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Briefing Paper, Volume 3: Improving the affordability, availability, and acceptability of health technologies

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

Financing and Coordination of Health Research
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Contents

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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Improving the affordability, availability, and acceptability of health technologies

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

Purpose and aims

The Global Health Technologies Coalition's "financing and coordination of health research" briefing papers provide examples and perspectives from nonprofit product development organizations (NPPDs)—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 is meant to inform discussions aimed at improving the coordination and financing of health research and development (R&D) addressing the needs of LMICs, and the 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 the recommendations included in the 2012 report from the World Health Organization (WHO) Consultative Expert Working Group (CEWG) on R&D. The main functions of the CEWG were to identify major challenges to advancing R&D for health needs of LMICs and make recommendations to improve the coordination of priorities and activities, financing of all phases of research, and monitoring of R&D investments. The resolution called for:

- Establishment of a global R&D observatory at the WHO that would act as a central coordinating mechanism to monitor and analyze relevant information on health R&D. The observatory would contribute to the identification of gaps and opportunities for R&D and define priorities in consultation with relevant stakeholders, as appropriate.
- Implementation of several health R&D demonstration projects to address identified gaps that disproportionately affect LMICs.
- Establishment of long-term, sustainable coordination and financing 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 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. This third paper describes how NPPDs and their partners try to ensure access in LMICs to the knowledge and technologies they develop. Subsequent papers will explore how NPPDs:

- Address regulatory challenges throughout the product development process.
- Work with partners in LMICs to strengthen local research and manufacturing capacity.

[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 conducted with representatives from 14 NPPDs (see Appendix 1 for list of interviewees). Interviews were conducted to capture the organization's approach to access and the most significant lessons learned. During interviews, respondents from NPPDs also provided input on how they manage partnerships and negotiate agreements to accelerate the development and improve the accessibility of technologies targeting the health needs of LMICs.

Introduction

The PDP Access Group—a forum for NPPDs to exchange information and share best practices in the area of access—defines access as "a coordinated set of activities needed to ensure that the products developed will ultimately have an equitable public health impact. Achieving that impact requires products that are *available, affordable*, and *acceptable* to end-users, and adopted into developing country health systems."[3] *Affordability* means that users and buyers are able to pay the cost of the product.[2,3] *Availability* includes activities to ensure a reliable and regular supply of the technology, and may take place at the local, national, regional, and global level.[3,4] Finally, *acceptability* ensures that there is demand and willingness from beneficiaries, end users, health systems, and buyers to adopt the product.[3]

The establishment of NPPDs and a number of market-shaping initiatives—such as the Global Fund to Fight AIDS, Tuberculosis and Malaria and the GAVI Alliance—have accelerated the development and the accessibility of new health technologies targeting poverty-related diseases and conditions. Historically, the introduction of new health technologies in LMICs relied on a trickle-down approach, which assumes products will eventually be accessible to poorer populations. This trickle-down approach delays wide-scale adoption of much-needed health interventions, as opposed to a scale-up approach in which new products are made available to the general population upon introduction.

NPPDs were created to speed the development and adoption of new technologies to address public health needs in LMICs and market-shaping initiatives were created to guarantee a viable market for these products. Since the late 1990s, when many NPPDs were created, the pipeline of products addressing the health needs of LMICs has grown substantially—including more than 450 technologies currently in development by the NPPDs contributing to this analysis.[5] As of 2013, NPPDs and their partners have contributed to the development, evaluation, and/or introduction of 42 new health products.[6]

Because NPPDs range in approach (from coordinating a virtual R&D network to having in-house R&D capacity) and focus (e.g., types of products), there is no "one size fits all" model for how they operate. However, NPPDs employ some common strategies to ensure that the resulting products benefit those most in need. Similar to commercial product developers, NPPDs spread investment in R&D across a portfolio of technologies, thereby allowing them to select only the most promising products to advance through the pipeline. In contrast to typical commercial product development, NPPDs also prioritize improving access to these technologies for poor populations.

