

Priority Review Voucher:

Policy Barriers and Opportunities to Increase Access to Voucher-Winning Medicines

by

Shashika Bandara

Duke Global Health Institute  
Duke University

Date: \_\_\_\_\_

Approved:

---

Jeffrey Moe, Supervisor

---

Gavin Yamey

---

Bronwyn Kaiser

Thesis submitted in partial fulfillment of  
the requirements for the degree of  
Master of Science in the Duke Global Health Institute  
in the Graduate School  
of Duke University

2018

ABSTRACT

Priority Review Voucher:

Policy Barriers and Opportunities to Increase Access to Voucher-Winning Medicines

by

Shashika Bandara

Duke Global Health Institute  
Duke University

Date: \_\_\_\_\_

Approved:

---

Jeffrey Moe, Supervisor

---

Gavin Yamey

---

Bronwyn Kaiser

An abstract of a thesis submitted in partial  
fulfillment of the requirements for the degree  
of Master of Science in the Duke Global Health Institute  
Graduate School of  
Duke University

2018

Copyright by  
Shashika Bandara  
2018

## Abstract

Background: Access to medicines is a vital component of upholding the right to health. However, there is a gap in access to medicines, especially in resource poor settings, that leads to poor health outcomes. The priority review voucher (PRV) is a ‘pull’ incentivizing mechanism designed to encourage new drug development for otherwise neglected diseases. This mechanism also reduces the cost of the end-product via incentives provided after the product has been developed. This study aims to understand policy and implementation barriers related to access to the PRV-winning drug bedaquiline. Bedaquiline is the first drug approved for multi-drug resistant tuberculosis (MDR-TB) in over 40 years. Based on an understanding of access barriers to this new drug, the study also aims to suggest policy recommendations to improve access for PRV winning drugs for tropical diseases.

Methods: The study used semi-structured qualitative interviews with multiple stakeholders at the global level and at the country level in South Africa. These were combined with data from research literature and advocacy materials and analyzed using thematic analysis, organized using Kingdon’s three streams model. The model includes three streams: the problem stream, politics stream, and policy stream. The model also identifies policy entrepreneurs and policy windows. The data were further analyzed using Lewin’s forcefield analysis (FFA) identifying supporting and opposing forces related to increasing access to bedaquiline.

Results: Overcoming policy and implementation access barriers related to bedaquiline is the responsibility of multiple stakeholders. The main barriers to access for bedaquiline currently include (i) barriers to registration of the drug at the country level, (ii) lack of research data (especially phase III trial data), (iii) weak health systems, and (iv) the lack of a sustainable pricing model. The manufacturer has a significant role to play, and this role is common among other PRV winners for tropical diseases as well.

Conclusion: PRV as an incentivizing mechanism to develop drugs for otherwise neglected diseases should strongly consider including an access plan requirement as part of the application process. The plan should be made available to the public for evaluation.

# Contents

Abstract .....	iv
List of Tables.....	viii
List of Figures .....	ix
Introduction .....	1
1.1. <i>Access to Medicine</i> .....	1
1.1.1.    Definition of Access to Medicine .....	1
1.1.2.    Existing mechanisms to increase access.....	3
1.2. <i>The Priority Review Voucher (PRV)</i> .....	5
1.2.1.    Economic Impact of the PRV .....	6
1.2.2.    Existing Criticisms .....	7
1.2.3.    Tropical Disease PRV Winners .....	8
1.3. <i>MDR-TB and Sirturo (bedaquiline)</i> .....	10
1.4. <i>Analyzing access gaps</i> .....	13
1.5.    Rationale and Study Aims .....	16
2.    Methods.....	18
2.1.    Participants .....	18
2.2.    Setting .....	20
2.3.    Recruitment.....	20
2.4.    Data Collection .....	21
2.5.    Qualitative Data Analysis .....	21
2.6.    Kingdon's Three Streams model.....	22
2.7.    Forcefield Analysis .....	22
2.8.    Literature review .....	23
3.    Results.....	23
3.1. <i>Categorizing results based on Kingdon's three streams model</i> .....	23
3.1.1.    The Problem Stream .....	23
3.1.2.    Political Stream.....	37
3.1.3.    Policy Stream .....	40

3.1.4 Policy Entrepreneurs and Policy Windows.....	42
3.2. <i>Understanding access barriers via forcefield analysis</i> .....	44
4. Discussion .....	46
4.1. <i>Implications for Policy and Practice</i> .....	46
4.1.3. Necessity for an access plan by the manufacturer .....	46
4.1.3. The role of the regulator.....	50
4.2 <i>Strengths and Limitations</i> .....	51
5. Conclusion .....	52
Appendix A: List of PRV Eligible Tropical Diseases .....	53
Annex B: Publicly available tier pricing data by Janssen therapeutics (J&J) .....	55
Annex C: Interview guide for semi-structured interview questionnaire.....	57
References .....	59

## List of Tables

Table 1: PRV mechanism separated into stages.....	6
Table 2: Overview of the five tropical disease drugs that won the PRV (16,22–24) .....	8
Table 3: Key stakeholder informant profiles (descriptive data are not provided to maintain anonymity) .....	18
Table 4: Overview of access barriers in the problem stream .....	24
Table 5: Overview of political actors related to access provision to bedaquiline .....	37
Table 6: Summary of control manufacturer has over each access barrier.....	45

## List of Figures

Figure 1: Kingdon's three stream model.....	14
Figure 2: Stakeholder interaction map in providing access to bedaquiline in South Africa .....	39
Figure 3: Timeline of key policies related to bedaquiline access.....	41
Figure 4: Summary of policy and implementation barriers to bedaquiline through Kingdon's three streams model .....	42
Figure 5: Forcefield analysis of providing access to bedaquiline.....	44

## **Introduction**

### **1.1. Access to Medicine**

Access to medicines is a vital component in upholding the right to health. As articulated in the preamble of the 1946 Constitution of the World Health Organization (WHO) “the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition” (1). The right to health is further recognized in the 1948 Universal Declaration of Human Rights and in 1966 International Covenant of the Economic Social and Cultural Rights (2,3).

Access to medicines is a key entitlement under the right to health (4). Both the Millennium Development Goals (MDG) and Sustainable Development Goals (SDG) have recognized access to medicines as an important aspect of health (5,6). SDG 3B outlines access to medicines as a key component in its 2030 agenda (5). In keeping with this agenda, in September 2016, the United Nations (UN) Secretary General’s High-Level Panel on Access to Medicines released a report outlining recommendations for all stakeholders to improve access (7). The objectives of this research project are aligned with the principles outlined in the human rights frameworks, global agendas and recommendations above.

#### **1.1.1. Definition of Access to Medicine**

The MDGs define access to medicine as “having medicines continuously available and affordable at public or private health facilities or medicine outlets that are

within one hour's walk from the homes of the population"(6). The SDGs do not have a clear definition of access to medicines. Access to medicines falls under SDG goal 3B that states its aim as to

“support the research and development of vaccines and medicines for the communicable and non-communicable disease that primarily affect developing countries, provide access to affordable essential medicines and vaccines, in accordance with the Doha Declaration on the TRIPS Agreement and Public Health which affirms the right of developing countries to use to the full the provisions in the Agreement on Trade-Related Aspects of Intellectual Property Rights regarding flexibilities to protect public health, and, in particular, provide access to medicines for all”(5).

In both global development agendas (the MDGs and SDGs), access to essential medicines is measured based on availability and affordability. However, the quality of the drugs and rational use are also considered as important aspects. Under the MDGs, absence of expired stock was considered indicative of quality, although not quantified. Implementation policies and national guidelines were considered to be indicative of rational use (8).

Further, scholars have argued that access is not just a technical issue of logistics of transporting drugs or technology from manufacturer to end user. Access also involves social values, economic interests and political processes (9). More importantly, access is also linked to services that are being provided and thus to the health system (9).

Based on the definitions and additional key aspects outlined above, this research uses the following the working definition of access to medicine: *availability, affordability of drugs and medical technologies that have prescribed quality standards, for rational use with sufficient services to ensure freedoms, entitlements and inclusions of right to health in each population*. This working definition aims to include the role of the health systems and to set a minimum standard across all populations.

However, this definition sets an aspirational standard for access, with the goal of achieving access to medicines for all populations. When considering the market price for any drug, it is placed at one point in the demand curve, assuming that there will be some who cannot buy at the market price (10). Therefore, there is a gap in consumers who will not be able to afford the medicine or technologies. Some of the key existing mechanisms to bridge the gap in access to medicines are outlined below.

### **1.1.2. Existing mechanisms to increase access**

At present, there are funding mechanisms that are designed to bridge the gap in affordability both at the country level and at the global level. At the country level, there are different social insurance and public subsidization mechanisms that aim to improve the affordability of medicines and services. However, over 90 percent of low- and middle-income countries (LMICs) must pay for medicines out of pocket due to inadequacy in social insurance or subsidization mechanisms (11,12). There are six categories of actors that aim to increase access by providing funding support to

governments in LMICs. These six categories are: I) bilateral aid agencies, such as the U.S. Agency for International Development (USAID), II) intergovernmental organizations, such as the World Bank, who provide support via grants or concessionary loans, III) global health partnerships (GHPs), such as Gavi, The Vaccine Alliance (Gavi) or the Global Fund To Fight AIDS, Tuberculosis (TB) and Malaria (Global Fund), IV) non-governmental organizations (NGOs), V) private foundations such as the Bill and Melinda Gates Foundation and, VI) the corporate sector. Funding support from the above mentioned actors is used for health system strengthening (HSS), to reduce costs of treatments, and to improve sustainability in healthcare delivery (13).

On the other hand, research and development (R&D) is also a vital part of access to medicines. Delinking the R&D cost from the end-product is one avenue to achieve affordability, availability and prescribed quality standards. 'Push' and 'pull' incentive mechanisms are two of the main methods that contribute to delinking costs from the end-product. 'Push' mechanisms, such as grants, provide funding at earlier stages of drug development to get a product into the market. 'Pull' mechanisms, such as advanced market commitments, promise financial or similar rewards after a product has been developed. These incentives contribute to lowering the price and encourage development of novel treatments. Other methods of delinking R&D costs include pooling (of data, funding and intellectual property), open collaborative research, public private partnerships and product development partnerships (7).

## **1.2. The Priority Review Voucher (PRV)**

The PRV is a 'pull' mechanism that provides a financial reward after a product goal has been reached. The voucher was originally designed as an incentive for pharmaceutical companies to develop therapies for tropical diseases (14). Since then, the PRV mechanism has been extended to include rare pediatric diseases and medical countermeasures (15,16). Medical countermeasures include emerging infectious diseases, biological, chemical and nuclear threats (16). As per the developers of the PRV, it has two objectives: "priority-review voucher provides two benefits: faster access to blockbuster drugs in developed countries, and faster access to cures for infectious diseases in developing countries,"(14).

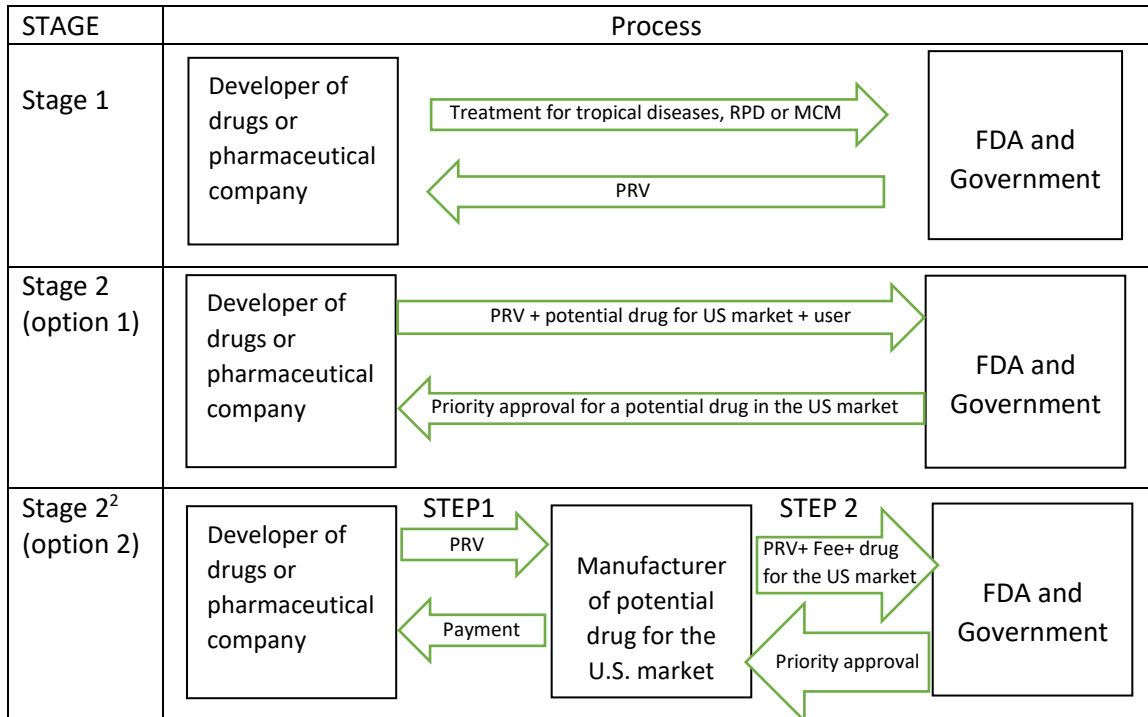
The PRV mechanism incentivizes pharmaceutical companies to develop drugs for any a) tropical diseases,<sup>1</sup> b) rare pediatric diseases or c) medical countermeasures by awarding a voucher that allows the company to gain priority review from the United States Food and Drug Administration (FDA) for potential therapies in the U.S. The PRV is also transferrable; therefore, the voucher itself has a market value. Hence, companies are incentivized to develop drugs for diseases that are otherwise neglected, and it allows the companies to receive priority approval for their potential drugs for the U.S. market. The normal approval process currently lasts about 10 months; the priority review process will shorten this to 6 months. When the mechanism was first introduced, the

---

<sup>1</sup> A complete list of tropical diseases eligible for the PRV and the new mechanisms through which new diseases can be added are include under Appendix A.

normal approval process lasted around 18 months (14,17). The PRV mechanism is illustrated in table 1.

