

Treating Patient, Not Disease: People-Centered Approach

7th TB Symposium – Ministry of Health of the Kyrgyz Republic
and Médecins Sans Frontières

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Access update, registration & procurement
strategies

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Access to bedaquiline

- Innovator: Janssen - Partnership in EECA countries, except Ukraine : Pharmstandard
- No voluntary license yet with generic companies (Janssen's patent ends in 2029)

Regulatory	<ul style="list-style-type: none"> . USFDA accelerated approval (2012) . EMA conditional approval (2014) Phase III clinical trial on-going (results due by 2021) 	<ul style="list-style-type: none"> . Registered in 21 countries . Pending in 13 others, including Belarus . Submission soon due in Ukraine . Blocked in Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan due to lack of phase III data
Guidelines	<ul style="list-style-type: none"> . WHO interim guidelines in DRTB (2013) . WHO review of available evidence (2017) . WHO best practice on off label use of BDQ and DLM (2017) 	<ul style="list-style-type: none"> . Translation in national guidelines needed . OOS 2017: National DRTB guidelines including BDQ (79%)
EML	<ul style="list-style-type: none"> Added on WHO EML for TB (May 2015) 	<ul style="list-style-type: none"> . Translation in national EML needed . OOS 2017: National Essential Medicines List with either BDQ or DLM (28%)

- Nov 2017: 6 month course at US\$1.815 to 2.000 in the Russian Federation
- April 2015, for all GFATM eligible countries: USAID/Janssen donation through GDF for **30.000** treatments till spring 2019 (Jan. 2018: **19.272** courses ordered)

Access to delamanid

- Innovator: Otsuka - Partnership in EECA countries: R-Pharm
- No voluntary license with generic companies (Otsuka's patent ends in 2031)

Regulatory	<ul style="list-style-type: none"> . EMA conditional approval (2014) . Phase III clinical trial: results published Q4 2017; on-going assessment at EMA 	<ul style="list-style-type: none"> . Registered in EU, Hong Kong, India, Japan, Philippines, South Korea, Turkey . Regulatory assessment on-going in China, Indonesia, South Africa, Turkmenistan . Submission soon due in Ukraine
Guidelines	<ul style="list-style-type: none"> . WHO interim guidelines in DRTB (2014) . WHO guidelines for use of DLM in children/adolescents (2016) . WHO best practice on off label use of BDQ and DLM (2017) 	<ul style="list-style-type: none"> . Translation in national guidelines needed . OOS 2017: National DRTB guidelines including DLM (62%)
EML	<ul style="list-style-type: none"> WHO EML (2015) WHO EML for children (2017) 	<ul style="list-style-type: none"> . Translation in national EML needed . OOS 2017: National Essential Medicines List with either BDQ or DLM (28%),

- February 2016, all GFATM eligible countries: 6 month course at US\$ 1700 through GDF (Jan. 2018: **2.633** courses ordered)

Access to linezolid

- Innovator: Pfizer
- Secondary patents could preclude importation of low-cost generics until 2021, but very likely to be ignored
- Quality-assured generics: Teva, Hetero, Cipla, Macleods
- No TB indication yet: repurposed medicine for DRTB

Guidelines	Upgraded as category C in the MDRTB WHO guidelines (June 2016)	Translation in national guidelines needed
EML	Added on WHO EML for TB for adults and children (May 2015)	Translation in national EML needed

- May 2016: thanks to enhanced competition across manufacturers, **price drop (- 75%)** from US\$ 3.253 per treatment course (20 months) to US\$ 838
- High price in some EECA countries (e.g. Belarus)
- Macleods pediatric dispersible tablets: Global Fund/GDF Expert Review Panel status by Q1 2018?

Access to clofazimine

- Innovator: Novartis
- No patent barrier, nevertheless no quality-assured generics yet (3 generic companies developing generic version: Macleods, Dong A, Lupin)
- No TB indication yet (repurposed medicine for DRTB), though in Jan 2017, USFDA granted fast-track assessment to Novartis's retrospective IPD due for submission in 2018

Guidelines	Upgraded as category C in the MDRTB WHO guidelines (June 2016)	Translation in national guidelines needed (some countries did so for the MDR shortened regimen)
EML	Added to WHO EML for TB indication, adults & children (March 2017)	Translation in national EML needed

- One set of price at Novartis, whatever the country: US\$ 597 per treatment (20 months) as per latest GDF negotiations

Access to imipenem/cilastatine

- Innovator: MSD (USA)
- Quality-assured generics incl. Demo (Greece), Fresenius (UK), Labatec (Switzerland), Panpharma (France), Sun Pharma (India)
- No TB indication: repurposed medicine for DRTB

Guidelines	In category D3 (add-on agent) in the MDRTB WHO guidelines (June 2016)	Translation in national guidelines needed
EML	On current WHO EML only as general anti-bacterial (watch group list)	

- “Best” price so far through GDF at Panpharma: US\$ 3.402 per treatment (for an average of 8 months)
- Major operational hurdle: need for infusion (Porth a Cath), with related complications for patient home care
- Transitory companion medicine to new DRTB ones till more efficient/safe new compounds are available?

