Global Health
Technologies Coalition

Advancing research and development to address poverty-related and neglected diseases and conditions

A summary of perspectives from nonprofits on accelerating product development and improving access for low- and middle-income countries

Financing and Coordination of Health Research
May 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 summary paper was authored by John Ballenot (PATH) and draws upon a series of papers 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), Kim Lufkin (GHTC), and Nick Taylor (GHTC). 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 series: Aeras, Dengue Vaccine Initiative, Drugs for Neglected Diseases *initiative*, European Vaccine Initiative, Foundation for Innovative New Diagnostics, Infectious Disease Research Institute, International AIDS Vaccine Initiative, International Partnership for Microbicides, International Vaccine Institute, Jhpiego, Medicines for Malaria Venture, PATH, Population Council, Sabin Vaccine Institute, TB Alliance, and TuBerculosis Vaccine Initiative.

Suggested citation: Global Health Technologies Coalition (GHTC). *Advancing Research and Development to Address Poverty-Related and Neglected Diseases and Conditions: A Summary of Perspectives from Nonprofits on Accelerating Product Development and Improving Access for Low- and Middle-Income Countries*. Washington, DC: GHTC; 2014. Available at: http://ghtcoalition.org/NPPD-briefing-paper-series.php.

Advancing research and development to address poverty-related and neglected diseases and conditions

A summary of perspectives from nonprofits on accelerating product development and improving access for low- and middle-income countries

Introduction

Although life expectancy in most countries has increased by about ten years over the past four decades, the gap in positive health outcomes between the richest and poorest countries remains wide. Closing the gap will require additional research and development (R&D) to advance health technologies and other products that can meet the specific needs of low- and middle-income countries (LMICs).

Nonprofit product development organizations (NPPDs) have been created to speed the development and adoption of new technologies to address public health needs in LMICs. Many of these nongovernmental organizations were formed in the late 1990s. NPPDs partner with the public, philanthropic, not-for-profit, and private sectors to advance health products such as diagnostics, drugs, devices, vaccines, and microbicides. They bring together the resources and expertise of various groups to advance and increase access to health products that would not otherwise be available for commercial reasons and to improve scientific understanding of health conditions affecting populations in LMICs.

To ensure that health products benefit those most in need, NPPDs employ some common strategies:

- Spreading investment in R&D across a portfolio of technologies, thereby ensuring only the most promising products are selected for advancement.
- Planning for access for poor populations from the beginning of the product development process.
- Working closely with manufacturing partners to guarantee that consistent supplies of high-quality, cost-effective products are available to target populations.
- Engaging end users and beneficiaries in the design and development of products.
- Strengthening the capacity of research and manufacturing partners in endemic countries.
- Working with regulatory stakeholders to clarify pathways and improve alignment of requirements throughout the product development process.
- Advocating for policies and investments to strengthen R&D for poverty-related and neglected diseases and conditions and to bring attention to the health needs of LMICs.

Although many NPPDs have effectively advanced R&D for poverty-related and neglected diseases over the past two decades, progress has been hindered by a number of challenges. These include insufficient funding, lack of consistent regulatory requirements and limited capacities of national regulatory authorities, and limited local capacity for research and manufacturing.

To explore these challenges and identify potential solutions, the Global Health Technologies Coalition (GHTC) collected available data and interviewed representatives of leading NPPDs (see

GHTC briefing paper series

The first paper in this series set the stage by providing examples of how nonprofit product development organizations (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 low- and middle-income countries (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. The fourth paper outlined the most significant regulatory challenges faced by NPPDs and partners throughout the product development process and described how these challenges affect their work. The fifth and final paper in the series describes NPPDs' efforts to strengthen the research and manufacturing capacity of academic, nongovernmental, and commercial partners in LMICs, and provides examples of the criteria that NPPDs consider when determining investment in capacity strengthening. All papers are available online at http://ghtcoalition.org/NPPD-briefing-paper-series.php.

appendix for complete list). Together, these NPPDs currently have more than 450 technologies under development,[1] and they have contributed to the development, evaluation, and introduction of 42 new health products for use in LMICs.[2]

The GHTC subsequently developed a series of briefing papers for policymakers and other stakeholders with an interest in advancing R&D to meet health needs in LMICs. This document summarizes findings from the briefing papers and provides an overview of the key challenges, lessons, and potential solutions identified by NPPDs.

Financing health research and development

The funding landscape for global health R&D is evolving. Although significant investments from governments and philanthropic organizations before the global financial crisis created robust pipelines of products intended for use in LMICs, recent budget constraints have threatened progress. In particular, traditional donors have scaled back their overall investments in NPPDs, and some donors have become more restrictive in how their money is spent. The changing funding landscape has prompted many NPPDs to reconsider their business models and funding structures.