Because NPPDs were established to develop, not deliver, health technologies, they are dependent on other stakeholders (e.g., national governments, local health systems, and manufacturers) to deliver the technologies they are helping to create. However, there are a number of ways that NPPDs have worked to ensure access as quickly as possible to the technologies that they and their partners develop. To date, NPPDs' efforts have focused on accelerating product development, establishing affordable pricing and sustainable supplies, and advocating for resources and policies to enable timely product adoption at the country level.

This paper will explore the approaches to access across a spectrum of NPPDs. It will also highlight the 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.

Findings

There is general agreement across NPPDs that access can be defined as the sum of the affordability, availability, and acceptability of a health product. However, there is less consensus about how access is measured and achieved. The spectrum of perspectives varies based on where along the R&D continuum the NPPD works, the state of the science, the types of technologies being developed, and the commercial potential of these products.

Access approaches

Because the technologies developed by NPPDs and their partners are aimed at addressing the health needs of resource-limited populations, it is just as critical to invest in high-quality manufacturing and affordable supply, and create demand for these products at the country level, as it is to develop an effective technology. The development of new (and improved) technologies alone is not sufficient to improve health outcomes in LMICs. Public health impact can be achieved only if the products developed by NPPDs and partners are integrated into the health system and widely adopted. Therefore, the resulting products must be affordable, available, and acceptable to those in need as a means to improve public health.

All of the NPPD representatives reported starting to plan for access to some degree at the beginning of the product development process. NPPDs collaborate with partners to implement access considerations and commitments from the initial design of the product through licensure and registration of the final product and, for some NPPDs, to wide-scale adoption. All of the respondents acknowledged that delays in planning and implementing an access strategy (for example, waiting until Phase III clinical trials are under way) can result in significant delays from licensure to actual delivery in country. A product that needs to be retrofitted for affordability, availability, and acceptability will result in a costly and time-consuming development process. It is critical that these principles are addressed from the beginning.

Table 1: Examples of access considerations included in target product profiles.

Access issue	Illustrative product characteristic	Example
Affordability	Establish the maximum affordable price point—as defined by the target countries and end users—that factors in the cost of manufacturing and the required materials to produce the product.	The maximum allowable price for MenAfriVac® (meningitis A vaccine) was US$0.50 per dose as defined by the national immunization programs.
Availability	Improve the thermostability of a product—the ability of a drug or vaccine to withstand temperature changes. This allows a product to retain its potency when outside of a temperature-controlled supply chain.	Stable formulations of rectal artesunate (antimalarial drug) should be able to withstand transient heat spikes above 40°C (e.g., during product transport), while still able to be administered at 37°C body temperature.
Acceptability	Simplify the preparation and/or administration of a product to limit incorrect use of product.	Provide clear instructions for preparation and administration to avoid incorrect use of injectable artesunate (antimalarial drug). Include saline vial in pre-packaged product to make reconstitution of product easier.

Target product profiles

NPPDs include access considerations in their target product profiles (TPPs), which outline the minimum and ideal clinical, technical, and scientific characteristics of a product required to achieve the desired public health impact. A number of the respondents noted that affordability, availability, and acceptability are considered to be equally as important as the efficacy and safety profiles of a technology. The TPP describes the safety and efficacy profiles, as well as the product characteristics that would improve the affordability, availability, and acceptability of a technology. It is important to note that the TPP is established at the start of the design process. It provides the framework for the final product and may be revised throughout the product development process in light of new clinical data and/or feedback from key stakeholders (e.g., local health care providers, patients, and ministries of health).

Affordability

Affordability is a moving target for NPPDs and their partners, and it is as much about value for those who will use the products as it is about cost to the buyers. For many of the NPPDs, cost-effectiveness is a critical characteristic of an affordable product. Respondents also stressed that it is critical to establish a product's value and that value must be defined by the end users and the countries that will use the product in order to facilitate adoption. NPPDs must ensure that these groups have a good understanding of the unique value the product will bring. The challenge for NPPDs and their partners is that many of the products they are developing should be considered

Improved access leads to greater health impact for sleeping sickness

Efficacy is a critical factor for any product, but it does not guarantee that a technology will reach those who need it most. Including access considerations in the design and development of new products may result in increased coverage of much-needed health interventions. In 2009, the Drugs for Neglected Diseases *initiative* (DND*i*) launched the first new and improved treatment option for stage 2 human African trypanosomiasis (HAT), or sleeping sickness, called nifurtimox-eflornithine combination therapy (NECT).
Sixty million people, mostly in sub-Saharan Africa, are at risk of HAT.