Table 1: PRV mechanism separated into stages



### 1.2.1. Economic Impact of the PRV

The financial advantage of the PRV is due to a) early sales based on early entrance to the market, b) having an advantage over competitors by having an established brand and c) having a longer period in the market before the arrival of generics (18). In terms of the re-sale value of the voucher, it is estimated that if only one priority review voucher is available for a year, it will have a value more than \$200

<sup>2</sup> Step 1 and Step 2 occurs in chronological order

million. However, if more than four vouchers are available in the market, the value could be less than \$100 million (17,18). If just four vouchers are available in one year, the value can be as low as \$39 million. Therefore, expansion of the voucher program's eligibility criteria -- resulting in a higher number of vouchers per year -- will drive down the value of the vouchers (18).

From an access perspective, decreased value of the voucher could weaken the incentive for companies to develop drugs using the PRV mechanism. Additionally, new product development partnerships aim to use a portion of voucher sales towards ensuring access (19). If the value of the voucher were to be reduced, it could also negatively impact potential product development partnerships (PDP) and therefore access to those drugs.

### **1.2.2. Existing Criticisms**

The two main criticisms of the PRV program are that a) the PRV's definition of novelty as "drugs not registered in the U.S." means that vouchers can be received by companies who have not made investments in R&D and b) affordability and access are not regulatory requirements for the drugs that are eligible to win the PRV. Therefore, there are arguments for changing the novelty requirement of the PRV to ensure that the drugs are novel treatments (not just treatments that are have not been registered in the U.S.) and to require a commitment to provide access for the PRV winning drugs for tropical diseases (20–22).

### 1.2.3. Tropical Disease PRV Winners

At present (February 2018), 18 vouchers have been awarded: five vouchers for tropical disease drugs and 13 for rare pediatric diseases. The five tropical disease vouchers were awarded for malaria, MDR-TB, leishmaniasis, cholera, and Chagas disease (17). Table 1 summarizes the disease, company, drug, the year that the PRV was awarded, and use of the voucher.

*Table 2: Overview of the five tropical disease drugs that won the PRV (16,22–24)*

<b>Disease</b>	<b>Drug and compound</b>	<b>Company</b>	<b>Award Year</b>	<b>Use of the Voucher</b>
Malaria	Coartem: (artemether/lumefantrine) tablets	Novartis	2009	Voucher was used on Ilaris. The drug was not approved.
MDR-TB	Sirturo: bedaquiline tablets	Janssen (subsidiary of Johnson and Johnson	2012	Successful use to approve Trmefya
Leishmaniasis	Impavido: miltefosine tablets	Knight	2014	Sold to Gilead Science for \$125 million
Cholera	Vaxchora: Cholera oral vaccine	PaxVax	2016	Not publicly used <sup>3</sup>
Chagas	Benznidazole tablets	Chemo Research	2017	Unused

<sup>3</sup> The voucher was considered to have been sold to Gilead Science in 2017(23).

The voucher winning companies for tropical diseases has had varied approaches to providing access. The following is a brief overview of access efforts, criticisms, and responses for Coartem, Impavido, Vaxchora and Benznidazole (17,19,21,22).

#### Coartem (artemether-lumefantrine)

In 2001, Novartis made Coartem available without profit for distribution through the WHO to malaria-endemic countries (24). Coartem is registered in 86 countries; 30 out of 47 sub-Saharan African countries have adopted Coartem as first line therapy for malaria. 500 million treatments especially targeting children and infants have been delivered to over 60 malaria endemic countries (25).

#### Impavido (Miltefosine)

Knight therapeutics received the PRV for Impavido and holds the exclusive license to distribute in the US. Paladin Labs, a subsidiary of Endo pharmaceuticals, holds exclusive rights to distribute Impavido globally. Hence, the access responsibility to provide Impavido in developing countries falls to Paladin/Endo Pharmaceuticals (26,27). Paladin/Endo provides a significantly lower price on bulk orders of over 3500 courses. The price decreases from €2636 to €45-55 for an adult treatment course, and from €842 to €34-€40 for a treatment course for children (27,28). However, as NGOs have pointed out, the bulk order requirement leads to over-supply of the drug outside of countries with large high populations such as India. The company's response was to

indicate that NGOs “need to weigh the benefits of the discount against the risk of over-supply” (27).

### VaxChora

Cholera vaccine is targeted for those traveling from non-endemic areas to endemic areas such as humanitarian workers, military or tourists (29). Effectiveness of the vaccine has not been established in cholera affected areas, thus limiting the potential of the vaccine as a treatment in endemic areas (30). Currently, the vaccine costs \$225 at wholesale acquisition cost (30). It should be noted that PaxVax has been criticized by humanitarian actors as unwilling or unable to scale access in developing countries (31).

### Benznidazole

The Drugs for Neglected Diseases initiative (DNDi), the pharmaceutical company Chemo Group (since renamed Insud Pharma), and the non-profit foundation Mundo Sano had a pre-agreed access plan per their PDP (32). The plan stipulates that 50 percent of the financial returns of a future sale of the PRV will be allocated for access (for benznidazole or any trypanocide) plan under DNDi and Mundo Sano agreement (19).

### **1.3. MDR-TB and Sirturo (bedaquiline)**

This research analyzes the access challenges faced by bedaquiline and the efforts made in South Africa to improve access to bedaquiline as an informative case study. The information is used to develop recommendations for improving access to PRV awardee tropical disease drugs.

## Bedaquiline

Bedaquiline is one of the first new drugs to be approved for TB treatment in over 40 years (33). Bedaquiline uses a new method, targeting the ATP synthase enzyme of the *Mycobacterium* cells that cause TB (34). The other new drug that uses a new method of action at the cellular level is delamanid (33). Due to increasing drug resistance for first and second line drugs, bedaquiline with its new method is a life-saving drug. FDA approved bedaquiline based on phase IIb clinical trial data in 2012, granting a PRV(17,35). Bedaquiline is a new treatment indicated for MDR-TB, rifampicin resistant TB (RR-TB), and extensively drug resistant TB (XDR-TB). The WHO issued interim policy guidance for bedaquiline, as a lifesaving drug for MDR-TB/RR-TB and XDR-TB patients (35,36). Bedaquiline was developed by Janssen therapeutics, a subsidiary of Johnson and Johnson (J&J). Janssen (J&J) is the sole manufacturer and distributor of bedaquiline under the brand name Sirturo (37).

## Disease Burden: TB and MDR-TB

TB is the leading cause of death from a single infectious agent, killing over 1.4 million people in 2016, and ranking above HIV/AIDS in terms of mortality. Overall, TB is the ninth leading cause of death in the world (38). In 2016, MDR-TB/RR-TB incidence was estimated at 600,000 in total, with 490,000 (82%) accounted for MDR-TB (38,39).

### **1.3.1. Access challenges for bedaquiline globally**

FDA's approval of bedaquiline was based on phase IIb trial data, as opposed to phase III trial data, due to the lifesaving potential of bedaquiline especially for MDR-TB patients (40,41). The absence of research data on the drug's side effects and on interaction with other drugs resulted in a cautious approach by the WHO. As per WHO's interim policy guidance on the use of bedaquiline, it is considered an 'add-on' drug for those who do not have other treatment options, for people with XDR-TB and/or TB/HIV co-infection and for people who cannot tolerate other TB medicines (40,42). The threat of TB acquiring bedaquiline resistance requires pharmacovigilance (43), including strict and continuous monitoring and reporting of the drug's effects on patients (44). For bedaquiline, electrocardiograms (ECG), blood toxicity and liver toxicity monitoring are essential tests (40).

The uptake of bedaquiline has been limited when considering the demand. At present, only 5 percent of drug resistant TB (DR-TB) patients have access to life saving novel drugs (bedaquiline and delamanid) (41). The current challenges include but are not limited to lack of research data, lack of registration in each country, the cost of improving health systems based on WHO guidelines for pharmacovigilance, and the cost of the drug (41,45). Many of these challenges are associated with multiple stakeholders including the manufacturer and country governments.

To address the challenge of the cost of bedaquiline, the manufacturer, Janssen (J&J) created a donation program through a public-private partnership (PPP) with

USAID, fulfilled via the Global Drug Facility (GDF). The donation program, which provides 30,000 six-month treatment courses, is slated to end in 2019 (46).

### **1.3.2. Access challenges for bedaquiline in South Africa**

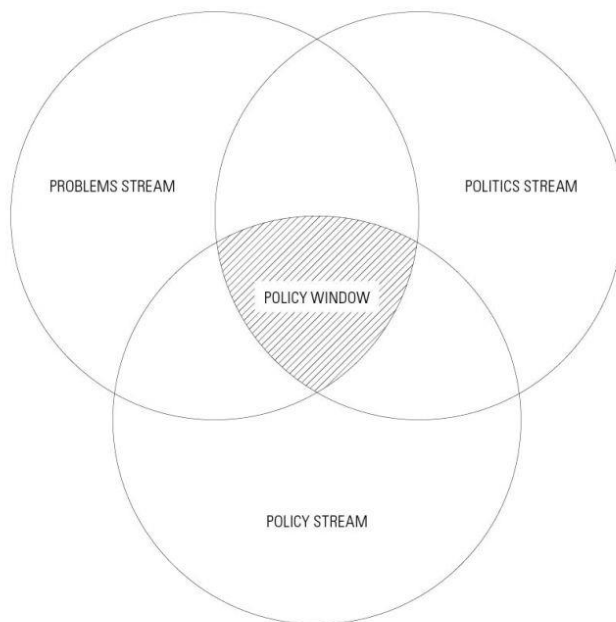
In 2016, South Africa's TB incidence, including HIV co-morbidity, was estimated at 438,000 (38). TB-only incidence was estimated at 180,000. Mortality, including HIV co-morbidity, was estimated at 101,000 (38). The incidence of MDR-TB/RR-TB was estimated at 19,000 (38). South Africa faced similar challenges regarding access to bedaquiline as outlined above, under global challenges. However, South Africa has led the way with its bedaquiline clinical access program since 2012, providing further research information on the use of bedaquiline on MDR TB patients (47). Since then South Africa has expanded its adoption of bedaquiline overcoming some of the access barriers (48).

### **1.4. Analyzing access gaps**

Thus, considering the challenges of access to bedaquiline globally, and in South Africa specifically, this research will explore the following question: *what are the existing policy and implementation barriers that affect patient access to the MDR-TB drug bedaquiline at the global level and at the country level in South Africa?* To answer this research question, qualitative data from key informant interviews and data from literature were organized using Kingdon's three streams model and analyzed using Lewin's forcefield analysis (FFA) (49,50).

### 1.4.1. Kingdon's three streams model

Kingdon's three streams model is used to organize and present the results of this research. Kingdon's three streams model observes or explains how an issue becomes prominent in the policymaking agenda. The three streams include I) problem stream, II) policy stream, and III) politics stream. Kingdon observes that the interaction of these three streams brings an issue to the top of the agenda, resulting in greater attention and potential solutions (49). Policy entrepreneurs who are powerful but interested individuals push this agenda forward using policy windows. Figure 1, illustrates the three streams and their interaction in the Kingdon's model.



*Figure 1: Kingdon's three stream model*

**The problem stream** includes indicators, focusing events or feedback mechanisms that help to further define or understand the problem. Indicators include statistical data from monitoring or investigations. Focusing events include catastrophic events or high-profile events that draw attention. Feedback mechanisms include experiences and commentaries from stakeholders on the current policies and challenges(49). In the case of bedaquiline and MDR TB, the indicators include disease burden, mortality and morbidity data. There have not been any focusing events, barring the fact that MDR TB, if untreated can result in the rise of mortality. Feedback from stakeholders are captured via qualitative interviews and advocacy documents.

