

Analysis of the Global TB Drug Market and Country-Specific Case Studies of TB Drug Distribution Channels

South Africa Case Study

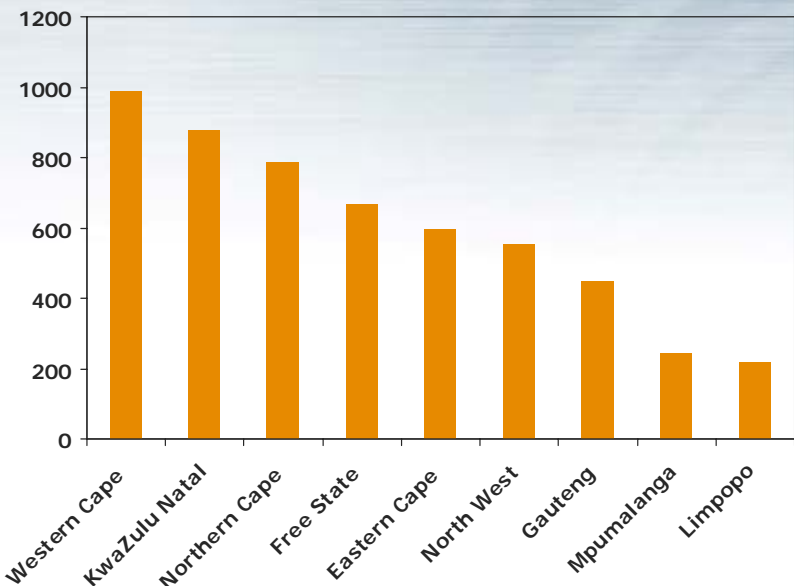


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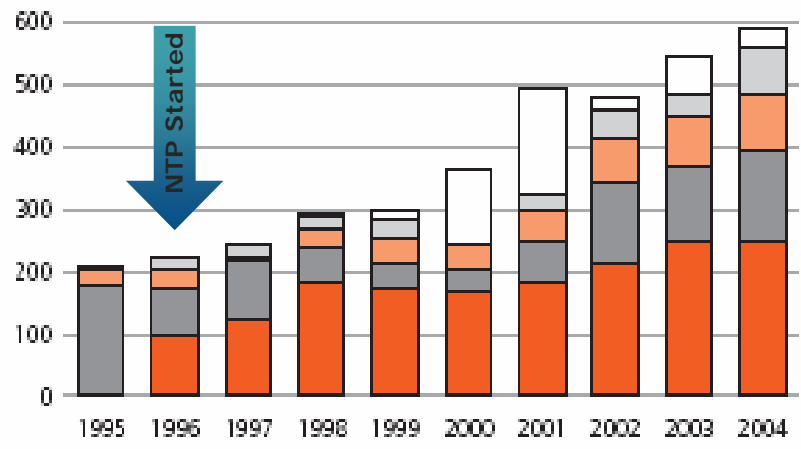
South Africa's TB burden is national, with each region suffering from high incidence of TB

Case Findings (All TB per 100K pop)



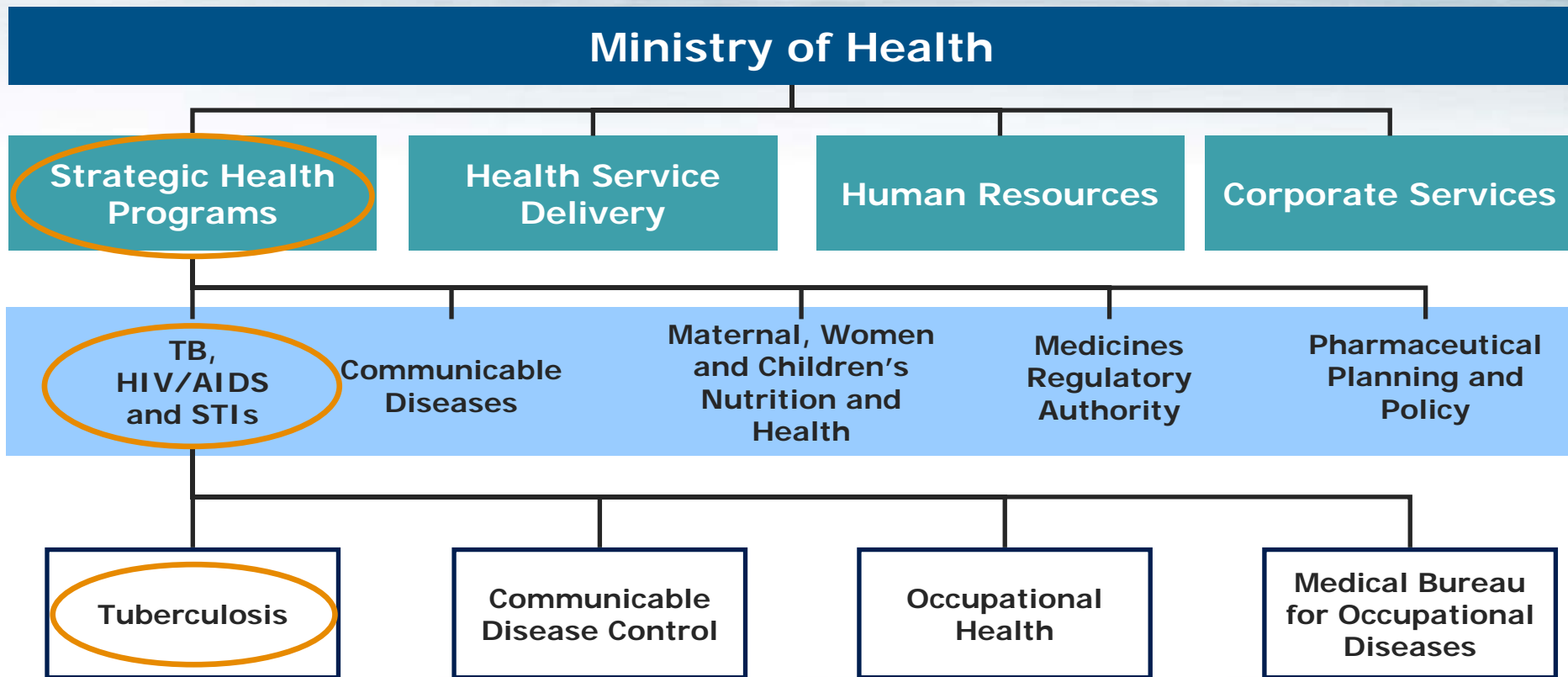
- South Africa is ranked 5th among countries with the highest TB burden (recently moved from 8th)
- There were approx 118,000 new smear positive TB cases in 2004 of which 60% were co-infected with HIV/AIDS
- Case notifications on the rise—partially due to start of NTP and prevalence of HIV
- Nearly all provinces have an incidence rate at or above 200 per 100K population

National Notification Rate (per 100K pop)



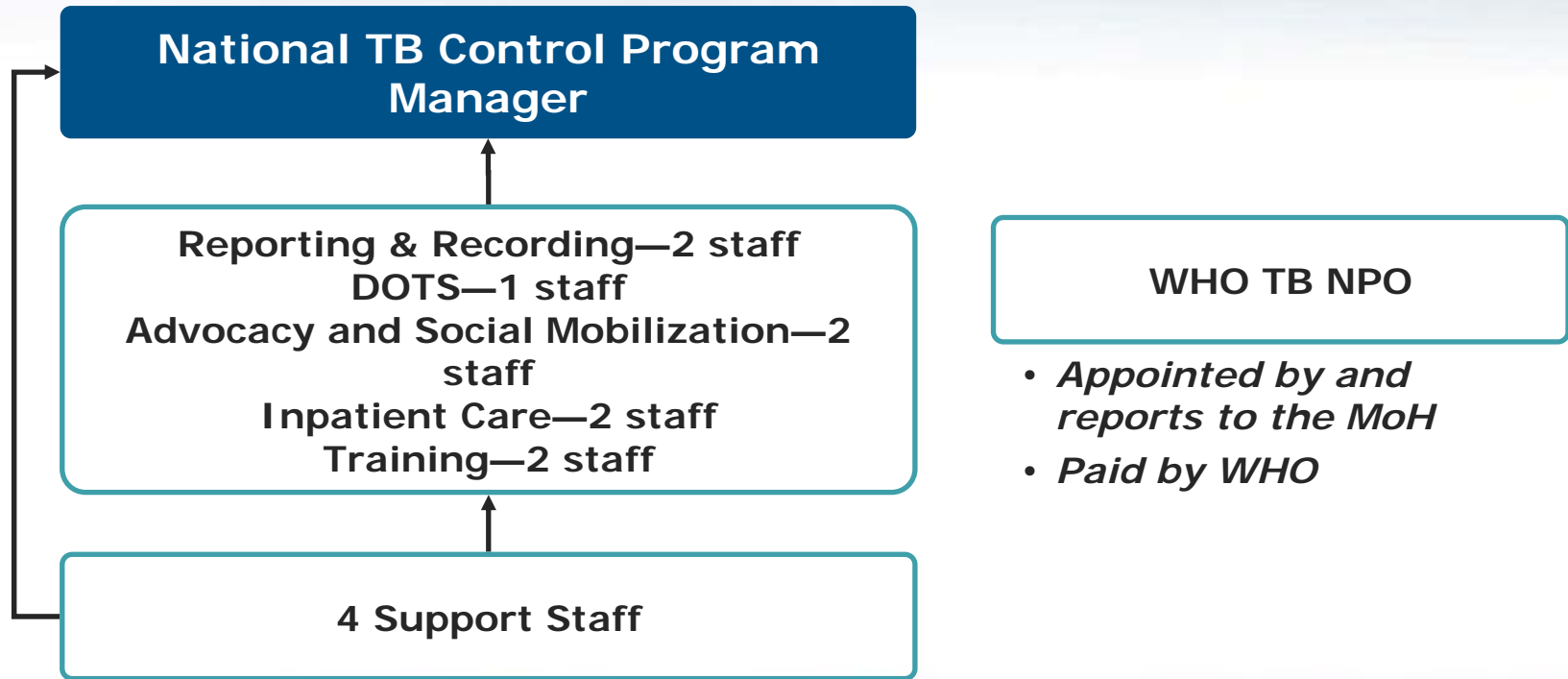
Source: WHO Country Profile; Global TB Control, Surveillance, Planning, Financing – WHO (2006)

The National TB Program is under the Ministry of Health, within a section called “strategic health programs”



