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## VIEWPOINT

# Regulating Medicines in a Globalized World With Increased Recognition and Reliance Among Regulators

## A National Academies Report

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**Research and development** of pharmaceuticals are now complex global endeavors, with drug companies operating worldwide using global supply chains.<sup>1</sup> Pharmaceutical companies source their products from many countries, conduct trials in multiple sites, and market essential drugs and vaccines globally. Yet oversight of drug safety and effectiveness is primarily the responsibility of national regulators of variable capacities. National agencies often undertake product reviews without recognizing that similar reviews are occurring elsewhere, sometimes simultaneously.<sup>2</sup> The result is duplication and redundancy, which benefits neither national nor global public health. Supported by the US Food and Drug Administration (FDA), the National Academies of Sciences, Engineering, and Medicine convened an expert committee to explore the benefits of mutual recognition and other reliance activities among regulators.<sup>3</sup>

Even well-resourced regulators (for example, the FDA, the European Medicines Agency, the Pharmaceutical and Medical Devices Agency Japan, and Health Canada) find it difficult to ensure the safety, efficacy,

and quality of medicines in a globalized world.<sup>1</sup> Regulatory failures cause harm to the population and undermine public trust in government. In 2008, following discovery of contaminated heparin originating from China, the Bush administration authorized the FDA to coordinate certain product manufacturing inspections with Australian and European regulators in China and India—setting the stage for “third country” inspections (ie, inspections conducted outside the jurisdiction of either regulator).<sup>4</sup> Yet concerns about the quality of active pharmaceutical ingredients and finished pharmaceutical products persist. For example, in 2018, the FDA recalled generic medications used to treat hypertension and cardiovascular disease because of contamination.<sup>5</sup>

ments to respond to the mounting complexity of regulatory oversight. Thus, agencies should increasingly rely on and actively cooperate with other trusted regulatory authorities.

Recognition and reliance leverage the work and work products (such as inspection or scientific assessment reports) of trusted regulatory authorities. Recognition and reliance can be informal (eg, scientific collaboration) or formal depending on the extent to which agencies are required by law to share information. “Recognition” is a formal type of reliance, with mutual recognition agreements (MRAs) being the most stringent. Countries negotiate MRAs typically as part of international trade agreements. National sovereignty is maintained because each government ultimately controls its own regulatory approvals based on its population's needs and legal traditions.

A country's strategy for reliance often depends on its capacities. Well-resourced and moderately well-resourced regulatory authorities should increase transparency and information sharing and ultimately share tasks like inspections. Lower-resourced regulatory authorities could consider unilateral recognition with trusted authorities. If the FDA or the European Medicines Agency, for example, were to approve a new product, a lower-resourced country might rely on, or even recognize, such approval. However, such recognition needs to be for the identical preparation or product.

Beyond government policy, industry and patient/consumer groups have major roles. Industry, for example, could reduce redactions in its reporting requirements by waiving unnecessarily broad definitions of trade secrets. Transparency would contribute to more informed decision-making. Patient and consumer groups should push for a public health framing of all recognition and reliance arrangements to secure the global public good of safe, effective medicines for all populations throughout the world. The public should have trust that pharmaceuticals everywhere are manufactured to the same high standards demanded by the best-resourced regulators.

### Building Better Reliance Arrangements

In an environment of limited human and financial resources, unprecedented globalization, and societal demands for faster drug approvals, medicines regulators have sought to improve and expedite regulatory oversight. The National Academies committee offered the following recommendations to help regulatory

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### Reliance Strategies to Enhance Regulatory Oversight

No regulator, even if highly resourced, has the capacity to fully protect the public's health. Given finite human and financial resources, the National Academies committee proposed recognition and reliance arrange-

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authorities cope with the growing workload and complexity of medicines regulation.

#### Improving Public Health Through Better-Designed MRAs

Mutual recognition agreements are legally binding agreements allowing one regulatory authority to trust the work products of another agency as equivalent to its own. Currently, 14 MRAs exist between well-resourced or moderately well-resourced regulatory authorities. The European Union has the most MRAs, including with Australia, Canada, Japan, Singapore, and, as of July 2019, the United States. Because MRAs are part of trade agreements, they are primarily negotiated by trade representatives. Because MRAs have strong public health implications, medicines regulators, rather than trade representatives, are in the best position to design, negotiate, and ultimately implement MRAs.

#### Responding to Evolving Science and Technology

Pharmaceuticals are rapidly evolving, presenting new challenges to regulators. Yet because they are embedded within trade agreements, MRAs cannot be easily adjusted. The committee therefore recommended that governments give broad and flexible powers to regulatory agencies to set up or amend MRAs and other reliance arrangements. Flexibility and agility will enable agencies to respond to the rapid pace of change in science and technology.

#### Better Utilization of the European Union–United States MRA

Mutual recognition agreements primarily focus on sharing inspection reports and certifications related to good manufacturing practices. The MRA between the European Union and the United States includes a limited range of products, although it does have provisions for expanding its product coverage and reliance measures, such as with third-country inspections. The committee urged the European Union and the FDA to immediately implement and expand oversight in countries with weaker regulatory systems and large production and manufacturing sites, like China and India. Because a growing share of new pharmaceuticals are sourced or manufactured in these countries, enhanced and shared international oversight is essential.

#### Information Sharing Among Medicines Regulators

Given large workloads and finite resources, it is important to maximize a regulatory authority's human and financial capital. Making work products of regulators easily accessible (eg, through limited redactions) to trusted authorities conserves scarce resources by avoiding duplicative work performed by other trusted agencies. The committee therefore recommended a systematic review of all agency policies and procedures to reduce the burden of regulatory redundancy.

#### Evaluating Public Health Influence of MRAs

Mutual recognition agreements have been in existence for 2 decades, yet there remains a dearth of quantitative data analyzing their public health influence. Anecdotally, multiple stakeholders report that MRAs are valuable tools for avoiding duplication of work. However, the committee recommends that regulatory authorities work cooperatively to create a results framework for monitoring and measuring outcomes and effects of recognition and reliance arrangements. Evaluating performance and then acting on high-quality evidence will ensure a stronger future for pharmaceutical regulation to improve global public health.

#### The Future of Regulatory Oversight

The public relies on regulators to ensure the safety and efficacy of essential vaccines and medicines. This core regulatory responsibility is placed at risk by the complex and rapidly evolving development of modern pharmaceuticals. Medicines have developed from simple molecules to highly complex elements requiring extensive expertise. At the same time, supply chains have become globalized. Elements of a medicine may be manufactured in various countries and then incorporated into a finished product in yet another country before being exported for sale. All of these advances require more efficient use of resources through recognition and reliance. In today's globalized world, regulatory authorities, regardless of resource level, cannot ensure rigorous public health oversight of medicines across the life cycle. In the view of this expert committee, well-evaluated reliance arrangements must now be considered a 21st century best regulatory practice.

#### ARTICLE INFORMATION

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