Systems Approach for Adoption, Introduction, and Implementation of New TB Medicines and regimens

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First Conference on Pharmaceutical Management for TB and M/XDR-TB for WHO European Region

Antalya, Turkey. December 10-13, 2013
Global TB Drug Pipeline

Preclinical Development

Early Stage Development  GLP Tox.  Phase I  Phase II  Phase III

CPZEN-45  PBTZ169  AZD5847\textsuperscript{N}
DC-159a  TBA-354  Bedaquiline\textsuperscript{N\,c\,R}
Q203  Linezolid
SQ609  PA-824\textsuperscript{N\,c}
SQ641  Rifapentine
TBI-166  SQ-109\textsuperscript{N}
Delamanid\textsuperscript{N\,R}
Gatifloxacin\textsuperscript{c}
Moxifloxacin\textsuperscript{c}
Rifapentine\textsuperscript{R}
Sutezolid\textsuperscript{N}

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

\textsuperscript{1}Details for projects listed can be found at http://www.newtbdrugs.org/pipeline.php and ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php.

\textsuperscript{c} Drug candidate currently in combination regimen in clinical testing

\textsuperscript{R} Submitted for approval or approved by stringent regulatory authority (i.e., FDA, EMA, WHO Prequalification)

\textsuperscript{N} New chemical entity

Updated: June 2013
Retooling Frameworks
Key Definitions of the Retooling Process

Adoption
- Analysis of benefits, risks, and health system capacities
- Making decisions to incorporate the new tool into the National Tuberculosis Program
- Communication of recommendation and policy

Introduction
- Regulatory and registration compliance
- Phase-in/phase-out plan preparation
- Guidelines, tools, and training materials revision
- Financial resources mobilization
- Procurement and logistics management
- Staff training
- Advocacy, communication, social mobilization

Implementation
- Carrying out phase-in and phase-out plans
- On-going operational activities
- Monitoring and evaluation of implementation progress and new technology performance

Adoption

A multi-sector process resulting in an explicit global and/or country policy decision to access and use new TB control technologies, following the analysis of:

- Benefits, risks, and costs of new medicines/regimens
- Health system’s capacity to finance, manage, and appropriately use the medicines
- Drug management systems’ capacity to ensure timely procurement, quality assurance, inventory control, and sustainable access
- Acceptance of new technologies by domestic markets, providers
Introduction

The set of coordinated activities that is carried out to prepare for effective and sustainable access to the new and improved health technology. Includes ensuring that—

• Plan is prepared to address the gaps and weaknesses of health and medicines management system
• There is appropriate new technology regulation and registration
• Phase-in/phase-out plans for procurement and supply management are prepared
• Guidelines, tools, and training materials are revised
• Financial resources are mobilized
• Initiation of staff training is initiated
• There are advocacy, communication, and social mobilization activities
Implementation

The activities that put into effect the policy and plan, and monitor and evaluate the progress of these activities and the impact on tuberculosis control. Implementation activities include:

- Execution of a phase-in/phase out plan
- On-going technical program and supply management procedures
- Monitoring and evaluation of program implementation and new health technology performance

Tailored Approach to Implementation—Potential Scenarios

• By type of new product and its impact on systems and markets
  – New MDR-TB medicine add-on (to existing regimen)
  – New MDR-TB regimen
  – New DS-TB regimen
  – New DS/DR-TB regimen

• By type of new medicines sources, procurement models, and international control (by GFATM, GDF, donors, etc.)

DS = drug susceptible. GFATM=The Global Fund to Fight AIDS, TB and Malaria. GDF=Stop TB Global Drug Facility
Rational Classification of Anti-TB Drugs

**Group 1:** First Line Drugs, Oral (H,R,E,Z) → All Possible

**Group 2:** Quinolones: High dose Lfx, or Mox → 1

**Group 3:** SL Injectables: Km, Ak, Cm → 1

**Group 4:** Other Second Line Drugs: Eth/Pth, Cs/Tz, PAS → Until 4 new

**Group 5:** Reinforcement Drugs:
- Linezolid, Clofaz., Carbapenem, Am/Cl, Bedaquiline?

Tailored Approach to Implementation – Potential Scenarios

• By type of new product and its impact on systems and markets
  – **New MDR-TB medicine add-on (to existing regimen)**
    – New MDR-TB regimen
    – New DS-TB regimen
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Types of Products and Potential Challenges:
New MDR-TB Medicine Add-On (to existing regimen)

- Minimum changes required to the existing normally functioning procurement and supply chain management system
- Least impact on existing market, less resistance—does not replace existing medicines