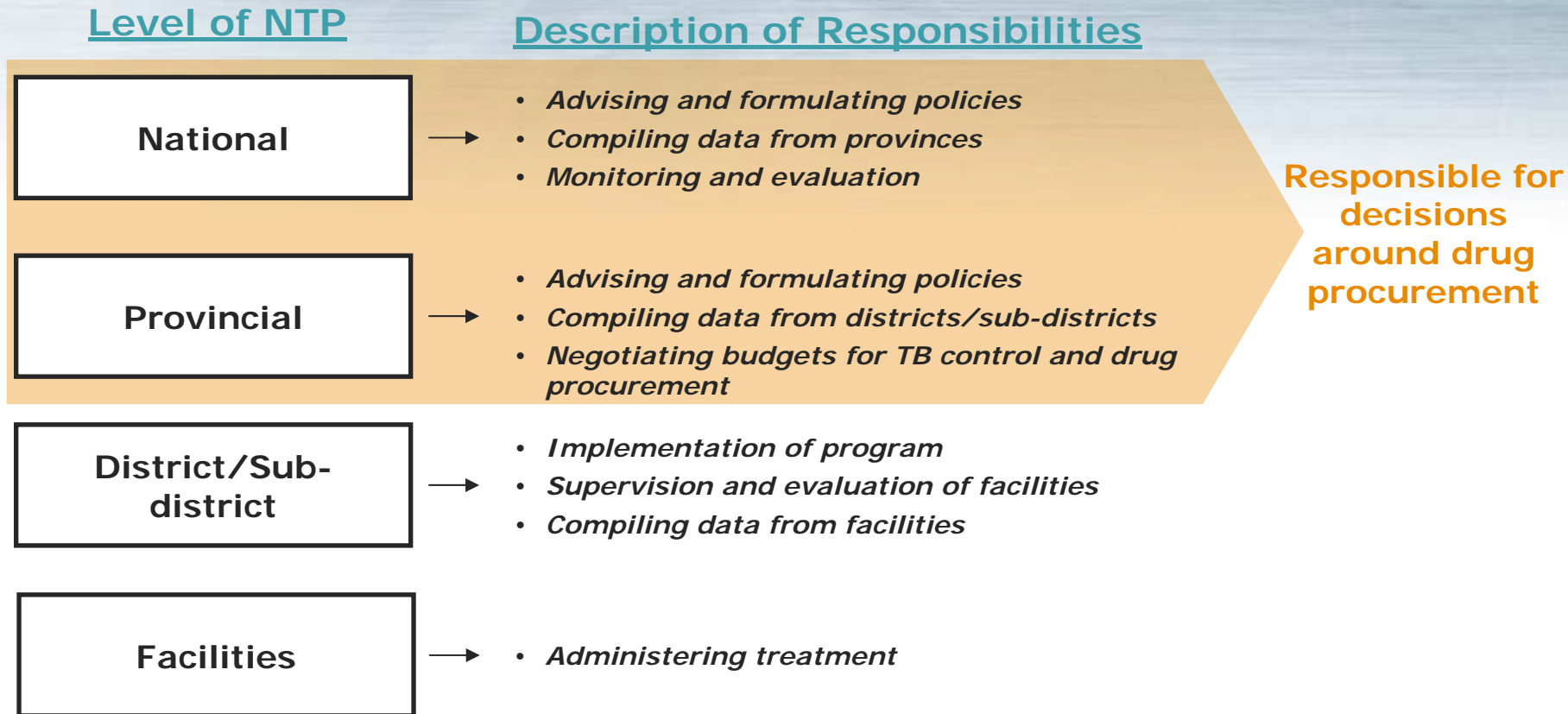
The program is staffed by a national program manager and 9 technical staff as well as a WHO national professional officer (NPO)

**National Level TB Staff and
Flow of Reporting**



Source: Interviews

Although policy is governed at the central level, like other health care issues, most decision making about services are decentralized to the provincial level



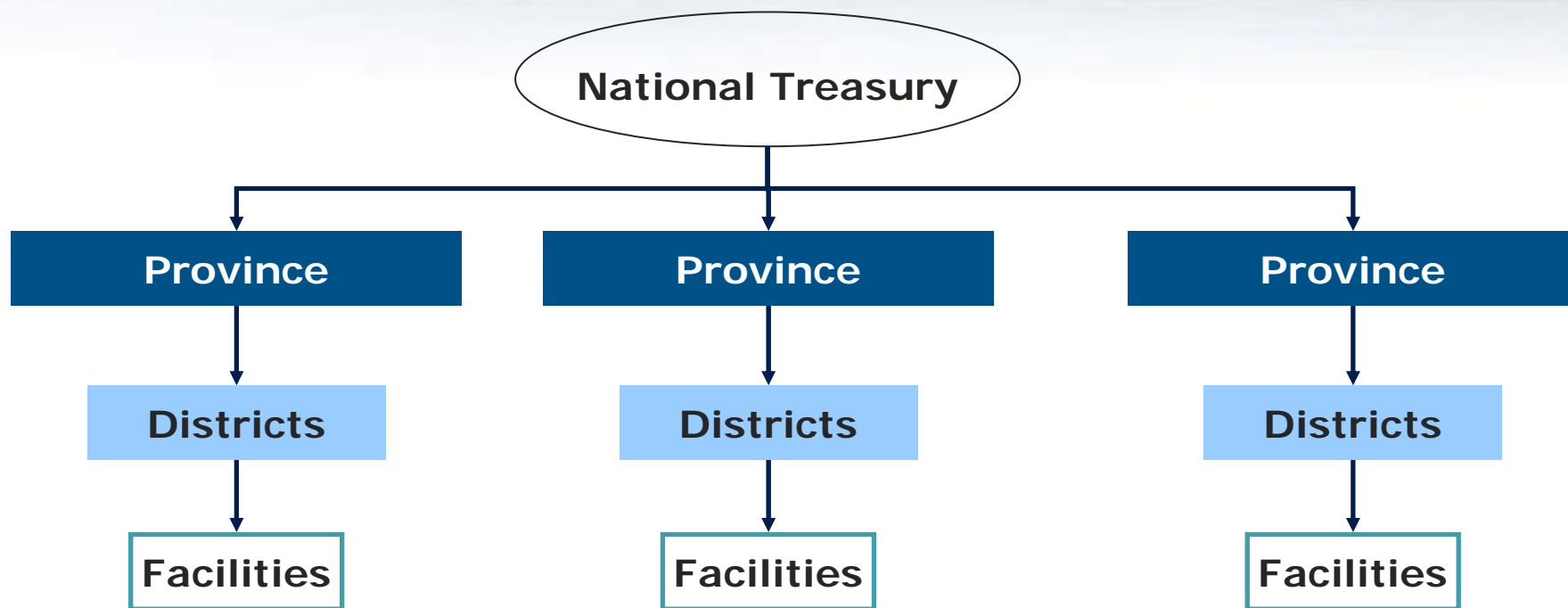
Source: Interviews

South Africa's annual TB expenses are estimated to be 250-300M USD

- **South Africa's TB control program receives technical assistance from a range of NGOs and multilateral agencies:**
 - International Union Against TB and Lung Disease
 - World Health Organization (WHO)
 - Management Sciences for Health (MSH)
- **HIV/TB is one area in which grant money is used to a significant extent**
 - South Africa has received three GFATM grants for HIV/TB, totalling approximately 91M USD (most of which has been disbursed as of last year)
 - The Provincial Health Department of the Western Cape is also the recipient of a GFATM grant of approximately 15M USD
- **However, the program derives the vast majority of its funding from national and provincial healthcare budgets**

Provinces are allocated an “equitable share” of resources from the National Treasury, which is distributed to the districts and facilities

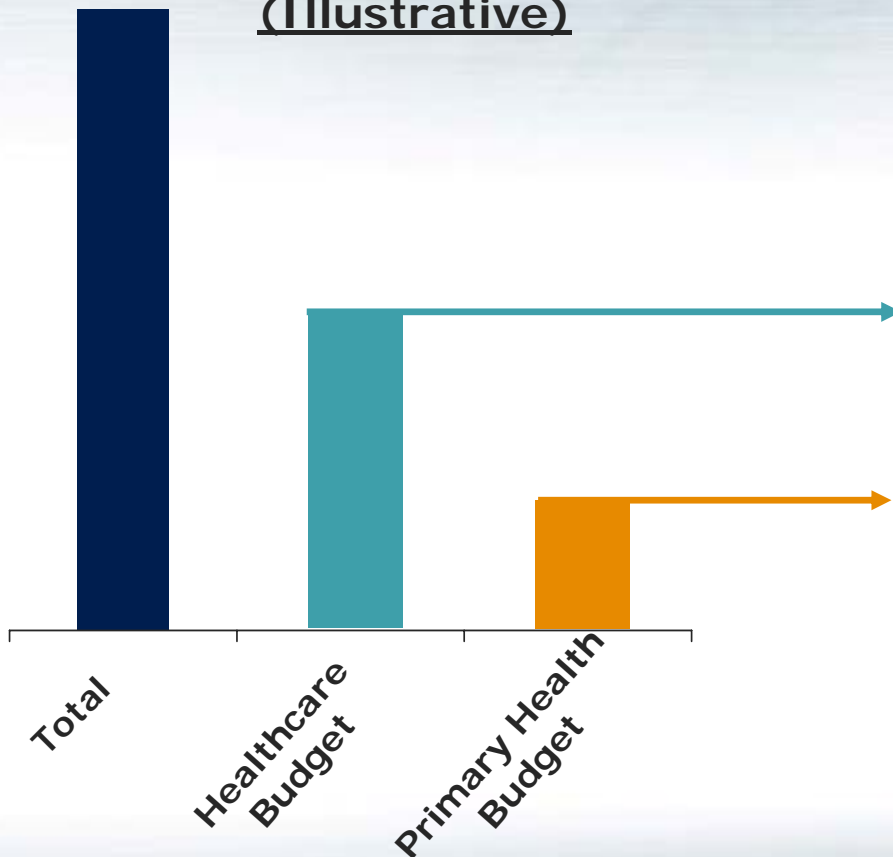
Illustrative Flow of Funding



Source: Interviews

Expenditures for TB are found within the category of primary health care

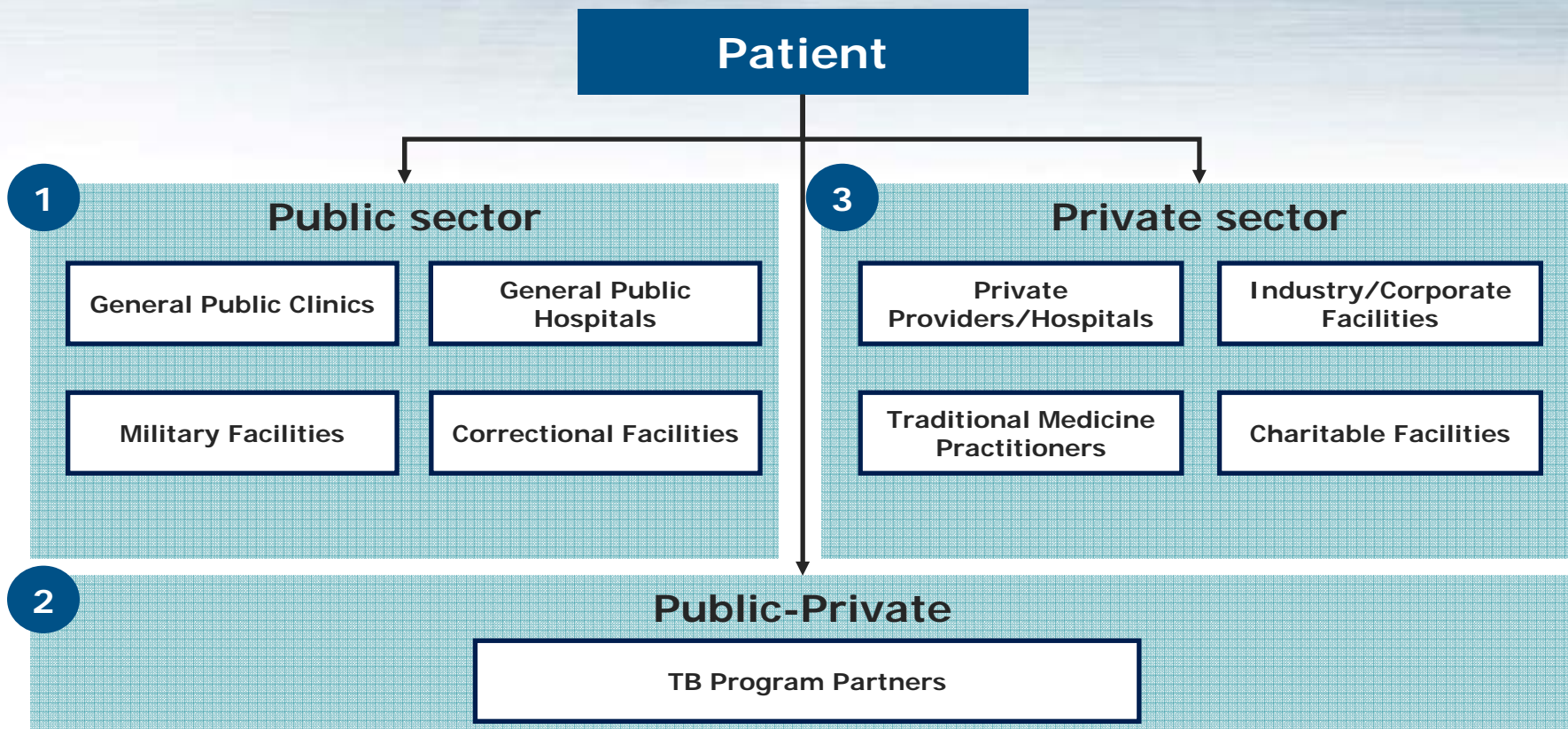
Provincial Budget Allocations
(Illustrative)