**The policy stream** includes potential solutions to the problem identified in the problem stream. The potential solution providers include but are not limited to experts both within and outside the government, inter-governmental organizations, special interest groups, international organizations and/or industry stakeholders. Adopted policy solutions depend on cost, past experiences, resulting reactions from different stakeholders including the public and the industry (49). I considered the existing policy solutions in South Africa, global solutions offered by the industry, and intergovernmental organizations.

**The politics stream** includes the contributory roles played by the stakeholders involved in the policy-making process. The stakeholders mainly consist of policy makers and other stakeholder groups who are supporting and opposing suggested policies.

Dominant global and national opinions, influential movements, and media can influence the politics stream (49). In the case of bedaquiline access, these stakeholders include state governments, WHO, NGOs and the industry.

These three streams interact with the support of policy entrepreneurs, which can be any one (or many) of the stakeholders who find effective ways to push the agenda forward. Policy entrepreneurs seize opportune moments, termed policy windows, to push forward the potential policy solutions and prioritize the problem at hand.

#### **1.4.2. Lewin's Forcefield Analysis (FFA)**

FFA is used to summarize the results of this research into categories of barriers and enablers of access to bedaquiline. FFA by Kurt Lewin is a technique that identifies key forces which oppose or support a preferred outcome. According to the theory, in any conflictual or stalemated situation, opposing forces are at play. The FFA first identifies these forces and secondly estimates the strength of each force. The analysis suggests two general approaches to shift the forces toward a preferred solution: either reduce the oppositional forces or strengthen the forces in support of the preferred solution (50).

### **1.5. Rationale and Study Aims**

This research examines the policy and implementation barriers of increasing access to bedaquiline at the global level and at the local level in South Africa. The access goals are in line with the access goals set under the Global Plan to End TB. The Global

Plan to End TB aims to reach 90% of all people who need TB treatment, including 90% of people in key populations, and achieve at least 90% treatment success by 2030 (51). In 2016, out of 97,000 patients who were eligible for bedaquiline treatment only 4,300 were on bedaquiline treatment (41).

Understanding barriers is the first step towards creating policy solutions and recognizing best practices. Since improving access to MDR TB treatments requires greater coordination between stakeholders, understanding barriers from the perspective of each stakeholder is important. Furthermore, as a drug that was awarded the PRV, understanding policy barriers and potential or existing solutions provides a basis for further recommendations to improve access to future drugs that win the PRV for tropical diseases.

Based on the above rationale, this research has two specific aims:

- I) To understand policy and implementation access barriers to bedaquiline**
- II) To analyze policy barriers and provide recommendations to improve access to PRV awardee treatments for tropical diseases**

At present, to the best of my knowledge, there are no analyses of policy and implementation barriers for bedaquiline through analyzing perspectives of stakeholders.

## 2. Methods

### 2.1. Participants

Interviewees were categorized into four main stakeholder groups: I) Health related inter-governmental organizations, II) Humanitarian organizations, III) Corporate sector (i.e. manufacturer), and IV) State level stakeholders (i.e. clinicians, local implementers and advocates).

Stakeholders interviewed include WHO, Médecins Sans Frontières (MSF) Global Access Campaign, MSF Access Campaign – South Africa, clinical doctors, Janssen therapeutics (J&J). All participants were of management level. I conducted informal interviews in addition to the recorded qualitative interviews of stakeholders. Informal interviews included human rights TB access advocates, pharmaceutical industry representatives, state officials from India, and WHO technical officers of the “End TB” program. Table 2 provides a summary of key informant profiles and their responsibilities.

*Table 3: Key stakeholder informant profiles (descriptive data are not provided to maintain anonymity)*

<b>Key Informant (KI)</b>	<b>Current Position</b>	<b>Type of organization</b>	<b>Experience related to access</b>
KI1	Senior leadership position of the global program related to TB	Intergovernmental organization; End TB program	Leadership in setting norms, policies and standards in global TB control; a leading academic in the field of tuberculosis; recognized by many multi-lateral

			organizations as a leader in the field of TB control.
KI2	Leadership position in the global program related to access to medicines	NGO	Medical Advisor and access to medicine expert with extensive implementation and policy level experience. Expert in TB treatment and implementing access related programs
KI3	Research leadership position related to TB	Intergovernmental organization; End TB program	Academic and implementation researcher; program research leader; author of many peer reviewed articles on health systems, access and TB treatment
KI4	Leadership position in the access to medicine program of Southern Africa region	NGO	Access to medicine advocacy expert and a coordinator of the policy efforts with stakeholders such as government, companies and human rights organizations.
KI5	Leadership position in regional clinical and healthcare delivery in South Africa	NGO/Clinician	Practicing clinician focusing on MDR TB in rural regions of South Africa; author of many published peer reviewed articles related to TB; leading clinician of the regional clinic

KI6	Leadership position in all regional operations including access to medicines in South and East Africa.	NGO	Leading policy advocate for access to medicine; key national level and regional level expert on TB, access to medicine and health policy
KI7	Leadership position in access to medicines, drug regulation and policy advocacy	Drug manufacturing company	Co-author of a book related to drug regulation, access and pharmacovigilance; leader within the company on policy making discussions related to drug manufacturing, marketing and access

## 2.2. Setting

Key informant qualitative interviews focusing on each stakeholder were conducted in a) headquarters of the relevant global institutions in Geneva, Switzerland, b) local offices and clinics in Johannesburg, Cape Town and Khayelitsha, South Africa and c) via tele-conference.

## 2.3. Recruitment

The key informants were identified based on the responsibilities they held due to their official position and relevance to the research. All key informants were recruited from official interview requests via academic or professional contacts.

## **2.4. Data Collection**

Interviews followed a semi-structured format<sup>4</sup> based on questions developed through policy literature review and included topics of disease burden, health system capacity, policy level access barriers, implementation level access barriers and other access barriers. The interviews also aimed to understand existing and potential solutions to improving access to bedaquiline. Interviews were conducted between May 2017 to February 2018. Interviewees were provided an overview of the research prior to the interview, and all interviews were anonymized in data analysis. The interviews were recorded with the consent of the participants and were transcribed by hand. Seven recorded interviews were included from all stakeholders for qualitative analysis. As this was a perspective analysis of diverse stakeholders, I used recognition of common policy/implementation barriers and enablers, with no new barriers and enablers arising in the last interview, as the data saturation indicator. Data saturation was achieved during data collection (52).

## **2.5. Qualitative Data Analysis**

I thematic analysis of the qualitative data. I used NVivo software to conduct qualitative data analysis using codes to categorize data. Codes were generated from a deductive process based on existing policy literature on access to medicine. The coding process followed themes of access barriers, enablers, and recommendations. A separate section named descriptions was set up with codes for health systems and disease burden

---

<sup>4</sup> Interview guide for semi-structured interviews is provided under Appendix C.

using an inductive process. I added additional codes related to access barriers, enablers and recommendations after inter-rater reliability rating process (IRR). Independent researchers (two in total) analyzed the data separately for IRR, based on which kappa score was calculated. I consolidated data from each interviewee under themes of barriers, enablers and recommendations. As an additional layer, I categorized each of the barriers, enablers and recommendation as being at the policy or implementation level.

## **2.6. Kingdon's Three Streams model**

Kingdon's three streams model is used to organize and present the analyzed qualitative data. The three streams model categorizes the data under problem, politics and policy streams; the results also outline policy entrepreneurs and potential policy windows as outlined in the introduction (49). The qualitative data are consolidated with the existing academic literature, reports and advocacy material on relevant access barriers to bedaquiline.

## **2.7. Forcefield Analysis**

Results section further summarizes the supportive and opposing forces of access to bedaquiline using a FFA. The strategy and the components of the FFA are described above as per the introduction.

## **2.8. Literature review**

For literature review, I used the international public policy literature database, Scopus search engine to focus on policy on access to bedaquiline. Additionally, I searched websites of the WHO, STOP TB Partnership, MSF, RESIST-TB, Janssen (J&J), and GDF for reports and policy announcements. I also used Google scholar and Google search engine with the advanced setting of sites ending with '.org.'

## **3. Results**

### ***3.1. Categorizing results based on Kingdon's three streams model***

Based on Kingdon's three streams model, the results are categorized into I) problem stream, II) politics stream, and III) policy stream. The problem stream identifies the main barriers based on feedback from key informant interviews and existing literature; the politics stream examines the main political actors, their role in barriers and enablers towards access; the policy stream examines existing policy solutions and potential solutions based on recommendations by the stakeholders. In addition, to these three streams, the final subsection discusses policy entrepreneurs and potential policy windows.

#### **3.1.1. The Problem Stream**

The problem stream in this model aims to understand the existing problem related to barriers of access to bedaquiline. These barriers are examined at the global level and at the country level in South Africa. As described earlier, the model uses indicators and stakeholder feedback to define the problem further. The main statistical

indicator related to MDR-TB indicating the need for access to bedaquiline is the disease burden. As stated in the introduction, in 2016, MDR-TB/RR-TB incidence was estimated at 600,000 in total, with 490,00 (82%) accounted for by MDR-TB(38,39). Apart from the disease burden, the survival rate of MDR-TB patients on treatment regimen is at 50 percent (53). In 2016, 1.7 million people died from TB. Globally, less than 5 percent of the DR-TB patients have access to treatment regimens that include novel drugs bedaquiline (and/or delamanid) (41).

The key barriers for access to bedaquiline, as identified in this research are a) pricing and funding, b) health system barriers, c) drug registration related barriers and d) research evidence related barriers. Table 3 provides an overview of barrier categories followed by detailed results.

*Table 4: Overview of access barriers in the problem stream*

<b>Pricing and funding</b>	<b>Health system barriers</b>	<b>Drug registration related barriers</b>	<b>Research evidence related barriers</b>
Tier pricing not reasonable for middle income countries with high burden	Lack of diagnostics leading to lack of treatment	Countries unwilling to allow registration	Lack of phase III data resulting in strict WHO interim policy guidance
Donation program's sustainability related challenges	Countries not up to WHO recommended health system standards	Slow process due to lack of interest or conservative approaches	Due to lack of data countries are taking a conservative approach in providing enabling policies
Reduction in overall global health funds	High cost of equipment maintenance in monitoring		

Changing political environment that affect partnerships			
---	--	--	--

**Pricing and Funding**

Janssen (J&J) initially introduced a tiered pricing system in which low and lower middle-income countries received the lowest price. While the final pricing is determined by the company after regulatory approval, available pricing indicates a tiered pricing range of \$18,000 – \$30,000 for high income countries, \$1500 – \$3000 for middle income countries and \$900 for lower middle and low-income countries.<sup>5</sup> Since then, Janssen (J&J) has introduced a donation program in partnership with USAID and GDF (46).

Within this subsection of the problem stream, we present stakeholder feedback focused on suitability of tiered pricing as a solution to access challenges, sustainability of the donation program, the evolving political climate affecting the donation program and the effect of the overall funding climate on bedaquiline pricing.

Global implementers highlighted the tiered pricing as a problem, saying, *“The majority of cases of MDR-TB are in big countries, and so there was this idea that the cost could be decreased for the middle-income countries, that’s what I meant, big middle-income countries. So, the idea was why don’t you cut this price and you also make (the price of) middle income that suffer the majority of cases same level as low income” (K11)*. The tiered pricing system, as first

---

<sup>5</sup> A complete list of countries and the pricing they receive under tier pricing for bedaquiline is included under Appendix B.

introduced, posed the challenge of not recognizing the overall high cost that high burden countries could face. The top three countries in terms of highest number of patients are China, India and Russia. India received the lowest marked price of \$900 per course, per patient. China and Russia were marked to receive the drug at \$3000 per course, per patient (54).

There was public opposition to the tiered pricing system for bedaquiline, especially by non-governmental healthcare organizations (55). As indicated above, the donation program was introduced after the tiered pricing system. However, key informants questioned the donation program's ability to solve the challenge of access to bedaquiline from a sustainability perspective. Multi-level stakeholders questioned the sufficiency of the donation program for high burden countries, for example: *"But the donation is just a step. It's a drop in the ocean you know. India has 25-27% of the global TB burden. So, they need a little bit more than 400 treatments"* (KI2). Further, the intergovernmental stakeholders highlight the need for sustainability in existing solutions:

*"They said okay here's thirty thousand regimens for three years I believe. So, what is going to happen in year four? If India wants to buy, how much will they pay? Will they pay you know eight hundred dollars? Would they pay three thousand dollars? Would they pay one hundred dollars? These are the big issues that no one knows and so I anticipate that unless Johnson & Johnson is already thinking about all of this, I'm pretty sure they are thinking about what to do, it*

*would be complicated no? Because again you will enter into a phase of transition. You don't know if you have the drugs," (KI1).*

The donation program started in 2015 provides 30,000, 6-month treatments and is slated to end in 2019 (46). The data indicate that there have been 21,565 orders, including the pending orders, as of February 28, 2018 (56). The slow uptake of bedaquiline is flagged by the manufacturing stakeholder, elaborated under research and health system barriers. The manufacturing stakeholder highlighted that the current program design limitation was not solely due to company requirements: *"There are many reasons why our donation program had to be time limited and they were largely reasons governed by the USAID and the way as an agency they needed to budget and had their own timeline"* (KI7). As per the manufacturer, the future and sustainability of bedaquiline supply including the donation program, is also dependent on multiple factors. Company highlights the ongoing challenges below, indicating a potential evolution of the donation program. *"All of this is under negotiation right now and US political environment as you probably know is a very uncertain environment and there have been a lot of cuts proposed to US global health programs and so forth - we would not put anything in stone - I think the donation program as it exists at this moment may not exist in an year from now,"* (KI7).