The NECT treatment is a simplified co-administration of two commonly used medicines—nifurtimox and eflornithine. Research showed that NECT had a comparable efficacy and safety profile to the best existing treatment, but it was much more accessible and affordable, and as a result it has greater health impact. NECT is an easier treatment to administer for health workers, as it requires a shorter number of intravenous infusions and can be taken in 10 days instead of 14 days, which is required by other treatments. Additionally, the infusions only need to be administered twice daily during the daytime. Other drugs require administration four times daily and need to be taken overnight. As a result, these factors make NECT less burdensome for patients and health workers.

In an effort to make NECT more accessible, the World Health Organization (WHO)—along with Doctors Without Borders/Médecins Sans Frontières—designed a kit for NECT that contains four full treatments, instead of two treatments, and all the materials needed to administer NECT to improve procurement and consolidate the product. Also, the actual volume of NECT treatment was reduced, allowing for improved logistics as the product is brought to remote areas. Because DND*i* and its partners were able to develop NECT using fewer ingredients, less equipment, and less medication, the final cost to produce NECT was reduced by half. This gives health systems in LMICs the opportunity to afford more treatment for a disease that is affecting significant portions of their populations. Reduced weight of the final product also lowered the cost to transport the treatment to patients in endemic countries.

Because NECT showed the potential to make a greater health impact, the WHO included the treatment on the Model List of Essential Medicines in 2009. NECT is now available in 12 African countries that account for 99 percent of HAT cases. NECT also represented 93 percent of HAT treatments distributed in the Democratic Republic of the Congo in 2011.

high-value products because they address significant health threats in LMICs, but there is not necessarily sufficient financing (from public, philanthropic, and private sources) available to pay for these products. Therefore, developers need to know what the health system, patient, and procurer want and are willing and able to invest to make a technology widely available.

A number of respondents from NPPDs that are developing products targeting diseases endemic in middle-income countries noted that establishing an affordable price in these countries can be challenging. Recent findings indicate that many of the world's high burdens of neglected diseases occur primarily in the poor living among the wealthy in middle-income countries.[7] Therefore, using the national average income status as an indicator for establishing an affordable price will not ensure access for those most in need in middle-income countries (and in some instance,s in high-income countries).

Respondents noted that affordability in terms of cost has different definitions across products and diseases. In other words, the price point at which one product is affordable does not translate to what is affordable for other health conditions, because the value proposition (or perceived value added) of products will vary. Some NPPDs use price points of current products as benchmarks (or points of reference) to guide their thinking about affordability. This is more straightforward for technologies that already exist, such as antimalarial drugs. Medicines for Malaria Venture has benchmarked the proposed pricing of new artemisinin-based combination therapies (ACTs) against the lowest-price, quality-assured ACTs available on the market. However, using a proxy for price can be problematic. For example, the Bacille-Calmette Guerin (BCG) vaccine against tuberculosis (TB) is not a good benchmark for a novel TB vaccine. Although the BCG vaccine is inexpensive, it provides limited protection against the disease, and therefore is too simplistic a comparison as it does not take into account the costs borne by the health system associated with TB prevention, care, and treatment.

Because the health system is critical to the introduction and integration of new technologies, the cost to the health system is an important consideration in determining a product's affordability, along with the costs to manage the product (e.g., training and improving delivery mechanisms). The NPPDs must work with their partners from both the public and private sectors to determine a price that ensures the product can be sustainably produced by manufacturers and used by countries well into the future, as needed. For instance, Aeras—an NPPD developing TB vaccines—is considering alternate routes of administration (e.g., needleless technologies) for new TB vaccines in addition to the traditional applications (e.g., intramuscular injection). In exploring these alternate routes, the potential exists for health care workers to administer TB vaccines faster and more easily. But Aeras and partners need to weigh the benefits and consider the costs of introducing new technologies, which may require updating manufacturing and storage facilities—as well as new equipment, training, and other system improvements—in under-resourced, overwhelmed health systems.