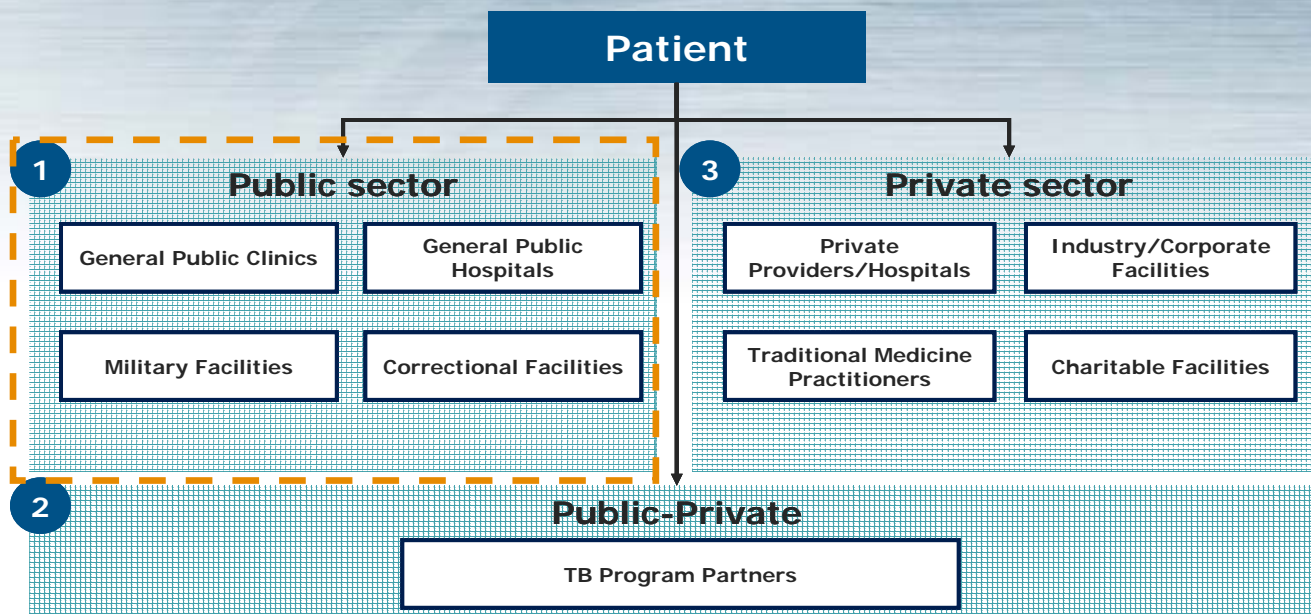
- *When the National Treasury allocates a province's "equitable share" of funds, it provides some guidance as to how those funds are spent*
- *However, provinces make the final decision as to how much to set aside for healthcare vs. education, social services, etc.*
- *Within healthcare, a certain budget is set aside for Primary Health, under which TB is folded*
- *In rare instances (e.g., North West Program), the Provincial TB Coordinator may secure a budget for the TB program and TB drugs*

TB control in South Africa leverages the primary healthcare system

Patient Flow Through TB Settings of Care



The government of South Africa considers TB control the mandate of the public sector



- TB control is primarily administered through public healthcare facilities—including those that cater to the general public, the military, and prisoners within correctional facilities
- Guidelines for TB diagnosis and treatment authored at the national level
- Funding is derived from provincial budgets

Patients are typically diagnosed and treated by a public health facility—most commonly in a clinic setting

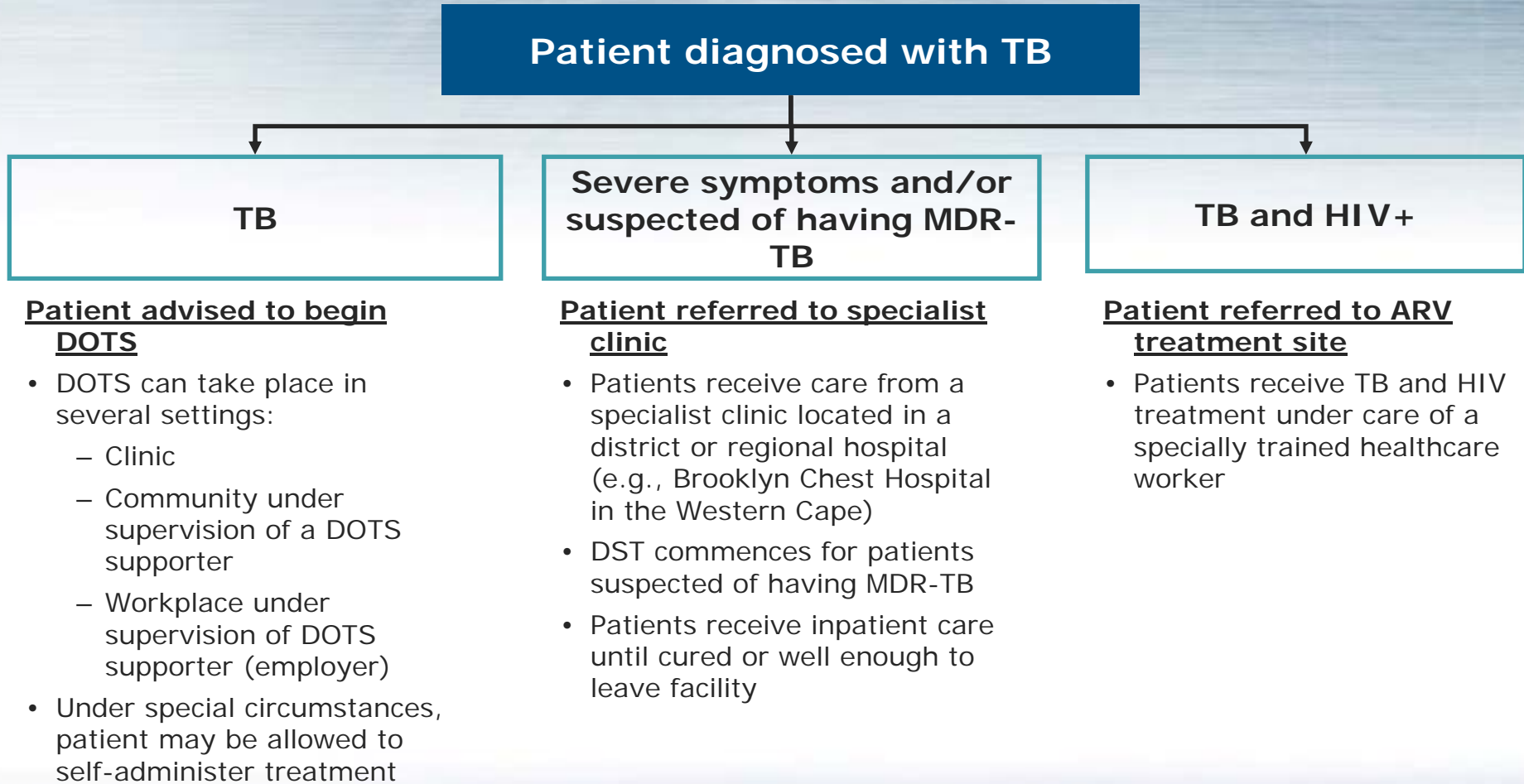
Consultation

- Patient approaches public health facility for consultation
- Clinics are usually the first point at which patients present—hospitals are generally far between and require travel time

Testing and Diagnosis

- Patients who are suspected of having TB are given a sputum smear test
- Sample is sent to microscopy lab for diagnosis
- Results are returned to the facility within 24-48 hours, though delays in the actual communication of those results to the patients are common

Patients who are confirmed as having TB may either be started on DOTS or referred to a specialist clinic



TB smear positive patients are given an FDC treatment regimen that is administered five times per week

NTP 1st Line Drug Treatment Regimen

<u>Patient Category</u>	<u>NTP Treatment Regimen</u>	<u>Method of administration</u>
Regimen 1: new smear positive, new smear negative, and extrapulmonary TB	2 (HRZE) ₅ / 4 (HR) ₅ or 4(HR) ₃	<ul style="list-style-type: none"> • <u>Use of FDCs</u> • Patients directly observed once per week by healthcare worker • Remaining doses in week are given to DOTS supporter who observes the patient
Regimen 2: previously treated TB patients after cure, after completion, interruption, and failure	2(HRZE) ₅ S ₅ / 1(HRZE) ₅ / 5(HRE) ₅ or 5(HR) ₃	
Pediatric (for patients below 8 years)	2(HRZ) ₅ /4(HR) ₅ or 4(HR) ₃	

Details on the 1st line Regimen

6-8 month treatment regimen. All treatment five times weekly unless patient resides far from health facilities and have no DOTS supporter.

Source: 2003 NTP Treatment Guidelines; DOTS Plus for standardised management of multidrug-resistant TB in South Africa (2004)

Those who are confirmed as having MDR-TB are treated with a standardized 2nd line treatment regimen

