

Blueprint for a Market-Driven Value-Based Advance Commitment (MVAC) for Tuberculosis

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Acronyms

AMC	Advance Market Commitment
BMGF	Bill & Melinda Gates Foundation
BRICS	Brazil, Russia, India, China, and South Africa
CIVETS	Colombia, Indonesia, Vietnam, Egypt, Turkey, and South Africa
DALY	Disability-adjusted life year
DST	Drug-sensitive treatment
HIC	High-income countries
HTA	Health technology assessment
LIC	Low-income countries
LMIC	Low- and middle-income countries
MDB	Multilateral development bank
MDR	Multi-drug resistant
MIC	Middle-income countries
MNC	Multinational companies
MVAC	Market-drive value-based advance commitment
NCDs	Non-communicable diseases
PDP	Product development partnerships
PR	Principal recipient
QALY	Quality-adjusted life year
R&D	Research and development
SoC	Standard of care
TB	Tuberculosis
TPP	Target product profile
UDR	Universal drug regimen
UHC	Universal health coverage

Glossary

Health Technology Assessment: a multidisciplinary process that reviews the medical, economic, organisational, social, and ethical issues related to the use of a health technology in a systematic manner whose main purpose is to provide policy-makers with evidence-based information, so they can formulate health policies that are safe, effective, patient-focused and cost-effective. It is also used by national authorities to help decisions on which technology should be reimbursed at national level.

Advance Market Commitment: a binding advance commitment, offered by governments and donors, for purchase of a health technology meeting specific pre-agreed parameters.

At-launch HTA: an updated HTA conducted at the time of product launch used to adjust pricing and volumes based on product efficacy against the pre-agreed TPP.

Ex-ante HTA: HTA conducted before the launch of a new treatment based on TPP characteristics.

Ex-post HTA: HTA conducted after product launch used to verify the product's clinical efficacy and confirm appropriate value-based pricing.

Governance arrangements: a range of explicit or implicit structures, institutions, organisations, or agreements that enable the governance functions to be executed.

Governance functions: processes that must be managed or decisions that must be taken for the overall model to work.

Governance model: a cohesive and complete set of governance arrangements that will ultimately guide execution of the entire model.

Impact/performance risk: risk that new drugs underperform once deployed.

IP risk: risk of patent infringement or compulsory licensing.

Market demand risk: risk of insufficient demand for volume/price to justify R&D.

Multi-entry risk: risk that multiple R&D actors produce the same product for the same target market.

MVAC: An AMC that is driven by MIC demand, informed by countries' willingness to pay, and allows pharmaceutical companies to reap higher revenues from a more effective product.

Payment risk: risk of non-payment or late payment.

Price risk: risk that prices demanded by R&D actors are unaffordable.

Product risk: risk that new products fail to address local needs.

Proof-of-concept: drug development up to Phase IIb

Scientific risk: risk that R&D does not lead to a viable product.

Value-based pricing: the idea that payers should be willing to pay a price that represents the value produced by a given treatment to their respective healthcare systems.

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Executive Summary

Background

Innovation—delivering new drugs, diagnostics, and devices—is a critical tool in the global fight against disease and premature death. Yet despite the potential for innovation to improve health around the world, the pharmaceutical industry’s investments in research and development (R&D) generally neglect diseases of the poor in favour of more lucrative high-income markets. Responding to this R&D gap, donor “push” investments have helped advance an innovation agenda to serve low- and middle-income countries (LMICs). Though these investments have helped accelerate market entry of several important innovations, other donor-push products have fizzled upon market entry due to unaffordable or cost-ineffective pricing, disappointing efficacy, lack of political will, or lower-than-anticipated country demand. And with many large middle-income countries (MICs) poised to soon transition from donor aid, the sustainability of the current donor-led model is in question.

Tuberculosis (TB), an infectious disease primarily affecting the poor and vulnerable, ranks among the top 10 global causes of death. Current TB treatment cycles are long and toxic, causing some patients to discontinue treatment, develop acquired drug resistance, and risk spreading a drug-resistant pathogen to others. Drug resistant strains are more difficult to treat, requiring long-duration toxic regimens and high-cost hospitalisation. Despite years of global investment in TB control, modelling suggests that global goals for TB cannot be achieved without major technological breakthroughs.[1] One particularly desirable innovation would be a short-course universal drug regimen (UDR)—equally capable of treating drug-susceptible and drug-resistant strains, with a two-month or shorter treatment duration. Donors, particularly the Bill & Melinda Gates Foundation (BMGF), have funded substantial early-stage R&D to source new treatment compounds that could contribute to a UDR, but substantial additional investments in late-stage trials would be required to bring the UDR to market.

The global market for TB therapies reached roughly \$1 billion in 2018 and is projected to grow over one-third by 2025—suggesting a potentially large and profitable market for better TB treatment.[2] Yet despite the clear health need and potential return, private sector actors have mostly shied away from the TB market. Industry perceives MICs—comprising the vast majority of the TB treatment market—as risky markets for an innovative product. Historically, many MICs have either aggressively negotiated down innovative drug prices; declined to purchase innovative therapies until they go off patent; imposed price controls; or exploited TRIPS flexibilities for compulsory licensing of on-patent drugs.

For MIC markets alone to generate private sector R&D investment, innovator companies will need assurance that MIC purchasers are willing to pay a value premium for innovation—potentially far higher than the cost of less effective generic competitors, but low enough to ensure local value and affordability. Notably, recent policy announcements by MIC governments signal their increasing willingness to engage with and contribute to global health initiatives, including the TB R&D agenda. This suggests a window of opportunity is opening to engage MICs in the development of a pathbreaking health technology to address the TB scourge.

Introducing the Market-Driven, Value-Based Advance Commitment

The Market-Drive Value-Based Advance Commitment (MVAC) builds on the Advance Market Commitment (AMC) mechanism previously used in global health with several important innovations and improvements. Most crucially, the MVAC is driven by MIC demand rather than donor contributions; informed by countries' willingness to pay rather than a single, "cost plus" price; and allows pharmaceutical companies to reap higher revenues from a more effective product.

The MVAC rests on four essential design pillars:

- **Health Technology Assessment:** Health Technology Assessment (HTA), already a well-established process in MICs including Brazil, China, India, and South Africa, is a mechanism by which payers evaluate the value of a new product through the application of globally accepted methods. The MVAC will use HTA—based on country-specific evidence and willingness to pay—to inform countries' purchase commitments.
- **Commitment Guarantees:** To drive engagement and investment in R&D by the pharmaceutical industry, it is critical industry perceive MIC commitments as highly credible. Commitment guarantees—underwritten by a financial intermediary—will help ensure that MICs credibly signal their demand and willingness to pay.
- **Industrial Policy Alignment:** Based on an initial landscaping analysis, we know that developing local industry (including home-grown research capacity and pharmaceutical industries) is a priority for many MICs.
- **Governance Structure:** An MVAC governance structure credible to both MICs payers and industry is required to drive and operationalize the MVAC. This requires it to be authoritative, open, and sufficiently flexible to place MIC governments in the driving seat.

The MVAC model is intended to serve as a bridge between the dysfunctional status quo and a more sustainable and effective R&D ecosystem—one which more closely emulates the positive characteristics of HIC markets for healthcare products. Many of its core elements (including the need to underwrite commitments and the development of a joint target product profile, or TPP) will become less relevant as markets mature and trust is built between payers and industry. The governance structure—a secretariat to pool HTA resources, set and signal joint priorities, and conduct country-specific value assessments—may endure but evolve as national payers build up their own institutional, human resource, and data collection and analysis capacities.

Health Technology Assessment: Estimating the Value-Based Market for a New TB Treatment Regimen

HTA is defined as a "a multidisciplinary process that reviews the medical, economic, organisational, social and ethical issues related to the use of a health technology in a systematic manner" whose "main purpose is to provide policy-makers with evidence-based information, so they can formulate health policies that are safe, effective, patient-focused and cost-effective. It is also *used by national authorities to help*

decisions on which technology should be reimbursed at national level.”[3] HTA is well established in many HICs; a wide range of MICs—including India (see Box 2), China, Indonesia, Thailand, South Africa, the Philippines, and most of Latin America and the Caribbean (LAC) (including Mexico, Brazil, Chile, and Colombia)—have also established HTA bodies linked to their national health insurance and pharmaceutical procurement agencies. In the context of the MVAC, early (or ex-ante) HTA conducted before the launch of the new treatment (based on the TPP characteristics) can then be applied to estimate the maximum justifiable size of a guaranteed purchase commitment given treatment alternatives, expected patient numbers, and local ability to pay.

We engaged a team of world-class epidemiological and economic modelers to undertake HTA and estimate the value-based market for a new TB drug treatment in line with the TPP in three countries—India, Russia, and South Africa.^a The modelling approach is rooted in “**value-based pricing**”—the idea that payers should be willing to pay a price that represents the value produced by a new TB drug regimen to their respective healthcare systems. The model evaluates the UDR from a healthcare perspective, considering two sources of value: (1) additional health gains of the UDR compared to alternative therapies, valued at country willingness to pay per Quality Adjusted or Disability-Adjusted Life Year (QALY or DALY) based on supply-side constraints/opportunity costs; and (2) health system savings (e.g., averted hospitalizations and a reduced need for drug sensitivity testing).

The full report includes extensive sensitivity testing, but we report our main (baseline) results based on a set of highly conservative assumptions, including launch of new and superior TB technologies before the TPP-based new drug treatment comes to market (Table 1). Based on these assumptions, the model estimates a total market in India, Russia, and South Africa of around \$6.3 billion for the first 10 years after launch (Table 2).

^a Note: Modelling work completed by Anna Vassall, Gabriela Gomez, Nim Pathy, and Lotte Steuten; report forthcoming

Table 1. HTA Model Assumptions and Parameters

	India	Russia	South Africa
Population (in terms of current burden and resistance)	High TB, TB/HIV, and MDR ^b Mainly resistance to first line drugs	High TB and MDR TB High levels of resistance to second line drugs	High TB, TB/HIV, and MDR Mainly resistance to first line drugs
Intervention	UDR as defined by the TPP		
Comparator	Standard of Care (SoC) at the time of UDR introduction: <ul style="list-style-type: none"> • New shortened regimen introduced in 2025 for DS and MDR^c • New vaccine 		
Outcomes	<ul style="list-style-type: none"> • Additional DALY averted • Net monetary benefit • Health sector cost savings 		
Context (National Strategic Plan)	Private sector engagement Patient support (nutritional supplement)	Scale up of Gene Xpert MTB/RIF in 2018 Standardisation of WHO MDR revised regimen	WHO symptom screening for all Standardisation of WHO MDR revised regimen

Table 2. Key Results from Early Stage (ex-ante) HTA

	100% value-based revenue (USD billions)	Maximum price per regimen (USD 2017)	Number of regimens 2030 to 2039 (millions)
India	3,24	501	6,467
Russia	0,6	2,498	240
South Africa	2,37	864	2,743
Total	6,30		9,450

The estimated value-based market for India, South Africa, and Russia is significantly larger than the expected cost of late-stage R&D. It could be possible, therefore, to pull a product to market with volume and/or price commitments that represent only a portion of total market demand.

^b MDR-TB (i.e. resistance to at least both isoniazid and rifampicin), which leads to substantially longer treatments and costs to the health service and patients compared to drugs sensitive TB.

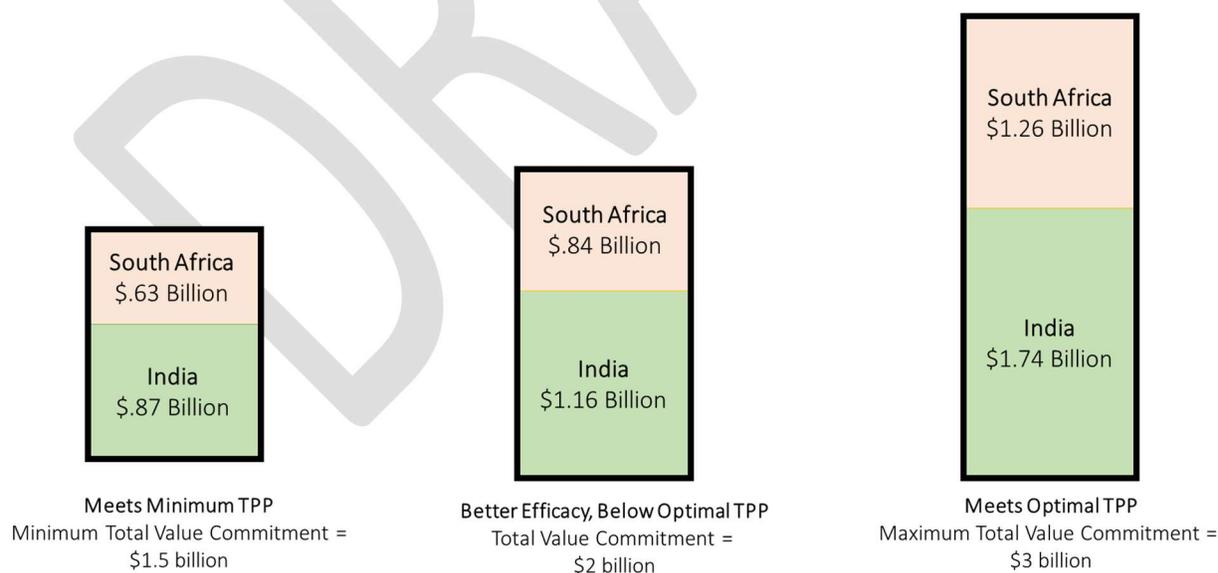
^c The SoC in 2030 was defined as new shortened regimens for first line treatment (4 months) and for MDR (9 months, new drugs with no pre-existent resistance) in 2025. These regimens are similar to the BPAmZ and BPAL currently trialled by the Global Alliance for TB drug development. In addition, we assume there will be a new vaccine coming to the market in 2027. This vaccine has clinical characteristics similar to the recently trialled M72/AS01E(18).

Calculating and Securing the Advance Purchase Commitment

Drawing from the ex-ante HTA results, participating countries must set a reasonable and sufficient purchase commitment to incentivize industry investments. The HTA results provide an upper-bound estimate for the size of that commitment; the lower-bound of the commitment size must be expected to provide a risk-adjusted return for the successful innovator company. Given the large overall value proposition, there are many different commitment models that could deliver shared value to all parties.

We suggest a relatively simple and powerful model—a predictable revenue commitment pool, tied to product efficacy—that could serve as a starting point for negotiations. As a first step, one or more high-burden countries would need to take a leadership role as “first-movers”—for example, India and South Africa. Ex-ante HTA for those two countries would reveal the total value-based market; the relative value of the TPP-based new drug treatment by country; and the relative value of the new drug treatment for each country vis-à-vis specific attributes of the TPP. Using the ex-ante HTA results as a starting point, the first mover countries would set and divide up a total “commitment pool”—essentially, an advance purchase commitment (price x volume) tied to product efficacy. A minimum commitment pool would be offered for a product meeting a minimal TPP; a maximum commitment pool would be offered for a product meeting the entirety of the TPP. The two countries would assume “shares” of the total commitment pool based on the relative value propositions in their respective health systems (Figure 1). Potentially, additional countries could join the commitment pool at a later date—leaving the total revenue guarantee unchanged but reducing each country’s specific commitment.

Figure 1. Indicative Schematic for Defining and Dividing a Value-Based Commitment



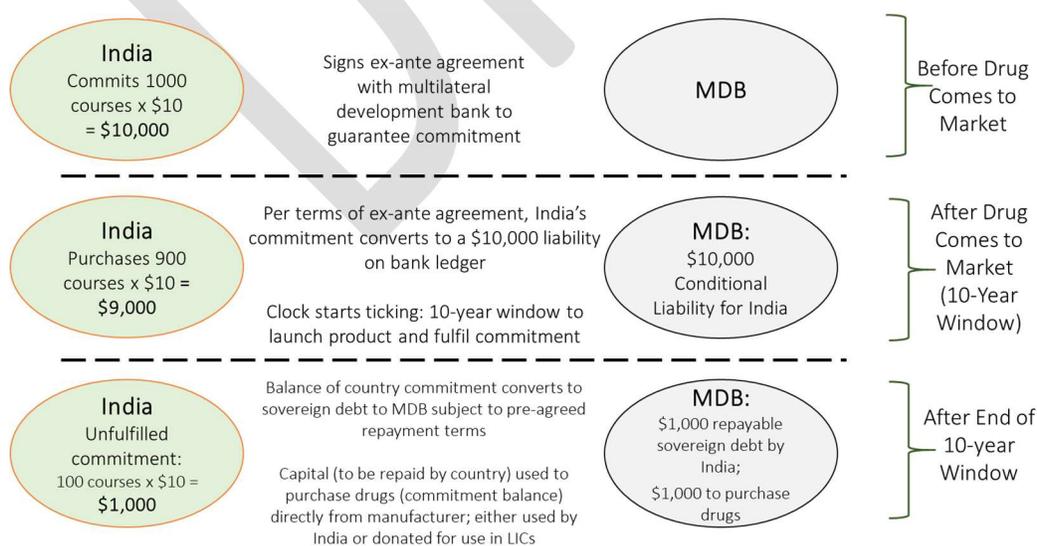
At the time of product launch, a form of at-launch HTA would be undertaken. Countries would rerun the early-HTA model with up-to-date efficacy data, based on the clinical trial results with appropriate modelling. The value-based price in each country would be adjusted for efficacy. Countries would be responsible for fulfilling their prior volume commitments by purchasing a sufficient quantity of the

product at the efficacy-adjusted value-based price. After fulfilling their commitments, countries would receive access to the product for the remainder of their demand at a discounted price (30 percent of the value-based price in the illustrative example) for a specified period. Ex-post HTA (say 2-5 years later) using post-launch evidence collection could be used to assess whether the product is meeting the at-launch efficacy expectations; efficacy either exceeding or failing to achieve anticipated levels could prompt pricing adjustments for future purchases from a pre-agreed time point.

A more complicated (but potentially advantageous) approach would involve conducting a full HTA at launch, inputting up-to-date data reflecting the current situation in 2030. This approach creates additional complexity but offers a better precedent for value-based pricing by incorporating accurate parameters at the time of launch. Country-guaranteed revenue commitments would still be calculated based on baseline assumptions, with volume adjustments to reflect any price change, to ensure predictability to countries, industry, and the financial intermediary for overall guaranteed revenue.

To guarantee countries' purchase commitments, countries would leverage their own sovereign creditworthiness—intermediated through a AAA-rated intermediary guarantor such as a multilateral development bank (MDB)—to underwrite the advance commitments (Figure 2). As a first step—well before the drug comes to market—each country government would sign a contractual agreement with such an MDB laying out the terms of the commitment and clearly defining the country's obligations after the drug becomes available. After the drug comes to market, the country's commitment would convert to a conditional liability on the MDB ledger; the country would have 10 years (illustratively) to fulfill the entirety of its purchase commitment by purchasing drugs directly from the originator company or a local licensee authorized by the originator. If a commitment balance remains at the end of the 10-year window—that is, if a country were to partially or fully renege on its purchase commitment—the remaining balance would convert to a loan by the MDB, subject to repayment by the commitment-making country under pre-agreed terms. The remaining drug purchase commitment would be honored by the MDB on behalf of the country, and the drugs would be supplied for the country to use as it thought appropriate.

Figure 2. Model to Underwrite Country Commitments



Based on a needs assessment and preliminary conversations with relevant stakeholders, the World Bank and the Asian Development Bank emerge as promising candidates to serve as MDB partners.

The MVAC model mitigates and distributes risk, reducing total risk to a more acceptable level for all parties. Along several dimensions, the MVAC is fully de-risked:

- The commitment guarantees offer clarity on market demand for a product that meets TPP efficacy expectations.
- The commitment ensures that countries can access the new products at affordable prices.
- The TPP ensures that products will meet local demand.
- The entire structure is premised on respect for the originator's intellectual property.

Along other dimensions, risk is reduced and redistributed efficiently across parties:

- Suppliers continue to face the scientific risk that products will fail in late-stage trials; however, their risk is substantially reduced with financial subsidies from global donors through early-stage pipeline development to proof of concept.
- Market entry of competitor products remains possible but unlikely given the stringent TPP requirements, including the likely nature of the TPP-based new drug treatment being a three-product combination; a more likely scenario would involve market entry of a vaccine (reducing the pool of people to be treated).
- We have assumed that at-launch HTA only leads to price adjustments from the full TPP price based on efficacy. However, the potential use of ex-post HTA after the product is launched could redistribute some performance/impact risk from countries to suppliers (e.g., if there are toxicity concerns).
- The MDB would reduce and absorb payment risk by transforming a verbal commitment to a sovereign debt obligation.

