



New treatments and approaches to Tuberculosis

Tuberculosis Symposium – Eastern Europe and Central Asia
RA Ministry of Health and Médecins Sans Frontières

Importation of new drugs including compassionate use.

Countries' experience of accessing the new drugs

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Agenda

- Importation mechanisms and compassionate use background
- Overview of the "status" of the new drugs in the region (marketed, importation mechanism, CU, etc.)
- Country experience with new drug access (Georgia, Armenia, Chechnya, Kyrgyzstan)

Importation Mechanisms



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Importation mechanisms

- Importation of medicines registered by the NMRA
 - ↳ content of the registration dossier defined by NMRA
- Importation of non registered medicines through flexible mechanisms as humanitarian access
 - ↳ under justification of the origin of the product, quality documentation
- Importation of non registered medicine for individual use through :
 - CU
 - Specific law for individual use
 - ↳ Required medical dossier

Compassionate use for TB patients

Сострадательная терапия



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Current situation for DRTB treatment

- Long treatment, many side effects hardly tolerated, low effectiveness for most drugs
 - ↳ but these are the only medicines available
- Urgent need to develop, validate and approve more effective and more tolerable treatments for drug-resistant TB (DRTB)



New drugs eligible for CU

2 promising drugs completed phase 2 and are currently on phase 3 clinical study

- Bedaquiline :
 - December 2012 → registration for conditional use by the United States Food and Drug Administration for official use in DRTB patients
- Delamanid :
 - April 2014 → registration for conditional use by the European Medicines Agency
 - July 2014 → registration by the Japanese Pharmaceuticals and Medical Device Agency

↪ But very few other countries registered Bedaquiline (Russia, RSA,...) and some files submitted by Pharmastandard in the region

↪ Before these two products could be formally included in the countries medical register it could be made available through CU

What is compassionate use (CU)?

CU is a mechanism aiming at providing a medicine:

- still under clinical development, for which phase II studies proved efficacy and acceptable safety profile,
- to patients suffering from a life-threatening disease and for whom no satisfactory authorised therapy exists.

↪ CU is a way to save lives before a new effective drug is fully registered by local Ministries of Health in all affected countries.

↪ It can be considered as a last hope treatment

Definition according to WHO

- ‘provide potentially life-saving *experimental* treatments to patients suffering from a disease for which no satisfactory authorised therapy exists and/or who cannot enter a clinical trial’
- ‘The terms “compassionate use,” “expanded access” or “special access” programmes have essentially the same meaning’

What is compassionate use ?

- CU is NEITHER a clinical trial, NOR an experimental therapy
- Minimal data are collected on patients, since CU is not research-oriented
 - ↳ Ministries of Health and pharmaceutical companies usually only asked to get final treatment outcome and Serious Adverse Events
- There is no economical interest from pharmaceutical companies: a drug under CU is generally provided for free (included transport cost)
- CU is not palliative care: the drug under CU can cure patients



MSF system: Indications outlines

CU considered for M/X DRTB patients

- presenting a life-threatening condition and for whom
- available treatments have failed or are very likely to be ineffective
- no medical or surgical options are appropriate
- susceptibility to at least one effective drug confirmed (never mono-therapy). To be considered on a case by case basis



MSF system: Minimal program requirements

- **Adequate management of DR TB in place**
 - Optimal treatment regimen and internationally quality assured drugs
 - EQA Drug Susceptibility Testing and bacteriological follow-up
 - Clinical and biological monitoring
 - Management of side effects
 - Adherence support
- **Specific monitoring if required**
- **Reporting system for adverse events**



MSF modus operandi

Patient

Practitioner + MSF medical coordinator

MSF medical committee for CU

Request to the drug developer

Patient

- **Must be well-informed about**
 - CU drug intended actions
 - CU drug potential adverse effects
- **Understands that there is no guarantee of benefit from the experimental drug**
- **Written consent**