Product development spans many years (sometimes decades) and may require significant amounts and multiple sources of funding. Some of the funding challenges now being encountered by NPPDs are new, and others—such as an overreliance on a small number of funders—have consistently hampered their work. In response to these challenges, NPPDs are pursuing innovative financing models to sustain progress in developing new products and to attract new investment, both to fill the funding gap and to increase resource flexibility. The most significant funding challenges affecting NPPD portfolios are:

- Donor shifts away from core funding to more narrowly restricted funding. Donors are increasingly awarding project-specific funding, which can only be used for a designated activity, as opposed to core funding that gives NPPDs the ability to support multiple projects at different stages of development.
- An overall decline in funding and a relatively small number of major funders of R&D. A shrinking pool of resources means that NPPDs cannot keep pace with the increased costs of advancing new health products through all phases

of development. Funding for NPPDs is declining just as promising products are progressing through the research pipeline to reach large-scale studies needed to demonstrate safety and efficacy in diverse populations.

- Discordant funder priorities and requirements. As some funders scale back on their support, NPPDs are increasingly seeking multiple donors and funding sources. Although funding diversification can help provide independence, it can result in a misalignment of funder requirements. NPPDs with varied funding sources can experience challenges in managing multiple funder requirements, which creates the need for more administration and staff resources.
- Limited capacity to identify, cultivate, and sustain funding. As NPPDs seek new funding opportunities, they must invest in a new configuration of skills—including managing, identifying, and cultivating new sources of support. This involves dedicating additional staff time, sometimes from researchers (detracting from their focus on scientific work), and establishing new systems to cultivate new donor relationships.

NPPDs have made progress despite these challenges and the inability of current funding mechanisms to accommodate the limited (or lack of) commercial incentive to invest in developing new technologies for use in LMICs. Interviewed NPPD representatives also highlighted many new investment and partnership opportunities.

To ensure that the goal of creating cost-effective, culturally relevant, affordable, and accessible products is driving their work, NPPD representatives outlined criteria that can be used to design and evaluate financing. They noted that funding mechanisms and donor support should:

- Support a portfolio of products at different stages of development. This ensures that only the most promising products advance through the research pipeline and allows NPPDs to shift funds to more promising projects. It also ensures that the entire product development lifecycle—from preclinical studies through introduction and wide-scale adoption—is funded.
- Provide sustainable funding commitments. The duration of funding commitments should be guided by scientific need. This will require multiyear funding commitments that align with the timelines of the product development process.
- Support core activities. These activities—including administrative and facility costs, advocacy and public awareness activities, and the cultivation of new funding sources—are critical to the success of any organization. All funding should include a proportionate level of support for the overall costs of running the organization or specific program.
- Incentivize new investment. Funding is most effective when it can be used to attract new financial support and other investments. The more flexible the funding, the greater the recipient's ability to create opportunities to complement existing investment.

NPPD representatives further noted that exploring new financing models is not new to NPPDs but that they must continue to adapt their models and explore new opportunities to respond to an evolving funding environment. They also highlighted that better collaboration among stakeholders—including NPPDs, governments, academia, foundations, and the private sector—is critical to maximizing R&D funding to improve health and well-being in LMICs.

Improving the affordability, availability, and acceptability of health technologies

To achieve impact, a health technology must be more than just safe and effective. To ensure access, it must be affordable, available, and acceptable to those who need it.

The R&D value chain

Organizations conducting research and development (R&D) targeting health needs in low- and middle-income countries (LMICs) include government agencies, academic institutions, nonprofit organizations, and private companies in high-, middle-, and low-income countries. Because the perceived financial risks of developing products for LMICs are often too high relative to the potential economic returns, and the scientific challenges are daunting for many poverty-related diseases and conditions, it is impossible to rely solely on one organization or sector. Therefore, many organizations partner to share risk, leverage expertise, and maximize impact. These organizations work across the product development value chain, from upstream research exploring fundamental understanding of a disease to more downstream operational research aimed at optimizing the use of new technologies within a health system. Nonprofit product development organizations (NPPDs) play an important (and often unique) role in bridging the gap between early basic science and late-stage research. Along the value chain, NPPDs and their private- and public-sector partners conduct trials of new tools across all phases of clinical and field trials to prove the concept, evaluate safety and efficacy, and validate that the proper production process is in place to ensure manufacturing quality.