Availability

NPPDs that have developed and delivered products work closely with their manufacturing partners to guarantee that consistent supplies of high-quality products are available to target populations. This may mean providing technical support to manufacturers to improve local capacity to produce quality-assured products and increase competition among local producers to drive down prices, or it may mean working with a multinational pharmaceutical company that is capable of producing massive quantities of product in a short amount of time. Strengthening local manufacturing capacity is important but is not always a priority for achieving access—in some instances, local manufacturing solutions may result in more costly

Critical drivers of success in ensuring access to MenAfriVac®

For years, meningitis has been a major cause of death and disability in sub-Saharan Africa, threatening the lives of the 450 million people living in the 26 countries that comprise the "meningitis belt." As a result, poor countries with overburdened health systems have had to divert funds, often too late, during epidemics to combat outbreaks. The World Health Organization (WHO) and PATH—an NPPD developing drugs, diagnostics, vaccines, and devices—established the Meningitis Vaccine Project (MVP) with the aim of developing and bringing to market a vaccine that would provide long-lasting protection against Group A Neisseria meningitis, the most common epidemic strain in Africa.

The collaboration brought together more than two dozen partners from African country governments, scientists, and manufacturers across four continents with the mission to develop the first vaccine specifically designed for Africa. Within a decade, the MenAfriVac® vaccine was developed at one-tenth of the US$500 million usually needed to develop and bring a new vaccine to market, and is currently available for less than $0.50 per dose.

The key factors of success:

- **Choose the right partners.** One of the most critical partners in ensuring the affordability and availability of the product was the manufacturer, Serum Institute of India, Ltd. (SIIL). SIIL has been manufacturing vaccines for use in LMICs for decades and therefore had the necessary experience, expertise, and understanding of the fluctuations of these markets.
- **Establish volume and price.** MVP worked with countries in the "meningitis belt" to determine how much product would be needed to make a public health impact. Based on this forecast, MVP and partners were able to guarantee volume, as well as determine an affordable price that the countries were willing to spend and would allow SIIL to recoup its costs and to generate a profit.
- **Engage local partners.** MVP began planning for access from day one. Before developing the target product profile, MVP engaged in-country partners (from governments and the target communities) to create demand and identify what they needed to value the product. Community forums and meetings with national authorities and directors of immunization programs convinced MVP staff that if a good product could be supplied at an affordable price, it would be rapidly adopted.

MenAfriVac® was prequalified by the WHO in June 2010 and six months later, the product was rolled out in a massive vaccination campaign in three countries in West Africa: Mali, Niger, and Burkina Faso. Within a month of introduction, nearly 20 million people were vaccinated. By the end of the meningitis season in 2011, WHO data showed no confirmed cases of meningitis A in people who received the vaccine. Since then, almost 110 million people within the meningitis belt have received MenAfriVac®.

production and thus negatively impact product pricing. Over the long term, companies (whether they are local or international) must have the capacity to meet demand in the countries of need.

Respondents acknowledged the need to ensure that their manufacturing partners are able to cover their costs. This may be done by allowing manufacturers to recoup their investment through a variety of strategies. For example:

- **Establish the price of the product based on the cost of goods plus limited profit margin.** The manufacturer is allowed to sell the product for a slight margin above what it costs the company to produce the technology. For instance, if it costs a diagnostics manufacturer US$2.00 per test to produce the technology, it will be allowed to charge an additional 10 percent, or $0.20, on top of the cost of goods for the final product.
- **Negotiate price controls or limits on how high a price can be charged for a product.** NPPDs and partners will establish the maximum price of a product based on a variety of factors—including the cost to produce, target geography or market, and demand estimates. By establishing the maximum cost that the manufacturer can charge

based on what the buyer is willing and able to pay, the NPPDs and partners ensure the price of the technology cannot exceed what is affordable. For example, Serum Institute of India, Ltd. agreed to charge no more than $0.50 per dose for MenAfriVac®—a price that African ministers of health and national immunization program managers told developers they could afford. It is important to note that NPPDs do not negotiate the lowest price possible but rather the maximum price that can be charged in order to encourage competitive pricing.

