Global Health
Technologies Coalition

Briefing Paper, Volume 4: Addressing regulatory challenges throughout the product development process

Perspectives from nonprofits on accelerating product development and improving access for low- and middle-income countries

Financing and Coordination of Health Research
March 2014

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About the Global Health Technologies Coalition

The Global Health Technologies Coalition is a group of more than 25 nonprofit organizations working to increase awareness of the urgent need for tools that save lives in the developing world, as well as the most effective policies and programs needed to develop and deliver new health tools. These tools include new vaccines, drugs, microbicides, diagnostics, insecticides, and devices. Housed at PATH and funded in part by the Bill & Melinda Gates Foundation, the coalition advocates for increased and effective use of public resources, incentives to encourage private investment, and streamlined regulatory systems.

The Global Health Technologies Coalition can be found online at **www.ghtcoalition.org**.

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Acknowledgments

This paper was authored by Claire Wingfield from PATH in consultation with Kaitlin Christenson from the Global Health Technologies Coalition (GHTC) and with support from Tricia Aung (GHTC), Nick Taylor (GHTC), and John Ballenot (PATH). We would like to thank our paper series advisory committee members: Rachel Cohen (Drugs for Neglected Diseases *initiative*), Mary Moran (Policy Cures), Eileen Quinn (PATH), Judit Rius (Médecins Sans Frontières), John-Arne Rottingen (Harvard University), Jane Rowley, Katharina Scheffler (Deutsche Stiftung Weltbevoelkerung), and Rachel Wilson (PATH). The views expressed in this paper are not attributed to any one individual or organization represented on the committee. We would also like to thank the nonprofit product development organizations that participated in this analysis: Aeras, Drugs for Neglected Diseases *initiative*, Infectious Disease Research Institute, International AIDS Vaccine Initiative, International Partnership for Microbicides, International Vaccine Institute, Jhpiego, Medicines for Malaria Venture, PATH, Sabin Vaccine Institute, and TuBerculosis Vaccine Initiative. Finally, we would like to recognize contributions made by Loren Becker (GHTC) who advised this work in an informal capacity.

Suggested citation: Global Health Technologies Coalition (GHTC): *Addressing Regulatory Challenges Throughout the Product Development Process: Perspectives From Nonprofits on Accelerating Product Development and Improving Access for Low- and Middle-Income Countries Vol. 4*. Washington, DC: Global Health Technologies Coalition; 2014. Available at http://ghtcoalition.org/NPPD-briefing-paper-series.php.

Addressing regulatory challenges throughout the product development process

Perspectives from nonprofits on accelerating product development and improving access for low- and middle-income countries

Background

Purpose and aims

The Global Health Technologies Coalition's briefing papers on financing and coordination of health research provide examples and perspectives from nonprofit product development organizations (NPPDs). NPPDs are nongovernmental organizations that partner with the public, philanthropic, not-for-profit, and private sectors to develop technologies targeted at neglected diseases and conditions of high morbidity and mortality in low- and middle-income countries (LMICs).[a]

This series of papers is meant to inform discussions aimed at improving the financing and coordination of health research and development (R&D) addressing the needs of LMICs. These papers may also inform implementation of activities as called for in a resolution passed at the 66th World Health Assembly in May 2013.[1]

The actions outlined in the World Health Assembly resolution are based on recommendations in the 2012 report from the World Health Organization (WHO) Consultative Expert Working Group (CEWG) on R&D. The CEWG identified major challenges to advancing R&D to meet the health needs of LMICs and made recommendations to improve the coordination of priorities and activities, increase financing of all phases of research, and enhance monitoring of R&D investments.[2]

The World Health Assembly resolution called for:

- Establishing a global R&D observatory at WHO that would act as a central coordinating mechanism to monitor and analyze relevant information on health R&D. The observatory would help to identify gaps and opportunities for R&D and define priorities in consultation with relevant stakeholders, as appropriate.
- Implementing several health R&D demonstration projects to address identified gaps that disproportionately affect LMICs.
- Establishing long-term, sustainable financing and coordination mechanisms, including pooling resources and voluntary contributions, to be assessed and considered at a later date.

The first paper in this series set the stage by providing examples of how NPPDs approach product development and describing the key challenges that NPPDs and their partners face in developing and introducing technologies that address the health needs of LMICs. The second paper provided the perspectives of NPPDs on the most significant funding challenges and the types of financing mechanisms that support their work. The third paper described how NPPDs and their partners try to ensure access in LMICs to the knowledge and technologies they develop. This fourth paper outlines the most significant regulatory challenges faced by NPPDs and partners throughout the product development process and describes how these challenges affect their work.

[a] The list of diseases is based on the list referenced in Policy Cures's *Neglected Disease Research and Development: A Five-Year Review* (available at: http://www.policycures.org/downloads/GF2012_Report.pdf) and is not an exhaustive list of neglected diseases. Those covered by surveyed NPPDs include bacterial pneumonia and meningitis, dengue fever, diarrheal diseases, helminth infections, HIV, kinetoplastids, leprosy, malaria, trachoma, tuberculosis, and typhoid. We also included technologies that address maternal, newborn, and child health, and sexual and reproductive health conditions.

Methodology

This analysis relies on publicly available data and information collected through interviews with representatives from five NPPDs and reviewed by representatives from an additional six NPPDs (see Appendix for list of NPPD contributors). Interviewees and reviewers were asked to identify the most significant regulatory challenges and describe how they affect the work of each organization. They also described lessons learned and recommendations for improving regulatory pathways.