Outside of high income countries, non-governmental stakeholders see a potential problem for countries with limited budgets. They highlight these challenges pointing out that *"budgets in places like Malawi and Mozambique is the biggest issue. They obviously get*

*most of it via donation, but as you know funding is an issue. GDF, Global Fund, PEPFAR, all of those places are cutting funding and benchmarking it," (KI6).*

### **Health System and Infrastructure Barriers**

Indicators of health system barriers are mainly in the sectors of diagnostics and monitoring. As per reports 40 percent of people living with TB are not diagnosed and in 2015, more than 4 million people were living with undiagnosed TB (41). *Out of Step, 2017* report which surveyed 29 countries point out only 15 countries have WHO recommended rapid Xpert diagnostic system (38,41). Out of the 15, only 7 have implemented the relevant rapid diagnostic policies widely (41). Stakeholder feedback below complement the indicator data and further elaborate on health system barriers and how they affect access to bedaquiline.

The need for improving diagnostics is a key part of the WHO strategy. Therefore, implementers, as indicated below, observe challenges in improving access due to lack of diagnostic facilities in many of the countries. As they point out diagnostics lead to better reporting which is key for better access.

*"However, going back to the burning question, how many cases are notified, reported by countries. Why is that? Because the accessibility testing is not widely available, or is not done regularly, systematically. Our strategy and what countries have signed off is that there should be universal accessibility testing, meaning everyone with TB like if you had in the United States, you would be tested for drug resistance," (KI1).*

Concerns of drug resistance have led to strict guidelines on monitoring by the WHO to improve pharmacovigilance (57). Additionally, as indicated in the introduction, since bedaquiline was approved based on Phase IIb trials further monitoring is required to understand side effects of the drug. These monitoring include monitoring of the QT interval of heartbeats via ECG, blood toxicity test and liver toxicity test (40).

Stakeholders point out that these requirements are a heavy ask from the country level healthcare system, especially in high MDR-TB countries.

*“Pharmacovigilance requirement was something that exceeded South Africa’s capacities from a practical stand point and from a cost stand point. It’s a warning signal because it is a challenge for any country - South Africa included - to figure out how to input this pharmacovigilance system that WHO rules mandate - again that is another limiting factor as we attempt to bring this drug to a patient,” (KI7).*

Even in South Africa where there is a high uptake of bedaquiline, stakeholders at the ground level point out that ECG equipment maintenance cost and the constant need for supplies have become an implementation challenge.

*“One of the obstacles is definitely still ECGs. Which I just wanted to touch on, because even though we’ve put a lot of money in the Western Cape into providing clinics with ECGs, but they’re expensive. And they always need paper and electrodes, and we’re constantly having problems with ECGs breaking and then patients having to go to other clinics for their ECGs, and*

*so I do think at a provincial, national and global level, we have to consider how much are we going to focus on ECGs,” (KI5).*

However, global implementation level stakeholders point out that pharmacovigilance and improving systems are vital in the fight against TB yet must be balanced with providing access to patients. Hence, countries should not approach this in a stepwise fashion.

*“But there needs to be some monitoring as well. At the same time in parallel, it doesn’t have to be one step leading to another, countries should be putting in place more robust systems to introduce bedaquiline and any other new drug properly, pharmacovigilance, reporting systems, guidelines, trainings, side effects reporting. So, this needs to be put in place at the same time as well, to anticipate wider use. We’ve been following the issues in India as well. There are concerns that if we don’t do this properly, we might actually lose the drug to resistance as well. Sooner than later. So, this is a real concern, but it doesn’t take away the need for those patients who need the drug now. So, again there needs to be a balance between immediate patient care, and proper pharmacovigilance,” (KI2).*

While the global TB program(GTB) of the WHO provide guidance and support challenges remain within country systems. As stakeholders point out active technical support is required in addition to policy guidance at the country level.

*“I think to go with interim policy for bedaquiline, delamanid, and also the WHO recommendation for the use of shorter regimen, we developed framework for active TB drug safety monitoring and*

*management. I think still in number of countries system is not available. Like what I just described. However, we don't hear from the countries. That's a key barrier for implementation. And part of my work now in the team is to support a country to set up that kind of system," (KI3).*

Drug procurement and managing of existing stocks also pose challenges to country level implementation teams. As observed by global implementation level stakeholders, the cost of having to move from one regimen to another with novel drugs results in waste. This excessive cost has budgetary implications for local level personnel.

*"And the third thing is related to the drug procurement. In some countries the problem happened when they already procured second line drugs for the old regimen and they fear about losing a lot of investment in the second line drugs because when you move to the new drugs or new regimens some drugs will not be used anymore, and that's a waste of the money. For example, I was in Nepal two months ago to help them with the plan to transition to the new drug and shorter regimen. The procurement officer, they very frightened because he worries about his role because he is the person who ordered the drug." (KI3)*

Additionally, bureaucratic challenges related to drug importing and procurement interfere with timely importing of drugs for treatment. In the case of India, as stakeholders point out WHO had to play a unique role to import bedaquiline in a timely manner. However, it remains to be seen if these exceptions related to supporting importing of the drug will become the norm.

*“So, WHO now intervened using WHO’s money, you know not Johnson & Johnson money or USAID but WHO money they had in the country office in India to pay for the import and the distribution which is in the range of five six thousand dollars altogether. It’s the first time. It might happen in some other countries that they come back and say look the drug is at the airport, but we need to import it officially, can you WHO please help? So, it could happen again, and this is actually one of the concerns of legal, I mean ‘is this becoming a rule?’ and in that case would all country offices be equipped to do that job? Have the money or the goodwill to do that thing?”*

(KI1)

### **Drug Registration Barriers**

Bedaquiline’s slow registration process has been highlighted by the non-governmental organizations (45). Stakeholder feedback highlight the need for registration and that the responsibility falls on the manufacturer, country administration and the relevant regulatory authority of each country.

Non-registration of bedaquiline, as stakeholders point out is a significant barrier, especially in high burden countries.

*“So bedaquiline now is officially registered in 19 countries but only 10 of those countries are on the WHO high burden list. Dossiers for registrations have been submitted for 19 other countries and is being rejected in 4 countries. So out of all those countries that bedaquiline is registered, the most successful in terms of its uptake and use is probably South Africa, and then maybe we have Georgia and maybe Russia as well,”* (KI2).

One reason cited by global implementation and technical support stakeholders is the length of the process, especially as the drug is new.

*“The survey by the Stop TB partnership and MSF I think they conducted a study in 2015, and one of the findings of the survey is among the high burden and high MDR-TB burden countries. And they report that more than 50% of the countries surveyed identified registration as a barrier for introduction of bedaquiline and delamanid. So I think that the situation is that’s a lengthy process for the registration of the drug. Specially the drug like new drug like bedaquiline in the countries,” (KI3).*

Other stakeholders point to the WHO interim policy guidelines for the use of bedaquiline for treatment issued based on phase IIb data as a reason for registration barriers (42).

*“The bulk of the registration challenges are situated around the WHO guideline - and almost total refusal on the part of even the high burden market to support our registration of the drug until those guidelines are changed,” (KI7).*

Global level implementing stakeholders explain that lack of registration at the country level leads to slow uptake of the drug despite the drug being free. They also point out that responsibility also lies with the country governments.

*“Our latest information we have is that only about 30% of the donated bedaquiline has been used and is again because there is no uptake at country level. It’s particularly free and WHO guidance is there, so in addition to this low uptake and concerns about enabling policies, there is also issues*

*about registration in countries. Some countries use WHO guidance. Bedaquiline is also on the WHO central medicines list, so some countries also use this as a proxy for importation into their countries, but some are very strict and they want the medicines to be registered in the country before it can be imported. So these are again country level barriers which go either way, if the owners want Janssen to register in the countries, then it's also for the countries to make registration processes smoother," (KI2).*

As local implementation level stakeholders point out, South Africa initially also faced the registration barrier which they eventually overcame via advocacy coalitions in addition to the support from the manufacturer.

*"So, there was some resistance put up by the regulatory authority just because I think it was something very new and it tends to be a somewhat conservative body that is cautious about trying things that are untested. So even though the government – the government being the department of health – had champions that really wanted to be at the forefront of new TB treatment. It took pressure from civil society on the Medicines Control Council (MCC) and I think a lot of academic - I mean we're very blessed in South Africa to have so many people that are really top of their field in TB, and so I think having that academic cohort of people, as well as very active civil society that could push combined with the political will, it eventually brought the MCC around to cooperating and be a bit more flexible," (KI6)*

## **Research related barriers**

WHO due to the unavailability of the phase III research data has only issued interim policy guidance on the use of bedaquiline (42). Furthermore, registration barriers also exist due to lack of research data. At the global level, stakeholders point out that the lack of phase III data has resulted in lack of knowledge with regard to drug interaction.

*“You know the treatment regimen for TB is normally composed by 5, 7, or 8, many drugs together and it’s a different combination of the drugs. We don’t know very well how interaction between the drugs and specially when bedaquiline use in the same regimen as a drug with similar toxicity. For example, when you use fluoroquinolone, clofazimine, that also has cardiac toxicity similar to bedaquiline. So that’s why we have in the interim policy, one condition is that we need to monitor the patient carefully,” (KI3).*

The reasons behind delayed phase III trial as per corporate stakeholders are partly due to the criticism received by the FDA and the manufacturer due to the approval of the drug based on phase IIb data. *“That external criticism fired at FDA, certainly fired at us, had the unintended effect of slowing phase III discussions, clinical trial designs, structuring and so forth. We have the full-fledged research up and running at the moment and we have 10 years of research commitment going forward,” (KI7).*

Global non-governmental stakeholders express doubt of manufacturers continuing phase III trials in the traditional sense: *“Where we are now with the use of bedaquiline is, I’m not convinced Janssen is going to change their mind about doing further trials. So, the only way*

*we can get more information on the use of this medicines is through programmatic use, and the more countries use this medicine, the more information we get to feed into the knowledge pool,”* (KI2).

Manufacturing stakeholders also point out that the ‘real world evidence’ should be a new standard in drug approval processes. ‘Real world evidence’ is data derived from real life clinical practices on potentially riskier drugs (58).

*“Real world evidence is important [to] look beyond expensive, cumbersome phase III trials in a traditional sense, especially when phase III trials are approached with regulatory conservatism - there is an opportunity for real world evidence to maybe set a standard,”* (KI7).

However, at the ground level in South Africa, despite the clinical experiences indicating less adverse reaction to the drug than expected, stakeholders believe proper monitoring should still be performed. *“Our clinical experience is that bedaquiline doesn’t have very many adverse events and I know there’s a lot of concern around you know, there not being phase III trials and QT intervals. In our experience on the ground we don’t see a lot of QT prolongation. I think ideally until we have those phase III trials, ideally we should be monitoring QTs,”* (KI5).

However, as indicated under health system and infrastructure barriers extensive monitoring places a significant demand on the health system. All stakeholders cited political will as a key factor affecting all the barriers listed above. Aspects related to political will are further examined under the political stream of this model.

### 3.1.2. Political Stream

The stakeholders identified in the data collection process are categorized by two main levels: I. Global level II. Country level. Some stakeholders function at the global level and some at the country level. WHO and similar organizations have their main mandate at the global level, therefore are categorized at the global level. Following table provides an overview of the main actors and their respective categories.

*Table 5: Overview of political actors related to access provision to bedaquiline*

Global Level	Country Level
WHO	Country Government
Global Drug Facility	Drug Regulatory Body (i.e. FDA, MCC)
USAID	Clinicians
	Local Civil Society
Drug manufacturer	
Researchers	
Global NGOs (i.e. MSF)	
STOP TB Partnership	

WHO through its global, regional and country offices and technical experts aim to provide guidance for procurement to use of drugs. Coalitions such as STOP TB Partnership consists of over 1500 members including governments, technical organizations, funders, researchers and foundations (59). While most of the key actors listed above belong to the STOP TB Partnership, to assess each actor's role in providing access to bedaquiline, they need to be considered individually.