Industrial Policy

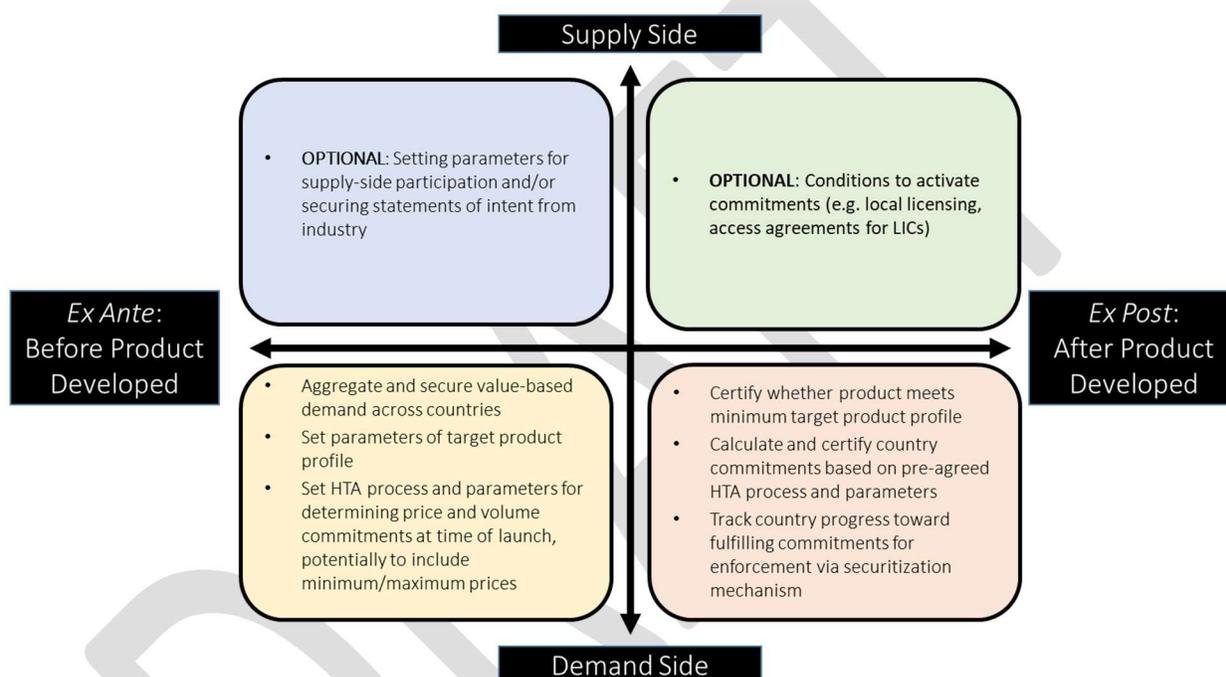
The proposed MVAC model raises several issues related to participating countries' industrial policy objectives. The MVAC will need to accommodate countries' preferential purchasing policies for local manufactures (as opposed to from multinational companies, or MNCs), plus any specific requirements for local research.

The successful innovator company could be expected to meet country industrial policy requirements by, for example, licensing production to local manufacturers. Development of the biopharmaceutical industry is a priority for the governments of India, China, and Russia. Russia is particularly protectionist in its policies, which results in a high need for localization by MNCs. In India, South Africa, and China, although localization is not required, there may be an expectation that MNCs would generate productive clinical development partnerships and local manufacturing arrangements. Given the high overall expected volumes, technology transfer models and license agreements between MNC developers and local manufacturing companies could be a useful route to secure long-term supply.

Governance

The MVAC is a vehicle for multinational cooperation; ultimately, its structure and operations must be owned and governed by participating country governments in partnership with relevant trusted global experts and institutional stakeholders. Yet for the model to work in practice, country governments must delegate key authorities to a permanent technical body that can manage day-to-day governance functions (Figure 3).

Figure 3. Essential MVAC Governance Functions



To serve its core functions—and successfully manage a complex and politically sensitive negotiation process—the MVAC governance model would benefit from being

- open and credible to BRICS/CIVETS and other MICs
- credible to industry
- relevant to, or expert in, tuberculosis
- flexible
- able to minimize transaction costs
- capable of attracting (or offering) long-term operational resources

Based on a needs assessment, we identified a World Bank trust fund as the best fit for MVAC operational needs. The World Bank is a credible multilateral institution—both for potential industry partners and for MICs, which already participate in institutional governance and could oversee a dedicated trust fund. The trust fund model is widely used to steward development resources and is well-trusted by the donors who might subsidize the secretariat’s operational costs. Trust funds offer predictable multi-year funding—

potentially using a single up-front investment to finance the MVAC secretariat over the entirety of its long-term lifecycle.

The trust fund would be governed by an **MVAC board**, primarily comprising participating country governments; it may also include representation from external technical and funding partners plus independent technical advisors. The board would be responsible for setting the secretariat mandate and broad policy direction, plus overseeing secretariat operations. To ensure that decision points are insulated from conflicts of interest—and thus credible to market actors looking to invest in TB R&D—the board would be supported by an independent technical advisory group.

In the first year, there would be a need to establish, test, and gradually expand a **transitional secretariat**, with costs of about \$2–3 million over a period of 12–18 months. This would build on the thinking and analysis delivered so far and would include (i) further modelling through modelling consortia; (ii) contract drafting; (iii) socialization and outreach to countries, industry, and MDBs; and (iv) recruiting the core team at the secretariat.

Once fully functional, the secretariat would migrate in full to a **permanent home**, ideally within a World Bank trust fund. During high-intensity periods, we expect that the secretariat would need approximately 15–20 full-time staff members, including technical, legal, and country-specific staff, and it would commission and administer research grants from third parties.

Next Steps

The Center for Global Development and Office of Health Economics released this consultation draft of the MVAC blueprint in March 2019 for public review and comment; the document is still preliminary, with many outstanding questions and unresolved issues. Through mid-2019, we welcome constructive feedback and dialogue to further hone the proposal and ensure it is responsive to the interests and concerns of all stakeholders. During this period, we will also work proactively to engage with stakeholders in target countries, international institutions, and within the pharmaceutical industry.

Please contact Rachel Silverman (rsilverman@cgdev.org) to share feedback or arrange a call and/or in-person meeting with the MVAC team.

Chapter 1. A Failing R&D Model for Tuberculosis

How Global Research and Development Excludes the World's Poorest

Innovation—delivering new drugs, diagnostics, and devices—is a critical tool in the global fight against disease and premature death. Yet despite the potential for innovation to prevent disease and improve health around the world, industry's research and development (R&D) investments disproportionately serve high-income markets, where the burden of disease is predominately concentrated in non-communicable diseases (NCDs) such as cardiovascular disease, cancer, and diabetes. High-income country (HIC) markets are characterised by high profit margins (particularly in the United States [1]) and ever-growing demand from patients for new, innovative treatments. These markets are sufficiently large and profitable to incentivize R&D.

Low- and middle-income countries (LMICs) carry a burden of disease that sometimes overlaps with HICs—for example, several major NCDs, plus infectious diseases such as hepatitis C and HIV. However, LMIC patients often lack access to the innovative products for these conditions that are available in HICs. Access is partly constrained by pricing, but also by system inefficiencies, limited budgets, and weak regulation. Nonetheless, LMIC patients and payers can opt for many effective, relatively low-priced generic products to meet part of this need (at least for NCDs), although inefficient procurement often leads to unnecessarily inflated prices even for off-patent products.^d For the poorest countries, voluntary licensing arrangements by multinational companies (MNCs) to low-cost generic producers, coupled with pooled procurement through global institutions such as GAVI and the Global Fund, have also greatly expanded access to innovative vaccines, treatments, and diagnostics targeting infectious diseases. In addition, there is the potential for differential (“tiered”) pricing of products that remain under patent and outside the scope of large global health institutions. This is a “win-win” solution in theory for countries and manufacturers, but the potential is often unrealised.

At the other end of the spectrum, diseases afflicting almost exclusively the world's poorest, for which treatments are not available in HICs, have received targeted R&D investment funded by the global health donor community. This has typically come in the form of “push” investment—grants or loans provided by donors for early-stage pharmaceutical R&D. Yet 75 percent of those suffering from extreme poverty in the world are now living in MICs[4]—many of which will “transition” from global health assistance over the next decade.[5] To the extent that donor “transition” leads to a reduction in push funding, R&D investment for diseases of the poor in MICs is likely to decline—slowing the pace and/or reducing the likelihood of breakthrough innovation.[6]

Tuberculosis: Addressing the Innovation Gap

Tuberculosis—an infectious disease primarily affecting the poor and vulnerable—ranks among the top 10 global causes of death. Although there is no effective vaccine, tuberculosis is curable with inexpensive and effective drugs; on average, the current first-line treatment regimen is reported to generate an 85 percent cure rate in drug-susceptible TB. However, the treatment cycle is long and toxic, causing some patients to discontinue treatment, develop acquired drug resistance, and risk spreading a drug-resistant pathogen to others. The treatment cycle for drug-resistant cases is even longer (9–12 months), more expensive (over US\$1,000 per person), and less effective (55 percent success rate).[7] This is particularly concerning in high-burden countries such as South Africa and India, where demand for second line TB treatment is

^d Forthcoming CGD Working Group Report on the Future of Global Health Procurement

expected to grow by 6.8 percent and 6.7 percent per year, respectively, over the next 10 years. As a result—and despite years of global investment in TB control—modelling suggests that global goals for TB cannot be achieved without major technological breakthroughs.[1]

In 2016, to help guide global R&D investments and following an expert consultation, the WHO published a target product profile (TPP) for a pan-TB regimen.[8] The TPP describes a *universal drug regimen* (UDR) to tackle both drug-sensitive (DS) and drug-resistant strains, with a treatment cycle of less than two months. In addition, it specifies a drug combination of up to three distinct molecules, with no toxicity or drug interaction. For the full TPP specification that we use in this report, based on the WHO version and with input from the Bill & Melinda Gates Foundation (BMGF), see **Appendix 1. Target Product Profile**.

With “push” funding from the BMGF, several candidate molecules are already at phase I or beyond; there are also 20 programmes in early development (discovery and pre-clinical) which may yield additional candidates. According to our estimates, informed by BMGF and its partners, development of a new product to meet the TPP would cost roughly \$1.6 billion—accounting for (i) the cost of capital (ii) an attrition rate that reflects the expected degree of scientific risk. However, this would drop to \$0.6 billion with a continuing commitment by BMGF to support development with push funding up to the end of phase IIb.

A Risky Market? Barriers to Private Sector R&D Investment

On paper, the numbers suggest a large and potentially profitable market for the proposed UDR. The global market for TB therapies reached roughly \$1 billion in 2018, projected to grow by over one third by 2025.[2] Almost three quarters of this growth will be driven by increased expenditure on second-line therapies [2]—reflecting the ballooning burden of drug resistance. Given the projected risk-adjusted development cost (\$1 billion), sales could—in theory—cover industry outlays for R&D if a new therapy was able to displace much of this market. Yet with the burden overwhelmingly concentrated in MICs (just nine MICs account for almost 70 percent of all TB incident cases)[7], innovator pharmaceutical companies are reluctant to invest, perceiving high commercial risk and limited upside potential.

The concentration of TB in MICs (North America and Europe combined represent just 13 percent of global sales) creates several distinct sources of risk for innovator pharmaceutical companies. The first source relates to donor transition from the highest burden countries. Historically, TB treatments have been largely donor funded, with TB regimens purchased in bulk through large-scale mechanisms for pooled procurement (e.g., the Global Drug Facility). Donors have also invested heavily in R&D for TB, helping accelerate the introduction of new treatments and diagnostics. But with most MICs already or soon transitioning from global health assistance, donor investment may soon dry up, leading to both a more unreliable and fragmented TB market and a reduction in donor funding of R&D. Pharmaceutical companies are increasingly forced to deal directly with MIC governments and payers, rather than a global purchasing entity, where they must confront local purchasing preferences for low prices and buy from local industry. This dynamic increases the risk and complexity of entry into the TB market.

Second, most MICs are undergoing rapid *epidemiological transition* paired with rising citizen expectations for universal health coverage (UHC). Citizens are demanding cancer treatment, dialysis, and other expensive care—placing competing demands on growing but still scarce health budgets. Since TB is concentrated among poor and marginalized populations—groups with less power and visibility—there is

a real risk that MICs will underprioritize TB within UHC benefit packages and overall health expenditure, constricting the market for an innovative TB therapy. Innovative pharmaceutical companies do not necessarily trust that TB will be prioritized by MICs into the future.

Finally, MICs are not yet sending strong and reliable signals about their willingness to pay for health innovation. Historically, many MICs have either aggressively negotiated down innovative drug prices; declined to purchase innovative therapies until they go off patent; imposed price controls; or exploited TRIPS flexibilities for compulsory licensing of on-patent drugs. These risks are tolerable to innovator pharmaceutical companies for products where they have a large market in HICs which can give a return on R&D investment, but may be prohibitive when profitability is exclusively tied to MIC sales. For MIC markets alone to generate private sector R&D investment, innovator companies will need assurance that MIC purchasers are willing to pay a value premium for innovation—potentially far higher than the cost of less effective generic competitors, but low enough to ensure local value and affordability.

A Political Window of Opportunity

This year, the United Nations hosted its first ever [high-level meeting on TB](#),^[9] a signal of global momentum to tackle this global challenge. Through policy announcements, MICs are also signalling their willingness to engage with and contribute to global health initiatives, including the TB research and development agenda. For example:

- TB has featured [prominently](#) in discussions and [communiqués](#) at the annual [BRICS summits](#);
- Last year Russia hosted the [WHO Global Ministerial Conference on Ending TB](#);
- India's Prime Minister Narendra Modi has [announced](#) a plan to end TB in India by 2025, and India has [added \\$740 million](#) to its national TB program, roughly *quintupling* its investment to fight TB;
- BRICS' respective ministers of health [announced](#) a TB cooperation plan in 2014; and
- The BRICS have launched a joint TB [Research Network](#), meeting annually since 2016.

These recent events and commitments (Box 1) signal an opportunity to develop and test a new business model for investing in improved treatment of TB, which we detail in this report and which has significant implications for the way pharmaceutical markets for different diseases and technologies operate in emerging markets in the future.

Box 1. Commitments to End Tuberculosis

"Prime Minister Narendra Modi on Tuesday launched a campaign to eradicate TB from India by 2025, five years ahead of a globally-set deadline. After inaugurating the Delhi End-TB Summit here, the Prime Minister launched the TB-free India Campaign to take the activities under the National Strategic Plan for TB Elimination forward in a mission mode for ending the epidemic by 2025." – [Times of India](#)

"The (BRICS) Ministers approved the development of a cooperation plan that includes a common approach to universal access to first line tuberculosis medicines for all people with TB in BRICS countries, as well as in low- and middle-income countries... Ministers also agreed to cooperate on scientific research and innovations on diagnostics and treatment, including drug resistance and service delivery of TB. They identified sharing technologies, identifying manufacturing capacities, and TB financing as key priorities." [2014 BRICS Health Ministers' Meeting, Brazil](#)

Chapter 2. A New Business Model for Global Health Innovation: The Market-Driven Value-Based Advance Commitment (MVAC) for TB

Chapter 1 described how the global R&D system is failing to produce desperately needed innovation to address the global TB burden. In this chapter we introduce a potential solution: the MVAC—a new business model for global health innovation.

The MVAC is in part inspired by the Advance Market Commitment (AMC) mechanism previously used in global health, but with several important innovations and improvements. Most crucially, the MVAC is driven by MIC demand rather than donor contributions; informed by countries' own willingness to pay rather than a single, "cost plus" price; and allows pharmaceutical companies to reap higher revenues from a more effective product.

This chapter proceeds as follows:

- First, we describe how the MVAC builds on the AMC approach, including a discussion of key differences and innovations.
- Second, we provide a high-level overview of the MVAC structure—built on four design pillars—that will be built out in greater detail throughout this report.
- Third, we describe the conceptual basis of the MVAC as a "bridging mechanism" between the dysfunctional status quo for R&D investment in products aimed at MICs and a more sustainable, effective, and efficient structure that can better serve the needs of MIC systems.
- Finally, we argue in favour of the MVAC over late-stage push funding.

From the AMC to the MVAC: Key Points of Evolution

The idea of an advance market commitment (AMC) first gained momentum in 2005 with the publication of a Center for Global Development working group report, [Making Markets for Vaccines: Ideas to Action](#). The AMC was conceived as a binding advance commitment, offered by governments and donors, for purchase of a health technology meeting specific pre-agreed parameters. The AMC was intended for markets perceived as "risky"—that is, markets where private sector actors would be unwilling to invest in upfront R&D without a guaranteed post-launch revenue stream.

In 2007, Italy, the United Kingdom, Canada, Russia, and Norway, in collaboration with the BMGF, committed US\$1.5 billion to launch an AMC for pneumococcal vaccines. GAVI, the World Bank, and the AMC donor committee organized and oversaw the initiative. Participating manufacturers made a 10-year commitment to supply a share of the required 200 million doses annually at a price no higher than US\$3.50 per dose,^e intended to reflect their manufacturing and distribution costs. In return, each manufacturer received a share of the AMC funds (allocated in proportion to their respective supply commitments) at an initial premium price of US\$7 per dose, intended to provide a return on R&D costs. The pneumococcal vaccine AMC targeted a product that was already in the late stages of clinical development; as anticipated, two eligible products (from GSK and Pfizer) entered the market in 2010 and received shares of the AMC commitment pool. An evaluation of the initiative found that the AMC had helped accelerate investments

^e Paid for by GAVI with a co-financing contribution from the recipient country governments, although in practice donors have met all of the \$3.50 cost

in manufacturing capacity for the vaccine but had not influenced R&D investments or the innovation timeline. Nonetheless, the evaluation suggested that the AMC contributed to rapid uptake of the vaccine in LMICs; the vaccine is projected to avert 3 million under-5 deaths by 2030.[10]

The MVAC builds on the core insight of the AMC model: that credible advanced commitments can solve a market failure for R&D and accelerate the introduction of new health technologies that service the world's poor. Informed by the pneumococcal disease experience and evaluation, however, the MVAC makes several important modifications, including additional design characteristics to help measure, aggregate, monetize, and underwrite future MIC demand for better TB treatment. Key differentiating factors are outlined below in Table 3. These include:

- Stimulating earlier stage R&D, thereby encouraging more competition
- Using value assessment of expected health and related gain, rather than “cost-plus,” as the basis for setting guaranteed prices and volumes
- MICs rather than global donors driving the process, creating a transition to a “normal” market for innovative drugs and vaccines in these countries
- Guarantees issued by financial intermediaries, on behalf of MICs, rather than by global donors

There are, of course, important similarities, including:

- Early registration of manufacturer interest to create awareness of progress
- Effective governance arrangements in place to provide assurance to all stakeholders

Table 3. Leveraging the Lessons Learned from Advance Market Commitments to New Models

Key factors	AMC pilot for pneumococcal vaccines	A market-driven value-based commitment for TB
Timeframe for meeting the TPP	Short as products were in <u>late stage</u> of development	Long as potential candidates are in <u>pre-clinical/early stage</u> of development
TPP	Product specifications defined by WHO experts including minimal characteristics to get reward	Product specifications defined by country payers, drawing on expert advice. Expert group to decide (as part of the governance) the minimum characteristics to get some reward
Price	AMC price (paid by donors to recover manufacturing investment) was effectively a minimum price. Tail price (set at marginal cost of production).	Price based on HTA value assessment of the TPP and on local willingness to pay of BRICS. Different price in different countries. Prices adjusted to reflect % of TPP met in practice by the products.
Competition	<ul style="list-style-type: none"> • Non-exclusive scheme to cover first and second-generation products • Initial contract not to take all of the commitment • Companies can compete on price and quality • Effectively rewarding two companies 	<ul style="list-style-type: none"> • Non-exclusive scheme to cover first and second-generation products • Companies can in principle compete on price and quality, however complexity of meeting TPP means combinations are likely and competition unlikely.
Countries it is designed for	Designed to engage donor countries	All except high income countries, with a focus on large MICs, but in particular countries transitioning away from aid; TB burden concentrated in large MICs and LICs
Governance	<ul style="list-style-type: none"> • WHO experts defined the TTP • GAVI served as secretariat and supported eligible countries to purchase the product • The World Bank guaranteed the AMC fund • UNICEF managed the supply agreements 	<ul style="list-style-type: none"> • Global secretariat (TBD) and decision-making function on key scheme elements • Advisory /expert committee (with MICs, global TB and HTA experts, donors, other stakeholders) to provide recommendations on the extent to which the new product meets the TPP
Role of companies (developers and/or manufacturers)	<ul style="list-style-type: none"> • Enter the AMC Registered Manufacturers Agreement • Scale-up manufacturing capacity to meet GAVI eligible countries demand for 10 years 	<ul style="list-style-type: none"> • Register interest at an early stage • Develop and submit regulatory and HTA dossiers for the new product • Commit to develop manufacturing capacity for the agreed period of time and price • Show willingness to engage in a commercial agreement involving post-launch evidence collection
Who bears the risk?	<ul style="list-style-type: none"> • Manufacturer bears R&D and manufacturing risk, donor bears volume risk 	<ul style="list-style-type: none"> • Multilateral development banks underwrite, companies bear R&D risk, countries bear volume risk
Role of donors	<ul style="list-style-type: none"> • AMC definition and governance (WHO, GAVI, UNICEF) • Price top-up to reward innovation (global donors) 	<ul style="list-style-type: none"> • Facilitating scheme establishment • Help mobilize political support for the proposal • Potentially help cover costs for MVAC secretariat; subsidize/cover commitment fees for development bank guarantees; provide research grant funding for BRICS research bodies
Role of LMIC countries	<ul style="list-style-type: none"> • Originally expected to contribute with a co-pay as a share of the tail price but in practice this has been met by global donors 	<ul style="list-style-type: none"> • Actively involved in the definition of the scheme • Committing to pay a pre-defined price based on their budget constraints and value offered by the prospective intervention/s
Role of financing intermediaries	<ul style="list-style-type: none"> • Donors guaranteed funding to GAVI. No intermediary. 	<ul style="list-style-type: none"> • Potential role for a DFI / bank to provide loan finance to assist in guaranteeing the recipient commitments

The MVAC: Four Design Pillars

The MVAC is an advance purchase commitment built on four essential design pillars: health technology assessment (HTA) to assess value from the country perspective; third-party guarantees to underwrite the country purchase commitments; industrial policy alignment to strengthen the case for investment; and an appropriate governance structure to coordinate the effort. The design considerations for these components are briefly detailed below, while the actual design will be further explained in the forthcoming chapters.