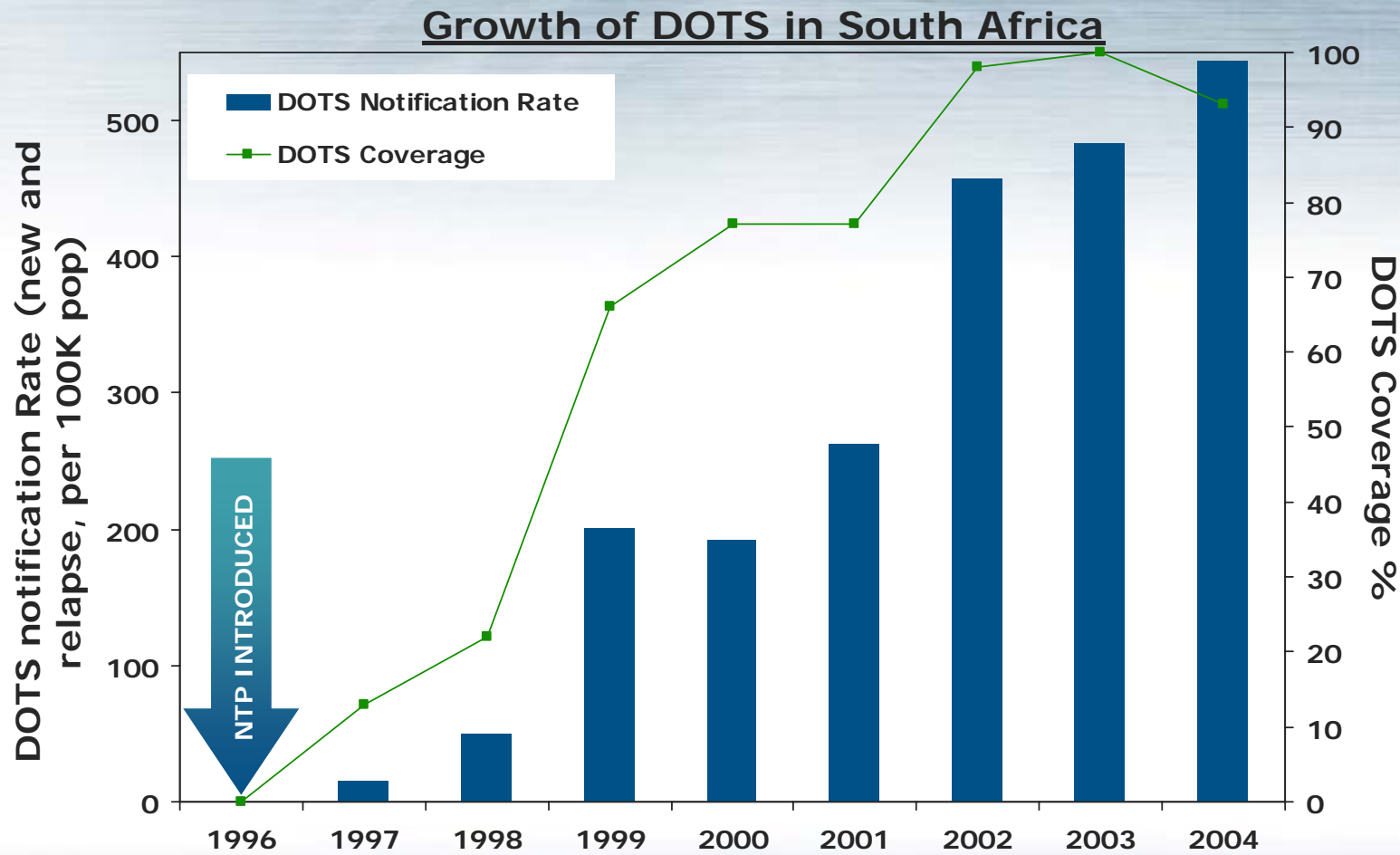
NTP 2nd Line Drug Treatment Regimen

<u>Patient Category</u>	<u>Initial Phase</u>	<u>Continuation Phase</u>	<u>Method of administration</u>
MDR-TB Patient	<p><u>4 months (5 or 7 times per week)</u></p> <ul style="list-style-type: none"> • Kanamycin • Ethionamide • Cycloserine • Pyrazinamide • Ofloxacin • Ethambutol or terizidone 	<p><u>12-18(5 or 7 times per week)</u></p> <ul style="list-style-type: none"> • Ethionamide • Cycloserine • Ofloxacin • Ethambutol or terizidine 	<ul style="list-style-type: none"> • Patients are referred to special facility for inpatient treatment • 16-22 month personalized drug regimen based on DST

Details on the 2nd line Regimen

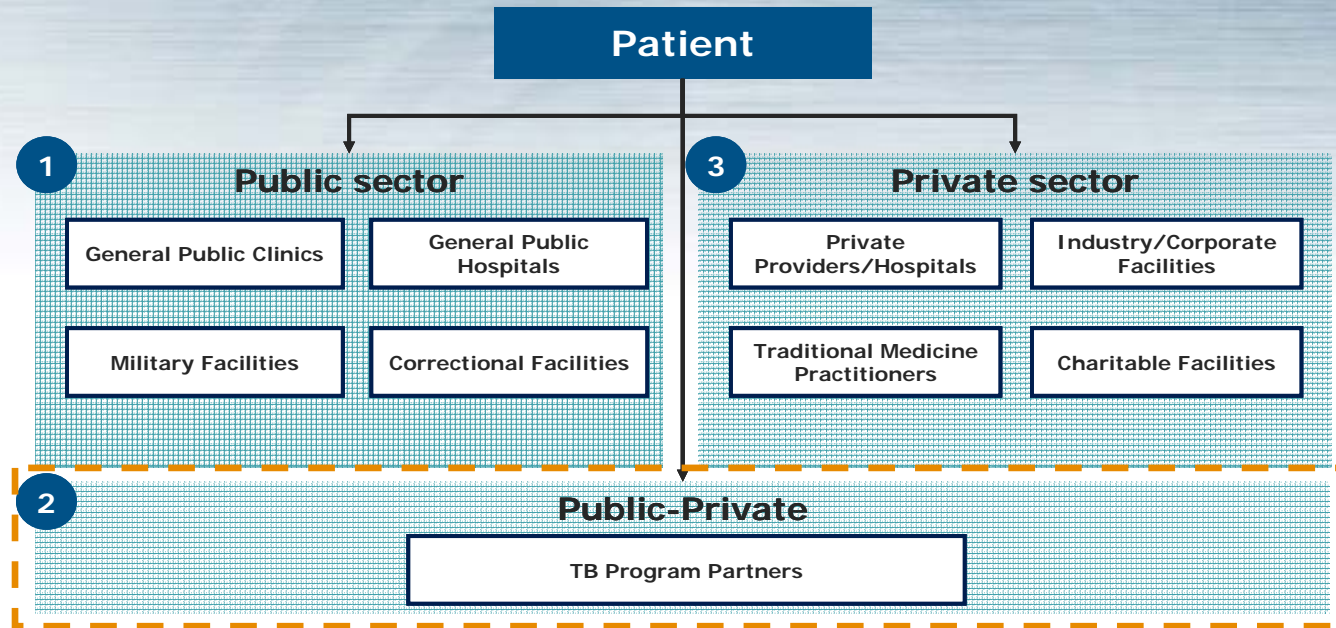
Terizidone used in patients who are resistant to ethambutol. In exceptional circumstances, amikacin can be used in place of kanamycin and ciprofloxacin can be used in place of ofloxacin.

Since the inception of the national program in 1996, DOTS notification rates have grown rapidly



Source: Global TB Control, Surveillance, Planning, Financing – WHO (2006)

Some provinces have chosen to incorporate private facilities into their TB programs



- Private providers—such as industry/corporate sponsored health facilities or charitable facilities—can be enlisted to provide TB treatment to patients
- These providers may receive funding from the government on a per patient basis to diagnose, categorize, and treat patients
- Some provinces have also recruited practitioners of traditional medicine—providing them with financial incentives to refer TB patients to the public sector and/or serve as DOTS supporters

These partners play various roles within the TB control program of any given province

Increasing level of involvement

Initial Diagnosis and Referral

- Some charitable facilities operating in regions in which the public sector resources are sparse may be enlisted to identify suspected TB patients and refer them to the public sector
- Traditional medicine practitioners may also be trained to recognize patients who have TB and refer them to the public sector

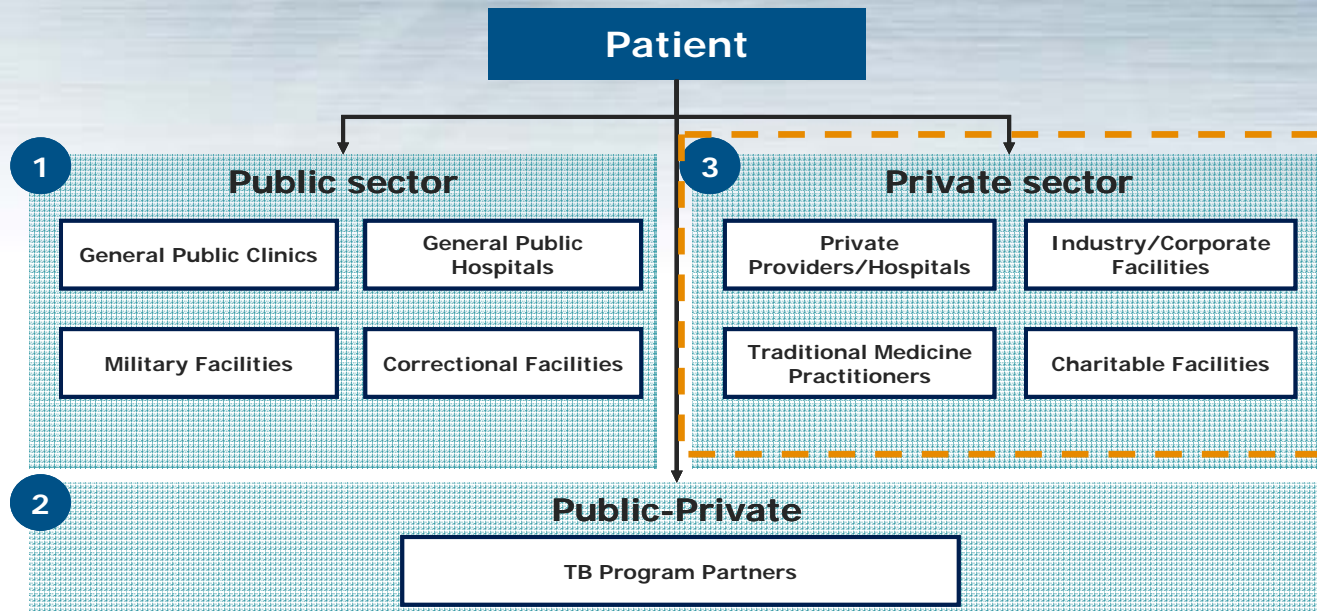
DOTS Supporters

- Because the direct-observation of all TB patients is often beyond the capacity of the public sector, it often relies on the help of other parties (i.e., DOTS supporters) to carry out observation once treatment has commenced
- Charitable facilities may either serve as DOTS supporters themselves or help to recruit, train, and supervise DOTS supporters
- Traditional medicine practitioners have also been enlisted to serve as DOTS supporters

Setting of Treatment

- Some charitable facilities, such as those that used to be under SANTA, are used by the program to serve as a specialty clinic
- In addition, industry/corporate-run facilities—e.g., large mining companies—may choose to partner with the government, receive funding on a per patient basis, and treat their employees with TB

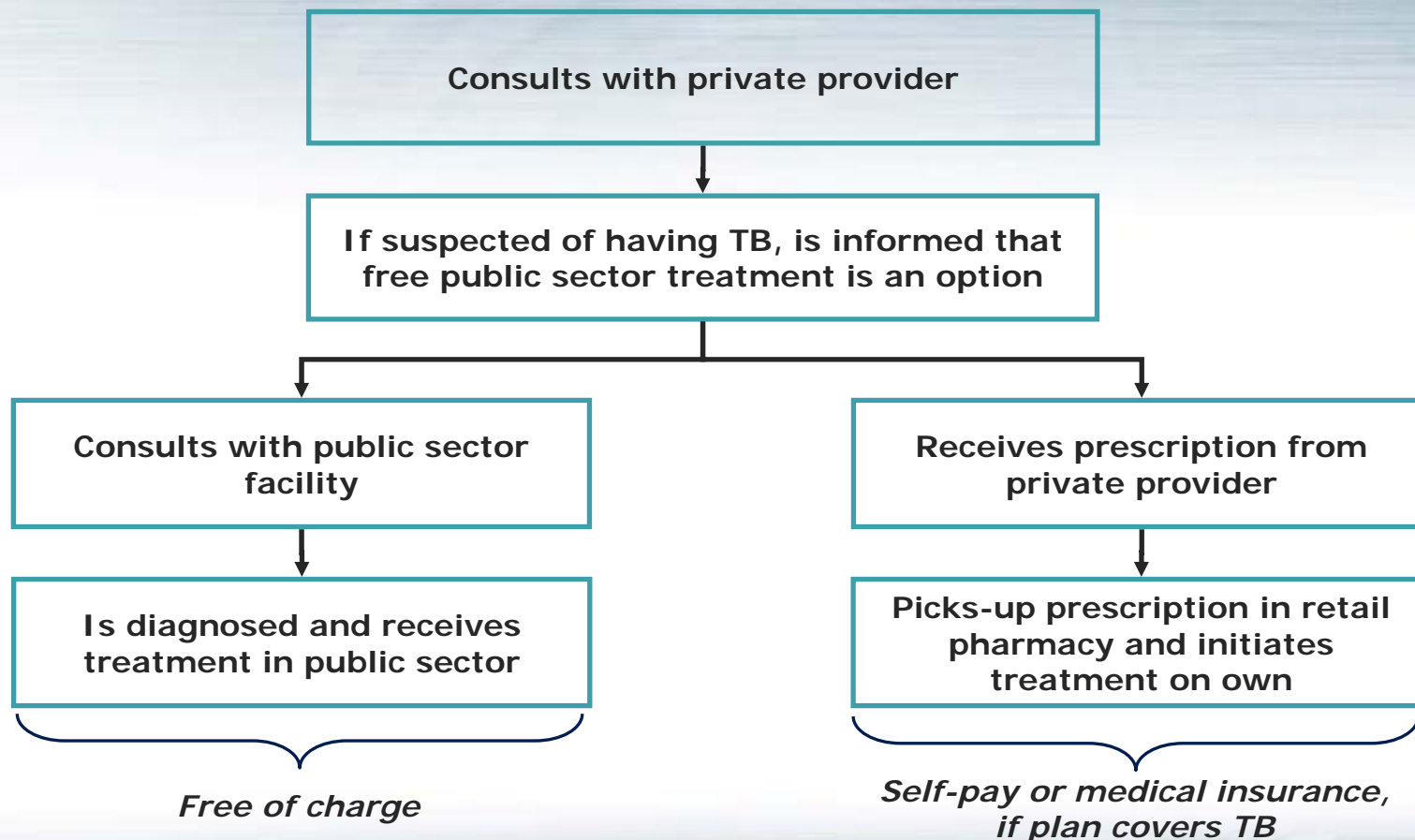
The private sector is not prohibited from prescribing and distributing TB drugs, but it is required to inform patients that they can receive free treatment in the public sector