Introduction

Regulatory review is an integral part of the product development process and plays a role at every step along the way, no matter the type of health technology (see Figure 1). Each step of the regulatory process depends on having the correct data. Product developers and manufacturers need to consider what information should be collected from the earliest stages to achieve final approval in accordance with international standards. Developers must design a study plan that will provide the data necessary to prove that the investigational product—whether a drug, vaccine, diagnostic, or medical device—is safe and effective. Before any clinical trial or field test can be initiated, regulatory authorities must review and verify the quality of and rationale for the proposed study. Likewise, regulators must approve a new health product before it can be used by patients. After a product has been registered, regulators (and manufacturers) are expected to monitor its use in the general population to ensure ongoing safety and efficacy.

National regulatory authorities (NRAs), stringent regulatory authorities (SRAs), and WHO are critical players who shape the regulatory landscape and monitor compliance with the regulatory requirements for technologies that address the health needs of LMICs (see Figure 2). The specific role and influence of these bodies depends on the regulatory strategy a developer chooses for a product. Product developers and manufacturers consider numerous factors when selecting a regulatory pathway, such as national regulatory capacity and requirements in the country where a product will eventually be distributed, whether the product needs to be eligible for purchase by global procurement institutions (which may require WHO prequalification), and in-country manufacturing requirements. As a result, developers often engage a combination of regulatory authorities as well as WHO throughout the regulatory process.

Although all countries have regulatory authorities that are responsible for monitoring the safety, efficacy, and quality of health technologies used

Figure 1. Examples of regulatory milestones throughout the R&D continuum.

Protocol review	Regulatory authorities review study protocols to assess whether: • The study design will answer the necessary clinical questions. • The preclinical data are sufficient to support the study design. • The study staff and site(s) meet international standards. • The manufacturing and testing processes meet international quality standards
Product registration	Regulatory authorities review a product dossier that contains efficacy, safety, and quality data and inspect manufacturing facilities to determine product eligibilty for registration in each country.
World Health Organization (WHO) Prequalification	If the product is eligible for consideration for prequalification, WHO reviews the product dossier to determine eligibility for prequalification for countries with procurement mechanisms.
Postmarketing surveillance	Regulatory authorities monitor the product's safety and efficacy in the general population. Regulatory authorities and WHO monitor manufacturers to ensure continued adherence to international standards of Good Manufacturing Practices.

Figure 2. Collaboration among important stakeholders in the regulatory landscape for products being developed for use in LMICs.

National regulatory authorities monitor the safety, efficacy, and quality of health technologies used within a country.

Stringent regulatory authorities are NRAs that are members, observers, or associates of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

The World Health Organization (WHO) provides guidance and support to countries to strengthen their regulatory capacity and ensure health products meet stringent international standards.

within a country, the capacity of NRAs varies greatly. WHO recently reported that 80 percent of WHO member states lack the capacity to effectively regulate health products domestically.[3] Many of these regulatory authorities are located in LMICs that are targeted by NPPDs and partners. For the purposes of this paper, the term NRA refers to regulatory authorities in LMICs with limited capacity, infrastructure, and resources to oversee multiple stages of the product development lifecycle, including testing and evaluation of products and product registration, and postmarketing surveillance in accordance with international standards.

SRAs are NRAs (with the exception of the European Medicines Agency, which is a regional regulatory body), but not all NRAs are SRAs. Officially, SRAs are members, observers, or associates of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[b] ICH is a joint initiative by the European Union (EU), Japan, and the United States that aims to harmonize international regulatory requirements by establishing agreed-upon core competencies within the three ICH regions—the EU, Japan, and the United States. The technical guidelines and requirements are based on consensus between regulatory experts, product developers, and manufacturers. Some NRAs have adopted these guidelines, but the extent to which the guidelines have been implemented and enforced by NRAs varies.

SRAs—such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMA)—provide additional regulatory support to facilitate development of technologies targeting the health needs of LMICs. SRAs have the resources and capacity to enforce strict regulatory requirements. They enhance the global regulatory environment in numerous ways, such as by providing technical guidance to groups developing health products intended for LMICs, engaging in regional harmonization initiatives, and strengthening capacity of regulators in LMICs.

Although not a regulatory authority, WHO can be a critical stakeholder in a product's regulatory pathway. The WHO prequalification (PQ) program certifies that certain health products—vaccines, drugs, diagnostics, and medical devices—for high-burden diseases and conditions meet global standards for quality, safety and efficacy, and PQ approval is required for these products to be procured by United Nations (UN) agencies. A product must be registered by a regulatory authority

[b] ICH members: EU member states, European Federation of Pharmaceutical Industries and Associations, Japan, and the United States. ICH observers: European Free Trade Association currently represented by Swissmedic, Health Canada, and WHO. ICH associates through mutual recognition agreements: Australia, Norway, Iceland, and Liechtenstein.