- Challenges:
  - Procurement regulation may need to be amended to allow direct procurement from international (single) source
  - Registration of add-on medicine (clinical trials?)
  - Justification of additional costs
  - Compulsory licensing, parallel import, and related issues
Tailored Approach to Implementation – Potential Scenarios

- By type of new product and its impact on systems and markets
  - New MDR-TB Medicine add-on (to existing regimen)
  - **New MDR-TB regimen**
  - New DS-TB regimen
  - New DS/DR-TB regimen
Types of Products and Potential Challenges: New MDR-TB Regimen

Strong impact on existing SLD market
- Reduction of demand for SLD with a shorter regimen
- Change of market players with a full new regimen

Challenges
- Resistance from domestic suppliers
- Serious revision of country procurement practices (international single source)
- Complete revision of SLD supply strategy
- Increased costs to programs: medicines, retraining
- Reduction of demand in existing SLD could push prices up

SLD = second-line drug
Tailored Approach to Implementation – Potential Scenarios

• By type of new product and its impact on systems and markets
  – Add-on to existing regimen
  – New MDR-TB regimen
  – New DS-TB regimen
  – New DS/DR-TB regimen
Types of Products and Potential Challenges: New DS-TB Regimen

- FLD market impact: drop in demand for some FLDs (depending on regimen) affecting suppliers
- Little or no impact on distribution and inventory management
- May not require changes in procurement procedures if medicines have already been registered and procured
- Challenges
  - Increased cost of treatment
  - Potentially increased prices for “traditional” FLDs
  - Lack of fixed-dose combination for new regimens and quality assurance issues
Tailored Approach to Implementation – Potential Scenarios

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Types of Products and Potential Challenges: New DS/DR-TB Regimen

- Market revolution?
- Challenges
  - Revision of national TB medicines management policies and regulations
  - Complete revision of country PSCM strategy, procurement practices, and standard operating procedures
  - Retraining of all staff
  - Cost of technical assistance to strengthen systems and implement changes may be very high
Shorter treatment regimens for multi-drug-resistant tuberculosis (MDR-TB)

What are the standard MDR-TB regimens?
The World Health Organization (WHO) currently recommends the use of at least four second line drugs which are effective, plus pyrazinamide, in the intensive treatment phase.

Treatment outcomes observed in Bangladesh for MDR-TB cases treated with a 9-month regimen

A regimen consisting of a minimum of 4 months of KmCfzGfxEHZPto, prolonged if necessary until conversion was achieved, followed by 5 months of GfxEZCfz, was reported to give high, relapse-free cure rate in MDR-TB patients [van Deun et al, 2010].

WHO CRITERIA TO BE APPLIED IN THE USE OF SHORTER REGIMENS FOR MDR-TB TREATMENT

WHO’s current position is that regimens which are markedly different from those that make up the current norm should be used only within the context of research and under close monitoring of the response to treatment, for a period of at least 12 months after treatment completion. The major concerns are that patients who do well after 9–12 months of treatment, with less drugs in the continuation phase than in the longer regimen, may have a higher risk of acquiring resistance in while on treatment and subsequently relapsing with TB.
COUNTRIES MAY BE CONFRONTED WITH REGULATORY CHALLENGES

ONE EXAMPLE:- COMPASSIONATE USE (CU)
European Regulation 726/2004/EC is clear on the intentions of CU Programs and aimed to harmonize them in the EU region....

However, different countries have adopted different requirements and CU is not interpreted in the same way across Europe.
ECRIN Survey on CU interventions (1)

- Responsibility is with the prescribing physician—single most common element

- 6 out of 10 countries allow CU programs on a “named individual patient” basis while only 3 countries specify that CU programs must be outside clinical trials
ECRIN Survey on CU interventions (2)

• Outcomes of CU programs do not need to be reported to the national regulatory authorities in most countries (not a desirable situation)

• Regulation 726/2004/EC does not describe any aspects of what the required content is for the authorization application.

• Responsibilities of the physician, national authorities and product manufacturer are ambiguous.
ECRIN Survey—CU or Expanded Access? (3)

- Compassionate use is a misleading term and should be replaced with “expanded access”

- Expanded access cannot replace clinical trials

- Regulation 726/2004/EC separates expanded access from clinical trials but many member states do not
Compassionate use of and expanded access to new drugs for drug-resistant tuberculosis


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SUMMARY

Several new classes of anti-tuberculosis agents are likely to become available in the coming decade. Ensuring prompt access to these drugs for patients without other treatment options is an important medical and public health issue. This article reviews the current state of ‘compassionate use’ and ‘expanded access’ programs for these new drugs, and identifies several shortcomings that will limit patient access to the drugs. A series of five steps is outlined that will need to be taken by national health bodies, international agencies and non-governmental organizations to prevent undue delays in access to new tuberculosis drugs for patients who could benefit from them. Following these steps can ensure that patients will be able to benefit from access to these drugs, while minimizing the risk of emergence of resistance to the drug.

