CHAPTER 11

OVERCOMING BARRIERS TO MEDICAL INNOVATIONS FOR LOW-RESOURCE SETTINGS

David C. Kaslow, PATH

Advancing health equity by improving health outcomes of those living in the lowest resource settings is a defining moral imperative of our current epoch. By identifying and overcoming barriers to health equity, individuals, families, and communities benefit from lifelong opportunities to improve well-being and increase economic development and security. A key determinant in achieving health equity in low- and middle-income countries is the successful development, introduction, and uptake of essential biologics, drugs, and vaccines—referred to herein as essential medicines—as well as diagnostics, devices, and health systems and services designed for the specific contexts and needs of those living in low-resource settings.

Developing and increasing access to health technologies for use in low-resource settings presents multi-dimensional challenges. For the subset of health innovations known as essential medicines, these challenges are even greater, and additional interventions are required due to the lack of robust and compelling market-based financial incentives that historically drive innovation and uptake of new technologies. Despite clear and present unmet health needs, innovation in essential medicines and other health technologies for disenfranchised populations has historically remained stagnant. Evolving traditional models of—and/or creating new paradigms for—product development, approval, and access are critical to reduce uncertainties and risks and to create sustainable incentives for public, private, and local stakeholders to significantly improve the pace of development and impact of new health technologies.

Three types of challenges to innovation

Challenges to product development for low-resource settings present in myriad ways throughout the product life cycle. Often, analyses of these challenges focus disproportionately on intellectual property and price, while important drivers of access, affordability, and availability of generic options alone are not sufficient to ensure widespread access and uptake of new health products.

A more holistic and systematic approach to identifying barriers and solutions to innovation and successful multisector collaboration reveals diverse opportunities to develop new products or significantly improve access to health technologies in low- and middle-income countries (LMICs). These barriers can be divided into three main categories.

1. **Biological uncertainties:** include biological hurdles or host response limitations imposed by the target disease or population that create uncertainties or currently insurmountable barriers to the development of new health technologies. For example, available scientific evidence may suggest it is biologically implausible to develop a universal, durably protective vaccine of sufficient safety and efficacy for a given disease. Increased investment in product development activities or changes to regulations or policies will have little to no impact on traversing these biological barriers absent further scientific advances or insights.

2. **Technical uncertainties or risks:** refer to challenges related to processes and/or attributes of health technologies in development or inherent in existing products that limit their production, safety, efficacy, or quality. Such issues include, but are not limited to, manufacturing, formulation, product analytics, stability, bioavailability, or half-life of a product candidate as well as dosing schedules and processes for conducting clinical trials. For example, an effective compound may have a complex and costly synthesis process, rendering production expensive and presenting a barrier for uptake in low-resource settings.

   Some technical challenges can be overcome with increased investment. In many cases, effective therapies exist for diseases present in low-resource settings, but in formulations that are resource intensive or burdensome to store or administer. For example, pulmonary surfactant for the treatment of infant respiratory distress syndrome (IRDS) is generally affordable and available. But it requires advanced healthcare infrastructure, such as ventilation equipment, to administer and monitor the treatment, which limits its suitability in low-resource settings. In such cases, reformulations or innovations to existing products may be the optimal investment to overcome an access barrier.

3. **Human-controlled uncertainties and risks:** relate to recommendations and decisions that drive approvals, investments, or allocation of resources that support product development, accessibility, availability, affordability, acceptability, or sustainability of health technologies. Such decisions can significantly create or overcome barriers to medical innovations in all settings. Political will, appropriate and relevant incentives, sufficient or insufficient allocation of financial and human resources, cost- and risk-sharing—or lack thereof—and favorable or unfavorable ethical, regulatory, and policy decisions can either advance or stall innovation. Evidence-driven shifts in the collective understanding of what is truly impeding access in low-resource settings today and more comprehensive analyses of the value proposition that a particular health technology brings to advancing health equity are needed to overcome these human-controlled uncertainties and risks.

Understanding human-controlled uncertainties and risks

Human-controlled factors act as barriers to innovation and access to new health products—especially those considered essential medicines—throughout the various stages of the product life cycle.

Meta challenges

While some challenges to innovation or access are primarily present at a particular point in the life cycle of a product, this section highlights two challenges—funding and political will—that are omnipresent, manifesting in various ways at each stage.