Table 1. Overview of regulatory initiatives and mechanisms aimed at streamlining and harmonizing regulatory processes for products targeting LMICs.[c]

Regulatory initiative/ mechanism	Description
Capacity strengthening	
African Vaccine Regulatory Forum (AVAREF)	AVAREF supports national regulatory authorities (NRAs) in the assessment of clinical trial applications, the monitoring of clinical trials, and the evaluation of clinical data in registration dossiers of vaccines. It provides a forum for African regulators to strengthen their capacity and align regulatory opinions to expedite the review of clinical trials and new vaccines. AVAREF has made considerable progress toward the harmonization of regulation of clinical trials. Furthermore, as more products progress through clinical development stages, AVAREF plays a larger role in organizing joint reviews of clinical trials of vaccines.[4]
Developing Country Vaccine Regulators' Network	Through collaboration, the Developing Country Vaccine Regulators' Network strengthens NRAs in developing countries where vaccines are manufactured. Member countries include Brazil, Cuba, India, Indonesia, Iran, China, Korea, South Africa, and Thailand.[5]
Expediting regulatory review	
European Medicines Agency (EMA) Article 58	Article 58 is a mechanism in which the EMA, in cooperation with WHO, can provide a scientific opinion for the evaluation of drugs and vaccines intended for use exclusively in markets outside of the European Union. This scientific opinion must then be adopted by NRAs. To be eligible for this mechanism, products must be used to treat diseases of major public health interest, including HIV/AIDS, malaria, tuberculosis, and other neglected diseases.[6]
US Food and Drug Administration (FDA) Accelerated Approval	The FDA's accelerated approval process allows expedited registration of drugs based off surrogate endpoints. Drugs must be treatments for serious and life-threatening diseases, such as multidrug resistant tuberculosis, for which there are few—if any—treatment options.[7]
FDA Priority Review	The FDA's priority review designation requires the FDA to review final drug dossiers within six months (compared to a standard review time of ten months). The FDA has implemented a related but separate program—the Priority Review Voucher—to incentivize investment in developing products for LMICs. Priority Review Vouchers are awarded to the regulatory sponsor of a newly approved drug or vaccine that targets a neglected tropical disease and can be used for a future product of its choosing.[7]
FDA Breakthrough Therapy	The FDA's breakthrough therapy designation allows for expedited development and review of a drug if it is intended to treat a serious and life-threatening condition and preliminary clinical evidence demonstrates that the drug may provide substantial improvement over existing therapy.[7]
World Health Organization (WHO) Prequalification	WHO prequalification is a mechanism to ensure that products are safe, appropriate, and meet stringent quality standards. It is not meant to replace the work of NRAs. A product must receive prior approval from a regulatory authority before being reviewed by WHO. The prequalification process involves a product dossier assessment, inspection of manufacturing and testing sites, and quality control testing. It is important to note that the list of products—including drugs, vaccines, diagnostics, and medical devices—included on the WHO prequalified list does not include all essential tools.[8]
Harmonization	
African Medicines Regulatory Harmonization (AMRH)	The AMRH initiative aims to increase access to essential medicines in African countries and regional economic communities by building medicine regulatory systems. This is achieved through harmonization of application formats and technical requirements, as well as capacity strengthening.[9]
Association of Southeast Asian Nations (ASEAN) Pharmaceutical Product Working Group	ASEAN is a union of ten Southeast Asian nations that aims to accelerate economic growth, social progress, and cultural development within the region. The ASEAN Pharmaceutical Product Working Group is working to harmonize regulation of drugs within ASEAN member countries. Specifically, the group aims to eliminate technical barriers to trade brought on by these regulations, without compromising drug quality, safety, and efficacy.[10]
Pan American Network for Drug Regulatory Harmonization (PANDRH)	PANDRH is an initiative of regulatory authorities within the Pan American Health Organization that supports the harmonization of pharmaceutical regulation in the Americas. PANDRH aims to promote harmonization of pharmaceutical regulation, strengthen regional NRA capacity, and recognize advances in science and technology.[11]

[c] The majority of the initiatives and mechanisms established to streamline regulatory pathways in LMICs have targeted vaccines and drugs and only minimally address regulatory issues for medical devices and diagnostics.

before it can be reviewed by the PQ program. A product that receives prequalified status from WHO is eligible to be purchased by UN procurement agencies. Because this has a significant impact on product access and market shaping, the WHO PQ program is an early and important consideration in the product regulatory strategy of some NPPDs. It is important to note that some products targeting poverty-related and neglected diseases and conditions are not eligible for consideration by the WHO PQ program, and WHO thus plays a less important role in their regulatory pathway.[8]

For many new health products used in LMICs, NRAs have relied on approval by well-resourced and more experienced regulatory authorities as a proxy for product registration. But as NPPDs and other developers create new technologies specifically designed to address health needs in LMICs, there is growing interest among NRAs to rely less on regulators in high-income countries and strengthen their own capacity to take on more responsibility for regulating products being used in their countries.[12] Additionally, NRAs are increasingly being expected to play a role in regulating products being used globally as manufacturing of products (or components of these products) used in all countries is shifting to LMICs.[13]

Although costs for product developers and manufacturers to comply with regulatory requirements are a large—and growing—component of R&D costs, and regulatory challenges can delay timely access to technologies for patients, regulatory reform was largely absent from the 2012 WHO CEWG report and the resolution passed at the 66th World Health Assembly in 2013. The CEWG acknowledged the need to strengthen regulatory capacity, particularly within national regulatory bodies in many LMICs, but it did not consider regulatory harmonization as contributing to improved financing or coordination of health R&D and, therefore, did not consider this within its mandate.[2] A number of NPPDs, their partners, and R&D advocates have noted that the failure of the CEWG to address regulatory systems in LMICs in its recommendations was a significant weakness. This paper will outline the most significant challenges that NPPDs and partners encounter throughout the R&D continuum to demonstrate how regulatory challenges impede their ability to accelerate R&D and increase the costs of product development.