As South Africa remains a rare success story, using a successful political process centered on coordination between multi-level stakeholders. Figure 2 maps the collaboration between all stakeholders to overcome barriers to access to bedaquiline. Figure 2 illustrates the political process through which South Africa was successful relative to other countries with low or no access to bedaquiline.

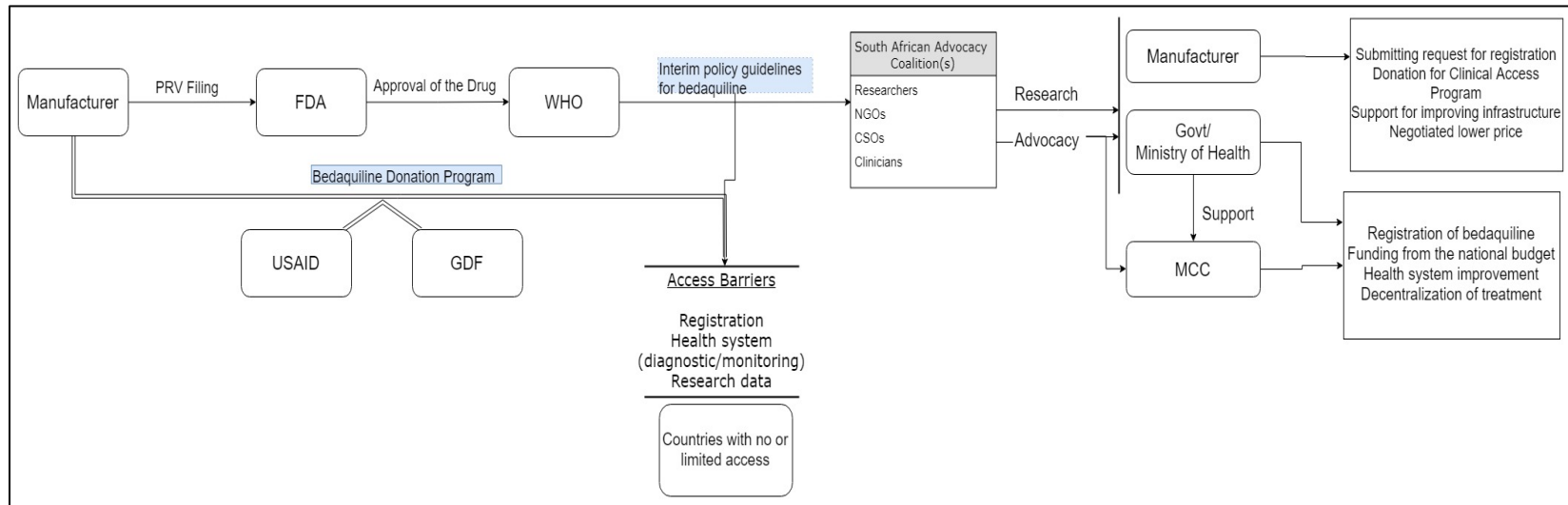


Figure 2: Stakeholder interaction map in providing access to bedaquiline in South Africa

As illustrated in figure 2, research and advocacy support by academics within the country, NGOs and civil society organizations, combined with the responsiveness of the government have provided successful results in South Africa. Both local stakeholders and manufacturer in interviews cited political will of the government as a key contributory factor. This coordinated effort was vital in improving access to bedaquiline. Additionally, figure 2 illustrates, multi-level involvement of the manufacturer, thus highlighting the important role the manufacturer plays in providing access.

### **3.1.3. Policy Stream**

After the approval of bedaquiline by the FDA in 2012, two main policies directly impacted access to bedaquiline at the global level (60). First, was the WHO interim policy guidance on the use of bedaquiline to treat MDR-TB in 2013; second, was the inclusion of bedaquiline in the essential medicines list by the WHO in 2015 (42,61). At the regional level the approval of bedaquiline by the European Union Medicines Agency (EMA) in 2013 positively impacted access to bedaquiline (62). Additionally, as confirmed by implementers during this research approval of bedaquiline by the MCC of South Africa in 2014 also positively impacted access to bedaquiline in East and Southern Africa (63). The policy guidance by the WHO for Xpert rapid diagnostic system for MDR-TB in 2011 preceded bedaquiline approval yet had an impact on access to bedaquiline (41). This impact was due to the significant role diagnostics play in treating

MDR-TB (38). Furthermore, outside of regulatory approvals and policy guidelines by global bodies, the decision to initiate the donation program in 2015 by Janssen (J&J) is also a key factor in the policy stream (46). As per the feedback from stakeholders and the current national policy South Africa opted out of the donation program despite being eligible, in favor of having a more sustainable approach to providing access to bedaquiline (64). Figure 3 provides a summary timeline of policies that affect access to bedaquiline.

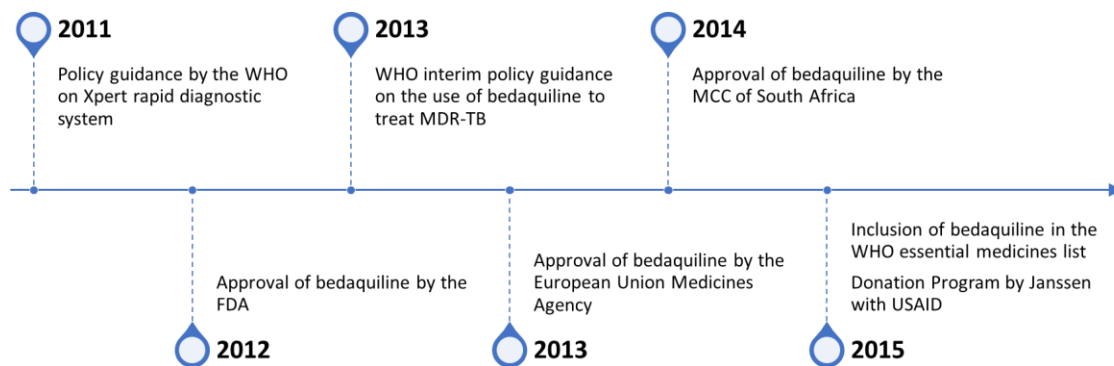


Figure 3: Timeline of key policies related to bedaquiline access

As per the latest TB related local policy survey report of 29 countries, bedaquiline has been included in the national guidelines of 23 countries. However, only 7 countries include bedaquiline in their national essential medicines list (38,41). The stakeholder data reviewed above in the problem stream, and monitoring data indicate that the conservative approach by countries when implementing newer MDR-TB drug regimens have led to low uptake of bedaquiline (38,41,45). Figure 4 summarizes the key findings according to the three streams outlined above.

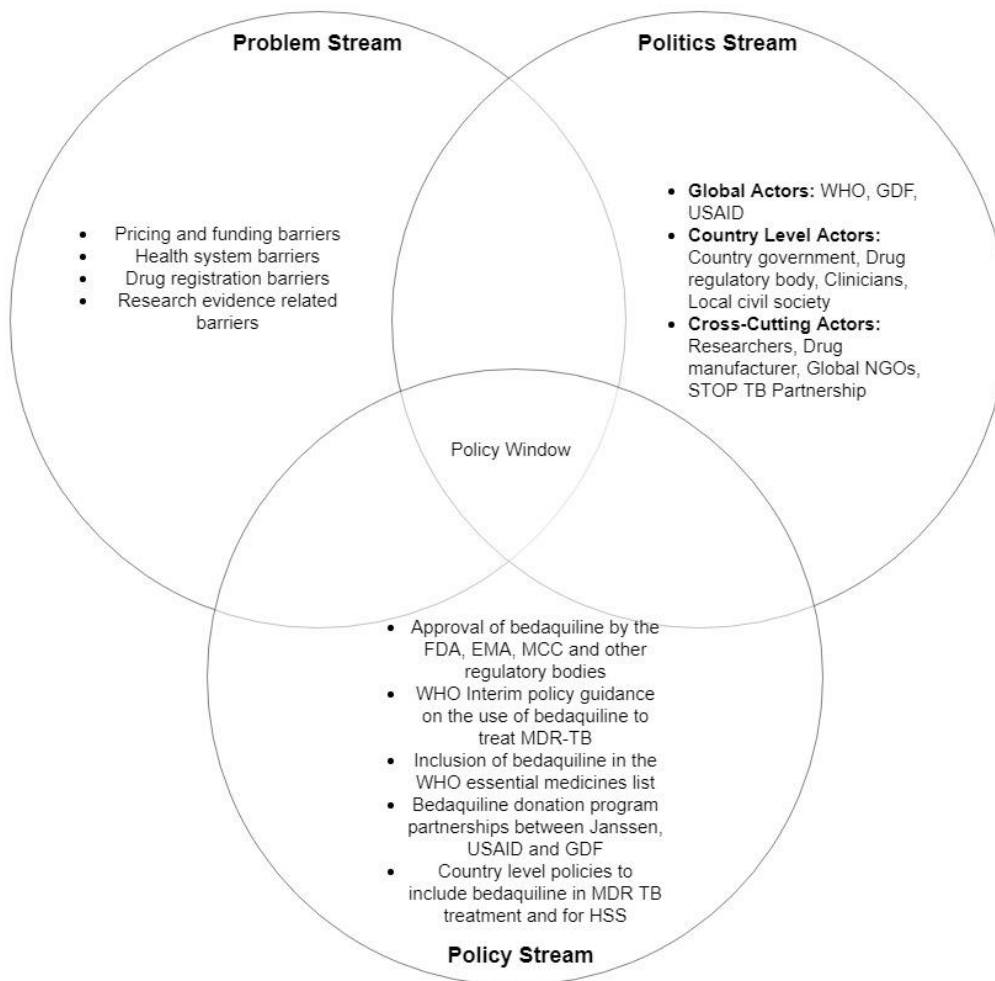


Figure 4: Summary of policy and implementation barriers to bedaquiline through Kingdon's three streams model

### 3.1.4 Policy Entrepreneurs and Policy Windows

**Policy Entrepreneurs:** WHO, Janssen therapeutics (J&J), local and global NGOs.

Since access to bedaquiline remains low, it can be argued that the three streams above have not aligned with each other to make access to bedaquiline a global priority. Based on the political stream we can observe that WHO and the manufacturer has a key role to play in improving access to bedaquiline. Hence, they are two of the three main policy entrepreneurs. The third policy entrepreneur are global and local NGOs. As figure 2 and

figure 4 indicate without the advocacy push from these stakeholders remain vital to improve access to bedaquiline. Additionally, the advocacy, research and clinical support by non-governmental organizations remain a vital part of MDR-TB treatment (45,53).

**Policy Windows:**

There are two main prospective policy windows identified in this research:

- a) The conclusion of the Standardized Treatment Regimen of Anti-TB Drugs for Patients with MDR-TB (STREAM) trial in 2021
- b) The first ever high-level UN meeting on TB in 2018

The STREAM trial is the world’s first multi-country randomized clinical trial to test the efficacy, safety and economic impact of shortened MDR-TB treatment regimens. The trial was initiated by the International Union Against TB and Lung Disease (The Union) with its main partner, the Medical Research Council Clinical Unit and University College London (65). Currently, phase III trials for a 9 month regimen with bedaquiline are being conducted under the STREAM trial slated to conclude in 2021 (66). Many of the stakeholders both at the global and the local level indicated that the ongoing STREAM trial data will end the “wait and see” approach by the countries. Additionally, stakeholders indicated that the results of the STREAM trials will be instrumental in expanding WHO guidelines and allow wider use of bedaquiline.

The high-level UN panel meeting decided through the UN General Assembly Resolution A/7/L/41 is scheduled for September 2018 in New York (67). The high-level panel is expected to improve political commitment of high burden countries to combat

MDR-TB by improving health systems and introducing novel drugs such as bedaquiline (68). Continuous evaluation reports by the WHO of the available evidence on the use of bedaquiline which have indicated high efficacy will be useful in terms of improving political commitment at the meeting (69).

### 3.2. Understanding access barriers via forcefield analysis

As per the introduction FFA aims to understand the supporting and opposing forces in achieving an objective. The objective in this research is improving access to bedaquiline. Understanding these barriers further in conjunction with the opposing forces will also provide a better idea as to how to address the existing challenges. Figure 5 depicts the results of the forcefield analysis.