Health Technology Assessment (Chapter 3): Health Technology Assessment (HTA), already a well-established process in MICs including Brazil, China, India, and South Africa, is a mechanism by which payers evaluate the value of a new product through the application of globally accepted methods. The MVAC will use HTA—based on country-specific evidence and willingness to pay—to inform countries' purchase commitments. In the context of the MVAC, HTA can improve the confidence of national payers that the product they are committing to buy is appropriately priced and affordable given its incremental value for their setting and their country's budgetary constraints.

Commitment Guarantees (Chapter 4): To drive engagement and investment in R&D by the pharmaceutical industry, it is critical industry perceive MIC commitments as highly credible. Commitment guarantees—underwritten by a financial intermediary—will help ensure that MICs credibly signal their demand and willingness to pay. Key considerations include the total size of the purchase commitment, informed by HTA results; the expected return on investment by the manufacturer (which will need to be reconciled with MICs' willingness to pay); the choice of financial intermediary; and transaction costs associated with the guarantee structure.

Industrial Policy Alignment (Chapter 5): Based on an initial landscaping analysis, we know that developing local industry (including home-grown research capacity and pharmaceutical industries) is a priority for many MICs. To get the support of these MICs for prices that enable the recovery of global R&D costs, MICs would need to adjust to varying degrees of localization requirements.

Governance Structure (Chapter 6): An MVAC governance structure credible to both MICs payers and industry is required to drive and operationalize the MVAC. This requires it to be authoritative, open, and sufficiently flexible to place MIC governments in the driving seat. Key features of a successful governance model include relevance to/expertise in TB; ability to leverage established bureaucracies or operational systems to minimize transaction costs without compromising programmatic quality; and a strategic commitment to and technical capacity to address value for money and affordability concerns.

A Bridging Model to a Sustainable R&D Ecosystem

The MVAC model is intended to serve as a bridge between the dysfunctional status quo and a more sustainable and effective R&D ecosystem—one which more closely emulates the positive characteristics of HIC markets for healthcare products. Many of its core elements (including the need to underwrite commitments and the development of a joint TPP) will become less relevant as markets mature and trust is built between payers and industry. The governance structure—a secretariat to pool HTA resources, set and signal joint priorities, and conduct country-specific value assessments—may endure but evolve as national payers build up their own institutional, human resource, and data capacities. Table 4 describes

how the MVAC helps accelerate and shape a constructive evolution in MIC markets across three time periods: (i) the status quo; (ii) the bridging MVAC model; and (iii) a sustainable MIC market for innovation.

Table 4. The Bridging Model for Investments in Pharmaceutical Innovation for MICs and LICs

Description	<i>Status Quo:</i> Donors pay disproportionately for innovations for MICs and LICs	<i>MVAC:</i> Donors pay for early stage push investments and countries pull UDR to market using credible and underwritten signal of WTP	<i>Future:</i> Countries have established HTA bodies that can assist pulling new innovations to market without the intervention of donors
Industry R&D investment	Limited for MICs/LICs[6]	Piloting in MICs	MICs signal own priorities and investors and innovators respond
TPP	TPP developed for small subset of priority disease by WHO and DPs	Collaboratively developed TPP with country payers	Investors invest where credible demand is signaled by countries, potentially to include joint priorities decided and signaled by a multinational coordinating body
HTA/Pricing	Limited, but growing, use of, or country capacity for HTA; default preference is generic pricing <i>(Note: Ineffective markets drive up generic prices for consumers, while some very high on-patent prices target the wealthy)</i>	Country HTA bodies used to measure and signal a justifiable value-based price with support from central secretariat.	Country HTA bodies are well-established and systematically inform purchasing decisions; affordability and value drives P/V negotiations which result in higher/sustainable returns on investment for investors and affordable prices to local purchasers.
MIC WTP for innovation	Not (clearly) signaled	Increasingly signaled through policy choices	Signaled through established HTA body coupled with track record of evidence-based coverage and purchasing decisions
Role of MDBs	None	Underwriting \$2bn commitment	Limited
Who bears the scientific/commercial risk	Scientific: Early stage – donors through push and PDPs; late stage – industry (if it is willing to invest) Commercial: industry (if it is willing to invest)	Scientific: Early stage – donors; late stage – industry Commercial: Shared between industry and payers, but underwritten by MDB	Scientific: Industry Commercial: Industry, provided payers have established “normal” markets, but some role for payer guarantees may continue
Role of the secretariat	None – does not exist	Aggregates/secures country demand; manages HTA/pricing negotiations; sets TPP parameters and certifies TPP compliance; tracks fulfilment of country commitments; helps build HTA capacity in MICs	Helps aggregate and signal demand; assists countries in signaling interest in new innovations; helps build HTA capacity in LICs
Who pays when	Donors pay for push <i>now</i> Downstream: donors purchase innovative products; out-of-pocket spending on ineffective, overpriced generics; little innovation diffusion despite significant spend	Donors pay for push <i>now</i> , countries pull and pay <i>later</i> if treatment reaches market	Countries pay <i>later</i> if/when treatments come to market

Push/pull split	Significant donor-funded early stage push Limited pull	Continued significant push from donors Strong pull from MIC markets	MICs expand investments in basic scientific research (global public good, as in HICs e.g., the US NIH). No targeted MIC or donor push investments for specific products. Pull brings products to market
MIC industrial production	Limited for innovative products	MVAC complies with and boosts industrial policies of participating countries	Increased industrial production/cooperation in MICs; innovative MICs industry is strengthened

The MVAC versus a \$1 Billion Push

The MVAC is a bridging mechanism designed to mimic the pharmaceutical market in HICs. In HICs, industry bears the standard innovation risk and invests in R&D, anticipating a reward for that innovation that exceeds the cost of its development, sometimes significantly. Through our bespoke model, rather than simply paying industry the amount it costs to develop a UDR, MVAC accelerates the establishment of a sustainable global R&D paradigm that works for MICs and their citizens as well as for industry. Below are a few key reasons why the MVAC model for TB is superior to a large push investment as a bridging mechanism, though not suitable for perpetual replication.

First, whilst the TB market has received significant push investment, aid transitions are likely to reduce the future availability of push funding. The MVAC complements push funding and helps introduce pull funding as the predominant driver of innovation in MICs.

Second, MVAC uses HTA to estimate the size of a value-based market, helping secure country participation and a sufficiently large guaranteed market to justify private investment in the required R&D costs (estimated at about \$1 billion in addition to already committed push funds). A credible argument is needed to convince MICs to pay the \$1 billion price tag without tangible evidence of value conferred to their national healthcare systems by the innovation. Further, the MVAC approach allows flexibility in adjusting the value-based market size to reflect the performance of the final UDR against the target TPP. Without an HTA model and the accompanying process such adjustment would not be possible.

Third, the MVAC will help build capacity in evidence-informed product selection and price negotiations in MICs, an area where lack of transparency and weak governance have been identified as major causes of an underperforming market with resulting obstacles to access and significant out-of-pocket spending.

Fourth, a cost-plus pricing approach based on industry-quoted US dollar figures for R&D costs and an “adequate” return on investment is not a sustainable or desirable approach. Nor is a substantial increase in push funding by global donors realistic or sustainable. Both risk inefficiencies by rewarding inputs rather than outputs. An HTA-based value-driven approach instead assesses value to the system and rewards innovators along a scale commensurate with locally experienced benefits.

Finally, a repeat of the AMC—albeit with pooled MIC and donor procurement—is unlikely to drive industry and investors in the market. The pneumococcal vaccine AMC example showed limited price competition and no new entrants. In addition, industry remains averse to pooled procurement arrangements with a single price applied across countries despite different wealth levels and healthcare spending, making such an approach less likely to reflect future MIC markets.

As the MVAC gets underway, the world will not need to wait until 2030 to see whether it “worked.” The MVAC is instead designed as a dynamic model that supports development of MIC markets as they evolve. Already, expanded HTA capacity at the country level is informing purchasing decisions in China, India, Indonesia, Philippines, Latin America, and elsewhere, supported by a [WHO resolution](#) on HTA-informed purchasing decisions. Drawing on this political commitment, the secretariat can scope out other disease and technology opportunities, evolving into a demand aggregation and signaling center whilst also helping expand technical and institutional capacity for HTA across MICs.

Ultimately, the MVAC approach will help transition industry and national payers toward an R&D ecosystem where MIC market demand can drive private-sector innovation to address local needs and priorities, all within local affordability and resource constraints.

Looking Forward

The remainder of this report offers one chapter for each of the four components of the MVAC model. Chapter 3 uses HTA to evaluate the potential price and revenues for a UDR; chapter 4 details how country commitments will be calculated and guaranteed; chapter 5 describes how the MVAC will be aligned with industrial policy; and chapter 6 outlines the proposed governance arrangements for the MVAC secretariat. The report concludes with practical next steps to operationalize the model.

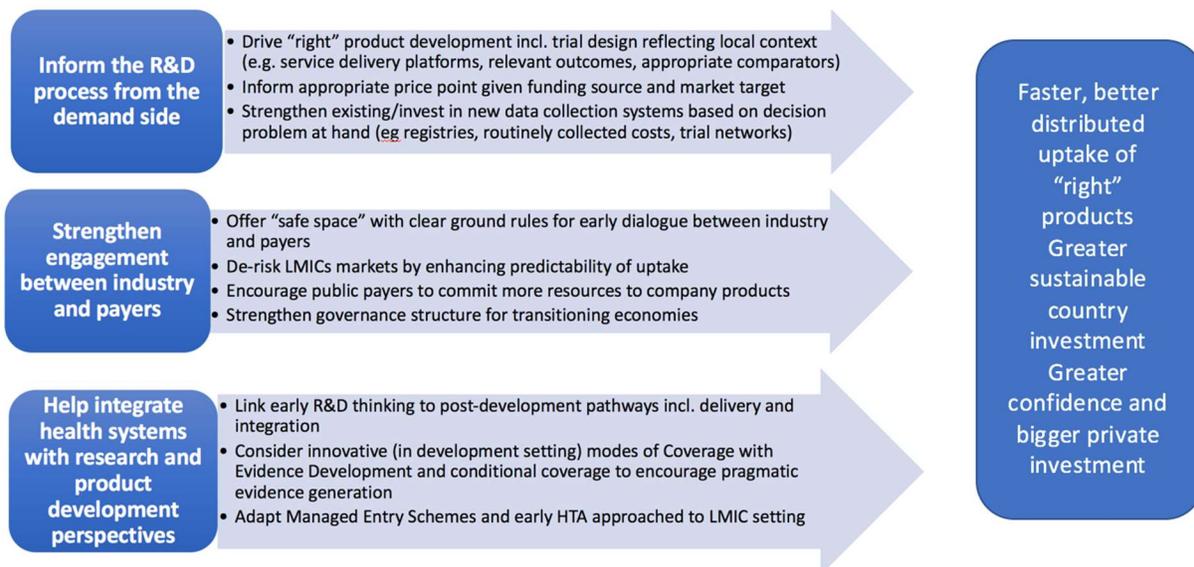
Chapter 3. Health Technology Assessment: Estimated the Value-Based Market for a UDR

What Is Health Technology Assessment (HTA) and Why Is It Important for the MVAC?

HTA is [defined](#) as a “a multidisciplinary process that reviews the medical, economic, organisational, social and ethical issues related to the use of a health technology in a systematic manner” whose “main purpose is to provide policy-makers with evidence based information, so they can formulate health policies that are safe, effective, patient-focused and cost-effective. It is also *used by national authorities to help decisions on which technology should be reimbursed at national level.*” [3]

In the context of the MVAC, HTA is a mechanism that can improve the confidence of national payers that the product they are committing to buy is appropriately priced and affordable, given its incremental value and the country’s budgetary constraints. Early (or ex-ante) HTA conducted before the launch of the new treatment (based on the TPP characteristics) requires stakeholders to agree on assessment processes and key features of the assessment model. HTA can then be applied to estimate the maximum justifiable size of a guaranteed purchase commitment given treatment alternatives, expected patient numbers, and local ability to pay. It can also inform the design of post launch studies to prove the regimen’s value in clinical practice. Figure 4 further elaborates on the role of HTA in helping drive innovation.

Figure 4. Health Technology Assessment/Value-Based Pricing Process: Why it matters for driving innovation in LMICs



Health Technology Assessment is already well-developed in HICs, with Australia, Canada, France, Germany, the UK, Norway, and, most recently, Japan, requiring HTA to inform pricing and reimbursement decisions for major new technologies (for an overview of HTA in HICs see [here](#)). In addition, some HICs

already collaborate^f to carry out joint horizon scanning and evidence assessments, helping inform product selection and price negotiations at the country level. For example, Belgium, the Netherlands, Luxembourg, Austria, and Ireland conduct joint HTA through the [BeNeLuxA](#) initiative, informing local coverage decisions. Unlike arrangements supported by donors in LMICs, where a single price per product may be offered to all participating countries (e.g., [PAHO Revolving Fund](#) for vaccines), these HIC partnerships allow differential pricing based on each country’s budget allowance and local value.

Many MICs—including India (see Box 2), China, Indonesia, Thailand, South Africa, the Philippines, and most of LAC (including Mexico, Brazil, Chile, and Colombia)—have also established HTA bodies linked to their national health insurance and pharmaceutical procurement agencies. Payers in these countries should be familiar with the MVAC approach to value assessment and supportive of deploying their own national agencies within the assessment process. Further, by offering to strengthen in-country HTA capacity, the MVAC builds on the current momentum for evidence-informed coverage decisions, helping drive the local institutionalization of evidence-based decision-making that may accelerate uptake of cost-effective innovations across LMICs. For a worldwide summary of HTA initiatives, see Appendix .

Box 2. India’s HTA launch

India recently launched an HTA agency at the Ministry of Health and Family Welfare—[HTAIn](#)—to inform ceiling rates for reimbursement via a [clearly defined](#) process and set of methods. One of its earliest [assessments](#) evaluates lenses for cataract operations based on “clinical efficacy, cost-effectiveness, accessibility, availability, and feasibility.” The assessment concludes that “[small-incision cataract surgery (SICS)] with rigid lenses is the most appropriate intervention to treat cataract patients in India in [the] current scenario,” and recommends that the benefits package cover both Phacoemulsification surgery and SICS at a cost of 9606 INR and 7405 INR, respectively.

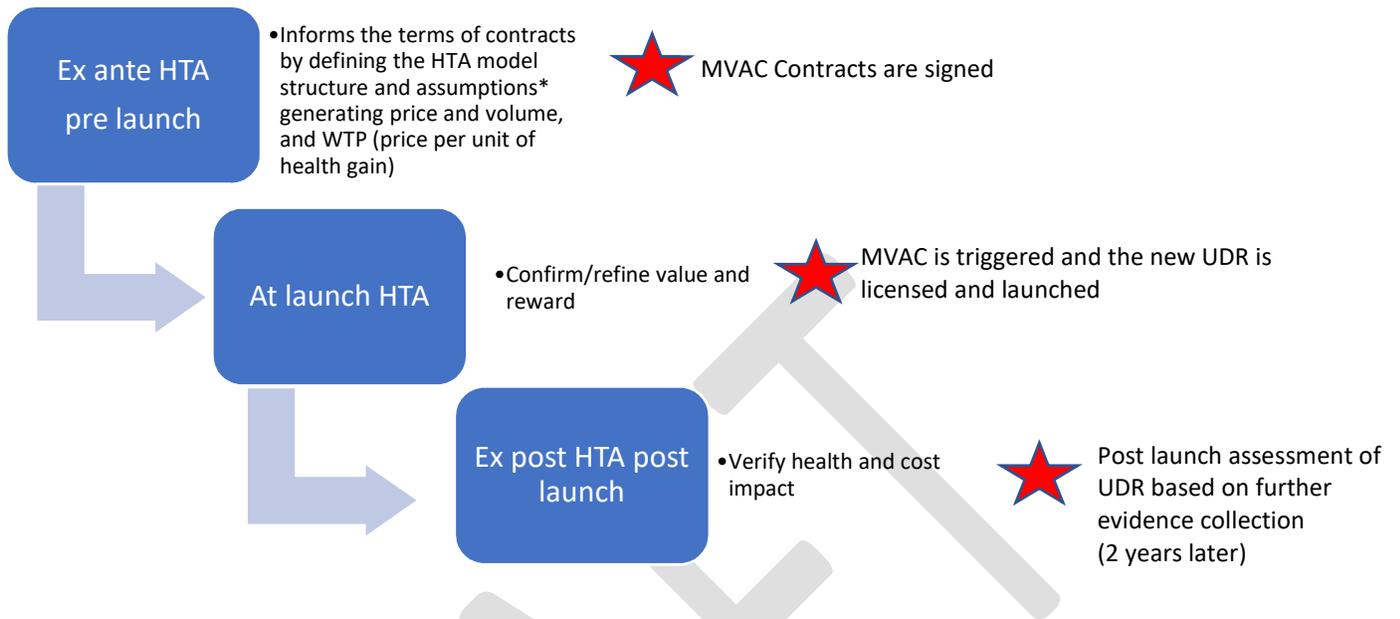
In the MVAC model, early (or ex-ante) HTA would first measure the value that the new UDR treatment would add in the participating countries—thereby estimating the size of the market for a UDR, including value-based prices and volumes for each country. The prices and volumes would incorporate two drivers of value:

1. additional health gains of the UDR compared to alternative therapies, valued at country willingness to pay per Quality Adjusted or Disability-Adjusted Life Year (QALY or DALY) based on supply-side constraints/opportunity costs
2. health system savings (e.g., averted hospitalizations and a reduced need for drug sensitivity testing).

The MVAC secretariat (see chapter 6) would facilitate negotiations that would translate country-level value assessments into minimum and maximum advance purchase commitments (floor and ceiling prices and volumes) for each country. Following launch of the UDR, at-launch HTA would be used to adjust pricing and volumes based on product efficacy against the pre-agreed TPP; depending on the specific design of the commitment (discussed in chapter 4), the at-launch HTA may hold a set of other parameters constant to limit complexity and reduce uncertainty. Potentially, ex-post HTA could be used to verify the product’s clinical efficacy and confirm appropriate value-based pricing (Figure 5).