Funding

Funding for product research and development, implementation and outcomes research, and market analyses for uses of health technologies in low-resource settings remain insufficient. Global funding for basic research and product development for neglected diseases in 2017 was just below US$3.6 billion, with over two-thirds directed to HIV/AIDS, malaria, and tuberculosis (TB),[1] leaving roughly $1 billion remaining for product development for all other neglected diseases. It is estimated that the funding gap between current investment and what is needed to launch one of each of 18 key missing neglected disease essential medicine products in the next five years is at least $1.5 to $2.8 billion annually.[2] This shortage of funding creates and exacerbates challenges throughout every stage of the product development life cycle.

Weak or absent profit incentives for new products for use in LMICs make it difficult to engage private-sector partners and secure their financial investment, capital infrastructure, and human resource capabilities for these products. Product developers are often able to secure partners who provide expertise and resources for work early in the product development life cycle. However, as a product progresses into later and more expensive stages of development and introduction, it becomes harder to secure private-sector funding to advance products. For context, a phase 3 vaccine trial conducted to standards that would suffice for WHO Listed Authorities who perform at a Maturity Level 3 or 4 (WLA-ML 3-4)[3] can cost $200 million or more.[4]

Funding to develop products for low-resource settings comes primarily from a rather short list of donor governments and foundations, such as the Bill & Melinda Gates Foundation (Gates Foundation). This puts product development for specific use in low-resource settings at a severe resource disadvantage as compared to for-profit product development. For perspective, in 2017, the Gates Foundation invested nearly $1.3 billion on global health,[5] but for-profit pharmaceutical developers now spend an average of $2.6 billion per drug.[6]

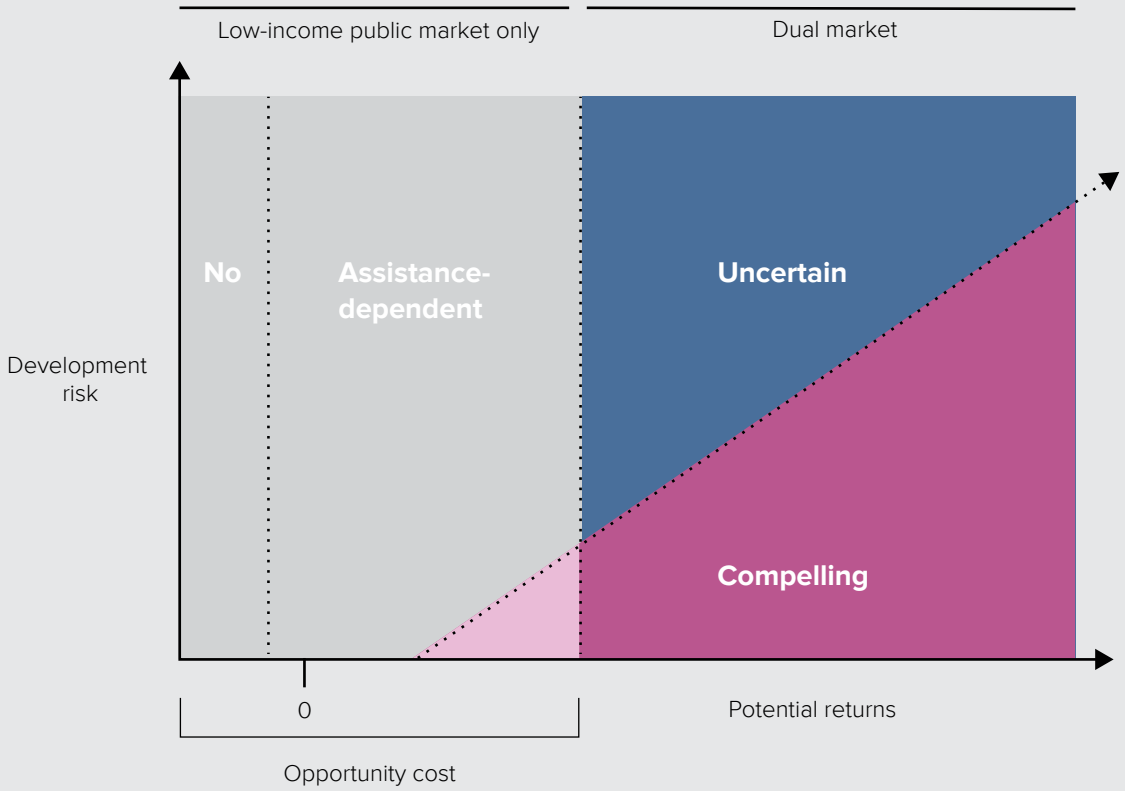
The complexity of challenges related to supporting product development for use in low-resource settings is further complicated by nuanced, but important, differences in the business cases for those products. For example, a product may have use in dual markets—both LMICs and high-income countries (HICs) and both private and public markets—or may have use only in LMIC public markets. Depending on the business case, different solutions have been, or could be, applied to provide sufficient incentives to drive development and introduction investments. Figure 10.1 illustrates these differences. The type of intervention and the epidemiology of the disease also can significantly impact the types of challenges and incentives most applicable to a particular product.