- Though most TB patients present to public facilities, TB diagnosis and treatment is possible in for-profit facilities and industry/corporate-run facilities
- These private providers are required to report all cases of TB to the government and inform patients that free treatment is available in the public sector
- In some cases, medical insurance will pay for TB drugs but will list it as "acute disease drug treatment" for which patients only receive a yearly allowance

Although very uncommon, patients do have the option to receive treatment in the private sector

Patient Flow between Public and Private Sector



Source: The Stop TB Partnership in South Africa, Interviews

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There are three mechanisms through which TB drugs are procured in South Africa

Procurement mechanisms

**National
Tender**

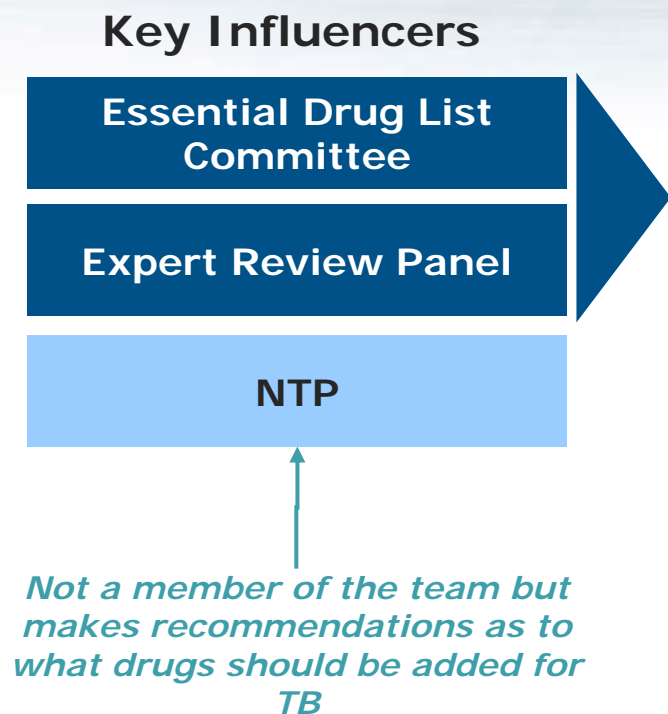
**Direct
Negotiations**

**Distributor/
Wholesaler**

- *General Public Facilities*
- *Correctional and Military Facilities*
- *TB Program Partners*

- *Private facilities*
- *Retail Pharmacies*
- *Other*

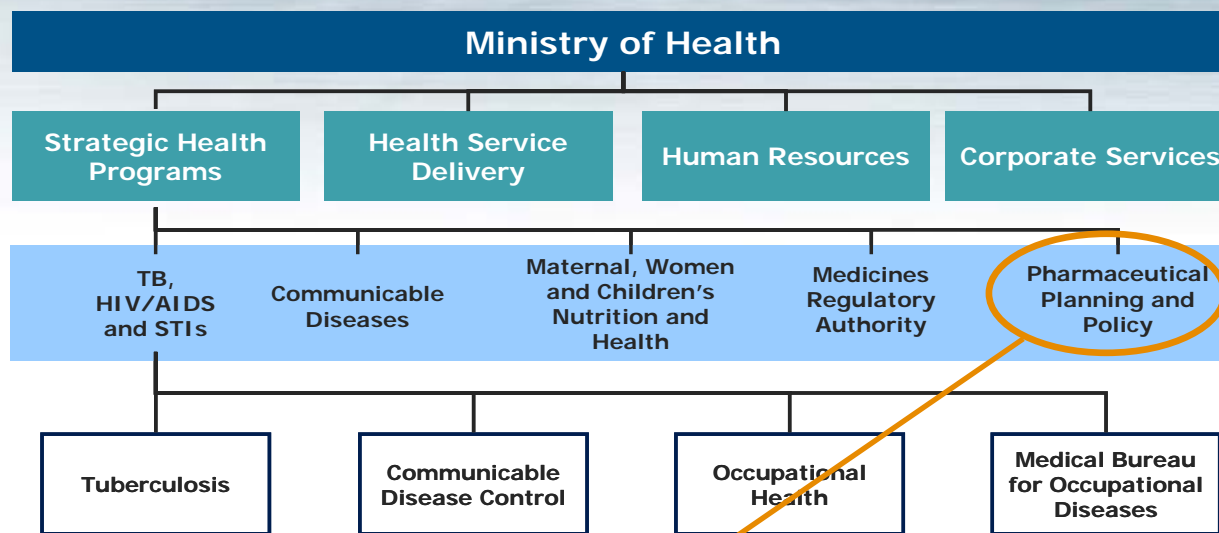
TB drugs are part of SA's Essential Drug List (EDL) and thus are available through the public health system



Essential Drug List

- Exists for non-TB as well as TB indications
- Exists in two forms: one for primary healthcare facilities and one for hospitals
- Published at regular intervals by the Ministry of Health's National Essential Drug List Committee, with the assistance of an expert review committee
 - Primary Healthcare EDL last revised in 2003
 - Previous version released in 1998
- Criteria for EDL status are based on the WHO guidelines:
 - Proven safety and efficacy
 - Cost effectiveness
 - Meets the needs of a majority of the population

TB and other drugs on the EDL are usually procured by Pharmaceutical Planning and Policy Cluster in conjunction with the National State Tender Board



The Pharmaceutical Planning and Policy Cluster conducts the forecasts of drug needs based on reported used from provinces. It collaborates with the National State Tender Board—a government body that administers public tenders in all areas(not just pharmaceuticals)—to procure pharmaceutical products on behalf of the public healthcare system. In addition, the cluster negotiates with suppliers for pharmaceutical products that are not on tender.

Separate tenders for 1st and 2nd line drugs are floated once every two years

Public Tender

Who administers the tender?

- National State Tendering Office

International or national tender?

- National
- Under exceptional circumstances, will issue and international bid

Pre-qualification required?

- Yes
- Companies and drugs must have marketing approval in South Africa

How often is tender floated?

- Once every two years
- When new treatment regimen introduced, contract can be shortened

How is tender awarded?

- 90% on price
- 10% on other factors (e.g., points accumulated under Preferential Procurement Policy Framework Act (2000)*)

Applies to all 1st line TB drugs and most 2nd line TB drugs

**See appendix for full listing of pre-qualification requirements and more details on Preferential Policy Framework Act*

The tenders for 1st line TB drugs are currently held by Sandoz and Sanofi-Aventis, while the 2nd line tender includes a greater mix of suppliers

1st Line Drug Suppliers

- Sandoz
- Sanofi-Aventis

2nd Line Drugs Suppliers

- Be-tabs Pharmaceuticals
- Biotech Laboratories*
- Bizshelf Pharmaceuticals
- Caps Pharmaceuticals*
- Pfizer Laboratories*
- Sandoz
- Sanofi-Aventis
- International suppliers

**Suppliers of streptomycin, which is also used in the 1st line treatment of relapse patients*

Starting in the next one to two years, the two 2nd line drugs that are not currently on tender will be manufactured in South Africa by Aspen Pharmacare

Up to 2007

- A separate tender is run for 2nd line drugs that are manufactured by a local company and are needed in large enough quantities to run a tender
- At this time, the public tender includes terizadone, ethambutol (loose), pyrazinamide (loose), streptomycin, and kanamycin are on tender
- Capreomycin and cycloserine are procured via direct negotiations with international suppliers

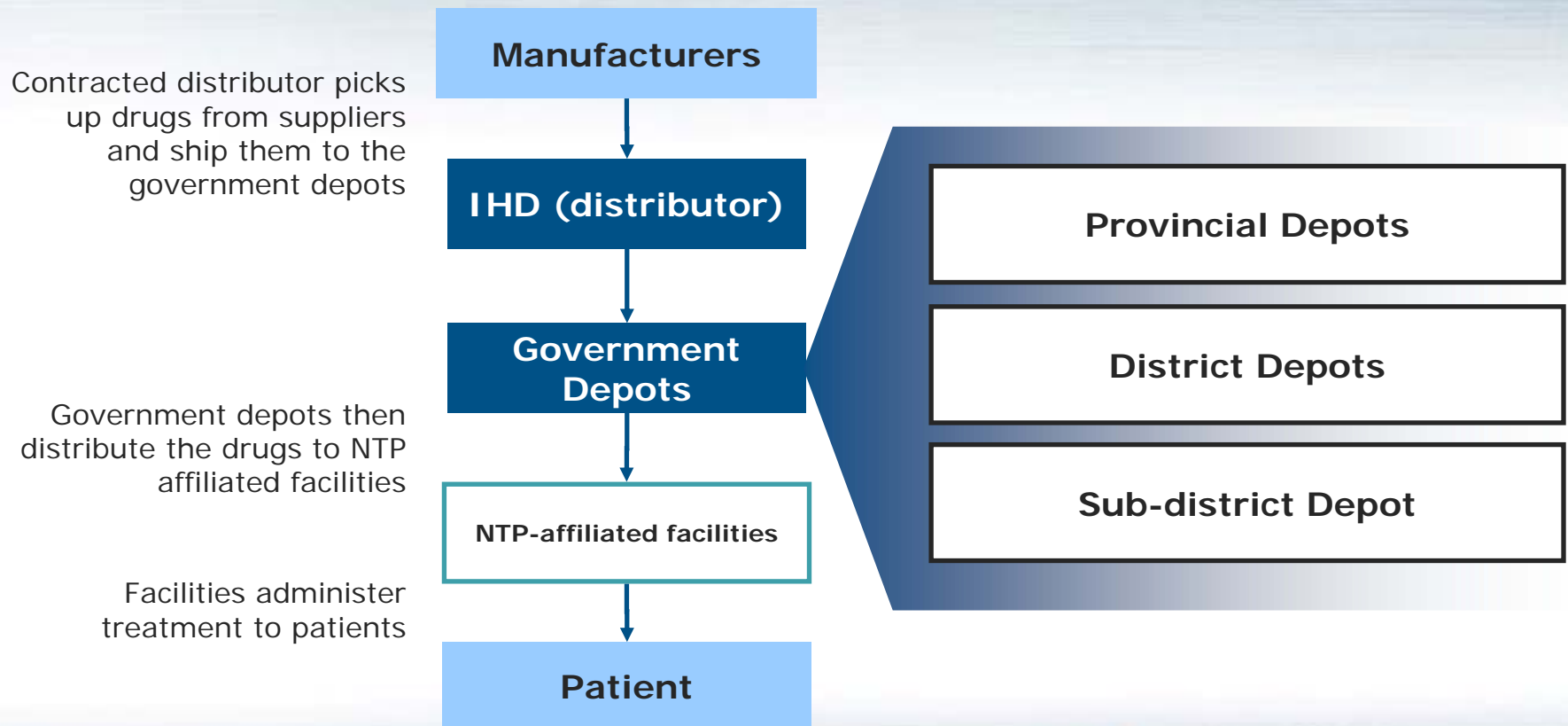
2007 and onwards

- Eli Lilly has agreed to a technological transfer of two second line drugs—capreomycin and cycloserine—to Aspen Pharmacare*

**Aspen is also in discussions with Lupin to receive a technological transfer for 1st line FDCs, though the agreement is still being finalized*