Findings

Regulatory processes and challenges can vary widely by product platform as well as geography. Each organization's regulatory experience, expertise, and investment will vary depending on where its work is focused. For instance, an organization that is primarily working on late preclinical and early clinical phase research will be more focused on clinical trial protocols as compared to an organization that is in late-stage development and preparing to register a new product. Competing definitions (and priorities) can make it difficult to understand what expertise is needed to successfully navigate the regulatory landscape at the country level where the products are going to be used. And although many regulatory authorities (SRAs and NRAs in LMICs) encourage developers to approach them at the earliest stage possible, NPPDs often feel they do not have sufficient access.

Even when NPPDs can get access to regulators, there are challenges. SRAs have the technology-specific expertise needed to provide technical guidance but may lack clinical understanding of many neglected diseases, and they are located in countries that are less likely to register the products being reviewed. Given that most products developed by NPPDs are destined for LMICs with limited regulatory capacity, this lack of capacity and resources to provide developers and manufacturers with guidance can be a significant hurdle and lead to considerable, costly delays in product development and introduction and could mean reduced protection for patients.

NPPDs are strengthening their capacity to navigate the regulatory pathways to product approvals.

These organizations are increasingly the sponsor for new product registration and are working more with partners from academia and the private sector in LMICs who have little regulatory experience in developing and testing (in accordance with international standards) and registering new technologies. In addition, as their product pipelines evolve, so does the need for greater regulatory capacity within NPPDs.

Many NPPDs are already the regulatory sponsors for clinical trials and field studies. In this role, NPPDs are responsible to the relevant regulatory authority for compliance with all requirements, including ensuring these studies are implemented in line with ICH standards of Good Clinical Practices and Good Laboratory Practices. Increasingly, some NPPDs are the regulatory sponsor for registration of new products. For example, the International Partnership for Microbicides is taking the lead on registering the Dapivirine Microbicide Ring in select African countries as well as with one or more SRAs upon completion of phase 3 studies. As NPPDs take on more responsibility for the full development of technologies in their portfolios and partner more with small to midsize companies and research institutions with less regulatory experience, they will also be taking on increasingly complex regulatory challenges to ensure adherence to globally recognized standards.

Because every step of the product development process has a regulatory component, respondents from each of the contributing NPPDs noted the importance of including a regulatory plan in their broader development strategy that outlines how a new technology will be validated as well as accessed by patients and health systems. This plan is an integral part of each phase of the development strategy and should indicate when NPPDs will engage with which regulatory bodies in LMICs as well as with which experts within SRAs and WHO. Ideally, NPPDs and partners should engage with regulators throughout the product development process to develop and implement their regulatory strategy to ensure alignment with international standards and shared expectations among regulators, developers, and manufacturers.

The regulatory challenges identified and validated by our respondents follow three broad themes: a complex global regulatory environment, weak regulatory capacity in LMICs, and the need for increased investment in regulatory capacity within NPPDs (see Table 2). Each of these challenges has a significant impact on the ability of NPPDs and partners to conduct their work. These challenges increase the costs of product development, cause delays in product introduction, and complicate an already difficult process.

Table 2. Key regulatory challenges identified by respondents.

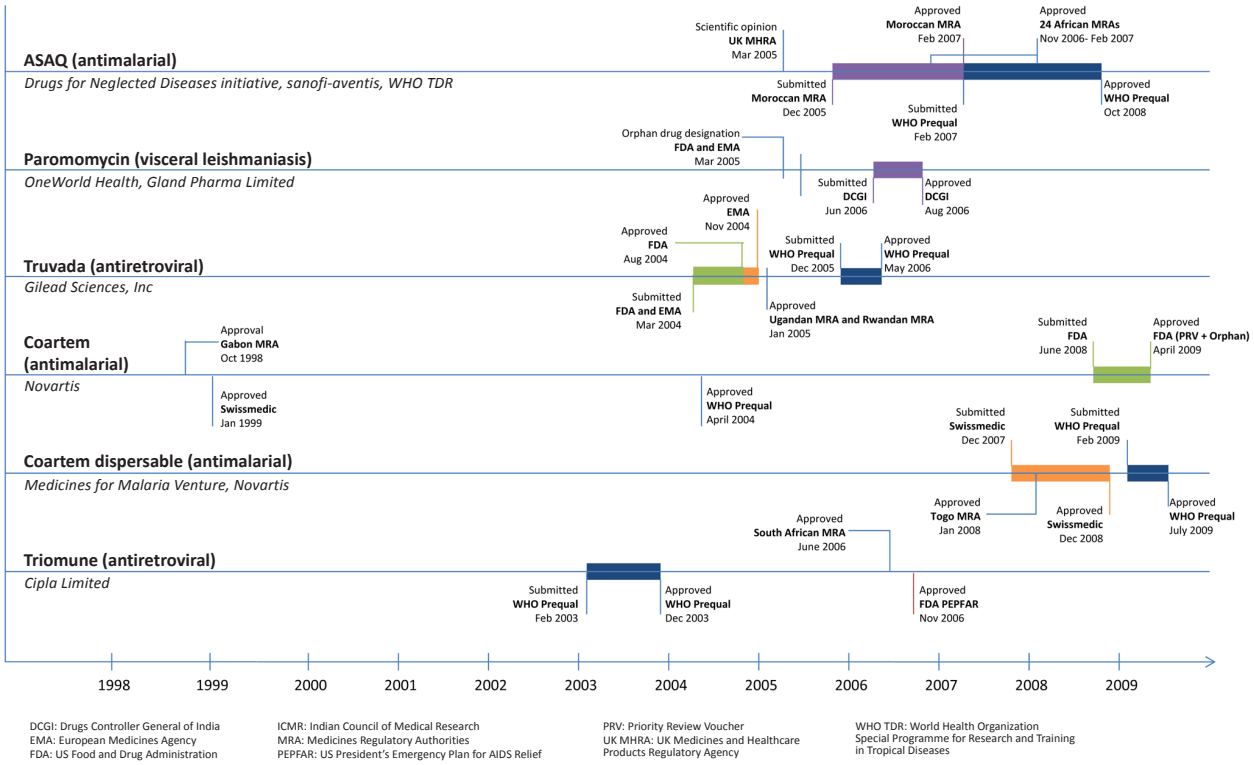
Complex global regulatory environment: the regulatory landscape for products targeting the health needs of LMICs is difficult to navigate because of the different levels of regulatory oversight across a spectrum of experience and expertise.
Weak regulatory capacity in LMICs: regulatory authorities in LMICs lack sufficient resources to reliably evaluate and monitor the safety, efficacy, and quality of all types of health products.
The need for increased investment in regulatory capacity within NPPDs: the robust pipelines and increasing product responsibilities necessitate strengthening internal regulatory capacity of the NPPDs.