Practitioner

- Is responsible for initiating a request on behalf of the patient
- Should provide :
 - ✓ a description of the conditions necessitating CU
 - ✓ a discussion of why existing therapies are unsatisfactory
- Must agree to report on the results of the use of the drug (follow-up forms) and to report immediately to the MSF medical committee any SAE
- Send request to MSF medical committee for CU

MSF/PIH medical committee for CU

- **Terms of reference**
 - Reviews the requests from MSF projects
 - Formulates recommendations for individual patients based on indications and requirements
 - Reports to the (MSF) ERB (Ethical review Board) every 6 month or 15 requests
- **Decision making process**
 - 7 members, quorum of 5, decision made if no more than 2 negative votes
 - Decision in 2 working days
 - Second recourse: advise from 2 other external experts

Drug developer

- Has the final word on whether the drug will be supplied and under which conditions
- Is responsible for providing information on pharmaceutical quality of the product for CU
- Is responsible for providing all information to practitioners and patients



Regulatory framework for CU

- CU is already a well proven treatment step for cancer, Alzheimer's disease, HIV/AIDS in a series of countries: USA, Canada, Western Europe, Australia, ...
- According to Janssen datas (2013)
 - More than 40 countries with patients under CU for Bedaquiline
 - Among them Armenia and Georgia
 - Around 500 patients under CU for Bedaquiline worldwilde by October 2014



Regulatory framework for CU

- **In South Africa**

- Apply for access to the drug via an application to the Medicines Control Council (MCC) under Section 21 of the Medicines and Related Substances Act 101 of 1965.
- **Clinical access program** for bedaquiline (equivalent to CU for a cohort of patients) started in March 2013 (5 sites, 200 patients treated by October 2014)
- Bedaquiline registered by the Medicines Control Council in October 2014

↳ Early access to Bedaquiline through the clinical access program in addition to the clinical trials run in the country facilitated the registration of Bedaquiline

Regulatory framework for CU

Unfortunately very few countries have a legal framework for CU **but** for some, practicalities are in place to implement CU :

- **India**

- No specific CU legislation but practicalities in place to import unregistered medicines which can be used for a particular patient, based on rules and standard forms of the Drugs and Cosmetics Act, 1940, and Drugs and Cosmetics Rules, 1945.
- Bedaquiline already imported based on this rule
- Delamanid will follow the same process

Regulatory framework for CU

- **Georgia and Armenia**
 - MOH authorised the CU from 2011
 - Practicalities have been put in place to implement the CU (e.g. medical committee of TB experts to review each clinical case)
 - For Bedaquiline
 - 30 (12 NTP and 18 MSF) patients were treated with Bedaquiline under CU in Georgia and 50 in Armenia
 - For Delamanid CU is initiated with Otsuka
 - Confidential agreement signed between MoH and Otsuka
 - PV training received
 - 2 first patients from Georgia approved for CU by Otsuka in January 2015

Requisites to fulfil in country before doing CU for TB?

- Decision to be made at MoH level on the medical added value of doing CU in TB for the patients
- As per international standards for CU, it is needed to set up:
 - evaluation of CU projects by an Ethics Committee,
 - review of Phase II pharmaceutical data by MoH for each drug which is a candidate for CU,
 - informed consent procedure with patients,
 - requirements for the importation of drugs under CU



Conclusion

- Only some countries have regulatory framework or practicalities for CU in place, but some are open to change
- Process aimed at a smaller number of patients compared to expanded access programs
- Time window for CU program: likely narrow in countries that approve shortly after USFDA/EMA approval; longer time in countries that will be slow in drug approval
- Important benefits:
 - Benefit for patients suffering from DRTB, HIV/AIDS, cancer, hepatitis,...
 - “Priming” the system (NTP, regulatory agency, clinicians, patient groups) for the new drugs and not only for DRTB

