyzed comprehensively (11), as opposed to one in which each component operates independently, without consideration for linkages among activities. Alignment of governance and incentives are critical value-chain characteristics. Value is added along the course of the chain by different clusters of activities until a final product (or health outcome) is produced. In the case of the regulatory value chain, one can conceptualize the final output as safe, effective, available medicines that meet quality standards. A value chain integrates the full set of activities needed to deliver this output—the chain is only as strong as its weakest link—while acknowledging that individual segments of the value chain may be resourced, measured, and managed in quite different ways, depending on a nation's needs, costs, policy preferences, and capacity.

The RVCM proposed here incorporates the nine IOM-identified core functions into five modules (Figure 2). These modules are: (i) clear guidelines and requirements; (ii) control of clinical trials; (iii) market authorization of medical products; (iv) pre-market quality control; and (v) post-market activities. The general functions of each of the five modules, as well as the overarching enabling factors necessary for implementation, are elements of analysis and function within a regulatory value chain. This model provides a framework for stakeholders to assess the effectiveness of the entire regulatory continuum and of each module independently.

Fundamentally, the systematic application of the RVCM offers national stakeholders a means to ask questions about the priorities for their regulatory system and where supranational harmonization programs or investments to strengthen the system are most appropriate. The value chain allows stakeholders to imagine options for bundling or unbundling various modules and managing them differentially. Depending on a country's economics, capacity, and needs some functions can be elevated to a regional or supranational level, while others can be maintained at the national level or devolved to subnational authorities. This contrasts the "one size fits all" approach to regulation systems in which each country manages the full regulatory value chain at the national level without leveraging the expertise or capabilities of other nations.

FIGURE 1. Iron triangle of health systems adapted for medicines regulation, showing the function and value of medicines regulatory authorities (MRAs) in public health.



Note: Triangle shows the four mandates of a public health system as related to MRAs. MRAs operate in a complex environment and must work to (i) enhance value to the health system, (ii) improve public health, and (iii) ensure equitable access for all. MRAs work in a public health system that must balance the triangle's three corners (affordability, accessibility, and product safety, efficacy, and quality), while ensuring timely availability of health products to patients (center).
Source: Produced by the authors from study data.

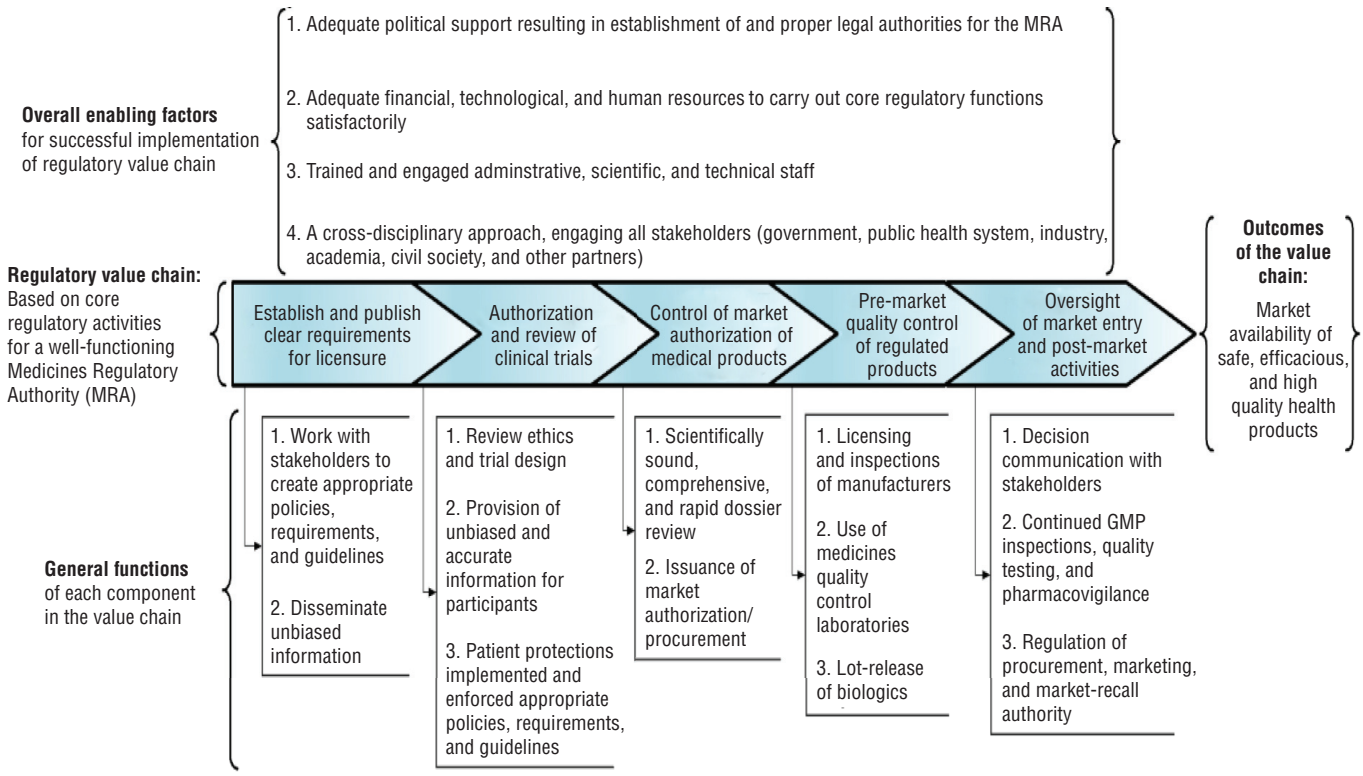
RVCM APPLIED TO NATIONAL AND REGIONAL NEEDS