Insufficient donor and health-related funding also impacts health systems and creates challenges specific to research, evaluation, procurement, and administration of health technologies. For example, a consortium of research and development

FIGURE 11.1

Four vaccine business cases

Compelling—Uncertain—Assistance—No



Assistance-dependent business case	**Uncertain** business case	**Compelling** business case
(LMIC only; Outbreak)	(LMIC ↔ HIC)	(HIC → LMIC)
(e.g., LMIC: cholera, malaria, meningitis A, Shigella; Outbreak: Ebola, MERS, Nipah, Lassa fever)	(e.g., group A strep, group B strep, TB)	(e.g., HBV, HiB, HPV, PCV, RSV, rotavirus)
Solutions: Public funding Priority review vouchers LMIC manufacturers Push and pull mechanisms	**Solutions:** Reverse tiered pricing Push and pull mechanisms	**Solutions:** Tiered pricing Push and pull mechanisms

Source: PATH/David Kaslow.
Note: Four vaccine business cases determine the types of incentives and partners most appropriate to advance a product.

organizations, including PATH, identified the lack of support for implementation research as a formidable barrier which reduces access to and impact of new health technologies.[7]

At the same time, government budgets and healthcare systems may not have sufficient funds to procure or administer all the drugs on Essential Medicines Lists (EMLs), nor to train local healthcare providers to use new technologies, nor to provide the infrastructure needed to maintain supply and delivery of products—all of which impact access.

Political Will

The challenge of building political will to fully recognize health inequity as both a moral imperative and a barrier to social and economic development also impacts many facets of access to health technologies at the global and local level. When assessing competing funding priorities, both donors and governments may operate in an evidence- or awareness-scarce space on health's broader impact on national and global economies, security, and stability. This scarcity isolates and restricts resources, and it limits potential for innovative cross-sector collaboration to overcome challenges to product development and access.

Pre-approval challenges

This section focuses on the many challenges that exist in the process of developing and getting new health technologies approved for use in a particular market. Developing products designed specifically for use in LMICs poses unique research, development, regulatory, policy and financing challenges.

Regulatory practice

When developing or reformulating health technologies, strong regulatory systems are integral to protect patient safety and privacy and to ensure favorable benefit-risk profiles and quality of interventions. Challenges—related to consistency and suitability of regulatory practice for products designed specifically for LMICs—manifest in several ways that cause delays and increase the cost of product development.

Undefined regulatory or impractical development pathways

Registering a product for dual use (i.e., HIC and LMIC) often begins with regulatory approval from an influential WLA-ML 4 regulatory authority, most commonly the United States Food and Drug Administration (FDA) or the European Medicines Agency (EMA). Development of a product for low-resource setting use only, may also start with regulatory review (e.g., U.S. FDA review of an investigational new drug (IND) application) by a prominent WLA-ML 4 regulatory authority, and may also include a comprehensive evaluation of the quality, safety, and efficacy of certain medicinal products for use intended exclusively for markets outside their jurisdiction—for example, the EMA Article 58 procedural advice. Reviews by these or other WLA-ML 3 or 4 authorities significantly assist approval in many low-income countries that lack the capacity and resources to conduct comprehensive independent regulatory reviews.

While WLA-ML 4 regulatory authorities may assist other countries' registration and adoption of new products, the WLA-ML 4 regulatory authority's mandates are typically legislated to ensure quality, safety, and efficacy of products to be used in their own jurisdiction. Although there are mechanisms for evaluation of candidates in other jurisdictions (e.g., see U.S. FDA *Guidance for Industry: General Principles for the Development of Vaccines to Protect Against Global Infectious Diseases*[8]), HIC national regulatory authority standards may not reflect the specific population needs, local infrastructural and administration limitations, or various other context-specific dynamics of products designed for use in LMICs. As noted above, EMA's scientific opinion procedure was designed to apply EMA's scientific review capabilities and the local epidemiology and disease expertise of WHO and national regulators to provide a development and assessment pathway for products intended for use in LMICs. This procedure facilitates both WHO Prequalification (PQ) and local approval.[9] Yet challenges remain.