Complex global regulatory environment

The regulatory landscape for health products targeting the needs of LMICs encompasses many stakeholders, mechanisms, and levels of oversight on the global, regional, and national levels. The role and impact of each varies based on the type of technology, the health condition being addressed, and the targeted geographies. Subsequently, developers often engage a number of regulatory stakeholders throughout a product's lifecycle.

Because the technologies being developed by NPPDs and partners are targeting the health needs of LMICs, most will not be implemented in high-income countries like the United States and many European countries. Despite this, NPPDs and partners often seek advice from SRAs on regulatory strategies and protocol design, and in some cases,

Figure 3. Examples of drug registration timelines.[14]



DCGI: Drugs Controller General of India
EMA: European Medicines Agency
FDA: US Food and Drug Administration

ICMR: Indian Council of Medical Research
MRA: Medicines Regulatory Authorities
PEPFAR: US President's Emergency Plan for AIDS Relief

PRV: Priority Review Voucher
UK MHRA: UK Medicines and Healthcare Products Regulatory Agency

WHO TDR: World Health Organization Special Programme for Research and Training in Tropical Diseases

they submit applications for product registration. NPPDs may target SRAs for initial product registration because their approval can facilitate (and at times expedite) regulatory processes in LMICs with limited regulatory infrastructure as well as the WHO PQ process.

NPPDs and partners may also engage with regional harmonization efforts through initiatives such as Association of Southeast Asian Nations (ASEAN), Pan American Network for Drug Regulatory Harmonization (PANDRH), and African Medicines Regulatory Harmonization (AMRH) to clarify and align requirements and processes across regions. Finally, at the country level, developers must work with the NRA in each country where they want to conduct a study and in each country where they plan to register a technology. Depending on the expertise, experience, and requirements across each of the NRAs, this could entail multiple application filings and regulatory reviews.

Because of the complexity of the regulatory landscape, many NPPDs and partners face unclear signals about which regulatory body to approach first for product registration, what the requirements are for each review, and whether these reviews can take place concurrently or must be conducted sequentially. Because concurrent reviews require resources that many NPPDs do not have, these reviews may be conducted sequentially, prolonging the time from first regulatory approval to the product being available in LMICs (see Figure 3).

The WHO PQ program has different pathways for vaccines than for other technologies.[15] Vaccines must first be approved by a regulatory authority that has demonstrated competency in six critical functions in ensuring vaccines are evaluated properly and meet international standards of quality and safety. If WHO has determined that an NRA can implement and enforce these requirements, then the regulatory authority is deemed functional.

By contrast, drugs and medical device technologies that are included on the WHO PQ list may by prequalified regardless of the functional status of the NRAs giving prior approval. For example, the Drugs

for Neglected Diseases *initiative*, in partnership with Sanofi, was able to get ASAQ (artesunate-amodiaquine antimalarial fixed-dose combination therapy) prequalified even though it had only been approved by the Moroccan regulatory authority, which has not been deemed functional by WHO. The WHO PQ program requires that manufacturers of drugs and medical devices are able to produce a product that meets quality standards and the manufacturing facilities and procedures comply with Good Manufacturing Practices, but it does not assess the capacity of the regulatory authority.

To demonstrate the challenge of determining the best regulatory pathway, one respondent described the multiple routes that her organization, which is developing vaccines targeting LMICs, is considering for registering its vaccines (see Figure 4). Although the NPPD could file with the NRA in the country of manufacture, because the technology is a vaccine, the NRA must be considered functional to be eligible for eventual WHO PQ approval. Given the limited number of NRAs that are deemed functional, this approach limits the organization's options, particularly in many of the target LMICs.

Another option is for the NPPD to submit an application for product registration to the US FDA, which has a program that allows for review of products that will not be used in the United States as long as studies are conducted under the ICH definitions of Good Clinical Practices and Good Laboratory Practices. Unfortunately, this review may not be a priority for the FDA, which is already overburdened regulating products being used in the United States.

