ACCESSING NEW DRUGS FOR TB

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RATIONAL INTRODUCTION OF A NEW DRUG AND APPROPRIATE USE

To ensure effectiveness and preserve efficacy of the new drug

- Minimize the risk of treatment failure
- Minimize risk of emergence of resistance to the drug
- Increase benefit to patients

NEW DRUGS IN TB TREATMENT

Guidance on the appropriate use of the new drug

- WHO interim guidance on the use of bedaquiline to treat MDR-TB

Programmatic requirements

- **Adequate management of DR TB in place, like**

  - Access to quality-assured in vitro drug susceptibility testing and bacteriological follow-up
  - Clinical, biological and bacteriological monitoring
  - Management of side effects
  - Adherence and psychosocial support
- **Optimal treatment regimens available**
- **Availability of quality-assured second- and third line anti-tuberculosis agents**

  Comprehensive list of quality assured TB medicines sources on Global Fund website (*http://www.theglobalfund.org/en/procurement/quality/pharmaceutical/*)

C. R. Horsburgh Jr, et al ***Compassionate use of and expanded access to new drugs for drug-resistant tuberculosis***
INT J TUBERC LUNG DIS 17(2):146–152; 2012
WHO The use of bedaquiline in the treatment of multidrugresistant tuberculosis, Interim policy guidance 2013

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ACCESSING NEW DRUGS - Bedaquiline

Clinical and Development Phases of Drugs

Type	Endpoint	Size	Duration of study	What is being studied?
Phase I	Establish safety/tolerability, dosage and routes of administration	Up to 50 normal healthy volunteers	Up to 1 year	Drug in healthy human beings
Phase II	Adverse effects, assessment of clinical potential	100- 300 patients	2 years or more	Drugs and regimen in patients
Phase III	Efficacy & safety profiles	Around 500 to 1000 patients, or more	Up to 3 years	Drugs and regimen in patients
Submission of new dossier for country registration approval : in average 3 years till registration completed				
Phase IV	Post-marketing	large	years	Drugs and regimen in patients

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Access to Bedaquiline

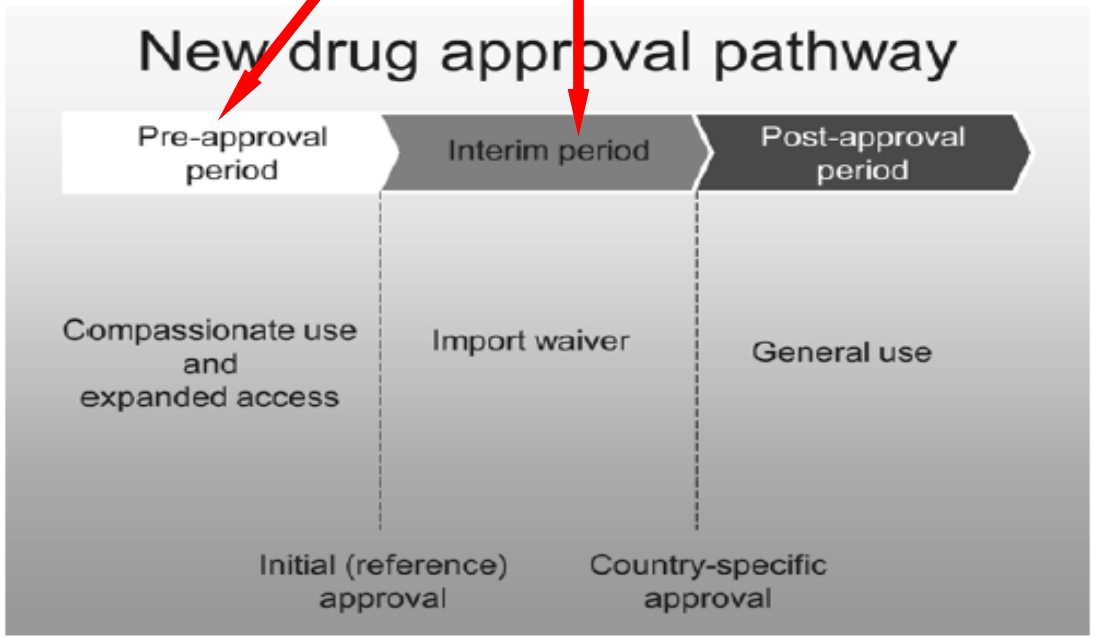

Figure Types of programs allowing access to new drugs and their relationship to the new drug approval pathway.