^f Forthcoming CGD paper on group purchasing organizations

Figure 5. Three key points at which HTA would be performed

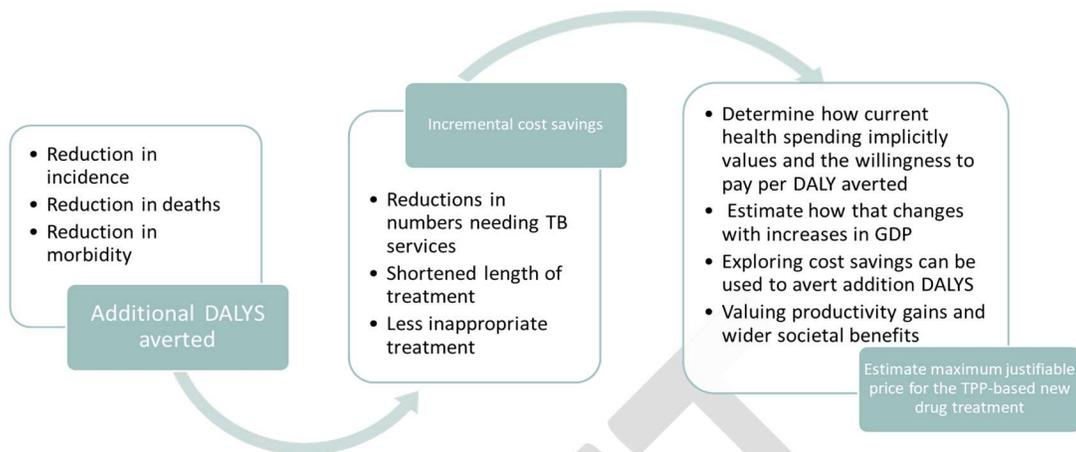


Early Stage Economic Model – Overview and Aims

We engaged a team of world class epidemiological and economic modelers to estimate the value-based market for a TB TPP-based new drug treatment in three countries—India, Russia, and South Africa. We selected these countries from among the BRICS based on their high TB burden, data availability, and access to previous modelling. The modelling approach used is rooted in “**value-based pricing**”—the idea that payers should be willing to pay a price that represents the value produced by the UDR to their respective healthcare systems. The team’s full report is forthcoming.

We assess the UDR value using conventional cost-effectiveness analysis from a **healthcare perspective** (Figure 6). First, we estimate health gain (incremental DALYs averted) from the TPP-based new drug treatment as compared to the standard of care at introduction. Second, we examine ways in which the introduction of the TPP-based new drug treatment will change the health system costs associated with TB diagnosis and treatment; for example, we expect that the new drug treatment’s shorter treatment duration and reduced need for drug susceptibility testing will generate significant health system savings.

Figure 6. Overall approach for the analysis



Finally, we use these costs and effects to estimate the value of the TPP-based drug treatment to public payers. We first convert health gains into (monetary) health benefit by determining the **willingness to pay for a DALY averted**. We estimate the available health budget in the year at which the TPP-based drug treatment becomes available, and then derive the willingness to pay by estimating an opportunity cost threshold, using several different approaches. In principle, the threshold represents the least efficient intervention within the health budget, i.e., the value forgone if those resources were re-allocated to fund the TPP-based drug treatment.

Our estimates of the TPP-based drug treatment value in 2030, when it is expected to be launched, are highly uncertain. Many factors that influence the value of the new regimen will change considerably in the next decade in ways that are hard to predict, including **launch of other TB technologies, the evolution of the TB epidemic, national healthcare strategies to tackle TB, and the future growth of health budgets**. Sensitivity analyses are used to explore different types of uncertainty; and scenario analyses are used to explore the impact of (i) existing and (ii) **future comparator technologies**. Our exploration of uncertainty is intended to draw out sources of risk and inform contracts which appropriately distribute risk between different stakeholders.

The economic model, described above, estimates the maximum justifiable price (from now on called the “value-based” price) for a TPP-based drug treatment, the number of patients to be treated, and the associated revenue/expenditure stream (representing the size of the market) over 10 years post-launch (2030 to 2039) in India, Russia, and South Africa. To reduce risk for commitment-making countries, our primary/baseline estimates—reported in this section—rely on a series of conservative assumptions around future technology availability and the evolution of the healthcare systems in the selected countries, all of which effectively reduce the projected market size for the new drug regimen.

Early Stage Economic Model – Methods

Defining the baseline scenarios

Table 5 defines the model's population, intervention, comparator, and outcomes (as part of the PICO statement) for each of the three countries.

Table 5. PICO statement of TPP-based drug treatment and National Strategic plans

	India	Russia	South Africa
Population (in terms of current burden and resistance)	High TB, TB/HIV, and MDR ^g Mainly resistance to first line drugs	High TB and MDR TB High levels of resistance to second line drugs	High TB, TB/HIV, and MDR Mainly resistance to first line drugs
Intervention	UDR as defined by the TPP		
Comparator	Standard of Care (SoC) at the time of TPP-based drug treatment introduction: <ul style="list-style-type: none"> • New shortened regimen introduced in 2025 for DS and MDR^h • New vaccine 		
Outcomes	<ul style="list-style-type: none"> • Additional DALY averted • Net monetary benefit • Health sector cost savings 		
Context (National Strategic Plan)	Private sector engagement Patient support (nutritional supplement)	Scale up of Gene Xpert MTB/RIF in 2018 Standardisation of WHO MDR revised regimen	WHO symptom screening for all Standardisation of WHO MDR revised regimen

Importantly, our choice of comparator is drawn from the most optimistic scenario, assuming successful introduction of several new technologies to tackle TB. This choice of comparator results in a relatively smaller estimated market, as better comparator treatments (compared to the current standard of care) and a vaccine would reduce the marginal benefit of the TPP-based drug treatment and, in the long run, decrease the size of the patient population in need of treatment.

In addition, the incremental effect of the TPP-based drug treatment will depend on the state of country-specific TB and/or healthcare systems at the time of its introduction (estimated for 2030). The modelling team explored several scenarios and used the most likely outcome for each country given current trends in national policy. In India, we considered a scenario (the “National Strategic Plan scenario”) with an increase in private sector engagement (achieved via incentives to private providers to improve notification and treatment completion rates) and patient social and nutritional support. In South Africa, we use a scenario with scale-up of WHO symptom screening for all clinic attendees and a standardisation of MDR regimens based on WHO revised guidelines. In Russia, we modelled standardisation of MDR regimens and scale-up of Gene Xpert MTB/RIF for diagnosis of tuberculosis and rifampicin-resistance.

In all three countries a key output of the HTA modelling is the estimation of potential health system savings each country can capture following the introduction of the TPP-based drug treatment. In Russia, those savings are mainly due to avoiding or reducing hospitalization of TB patients.

^g MDR-TB (i.e. resistance to at least both isoniazid and rifampicin), which leads to substantially longer treatments and costs to the health service and patients compared to drugs sensitive TB.

^h The SoC in 2030 was defined as new shortened regimens for first line treatment (4 months) and for MDR (9 months, new drugs with no pre-existent resistance) in 2025. These regimens are similar to the BPamZ and BPaL currently trialled by the Global Alliance for TB drug development. In addition, we assume there will be a new vaccine coming to the market in 2027. This vaccine has clinical characteristics similar to the recently trialled M72/AS01E(18).

Estimating the value of DALYs averted – the opportunity cost threshold

Three approaches were used to estimate an “opportunity cost” value of a DALY averted, by estimating the least efficient investment (or the marginal productivity of expenditures within the public health sector budget) that the UDR would replace in 2030.

We present here the approach used in the primary estimates, which bases the value of DALYs averted as the opportunity cost at the health sector level and assumes that TB budgets are flexible within overall healthcare spend. These thresholds estimate the least efficient investment (or the marginal productivity of that expenditures, within the public health sector budget) that the TPP-based drug treatment would replace in 2030. We use recent work by Ochalek et al.[11] that estimates the elasticity of health outcomes to changes in health sector budgets. We then estimate the size of the health sector budget considering GDP growth and increased public sector revenue and use these elasticities to estimate marginal productivity of the health sector, in each country, in 2030.

Early stage economic model – Primary Results

We combine maximum justifiable price with number of patients treated between 2030 to 2039 to estimate revenues. We present revenues undiscounted from 2030 to 2039.

Our early stage HTA modelling estimates that the market size in India, Russia, and South Africa can total around \$6.3 billion for the first 10 years after launch, using the conservative assumptions described in the previous section (Table 6). The value-based calculations include only health gains and savings within the health system, excluding productivity gains and non-health impacts on patients. Across different scenarios, revenue estimates range between \$3.24 - \$7.19 billion for India, between \$0.69 - \$2.62 billion for Russia, and between \$2.37 - \$5.46 billion for South Africa (USD 2017). These projected revenues are potentially transformative as compared to current expenditure on TB treatments and tests (estimated at around \$750 million per year).

Table 6. Key results from early stage HTA model¹

	100% value-based revenue (USD billions)	Maximum price per regimen (USD)	Number of regimens 2030 to 2039 (millions)
India	3,24	501	6,467
Russia	0,6	2,498	240
South Africa	2,37	864	2,743
Total	6,30		9,450

It is important to note the quality of data used to model cost and health gains. There are substantial data limitations for Russia, while more robust evidence is available in India and South Africa.

¹ In Table 6 total revenues are not discounted. We note that in the economic model presented here health gains and costs were discounted at 3% to obtain the maximum justifiable price (or “value-based” price), in line with HTA methods guidelines.

Sensitivity Analysis around the TPP-Based Drug Treatment

In the previous section, we estimated the value-based market for a new drug regimen meeting the full TPP. In the full (forthcoming) modelling report we also explore sensitivity of the maximum price to changes in product characteristics, e.g. the value of a product that meets part but not the entirety of the TPP.

Overall, we find that the main value-driver of the TPP-based drug treatment is its shortened duration. In India, a 6-month variant of the TPP-based drug treatment (compared to the optimal 2-month duration) would lose up to 80 percent of its maximum regimen price. In South Africa, a 6-month new drug regimen would become more expensive than the comparator standard of care (including a 4-month regimen for first line treatment and a 6-month regimen for second line treatment). In Russia, the longer treatment duration would reduce the value of the new drug regimen by at least 40 percent. In Russia and India, we also find that the need for DST and ineligibility of XDR-TB patients would result in larger value reductions than a need for lab monitoring. In South Africa, the presence of GeneXpert at scale reduces the cost impact of DST.

Results from this sensitivity analysis can inform selection of the minimum and optimal TPP and corresponding purchase commitments.

Size of the Commitment Required to Incentivize Private Investment – Net Present Value Scenarios

The global pipeline for new TB treatments has improved substantially in the last five years and is summarised in Appendix 3. Based on recent industry estimates, the total cost of R&D for a successful TB drug is around \$1.6 billion. However, if current push funding by the BMGF is maintained through proof of concept (phase IIb), late stage R&D costs to develop a successful regimen may be as low as \$600 million, taking account of failures.

The estimated value-based market for India, South Africa, and Russia is therefore significantly larger than the expected cost of late-stage R&D. It could be possible, therefore, to pull a product to market with volume and/or price commitments that represent only a portion of total market demand.

Table 7 presents an estimated net present value (NPV) based on (i) covering only late-stage R&D costs; and (ii) covering all expected R&D costs. For the late stage costs, we show the results at 30 percent of the potential value-based revenue commitment (i.e., \$1.8 billion). For the total R&D costs we show the full \$6 billion commitment. For both we also show NPV with and without the possible additional pull incentive that successful companies can receive at registration: the Priority Review Voucher (PRV).^j These calculations are illustrative only and aimed at showing the possible size of the commitment.

^j “The priority review voucher (PRV) program, currently administered by the US Food and Drug Administration (FDA), was passed into United States law in 2007 as a pull mechanism to help promote R&D for new medicines targeting NTDs, malaria, and tuberculosis. Under this law, companies that receive FDA approval for a novel drug or vaccine targeting one of 16 tropical diseases are awarded a transferable voucher. This voucher can be sold to a second organization or can be redeemed to grant the bearer priority six-month review for a future medicine of their choosing. As average standard review periods can range between 10–16 months, the voucher could potentially allow drugs to reach the market up to eight months earlier. Economic models have predicted that this faster time to market could be worth between US\$50 million to US\$300 million.” <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3429395/>

Table 7. Estimated NPV

Assumptions	USD 2019 million
Cost of all R&D	1600
Cost of late stage R&D	600
Priority Review Vouchers (PRV) (x3) *	300
Cost of capital per annum	8.50%
Gross margin	50%
Scenario 1: Late stage R&D; Gross sales \$1.8bn; No PRV; NPV**	-217
Scenario 2: Late stage R&D; Gross sales \$1.8bn; PRV; NPV**	40
Scenario 3: All R&D; Gross sales \$6bn; No PRV; NPV**	-271
Scenario 4: All R&D; Gross sales \$6bn; PRV; NPV**	-13

*Assuming a value of \$100 million for each of the three made available to the companies with a compound part of the regimen, sold 1,2, and 3 years after launch. **NPV calculations are as of 2030, the expected date of product launch.

The results suggest that industry NPV is sensitive to the amount of R&D, the value of PRVs, and the guaranteed revenues. With income from PRVs and only late-stage R&D to fund, then a commitment of 30 percent of the total market can produce a positive NPV. With full R&D funding to be met by the companies, then NPV is slightly negative (effectively breakeven) even with the full market guarantee of \$6 billion and income from PRV sales. As we noted, these calculations are only illustrative and should inform a dialogue between the parties involved to strike the right balance between appropriate return on investment for companies investing, and sustainable access to an innovative therapy for TB.

Chapter 4. Calculating and Securing the Advance Purchase Commitment

In the previous chapter, we used ex-ante HTA to estimate the potential value of the global TB market. Even under very conservative assumptions, our results show that three countries alone—India, South Africa, and Russia—could capture over \$6 billion of value in terms of health gains for their citizens and health system savings from access to a TB UDR. If these countries purchased a hypothetical regimen at prices and volumes commensurate with local value, pharmaceutical company innovators would easily recoup investments in late stage research and development—plus a healthy profit margin. Yet as we discussed in chapter 1, industry remains skeptical that LMIC markets alone will yield sufficient revenue to justify up-front investment, noting uncertainties around willingness to pay, intellectual property protection, industrial policy, and budgetary prioritization of health and of TB within health. The status quo represents a lose-lose-lose scenario: industry is scared off from developing products for a potentially profitable market; LMICs miss an opportunity to shape global R&D investments; and tuberculosis patients must make do with long, unpleasant, and increasingly ineffective treatment regimens, leading to both suffering and premature death.

In this chapter, we consider a model to bridge the gap between industry and LMICs, addressing the sources of mistrust and misalignment that prevent emergence of a mutually beneficial transaction—and, consequently, prevent development of a new, life-saving product. Through our proposed model, countries will make secured advance purchase commitments for a product meeting the prespecified product profile. As a result, industry will be offered an avenue to sell into MICs with market visibility, revenue guarantees, and respect of company intellectual property (IP) rights; countries, in turn, will receive guaranteed access to innovative drugs targeted to local disease and priorities, at locally affordable prices. Patients get access to treatment that will transform their lives. The value proposition is sufficiently large that all parties will benefit from the arrangement—a win-win-win for all involved.

This chapter proceeds as follows:

- First, we describe the challenges in transforming chapter 3's HTA results into country-specific commitments and lay out principles to guide and manage the negotiation process.
- Second, we discuss how a value commitment can be set and adapted over time.
- Third, we describe a mechanism, intermediated by an MDB, to secure countries' voluntary advance purchase commitments using their own sovereign credit-worthiness.
- Fourth, we consider how to “crowd in” additional countries, suggesting a relatively simple incentive-compatible model—a set *value* commitment that varies with product efficacy— helping to sidestep common free-rider/first-mover problems, producing value for all parties to the transaction.
- Finally, we analyze how this set of arrangements redistributes and mitigates risk, overcoming the market failures that have heretofore hampered innovation.

From HTA to a Value-Based Commitment: Challenges and Principles

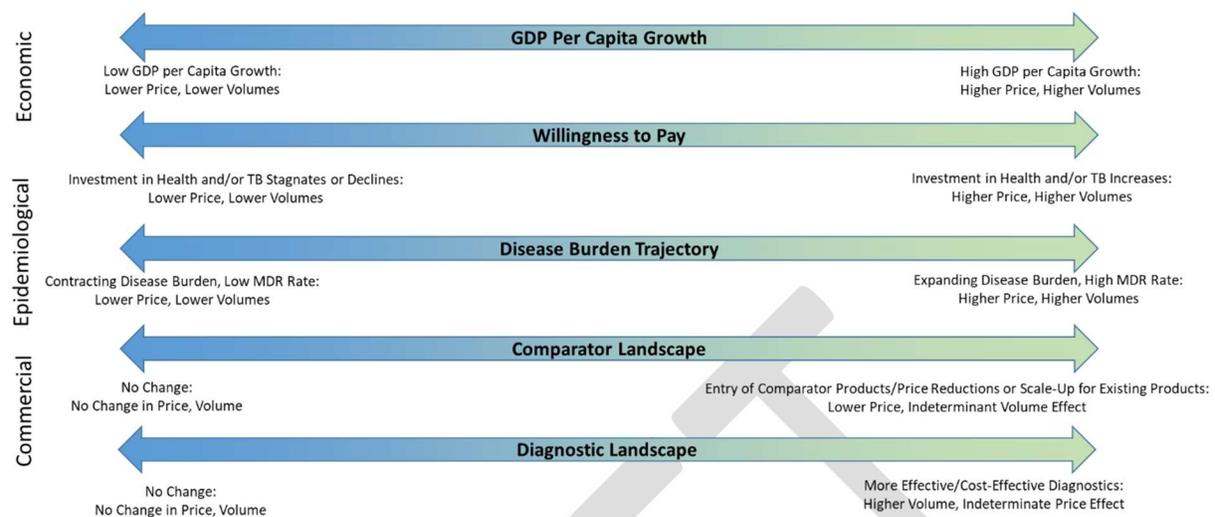
As a first step, participating countries must set a reasonable and sufficient purchase commitment to incentivize industry investments. The HTA results based on the TPP and opportunity cost provide an upper-bound estimate for the size of that commitment; theoretically, countries would be expected to “break even” (i.e., net benefit to countries would in this case be zero) in value terms if they were to pay

those maximum justifiable prices at the given volumes.^k There are several challenges to be tackled before the results of the ex-ante HTA can be translated into fixed purchase commitments:

- **Uncertainty and Complexity:** As described in chapter 3, early HTA results necessarily rely on many assumptions and are therefore vulnerable to uncertainty about how the market will evolve between now and the time of product entry. Sources of uncertainty include questions about the efficacy of the product; exogenous factors such as GDP growth and other factors that will influence health expenditure; programmatic choices around the investment in TB services prior to the arrival of the TPP product; the TB disease burden trajectory; market entry of comparator products; and diagnostic advances (Figure 7). Fixed price and volume commitments—directly derived from the early HTA results—would transfer a high proportion of that risk directly to the commitment-making countries, without offsetting benefits that justify that risk absorption. At the other extreme, overly flexible commitments—essentially guaranteeing use of a standard HTA process at launch but opening all other parameters to variation—would mean that country commitments directly corresponded to actual conditions at the time of purchase. This would insulate countries from all exogenous risk factors—but given the high level of uncertainty, and industry fears about opportunistic behavior, such a process is likely to be seen by industry as shifting all of the commercial risk back to them and rendering the early HTA process of no practical value. Full flexibility at launch would therefore be insufficient to change industry incentives, and overly complicated and contentious to contractually guarantee and execute in practice.
- **Shared Surplus:** Country governments might wish to negotiate or otherwise set a “discount” from opportunity cost-based (break-even) price points, allowing payers to capture a larger portion of the economic value (the health gain and cost savings) generated by the innovator product.
- **Transaction Costs:** The MVAC model uses a financial intermediary—likely an MDB—to guarantee countries’ advance purchase commitments. The financial intermediary is likely to charge a commitment fee for its services; the size of the fee would be directly proportional to the total size of the guaranteed purchase commitment. Reducing the size of the guaranteed purchase commitment may thus be advantageous as a strategy to minimize transaction costs.
- **Subsidy and Commercial Risk Mitigation:** As the MVAC is designed to mitigate companies’ commercial risk, intending to provide a guarantee of a profitable return for a good product, and push funding is available to reduce R&D financial risk (giving companies a pipeline of early-stage compounds, pushed to phase 2a with direct donor support), it may be considered reasonable to limit industry’s upside profit margin—though industry must be assured of sufficient expected returns to justify the R&D investment.

^k We can note that strictly the opportunity cost we have used is relevant within the context of the health budget and applies only to health expenditure. TB may bring other benefits (for example in productivity gains) that are much greater than those from any displaced health expenditure. We are also assuming, conservatively, that the availability of a breakthrough TB treatment does not lead to an increase in the health budget over and above the trend growth we have assumed.