- **Implement tiered pricing within specific geographic areas or markets.** NPPDs and partners will agree on different price points based on the economic status of countries or markets (i.e., prices are set higher in private markets than in public health systems). For instance, the European Vaccine Initiative uses a regulation adopted by the Council of the European Union that regulates tiered pricing for pharmaceutical products as a benchmark. The regulation outlines options for tiered pricing of products to ensure equitable access to medicines and vaccines at affordable prices in developing countries (based on criteria outlined in the regulation). This allows partners to set a competitive market price for high-income markets and simultaneously offer a preferred price in NPPD target countries and markets.

Respondents noted that setting the price based on what the buyer can afford rather than on the costs associated with developing the product is in line with the principle of "de-linkage" that underlies the CEWG recommendations. Simply put, when applying this principle, the costs of R&D are not associated with the price of the final product. NPPDs play a critical role in de-linking, at least partially, the costs of product development from the final price. Most respondents felt that complete de-linkage can be achieved only when R&D is fully funded through public and philanthropic sources. However, many respondents noted that when a commercial partner financially supports the process of getting a product to market with its own direct funding, allowing a company to recoup its costs, at least in part, is an important factor to ensure a sustainable commitment to the collaboration. It is important to note that respondents felt this should not be the case when industry partners provide in-kind investments, such as technical support and pro bono services, rather than financial investment.

Acceptability

Respondents emphasized that it is critical to engage end users and beneficiaries (e.g., health care workers administering immunizations or patients seeking better treatments) in the design and the development of the product. It is important to know who will be the ultimate implementers and users of any new technologies, and how technologies are going to be delivered. Unless tailored to meet such specifications, a product risks sitting on the shelf. PATH and Population Council—NPPDs that have developed and introduced technologies to meet the reproductive health and maternal, newborn, and child health needs of LMICs—stressed that access includes ensuring the health system is ready to take up a new technology. NPPDs and partners must consider who will buy the product and buyers' key drivers. For instance, how does a health system decide to purchase a product? What needs to happen for the new technology to be integrated into the health system (e.g., do health care providers need additional training to administer the product)? These considerations also need to be taken into account when developing simpler manufacturing processes that are adjusted to developing-country conditions to ensure that a high-quality product can be produced locally at lower costs to improve access.

Partnerships

Because NPPDs are not manufacturers or distributors, they cannot be solely responsible for implementing access activities.[b] Therefore, NPPDs negotiate collaborations with partners from the public and private sectors that are designed to ensure access to the resulting products and

[b] Aeras is an exception, in some cases, as they have in-house pilot manufacturing capabilities that can be utilized for process development and Phase I and II clinical manufacturing runs. However, this will also depend on the capabilities of its collaboration partners, who may have clinical and/or commercial manufacturing capabilities of their own, or already have manufacturing partnerships established.

Medicines for Malaria Venture partnering to improve access

Access activities at Medicines for Malaria Venture (MMV) are driven by a belief that a drug becomes a medicine once it gets to the right patient. MMV weaves this principle throughout its approach to all stages of the product lifecycle, and as evidenced by the successful development and launch of Coartem® *Dispersible*.

Even though more than 85 percent of those who die from malaria are children, antimalarial medication existed only in tablet formulations until the development of Coartem® *Dispersible*. Tablet formulations need to be broken up for children, leading to poor compliance and imprecise dosing. Furthermore, antimalarial drugs typically taste bitter, making them difficult for children to swallow. With these considerations in mind, MMV and Novartis launched Coartem® *Dispersible*—the first fixed-dosed artemisinin-based combination therapy (ACT) specifically developed for children. Coartem® *Dispersible* is as effective as Novartis' fixed-dose ACT Coartem® but is a child-friendly formulation that tastes sweet. Coartem® *Dispersible* received Swissmedic (Swiss Regulatory Agency) approval in December 2008 and World Health Organization (WHO) prequalification in February 2009. The WHO included Coartem® *Dispersible* on the WHO Model List of Essential Medicines for children in April 2009. Since the launch of Coartem® *Dispersible* in 2009, 200 million treatments have been delivered to 50 malaria-endemic countries.