Challenges in access

- **Green Lights easing up dispensation of new /repurposed DRTB medicines**
 - ✓ WHO guidelines on how to dispense new /repurposed DRTB medicines
 - ✓ Listing on WHO EML for TB (except imipenem)
 - ✓ Quality-assured (QA) sources on the international market
- **Red Lights blocking importation and/or dispensation of new /repurposed DRTB medicines**
 - ✓ Delay in updating national TB guidelines & EML
 - ✓ Lack of TB indication for repurposed medicines
 - ✓ Delay in national registration & lack of importation waiver provision
 - ✓ High cost per patient per month

Cost / patient /month

-best current prices for quality-assured medicines-

Linezolid	Clofazimine	BDQ 1st potential generic	BDQ - outside donation	DLM	BDQ - outside donation	Imipenem	BDQ - outside donation
US\$ 42	US\$ 66	US\$ 90	<u>Janssen</u> US\$ 150 (LIC)	<u>Otsuka</u> US\$ 283	<u>Pharmstandard</u> US\$ 303 (Russian Federation only)	US\$ 425	<u>Janssen</u> US\$ 500 (MIC)
Gotham target price: US\$ 5 - 13	Gotham target price: US\$ 6 - 16	Gotham target price: US\$ 9 – 16		Gotham target price: US\$ 3.5 - 9			

- **!! Complicated patients need more than only 6 month treatment with new medicines to be cured !!**

- For moxifloxacin which used to be very costly for DRTB use:

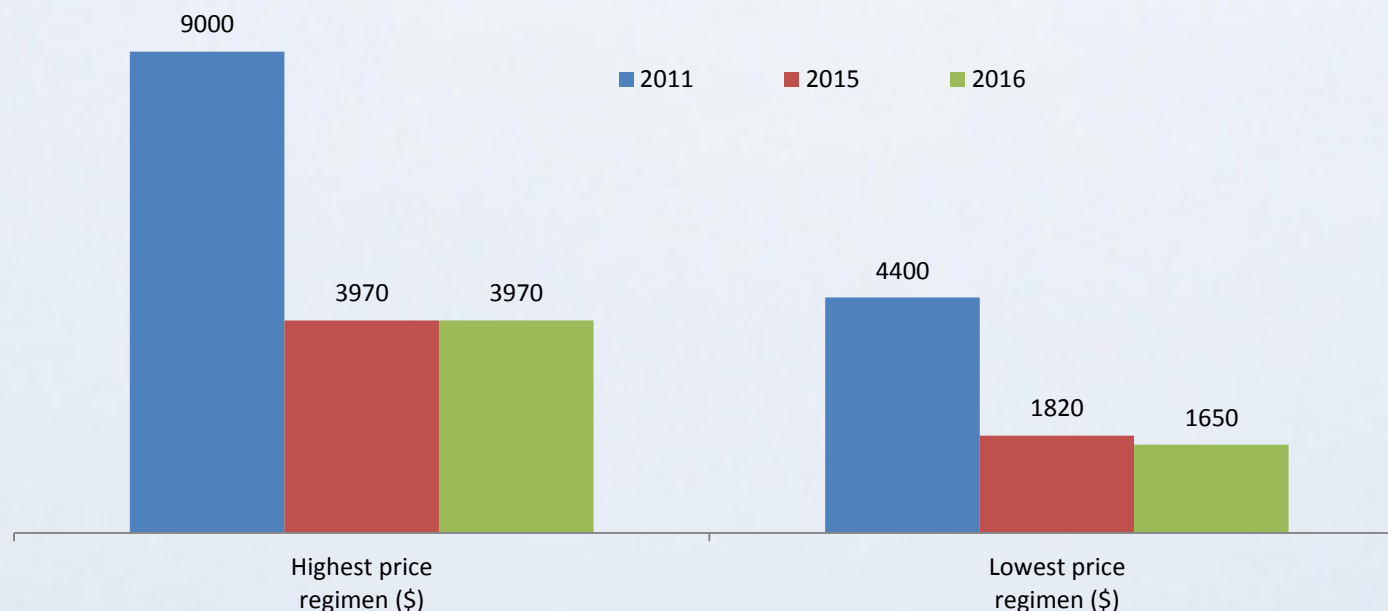
Cost / Patient / Month = currently US\$ 9, thanks to healthy competition across manufacturers (Gotham target price = US\$ 3.5 – 9.4)

Source: Gotham Estimated generic prices for novel treatments for DRTB [J Antimicrob Chemother.](#) 2017 Apr 1;72(4):1243-1252

How to do better on price?

- Considering the relatively small DRTB market, only one way forward:
competition across manufacturers & pooled procurement across countries
- GDF, global example of pooled procurement of QAed TB medicines at the lowest global prices by setting up international yearly bids across manufacturers

Decrease of preferred regimen prices (**2 year Standard Of Care**) through GDF from 2011 till 2016, in US\$:



Note: with 2016 GDF prices, short regimen cost: 600 to 800 US\$

How to do better on regulatory components?