Figure 7. Value-Based Price and Volume; Axes of Exogenous Long-Term Uncertainty



These inherent challenges make direct translation of HTA into a purchase commitment prohibitive. To manage this complex question, we suggest a few principles to guide negotiations, helping create a viable purchase commitment while also setting important precedents for the healthy long-term development of MIC pharmaceutical markets:

- **Upper Bounding Not to Exceed Ex-Ante Value:** Countries should not, under any circumstances, make purchase commitments that exceed a product’s expected local value based on the ex-ante HTA assessment.
- **Lower Bounding Required to Deliver a Return on Investment:** Subject to the upper bound constraint, total commitments must be set a sufficiently high level to ensure a risk-adjusted return for the successful innovator company. Countries should pay a price premium for innovation that is not directly tied to the marginal cost of producing the product. In effect, we need to establish a “reserve price,” or more strictly a reserve revenue, for the MVAC.
- **Minimum TPP (and Corresponding Revenue Commitment) Must Offer Value to Countries:** The minimum TPP to trigger the MVAC commitment must be set at a level that offers meaningful clinical and economic benefits.
- **Rewarding Value:** Companies should be rewarded for developing a more efficacious product; the purchase commitment should scale in a way that is commensurate with the value produced by a more effective product compared to the standard of care (however defined).
- **Minimizing the Collective Action Problem:** To the extent possible, the commitment model should work to minimize the collective action problem by providing clear incentives for countries to be first movers, with long-term incentives to “crowd in” additional countries.
- **Differential, Value-Derived Pricing:** Country-specific pricing should be connected to country-specific value; this necessarily implies differential pricing across countries.

- **Simplicity and Predictability:** To the extent possible, commitments should be simple and predictable, allowing payers to plan for their own fiscal liability and industry to make informed investment decisions.
- **Risk Compensation:** Parties (in this case country payers) that assume additional risk should be compensated with a larger share of overall value.

How a Value Commitment Can be Set and Adapted Over Time: A “Commitment Pool” Tied to Product Efficacy

Given the large overall value proposition, there are many different commitment models that could deliver shared value to all parties. Here we suggest a relatively simple and powerful model—a predictable revenue commitment pool, tied to product efficacy—that could serve as a starting point for negotiations.

Step 1: First Movers Assess Value: As a first step, one or more high-burden countries would need to take a leadership role as “first movers”—for example, India and South Africa. Ex-ante HTA for those two countries would give several important pieces of information:

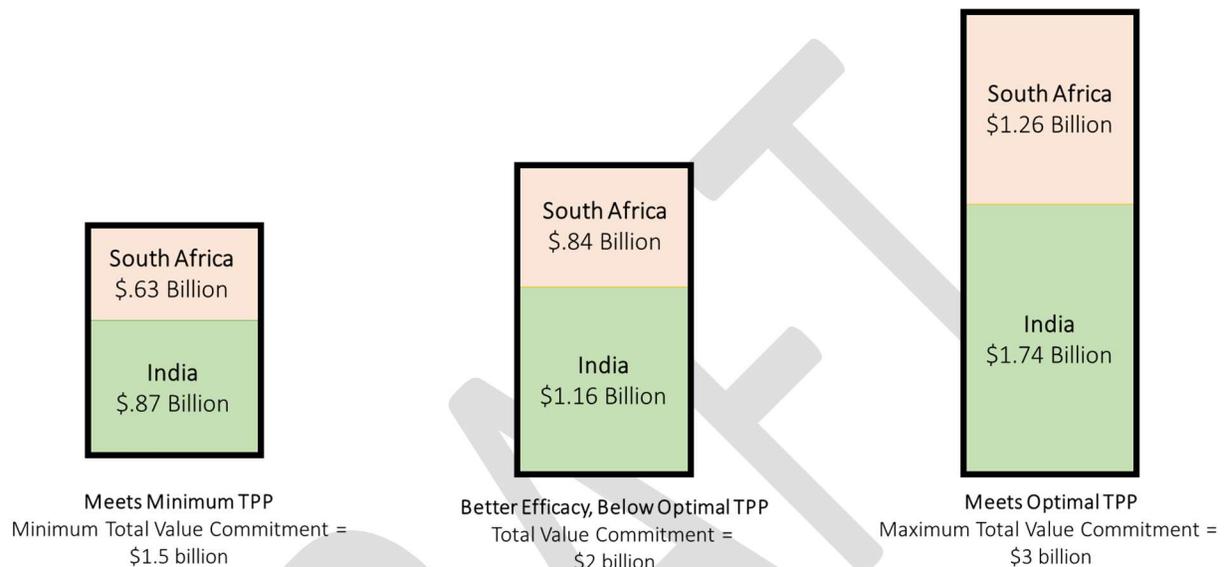
1. The total value-based market: HTA would provide an upper bound for value-based commitments. As we show in the previous section, the total value-based market for India and South Africa could exceed industry’s “reserve price” for pharmaceutical investment.
2. Relative value by country: HTA would show how the total value proposition of a UDR varies across countries.
3. Relative value by product profile: HTA would show how the total value proposition of a UDR varies vis-à-vis specific product characteristics. For example, it might show that the value of the UDR is closely tied to regimen duration.

Step 2: First Movers Define and Divide a Value-Based Commitment Pool: Using the HTA results as a starting point, the first-mover countries would set and divide up a total “commitment pool”—essentially, an advance purchase commitment (price x volume) tied to product efficacy. The total commitment pool would need to be sufficiently high to incentivize industry investment. In the next section, we consider issues involved in calculating the total size and form of the commitment pool. For now, for the sake of illustration, Figure 8 offers an indicative schematic for how countries would divide up the total commitment pool using arbitrary numbers.

Imagine that a product meeting the minimum TPP would be entitled to a minimum total value commitment (e.g., \$1.5 billion) and a product meeting the optimal TPP would be entitled to a maximum total value commitment (e.g., \$3 billion). Between those two extremes, the total value commitment would vary based on different product characteristics/levels of efficacy. The schematic here is based on illustrative numbers, but in practice the scale should reflect real HTA-derived value differences between different iterations of the product. Country-specific commitment “shares” would also be derived from HTA results. For example, our preliminary HTA results suggest a total value-based market of \$3.24 billion

for India and \$2.37 billion for South Africa—a 1.37:1 ratio. For the sake of simplicity, Figure 8 assumes that the ratio (1.37:1) holds constant across different levels of product efficacy; in reality, different permutations of product characteristics will create differential value for different countries, and the ratio between commitments should reflect relative value between countries. In this example, for the minimum TPP, India would be liable for a \$.87 billion purchase commitment and South Africa for \$.63 billion; for the maximum TPP, India would pay \$1.74 billion and South Africa \$1.26 billion.

Figure 8. Indicative Schematic for Defining and Dividing a Value-Based Commitment



Setting and Adjusting the Commitment Pool: A Recommended Model

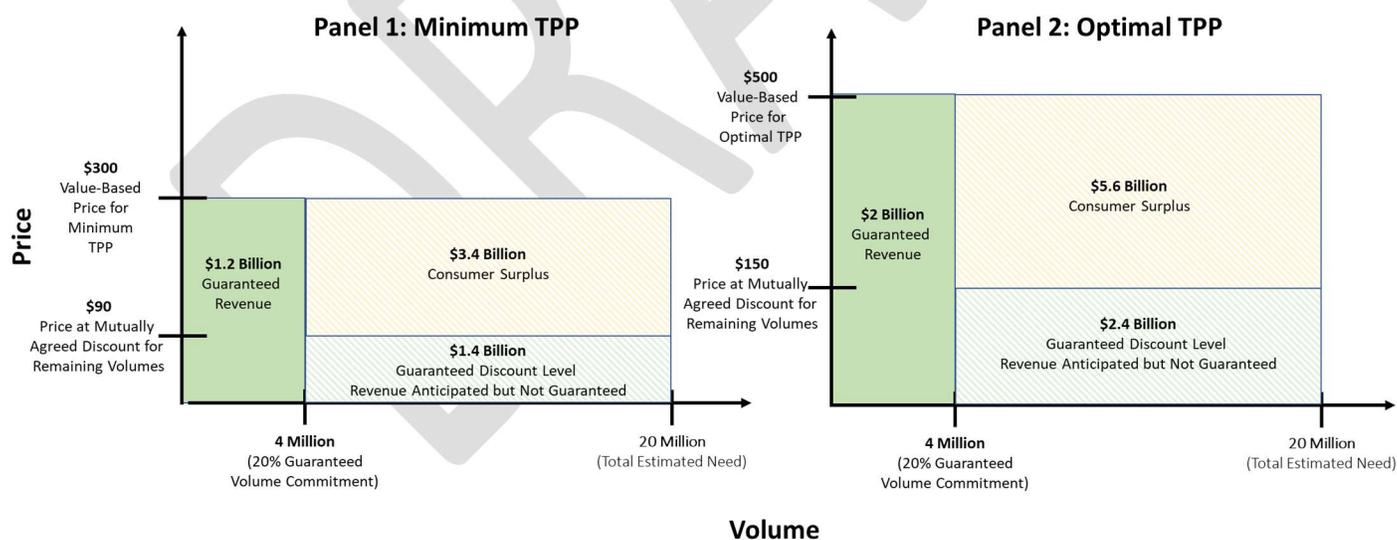
In the previous section, we explained our rationale for setting a fixed-value commitment that would vary based on product efficacy. Yet this approach still leaves several unanswered (and intertwined) questions that will need to be resolved during negotiations:

1. How large should the total commitment pool be?
 - Should the commitment pool represent the entirety of the expected market? Or is it sufficient to guarantee just a portion thereof?
 - Within the general principles laid out earlier in this section, what is the total value commitment for a product meeting the minimum TPP? What is the total value commitment for a product meeting the optimum TPP?
2. Value is calculated as price x volume. If the total value commitment for each country is indeed below the total value-based market, does the reduction occur via a *smaller volume commitment*, a *reduced price*, or some combination of the two?
3. Each country's share of the value commitment is calculated via ex-ante HTA. Are these shares "locked" based on prospective modelling, or are they re-calculated at the time of launch to reflect changing circumstances?

In this section we suggest one plausible model that we believe effectively balances these interests while creating important precedents for use of HTA and value-based pricing. For illustration, imagine a simplified scenario where all countries have the same value-based price, though in reality there will be a country-specific value-based price given the different country characteristics. For the optimum TPP, imagine that ex-ante HTA shows a total \$10 billion market in participating countries (at value-based prices) over 10 years (\$500 per course x 20 million courses); for the minimum TPP, the value-based market is \$6 billion (\$300 per course x 20 million courses).

These countries agree to guarantee 20 percent of the total projected value-based market at the value-based price; collectively, they thus commit to a total (fixed) commitment pool of \$2 billion for a product meeting the optimum TPP (\$500 per course x 4 million courses) and \$1.2 billion for a product meeting the minimum TPP (\$300 per course x 4 million courses); see Figure 9. To access the purchase commitment, the successful innovator must agree that any volumes beyond the guaranteed commitment pool—up to a pre-agreed maximum or for a pre-agreed time period—will either receive a heavily discounted price (e.g., a 70 percent discount as illustrated in Figure 9) or be made available to local licensees for a pre-defined royalty rate. In this illustrative example, industry would be guaranteed \$2 billion in revenue and could reasonably expect another \$2.4 billion from participating countries if it met the optimal TPP; participating countries would capture \$5.6 billion in economic surplus if they purchased sufficient quantities to treat their entire population in need. Industry would be guaranteed \$1.2 billion and could reasonably expect another \$1.4 billion in revenue if they met the minimum TPP; Participating countries would capture \$3.4 billion in value.

Figure 9. Model to Define Commitment



Using a simple version of this approach (

Figure 10), ex-ante HTA would estimate the future size of the market and inform the guaranteed value commitment (e.g., revenue) for products of different efficacy. At the time of product launch, countries would rerun the model with up-to-date efficacy data, based on the clinical trial results with appropriate modelling. Countries would be responsible for fulfilling their prior value commitments by purchasing a

sufficient quantity of the product at the efficacy-adjusted value-based price. After fulfilling their commitments, countries would receive access to the product for the remainder of their demand at a discounted price (30 percent of the value-based price in the illustrative example). Ex-post HTA could be used to ensure the product is meeting efficacy expectations; efficacy either exceeding or failing to achieve anticipated levels could prompt pricing adjustments for future purchases.

Figure 10. Process for Calculating and Fulfilling Advance Purchase Commitments



A more complicated (but potentially advantageous) approach would revise steps 4 and 5 in

Figure 10. In this revised approach, country revenue commitments (GR_Country) would still be calculated based on baseline assumptions (Step 1) and realized product efficacy (Step 3); this would provide predictability to both countries, industry, and the financial intermediary for overall guaranteed revenue. However, countries using a standardised methodology and the original model and supported by the Secretariat (see Chapter 6) would also conduct a full HTA at launch, inputting up-to-date data reflecting the current situation in 2030. This process would yield an updated value-based price (VBP) for each country. Countries would fulfill GR_Country by purchasing a sufficient product volume at the updated VBP (VBP_Country) instead of the 2019-projected price (pP_Country); the pre-agreed discount (Step 5) would also be applied to the updated VBP_Country instead of the projected pP_Country. This approach creates additional complexity but offers a better precedent for value-based pricing by incorporating accurate parameters at the time of launch. It would also offer an opportunity to engage country payers and HTA agencies through a thorough at-launch HTA process similar to the one HICs are likely to apply as a starting point for their negotiations with manufacturers.

Overall, our suggested model has several advantages:

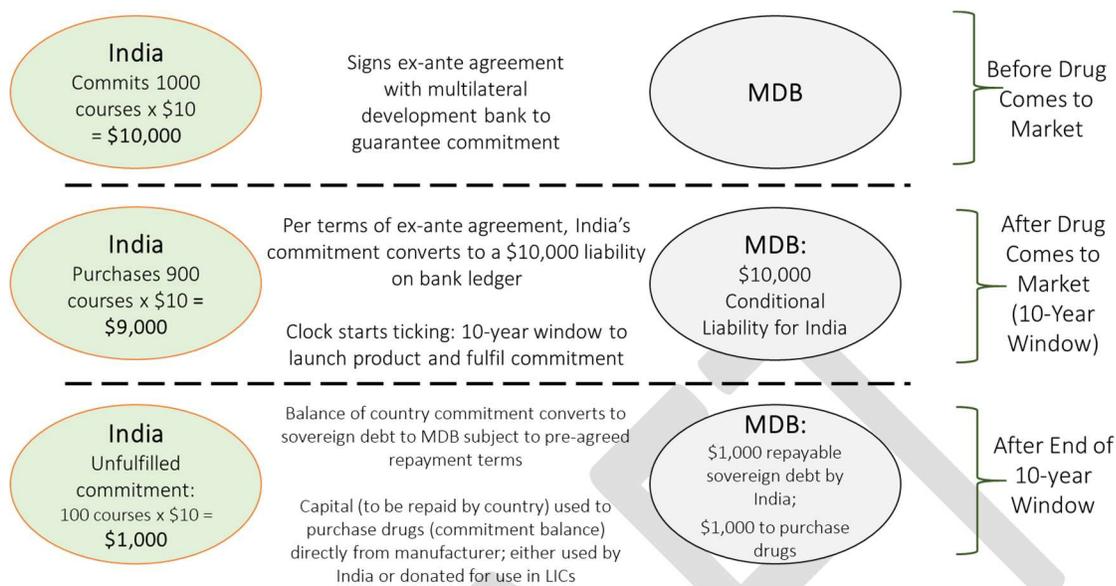
- Importantly, it establishes the precedent and principle of value-based pricing; each country pays the entire value-based price *for a portion* of their total projected demand, and a discounted value-based price for additional volumes. Each country pays a country-specific price.
- The revenue commitments de-risk the market for industry and guarantee profitability for the successful innovator, while the substantial discounts for additional volumes create large consumer surplus for country payers.
- The model is simultaneously flexible and predictable; it caps countries' financial exposure and guarantees a minimum level of industry revenue, but it enables countries to adjust pricing based on product efficacy.
- By limiting the "guarantee" to just a portion of the overall market, it also helps reduce transaction costs from commitment fees (discussed in the next section).

Underwriting the Commitment

Countries' verbal purchase commitments send an important market signal about their priorities and willingness to pay for an innovative product. Nonetheless, industry is unlikely to make significant R&D investments without a firmer purchase guarantee. Political leadership and priorities can change dramatically over a 10- to 15-year time horizon, with verbal commitments from previous governments easily disregarded or overturned. Industry will need assurance that today's purchase commitments will be honored 10 to 15 years in the future—withstanding political, economic, and social winds of change.

Here, we propose a model wherein countries leverage their own sovereign creditworthiness—intermediated through a AAA-rated intermediary guarantor such as an MDB—to underwrite their purchase commitments. Figure 11 presents a simplified strawman for how the guarantee would be structured (indicative numbers only, using India as an example; in practice, the commitment amount and structure would vary as described in the previous section). As a first step—well before the drug comes to market—each country government would sign a contractual agreement with such an MDB. The contractual agreement would lay out the terms of the commitment, clearly defining the country's obligations after the drug becomes available.

Figure 11. Simplified Strawman of Model to Underwrite Country Commitments



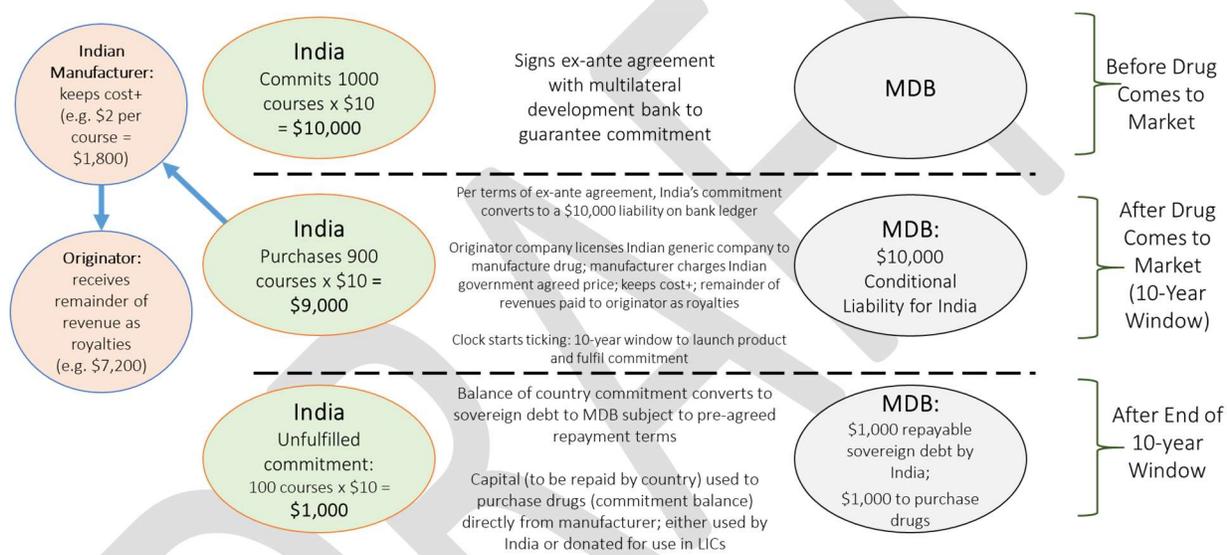
After the drug comes to market, the country's commitment would convert to a conditional liability on the MDB ledger; no money would change hands. From that point forward, the country would have 10 years (illustratively) to fulfill the entirety of its purchase commitment. The country would purchase drugs directly from the originator company or a local licensee; in turn, the value of its purchases would be deducted from the country's conditional liability. Countries that fulfill the purchase commitments would thus erase the entirety of their conditional liability, subsequently ending their contractual relationship with the MDB.

If a commitment balance remains at the end of the ten-year window—that is, if a country were to partially or fully renege on its purchase commitment—the remaining balance would convert to a loan by the MDB, subject to repayment by the commitment-making country under pre-agreed terms. The capital would be used to fulfill the remainder of the purchase commitment, ensuring that the originator company receives the entirety of the guaranteed return; the drugs could either be used in the commitment-making country or donated for use in LICs (if the commitment-making country is unable to absorb/effectively use the product).

This specific guarantee model has several advantages. The model relies on MICs' own credit-worthiness; the development bank will accept the arrangement only if it has confidence that the MIC will make good on sovereign debt payments. In this role, the development bank is acting as a financial intermediary—not a donor. The model is also transactionally simple; if voluntary commitments are met, no money ever changes hands except between countries and the successful company. Countries can continue to manage contracting, appropriation, and payment through their own standard year-by-year budgetary and appropriation processes, sidestepping potential legal challenges with multi-year contracting.

In addition, commitment-making countries can use their contracts with the MDB to set out specific conditions for their participation. Commitment-making countries could ensure the contracts align with local industrial policy (see next chapter), for example by conditioning their commitment on local licensing (whilst respecting IP) or use of local clinical trial networks. Figure 12 suggests how the underwriting mechanism would work with local licensing as it happens in many MICs nowadays and without challenging the innovator’s IP). The contract could specify pricing conditions after the commitment is exhausted, potentially including further pricing reductions for later purchases (as described earlier in this chapter). It could also require the originator companies to offer the drugs at cost for use in LICs—an in-kind contribution to global health that could be recognized as a contribution to the Global Fund credited perhaps to the early MICs (e.g., India) entering MVAC.