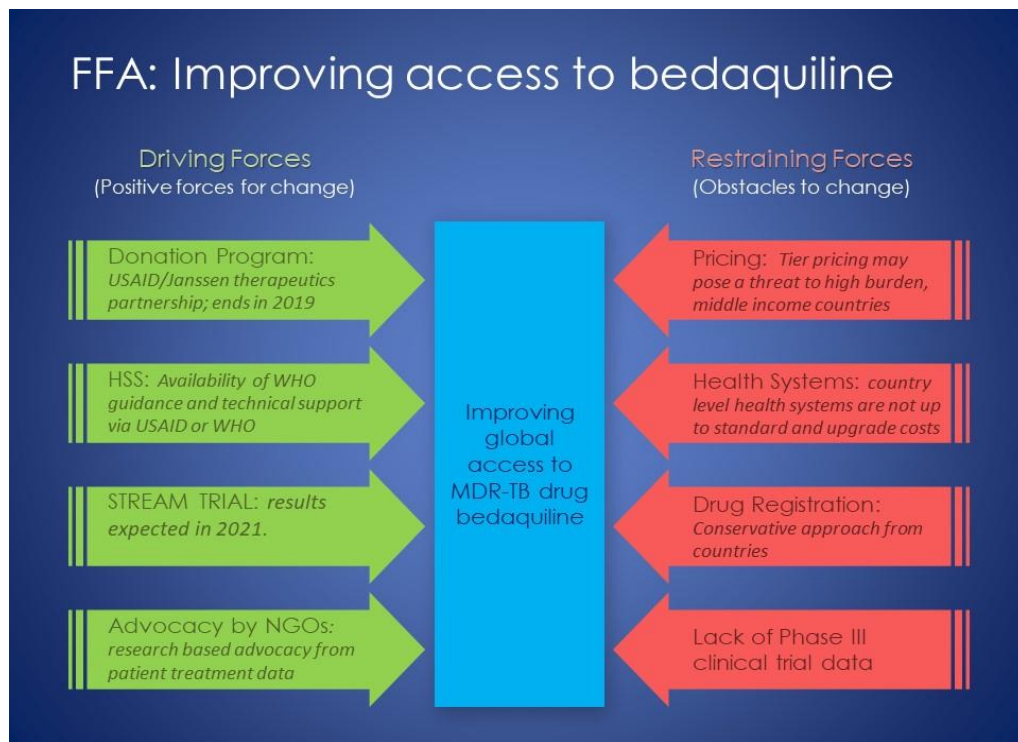


Figure 5: Forcefield analysis of providing access to bedaquiline

As this research aims to propose avenues to improve the access to the PRV winners for tropical diseases, understanding the manufacturer’s role in facilitating access to bedaquiline is vital. Thus, combined results from Kingdon’s three streams and forcefield analysis, are further categorized below in table 6. This categorization is based on the amount of control that the company had over the existing barriers.

Table 6: Summary of control manufacturer has over each access barrier

Access barrier	Level of control the manufacturer has over each access barrier		
	High	Partial	Low or none
Pricing	Has high control		
Sustainability of the donation program		Has partial control as countries are also responsible. However, can be overcome through different pricing models.	
Political climate affecting the donation program			Has very little control as the power lies with the U.S. government
Countries not meeting WHO guidance on health systems		This is mostly the country’s responsibility. However, the company can provide technical and funding support as they have done in South Africa.	
Drug registration barrier		Has partial control as the company is required to file dossiers to be approved by each country’s regulatory body	
Lack of research data (phase III trials)	Has high control as the company usually invests in		

	<p>phase III trials prior to approval. However, the initial phase III trials required recruitment for 24 months. The length of trials acted as a barrier. Currently, clinical trials have shifted to new 9-month regimen.</p>		
--	---	--	--

## 4. Discussion

### 4.1. Implications for Policy and Practice

#### 4.1.3. Necessity for an access plan by the manufacturer

The working definition of access in this research is *availability, affordability of drugs and medical technologies that have prescribed quality standards, for rational use with sufficient services to ensure freedoms, entitlements and inclusions of right to health in each population.*

The goal set under the Global Plan to End TB is to reach 90% by 2030 of those who require treatment for TB (51). As of 2016, only 5 percent of eligible MDR-TB patients had access to both delamanid and bedaquiline (41). Based on the results analysis we observe that many significant barriers to access can only be overcome through a collaborative effort. This idea is supported by arguments of access being inclusive of political, economic, social and cultural processes (9). This argument is further highlighted in the results of this research where multiple stakeholders are required to overcome access to

bedaquiline barriers. Therefore, the manufacturer or the company is not solely responsible for all the access barriers of providing a drug to communities in LMICs. However, as per the analysis in Kingdon's three streams model, the manufacturer as a 'policy entrepreneur' has a significant role to play in facilitating access.

Further demarcation of access barriers based on company control in the FFA indicates that out of the main barriers, pricing and research barriers are directly under the control of the manufacturer. When considering registration, the country regulatory body and the manufacturer share the responsibility. However, in health infrastructure improvement related to the use of the manufactured drug, the company can opt to support to develop health system infrastructure. In an ideal setting a country will improve its health system to improve access to medicine. Yet, in LMICs, this is not always possible, thus private sector partnerships are essential (70).

Therefore, from a practical stand point we can argue that the company has a role to play in improving health systems related to the use of its manufactured drug, at the minimum. Janssen therapeutics (J&J) continues to be involved in improving the health system infrastructure in South Africa to be able to administer bedaquiline effectively and to avoid building resistance (71). As all the drugs under the PRV are developed for diseases that are in LMICs, manufacturer commitment to facilitate access is vital, to reduce the impact of the barriers outlined above (22). Thus, reforming the PRV to

require the company to provide an access plan is overdue (20,21,72,73). The access plan can be based on best practices or novel methods to increase access.

When considering the PRV winning drugs for tropical diseases we can observe that many of the access barriers such as pricing, registration and infrastructure are common (25,26,31). While these barriers are common, different manufacturers have found innovative and diverse solutions to resolve the access challenges (19,25,33). In the case of Novartis the solution was a partnership with the WHO for distribution support (25). Insud Pharma (Chemo Research) partnered with local and global not-for profit organizations to facilitate access (19,25,33). Janssen therapeutics (J&J) partnered with USAID to provide technical support and with GDF for distribution (46). Thus, many of these solutions which are independently devised, focus on leveraging expertise to find viable access solutions through partners. From the results of this research we can observe that all 'driving forces' of access provision in the FFA for bedaquiline require partnerships.

Based on the access challenges that PRV winning tropical disease drugs face and observing their solutions, an access plan is required to improve access to the above-mentioned drugs. This access plan based on results and common barriers identified in the discussion should include plans to address i) pricing and distribution barriers ii) registration barriers iii) research data barriers. Four processes can be suggested to add an access plan to the PRV winning drugs for tropical diseases. First, the FDA could

require an access plan from the manufacturer (addressing above mentioned three components), with the PRV application. Under the first option the FDA will monitor the progress of the access plan. If the manufacturer does not abide by the access plan the FDA will then have to enforce penalties. A second option is for the FDA to require an access plan with the PRV application but not monitor it or enforce penalties. Instead, the FDA will make the access plan public, making it available for organizations such as the Access to Medicine Index to evaluate the progress. Access to Medicine Index already monitors the complete drug portfolios of many drug companies including Johnson and Johnson. The latest report cards on manufacturers indicate areas the companies have improved since last report and areas for potential improvement (74). A third option, which already exists, is to allow the company to address the access plan components via its own strategies such as lower pricing for bulk orders (Impavido and VaxChora), free distribution (Coartem) or use of donation programs (Sirturo). These methods, however, have already been tried with lower level of success. A fourth option is for companies to voluntarily build PDPs with NGOs and commit a portion of PRV earnings towards provision of access. Provision of access include addressing the access components outlined above. As mentioned earlier Insud Pharma, DNDi and Mundo Sano is an example of this model (19,75). Another example is the collaboration between PATH, Global Health Investment Fund, and life science investment firm, Clarus to develop improved treatment for hookworm infections (76). The investment firms, provide

funding expecting a PRV monetization based return, and PATH will use a portion of the PRV monetization to facilitate access (76).

#### **4.1.3. The role of the regulator**

However, when requiring an access plan, it is also important to consider the agency or institution expected to enforce the regulatory requirement. In this case as the FDA is responsible for issuing PRVs, the responsibility of requiring an access plan naturally falls on the FDA (14,20). Currently, FDA do not possess any regulatory measures or the man power to evaluate access plans and to ensure accountability (77). Thus, one option is to outsource both the evaluation of a submitted access plan and monitoring the fulfillment of such a plan. FDA can outsource to either their partners who has the expertise within the US government (USAID or NIH) or to outsider expert groups. These expert groups include expert coalitions around neglected tropical diseases, global non-profit organizations with expertise in access provision in LMICs. As recognized in the 'politics stream' in the Kingdon model related to bedaquiline NGOs are also 'policy entrepreneurs' for access facilitation. Therefore, NGOs are well suited to partner with to facilitate access. However, the current funding climate for global health from the U.S. government, may pose challenges for outsourcing (78). The prospect of outsourcing to other partners also require a higher-level coordination and effort which may not be currently available from within the U.S government.

As a second option, the FDA can require an access plan and make it publicly available for scrutiny. This will increase accountability from the side of the manufacturer to avoid public criticism. Companies can also use this opportunity to illustrate their commitment to increasing access, thereby also improving its public profile. Organizations such as Access to Medicine Index have already illustrated that public evaluation can be a factor in improving access related practices of companies. However, the idea of a publicly available access plan requirement may not be well received from industry as it opens the manufacturers up for criticism based on a prospective access plan.

#### ***4.2 Strengths and Limitations***

The main strength of this research is the inclusion of multiple stakeholder perspectives combined with research literature and advocacy material on policy and implementation level challenges to access. This method allowed me to understand policy and implementation barriers holistically and provide a balanced output. Another strength of this research is the use of Kingdon's three streams model and FFA to organize results. The model was an important tool to separate multi-faceted access barriers improving clarity of the research results. Through the FFA, the I was able to synthesize results and orient them to better implicate required policy changes.

The weaknesses of this research include the limited sample of interviewees, as many interviewees preferred informal interviews over recorded interviews. Further, as the

research topic was considered as a sensitive topic by some stakeholders, some information was withheld or not explicitly stated. This limitation was addressed to an extent by filling the gap of information via research literature or publicly available advocacy material.

## **5. Conclusion**

Therefore, considering the future voucher winning drugs for tropical diseases under the PRV, the four processes outlined above can be used as methods to improve access. However, since the FDA do not have the authority to enforce penalties or to monitor an access plan the first option becomes impractical under the present legal framework. The third and fourth options are voluntary efforts by companies which can still leave the access gap that we experience today. Therefore, the second option of requiring an access plan with the PRV application and making it available for public evaluation remains the best option moving forward. In order to produce a credible public evaluation of an access plan by a manufacturer for a PRV winning drug for tropical diseases, existing algorithms can be customized in partnership with organizations such as Access to Medicine Index.

Therefore, requiring an access plan as part of the PRV application and making the plan available for public scrutiny should be a starting point for an amendment of the section 524 of the Food and Drug Cosmetic Act.

## **Appendix A: List of PRV Eligible Tropical Diseases**

Following information on tropical diseases eligible for the priority review voucher is based on Tropical Disease Priority Review Vouchers Guidance for Industry, issued on October 2016, prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA).

Information below is relevant to the implementation of section 1102 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), which added section 524 to the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360n). Section 524 authorizes the FDA to award priority review vouchers to sponsors of certain tropical disease product applications that meet the criteria specified in that section.

### **Diseases are considered tropical diseases for priority review voucher purposes**

A tropical disease is any of the following diseases (see section 524(a)(3) of the FD&C Act):

- Tuberculosis
- Malaria
- Blinding trachoma
- Buruli Ulcer
- Cholera
- Dengue/Dengue haemorrhagic fever
- Dracunculiasis (guinea-worm disease)
- Fascioliasis
- Human African trypanosomiasis
- Leishmaniasis
- Leprosy
- Lymphatic filariasis
- Onchocerciasis
- Schistosomiasis
- Soil transmitted helminthiasis
- Yaws
- Filovirus Diseases
- Zika Virus Disease
- Any other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations, designated by order of the Secretary.

### **Adding a new disease to the PRV eligible tropical diseases**

Section 524 allows the FDA to designate by order any other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations. On August 20, 2015, the FDA issued the final order “Designating Additions to the Current List of Tropical Diseases in the Federal Food, Drug, and Cosmetic Act” in the Federal Register (80 FR 50559). The order sets forth the criteria for adding a disease to the list, added Chagas disease and neurocysticercosis to the list, and opened a docket to receive recommendations from the public for future additions to the list (FDA-2008-N-0567). FDA will review these recommendations and make future additions to the list, as appropriate.

### **Amendment of the PRV to include Ebola as an eligible disease**

Section 524 of the FD&C Act subsequently was amended December 16, 2014 (Public Law 113-233) to include filoviruses (family of viruses that include Ebola) as a PRV eligible disease. The amendment is as follows:

“Public Law No: 113-233 (12/16/2014)

**(This measure has not been amended since it was introduced. The expanded summary of the Senate reported version is repeated here.)**

Adding Ebola to the FDA Priority Review Voucher Program Act - (Sec. 2) Amends the Federal Food, Drug, and Cosmetic Act to add filoviruses, a family of viruses that includes the Ebola virus, to the list of tropical diseases under the priority review voucher program, which awards vouchers to sponsors of human drug applications that are approved to prevent or treat tropical diseases. (A voucher entitles the holder to have a future human drug application acted upon by the Food and Drug Administration (FDA) within six months.)