The successful introduction of Coartem® *Dispersible* is attributable to strategic packaging considerations, as well as key regulatory and policy activities that supported product uptake. MMV and Novartis conducted field research in Kenya, Tanzania, and Uganda to inform the design of packaging and supplemental training materials. Following product introduction, appropriate packaging remains an ongoing consideration. Two years after initial rollout of Coartem® *Dispersible* in Malawi, MMV partnered with the country's Ministry of Health and Population Services International (PSI) to expand integrated community-level treatment. MMV and Novartis worked with PSI to develop packaging that would facilitate rollout. MMV and Novartis also partnered with the Malawi regulatory authority to get fast-track approval, and MMV simultaneously provided technical guidance to change national treatment guidelines and support health care worker training. By advocating for a supportive policy environment and regulatory activities, and by designing packaging to promote delivery within health systems, MMV and Novartis further ensured access long after the original development of the product.

knowledge. For instance, commercial partners may establish a new manufacturing process to improve production. In addition, government partners may need to develop or revise policies to strengthen the procurement systems of new technologies. Collaboration is a key element in all NPPDs' access strategies.

Access commitments

Many of the respondents said that it is often difficult to tie partners to measurable access commitments early in the development process because all of the specific characteristics of the final product may not be known in the early phases. For example, it may be expected initially that a product will require one dose, but results from clinical studies may reveal that it actually requires two doses to achieve the desired health outcome. This added dose could increase the cost of the treatment and add complexity to the storage and the delivery of the product, and thereby impact the accessibility of the technology. Respondents stressed that although access commitments early in the R&D process are necessary—to ensure affordability, availability, and acceptability of the product—flexibility is required in how they are implemented as the product progresses through the pipeline.

The access commitments that NPPDs ask from manufacturing partners generally fall into two categories: ensuring supply and establishing affordable price. NPPDs seek to ensure that their manufacturing partners guarantee adequate supply of products to meet the needs in LMICs. NPPDs may ask their partners to provide sufficient supply for the public health system or specific LMICs, or agreed-upon volume to meet demand forecasts. If possible, NPPDs may opt to work with multiple manufacturers in order to increase competition. The presence of multiple manufacturers that are able to produce a technology in a market can increase an

NPPD's leverage to secure an affordable price and sustainable supply.

As previously discussed, an NPPD will often negotiate a price ceiling (the maximum allowable price) or tiered pricing schemes (differential pricing based on geographic economic status) with partners. This may mean that partners agree to sell a product at cost in select regions or markets, whereas it may be sold at higher cost in high-resource settings. In some situations, NPPDs may establish a limited profit margin above the cost to produce the product. No matter how the agreement is structured, NPPDs try to negotiate the best supply and pricing terms in favor of LMICs in order to achieve access.

These agreements define the expectations, commitments, and investments among partners, and are critical to sustaining effective collaborations and creating a framework to make products available for public health impact. Respondents noted that they will often stagger agreements by phase of research. Early in the development process agreements may focus more on the process for moving forward, with specific predetermined milestones to be reached. General global access commitments will be included in early research agreements but may not include much detail because it is difficult to determine the specific characteristics of the product at early research stages. If the access plan is too concrete too early, there is increased likelihood that developers may be more risk averse when there are many uncertainties and that too much specificity at that stage may lead to overly conservative access plans (e.g., overestimates of costs or underestimates of need). In order to hold partners accountable, agreements include exit provisions that allow NPPDs to discontinue the partnership if the partner is not complying with access commitments.

Critical leverage points

Every respondent noted that the most significant keys to attracting and leveraging partner commitments are their expertise and experience. They identified a number of other critical leverage points that they use to ensure that partners implement access principles. It was noted that some of these commitments can be written into a contract, whereas others are considered "soft leverage" that may be less tangible but no less important. For example, access to intellectual property (IP) rights and funding commitments can be written into a contract but the value of reputation building for partners (particularly less well-known organizations) through association with an NPPD is harder to define and quantify.