Figure 12: Simplified Strawman Underwriting Model with Local Licensing



Potential MDB Partners:

The underwriting model relies on the existence of MDBs with a set of specific capabilities and characteristics. These include:

- **High credit rating:** To drive private sector investment, industry would need to perceive the MDB-issued guarantee as highly credible and reliable.
- **Sufficient capitalization:** Guaranteed commitments could easily total \$2-\$3 billion. The MDB would need sufficient capital to cover these expenditures in the case of country default.
- **Low opportunity cost of capital:** The MDB would essentially need to “hold” a large sum of capital for potential (but unlikely) deployment 20 or more years in the future. A high opportunity cost of capital might prohibit use of funds for this purpose.
- **Appropriate instruments:** The MDB would need to have appropriate financial instruments that could be deployed or adapted to meet MVAC needs.

- **Country eligibility/regional purview:** Many development banks serve only a subset of countries. Regional development banks may be unable to serve all participating MVAC countries.
- **Exposure limits:** Some development banks cap total lending for any given country. The MDB would need sufficient lending space for all participating countries.
- **Low commitment fees:** MDBs “commitment fees” are typically charged at the time of issue and subsequently on an annual basis. Commitment fees are typically 100 basis points per year or less; nonetheless, even small fees could quickly accumulate given a large overall commitment and a long-term time horizon. Depending on total commitment size, time horizon, and how the commitment is structured, commitment fees could range from about \$22 million (.15 percent annual commitment fee, \$1.5 billion commitment, 10 years) to \$600 million (1 percent annual fee, \$3 billion commitment, 20 years). Identifying guarantee structures with relatively low commitment fees will be important for the overall feasibility of the model.

Given these characteristics—and based on preliminary conversations with relevant stakeholders—the World Bank and the Asian Development Bank emerge as promising candidates to serve as MDB partners (Table 8). Based on their respective comparative advantages—and the large overall commitment size—it may be desirable for different countries to underwrite their conditions using different development banks, essentially splitting the total commitment value across the two institutions. The Asian Development Bank could serve countries within its regional scope (e.g. potentially India, China, Indonesia, the Philippines, and Pakistan, among others), while the World Bank could serve countries ineligible for ADB lending (e.g., South Africa, Russia, and Brazil, among others). The World Bank may also be an appropriate host institution for the MVAC secretariat (see chapter 6) – we assume that the regional remit of the ADB makes it ineligible as a candidate.

Table 8. Assessing Potential MDB Partners

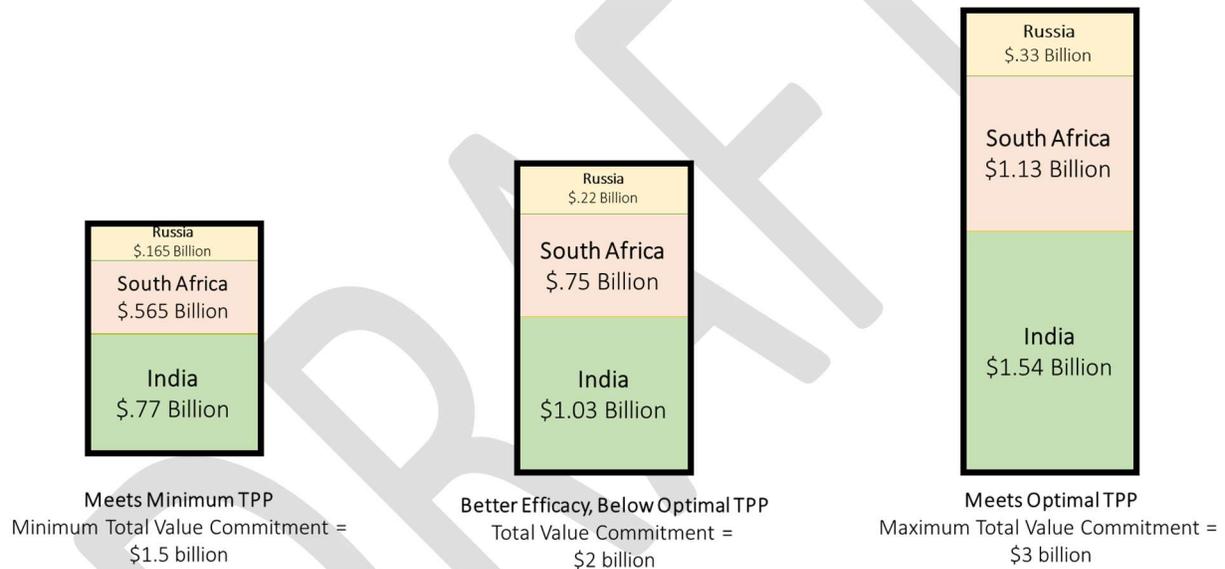
	World Bank	Asian Development Bank
Opportunities	<ul style="list-style-type: none"> • AAA credit rating • Global scope • High capitalization • Large health practice 	<ul style="list-style-type: none"> • AAA credit rating • No firm exposure limits • Decreasing need for concessional financing among its members; interested in alternative models to add value • High capitalization • Commitment fees potentially as low as .15 basis points for a standby credit facility (requires further exploration)
Challenges	<ul style="list-style-type: none"> • Firm exposure limits; may not be able to offer additional lending to India, specifically • Potential conflict of interest if Secretariat is also housed in the World Bank 	<ul style="list-style-type: none"> • Cannot serve countries outside its regional scope

A Mechanism to Crowd In Additional Countries

Once the MVAC is underway, additional countries may see benefit for their populations in joining the commitment pool; participation in the pool guarantees affordable access to a pathbreaking technology, whereas non-participating countries could face higher prices from industry. The MVAC could create a mechanism that enables and incentivizes other countries to join the pool, expanding the beneficiary population and helping push prices lower across all parties.

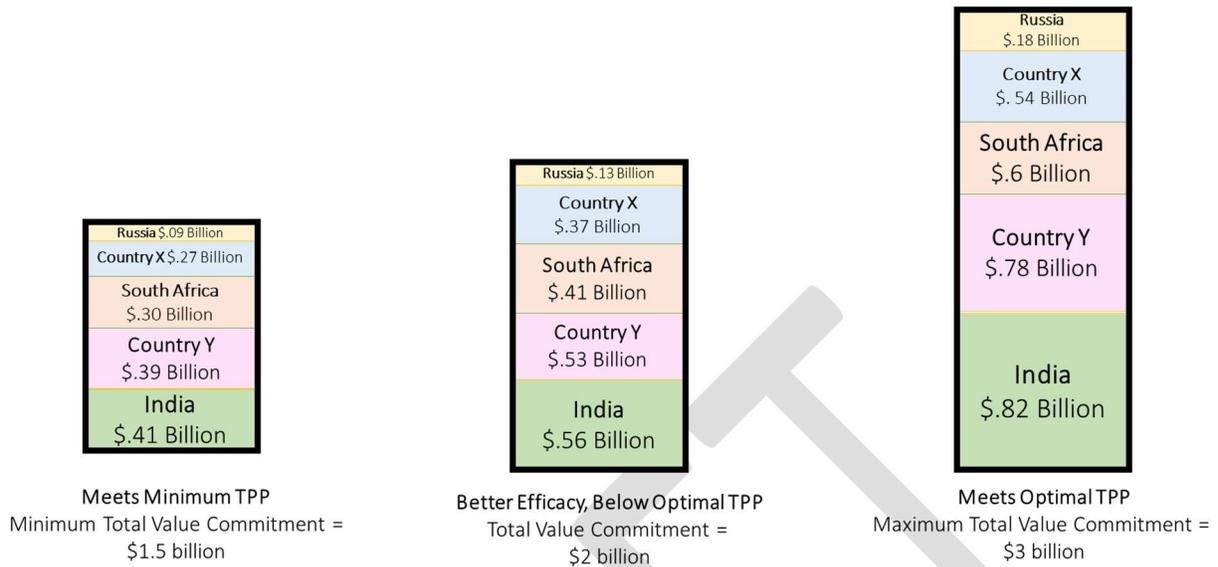
For example, imagine that Russia wishes to join in a few years after the MVAC is launched. HTA results (see previous chapter) show that Russia's value-based market totals \$.69 billion, compared to \$3.24 billion for India and \$2.37 billion for South Africa. The three countries now agree to a three-way split of the purchase commitment; once again, the relative commitment shares would be based on relative value, so a ratio 1.37 (India) to 1 (South Africa) to .29 (Russia); see Figure 13.

Figure 13. Expanding the Value-Based Commitment Pools to Include an Additional Country



This process could repeat multiple times; entry would be open to all middle-income countries up until market entry of the successful product. Potentially, countries could receive an additional incentive/reward for entering the pool early, or late entrants could owe an additional fee. After several additional entries, the pool might look something like Figure 14 (indicative numbers only).

Figure 14. The Value-Based Commitment Pools After Several Additional Entries



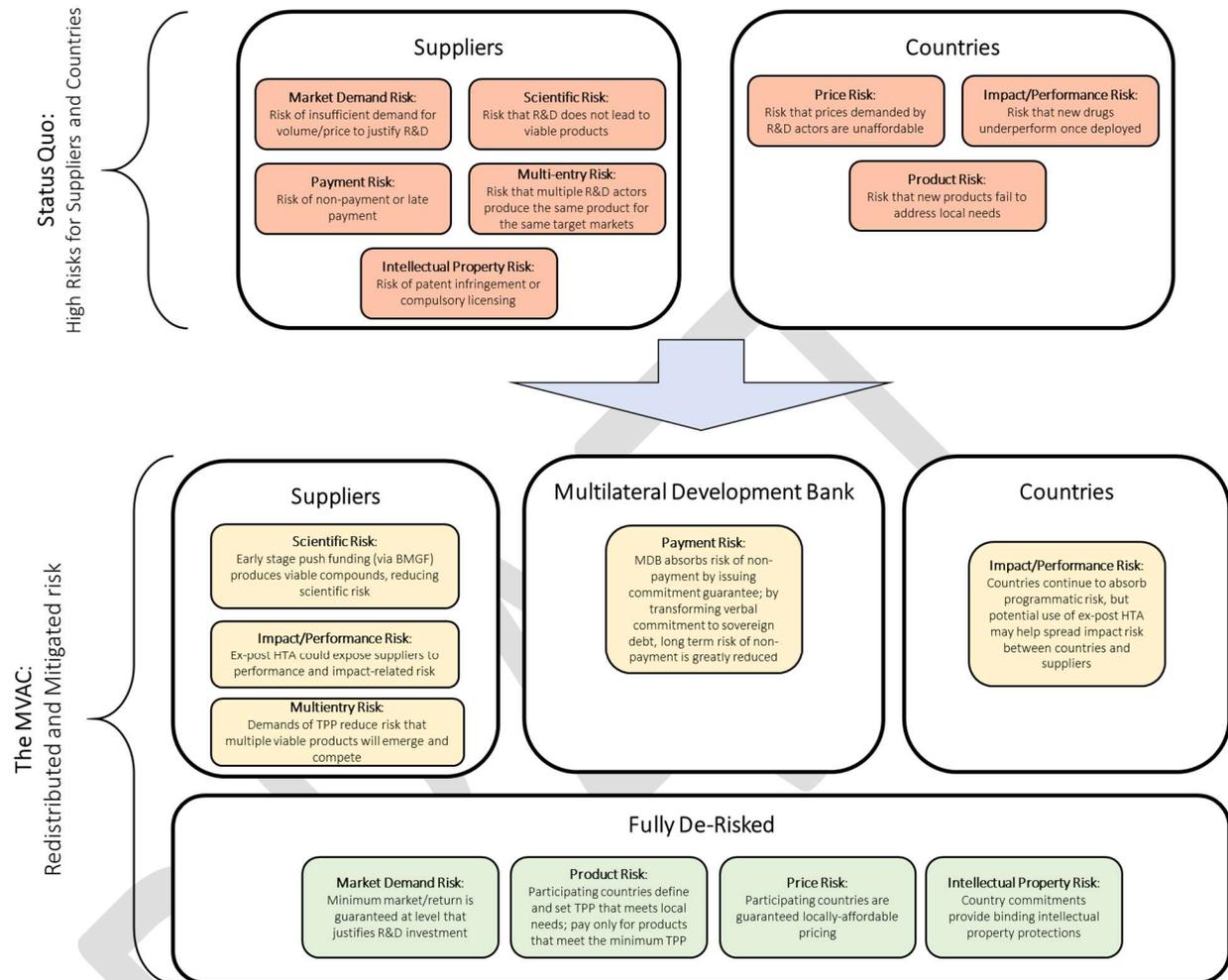
This commitment pool model we describe here has several benefits. First, it maintains a strong incentive to industry to develop the best possible product; a more efficacious product will lead to higher guaranteed returns. Second, there is a powerful mechanism to crowd in additional countries, reducing each country's purchase liability without affecting guaranteed industry returns. Finally, the model is simple and predictable for both countries and industry; countries have a clear limit on their financial exposure, while industry is guaranteed a minimum return for a product meeting the TPP.

When additional countries enter the pool, each of the existing country's volume commitment is reduced, but the price for the guaranteed segment remains unchanged. The level of discount for volumes beyond the purchase guarantee becomes more important. We assumed in our earlier discussion an illustrative discount of 70 percent but this will need to be subject to negotiation.

A Distributed and Mitigated Risk Model

Prior to the MVAC, several types of risk are concentrated among suppliers and countries (Figure 15). The risks are sufficiently high to prevent a desirable product—the TB universal regimen—from coming to market.

Figure 15. Risk Transformation Under the MVAC Model



The MVAC model mitigates and distributes risk, reducing total risk to a more acceptable level for all parties. Along several dimensions, the MVAC is fully de-risked:

- The commitment guarantees offer clarity on market demand for a product that meets TPP efficacy expectations.
- The commitment ensures that countries can access the new products at affordable prices.
- The TPP ensures that products will meet local demand.
- The entire structure is premised on respect for the originator's intellectual property.

Along other dimensions, risk is reduced and redistributed efficiently across parties:

- Suppliers continue to face the scientific risk that products will fail in late stage trials; however, their risk is substantially reduced with financial subsidies through early stage pipeline development to proof of concept.

- Market entry of competitor products remains possible but unlikely given the stringent TPP requirements, including the nature of the UDR as a three-product combination; a more likely scenario would involve market entry of a vaccine (reducing the pool of people to be treated).
- We have assumed that at-launch HTA only leads to price adjustments from the full TPP price based on efficacy. However, the potential use of ex-post HTA after the product is launched, could redistribute some performance/impact risk from countries to suppliers (e.g., if there are toxicity concerns).
- The MDB would reduce and absorb payment risk by transforming a verbal commitment to a sovereign debt obligation.

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Chapter 5. Industrial Policy

BRICS Industry Policy in Relation to Biopharmaceutical Innovation and Manufacture

The proposed MVAC model raises several issues related to participating countries' industrial policy. The MVAC will need to accommodate countries' preferential purchasing policies for local manufactures (as opposed to MNCs, plus any specific requirements for local research or manufacturing. Overall, most BRICS countries have industrial strategies to support domestic companies, including those in the pharmaceutical sector. We describe the key issues below, largely based on a landscape analysis commissioned by the BMGF from McKinsey.

Overall, localization requirements in Russia are significant and are likely to become more stringent going forward. Since 2014, Russia has offered a 15 percent price preference for locally-produced products; suppliers with an insufficient level of localisation must therefore bid at least 15 percent below the price of any local player to win government tenders. Local manufacturing is therefore critical for MNCs that seek access to the Russian market as there is a clear pricing advantage to firms that have local manufacturing facilities. Many MNCs use a local manufacturer to package drugs, enabling preferential pricing and market access. Some MNCs are beginning to produce drugs in Russia for export to other Commonwealth of Independent States (CIS) and Eastern European countries. Additionally, in-country clinical trials are a prerequisite for drug reimbursement by Russian government payers. The state has used compulsory licensing for some specific disease areas to increase access for patients (e.g., anti-HIV therapies). There is a small but growing R&D presence in Russia, with a few local companies undertaking R&D in labs in Moscow and St. Petersburg. The state has been supportive of this trend but we are not aware of specific policy initiatives.

In China, MNCs benefit from partnerships with local manufacturers, as they enjoy access and distribution advantages (e.g., Chinese distributors have better, more entrenched distribution networks and relationships that are almost impossible for MNCs to replicate, given the complexity of the Chinese market). At the provincial level, localizing production can also help secure preferential placement within regional formularies. Intellectual property rights are not strongly enforced in China and violators are often not prosecuted, though there is no compulsory licensing. For some new advanced therapies, the Chinese state prioritizes having local supply (e.g., in December 2017 the government instituted a regulation that all cell therapies need to be manufactured locally). Developing the domestic Chinese pharmaceutical industry is a priority for the Chinese government and is included in the 12th and 13th 5-year plans. Chinese R&D for innovative therapies is growing, with institutions such as the Shanghai institute of Materia Medica and the Beijing Institute of Technology producing globally recognized research.

Though local manufacturing is not mandatory in South Africa, showing an effort to develop local supply is a requirement for participation in government tenders. This will become increasingly important as the fledgling National Health Insurance (NHI) scheme expands coverage. The country is also experiencing drug registration delays with registration taking approximately five years, though registration of drugs to address an unmet need or treat life-threatening illnesses have historically benefited from fast track registration. To ensure drug and vaccine supply, the South African government has promoted public-private partnerships (PPPs) (e.g., the Biovac Institute's partnerships with MNCs for vaccines). Other than these PPPs, the South African government has not yet taken significant policy action to date to promote

biopharmaceutical innovation or manufacture. Most efforts have been related to import substitution and to lowering the cost of health products.

No localization requirements are currently in place in India, although indigenous manufacturing is a growing priority for the government. India is among the top pharmaceutical producers in the world (ranked 3rd in volume and 16th by value with more than 10,000 manufacturers and more than 500 FDA-approved manufacturing facilities). Although India's IP climate is improving, it is still unpredictable and can be unfavourable for innovative drugs given recent trends in compulsory licensing and delays in patent approval. This environment has driven some companies to opt for voluntary licensing (e.g., Gilead for its drug Sovaldi).

Many MNCs have manufacturing plants in Brazil, although they are primarily "fill and finish" or packaging plants. Although localisation is not required for market access and joint ventures (JVs), the government has promoted agreements between MNCs and local manufacturers (so called Product Development Partnership – PDPs) to facilitate local production via technology transfers and royalty arrangements. This approach was successful for vaccines in the 1980s and led to more PDPs for drugs and biologics in 2009. However, due to the added manufacturing complexity of drugs and the high volume of contracts signed, there have been some delays and cancellations. Local industry players dominate due to their low-cost structures, low prices, and brand recognition, making it difficult for MNCs to compete. Brazil has used the threat of compulsory licensing to pressure companies to lower prices of patented medicines, including Abbott's HIV/AIDS drug Kaletra; compulsory licensing was ultimately used in 2007 for Merck's HIV/AIDS drug Stocrin when Merck and the government could not agree on a price. This practice is now less common.

How Can MVAC Align with National Industrial Policy?

Industrial policy alignment would mean that the MVAC design accommodates country-level industrial policy goals and local purchasing preferences. The successful innovator company could be expected to meet country industrial policy requirements by, for example, licensing production to local manufacturers. As already described, developing their biopharmaceutical industry is a priority for the governments of India, China and Russia. Russia is particularly protectionist in its policies, which results in a high need for localization by MNCs. In India, South Africa, and China, although localization is not required, there may be an expectation that MNCs would generate productive clinical development partnerships and local manufacturing arrangements. Given the high overall expected volumes, technology transfer models and license agreements between MNC developers and local manufacturing companies could be a useful route to secure long-term supply.

Chapter 6. Governance

The MVAC is a vehicle for multinational cooperation; ultimately, its structure and operations must be owned and governed by participating country governments in partnership with relevant trusted global experts and institutional stakeholders. Yet for the model to work in practice, country governments must delegate key authorities to a permanent technical body that can manage day-to-day functions. In this chapter, we outline and map the requisite governance arrangements required to drive forward the MVAC model from concept to operational reality. Based on a comprehensive needs assessment and comparative options analysis, we propose a Secretariat housed within a World Bank Trust Fund, governed by participating countries in partnership with trusted technical and development partners.