Early access mechanisms before local marketing authorisation is granted

✓ **Compassionate Use for new coming DRTB molecules (e.g. pretomanid)**

- . When no satisfactory authorised therapy in the context of a serious, life-threatening condition for patients who cannot enter a clinical trial
- . Possible on an individual basis once Phase II data are available for a new medicine
- . Guidance in 2014 WHO Companion handbook to the WHO guidelines for the programmatic management of DRTB

✓ **Expanded Access**

- . Like Compassionate Use for a cohort of patients
- . Expanded Access also used to collect safety data after registration (e.g. China, India, South Africa)
- . Guidance in 2014 WHO Companion handbook to the WHO guidelines for the programmatic management of DRTB

✓ **Import waiver**

✓ **Temporary access under a national research framework**

How to do better on regulatory components?

Expedited registration (1/2)

✓ **Mutual recognition between regulatory authorities**

- Take benefit of assessment already performed by stringent regulatory authorities (SRA)

→ Example: bill N°4484 in Ukraine

« For public health priority diseases such as TB, the law allows medicines already authorized in the European Union, United States, Japan, Australia, Canada and Switzerland to be authorized in Ukraine under a simplified procedure in less than a month »

✓ **Regional harmonisation regulatory framework**

- Eurasian Economic Union harmonised registration procedure for medicines

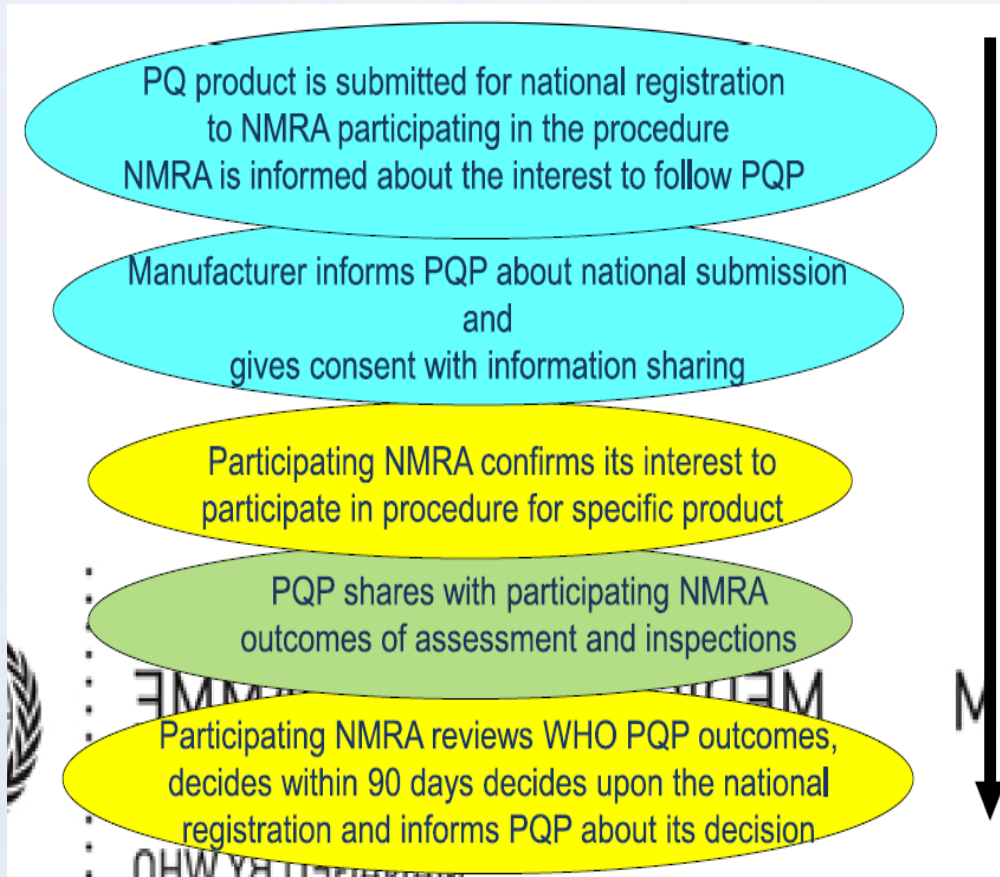
. To start in 2018

. So far Armenia, Belarus, Kazakhstan, Kyrgyzstan, Russian Federation are part of the process

How to do better on regulatory components?

Expedited registration (2/2)

✓ Collaborative Registration Programme with the support of WHO Prequalification



- For WHO prequalified & SRA registered medicines
- 33 participating countries, including Armenia, Georgia, Kyrgyzstan, Ukraine
- **More than 300** marketing authorisations approved, including **more than 50** for TB & DRTB medicines
- 93 days as a median time from information sharing to registration (2014 survey)

Global Fund co-financing / transition policies



- Need for countries to anticipate best ways to secure long term access to quality-assured DRTB medicines at an affordable price
 - explore ways to keep GDF as a bidder in national public tenders
 - anticipate the local registration of WHO-prequalified and SRA approved DRTB medicines to allow manufacturing companies to bid in national tenders