Tuberculosis in 2017: Searching for new solutions in the face of new challenges

6th TB Symposium – Ministry of Health of the Republic of Belarus, Republican Scientific and Practical Center for Pulmonology and Tuberculosis, and Médecins Sans Frontières

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Access update, registration & procurement strategies

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MEDECINS SANS FRONTIERES

Access to bedaquiline

- Innovator: Janssen - Partnership in CIS countries: Pharmstandard
- No voluntary license yet with generic companies (Janssen's patent ends in 2029)
- **Jan. 2017: 7597 patients in programmatic use – 766 patients in compassionate use**
- Phase III Clinical trial (extended STREAM trial): results due by 2021

WHO interim guidelines (June 2013) based on current conditional approvals at EMA (March 2014) and USFDA (Dec. 2012) **Updated WHO guidelines expected Feb. 2017**	Translation in national guidelines needed
Added on WHO EML for TB (May 2015)	Translation in national EML needed
Beyond USA & Western Europe, registration in 12 countries including Armenia, **Moldova,** Russian Federation, Turkmenistan & Uzbekistan	. On-going dossier assessment at Regulatory Authorities **in 17 countries, including** Belarus . Lack of Phase III, a problem in Azerbaijan, Kazakhstan, Kyrgyzstan; possibly Georgia?

- January 2015, for CIS countries: 6 month course at US$ 1700 in the Russian Federation & US$ 1351 in other CIS countries
- April 2015, for all GFATM eligible countries: USAID/Janssen donation through GDF for **30.000** treatments till spring 2019 (Jan. 2017: **6385** courses ordered)

Access to delamanid

- Innovator: Otsuka - Partnership for CIS countries: under negotiation
- No voluntary license yet with generic companies (Otsuka's patent ends in 2031)
- **Jan. 2017: 469 patients in programmatic use – 1800 patients in compassionate use**
- Phase III Clinical trial: results due by Q4 2017

WHO interim guidelines (Oct.2014) based on current conditional approvals at EMA (April 2014); update for children (Oct. 2016)	Translation in national guidelines needed
Added on WHO EML for TB for adults (May 2015); submission for children (March 2017)	Translation in national EML needed
Beyond Japan & Western Europe, registration in **South Korea (Republic),** Hong Kong	. On-going dossier assessment at Regulatory Authorities in China, Indonesia, Philippines, Turkey . Evaluation whether to go for EAEU harmonised procedure by Q2 2017

- February 2016, all GFATM eligible countries: 6 month course at US$ 1700 through GDF (Jan. 2017: **1648** 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, still ERP status till Oct. 2017)
- No TB indication : repurposed medicine for DRTB

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

- May 2016: thanks to enhanced competition across manufacturers, **price drop (- 75%)** from US$ 3253 per treatment course (20 months) to US$ 838

Access to clofazimine

- Innovator: Novartis
- No patent barrier, nevertheless no quality-assured generics yet (2 companies developing generic versions, one could submit its dossier to WHO Prequalification Programme by Q2 2017)
- No TB indication yet (repurposed medicine for DRTB), though in Jan. 2017, USFDA granted fast-track assessment to Novartis's retrospective individual patient data due for submission by Q4 2017

Upgraded as category C in the MDRTB WHO guidelines (June 2016)	Translation in national guidelines needed
Submission to WHO EML for TB indication, adults & children (March 2017)	If successful, translation in national EML needed

- One set of price at Novartis, whatever the country: US$ 666 per treatment (20 months)

Access to imipenem

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

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

- "Best" price so far through GDF at Panpharma: US$ 3402 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 clofazimine & *imipenem if DRTB need confirmed*)

✓ 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 (best current prices for QA medicines)

When currently for moxifloxacine: US$ 9 of cycloserine: US$ 25,

Linezolid	Clofazimine	Bedaquiline (outside donation)	Delamanid	Imipenem
US$ 42	**US$ 66**	**<u>Pharmstandard - CIS countries</u>** **US$ 225 (CIS, not Russian Federation)** **US$ 283 (Russian Federation only)** **<u>Janssen – non CIS countries</u>** **US$ 150 (Low Income Countries)** **US$ 500 (Middle Income Countries)**	**US$ 283**	**US$ 425**