C. R. Horsburgh Jr, et al ***Compassionate use of and expanded access to new drugs for drug-resistant tuberculosis*** *INT J TUBERC LUNG DIS 17(2):146–152; 2012*

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Clinical trials 'pre-approval phase'

Phase I **Phase II** **Phase III**

2 months of safety data

Compassionate Use

Application for country approval

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COMPASSIONATE USE

Definition

- Access and provision to Investigational New Drugs (IND) prior to regulatory approval in a country

  Drug still under clinical development, for which phase II studies ***proved efficacy and acceptable safety*** profile

- Patients suffering from a ***life-threatening disease*** and whose treatment option have been exhausted.

  Specific individual patient, prescribed by one physician and provided by the manufacturer for the use in that specific patient

Scientific benefit

- Minimal data are collected on patients, data will not be considered for research, as CU is not research-oriented
- MoH and pharmaceutical companies usually only asked to get ***final treatment outcome and Serious Adverse Events***.

Economic interest

- Medicine under CU should be provided for free (included transport cost)

Drug Developer' Responsibility

- 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 drug
- Is responsible for providing all information to practitioners and patients

Countries' Responsibility

Regulatory mechanisms

- In most countries, only drugs for which a marketing authorization has been granted by the national regulatory agency can be used in humans.
- Many countries have established ***processes and/or put a legal framework in place to allow CU*** in the country
- Each country decides ***its own regulations and definitions***:
  CU, ***Expanded Access Programs*** (EAP), ***Special Access Program*** (SAP)

Prerequisites as per international standards before CU can be implemented:

- Evaluation of CU projects by a ***Medical and Ethics Committee***
- ***Review of Phase II pharmaceutical data*** by MoH for each drug which is a candidate for CU
- ***Informed consent procedure with patients***
- Regulatory requirements for the ***importation of drugs*** under CU

WHO Guidelines for the programmatic management of drug-resistant tuberculosis 2008 Emergency up-date 2008 ANNEX 5 Use of experimental drugs outside of clinical trials (“compassionate use”)

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Countries' Responsibility con't

Pharmacovigilance

- Patient monitoring and pharmacovigilance
  - adequate clinical, biological and bacteriological monitoring in place
  - adverse events reporting system

Patient protection

- Patient must be well-informed about the drug
  - potential adverse effects and its possible impact on other conditions or treatments
  - safety and/or efficacy have not been scientifically proven
- *Informed consent*
- *Ethical review board approval recommended*

WHO Guidelines for the programmatic management of drug-resistant tuberculosis 2008 Emergency up-date 2008 ANNEX 5 Use of experimental drugs outside of clinical trials ("compassionate use")

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Countries	Patients that started treatment with TMC207		
	2011	2012	2013
Argentina		1	
Armenia			33
Austria			13
Bangladesh	2	2	1
Belgium		3	1
Botswana			4
Canada			2
Estonia			1
Ethiopia			1
Germany	3	7	6
Georgia	2		4
Greece	1		
India			9
Italy	1	3	1
Ireland	1		
Kazakhstan			9
Latvia			14
Lebanon			1
Nepal	1	1	
Netherlands		1	1
Niger		2	2
Nigeria			1
Peru		1	
Papua New G.			1
Portugal			1
Romania		1	
South Africa	4		44
Sweden		1	2
Switzerland	1		
Taiwan		1	1
UK	5	1	5
USA		1	3
Sub Total	21	26	161
France	14	31	26
Sub Total			
Total	35	57	187

Data provided by Janssen December 2013

33 countries

2011 *35 patients*

2012 *57 patients*

2013 *187 patients*

2011 MSF Assessment on CU framework

Regulatory framework in 6 countries:
Swaziland, Georgia, Abkhazia, Armenia, Uzbekistan, India, South Africa