Funding: Because private-sector companies are less likely to assume the full risks and costs of product development targeting LMICs, NPPDs take on this risk by covering costs through public and philanthropic investments. The funding that NPPDs bring to the partnerships incentivizes partners who may not otherwise engage in R&D with limited commercial potential to invest their expertise and resources. This funding also ensures, to some extent, that the costs of product development are not associated with the final price of the product. These funds are conditional on partners complying with access clauses as outlined in agreements.

Intellectual property and know-how: Intellectual property rights may be leveraged in return for supply and pricing commitments from commercial partners to ensure that products will be available in sufficient volume and at an affordable price. In addition to licensing their technologies to partners, NPPDs may also transfer critical know-how and provide access to data that can enable partners' research. For instance, an NPPD may have developed a simplified process for producing a vaccine and will transfer that technical knowledge to partners to help increase their manufacturing capacity to produce an affordable, quality-assured supply of product. Some NPPDs may not have IP to license but have generated data that can accelerate a partner's research. The aim of sharing knowledge is to expedite the broader research agenda.

As was mentioned, not all NPPDs hold exclusive or any IP rights on the products in their pipeline. IP ownership may be simple and lie with one organization, or it may be more complex and shared

among multiple entities—from the commercial, public, and academic sectors—including an NPPD. Those NPPDs that do manage IP acknowledge that, although IP rights can be an important driver, it is never enough for true product access, particularly for neglected diseases where there is little to no commercial profit potential.

Capacity strengthening: All of the NPPDs engage in some capacity strengthening with their in-country research and manufacturing partners. International AIDS Vaccine Initiative has established a global network of clinical facilities and labs to strengthen AIDS vaccine research by providing training for clinicians, nurses, scientists, and technicians to conduct trials and studies in line with international standards. PATH has worked with manufacturing partners in India and China to expand their capacity to manufacture vaccines against Japanese encephalitis and meningitis group A that have both achieved WHO prequalification.

Field presence: A number of the NPPDs have national and regional offices that serve as platforms for innovation and can help create demand for new products and implement access activities. The International Partnership for Microbicides (IPM) established a significant presence in South Africa for the purposes of implementing its Phase III clinical trial for the dapivirine ring. A local field presence in South Africa allows IPM to be close to the clinical trial sites as well as the local community, stakeholders, and regulators. Local presence allows IPM to understand product use and adoption, and will help ensure timely uptake. Drugs for Neglected Diseases *initiative* has regional platforms that coordinate its product development activities and engage policymakers in preparing for the introduction and adoption of new technologies. TB Alliance is an NPPD developing TB drugs that does not have regional or country offices but is working with other nongovernmental organizations, including other NPPDs, to access their in-country networks to prepare countries for the rollout of new TB treatments.

Critical partnerships: NPPDs work with a range of stakeholders who are engaged in ensuring access to new technologies at the national, regional, and global levels, and with whom many of their private sector or academic partners may not normally interact. These individuals and organizations include:

- Local health providers who are implementing many of the health technologies developed by NPPDs and their partners.
- Local communities who are the beneficiaries and end users of these products.
- Normative agencies like the WHO that establish global policy frameworks for the adoption of new health interventions.
- Global procurement institutions, such as the United Nations Children's Fund (UNICEF) and the Pan American Health Organization (PAHO), that provide funding to low-income countries to buy and distribute health technologies.
- National regulatory bodies that approve new health technologies for use and monitor their implementation.
- National ministries of health and finance that make the decision to adopt and fund new health technologies.
- International development organizations, such as Clinton Health Access Initiative (CHAI) and UNITAID, that work with governments to improve markets for new health technologies.

Entry into new markets: Working with an NPPD to develop and introduce a new technology may allow a partner to build its presence and experience in LMIC markets. This can help partners gain experience in working in these markets and enable them to introduce other products, potentially products with commercial value like drugs for asthma or heart disease, in the future.

Whether it is their understanding of how to move a product from the lab into clinical trials (of particular interest to academic partners) or working in LMIC markets, NPPDs play a critical role in working with partners to navigate the policy environment, build research and manufacturing capacity, and provide access to key decision-makers on the global and local levels who can facilitate the introduction and integration of new technologies.