The NPPD could also use the EMA's Article 58, which allows for the EMA to provide a scientific opinion on a technology that is not to be marketed within the European Community. Although Article 58 can be used to fast-track WHO PQ approval, there are a number of caveats. To be eligible, the entity seeking approval must have a point of contact registered in the EU. In addition, because the EMA provides an opinion rather than regulatory approval, the EMA's decision may not be adopted as readily by NRAs. It is important to note that these FDA and EMA mechanisms do not cover reviews of diagnostics and other medical devices and do not monitor manufacturing or conduct postmarketing surveillance—both critical regulatory activities.

As previously noted, competing and misaligned requirements across regulatory authorities in high-, middle-, and low-income countries have created a confusing landscape for NPPDs

Figure 4. Examples of potential regulatory pathways for product registration.

Expediting regulatory review: European Medicines Agency Article 58

Through Article 58 of the regulations governing the European Medicines Agency (EMA), the EMA can give a scientific opinion—with the cooperation of the World Health Organization (WHO)—for the evaluation of drugs and vaccines intended for use outside the European Community. The EMA enacted Article 58 in 2004 in response to the need to protect public health and to give scientific assistance to nonmember countries while allowing for faster access to important new medical products for countries outside the European Community. The EMA and WHO decide on a case-by-case basis whether a product falls within the mandate of Article 58.

Article 58 is an appealing resource given that the quality, safety, and efficacy criteria are the same ones used for any other EMA evaluation. Although the use of Article 58 does not result in product approval, the national regulatory authority approval process may result in a more positive outcome due to WHO involvement. Furthermore, for vaccines evaluated under EMA's Article 58, the WHO prequalification process can be significantly reduced.

Because of limited awareness and understanding of Article 58, it has not been widely used by developers. This mechanism has been instrumental, however, in the regulatory strategy of some NPPDs. NPPDs such as Drugs for Neglected Diseases *initiative*, International Partnership for Microbicides, and Medicines for Malaria Venture (MMV) have received valuable guidance and scientific advice through Article 58 to inform their regulatory strategies. MMV used the favorable Article 58 scientific opinion of Pyramax®—a fixed-dose artemisinin-based combination therapy approved to treat *Plasmodium falciparum* and *Plasmodium vivax* blood-stage malaria. Within a year, MMV received approval by the Korea Food and Drug Administration, and Pyramax® is included on WHO's list of prequalified medicinal products. Article 58 has the potential to substantially expedite the process of getting new health technologies to people in need.

and partners. Respondents cited duplicative efforts—ranging from regulators reviewing the same information against different standards to repetitive manufacturer inspections—as straining the overstretched resources of NRAs and SRAs as well as the resources of NPPDs and their partners. Respondents are encouraged by regional harmonization efforts under way among NRAs as well as efforts by SRAs to streamline information sharing, but they warn that because consensus requires compromise, it also requires patience from all stakeholders. As a reminder, one respondent noted that it took the EU decades to establish the EMA and harmonize its regulatory efforts across the region.

Weak regulatory capacity in LMICs

Because many NRAs in LMICs are often poorly funded, understaffed, and overburdened, they lack the resources to provide adequate guidance to developers and proper oversight over many of the products being studied, introduced, and used in their countries. This is particularly true for medical devices, which are less likely than drugs and vaccines to be regulated in LMICs. Respondents noted that many of the capacity issues facing NRAs are often a result of lack of political will from other branches of government (e.g., ministry of finance) to adequately invest in strengthening regulatory capacity and ensuring harmonization with other regulatory authorities. There is also the challenge of balancing the needs of the central and subnational governments, which may have overlapping duties and responsibilities for inspecting manufacturing sites, clinical trial oversight, and regulatory review. This makes it more difficult to navigate the regulatory requirements, especially if there is duplication of responsibilities. The limited ability of and resources available to NRAs often result in significant delays in starting trials and registering much-needed interventions. These delays may result in financial costs and ultimately health costs in terms of delayed access to products.

For instance, before the Infectious Disease Research Institute was able to initiate a phase 1 clinical trial of its *Leishmania* vaccine in India, eight separate institutions were required to review the protocol: (1) Central Ethics Committee on Human Research

of the Indian Council of Medical Research, (2) the Indian Council of Medical Research, (3) Ministry of Science and Technology, (4) Drugs Controller General of India–Import License, (5) Drugs Controller General of India–Clinical Trials, (6) Health Ministry Screening Committee, (7) Genetic Engineering Approval Committee, and (8) Banaras Hindu University Institutional Ethics Committee. This review process took more than one year to complete.

The inability of most NRAs in LMICs to provide effective oversight of the quality, safety, and efficacy of products in accordance with ICH standards means that NPPDs and partners often seek guidance from regulators and partner with manufacturers outside of their target geographies. To identify the NRAs that can enforce regulations in accordance with stringent international standards, WHO has established core competencies that define what it takes for a regulatory authority to be deemed functional. As was previously mentioned, this designation is only relevant to vaccine regulation.[d] This functional status not only certifies that the NRA is enforcing international standards of quality, safety, and efficacy but also serves as a prerequisite for local manufacturers to supply vaccines to countries through UN procurement agencies. The ability of UN agencies to procure technologies from manufacturers in LMICs can have a significant, beneficial impact on the global supply of quality-assured products, as well as contribute to local economies.

In 2011, the NRA of China, the State Food and Drug Administration (now known as China Food and Drug Administration), received a functional status designation by WHO. As a result, vaccine manufacturers in China became eligible to apply for WHO prequalification as long as their products meet WHO quality and safety standards. WHO added the first Chinese-manufactured vaccine—against Japanese encephalitis—to its list of prequalified vaccines in December 2013. This will enable millions of people living in poor rural communities in Asia to access this vaccine.