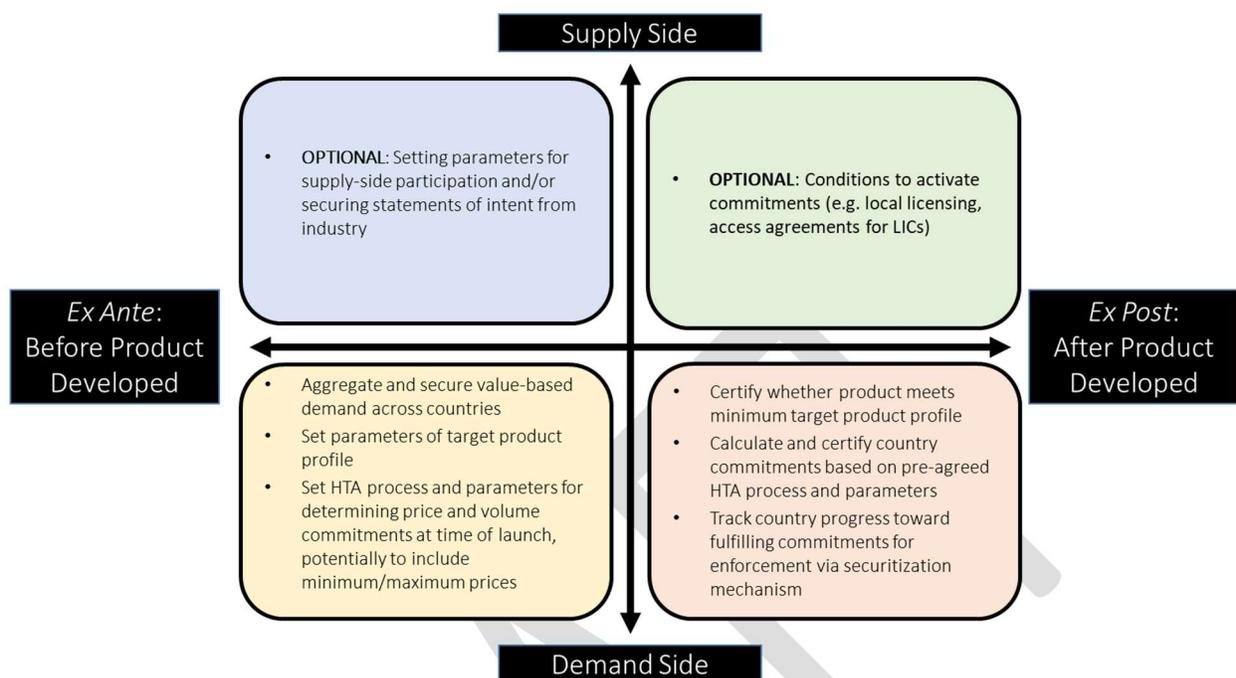
Defining Terms and Scope

The term “governance” is widely used in global health, but does not have a single, agreed-upon definition. For the purposes of this report—and the MVAC, more generally—we put aside the broader definitional debate and set our own functional vocabulary. In this chapter:

- “Governance functions” refers to processes that must be managed or decisions that must be taken for the overall model to work.
- “Governance arrangements,” in turn, refer to a range of explicit or implicit structures, institutions, organizations, or agreements that enable the “governance functions” to be executed.
- The “governance model” we propose for the MVAC refers to a cohesive and complete set of governance arrangements that will ultimately guide execution of the entire model.

Many different governance functions are required to refine and operationalize the proposed model; for simplicity, they can be mapped along two axes: supply side versus demand side, and ex ante (before the product is developed) versus ex post (after the product is developed; Figure 16). The MVAC is primarily a demand-driven instrument; as a result, its *essential* governance functions are exclusively found on the demand-side. Demand-side governance arrangements are initially needed to aggregate and secure value-based country commitments, set parameters of the target product profile, and set HTA processes and parameters for determining price and volume commitments at the time of launch—essentially creating the “market” that can be guaranteed/secured and subsequently drive industry investments in research and development. Following development of a therapy matching the TPP, demand-side governance structures must certify that the product meets the minimum TPP, calculate and certify country commitments based on pre-agreed HTA processes and parameters, and track country progress toward fulfilling purchase commitments.

Figure 16. Mapping Essential and Supplementary Governance Functions



Beyond the essential demand-side governance functions, some variants of the MVAC structure could benefit from additional/supplementary supply-side governance arrangements. As a general principal, before a product is developed, a true “pull model” does not need supply side governance. The incentive provided by the “pull” is, in theory, sufficient. The aggregation of and guarantee of demand is intended to mimic the market forces that typically stimulate private sector investment in research and development, with companies competing for the “pull” rewards. As a “light touch” option, however, we recognize it may be desirable for the MVAC secretariat to engage directly with potential suppliers at the outset—for example, to negotiate parameters for supply-side participation or secure statements of intent from interested companies. The expected continued existence of “push” incentives from global donors increases the case for early engagement by the MVAC secretariat.

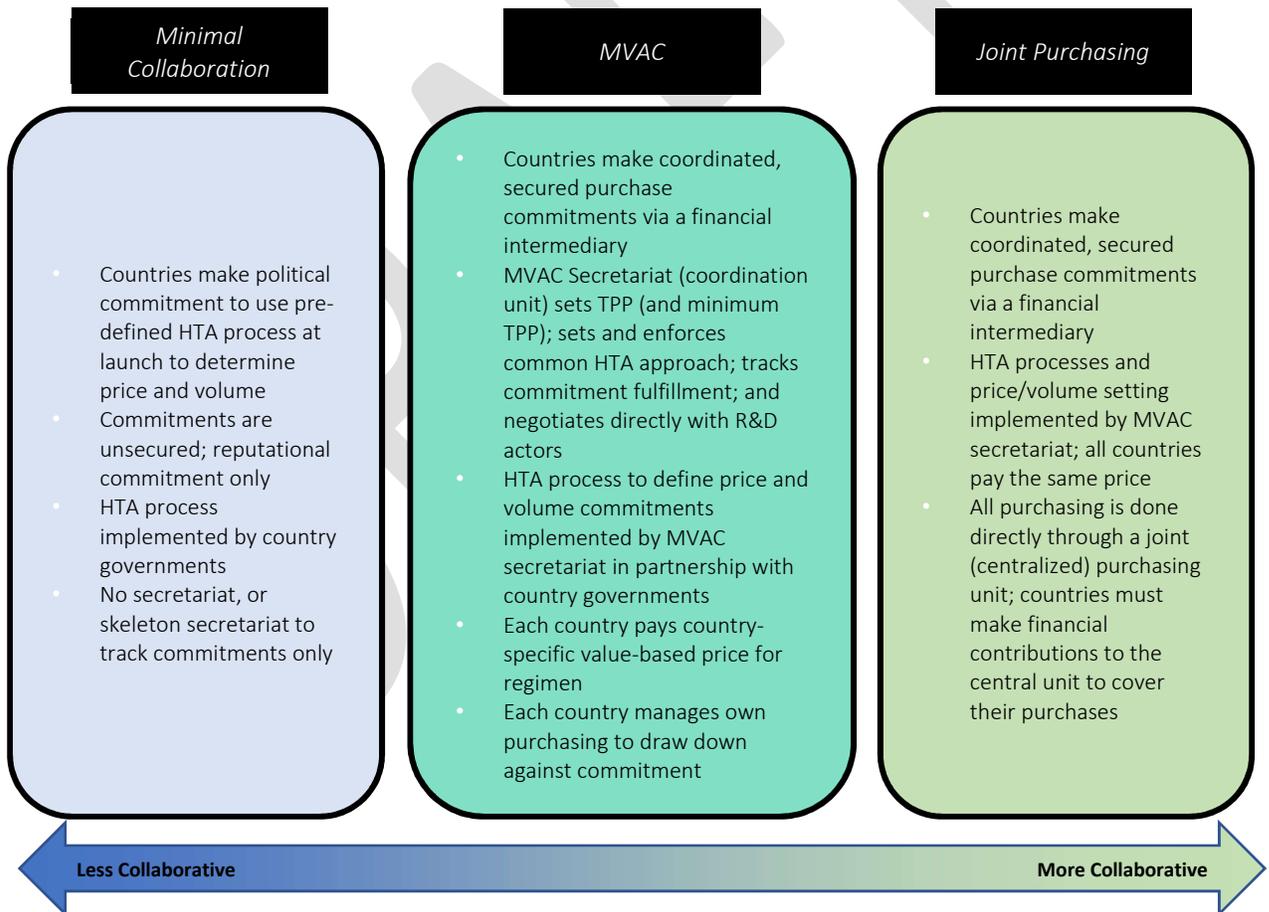
Once the drug comes to market, suppliers may be bound by certain “conditionalities” to activate the purchase commitment. Any conditions on supplier participation must be set at the outset, creating a clear and consistent set of market incentives. Potential conditions for supplier participation may include:

- Supplier commitment to supply the entire MVAC-guaranteed volume at the agreed prices, either directly or via licensed intermediaries
- Access agreements for LICs, perhaps linked to global donor purchase agreements
- Sustained or further reduced pricing for participating countries once the purchase commitment is exhausted (for a specific total volume or a specific period of time)
- Alignment with industrial policy priorities, potentially including licensing to local manufacturers, technology transfer, or partnerships with local clinical trial networks (see previous chapter)
- Agreement that a portion of payment (if any) would be tied to ex-post HTA
- Acceptance of contingency arrangements for:

- Adverse events;
- Development of drug resistance; or
- Introduction of new/superior therapies.

The proposed governance model is also notable for the functions it *excludes*—that is, the functions that remain vested with participating country governments outside the proposed secretariat. Most importantly, national governments will continue to directly manage their own purchasing (drawing down against the agreed commitments) through standard local procurement systems, in compliance with all national regulations as well as with the terms of the MVAC agreement. Countries will also maintain direct control and management over their own budgets; there will be no need to transfer funds to the MVAC secretariat, except (potentially) to help cover operational costs. In total, our model proposes a moderate level of collaborative but not pooled purchasing (Figure 17).

Figure 17: Moderate Level of Collaborative Purchasing Managed by the MVAC



Scoping the MVAC Governance Model: Needs Assessment

To serve its core functions—and successfully manage a complex and politically sensitive negotiation process—the MVAC governance model would benefit from the following essential characteristics:

- **Open and credible to BRICS/CIVETS and other MICs.** The success of this entire model is contingent upon successful engagement of middle-income countries with high tuberculosis disease burdens, including countries which: (i) have successfully transitioned away from Global Fund support (e.g. China, Russia); (ii) are in the process of doing so (e.g. South Africa and Indonesia); or (iii) are still largely eligible but are committing increasing domestic resources through co-financing requirements (e.g. India and Nigeria). A successful governance model will allow these countries to lead or at least share responsibility/power and offer prestige to participating country governments. This implies that the model must also have enough operational and strategic flexibility to engage with non-governmental, PDP, and private sector players in HICs and MICs.
- **Credible to industry.** The MVAC model is designed to respond to a market failure: the lack of trust from industry that MICs will pay value-based prices for innovative products, hampering investments in research and development. Secured country commitments (see previous chapter) are the primary vehicle through which the MVAC mitigates this “counterparty risk”; nonetheless, credibility of governance arrangements remains an important lever to stimulate industry participation. For example, the governance structures will hold ultimate responsibility for certifying whether a product meets the minimum TPP; industry may remain wary of investment if it believes the decision-making process would be vulnerable to conflicts of interest or unpredictable political forces.
- **Relevance to/expertise in tuberculosis.** Determining the appropriate product profile and managing the aggregation of demand will require substantial expertise in tuberculosis as a disease. This could be accomplished in two ways: (i) by leveraging existing expertise at existing institutions, or (ii) by creating a new mechanism that can attract or leverage outside expertise.
- **Flexibility.** By design, the activity/intensity level of the MVAC would vary substantially over time. Early on, there would be a flurry of activity as the secretariat scrambled to recruit countries, agree to a target product profile, and “kick off” the MVAC process. Immediately thereafter, the MVAC would enter a period of dormancy, with perhaps just a skeleton staff needed to maintain operations, interface with industry, monitor R&D, and recruit additional countries. Several years later, when a candidate drug emerged from late-stage trials, the MVAC secretariat would need to rapidly ramp up once again. The governance structures thus require significant flexibility to expand and contract across the project cycle.
- **Minimize transaction costs.** To direct as many resources as possible toward research and development and the subsequent purchase of innovative TB therapies, the governance arrangements should be designed to minimize unnecessary transaction costs. This could potentially be achieved by taking advantage of well-established bureaucracies/operational systems, or by establishing new, light-touch organizations. However, efficiencies in operational costs should not be achieved at the expense of cutting programmatic corners.

- **Attract (or offer) long-term operational resources.** We estimate that Secretariat costs over a 15-year time horizon would total about \$40 million. Though this is a relatively modest sum by global health standards (and compared to the anticipated value of the commitment), it may nonetheless be difficult to secure predictable, long-term resources. The MVAC would benefit from a host institution that either (i) had dedicated, predictable income streams to fund secretariat operations; or (ii) could attract and manage a dedicated long-term trust fund, disbursed over many years.

Options Analysis

Based on the needs assessment (see above) we identified and evaluated three potential options for housing the MVAC secretariat. The following section (summarised in Table 9) presents an options analysis for the three potential hosts, including description, advantages, and disadvantages. The analysis suggests that a World Bank trust fund (option 1) offers the best fit for MVAC operational needs. Accordingly, it is our recommended structure.

Option 1: Recommended - World Bank Trust Fund

Description: “Trust funds are vehicles used to manage funds contributed by development partners for specific development activities and administered by the World Bank.”[12] Though they are housed within World Bank fiscal and administrative systems, trust funds are governed based on an agreement between donors and the World Bank and can thus include direct oversight by external parties.

Advantages: The World Bank is a credible multilateral institution—both for potential industry partners and for middle-income countries which already participate in institutional governance and could oversee a dedicated trust fund. The trust fund model is widely used to steward development resources and well-trusted by the donors who might subsidize the secretariat’s operational costs. Trust funds offer predictable multi-year funding—potentially using a single up-front investment to finance the MVAC secretariat over the entirety of its long-term lifecycle.

Disadvantages: Though the World Bank finances many health programs, it has no specific expertise in either tuberculosis or health procurement. There are potential conflicts of interest if the secretariat and underwriting mechanism are housed within the same institution.

Option 2: Existing Donor-Led Secretariat

Description: The new purchase commitment would be embedded as a unit or program within an existing donor-led global health institution/secretariat. This would essentially follow the model of the AMC for pneumococcal disease, which was hosted by Gavi. Candidate host organizations for the model include:

- *The Global Fund to Fight AIDS, Tuberculosis, and Malaria:* The Global Fund has a long history in the fight against tuberculosis, and substantial in-house expertise. Its financial resources are also relatively large; in total, \$1.84 billion was allocated to TB programs for the 2017-2019 cycle,[13] and additional \$800 million was made available for “catalytic investments”, which includes “strategic initiatives that are needed to support the success of country allocations but cannot be funded through country grants.”[14] The Global Fund could potentially use its existing resources to guarantee country commitments; it could also “commit” parts of country TB allocations to purchase of an innovative TB therapy. The Global Fund has also shown its willingness to support market-shaping efforts in the past. However, many of the target countries have already graduated

from Global Fund support or are positioned to do so shortly. In addition, anecdotal reports suggest that the Global Fund is now resistant to purchasing first-line TB drugs.

- *UNITAID*: [UNITAID](#) describes itself as a mechanism that “invests in new ways to prevent, diagnose and treat HIV/AIDS, tuberculosis and malaria more quickly, more cheaply and more effectively.” Its mission—to accelerate and facilitate the development and market entry of innovative tools—is clearly aligned with the goal and structure of this model. However, UNITAID is relatively small (average spend of about \$250 million per year over the past 10 years).[15] It is also widely perceived as a French-led initiative, as France provides the majority of its funding; this might constrain its credibility and ability to engage with BRICS/other MICS, and its ability to secure other donor commitments, for example from the United States.
- *Global Drug Facility*. Hosted within the StopTB Partnership, the Global Drug Facility (GDF) is a pooled procurement mechanism for quality-assured TB drugs, servicing many Global Fund principal recipients (PRs). The GDF is specialized in TB and experienced in managing procurement and distribution of innovative formulas.

Advantages: Use of an existing donor-led secretariat would facilitate access to existing concentrations of tuberculosis-, market shaping, and procurement-related expertise, and existing bureaucracies/operational structures; this could help minimize transaction costs and enable rapid set-up. Current donors are already comfortable channeling funding through these organizations; their use could help mitigate perceived fiscal and operational risk. Existing secretariats may have their own pre-existing funding pools that can be used to help guarantee country commitments.

Disadvantages: Although some mechanisms, such as the Global Fund and UNITAID, include recipient countries within their governance structures, they are widely perceived as donor-driven mechanisms. Many of the target MICS are no longer eligible for their assistance or will be graduating shortly; as a consequence, they no longer engage directly with these mechanisms and may see themselves as no longer “needing” their assistance. Existing bureaucracies may have operational constraints that prevent flexibility/could prove problematic in managing this initiative.

Option 3: New Secretariat

Description: Following the model of previous global health funding mechanisms, MICS and donor governments/representatives could jointly create and govern a new mechanism with a permanent secretariat. Representatives from MIC governments and donors would sit on the board of organization and set broad direction, but day-to-day operations would be managed by the secretariat.

Advantages: A “clean slate” offers the opportunity to create purpose-build, agile mechanism, avoiding bureaucratic entanglement. Opportunity to co-found and co-lead a new mechanism may be more attractive to BRICs/MICs than working with existing, donor-driven institutions, and may create greater sense of ownership to mitigate risk that they will renege on commitments. Creation of a secretariat offers an opportunity to insource most relevant expertise.

Disadvantages: Need to start from scratch building operational capacity. No established funding base to support initiative, and no track record of attracting donor funds. May have less credibility engaging with pharma/industry than an established organization. May have limited ways to engage with countries not directly involved in governance arrangements.

Table 9. Options for MVAC Secretariat Host Institutions

Option	Strengths	Weaknesses
RECOMMENDED: World Bank	<ul style="list-style-type: none"> • Credible to MICs; MICs already participate in governance. Dedicated trust fund could be governed by MICs. • Credible to industry. • Significant capitalization/fiscal resources. • Easy to coordinate with underwriting function if housed with same institution. • Flexibility to expand/contract given differing needs over MVAC duration. 	<ul style="list-style-type: none"> • No specific TB or health procurement expertise. • Potential conflicts of interest if secretariat and underwriting mechanism housed within the same institution.
Existing Secretariat-based institution (e.g. Global Fund, UNITAID, GDF)	<ul style="list-style-type: none"> • Experience and expertise in tuberculosis. • Existing infrastructure and expertise in procurement. • Fiscal resources to help secure commitments (e.g. Global Fund catalytic funding; TB allocations for LICs). • Track record raising money from donors; credibility with donor institutions. • Credibility/track record with pharma companies. 	<ul style="list-style-type: none"> • Perceived as donor-driven mechanisms; may not be credible to MICs or sufficiently flexible to include them in governing bodies. • Existing bureaucracies may have operational constraints that prevent flexibility. • Existing bureaucracies are disease-specific (mostly infectious diseases), which limits generalizability of the model.
New Secretariat-based institution	<ul style="list-style-type: none"> • “Clean slate” offers the opportunity to create purpose-built, agile mechanism, avoiding bureaucratic entanglement. • Opportunity to co-found and co-lead a new mechanism may be more attractive to MICs than working with existing, donor-driven institutions. • Creation of a secretariat offers an opportunity to insource most relevant expertise. 	<ul style="list-style-type: none"> • Need to start from scratch building operational capacity. • No established funding base to support initiative, and no track record of attracting donor funds. • May have less credibility engaging with pharma/industry than an established organization. • May have limited ways to engage with countries not directly involved in governance arrangements.

Governing Board and Independent Advisory Committees

The board would primarily be comprised of participating country governments; it may also include representation from external technical and funding partners plus independent technical advisors. The board would be responsible for setting the secretariat mandate and broad policy direction, plus overseeing Secretariat operations.

However, there are some decision points where board members would have a natural a conflict of interest. These include:

- **Design and approval of HTA models and results:** Because price and volume commitments would be tied to HTA results, board members would have a fiduciary interest in HTA models that understate the local benefits of a new product.
- **Approval of a product as meeting the minimum TPP:** Because approval of a product activates the time-limited purchase commitment, board members may have an interest in rejecting a suitable product.

To ensure that these decision points are insulated from conflicts of interest—and thus credible to market actors looking to invest in TB R&D—the board would be supported by an independent technical advisory group. Comprised of independent tuberculosis and HTA experts, the independent advisory group would be responsible for approving HTA models; approving the results of country-level HTA; and certifying that a country meets the TPP and should thus qualify for MVAC value-based purchase commitments.