As an example, during the development of tribendimidine (TrBD) to control soil-transmitted helminth (STH) infections in LMICs, FDA registration standards originally called for the product to be evaluated for efficacy against the U.S. approved standard of care—which is a multi-dose, multi-day, licensed product regimen designed for individual-based treatment of active gastrointestinal infection. This is feasible to implement in HICs, however, TrBD is intended for use in LMICs where single-dose, mass drug administration for periodic presumptive treatment (PPT) is the most feasible approach for treating and controlling STH infections in an entire population. A mass drug administration campaign is not a licensed regimen in the United States. After a specific request to re-evaluate the acceptability of a PPT indication, U.S. FDA did recognize PPT as a new indication acceptable for approval. However, the development pathway for a registration of a PPT indication was complex from financial, regulatory, and scientific perspectives, which placed the project goal out of reach.

Multiple national regulatory authorities with differing regulations

Each regulatory system presents distinct logistical and technical requirements. The need for researchers and manufacturers to navigate multiple systems to register the same health products across multiple countries results in delays and increased cost to product access.

Gaps in regulatory capacity in LMICs

Gaps in regulatory capacity in many LMICs can lead to delays in accessing new health technologies. In situations where a product is intended solely for use in LMICs, first-in-human studies are often conducted in the United States or the European Union, with subsequent research often conducted locally. Reduced regulatory capacity means reviews may be longer and/or iterative, and the development pathway may be delayed or require more trials than in WHA-ML 3 or 4 settings. Some national regulatory authority (NRA) systems have insufficient capacity to efficiently regulate across all phases of development and licensure and provide adequate pharmacovigilance, or quality assurance, for products once marketed.

Resource-limited NRAs result in delays in other ways as well. For example, WHA-ML 4 NRAs have created mechanisms whereby product candidates for certain indications can obtain:

1) Accelerated approval based on a surrogate or intermediate clinical endpoint reasonably likely to predict a clinical benefit, followed by post-approval phase 4 confirmatory trials to verify clinical benefit (e.g., U.S. FDA accelerated approval pathway); or

2) Conditional approval, renewable annually, based on meeting certain specific requirements, including that the benefit to public health of the immediate availability of the product outweighs the risks due to a need for further data. This later pathway requires completion of ongoing or new studies and, in some cases, additional activities to provide comprehensive data confirming that the benefit-risk balance is positive.

Many LMIC NRAs do not have similar mechanisms and/or their healthcare systems are not able to provide the monitoring and standards stipulated as required for earlier access to essential medicines and health technologies. For products with markets and use cases in both HICs and LMICs, LMICs may have to wait for the confirmatory studies in HICs to be completed before LMICs approve access to these new health technologies.

Post-approval challenges

Once a product is developed, it must reach those it is intended to benefit to have an impact. This section highlights challenges that exist in the process of ensuring a newly developed and approved product achieves optimal use at scale.

Appropriate essential medicines lists at local levels

The WHO EML serves as a model for the development of national and institutional essential medicines lists. The most current WHO EML includes 433 products deemed essential for addressing the most important public health needs globally. Most countries have national lists and some have provincial or state lists as well. National lists of essential medicines guide the procurement and supply of medicines in the public sector, schemes that reimburse medicine costs, medicine donations, and local medicine production.[10]

Given the realities of budget limitations, it is often not possible for national or district health systems to procure an adequate supply of all medicines with WHO EML designation. Countries also may lack the data or expertise to assess their needs and prioritize their lists and supply accordingly.

Lack of workforce capacity and training

Widespread and responsible implementation of health technologies requires local healthcare providers who accept the value of new products and are appropriately trained and licensed in their use. Local healthcare workers may not have the specialized skills or licenses to administer the product. For example, local regulations in some countries preclude classes of health workers from administering injections. Program resources needed to support local capacity, product acceptance, and training around new products can be large and expensive. The process of scaling such programs can be lengthy, slowing uptake of new products.

Fragile markets

Market dynamics for many health technologies, particularly essential medicines, are not driven by traditional market forces and therefore may be fragile and require considerable additional efforts and interventions to shape and sustain them. The long-term availability of health technologies relies on sustainable markets for product manufacturers.

A product's price must be low enough to be affordable to the health system(s) or patients who must purchase it. However, if prices are pushed too low, manufacturers will exit the market, reducing competition and threatening supply security.