Overview of the "status" of the new drugs in the region



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	Armenia	Georgia	Kyrgyzstan	Russia
Importation mechanism	Humanitarian Access (HA)	Humanitarian Access (exemption letter for unregistered drugs)	Humanitarian Access	Humanitarian Access for registered drugs or life saving framework for specific drugs / specific patient
CU framework	Authorised and practicalities in place	Authorised and practicalities in place	No	No
Bedaquiline	Not registered but accessible through CU and HA	Not registered but accessible through CU and HA	Not registered but file submitted by Pharmastandard	Registered and marketed by Pharmastandard
Delamanid	Not registered but accessible through CU	Not registered but accessible through CU	Not registered and not available	Not registered and not available

	Tadjikistan	Ukraine	Uzbekistan	Belarus
Importation mechanism	Humanitarian Access	Humanitarian access procedure - emergencies, catastrophes, epidemics: can import non registered drugs.	Humanitarian Access	Humanitarian Access
CU framework	No	No	No	No
Bedaquiline	Not registered	Not registered/ Problem of access as Russian products were banned from market	Not registered but file submitted by Pharmastandard	Not registered but file submitted by Pharmastandard
Delamanid	Not registered	Not registered	Not registered	Not registered

Georgia experience with introduction of new MDRTB drugs



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Ways of importation of MDRTB drugs in Georgia

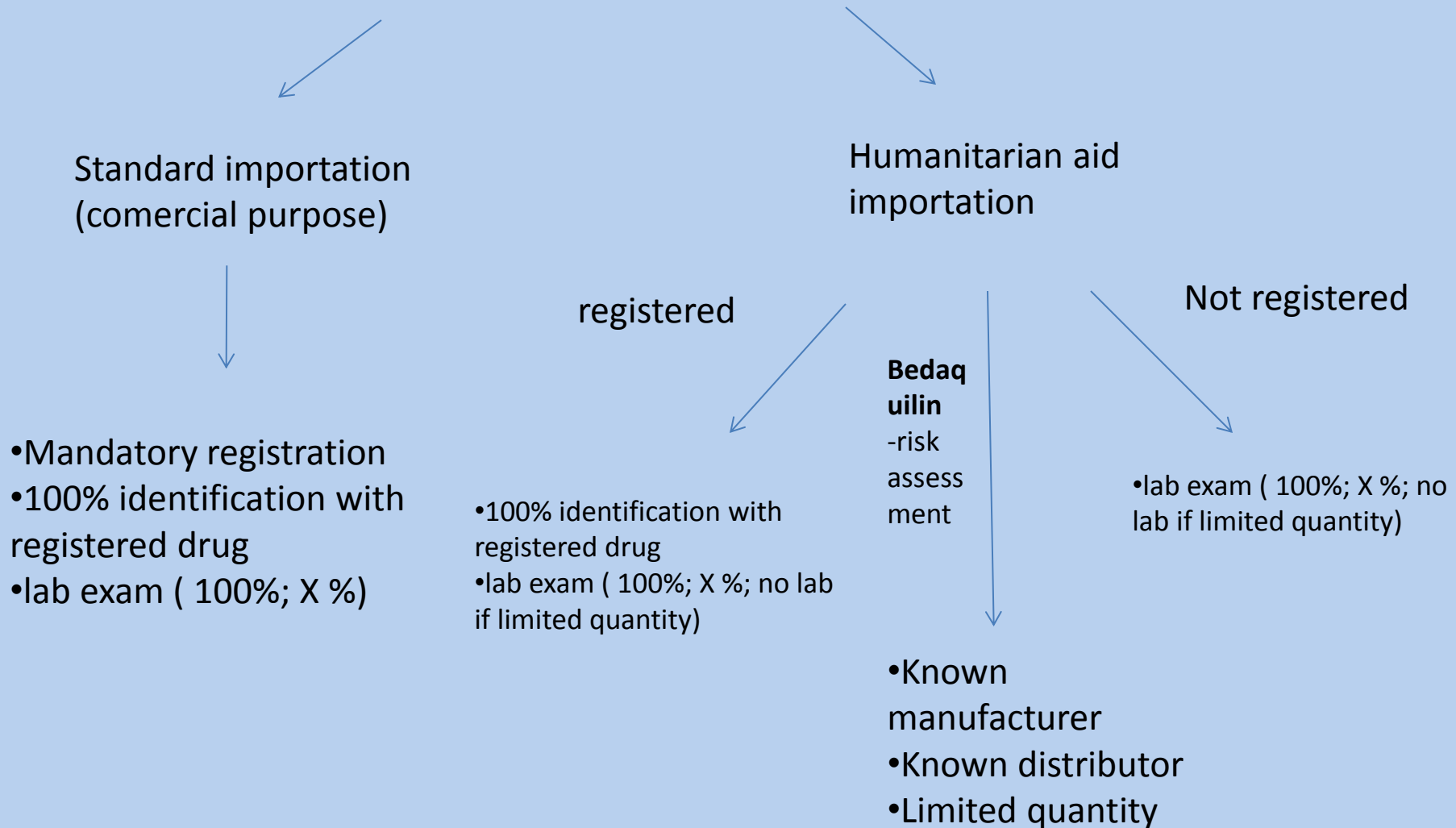
- Drugs already registered in Georgia can be imported without any approval.
- Non-registered drugs can be imported through the MoH special commission after submission of the relevant documents (so called “exemption” mechanism).
- Non-registered drugs with the q-ty less than 10 packs, can be imported for the individual needs of the patient without “exemption” permission, just presenting medical documents. This way of importation is used by NTP Georgia for importation of Bdq and will be used by MSF for importation of Delamanid.