As a first step to applying the RVCM, a comparative assessment of health priorities, existing regulatory frameworks, and resource capacities of each MRA should be undertaken. Understanding a system's current strengths and weaknesses allows informed and strategic allocation of resources with the aim of maximizing health benefit while minimizing resource input. It also enables more nuanced discussions of the appropriate focus of oversight for regulatory authorities and the potential benefits of supranational or regional models. For example, a country with significant FSM challenges that wishes to focus its limited MRA resources on post-market oversight activities, may choose to establish a mutual recognition regime or harmonization of product approval and market authorization processes with other countries. The result of applying the RVCM is better alignment of MRA resource allocation with country goals.

Once a comprehensive regulatory capacity assessment has been completed and current performance of the regulatory system is established, the RVCM can help policymakers determine how to best leverage limited resources for the greatest public health benefit. Standardized assessment tools, such as those made available by PAHO and WHO (18, 19), may be used to calibrate a regional model to the needs and strengths of the participating MRAs.

Analyses that forecast what incremental investments in various modules could yield in improved performance can change the nature of resource allocation decisions. Regulatory system strengthening should be viewed as an investment with a measurable return that improves medicines access and quality. A focus on measuring the return on investment in regulatory systems may justify committing additional national resources for certain regulatory activities, while also justifying the need for harmonization of

FIGURE 2. Regulatory Value Chain Model for a regional medicines regulatory system and its general functions and enabling factors.



Note: From left to right, the various modules (or links) of the regulatory value chain are described. Below each module are some general functions that a medicines regulatory authority (MRA) would be expected to perform to ensure optimal performance of that component of the value chain. Functions listed are at a high level, but could be further detailed. Above the chain are the overall enabling factors required for successful implementation of the entire value chain. Finally, to achieve the outcome of the value chain—market availability of safe, efficacious, and high quality health products—each module must be implemented completely. Visualizing the regulatory components in this manner helps determine the distinct and inherent overlap of some regulatory activities that could be performed by MRA partners to focus resources and achieve the outcome.
Source: Produced by the authors from study data.

others. These include activities that increase efficiency through integration of upstream regulatory processes (e.g., laws, policies, and regulations) or internal operations (e.g., technical review and approval of applications), or that expedite access to essential, life-saving therapies for patients (14).