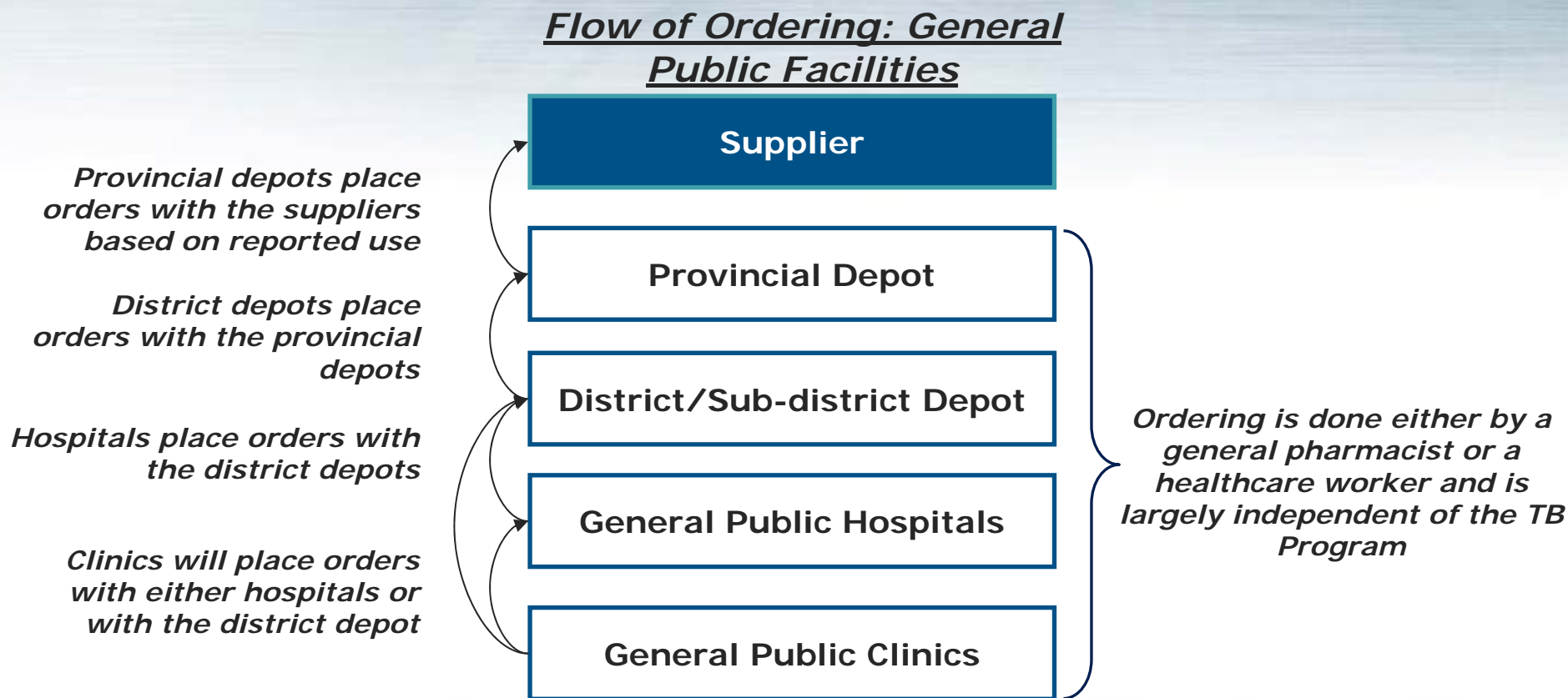
In the public sector, TB drugs flow through a series of government depots before reaching the facilities and patients

Drug Flow: Public Sector Channels



Source: Interviews

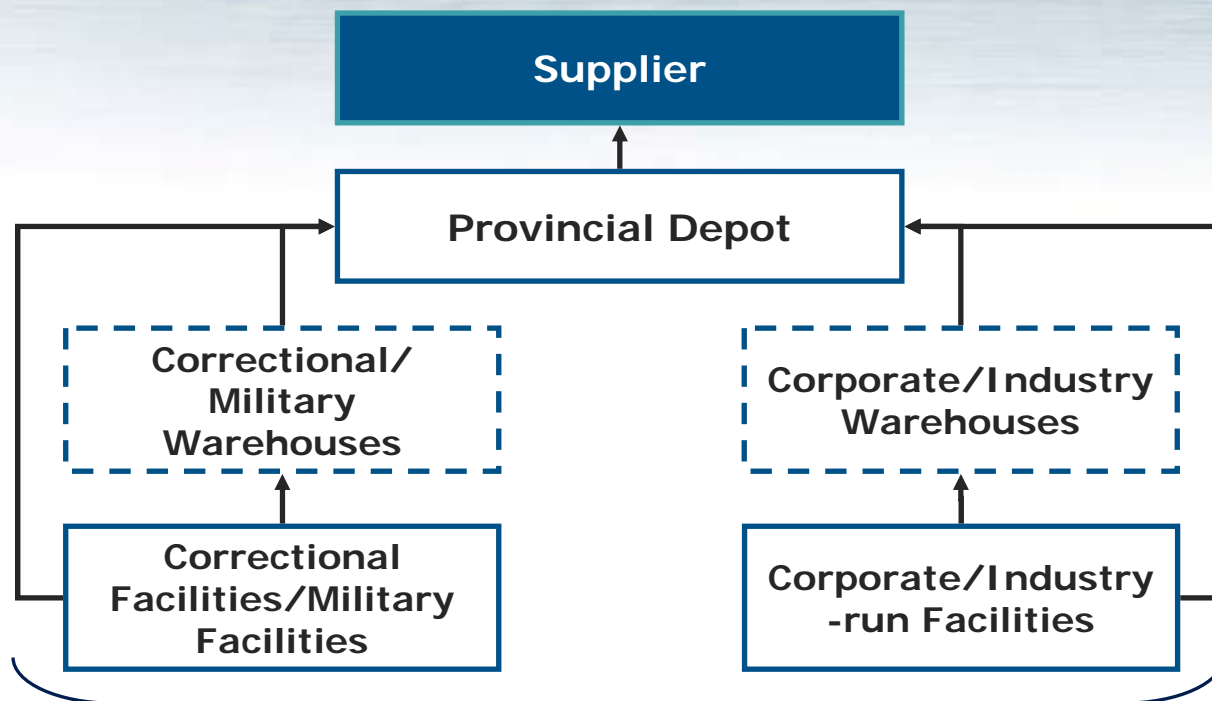
Provincial depots place orders with suppliers and serve as the starting point for drug distribution to the government depots and general public facilities



Source: Interviews

They also serve as the sourcing point for other facilities working in cooperation with the NTP

Flow of Ordering: Other NTP-affiliated Facilities



Orders with the provincial depots are placed either by warehouses acting on behalf of multiple facilities or a facility itself. In a few instances, the facilities may order directly from the suppliers at public tender prices.

In the private sector, TB drugs flow through the same routes as other pharmaceuticals and are subject to a set mark-up structure

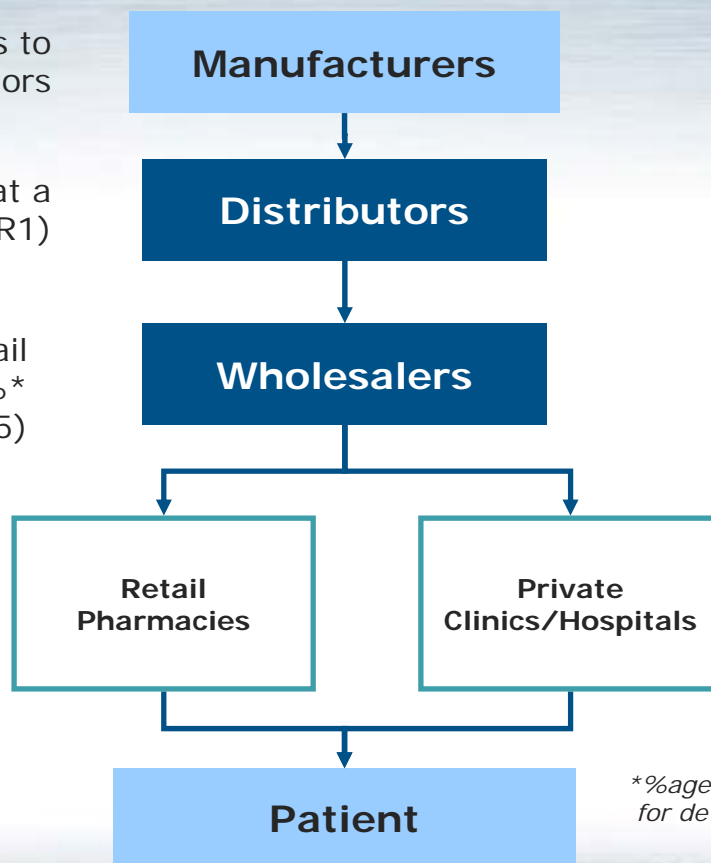
Drug Flow: Private Sector Channels

1st point of sale: Manufacturers sell their TB drugs to distributors

2nd point of sale: Distributors sell to wholesalers at a 2.5%* markup (no more than R1)

3rd point of sale: Wholesalers sell drugs to retail pharmacies and private clinics/hospitals at a 12.5%* markup (no more than R5)

Retail sale: Retail pharmacies then dispense drugs to patients at a 24%* mark-up (no more than R24 per pack). Dispensing doctors are limited to 16% (no more than R16)



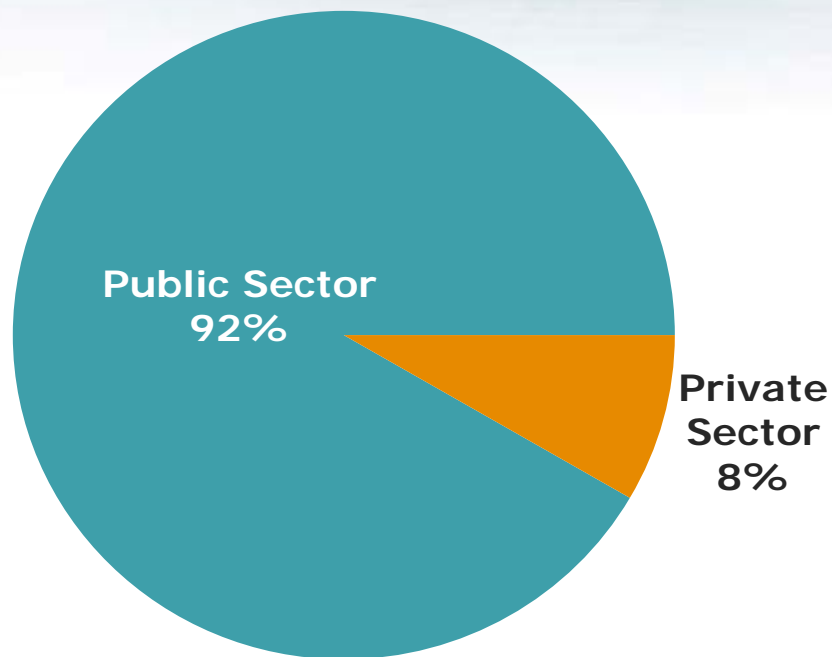
**%age of SEP, refer to appendix for details on Single Exit Pricing*

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The total TB market in South Africa is currently valued at approximately 21.8M USD , nearly all of which falls in the public sector

Total TB Market Value by Sector in 2004-2005 (Approx 21.8 M USD)



A publicly-driven market

- The vast majority of the value of TB drugs flows through the public sector
 - The public sector is estimated to hold 92% (20.0 USD) market value share
 - The private sector accounts for the remaining 8% (1.8M USD)
- When segmenting the market from a volume (standard units) perspective, the market is also primarily in the public sector
 - 95.7% of the market volume lies in the public sector
 - 4.3% of the market volume is in the private sector

Note: Segmentation is by product—does not account for use of 1st line products in 2nd line treatment and vice versa