Interviewed NPPD representatives shared lessons that they and their partners have learned in trying to improve the affordability, availability, and acceptability of new health technologies for those most in need:

- Defining the value of a technology must be driven by the local communities and countries that will use the product. Product developers must understand and address the needs and wants of those who will ultimately implement and benefit from the product.
- Achieving global access does not guarantee local access. NPPDs and their partners may achieve global access targets (such as receiving World Health Organization prequalification), but this does not guarantee that the technology will be accessible at the national or subnational level.
- Relying on national average income status can undermine access for the poorest populations. In many middle-income countries, the burden of disease is among poorer populations that have not benefitted from stronger economies. Therefore, the poorest populations, often the most at risk, are unable to access new technologies.
- Securing donor recognition of the need for early initiation of access activities is critical. To reduce the delay between registering a product and making it available in the health system, NPPDs and their partners must start planning for access from the beginning of the development process, and donor support for these activities is crucial.
- Demonstrating a niche in the market for manufacturers is essential to incentivize their investment. Manufacturing partners must understand the value that they bring to a market to enable them to invest time, effort, and money in developing products for poverty-related and neglected diseases and conditions.

Because it is impossible to predict all future access problems, NPPDs and their partners must try to articulate scenarios that will achieve access on the global and the local levels throughout the product development process. Therefore, it is critical that NPPDs and their partners address these principles from the beginning of the product development process.

Addressing regulatory challenges

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. There are regulatory milestones to be achieved at every step of the development process. Developers often engage a number of regulatory stakeholders throughout a product's lifecycle and encounter a number of challenges along the way.

Costs for product developers and manufacturers to comply with regulatory requirements are a large—and growing—component of R&D expenditures, and regulatory challenges can delay timely access to technologies for patients. Despite this, policymakers and donors have until recently paid little attention to regulatory reform in discussions on improving financing and coordination of global health R&D.

Regulatory processes and obstacles can vary widely by product platform, as well as geography. Nonetheless, NPPD representatives agreed on three thematic challenges that increase the costs of product development, delay product introduction, complicate an already difficult process, and—ultimately—result in fewer lives saved:

- Complex global regulatory environment.
- Weak regulatory capacity in LMICs.
- The need for increased investment in regulatory capacity within NPPDs.

Competing and misaligned requirements across regulatory authorities in high-, middle-, and low-income countries have created a confusing landscape for NPPDs. Because of the complexity of the regulatory environment, many NPPDs and partners face unclear signals about which regulatory body to approach first, the requirements for each review, and when these reviews can take place.

Because many national regulatory authorities in LMICs are poorly funded, understaffed, and overburdened, they lack the resources to provide adequate guidance to developers, as well as proper oversight over many of the products being studied, introduced, and used in their countries. This lack of capacity and resources can be a significant hurdle and lead to costly delays in product development and introduction, and could mean reduced protection for patients.

As their innovation pipelines grow, NPPDs are taking over more aspects of product development programs and recognizing the need to work more directly with regulators. Based on their experiences in navigating regulatory pathways for health products, NPPD representatives had several recommendations to strengthen processes:

- 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 national regulatory authorities in endemic countries, to ensure that expectations are understood by both groups and to build trust.
- All regulatory bodies should possess a foundational level of core competencies. Although all regulatory authorities do not need the same capacities, there should be a common minimum standard of oversight that all can enforce.
- Regulatory harmonization and capacity strengthening should encourage collaboration of poorly resourced regulatory bodies with better-resourced and more experienced regulatory authorities. This work should include expanding and leveraging existing innovative mechanisms to improve coordination and alignment across technologies and geographies and provide a platform for technical assistance.

- It is critical to educate nonregulatory 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. Regulatory reform has not been prioritized among the many competing demands for limited (and in some cases shrinking) resources by policymakers.

Regulatory challenges can cause significant delays and increase costs, and can ultimately end in fewer lives saved. There is a need for stronger regulatory systems and increased collaboration among stakeholders—including developers, manufacturers, regulators, and policymakers—to ensure that promising technologies in the innovation pipeline are being advanced at a reasonable pace to maximize health impact.

Strengthening local capacity for research and manufacturing

Further development of local research and manufacturing capacity in LMICs is key to accelerating the development and dissemination of high-impact, cost-effective health technologies appropriate for use in these settings. Unfortunately, many researchers and manufacturers in LMICs have limited experience following rigorous international laboratory, clinical, and manufacturing standards, and LMICs often have inadequate infrastructure to support high-quality innovation. It is estimated that only 25 percent of research on neglected diseases takes place in LMICs[3] and only 13 percent of manufacturers of medical devices are located in LMICs.[4]

Strengthening local capacity is an integral component to most NPPD projects, though the emphasis depends on the impact it has on achieving NPPDs' mission of accelerating the development and adoption of new technologies to address public health needs in LMICs. NPPDs typically collaborate with experienced commercial entities, academic institutions, and governments to conduct capacity strengthening with partners in LMICs.