Armenia experience with introduction of new MDRTB drugs



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There is 2 types of importation in Armenia. In both cases needed importation authorization by MOH



Chechen Republic experience with introduction of new MDRTB drugs



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New TB drugs use in Russian Federation

- 22.10.2013 – Bedaquiline (Sirturo) registered in Russia by Pharmastandard under license of Janssen
- Principal agreement had been obtained between MSF and MOH RF/MOH Chechen Republic about use of bedaquiline, clofazimine and imipenem/cilastatine and linezolid for treatment of TB
- Imipenem/ Cilastatine, linezolid and Bedaquiline accessible from local market ,
- Clofazimine is not registered in RF

New TB drugs use in Russian Federation

- Importation under lifesaving framework is the only choice for clofazimine
- Federal Law “On turnover of medicines” N 61 from 12.04.2010 determines possibility of importation of concrete batch of unregistered medicine for lifesaving medical aid for the concrete patient.
- The Decree of Government of RF N 771 from 29.09.2010 “On procedure of importation of medicines for medical use” is applying the procedure for import of unregistered medicines.

Kyrgyzstan experience with introduction of new MDRTB drugs



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Kyrgyzstan : Preparation for new TB drugs implementation

- Feb. 2014:
 - First presentation of concept of new TB drugs to MoH partners
 - MoU for Kara suu project signed with main objective of starting Day 1 ambulatory care for DRTB patients and implementation of innovative practices including new TB drugs
- May 2014: DDP informed about the intent of MSF using new drugs for XDR Treatment in Kara suu project and process of Registration initiated.
- June 2014:
 - pharma std and hetero group invited for registration
 - assessment of facilities and patients needs calculated in Kara suu region
 - Draft XDR Guidelines
- September 2014: IO for Bedaquiline and Linezolid placed for 4 XDR patients

Kyrgyzstan cont:

- October 2014:
 - registration of Bedaquiline stopped due to concerns on the PV in the country that needed to be strengthened .
 - It was decided that a special legal frame work will be developed with involvement of the MoH and DDP to allow the importation of the Bedaquiline under special humanitarian goods.

Thank You



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