Changes the process by which infectious diseases that do not significantly impact developed nations and disproportionately affect poor and marginalized populations can be designated as tropical diseases from rulemaking to order of the Secretary of Health and Human Services (HHS).

Allows priority review vouchers to be transferred between sponsors of human drug applications any number of times.

Reduces from 365 days to 90 days the advance notice required before submitting a human drug application subject to a priority review voucher.”

## Appendix B: Publicly available tier pricing data by Janssen therapeutics (J&J)

Source: Who Model List of Essential Medicines Application: Bedaquiline

Country	Price
<i>High Income Countries</i>	
Austria	EUR 22,585
Belgium	EUR 23,350
Czech Republic	EUR 22,191.60
Denmark	EUR 31,388.81
Finland	EUR 28,105.40
France	EUR 23,428.12
Germany	EUR 32,998.15
Italy	EUR 22,228.81
Luxembourg	EUR 23,350
Norway	EUR 22,664
Romania	USD 15,375
Russia	USD 2,800
Slovakia	EUR 22,191.60
Slovenia	EUR 24,768.13
Sweden	EUR 23,065.43
The Netherlands	EUR 23,350
The United Kingdom	GBP 18,700
United States of America	USD 30,000
<i>Low &amp; Middle Income Countries</i>	
Albania, Algeria, Azerbaijan, Belarus, Bosnia & Herzegovina, Brazil, Colombia, Ecuador, Kazakhstan, Serbia, Lebanon, Libya, Palau, Peru, Tunisia, TFYR Macedonia, Turkmenistan	USD 3,000
Thailand	USD 1,424.92

<p>Afghanistan, Algeria, Angola, Armenia, Bangladesh, Benin, Bhutan, Botswana, Burkina Faso, Burundi, Cambodia, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, Cote d'Ivoire, Democratic People's Republic of Korea, Democratic Republic of the Congo, Djibouti, Egypt, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Georgia, Ghana, Guinea, Guinea-Bissau, India, Indonesia, Kenya, Kiribati, Kyrgyzstan, Laos, Liberia, Madagascar, Malawi, Maldives, Mali, Marshall Islands, Mauritania, Mauritius, Micronesia, Moldova, Mongolia, Morocco, Mozambique, Myanmar, Namibia, Nepal, Niger, Nigeria, Pakistan, Papua New Guinea, Philippines, Rwanda, Samoa, Sao Tome &amp; Principe, Senegal, Seychelles, Sierra Leone, Solomon Islands, Somalia,</p>	<p>USD 900</p>
--	----------------

## Appendix C: Interview guide for semi-structured interview questionnaire

This guide is for semi-structured interviews, while these questions are used as starting points, more questions were asked based on the answers by the interviewees.

1. Can you give me brief idea about the disease burden of MDR-TB and the role that bedaquiline plays as a treatment?
2. In terms of access barriers to bedaquiline, what are the main barriers that you recognize in terms of policy and implementation?
3. Out of these barriers what are the global and what are the local level (country level) barriers?
4. Can you explain how the donation program works/helps and the strengths/weaknesses of this program?
5. What facilitators or enablers do you think exist in terms of bedaquiline to improve access at the policy and implementation level?
  - a. By countries
  - b. Company
  - c. WHO etc.
  - d. NGO
6. At the policy and implementation level what steps can the following stakeholders take to improve access?
  - I. What steps can the government take?
  - II. What steps can WHO take?
  - III. What steps can the NGO community take?
  - IV. Are there any other stakeholders that I did not mention –
7. What policy and implementation level gap do you see in terms of bedaquiline that is hindering its access to patients the most?
  - a. What recommendations would you have to fix them?

8. What are general barriers that are affecting access to medicine at large that we should prioritize?
9. What solutions can we explore in terms of policy recommendations to improve access to medicine?
10. What do you think of incentive mechanisms such as the Priority Review Voucher?
11. Do you have suggestions to improve access to voucher winning drugs such as bedaquiline?

## References

1. World Health Organization. The Constitution of the World Health Organization [Internet]. World Health Organization. 2006 [cited 2018 Feb 11]. Available from: [http://www.who.int/governance/eb/who\\_constitution\\_en.pdf](http://www.who.int/governance/eb/who_constitution_en.pdf)
2. The United Nations. International Covenant on Economic, Social and Cultural Rights [Internet]. 1966 [cited 2018 Feb 11]. Available from: <http://www.ohchr.org/EN/ProfessionalInterest/Pages/CESCR.aspx>
3. The United Nations. Universal Declaration of Human Rights [Internet]. The United Nations. 1948 [cited 2018 Feb 11]. Available from: [http://www.un.org/en/udhrbook/pdf/udhr\\_booklet\\_en\\_web.pdf](http://www.un.org/en/udhrbook/pdf/udhr_booklet_en_web.pdf)
4. Office of the High Commissioner of Human Rights. The Right to Health - Fact Sheet [Internet]. Office of the High Commissioner of Human Rights. 1944 [cited 2018 Feb 11]. Available from: <http://www.ohchr.org/Documents/Publications/Factsheet31.pdf>
5. The United Nations. Goal 3 :. Sustainable Development Knowledge Platform [Internet]. 2015 [cited 2018 Feb 11]. Available from: <https://sustainabledevelopment.un.org/sdg3>
6. United Nations Development Programme. Indicators for Monitoring the Millennium Development Goals: Definitions, Rationale, Concepts and Sources [Internet]. 2003 [cited 2018 Feb 11]. Available from: <http://mdgs.un.org/unsd/mdg/Resources/Attach/Indicators/HandbookEnglish.pdf>
7. The UN Secretary General's High Level Panel on Access to Medicines. Report of the United Nations Secretary General's High Level Panel on Access to Medicines [Internet]. 2016 Sep [cited 2018 Feb 11]. Available from: <http://www.unsgaccessmeds.org/final-report/>
8. World Health Organization. MONITORING THE BUILDING BLOCKS OF HEALTH SYSTEMS: A HANDBOOK OF INDICATORS AND THEIR MEASUREMENT STRATEGIES [Internet]. World Health Organization; 2010 [cited 2018 Feb 12]. Available from: [http://www.who.int/healthinfo/systems/WHO\\_MBHSS\\_2010\\_full\\_web.pdf?ua=1](http://www.who.int/healthinfo/systems/WHO_MBHSS_2010_full_web.pdf?ua=1)
9. Frost L, Reich M. Access: how do good health technologies get to poor people in poor countries? Harvard Center for Population and Development Studies; 2008.
10. Flynn S, Hollis A, Palmedo M. An Economic Justification for Open Access to Essential Medicine Patents in Developing Countries. *Artic Law Rev Acad J* [Internet]. 2009 Jan 1; Available from: [http://digitalcommons.wcl.american.edu/facsch\\_lawrev/211](http://digitalcommons.wcl.american.edu/facsch_lawrev/211)

11. McIntyre D, Thiede M, Dahlgren G, Whitehead M. What are the economic consequences for households of illness and of paying for health care in low- and middle-income country contexts? *Soc Sci Med* 1982. 2006 Feb;62(4):858–65.
12. World Health Organization, Health Action International. Measuring medicine prices, availability, affordability and price components - Second Edition [Internet]. 2008 [cited 2018 Mar 14]. Available from: [http://www.who.int/medicines/areas/access/OMS\\_Medicine\\_prices.pdf](http://www.who.int/medicines/areas/access/OMS_Medicine_prices.pdf)
13. McCoy D, Chand S, Sridhar D. Global health funding: how much, where it comes from and where it goes. *Health Policy Plan*. 2009 Nov 1;24(6):407–17.
14. Ridley DB, Grabowski HG, Moe JL. Developing Drugs For Developing Countries. *Health Aff (Millwood)*. 2006 Mar 1;25(2):313–24.
15. Issuance of Priority Review Voucher; Rare Pediatric Disease Product [Internet]. *Federal Register*. 2017 [cited 2018 Feb 12]. Available from: <https://www.federalregister.gov/documents/2017/09/11/2017-19130/issuance-of-priority-review-voucher-rare-pediatric-disease-product>
16. Commissioner O of the. Medical Countermeasures Initiative - Guidance and Other Information of Special Interest to MCM Stakeholders [Internet]. [cited 2018 Feb 12]. Available from: <https://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/ucm262917.htm>
17. Priority Review Voucher [Internet]. [cited 2018 Feb 13]. Available from: <http://priorityreviewvoucher.org/>
18. Ridley DB, Régnier SA. The Commercial Market For Priority Review Vouchers. *Health Aff Chevy Chase*. 2016 May;35(5):776-783,1-11.
19. DNDi. DNDi, Mundo Sano and Chemo team up to register benznidazole in US and Latin America – DNDi [Internet]. [cited 2018 Feb 13]. Available from: <https://www.dndi.org/2016/media-centre/press-releases/partnership-register-benzindazole-usa-latinamerica/>
20. Ridley DB. Priorities for the Priority Review Voucher. *Am J Trop Med Hyg*. 2017 Jan 11;96(1):14–5.
21. American Thoracic Society, Global TB Alliance, Medecines Sans Frontieres, Sabin Vaccine Institute, Center for Global Health Policy, Treatment Action Group, et al. Open Letter to the U.S. Senate HELP Committee Leadership: Suggestions to Fix the FDA PRV

- for Neglected Diseases [Internet]. [cited 2018 Feb 13]. Available from:  
[https://www.dndi.org/wp-content/uploads/2015/11/JointOpenPRV-Letter-to-HELP-Committee\\_web.pdf](https://www.dndi.org/wp-content/uploads/2015/11/JointOpenPRV-Letter-to-HELP-Committee_web.pdf)
22. Arnold CG, Pogge T. Improving the Incentives of the FDA Voucher Program for Neglected Tropical Diseases. *Brown J World Aff Provid.* 2015 Spring/Summer;21(2):224–35.
  23. Investors: Gilead SEC Filings [Internet]. [cited 2018 Feb 13]. Available from:  
<http://investors.gilead.com/phoenix.zhtml?c=69964&p=irol-SECText&TEXT=aHR0cDovL2FwaS50ZW5rd2l6YXJkLmNvbS9maWxpbnmcueG1sP2lwYWdlPTExMzY5MjQ2JkRTRVE9MCZTRVE9MCZTUURFU0M9U0VDVEIPTI9FTIRJUKUmc3Vic2lkPTU3>
  24. World Health Organization. Global supply of artemether-lumefantrine before, during, and after the Memorandum of Understanding between WHO and Novartis [Internet]. 2011 [cited 2018 Feb 13]. Available from:  
[http://www.who.int/malaria/areas/treatment/MoU\\_termination\\_report\\_may2011.pdf](http://www.who.int/malaria/areas/treatment/MoU_termination_report_may2011.pdf)
  25. Hamed K, Grueninger H. Coartem?: a decade of patient-centric malaria management. *Expert Rev Anti-Infect Ther Lond.* 2012 Jun;10(6):645–59.
  26. Patient Access to Miltefosine in Developing Countries Not Secure Despite Award of US FDA Priority Review Voucher Sold for USD 125 Million [Internet]. [cited 2018 Feb 13]. Available from: <http://www.msfaccess.org/resources/press-releases/2335>
  27. Doshi P. US incentive scheme for neglected diseases: a good idea gone wrong? *BMJ.* 2014 Jul 21;349:g4665.
  28. den Boer M, Argaw D, Jannin J, Alvar J. Leishmaniasis impact and treatment access. *Clin Microbiol Infect.* 2011 Oct 1;17(10):1471–7.
  29. Herzog C. Successful comeback of the single-dose live oral cholera vaccine CVD 103-HgR. *Travel Med Infect Dis Phila.* 2016 Jul 1;14(4):373–7.
  30. Cabrera A, Lepage JE, Sullivan KM, Seed SM. Vaxchora: A Single-Dose Oral Cholera Vaccine. *Ann Pharmacother.* 2017 Jul 1;51(7):584–9.
  31. Knowledge Ecology InternationalInternational, Médecins Sans Frontières. Comments to the National Institutes Notice of Prospective Grant of Exclusive Patent License: DNA-Based Vaccine for Prevention of Zika Virus Infection [Internet]. 2017 [cited 2018 Feb 14]. Available from:  
[https://www.keionline.org/sites/default/files/KEI\\_MSF\\_NIH\\_Zika\\_Vaccine\\_License.pdf](https://www.keionline.org/sites/default/files/KEI_MSF_NIH_Zika_Vaccine_License.pdf)