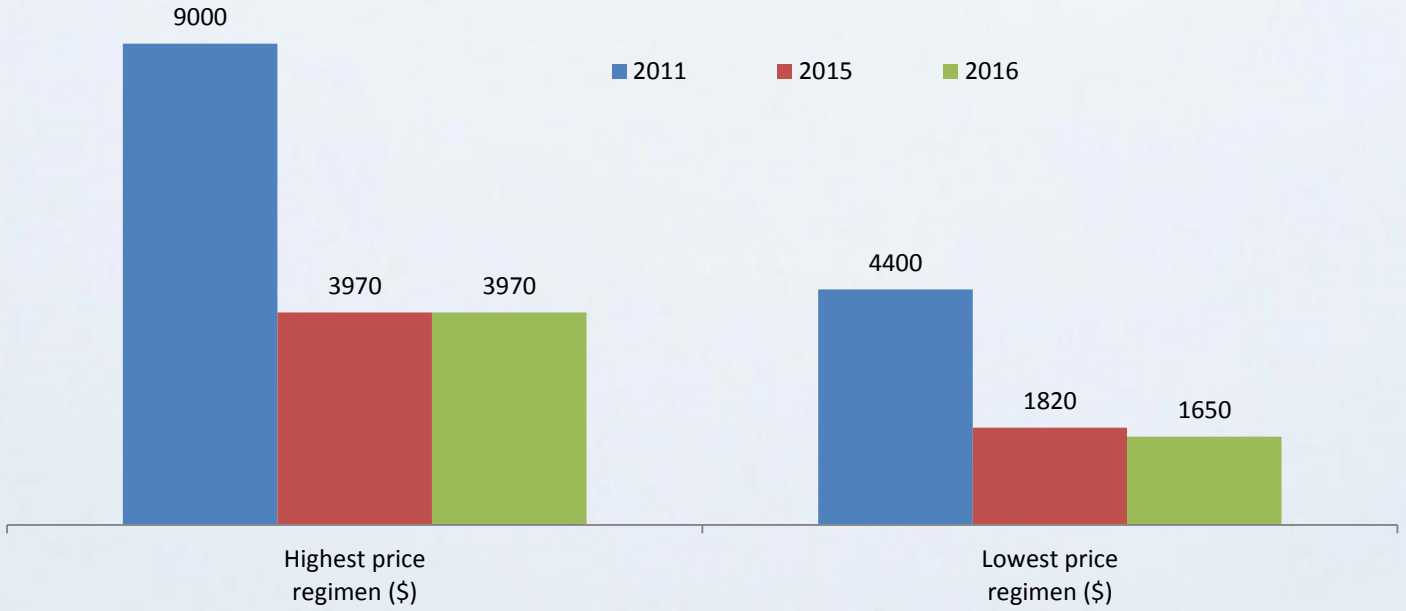
How to do better on price?

- 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 through GDF from 2011 till 2016, in US$:



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

- **Besides the Global Fund mechanism, how to keep GDF as a bidder in national public tenders?**

How to do better on regulatory components?

Early access mechanisms before local marketing authorisation is granted

✓ **Compassionate Use**

. When no satisfactory authorised therapy in the context of a serious, life-threatening condition for patients who cannot enter a clinical trial

. On an individual basis

. Possible 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

. 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 EU, United States, Japan, Australia, Canada and Switzerland to be authorized in Ukraine under a simplified procedure in less than a month »

✓ **Regional harmonisation framework**

- Eurasian Economic Union harmonised registration procedure for medicines

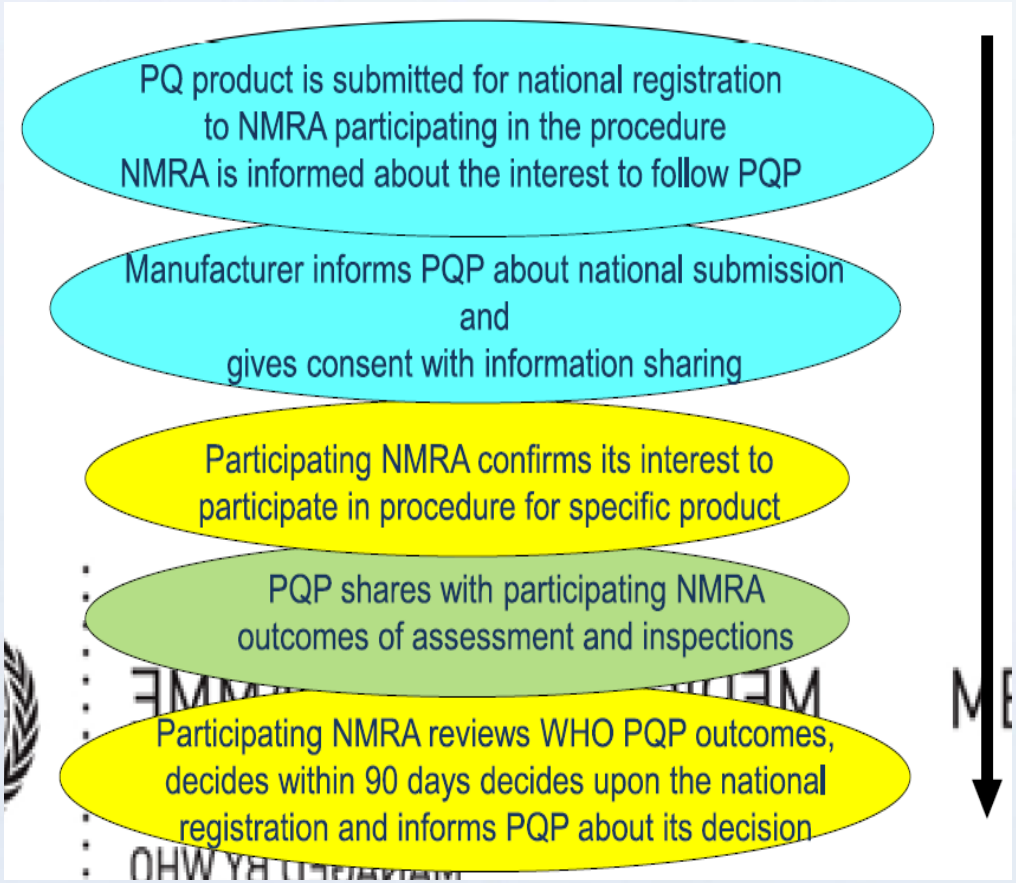
. To start by Q2 2017? (approval of chemical regulations still holding the process)

. So far Armenia, Belarus, Kazakhstan, Kyrgyzstan, Russian Federation are part of the process; will more CIS countries join?

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
- 30 participating countries, including Armenia, Georgia, Kyrgyzstan, Ukraine
- 185 marketing authorisation approved, including 46 for TB & DRTB medicines
- 93 days as a median time from information sharing to registration (2014 survey)