A potential application of the RVCM is to provide a blue print for the development of a regional regulatory system. In general, any function that is not best performed at the national level could be centralized at a regional or supranational level or "outsourced" to another MRA that has distinctive strength in that function. In the Region of the Americas, six regulatory authorities[3] have been recognized as National Regulatory Authorities of Regional Reference (NRA/RR), and another is in the process of joining the group (15, 16). Leveraging the capacity of NRA/RR would allow for increased regulatory capacity in the Region, with minimal additional investment. NRA/RRs could "un-bundle" the value chain modules to carry out different regulatory functions on behalf of all partners.

ECONOMIC BENEFITS

By applying the RVCM and measuring cost and performance at the module level, the cost of various approaches can be compared. For example, if Regional harmonization of particular modules is deemed most cost-effective overall, a net investment approach can be used to offset the savings from duplicative efforts against the initial investment required to set up a Regional authority (10). The economic benefits should also take into account the savings garnered from improvements to population health that result from a well-functioning regulatory system. For example, in a country with significant FSM problems, modest investments that address this challenge could offer substantial economic and health returns to the population. Finally, RVCM application gives countries a better understanding of the cost of establishing a self-sustaining Regional regulatory system. To ensure operational sustainability, the system must be flexible, responsive, and outcome-driven, while continuing to offer a favorable return on investment (3).

DISCUSSION

The value of regulatory harmonization of technical requirements for registration of medicines and other medical products is widely recognized (3, 6, 10, 12). Currently, several regional harmonization initiatives[4] exist to standardize registration procedures (17).

[3] Argentina, Brazil, Canada, Colombia, Cuba, and Mexico; United States is in the process of becoming a NRA/RR.

[4] Asia-Pacific Economic Cooperation (APEC); Association of Southeast Asian Nations (ASEAN); East African Community (EAC); Gulf Cooperation Countries (GCC); Pan American Network on Drug Regulatory Harmonization (PANDRH); and South African Development Community (SADC).

TABLE 1. Core functions of a Medicines Regulatory Authority (MRA), as identified by the Institute of Medicine,[a] and the Regulatory Value Chain Model

Core regulatory function[a]	Corresponding Regulatory Value Chain Model (RVCM) components[b]	Description/comment	Streamline the core regulatory functions to focus resources[c]	
			MRA level	Regional level
Publishing clear requirements for licensure	Establish and publish clear requirements for licensure	The regulatory authority must provide clear, consistent, and trustworthy information to all those attempting to access the market for sale of medical products.		X
Provision of unbiased information				X
Use and control of clinical trials	Authorization and review of clinical trials	A competent authority must make decisions on the basis of evidence from clinical trials and other methods that must comply with appropriate study design and ethical requirements.		X
Registration/market authorization	Control of market authorization of medical products	Registration of medical products to gain market authorization is key first step to ensuring the safety and quality of medicines.		X
Quality control testing	Pre-market quality control of regulated products	A competent regulatory authority must be able to conduct quality control on medical products to ensure safety and quality standards are met prior to approving market entry.		X
Good manufacturing practices compliance inspections of manufactures		Inspections of manufacturing facilities to ensure that standards and practices are met—a key component to ensuring quality of medical products.		X
Market entry notification	Oversight of market entry and post-market activities	After product approved for sale, appropriate actors (procurement agencies, health systems/providers, patients, etc.) must be made aware of its availability for purchase.	X	X
Lot release for biologics (e.g., vaccines)		When manufactured in a given country, the regulatory agency must ensure a traceable lot release system to ensure quality of biologic products.	X	
Safety and effectiveness surveillance (post-market)		After market entry, a pharmacovigilance mechanism (e.g., observational studies) must track and remove any product found to be deficient in safety and/or effectiveness. The regulatory authority must ensure such studies are methodologically sound and designed to evaluate outcomes of interest.	X	X

Source: Produced by the authors, except where otherwise noted.
[a] Institute of Medicine. Ensuring safe foods and medical products through stronger regulatory systems abroad. Washington, DC: IOM; 2012.
[b] The corresponding components of the proposed Regulatory Value Chain Model (RVCM); as noted, some core functions could be folded under the specified modules (links) of the value chain to bundle or unbundle regulatory functions at a national or Regional level, according to need.
[c] "X" indicates core functions that could be consolidated by a regional/central authority to minimize duplication at the national level.