When an NRA is deemed competent to regulate vaccines and is therefore considered functional, it does not guarantee that the NRA has the experience, knowledge, and infrastructure to review and register new vaccines. Respondents noted that a functional

Strengthening regulatory alignment: The African Vaccine Regulatory Forum

The African Vaccine Regulatory Forum (AVAREF) was established by the World Health Organization (WHO) in 2006 to strengthen the capacity of African regulatory authorities to regulate vaccines. It also provides a platform for increased alignment among national regulatory authorities (NRAs) in the region. AVAREF membership includes 21 countries that are targeted for or are currently hosting vaccine clinical trials but lack the capacity to provide comprehensive regulatory oversight. The WHO African regional office serves as secretariat for AVAREF and coordinates its activities. To date, three NPPDs have engaged with AVAREF—the Meningitis Vaccine Project (MVP), PATH's Malaria Vaccine Initiative (MVI), and Aeras.

MVP is a partnership between PATH and WHO that was created to accelerate the development and introduction of MenAfriVac®, a vaccine against meningitis A, the most common epidemic strain of meningitis in Africa. AVAREF conducted two joint protocol reviews and two joint reviews of clinical trial sites for MenAfriVac®. AVAREF also conducted a joint protocol review for a phase 3 study of the RTS,S/AS01 malaria vaccine candidate, developed by GlaxoSmithKline Biologicals in partnership with MVI. The clinical trial involved 11 sites in seven African countries. The clinical trial was approved and initiated in all participating countries within the next year. The joint reviews helped to standardize requirements among the participating NRAs and expedite regulatory reviews. Aeras—an NPPD developing tuberculosis vaccines—and partners consulted with AVAREF to get input on innovative trial designs as well as increase AVAREF member organizations' understanding and ability to critically review products as relevant to their country context.

[d] List of countries with functional NRAs producing vaccines prequalified for purchase by UN agencies: Africa (Senegal); Asia (China, India, Indonesia, Japan, Korea); Australia (Australia); Europe (Belgium, Bulgaria, Denmark, France, Germany, Hungary, Italy, The Netherlands, Russia, Sweden, Switzerland); North America (Canada, United States); South America (Brazil, Cuba). List is available at http://www.who.int/immunization_standards/national_regulatory_authorities/offices/en/.

NRA may have experience ensuring the safety and efficacy of products that already exist but not have expertise in licensing new compounds. In other words, the NRA may have met WHO standards for ensuring that the safety and efficacy of existing vaccines are in line with international standards but not have evaluated and registered a novel vaccine. To address this gap (in vaccine regulation as well as for other health products), NRAs have worked with NPPDs and partners, other NRAs, SRAs, and WHO to develop and implement innovative regulatory mechanisms to improve capacity and strengthen alignment among NRAs (see Table 1).

Engagement with NRAs through African Vaccine Regulatory Forum (AVAREF) has provided NPPDs and partners the opportunity to interact with regulators early in the development process. These consultations with regulators in their target countries have allowed NPPDs to get input from regulators on trial design and improve alignment among the NRAs, thereby building trust and creating more efficiencies within regulatory review processes for some products.

Many of these efforts focus on strengthening systems and processes for vaccine and drug regulation. However, regulatory systems for medical devices (including diagnostics) are less developed than those for drugs and vaccines. According to a WHO survey, only 65 percent of the 145 responding countries reported having a national authority that was mandated to implement and enforce medical device regulations.[16] In addition, few countries that have drafted regulations have actually implemented them. For instance, the only medical devices monitored by the South African regulatory authority, the Medicines Control Council, are a limited number of electromagnetic devices (or radiation emitting devices). In 2008, South Africa passed legislation to create a new regulatory agency, the South African Health Products Regulatory Agency, with a mandate to include medical devices in its portfolio, but regulations have not yet been formalized or issued. The quality and use of medical devices in many LMICs cannot be ensured to be in line with international standards.

Respondents also noted that some NRAs have lacked transparency and consistency in their processes and requirements. NRAs have unexpectedly changed requirements with little to no explanation or demanded additional studies that were not part of the original plan before registering a product. These changes make it challenging for NPPDs and partners to stay abreast of regulatory requirements and on schedule. Because these changes are beyond the NPPD's control and often cannot be accounted for in a regulatory strategy and timeline, these delays often increase costs.

Insufficient investment in regulatory capacity within NPPDs

NPPDs range in scope, focusing on research activities in various phases of product development. Therefore, the level of engagement and investment in regulatory activities varies across the spectrum of organizations. Regardless of their organizational experience and expertise, however, NPPDs are working more with regulators and deepening their understanding of requirements as their portfolios grow and products advance through the pipeline.

In their early days, NPPDs relied on private-sector partners or consultants for regulatory expertise, particularly in planning for product registration, and in-house regulatory expertise was not a high-priority area for investment. As a result, regulatory resources within NPPDs are fragmented, resulting in limited in-house capacity across the spectrum of regulatory activities, particularly in the later stages involving product registration and postmarketing surveillance. Most NPPDs have few staff dedicated to regulatory activities. In fact, regulatory functions are often split among several team members or outsourced completely.