KEY WORDS: pre-approval access; expanded access program; pre-marketing access; import waiver; open enrollment trial
CU and Expanded Access Programs (1)

There is no universally accepted definition for the terms CU or expanded access

- CU = physician request and responsibility
- Expanded access refers to programs that focus on enrolling groups of patients (like a clinical trial)

Each country decides its own regulations and applies its own definitions, leading to a wide variety of global programs using similar terminology

- USA—expanded access only
- EU region—CU programs are the primary mechanism
- Canada—CU and expanded access is distinct

Horsburgh et al, 2012 for RESIST-TB and CPTR.
CU and Expanded Access Programs (2)

What are the Goals?

- Protect patients
- Minimize the risk of treatment failure and emergence of resistance
- Exercise fairness
- Comply with regulatory guidance

Horsburgh et al, 2012. RESIST-TB and CPTR
COUNTRIES MAY BE CONFRONTED WITH PRICING CHALLENGES
We know the current offer price.....

Estimated cost of bedaquiline for 6-months

High Income country $30,000
Upper MIC $3,000
MIC Unknown*
LIC $900

Jaansen Pharmaceuticals will place countries in the respective World Bank classified income groups after Conclusion of regulatory efforts and where applicable, Completion of reimbursement process.
The “Middle-Income” Curse

MSF analysis revealed that several MNCs have “Shut Down HIV Drug Discount Programs In Middle-Income Countries”

• ViiV (Pfizer & GlaxoSmithKline) no longer offers reduced prices to middle-income countries, even when programs are fully funded by GFATM or PEPFAR
  
• Merck: Will no longer issue price discounts for 49 middle-income countries for raltegravir
  – Excludes India, Indonesia, Thailand, Viet Nam, Ukraine, Colombia, and Brazil
  – Brazil pays $5,870 per patient per year for raltegravir
  – In LICs, Merck charges $675 per patient per year for the drug,

• Access programs promoted as voluntary solutions offered by big pharmaceutical companies appear unreliable and unsustainable in the long term

K. Bhardwaj. IAS 2012 - WEAE0106.

MNCs = Multi-national companies
LICs = Low-income countries
REGIONAL AND GLOBAL STRATEGY FOR NEW TB MEDICINES/REGIMENS:

WHAT IS THE RELEVANCE AT COUNTRY LEVEL?
Among four objectives

- To support the timely and effective introduction of new tools for diagnosis, treatment, and prevention.

Relevance (page 36)

- Promptly update policy for commodity supply as new vaccines, diagnostic tools and drugs are developed.
Research to develop new diagnostic methods, drugs and vaccines (pg 39)

- Prepare and coordinate actions to introduce the use of effective new diagnostic methods, medicines, and vaccines in countries
Activity 3.3.1
• The Regional Office and partners will develop a long-term regional strategy for the development of the TB medicines market
SWOT analysis in relation to MDR/XDR-TB

Threats

• Existing pharmaceutical policies, regulations, and practices may not support the rapid adoption, introduction, and implementation of new TB tools and their proper utilization.
Development of new technology is insufficient; health policy-makers will need to develop new, robust delivery systems as part of the health service delivery function.
“We will need novel health systems designs that advance adoption and diffusion of new technologies”

Global Plan to Stop TB, 2011-2015, page 56
Global Strategy (2)

Highest Priority Research Question

Not just revolutionary new technologies but also

- Novel service delivery models
- Novel evidence-based health system designs that foster adoption and diffusion of new tools and technologies
Country Strategic Plans—What Do They State? Two Examples

Kyrgyzstan
Consider possibilities to apply new TB drugs for the DR-TB patients:
• Negotiations with the manufacturers
• Amendments in the legislation to allow import and use

Armenia
• Ensure availability of new anti-TB drugs by end of 2014
• Compassionate use of new TB drugs should be implemented with caution, there may be ethical and drug procurement issues
In Summary

- WHO Euro region countries need adequate preparation and systematic planning for adoption, introduction, and implementation of new TB medicines or regimens

- During break-out group discussion (Thurs, Dec. 12), we need to identify specific areas of
  - Shared challenges
  - Priority action areas by international and country level authorities