In the case of the live Japanese encephalitis vaccine (JEV), which PATH contributed to bringing to market, a single manufacturer, Chengdu Institute of Biological Products, is responsible for over three-quarters of the JEV global supply. The product is currently affordable and available, but any significant disruption in JEV supply from one manufacturer, including force majeure, could threaten global availability of this product, negatively impacting public health and increasing the threat of outbreaks of Japanese encephalitis.

Infrastructure maintenance

An often-neglected component of sustainable supply for essential medicines and other health technologies is ongoing maintenance and quality improvement in the infrastructure and capacity for production. Facilities that produce, store, and transport existing and future products must be rigorously maintained and routinely updated to new and evolving quality standards. Manufacturing facilities that produce low-margin essential medicines for low-resource settings face constant threats to their long-term sustainability. Without sufficient margins or other mechanisms to ensure access to low-cost capital and resources for maintaining or replacing aging facilities, sustainable supply and administration of health products is threatened.

Policy recommendations

Addressing barriers to access of health technologies, including essential medicines, in low-resource settings requires innovation and strengthening of systems throughout the product life cycle, as well as engagement from stakeholders at all levels and from various sectors and governmental agencies. The following is a list of recommendations to support and accelerate access to innovative health technologies for use in low-resource settings and further enable the multisector collaboration needed to tackle the complex and diverse challenges previously discussed.

1. Resources and commitment: Increase financial investment and political will to prioritize global health product development and access

The lack of adequate financial resources to drive the product development and access pipelines for new health technologies for poverty-related and neglected diseases impacts every challenge discussed. Unlocking greater funding for this work requires innovations to be valued not just on their direct, individual health benefits but also on indirect, population-based social and economic benefits. Funding to support this work must break out of silos, such as solely Ministry of Health or Department of Health budgets. A more holistic approach could enable new resource streams to sustainably fund innovation. Activities to support this shift include:

- Existing funders should continue to support research to further establish the evidence base and business case for investment in innovation of health technologies. This research should include cross-disciplinary work that frames the value of new products beyond individual health benefits and presents evidence of the positive impact health technology investment can have on other priorities like poverty prevention, security, global development, agriculture, education, and technology. Funders and thought leaders should highlight this research using high-visibility platforms to build political will and cultivate champions.
- More fit-for-purpose incentives and innovative financing mechanisms to support product development and provide incentives for private-sector participation are needed throughout the product life cycle. To ensure impact, each of these mechanisms need a focused and clearly understood scope to accomplish stated goals and limit unintended outcomes. Mechanisms should be deliberately coordinated such that there is a clear line-of-sight across development and introduction, with minimal gaps or delays during transitions in financing mechanisms. Both push (funding greater input) and pull (rewarding output) mechanisms are needed.

2. Regulatory affairs: expand efforts to converge regulatory standards across agencies and regions and support innovative initiatives to strengthen regulatory capacity in LMICs

Addressing regulatory challenges could simplify and clarify the development and regulatory pathways required for registration of health technologies (including essential medicines), facilitating quicker adoption and uptake, and increasing public health impact. A more convergent and/or integrated regional or even global regulatory system would reduce the cost and time of product development, as fewer country-specific clinical studies or chemistry, manufacturing, and control activities would have to be performed.

Efforts across regions to pool resources and expertise is a critical way to strengthen capacity and converge/integrate standards and processes. A recent PATH report, *Making the Case: How Regulatory Harmonisation Can Save Lives in Africa*, shows that harmonization of regulatory approvals for just two medicines could contribute to more than 23,000 lives saved in eastern and southern Africa. Initiatives such as the *African Medicines Regulatory Harmonisation* (AMRH) are advancing these goals and having an impact.[11] However, these efforts have only been piloted at a small scale and require further support. Activities to support strengthening regulatory systems include:

- Regulatory agencies should clearly and consistently communicate regulatory and licensure requirements to help clarify paths for developers and manufacturers.
- Regulatory convergence and ongoing harmonization initiatives should receive financial and political support, with a focus on building capacity and streamlining processes in LMICs.
- Regulatory convergence should create opportunities for third parties with experience developing and evaluating products in low-resource settings to help facilitate regional regulatory convergent/integrated processes. These opportunities include, but are not limited to, standardizing methodologies for evaluation, forms and filing protocol, review scheduling, and decision reporting systems.