However, some NPPDs are relying less on commercial partners based in high-income countries as products advance through the pipeline and regulatory requirements become more complex. Despite the fact that large, multinational partners often have extensive regulatory experience, they may not have an understanding of NPPDs' high-

Pioneering a regulatory pathway: International Partnership for Microbicides

While a regulatory strategy is important to any product development plan, regulatory planning is even more crucial when no pathway exists. Since 2002, the International Partnership for Microbicides (IPM) has focused on developing antiretroviral-based microbicides for use by women in LMICs, particularly those at high risk of HIV infection. Because microbicides for HIV prevention do not currently exist on the market, regulatory requirements for product development and licensure are unclear. Regulators from national regulatory authorities often have limited understanding of the microbicide field, which further challenges regulatory planning.

To navigate this difficult regulatory environment, IPM's strategy involves early engagement with numerous regulatory stakeholders. IPM has been working with the South African Medicines Control Council (MCC) to outline the clinical data needed to register the first-ever microbicide. The MCC will be the first regulatory authority to approve IPM's Dapivirine Microbicide Ring. IPM, with a five-year grant from the European Commission to support regulatory and ethics capacity strengthening, has held annual meetings with nine regulators from African countries. These meetings have facilitated knowledge sharing on microbicides and provided an opportunity for regulators to share expectations for clinical trials.

IPM is also pursuing joint scientific review for the Dapivirine Microbicide Ring through the European Medicines Agency's Article 58 and the US Food and Drug Administration (FDA). IPM's interactions with these bodies have highlighted the uncertainty of microbicide regulation and inspired development of regulatory pathways for microbicides. For example, the FDA released its first draft guidance on the development of vaginal microbicides for HIV prevention in November 2013.

IPM has additionally been actively engaged with the World Health Organization to ensure that the Dapivirine Ring will be prequalified and eligible for purchase by global procurement agencies. Through these activities, IPM has established a model for a microbicide regulatory strategy and built mutual trust and respect between the regulators and developers, facilitating regulatory planning for future microbicides.

priority diseases and target countries and may not prioritize investments in products targeting poverty-related and neglected diseases and conditions. Therefore, companies are less willing to invest regulatory resources in products that are not likely to generate significant profits. At the same time, commercial and academic partners based in LMICs may have extensive knowledge about the target disease but limited regulatory understanding and expertise outside their own geographies. So as their innovation pipelines grow, NPPDs are taking over more aspects of product development programs and recognizing the need to increase their role in regulatory affairs.

The lack of regulatory experience of smaller development partners and the lack of established regulatory policies to ensure compliance with international standards are of increasing concern for NPPDs. The lack of policies is an especially important challenge for the medical devices field because of the broad spectrum of products. For instance, one respondent noted that an academic research partner initiated preclinical research on a drug/device combination product and started to plan for clinical evaluation of the product without developing a target product profile (TPP). The TPP, which outlines the product requirements, should guide product development research efforts, including the regulatory strategy. The initiation of studies prior to establishing the TPP highlights the need for NPPDs and partners to implement structured and informed product development processes that adhere to recognized standards and practices.

Conclusion

The regulatory landscape for R&D of health products to address poverty-related and neglected diseases and conditions is a complex environment that is evolving as NPPDs and partners continue to grow their pipelines. Increased development of health products targeting the health needs of LMICs is highlighting the need for stronger regulatory systems and increased engagement with regulators to ensure safety, efficacy, and quality around the globe. Respondents outlined some key recommendations:

- **Best practice is to develop a regulatory strategy at the beginning of the development cycle that outlines activities through product registration.** The strategy should determine how and when developers want to engage with regulators, particularly within NRAs in target countries, to ensure that expectations are understood by both groups and to build trust. The strategy should also reference which standards will be followed by the product developers and manufacturers. This can result in more efficient and standardized regulatory pathways, which in return results in significant, long-term cost savings and health impact. Following this best practice also helps to ensure that regulators, NPPDs, and partners are held responsible for meeting quality standards.
- **All regulatory bodies should possess a foundational level of core competencies.** Not all regulatory authorities need the same capacities, but there should be some common minimum standard of oversight that all can enforce. These competencies can be leveraged across regions and among regulatory authorities. For instance, among the NRAs participating in the AMRH regulatory harmonization efforts in the East African Community, certain countries are taking the lead as technical experts on key regulatory activities so that they can provide regulatory support to other East African Community countries to improve alignment with international standards.
- **Regulatory harmonization and capacity strengthening should encourage collaboration of poorly resourced regulatory bodies in LMICs with better-resourced and more experienced regulatory authorities.** This work should include expanding and leveraging existing innovative mechanisms such as AVAREF and Article 58 to improve coordination and alignment across technologies and geographies and provide a platform for technical assistance among NRAs.
- **It is critical to educate non-regulatory stakeholders on the impact of regulatory delays on increasing the cost and length of product development and introduction to make the case for increased investment.** Because regulatory processes are not well understood by policymakers, regulatory reform has not been prioritized among the many competing demands for limited (and in some cases shrinking) resources.

Regulatory challenges can cause significant delays and increase costs for NPPDs and partners, and can ultimately end in fewer lives saved. As the pipeline of products aimed at addressing the health needs of LMICs grows, the more complicated the regulatory issues become. Therefore, stronger collaboration among regulatory stakeholders—including developers, manufacturers, NRAs, SRAs, and WHO—is key to improving regulatory processes and ensuring that the innovation pipeline is filled with technologies that have been developed according to stringent standards of quality. Regulatory oversight is an integral part of making sure that these products are properly designed and developed to be safe and effective to maximize health impact in LMICs.

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