The Pan American Network for Drug Regulatory Harmonization is an example of such an initiative (18). However, while regulatory harmonization is an important first step, it is not enough. While harmonization initiatives help develop common standards, execution of the standards is still the responsibility of individual nations (19). As such, there are persisting financial and technical challenges to enacting harmonized standards. These affect countries at all income levels, and many nations are not able to successfully implement the already harmonized standards set by International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (3, 6).

A value chain model has much to offer the Region of the Americas, which now has the opportunity to significantly improve health by strengthening its MRAs. Over the last decade, Latin America and the Caribbean have experienced remarkable economic and social development, with the middle class expanding over 50% (20). Despite this, expansion of the Region's medicines regulatory capacity is highly variable and lags behind its economic development (6). Given the substantial deficiencies observed in the PAHO basic indicators data, the Region of the Americas could benefit from using the RVCM as a tool for prioritizing regulatory system changes at national, regional, and/or subregional levels (6).

Application of the RVCM framework allows countries to pursue gradual, dynamic regulation, concurrently determining which functions benefit from regionalization and which should be preserved as sovereign, deemed essential to local needs and priorities. Instead of replacing MRAs, regional regulatory systems allow for efficient use of limited resources to provide high quality, consistent regulation of medical products. The European Medicines Agency and Gulf Central Committee for Drug Registration are successful entities that work in conjunction with their national counterparts to regulate medical products (21, 22). While these are based on the specific cultural and political context of their regions, it may be instructive to learn from the successes and challenges of these collaborations.

The RVCM provides a useful adaptive framework that takes into account the unique cultural and political characteristics of the Americas. The framework has the potential to provide specific metrics for data collection and analysis, enabling policymakers to conduct standardized evaluations throughout the Region. We believe policymakers and regulators will find this approach useful to striving toward and attaining the goal of safe, affordable, and rapidly accessible medicines for all the people of the Americas.

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Establecimiento de un modelo de cadena de valor reglamentaria: un enfoque innovador para fortalecer los sistemas de reglamentación farmacéutica en entornos de escasos recursos

RESUMEN

Los organismos de reglamentación farmacéutica son parte esencial de los sistemas nacionales de salud y se encargan de proteger y promover la salud pública mediante la reglamentación en torno a los medicamentos. Sin embargo, en lugares con pocos recursos, estos organismos suelen tener dificultad para supervisar eficazmente la entrada en el mercado y el uso de los productos sanitarios básicos. En el presente artículo se propone un modelo de cadena de valor reglamentaria (MCVR) que los responsables de las políticas y de la reglamentación pueden usar como marco conceptual para guiar las inversiones dirigidas a fortalecer los sistemas reglamentarios. El modelo incorpora en cinco módulos nueve funciones básicas de los organismos de reglamentación farmacéutica: (i) directrices y requisitos inequívocos; (ii) el control de los ensayos clínicos; (iii) la autorización de la comercialización de los productos médicos; (iv) el control de calidad antes de la comercialización; y (v) las actividades posteriores a esta. La aplicación del MCVR les permite a los interesados directos en los países determinar qué inversiones hacen falta y darles la prioridad debida teniendo presente dónde contribuirían en mayor medida a realzar el valor del proceso reglamentario. Si lo permiten la economía, la capacidad y las necesidades de un país, ciertas funciones pueden extenderse al nivel regional o supranacional, mientras que otras pueden seguir siendo nacionales. A diferencia de un método único para todos los casos, en el que cada país administra todo el proceso reglamentario en el nivel nacional, el MCVR promueve el aprovechamiento de la pericia y capacidades de otros organismos de reglamentación farmacéutica en áreas donde los procesos comunes fortalecen la reglamentación. Este método de la cadena de valor les proporciona a los formuladores de las políticas un marco para potenciar al máximo el efecto de las inversiones a la vez que se esfuerzan por lograr el objetivo de poner al alcance de todos medicamentos inocuos, asequibles y rápidamente accesibles.

Palabras clave Preparaciones farmacéuticas; normas; cooperación internacional; legislación, farmacia; aseguramiento de calidad, prestación de atención de salud; preparaciones farmacéuticas; Américas.