Capacity strengthening may require substantial investments in training and technical assistance and may prolong project timelines. This can create a tension—and a potential trade-off—between the need to make a new technology available as quickly as possible and the need to increase local capacity.

Strengthening local capacity for research and manufacturing has many benefits. NPPD representatives noted that strengthening the capacity of research institutions in LMICs helps to ensure that products are suitable for use in low-resource settings. Increasing local capacity to conduct studies in accordance with international standards improves the overall quality of research and helps to generate rigorous results and data to inform national regulatory reviews and product registrations. It also improves attention to study participants' rights, safety, and needs by increasing understanding of international clinical and ethical standards. If capacities can be maintained beyond initial projects, they may be redeployed to address new and emerging health issues, increase understanding of disease (i.e., incidence and prevalence patterns), and improve timelines for the development and uptake of new health products.

Technology transfers and enhancements of manufacturing facilities have helped to build competitive markets that include endemic-country manufacturers. The availability of high-quality manufacturing capacity at lower cost is critical to lowering prices and increasing access to health products by increasing competition among producers. This alleviates supply constraints created when only one or two manufacturers can produce high-quality products. This dispersed capacity also enables a more robust response to critical situations (e.g., outbreak of pandemic flu) by increasing product availability. Finally, improved local manufacturing capacity can increase employment opportunities and help to improve local economic conditions.

NPPD representatives noted a number of challenges in strengthening local research and manufacturing capacity. For example:

- It is difficult to ensure the sustainability of strengthened capacity following the conclusion of a specific study or project. Governments in endemic countries have limited ability to co-finance these complex, long-term efforts. If sustainable funding is not available, it is difficult to ensure the further employment of trained staff and maintenance of upgraded facilities.
- A weak regulatory environment can undermine capacity-strengthening investments. Many small manufacturers in LMICs have not complied with international standards because these are often not enforced by national regulators. Smaller manufacturers who adopt these standards are at risk of becoming less competitive in the local market because compliance increases production costs (i.e., upgrading facilities, training, and hiring more staff).
- The time and resources needed to provide equipment, training, and technical assistance to achieve appropriate standards is significant. Any setbacks (e.g. trained staff leaving for more lucrative employment opportunities or commercial partners shifting priorities as the business or competitive landscape changes) can delay or derail product development timelines.
- Because overall research and manufacturing capacity is low in most LMICs, in many cases, only a relatively small number of organizations and individuals can engage in capacity strengthening. At times, NPPDs find themselves competing to use the same set of partners.
- Cultural differences can influence capacity-building efforts. Different norms and business or research practices can create tensions between partners, and resolving these tensions requires patience and transparency. Likewise, different communication styles can lead to misinterpretation and confusion.

Recommendations from NPPD respondents included:

- Project partners must share a commitment to comply with international technical and ethical standards to ensure volunteers' safety, rights, and needs are protected and quality products are produced and accessible among those in need.
- Capacity-strengthening investments must weigh accelerating the availability of much-needed products against the potential of lengthier timelines when increasing capacity.
- Capacity strengthening should enable home-grown solutions and local product development to be responsive to existing needs and emerging challenges.
- Capacity-strengthening investments must be sustainable and enable LMICs to leverage this increased capacity for their continued future growth.

NPPDs and their partners have already made significant investments to increase the capacity of researchers and manufacturers in LMICs. But capacity strengthening is not an end in itself. Rather, it is integral to conducting high-quality research, product development, and manufacturing in challenging environments. Strengthening local capacity enhances engagement and ownership in the affected countries; ensures that studies can be performed directly in the populations and settings where the final products will be rolled out; and helps to build competitive markets that include endemic-country manufacturers, which lowers prices and accelerates the availability of new products.

Conclusion

Although NPPDs have advanced R&D for poverty-related and neglected diseases in LMICs, progress has been hampered by a number of challenges. These have included insufficient funding, shortcomings of regulatory systems, and limited local research and manufacturing capacity. Closing the health gap between the richest and poorest countries will require prioritizing and planning for access to needed health products within LMICs.

NPPDs have identified effective solutions to address these challenges and are working to implement needed changes. For example, NPPDs are working toward more predictable, stable, and long-term funding across all phases of product development, as well as diversified funding sources and improved coordination across funders. They are pursuing policy changes and sustainable funding to improve regulatory capacities and pathways for products targeting LMICs. And they are strengthening local partners' research and manufacturing capacities in line with international standards.

Implementing these solutions will further enhance R&D for poverty-related and neglected diseases and conditions and thereby increase access to needed drugs, diagnostics, vaccines, and devices in LMICs. This will not only help to save lives and improve health among vulnerable populations but also contribute to local economic development.

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a. Serum Institute of India Ltd. is not a nonprofit product development organization.

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