Georgia, Armenia
Exceptional waiver issued

Abkhazia, Uzbekistan
No legal framework in place for CU in general

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TO ACCESS NEW DRUGS FOR TB RECOMMENDATIONS

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Countries

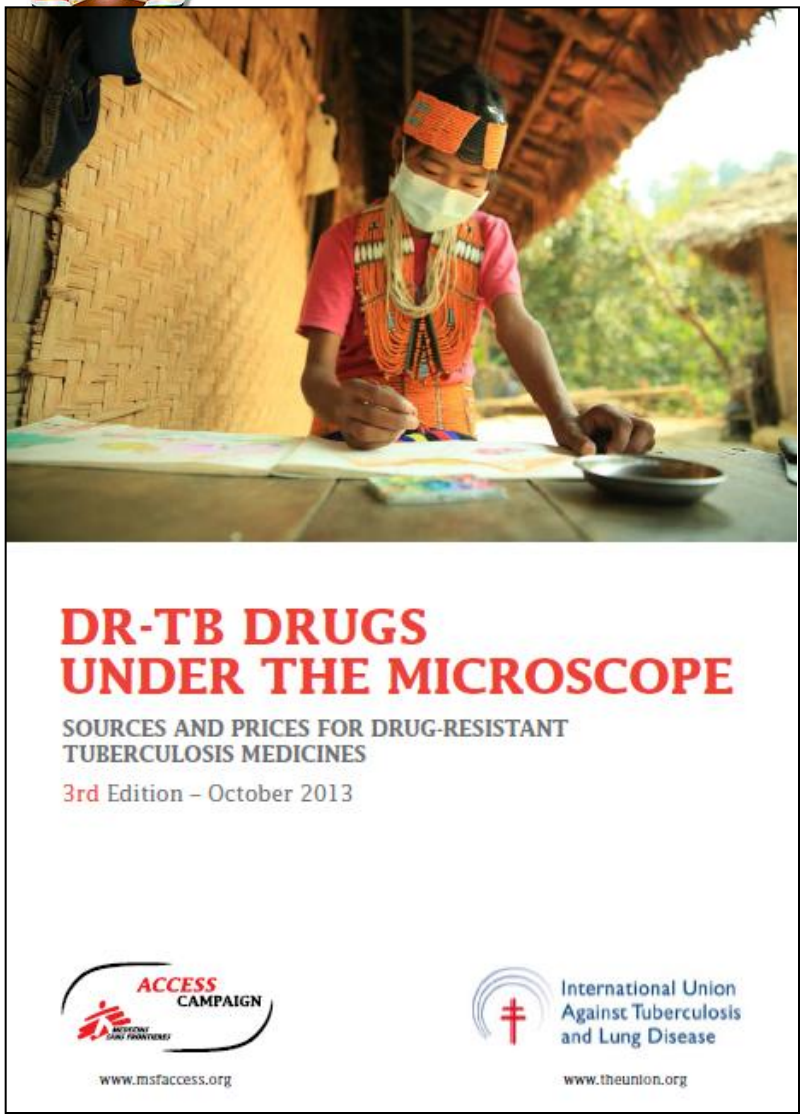
- To commit to the programmatic requirements for a rational introduction
  - Adequate management of DR TB in place
  - Ensure access to quality-assured second- and third line anti-tuberculosis agents
- To establish a framework for compassionate use programs

WHO

- To give guidance on appropriate use of new medicines
- To give guidance to countries about initiating a compassionate use programme and facilitating registration and appropriate scale up of the new compound

Drug developers

- To provide access to a new medicines for CU
- To provide the medicines free of charge for CU
- Ensure affordable access after registration



- Sources and prices of DR TB medicines and regimens
- Limited access to repurposed medicines as clofazimine and linezolid
- Access to new medicines
- Quality assurance of medicines
- Research&Development
  - Pipeline and clinical trials landscape
- Drug profiles and information on accessing quality assured DRTB medicines

http://www.msfaccess.org/sites/default/files/MSF_TB_Report_UTM3rdEdition-2013.pdf

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Scaling up and improving access to ambulatory and paediatric TB care in Central Asia and Eastern Europe

Regional Symposium on TB Care

Dushanbe 5- 6 December 2013

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