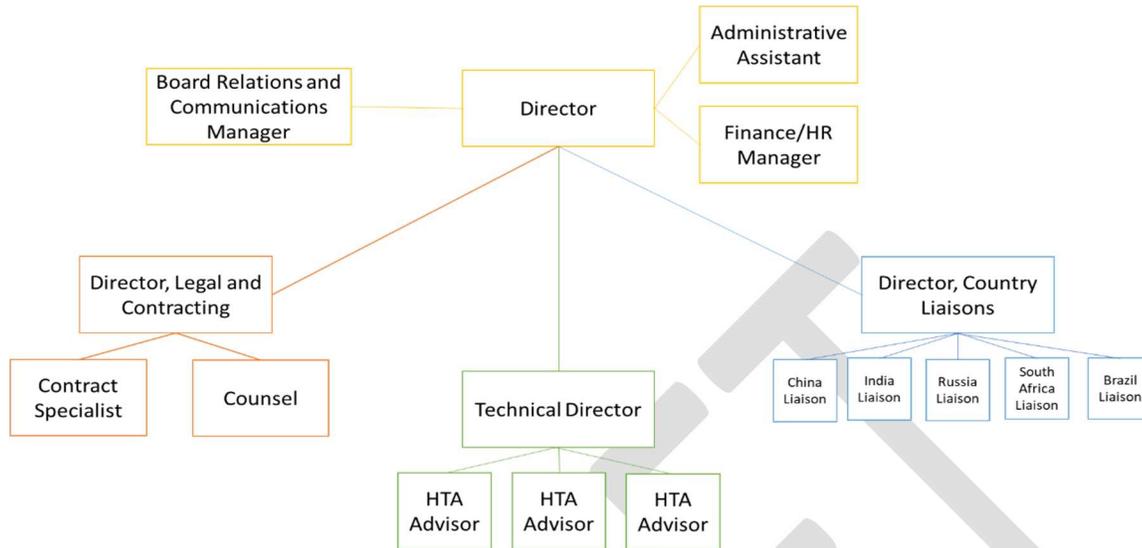
Secretariat Design and Operationalization

In the first year, there would be a need to establish, test, and gradually expand a **transitional secretariat**, with costs of about \$2–3 million over a period of 12–18 months. This would build on the thinking and analysis delivered so far and would include (i) further modelling through modelling consortia; (ii) the drafting of contracts; (iii) socialization and outreach to countries, industry, and MDBs; and (iv) recruiting the core team at the secretariat.

Once fully functional, the secretariat would migrate in full to a **permanent home**, recommended to be within a World Bank trust fund. During high-intensity periods, we expect that the secretariat would need approximately 15–20 full-time staff members, including technical, legal, and country-specific staff, and it would commission and administer research grants from third parties. The secretariat would be organized along regional and functional lines (Figure 18).

- **A country liaison team** would host dedicated liaisons for each of the participating countries; the designated liaisons would be the primary contacts for in-country technical and political stakeholders. The country liaisons would be responsible for building relations with relevant in-country stakeholders, requiring frequent travel; facilitating countries' access to technical resources from elsewhere in the secretariat (HTA advisors or legal/contracting experts); and knowledge management for all country-specific data and resources relevant to the MVAC.
- **A technical team** would host a dedicated team of HTA specialists. These specialists would partner with in-country HTA resources (e.g., universities, consultancies) to commission, build, validate, and implement HTA models for use by the MVAC, including ex-ante and ex-post HTA.
- **A legal and contracting team** would work with the underwriting partner to assess and review the terms of conditional liabilities and purchase commitments.
- **A front office team** would report directly to the director, handling finance, administration, human resources, board relations, and communications.

Figure 18. Proposed Secretariat Structure During High-Intensity Periods



During the low-intensity interim period, the secretariat would contract to a shell (e.g., a director, single legal advisor, and technical advisor). The shell secretariat could continue to recruit additional countries to join the mechanism even during low-intensity periods.

Chapter 7. Next Steps

The Center for Global Development and Office of Health Economics released this consultation draft of the MVAC blueprint in March 2019 for public review and comment; the document is still preliminary, with many outstanding questions and unresolved issues. Through mid-2019, we welcome constructive feedback and dialogue to further hone the proposal and ensure it is responsive to the interests and concerns of all stakeholders. During this period we will also work proactively to engage with stakeholders in target countries, international institutions, and within the pharmaceutical industry.

Please contact Rachel Silverman (rsilverman@cgdev.org) to share feedback or arrange a call and/or in-person meeting with the MVAC team.

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Sources

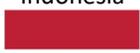
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Appendix 1. Target Product Profile

Attribute	Target
Indication	Regimen is 1 st line treatment without DST requirement
Target Population	All groups irrespective of HIV status
Efficiency	Not inferior to rif-sensitive TB standard of care (RS SOC) in ≤2mo regimen
Safety	<ul style="list-style-type: none"> - Incidence/severity of AEs better than DS SOC - No active clinical/lab monitoring for toxicity (except in special pops) - No ECG monitoring of QT interval
Drug-Drug Interactions and Metabolism	<ul style="list-style-type: none"> - No dose adjustment w/other meds - Ability to safely use regimen w/o active lab test monitoring
Barrier to emergence of drug resistance	<ul style="list-style-type: none"> - Mutation rates not > 1/10⁹; essentially no acquired resistance (<0.1%) - No pre-existing resistance
Formulation, dosage, route of administration	<ul style="list-style-type: none"> - Oral, once daily, no special weight banding - ≤ 3 novel antibacterial compounds; 2 of 3 or all in FDC
Stability/shelf life	Stable > 3 years in climate zones 3 and 4 at 30C / 75% RH

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Appendix 2. Summary of HTA Initiatives

Emerging Markets	
<p>China</p> 	<p>“We have fully utilized HTA...to balance financial sustainability and access to new cancer drugs...up to 30% price reductions compared to nearby countries”</p> <p>Director of Chinese Medical Insurance Bureau, Beijing, October 2018</p>
<p>India</p> 	<p>“the India Medical Technology Assessment Board for evaluation and appropriateness and cost effectiveness of the available and new Health Technologies in India...standardized cost-effective interventions that will reduce the cost and variations in care, expenditure on medical equipment...overall cost of treatment, reduction in out of pocket expenditure of patients...’.</p> <p>MTAB, Ministry of Health & Family Welfare, Government of India</p>
<p>Indonesia</p> 	<p>(5) Health Technology Assessment Committee provide policy recommendation to the Minister on the feasibility of the health service as referred to in paragraph (4) to be included as benefit package of National Health Insurance</p> <p>Indonesia: Minister of Health’s Decree No. 71 /2013 Article 34</p>
<p>Philippines</p> 	<p>Philippines: “The Corporation shall not cover expenses for health services which the Corporation and the DOH consider cost-ineffective through health technology assessment...”</p> <p>National Health Insurance Act of 2013, Section 11- Excluded Personal Health Services</p>
<p>South Africa</p> 	<p>Service coverage (5.3): South Africa “Detailed treatment guidelines, based on available evidence about cost-effective interventions, will be used to guide the delivery of comprehensive health entitlements. Treatment guidelines will be based on evidence regarding the most cost-effective interventions.”</p> <p>RSA National Treasury (HTA unit budgeted @R368m in 2018 Treasury budget)</p>

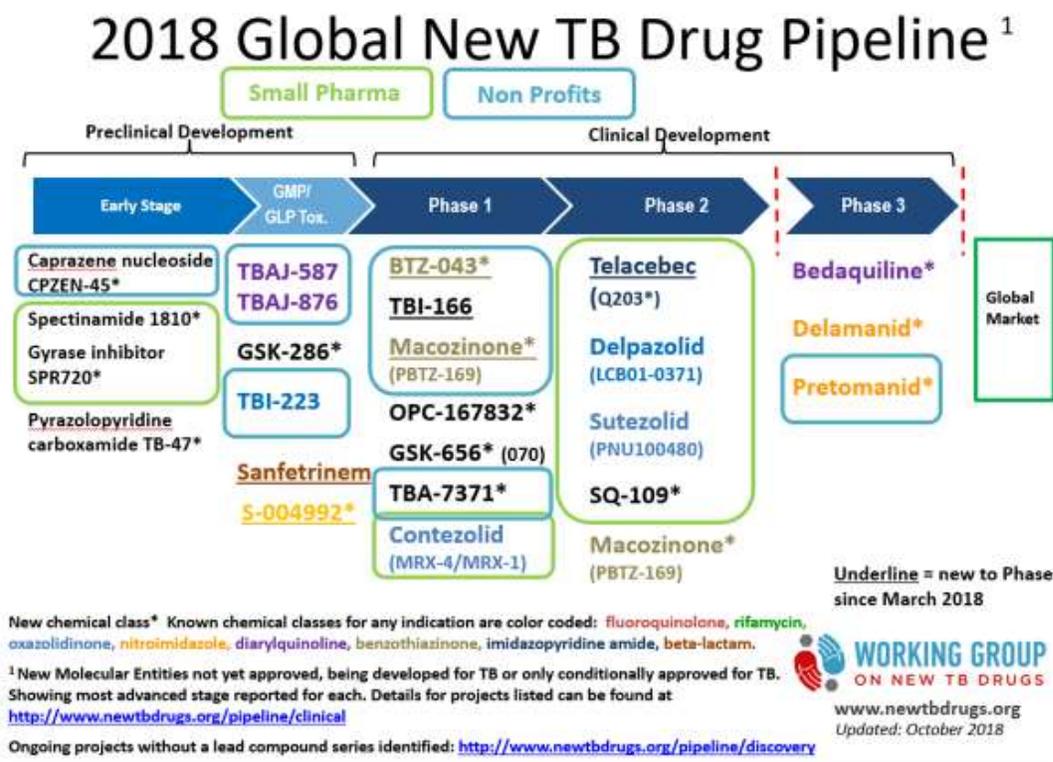
Low- and Middle-Income Markets	
<p>Ghana</p> 	<p>“MOH should develop a transition plan to ensure sustainable financing and operational management of the supply chain to transition to a government led supply chain system; MOH should establish a National Pricing Committee for Medicines; MOH should institutionalise Health Technology Assessment to provide technical advice to the NPC”</p> <p><i>Ghanaian National Medicines Policy</i></p>
<p>Kenya</p> 	<p>“Define an evidence-based benefit package for Kenyans under Universal Health Coverage: (A list of services that should be prioritized and made available taking into account the cost effectiveness, impact on financial protection, and equity in access across the population).</p> <p>- Define a framework for institutionalization of Health Technology Assessment (HTA).”</p> <p><i>Cabinet Secretary, Government Gazette, July 2018</i></p>
<p>Tanzania</p> 	<p>“The aim of the Tanzanian Health Technology Assessment Committee (THTAC) is to make evidence-informed recommendations to the MOHCDGEC based on the internationally recognized HTA framework. The committee will make recommendations about the public provision of health technologies that will contribute to maintaining and improving the health and well-being of Tanzanians, provide value for money and lead to the ultimate goal of Universal Health Care.”</p> <p><i>TANZANIA HEALTH TECHNOLOGY ASSESSMENT COMMITTEE (THTAC) Report, 2018</i></p> <p>“The government will improve adequate knowledge in health technology assessment (HTA) for evidence-based selection of quality and safe technology as well as realizing value for money.”</p> <p><i>2017 National Health Policy 5.14.3. Policy Statements</i></p>

High-Income Markets	
<p>European Union Commission</p> 	<p>“The outcome of HTA is used to inform decisions concerning the allocation of budgetary resources in the field of health, for example, in relation to establishing the pricing or reimbursement levels of health technologies. HTA can therefore assist Member States in creating and maintaining sustainable healthcare systems and to stimulate innovation that delivers better outcomes for patients”</p> <p><i>REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on health technology assessment and amending Directive 2011/24/EU</i></p>
<p>BeneLuxA + Ireland</p> 	<p>“The initiative aims to achieve its goals by ... increasing efficiency in the assessment, pricing, and reimbursement of pharmaceutical products by exchanging expertise and the mutual recognition of HTA...”</p> <p><i>BeNeLuxA Initiative on Pharmaceutical Policy Terms of Reference</i></p>

Appendix 3. Current Research and Development (R&D) pipeline in TB

The global pipeline for new TB treatments has improved substantially in the last five years. As shown in Figure 19 there are currently seven programmes in phase 1, led by a mix of organizations including research organizations and product development partnerships (PDPs), large and small pharmaceutical companies.

Figure 19: 2018 Global New TB Drug Pipeline[16]



A key role in this expansion of the global pipeline is due to the creation in 2012 of the TB Drug Accelerator program (TBDA), which is a partnership between pharmaceutical companies and research organizations with support from the BMGF.

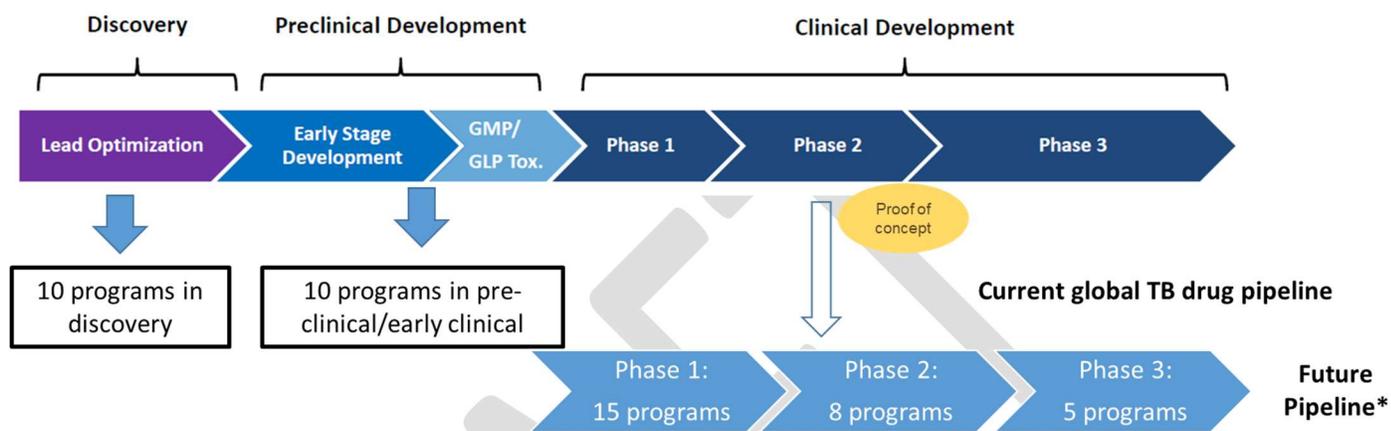
Launched in August 2012, TBDA is a ground-breaking partnership between eight pharmaceutical companies and seven research organizations with support from the BMGF. One of the fundamental aims of the initiative was to support the discovery and development of new compounds which could form the basis of new shortened regimens in the next five to ten years.

Based on the current clinical program (from phase I to III), it is expected that at least one new regimen will be introduced in around 7 years. The new regimen will not meet the TPP for a UDR but should have a better profile than those currently available for MRD/XDR-TB.

Based on the current discovery and pre-clinical development (lead optimization to toxicity tests), a UDR may potentially be developed in the next 12 to 15 years. As shown in Figure 20, below, when considering the 20 programs in early stages (including those supported by the TBDA) and the attrition

rates from a phase to the next (as predicted by pharma companies in recent calculations), it expected that 15 programs will enter phase 1, eight in phase 2, and five in phase 3, to subsequently lead to one successful new regimen meeting or close to meet the UDR TPP.

Figure 20. Current early discovery and pre-clinical global TB drug pipeline vs expected clinical development pipeline



*based on estimated on industry attrition rates. Source: Adaptation of <https://www.newtbdrugs.org/pipeline/clinical>

Appendix 4. Frequently Asked Questions

Why does this matter? According to the WHO, the SDG for tuberculosis “cannot be achieved” without a “major technological breakthrough.” BMGF funding and product development partnerships have helped source new and promising compounds, but major new investments are needed to bring drugs to market. In the absence of intervention, pharmaceutical companies will not invest the requisite financial resources to fund late state clinical trials and bring a pathbreaking drug (UDR) to market, and global TB goals will not be achieved.

What’s in it for industry? Industry receives a de-risked and guaranteed market for an innovative drug, protected from compulsory licensing and other threats to IP. In the long run, industry builds relationships, experience, and precedent for value-based pricing that would help expand sales in emerging markets.

What’s in it for countries? Participating countries get guaranteed access to innovative drugs, targeted to local needs, at locally affordable prices—driving multinational and domestic investments to address local disease and population priorities.

What is health technology assessment (HTA)? Where and how is it used? Is it realistic in MLICs? The WHO [defines](#) HTA as the systematic evaluation of properties, effect, and/or impacts of health technology. HTA informs decision making about the use of new products by helping payers quantify tradeoffs and draw informed comparisons between alternative potential uses of finite health budgets. HTA offers a starting point for product listing and price negotiation and for policy decision-making, but it is not an automated decision rule. Many of the largest MICs—including India, Brazil, China, Thailand, Vietnam, Indonesia, and South Africa—already use HTA to inform coverage and purchasing decisions within their health sectors. (See more [here](#)).

How is this different from the AMC for pneumococcal vaccines? The MVAC targets products in an earlier stage of clinical development; relies on commitments from country governments rather than donors, commitments guaranteed by a financial intermediary (e.g., a development bank); is led and governed by country governments; and determines pricing based on a local value and affordability assessment in participating countries, i.e., it is not cost-plus.

What happens to the IP? The innovator company retains IP rights. At the very least, participating countries are guaranteed pricing at MVAC levels in perpetuity (e.g., after their commitments are exhausted); potentially, participating countries could condition the guarantees on more aggressive price reductions once the commitment is fulfilled.

What exactly are countries committing to pay? Based on a minimum and optimal target product profile—paired with some conservative assumptions about GDP growth—the MVAC approach would set a floor and ceiling total revenue level for country commitments. Within that range, the final price and volume would be calculated via a pre-defined process and using the HTA model once the drug comes to market, based on its efficacy/product characteristics and other pre-agreed parameters that influence its value to country health systems, including local affordability constraints.

What is guaranteed in the MVAC model? The MVAC offers guaranteed revenue to a product developer; the total guaranteed revenue will only vary based on product efficacy, within a pre-set range (floor and ceiling).

Are there ways to continue downward pressure on pricing through the MVAC structure? Yes. The total value-based market—if appropriately de-risked—is likely to significantly exceed industry’s “reserve price” to make the requisite investments and bring the product to market. As a result, the MVAC can cap the guaranteed revenue at only a portion of the overall value-based market. The MVAC could then “crowd in” other middle-income countries into the same pool of a guaranteed market—lowering the revenue commitments for every participating country.

Would the MVAC involve pooled procurement? No. Although countries would collaborate to negotiate prices and agree to a common TPP, each participating country would procure the UDR directly from the originator or local licensee through its own national procurement procedures at a price which represents value for each country whilst complying with all relevant national regulations.

How does the MVAC compared to the Most Favoured Nation clause? MVAC relies on differential pricing based on locally determined value and affordability. Differential pricing (though not necessarily based on country budget realities and local value) is currently the norm for on patent products across MICs. A trend towards MFN would distort markets, possibly resulting in selective launches in higher income markets hence impeding access. By linking markets, it would also undermine R&D which addresses poorer/MICs needs.

How do we ensure access for LICs? To benefit from the guaranteed country commitments, the successful company must offer the drug at cost for use in LICs—either to a third-party or directly to country governments. By helping ensure access for LICs, participating countries would be credited for indirect contributions to the Global Fund. Global donor commitments would still be needed to enable LICs to purchase the new TB drugs at cost.

Does the MVAC involve tiered pricing? Yes. Each country would pay a country-specific price, calculated based on the value that the drug provides within its own health system. Tiered pricing is the norm for non-donor health products within and across MICs.

How does the MVAC align with countries’ industrial policy? To comply with countries’ industrial policy requirements, the successful innovator would work with in-country manufacturers—potentially including licensing agreements, investments in clinical trial networks, and joint ventures—to help build industrial capacity.

Is the MVAC only for large multinational companies? What about companies based in developing countries? The MVAC is a flexible, demand-based pull mechanism. All companies—including those based in developing countries—can participate, either as innovators or licensees.

Is there precedent for countries to pay differential prices through a collaborative purchasing arrangement? Yes. In the EU, several country groupings—most recently [Belgium, Ireland, Austria, Luxemburg and the Netherlands](#)—have come together to collaborate in their purchasing of high-priced pharmaceutical products. Countries share information on comparative effectiveness and budget impact but continue to purchase individually at a country-specific confidential prices.

Is there precedent for the development banks to serve as a guarantor/intermediary? Yes. Both the [ADB](#) and [World Bank](#) offer guarantees among their suites of financial products, using their AAA ratings to mitigate commercial risks. Representatives from have expressed confidence that the proposed guarantee instrument is technically feasible.