Conclusion

Partnerships across sectors and regions are critical to the successful development and integration of affordable, available, and acceptable health products. Since it is not possible 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 level throughout the product development process.

NPPDs identified some common lessons that are relevant for any organization trying to advance technologies to meet the health needs of LMICs:

- **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 be implementing and benefiting from the product. The end users must be engaged in the identification of need, design, and development of the solution, and access plans, in order to ensure that the resulting technology has impact for those most in need.
- **Achieving global access does not guarantee local access.** NPPDs and partners may achieve global access targets (e.g., receiving WHO prequalification) but this does not guarantee that the technology will be accessible at the national or subnational level. A global access plan is necessary to facilitate implementation at the country level, but it is also critical to work with country officials, local providers, and communities to translate need into demand, plan for introduction, and accelerate the uptake of new technologies.
- **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 who have not benefitted from strengthening economies. Conflicting criteria used to define developing countries has complicated price negotiations as countries transition from receiving donor funds to becoming donors. For some middle-income countries, the national gross domestic product does not reflect what local populations can afford to spend on public health programming. Therefore, the poorest populations, often the most at risk, are unable to access new technologies.
- **Securing donor recognition that access activities need to be initiated early is critical.** In order to ensure there is not a lag between licensing a product and making it available in the health system, NPPDs and partners must start planning for access from the beginning of the development process. Support from donors for these activities is critical.
- **Demonstrating a niche in the market for manufacturers is essential to incentivize their investment.** Manufacturing partners must understand the added value that they bring to a market to enable them to invest time, effort, and expense to developing products for poverty-related and neglected diseases and conditions. They need to be able to see long-term benefits to their business while at the same time achieving the access goals outlined by the NPPDs.

The examples and perspectives cited in this paper provide a high-level overview of how NPPDs and their partners try to ensure access to the technologies and knowledge that they develop. As illustrated, there are common lessons learned, and there is a spectrum of experience in how access is defined and pursued among NPPDs.

Appendix 1: List of interviewees

Aeras: Angeline Nanni, Director, Market Access; Kevin Sly, Vice President, Business and Corporate Development

Drugs for Neglected Diseases *initiative* (DND*i*): Jennifer Katz, Interim Regional Executive Director, North America

European Vaccine Initiative (EVI): Stefan Jungbluth, Business Manager

Infectious Disease Research Institute (IDRI): Erik Iverson, Executive Vice President, Business Development and External Affairs

International AIDS Vaccine Initiative (IAVI): Labeeb Abboud, Senior Vice President and General Counsel

International Partnership for Microbicides (IPM): Chris Camut, Chief Financial Officer; Karen McCord, Senior Director, Strategic Planning; Christine Woodward, Associate Director, Operational Risk and Asset Management

International Vaccine Institute (IVI): Christian Loucq, Director-General

Jhpiego: Brinnon Mandel, Team Leader, Innovations Development Program

Medicines for Malaria Venture (MMV): George Jagoe, Executive Vice President: Access and Product Management

PATH: Steve Brooke, Commercialization Advisor, Technology Solutions; Ray Cummings, Business Advisor, Technology Solutions and Drug Development; Linda Nyari, Director, Commercialization and Corporate Partnerships, Vaccine Development; Leander Lauffer, Head of Business Development, Malaria Vaccine Initiative; Chris Victor, Advisor for Epidemiologic Science and Clinical Trials, Vaccine Access and Delivery

Population Council: Jim Sailer, Vice President, Corporate Affairs; Martha Brady, Senior Associate

Sabin Vaccine Institute: Peter Hotez, President and Director; Maria Elena Botazzi, Director of Product Development

Serum Institute of India Ltd.:[c] F. Marc LaForce, Director, Technical Services[d]

TB Alliance: Elizabeth Gardiner, Vice President, Market Access

TuBerculosis Vaccine Institute (TBVI): Rene Coppens, Director, Resource Mobilization

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

[d] F. Marc LaForce was interviewed in his role as former Director of the Meningitis Vaccine Project

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