32. Spanish group defeats Shkreli in Chagas voucher race - Science in Context [Internet]. [cited 2018 Feb 14]. Available from: [http://ic.galegroup.com.proxy.lib.duke.edu/ic/scic/AcademicJournalsDetailsPage/AcademicJournalsDetailsWindow?disableHighlighting=&displayGroupName=Journals&docIndex=&source=&prodId=&mode=view&limiter=&display-query=&contentModules=&action=e&sortBy=&>windowstate=normal&currPage=&dviSelectedPage=&scanId=&query=&search\\_within\\_results=&p=SCIC&catId=&u=duke\\_perkins&displayGroups=&documentId=GALE%7CA513866504&activityType=BasicSearch&failOverType=&commentary=](http://ic.galegroup.com.proxy.lib.duke.edu/ic/scic/AcademicJournalsDetailsPage/AcademicJournalsDetailsWindow?disableHighlighting=&displayGroupName=Journals&docIndex=&source=&prodId=&mode=view&limiter=&display-query=&contentModules=&action=e&sortBy=&>windowstate=normal&currPage=&dviSelectedPage=&scanId=&query=&search_within_results=&p=SCIC&catId=&u=duke_perkins&displayGroups=&documentId=GALE%7CA513866504&activityType=BasicSearch&failOverType=&commentary=)
33. Lienhardt C, Raviglione M, Spigelman M, Hafner R, Jaramillo E, Hoelscher M, et al. New Drugs for the Treatment of Tuberculosis: Needs, Challenges, Promise, and Prospects for the Future. *J Infect Dis*. 2012 May 15;205(suppl\_2):S241–9.
34. Goulooze SC, Cohen AF, Rissmann R. Bedaquiline. *Br J Clin Pharmacol*. 2015 Aug 1;80(2):182–4.
35. World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis [Internet]. 2013 [cited 2018 Feb 14]. Available from: [drug re](#)
36. Tradeoffs in Introduction Policies for the Anti-Tuberculosis Drug Bedaquiline: A Model-Based Analysis [Internet]. [cited 2018 Feb 14]. Available from: <http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002142>
37. Johnson and Johnson. Products by Janssen Therapeutics [Internet]. Janssen. [cited 2018 Mar 10]. Available from: <http://www.janssen.com/products>
38. World Health Organization. Global Tuberculosis Report 2017 [Internet]. 2017 [cited 2018 Feb 14]. Available from: <http://apps.who.int/iris/bitstream/10665/259366/1/9789241565516-eng.pdf?ua=1>
39. World Health Organization. Global Tuberculosis Report 2016 [Internet]. 2016 [cited 2018 Feb 14]. Available from: [http://www.who.int/tb/publications/global\\_report/gtbr2016\\_executive\\_summary.pdf](http://www.who.int/tb/publications/global_report/gtbr2016_executive_summary.pdf)
40. Information NC for B, Pike USNL of M 8600 R, MD B, Usa 20894. “How-to” guide on the use of bedaquiline for MDR-TB treatment [Internet]. World Health Organization; 2014 [cited 2018 Mar 15]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK247434/>
41. Medecines Sans Frontieres, Stop TB Partnership. Out of Step 2017 - TB Policies in 29 Countries: A survey of prevention, testing and treatment policies and practices. 2017.

42. World Health Organization. WHO | Interim guidance on the use of bedaquiline to treat MDR-TB [Internet]. 2013 [cited 2018 Mar 9]. Available from: <http://www.who.int/tb/challenges/mdr/bedaquiline/en/>
43. Nguyen TVA, Anthony RM, Bañuls A-L, Vu DH, Alffenaar J-WC. Bedaquiline resistance: Its emergence, mechanism and prevention. *Clin Infect Dis Off Publ Infect Dis Soc Am.* 2017 Nov 8;
44. WHO | Pharmacovigilance [Internet]. WHO. [cited 2018 Mar 15]. Available from: [http://www.who.int/medicines/areas/quality\\_safety/safety\\_efficacy/pharmvigi/en/](http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/)
45. Medecines Sans Frontieres. Open letter to Johnson & Johnson on ensuring widespread access to bedaquiline for the treatment of tuberculosis | [msfaccess.org](http://msfaccess.org) [Internet]. [cited 2018 Mar 8]. Available from: <https://www.msfaccess.org/content/open-letter-johnson-johnson-ensuring-widespread-access-bedaquiline-treatment-tuberculosis>
46. USAID's Bedaquiline Donation Program in Partnership with Johnson and Johnson [Internet]. [cited 2018 Feb 16]. Available from: <https://www.usaid.gov/what-we-do/global-health/tuberculosis/technical-areas/bedaquiline-donation-program>
47. Conradie F, Meintjes G, Hughes J, Maartens G, Ferreira H, Siwendu S, et al. Clinical access to Bedaquiline Programme for the treatment of drug-resistant tuberculosis. *South Afr Med J Suid-Afr Tydskr Vir Geneeskd.* 2014 Mar;104(3):164–6.
48. Population implications of the use of bedaquiline in people with extensively drug-resistant tuberculosis: are fears of resistance justified? - *The Lancet Infectious Diseases* [Internet]. [cited 2018 Mar 17]. Available from: [http://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(17\)30299-2/fulltext](http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(17)30299-2/fulltext)
49. Kingdon JW. *Agendas, alternatives, and public policies* [Internet]. Boston: Little, Brown; 1984 [cited 2018 Feb 14]. Available from: <http://catalog.hathitrust.org/api/volumes/oclc/10277820.html>
50. Lewin K. *Field Theory in Social Science: Selected Theoretical Papers.*. Tavistock, London; 1952.
51. Stop TB Partnership. *Global Plan To End TB- The Paradigm Shift: 2016-2020* [Internet]. 2015 [cited 2018 Mar 15]. Available from: [http://www.stoptb.org/assets/documents/global/plan/GlobalPlanToEndTB\\_TheParadigmShift\\_2016-2020\\_StopTBPartnership.pdf](http://www.stoptb.org/assets/documents/global/plan/GlobalPlanToEndTB_TheParadigmShift_2016-2020_StopTBPartnership.pdf)

52. Saturation in qualitative research: exploring its conceptualization and operationalization | SpringerLink [Internet]. [cited 2018 Mar 10]. Available from: <https://link.springer.com/article/10.1007/s11135-017-0574-8>
53. Cox HS, Furin JJ, Mitnick CD, Daniels C, Cox V, Goemaere E. The need to accelerate access to new drugs for multidrug-resistant tuberculosis. *World Health Organ Bull World Health Organ Geneva*. 2015 Jul;93(7):491–7.
54. World Health Organization. WHO MODEL LIST OF ESSENTIAL MEDICINES APPLICATION: Bedaquiline [Internet]. 2014 [cited 2018 Mar 7]. Available from: [http://www.who.int/selection\\_medicines/committees/expert/20/applications/Bedaquiline\\_Janssen.pdf](http://www.who.int/selection_medicines/committees/expert/20/applications/Bedaquiline_Janssen.pdf)
55. Medecines Sans Frontieres. Open letter to Janssen on reducing the price of bedaquiline [Internet]. [cited 2018 Mar 8]. Available from: <http://www.msffaccess.org/content/open-letter-janssen-reducing-price-bedaquiline>
56. Global Drug Facility. Bedaquiline Donation Order Status Report - February 28, 2018 [Internet]. 2018 [cited 2018 Mar 8]. Available from: [http://www.stoptb.org/assets/documents/gdf/GDF\\_BDQ\\_Rpt\\_28-February-2018.pdf](http://www.stoptb.org/assets/documents/gdf/GDF_BDQ_Rpt_28-February-2018.pdf)
57. World Health Organization. Introduction of bedaquiline for the treatment of multidrug-resistant tuberculosis at country level: Implementation Plan. 2014 Nov.
58. Commissioner O of the. Real World Evidence [Internet]. [cited 2018 Mar 9]. Available from: <https://www.fda.gov/ScienceResearch/SpecialTopics/RealWorldEvidence/default.htm>
59. Stop TB Partnership. Stop TB Partnership | About Us [Internet]. [cited 2018 Mar 9]. Available from: <http://www.stoptb.org/about/>
60. Mahajan R. Bedaquiline: First FDA-approved tuberculosis drug in 40 years. *Int J Appl Basic Med Res*. 2013;3(1):1–2.
61. World Health Organization. WHO Essential Medicines List (2017) [Internet]. WHO. [cited 2018 Mar 7]. Available from: [http://www.who.int/medicines/news/2017/21st\\_essential\\_med-list/en/](http://www.who.int/medicines/news/2017/21st_essential_med-list/en/)
62. European Medicines Agency. European Medicines Agency recommends approval of a new medicine for multidrug-resistant tuberculosis [Internet]. 2013 [cited 2018 Mar 9]. Available from: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2013/12/news\\_detail\\_001999.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/12/news_detail_001999.jsp&mid=WC0b01ac058004d5c1)

63. National Institute for Communicable Diseases, South Africa. Communicable Diseases Communiqué - South Africa [Internet]. 2015 [cited 2018 Mar 9]. Available from: <http://www.nicd.ac.za/assets/files/TB%20update.pdf>
64. Department of Health. INTRODUCTION OF NEW DRUGS AND DRUG REGIMENS FOR THE MANAGEMENT OF DRUGRESISTANT TUBERCULOSIS IN SOUTH AFRICA: POLICY FRAMEWORK [Internet]. Department of Health - South Africa. 2015 [cited 2018 Mar 9]. Available from: <http://www.nicd.ac.za/assets/files/Acrobat%20Document.pdf>
65. The Union. STREAM Clinical Trials [Internet]. The Union. 2012 [cited 2018 Mar 10]. Available from: <http://www.theunion.org/what-we-do/research/clinical-trials>
66. RESIST-TB. Clinical Trials Progress Report [Internet]. RESIST-TB; 2018 Jan [cited 2018 Mar 10]. Available from: [http://www.resisttb.org/wp-content/uploads/2017/10/RESIST-TB-Clinical-Trials-Progress-Report\\_24-Oct-2017.pdf](http://www.resisttb.org/wp-content/uploads/2017/10/RESIST-TB-Clinical-Trials-Progress-Report_24-Oct-2017.pdf)
67. WHO | UN General Assembly high-level meeting on TB to take place in 2018 [Internet]. WHO. [cited 2018 Mar 10]. Available from: [http://www.who.int/tb/features\\_archive/unga-meeting-tuberculosis/en/](http://www.who.int/tb/features_archive/unga-meeting-tuberculosis/en/)
68. Stop TB Partnership. Stop TB Partnership | The 2018 UN High-Level Meeting on TB - Let's do this! [Internet]. [cited 2018 Mar 10]. Available from: [http://www.stoptb.org/news/stories/2017/ns17\\_037.asp](http://www.stoptb.org/news/stories/2017/ns17_037.asp)
69. Mbuagbaw L, World Health Organization. Review of available evidence on the use of bedaquiline for the treatment of multidrug-resistant tuberculosis: Data analysis report [Internet]. World Health Organization. 2017 [cited 2018 Mar 10]. Available from: [http://www.who.int/tb/publications/2017/Appendix\\_GDGReport\\_Bedaquiline.pdf](http://www.who.int/tb/publications/2017/Appendix_GDGReport_Bedaquiline.pdf)
70. Sekhri N, Feachem R, Ni A. Public-Private Integrated Partnerships Demonstrate The Potential To Improve Health Care Access, Quality, And Efficiency. *Health Aff Chevy Chase*. 2011 Aug;30(8):1498–507.
71. Working to close the TB diagnostics and treatment gap [Internet]. Devex. 2016 [cited 2018 Mar 10]. Available from: <https://www.devex.com/news/sponsored/working-to-close-the-tb-diagnostics-and-treatment-gap-87745>
72. Kesselheim AS, Maggs LR, Sarpatwari A. Experience With the Priority Review Voucher Program for Drug Development. *JAMA*. 2015 Oct 27;314(16):1687–8.

73. Kesselheim AS. Priority review vouchers: an inefficient and dangerous way to promote neglected-disease drug development. *Clin Pharmacol Ther.* 2009 Jun;85(6):573–5.
74. Access to Medicine Index. Report cards [Internet]. 2016 Nov [cited 2018 Apr 5]. Available from: <https://accesstomedicineindex.org/report-cards/>
75. Getting medicines to the people who need them [Internet]. *Financial Times.* 2018 [cited 2018 Mar 10]. Available from: <https://www.ft.com/content/c128ca0c-0a87-11e8-8eb7-42f857ea9f09>
76. Clarus and GHIF provide \$25 mln to PATH [Internet]. *PE Hub.* 2017 [cited 2018 Mar 10]. Available from: <https://www.pehub.com/2017/01/clarus-and-ghif-provide-25-mln-to-path/>
77. Tropical Disease Priority Review Vouchers Guidance for Industry. :14.
78. CDC to cut by 80 percent efforts to prevent global disease outbreak - The Washington Post [Internet]. [cited 2018 Mar 10]. Available from: [https://www.washingtonpost.com/news/to-your-health/wp/2018/02/01/cdc-to-cut-by-80-percent-efforts-to-prevent-global-disease-outbreak/?utm\\_term=.54d5dec5f1ee](https://www.washingtonpost.com/news/to-your-health/wp/2018/02/01/cdc-to-cut-by-80-percent-efforts-to-prevent-global-disease-outbreak/?utm_term=.54d5dec5f1ee)