1st line drugs represent the vast majority of the total market value today

Total TB Market

Almost entirely a 1st line market

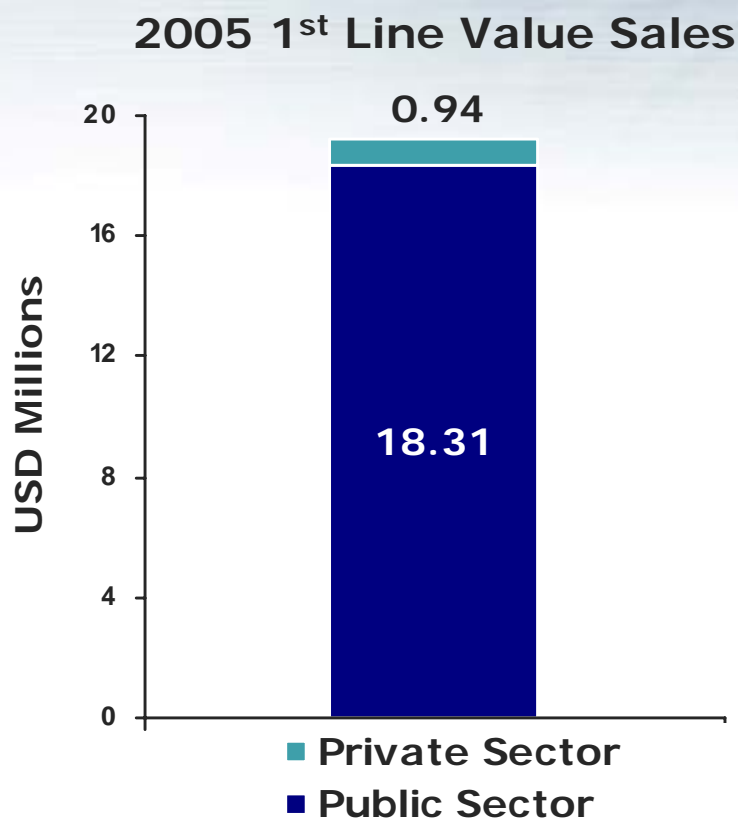
- 1st line drugs account for 19.3M USD or 94% of the total market
- Predominantly public sector
- Heavy use of FDCs in both the private and public sector (where FDCs are recommended)

Niched 2nd line market

- Data suggest that 2nd line drugs account for 2.5M USD or 6% of the total market
- Public share of market value rapidly growing

Note: Segmentation is by product—does not account for use of 1st line products in 2nd line treatment and vice versa

In terms of value, 95 percent of the 1st line market is in the public sector



1st Line Drug Market

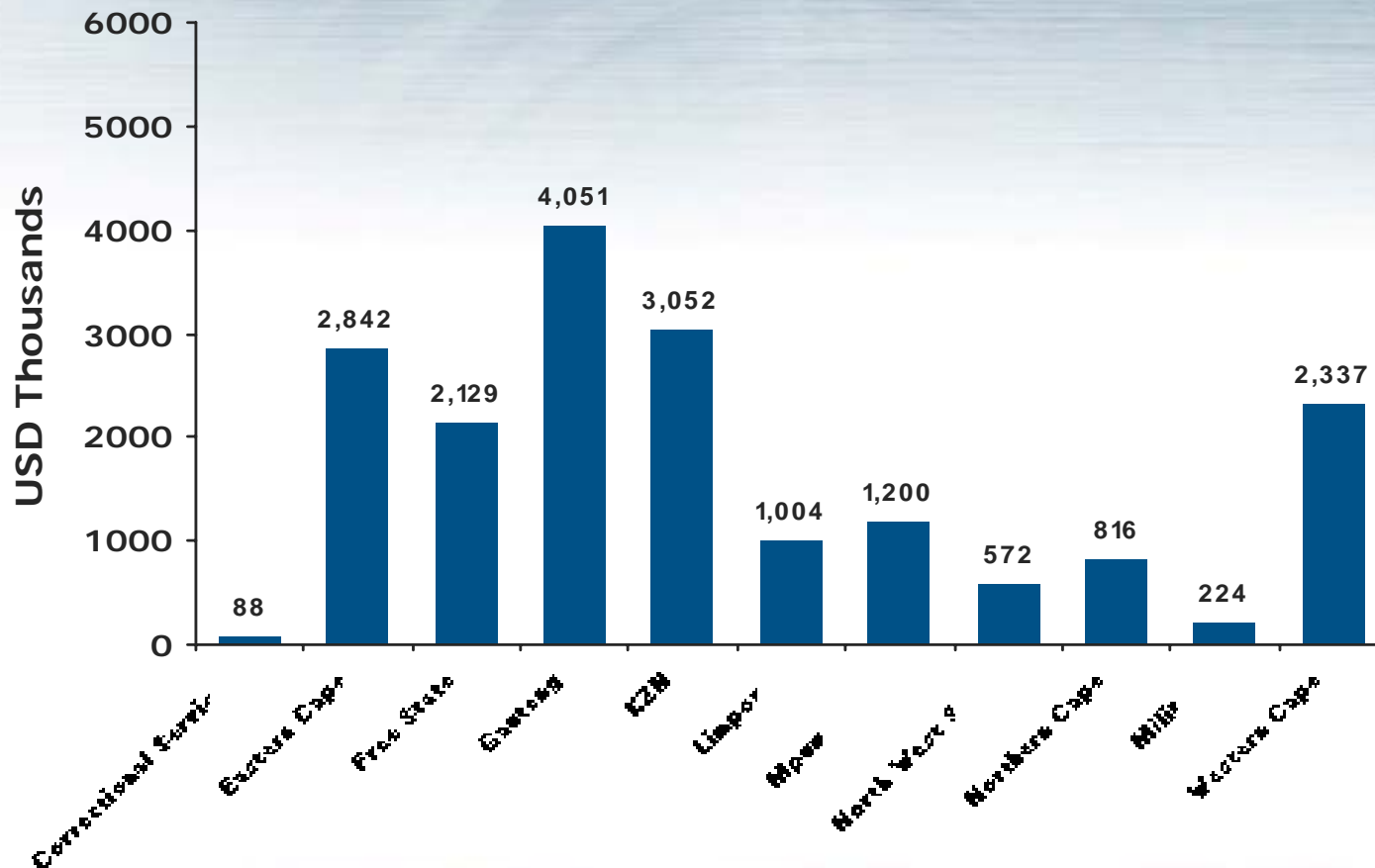
- 95% of the 19.25M USD 1st line market is in the public sector
- Approximately 250-260K new patients initiated on treatment each year
- Sanofi Aventis and Sandoz are the only players in the public sector:
 - Sanofi Aventis holds 49% volume share and 53% value share
 - Sandoz holds 51% volume share and 47% value share

Note: Includes 1st line drugs that may be used in 2nd line treatment of patients

Source: Supplier figures, IMS database, IMS Consulting analysis

Expenditures on 1st line drugs vary considerably between provinces

2005 1st Line Public Value Sales by Province

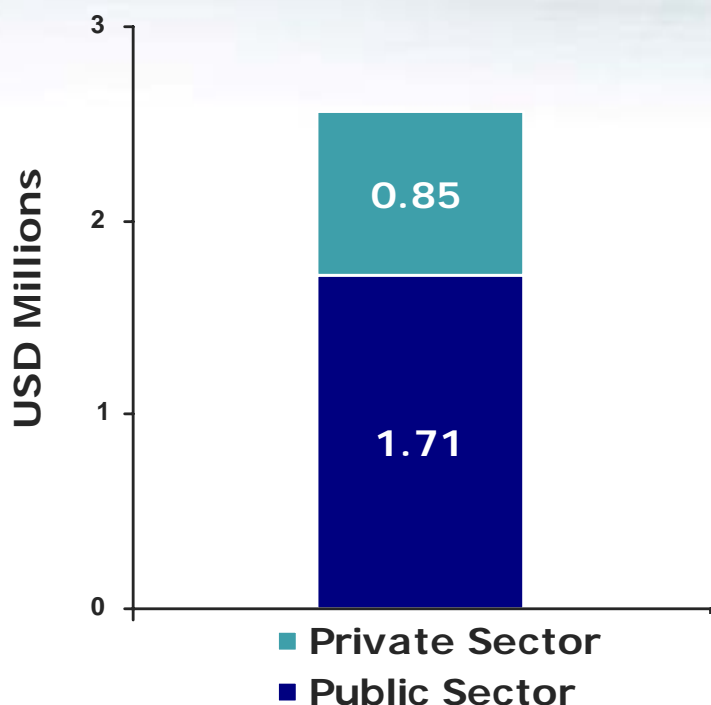


Note: Does not include 1st line drugs that may be used in 2nd line treatment of patients

Source: Supplier figures, IMS Consulting analysis

In the 2nd line market, the public sector holds the majority of the market value but by less of a margin than in the 1st line market

2005 2nd Line Value Sales*



2nd Line Drug Market

- 2nd line drugs account for 2.5 M USD or 6% of total TB market
- Approximately 66% of the 2nd line market value is in the public sector
- Tenders issued and awarded by product and do not distinguish between use in TB or non-TB indications**
- Market as a whole is led by Sanofi Aventis, though shared by a larger number of players such as Betabs and Biotech

Note: Includes 1st line drugs that may be used in 2nd line treatment of patients

*Sales of cycloserine or capreomycin not available

**Figures presented adjusted for use in non-TB indications

Source: IMS database, IMS Consulting analysis

The public sector's share of the 2nd line market has increased rapidly over the past five years



**2nd line drugs adjusted to screen out use in other indications*

Note: Does not include 1st line drugs that may be used in 2nd line treatment of patients

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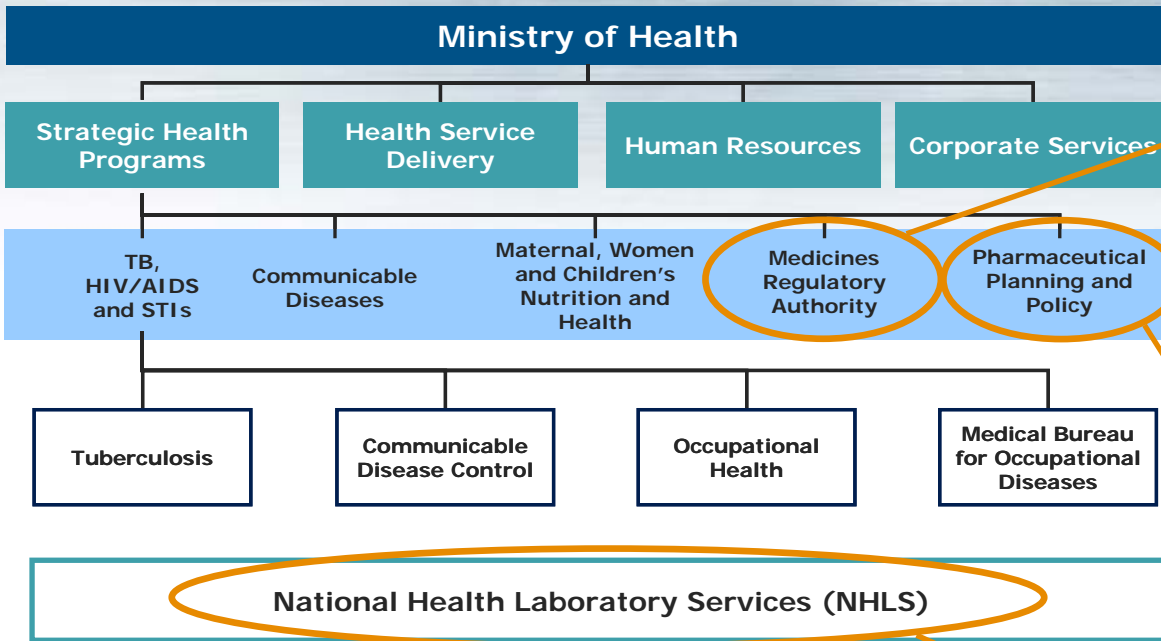
Appendix: Interviewed Stakeholders