3. Local capacity: Invest in growing local capacity to support the introduction, appropriate and responsible use, and sustainable supply of the most impactful health technologies

Public health impact is not achieved until those in need of interventions receive and benefit from them. Ensuring medical products are reliably delivered, consistently available, and appropriately and responsibly administered requires reliable and robust health systems. These health systems must include informed decision-makers, well-trained and resourced care providers, and anti-fragile infrastructure to support manufacturing, storage, and delivery. Activities to strengthen the capacity of local workforces, and systems to implement innovative health solutions, must include sufficient resources from donors and national governments to:

- Strengthen public health systems and aspire to achieve universal healthcare, which will enable widespread and responsible use of new health technologies.
- Develop national and provincial Essential Medicines Lists that ensure countries are selecting, prioritizing, and procuring the products necessary and appropriate for their health context and making these decisions based on current relevant evidence from real-life implementation of stated treatment standards.
- Address issues of deteriorating manufacturing infrastructure of legacy essential medicines (e.g., vaccine factories that are reaching the end of their useful life) and ensure the supply of essential medicines—particularly those with two or fewer manufacturers—remains secure. To stimulate competition and provide incentives or funding for the maintenance of infrastructure needed for manufacture, storage, and delivery, products in need of manufacturer diversity and repair of markets should be proactively identified. Such efforts should include actively seeking and supporting local manufacturers and investing in their capacity to produce essential medicines, to increase local product acceptance, promote consistent and sustainable local product supply, and achieve sustainable and affordable product prices.

Innovation is critical to driving gains in health equity and social and economic development around the world. However, product development is only the first step. A holistic approach that creates and supports the financial, economic, regulatory, and human resources to create an anti-fragile environment is needed to sustainably advance the development, approval, widespread adoption, and effective and responsible use of health technologies in LMICs.

Notes:

1 Chapman et al., 2019.

2 Young et al., 2018.

3 World Health Organization (WHO), n.d.-a.

4 Young et al., 2018.

5 Bill & Melinda Gates Foundation, 2017.

6 DeMasi, 2018.

7 PATH, 2018.

8 United States Food and Drug Administration (FDA), 2011.

9 European Medicines Agency (EMA), n.d.

10 World Health Organization (WHO), n.d.-b.

11 New Partnership for Africa's Development (NEPAD), n.d.

References:

Bill & Melinda Gates Foundation. (2017). Who We Are: Annual Report 2017. Retrieved from https://www.gatesfoundation.org/Who-We-Are/Resources-and-Media/Annual-Reports/Annual-Report-2017

Chapman, N., Doubell, A., Oversteegen, L. et al. (2019). *Neglected Disease Research and Development: Reaching New Heights.* Surry Hills NSW, Australia: Policy Cures Research; 2019. Retrieved from https://www.policycuresresearch.org/wp-content/uploads/Y11_G-FINDER_Full_report_Reaching_new_heights.pdf

DeMasi, J.A. (2018). Assessing pharmaceutical research and development costs. *JAMA Internal Medicine, 178*(4), 587. Retrieved from https://doi.org/10.1001/jamainternmed.2017.8703

European Medicines Agency (EMA). (n.d.) Medicines for use outside the European Union. Retrieved from https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/medicines-use-outside-european-union

New Partnership for Africa's Development (NEPAD). (n.d.) African Medicines Regulatory Harmonisation (AMRH). Retrieved from https://www.nepad.org/programme/african-medicines-regulatory-harmonisation-amrh

PATH. (2018). Investigating a Second Valley of Death in Malaria R&D: How Is "Research for Implementation" Funded? Seattle, WA: PATH 2018. Retrieved from https://www.malariavaccine.org/sites/www.malariavaccine.org/files/content/resource/files/Malaria_R&D_Funding_Report.pdf

United States Food and Drug Administration (FDA). (2011). *Guidance for Industry: General Principles for the Development of Vaccines to Protect Against Global Infectious Diseases.* Rockville, MD: FDA. Retrieved from https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM282995.pdf

World Health Organization (WHO). (n.d.-a.) WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems. Retrieved from https://www.who.int/medicines/regulation/benchmarking_tool/en/

———. (n.d.-b.) WHO Model List of Essential Medicines. Retrieved from https://www.who.int/selection_medicines/list/en/

Young, R., Bekele, T., Gunn, A. et al. (2018). Developing new health technologies for neglected diseases: a pipeline portfolio review and cost model [version 2; referees: 3 approved]. *Gates Open Research*. Retrieved from https://doi.org/10.12688/gatesopenres.12817.2