Individual	Organization	Position
Dr Lindiwe Mvusi	National TB Control Program	NTP Director
Mandisa Helle	Pharmacy Planning and Policy	Dir of Pharmacy Services
Ms. Alvera Swartz	Provincial TB Control Program, West Cape	Provincial NTP Coordinator, Assistant Director, TB Control
Liezel Channing	Provincial TB Control Program, West Cape	Pharmacist ARV Program
Ann Preller	Provincial TB Control Program, North West	Provincial NTP Coordinator
James Kruger	District TB Control Program(Boland Overberg)	District NTP Director (Boland, Overberg)
Virginia de Azeveda	Sub-district TB Control Program (Kylitscha)	Sub-district NTP Director (Kylitscha)
Dr. M. Makhetha	WHO	TB Program Coordinator / NPO - TB
John Heinrich	SANTA	CEO
Ethel Makoena	SANTA	Chairman
Mrs Ria Grant	TB Care Association	Director
Prof. Gavin Churchyard	Aurum Institute	CEO
Dr. Penny Mkalipe	ESKOM	Medical Officer
Prof. Deon Du Plessis	Netcare	Medical Director

Appendix: Interviewed Stakeholders (continued)

Individual	Organization	Position
Reuben Mawela	Sanofi Aventis	District Sales Manager, TB
Alan Beattie	Aspen Pharmacare	National Sales Manager (Public Sector)
Elaine Cross	Sandoz	Head of TB Supplies
Dr. Bernard Fourie	MRC	Research Associate/Clinical Trials Advisor to the MRC; Chief Scientific Officer/Dir of South African Operations of MEND
Jean-Pierre Sallet	MSH	Regional Technical Advisor
Tumi Molongoana	MSH	Senior Program Associate
Shabir Banoo	MSH	Senior Program Associate
Sipho Mthathi	TAC	CEO

Appendix: Other key stakeholders relevant to TB control



Cluster under which Medicines Control Council (MCC) sits:

- South African regulatory authority to whom new drug applications must be made
- Headed by Dr HZ Zokufa

Responsible for forecasting and working with National State Tender Board

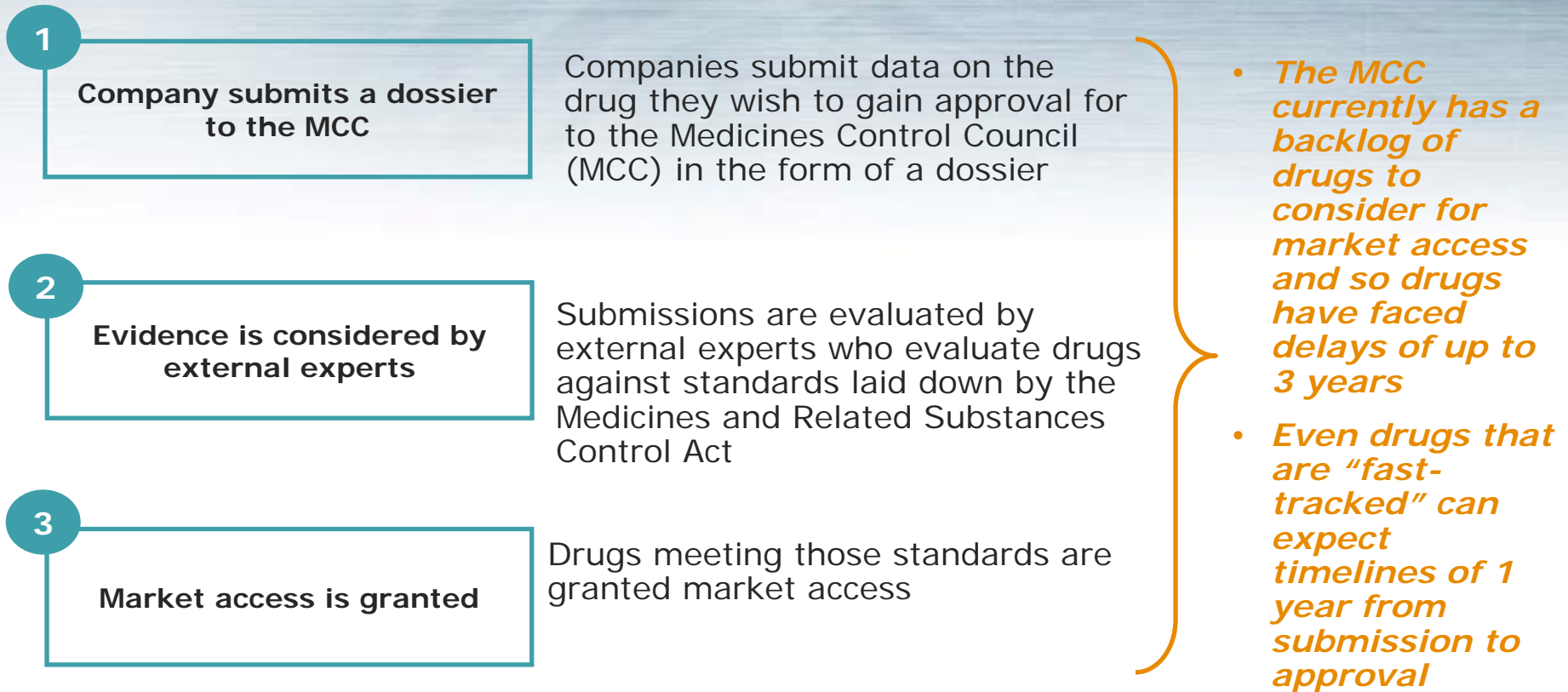
- Headed by Ms. Mandisa Helle

Network of laboratories providing diagnostic services to the NTP:

- Supports public health system but unclear to whom it reports

Source: Ministry of Health website, Interviews

Appendix: Medicines Control Council approvals process



Source: MCC Website

Appendix: Broad Based Black Economic Empowerment (BEE) Act

BEE SCORECARD

Direct empowerment through ownership and control of enterprises and assets

Management at a senior level

Human resource development and employment equity

Indirect empowerment: preferential procurement, enterprise development, corporate social investment

Details on the Broad Based Black Economic Empowerment Act

- Passed in 2004, designed to promote a more equitable distribution of wealth among all historically disadvantaged people (HDP)—i.e., women, disabled, black
- Operates via a scorecard with which a company's progress in BEE is measured
- Required by any private company wishing to do business in the public sector
- Employed by all state-run bodies and the government when making decisions on procurement, licensing and concessions, and the sale of state-owned assets or businesses
- Feeds into the Preferential Procurement Policy Framework

Source: www.southafrica.info – Black Economic Empowerment

Appendix: Preferential Procurement Policy Framework Act

Key Factors of Framework

Price

- Established in 2000 to provide a framework for state procurement

Functionality

- Preferential points are awarded to companies for price, functionality and HDP involvement (see BEE Act)

HDP
Involvement

- For cases in which price and functionality are comparable, companies demonstrating economic empowerment of HDPs are preferred choices for tenders

Nationality

- Joint ventures with companies demonstrating high HDP involvement are common—e.g., Enaleni manufactures and supplies all Merck products for the government pharmaceutical tender market

Appendix: Full treatment guidelines for Regimen 1 patients (new smear positive, new smear negative, extrapulmonary)

Pretreatment body weight	Initial Phase (2 Months)	Continuous Phase (4 months)			
	To be given 5 times per week	When given 5 times per week		When given 3 times per week	
	RHZE (150/75/400/275)	RH (150/75)	RH (300/150)	RH (150/150)	RH (300/150)
30-37 kg	2 tabs	2 tabs	--	2 tabs	--
38-54 kg	3 tabs	3 tabs	--	3 tabs	--
55-70 kg	4 tabs	--	2 tabs	--	3 tabs
Greater than 71 kg	5 tabs	--	2 tabs	--	3 tabs

Source: 2003 NTP Treatment Guidelines; DOTS Plus for standardised management of multidrug-resistant TB in South Africa (2004)

Appendix: Full treatment guidelines for Regimen 2 patients (relapse)

	Initial Phase (1 st 2 Months)		Initial Phase (3 rd Month)	Continuous Phase (4 months)			
Pretreatment body weight	To be given 5 times per week			When given 5 times per week			
	RHZE (150/75/400/275)	Streptomycin (g)	RHZE (150/75/400/275)	RH (150/75)	E (400)	RH (150/150)	E
30-37 kg	2 tabs	0.5	2 tabs	2 tabs	2 tabs	--	--
38-54 kg	3 tabs	0.75	3 tabs	3 tabs	2 tabs	--	--
55-70 kg	4 tabs	1.0	4 tabs	--	--	2 tabs	3 tabs
Greater than 71 kg	5 tabs	1.0	5 tabs	--	--	2 tabs	3 tabs
				When given 3 times per week			
				RH (150/150)	E (400)	RH (150/150)	E
				2 tabs	2 tabs	--	--
				3 tabs	3 tabs	--	--
				--	--	3 tabs	4 tabs
				--	--	3 tabs	4 tabs

Source: 2003 NTP Treatment Guidelines; DOTS Plus for standardised management of multidrug-resistant TB in South Africa (2004)

Appendix; Full treatment guidelines for pediatric TB patients

Pretreatment body weight	Initial Phase (2 Months)	Continuous Phase (4 months)	
	5 times per week	5 times per week	3 times per week
	RHZ (60/30/150)	RH (60/30)	RH (60/60)
3-4 kg	0.5 tab	0.5 tab	0.5 tab
5-7 kg	1 tab	1 tab	1 tab
8-9 kg	1.5 tabs	1.5 tabs	1.5 tabs
10-14 kg	2 tabs	2 tabs	2 tabs
15-19 kg	3 tabs	3 tabs	3 tabs
20-24 kg	4 tabs	4 tabs	4 tabs
25-29 kg	5 tabs	5 tabs	5 tabs
30-35 kg	6 tabs	6 tabs	6 tabs

Source: 2003 NTP Treatment Guidelines; DOTS Plus for standardised management of multidrug-resistant TB in South Africa (2004)

Sandoz private sector prices (USD)

Sandoz Trade Name	Pack Size	SEP Prices (VAT Excluded)	SEP Prices (VAT Included)
Rimactane 150	100	16.50	18.81
Rimactane 300 Vials	1	17.29	19.71
Rimactane 450	100	29.03	33.09
Rimactane 600	100	54.15	61.73
Rimactazid 150/75	60	7.00	7.98
Rimactazid 300/150	40	6.20	7.07
Rimactazid 60/30	40	5.27	6.00
Rimactazid Paed 60/60	80	11.92	13.59
Rimactazid Paed 60/60	120	17.88	20.38
Rimcure Paed 3-FDC	80	15.93	18.16
Rimcure Paed 3-FDC	120	23.90	27.24
Rimcure Paed 3-FDC	500	99.57	113.51
Rimstar 4-FDC	40	4.60	5.24
Rimstar 4-FDC	60	6.90	7.87

Source: Supplier figures

Sandoz private sector prices (USD) (continued)

Sandoz Trade Name	Pack Size	SEP Prices (VAT Excluded)	SEP Prices (VAT Included)
Rimstar 4-FDC	80	9.20	10.49
Rimstar 4-FDC	100	11.50	13.11
Rimstar 4-FDC	500	57.50	65.55
Sandoz Ethambutol HCl 400	100	12.67	14.44
Sandoz Pyrazinamide 500	100	14.72	16.78

Source: Supplier figures

Appendix: Sanofi-Aventis private sector prices (USD)

Sanofi-Aventis Trade Name	Pack Size	SEP Prices (VAT Excluded)	SEP Prices (VAT Included)
Rifafour e-275	40	4.43	5.05
Rifafour e-275	60	6.64	7.57
Rifafour e-275	80	8.86	10.10
Rifafour e-275	100	11.65	13.29
Rifafour e-275	500	55.35	63.10
Rifinah 300 mg	40	5.83	6.65
Rifater Junior	40	7.00	7.98
Rifinah Junior	40	5.78	6.58

Source: Supplier figures