



Development of a Risk-Based Approach and Tools for Improving Safe and Rational Use of Tuberculosis Medicines

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Development of a Risk-Based Approach and Tools for Improving Safe and Rational Use of Tuberculosis Medicines

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March 2013

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ACRONYMS AND ABBREVIATIONS

ADR	adverse drug reactions
AIDS	acquired immunodeficiency syndrome
ARV	antiretroviral
DOTS	WHO internationally recommended strategy for tuberculosis control
EML	Essential medicines list
EU	European Union
FDA	US Food and Drug Administration
FDC	fixed-dose combination
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
HCW	health care worker
HIV	human immunodeficiency virus
ICH	International Conference for Harmonization
MDR-TB	multidrug-resistant tuberculosis
PPPs	Public-Private Partnerships
STP	Stop TB Partnership
REMS	Risk Evaluation and Mitigation Strategy
RMP	risk management plan
RiskMAPs	Risk Minimization Action Plans
TB	tuberculosis
USAID	US Agency for International Development
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

BACKGROUND

More than 20 anti-tuberculosis (TB) medicines are being used today. These medicines are taken in different combinations simultaneously. There is a high probability of having an adverse reaction during therapy with anti-TB medicines because of the lengthy period of use required for a complete cure. The fact that most of these medicines have been in use for decades and clinicians are aware of the associated risk and adverse drug reactions (ADRs) is not a guarantee or assurance of completely safe use, as there are still gaps in the current information for these medicines.

Second-line anti-TB medicines that are used to treat the emerging drug-resistant forms of the bacteria are less effective and more costly with treatment lasting up to two years. The World Health Organization (WHO) and its partners have established programs to facilitate proper use of second-line medicines and curtail medicine resistance. However, more action is required to improve on existing efforts, particularly to reduce ADRs that affect treatment outcome.

Prevalence and Burden of Adverse Reactions and Side Effects

In 2011, an estimated 8.7 million new cases of tuberculosis were documented. Also in the same year, 1.4 million deaths occurred as a result of TB. The highest burden of TB is found in Asia and Africa with the latter accounting for 24 percent of TB cases worldwide. Since the implementation of the WHO global TB strategy (DOTS), approximately 51 million people have been successfully treated for TB in regions and countries where this strategy was adopted. The standard regimen for treating susceptible TB is 6 months and up to 24 months for the drug-resistant forms as it requires multiple medications with commitment and attention to details. Nevertheless, as is the case with all medicines, there is associated risk with the use of anti-TB medicines. These risks (adverse reactions/side effects) commonly develop during TB treatment and are a serious threat to treatment outcome.

Hepatitis is a common adverse reaction from some anti-TB medications. Its presence in a patient is usually confirmed by liver enzymes that are more than three times the upper limit of normal. Most frequently, the enzymes level returns to normal following discontinuation of the causal medicine, but sometimes the patient's condition may worsen and even result in death. Following a review of previously developed literatures on first-line anti-TB medicines, isoniazid was found to have a five percent hepatotoxicity-related mortality rate.¹ Severe side effects can equally be seen in the second-line anti-TB medicines.² An example is amikacin (an aminoglycoside) which causes increased kidney damage especially in patients with both normal and pre-existing renal failure at higher doses for over a long period. It is reported that about 86 percent of patients being treated with these second-line medicines do develop an adverse

¹ Forget, E. J., D. Menzies. 2006. Adverse reactions to first-line antituberculosis drugs. *Expert Opinion on Drug Safety* 5 (2): 231–49. <http://www.ncbi.nlm.nih.gov/pubmed/16503745>

² Awofeso, N. 2008. Anti-tuberculosis medication side-effects constitute major factor for poor adherence to tuberculosis. *Bulletin of the World Health Organization* 86(3): B–D. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2647396/>.

reaction.³ Generally, these side effects can lead to poor treatment adherence and to partially suppressive drug concentrations due to inadequate treatment.

Treatment adherence is also influenced by comorbidities such as HIV/AIDS. In 2011, 13 percent of TB patients were found to be co-infected with HIV. Worldwide, TB co-exists with HIV/AIDS in an estimated 40 million people and approximately 80 percent of these cases are found in Africa. Treatment of co-infected patients can be complicated as the side effects of the medicines used to manage both conditions and the potential for serious harm are magnified.

Poor adherence as a result of side effects can result in ineffective response and resistance to treatment over time which is commonly referred to as drug resistant TB (DR-TB). Also, termination of first-line TB therapy due to side effects, such as hepatitis, dyspepsia, exanthema, and arthralgia, is estimated to occur in up to 23 percent of patients during the intensive phase of treatment.⁴

DR-TB has the highest impact in some developing countries. About 60 percent of DR-TB occurs in Brazil, China, India, Russia, and South Africa. According to a 2012 publication by WHO,⁵ 3.7 million new TB infections worldwide are the resistant form of the disease, with previously treated individuals reflecting an increase of approximately 20 percent above new ones. The exact prevalence cannot be established because of laboratories lacking equipment or not being adequately equipped to confirm diagnosis.

The two forms of DR TB are multidrug-resistant (MDR)-TB which is treated with second-line anti-TB medicines that are very toxic and have severe side effects (as earlier noted), and extensively drug resistance (XDR)-TB, which develops following mismanagement of MDR-TB; this makes up approximately 9 percent of drug resistant cases.⁶ Successful treatment of these patients is difficult to achieve, only a 48 percent treatment success rate was reported by WHO for MDR-TB patients enrolled on treatment in 2009.⁷

National TB programs have adopted approaches to address issues related to adverse effects from anti-TB medicines that support efforts at combating the infection. However, the implementation of additional plans will be needed to improve the management of all forms of TB.

Promoting rational anti-TB medicines use through the application of WHO strategies for improving the use of medicines can also contribute towards preventing the development of anti-TB medicines resistance. This document therefore addresses how to develop a universally adaptable plan to reduce or prevent harmful effects from the use of anti-TB medicines, and to promote their efficient utilization. This process will require the development and implementation of risk management plans and tools to promote patient safety.

³ Leimane V., V. Riekstina, T. Holtz, et al et al. 2005. Clinical outcome of individualized treatment of multi-drug resistant tuberculosis in Latvia: a retrospective cohort study. *Lancet* 365: 318-26.

⁴ Awofeso, N. 2008. Available at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2647396/>.

⁵ WHO. 2012. Global Tuberculosis Report 2012. http://www.who.int/tb/publications/global_report/gtbr12_main.pdf

⁶ WHO. 2012. Multidrug-resistant Tuberculosis (MDR-TB) 2012 Update. <http://www.who.int/tb/publications/MDRFactSheet2012.pdf>.

⁷ WHO. 2012. Multidrug-resistant Tuberculosis (MDR-TB) 2012 Update. <http://www.who.int/tb/publications/MDRFactSheet2012.pdf>.

WHO Strategies for Improving Rational Medicine Use

WHO defines rational medicine use as when “patients receive medications appropriate to their clinical needs in doses that meet their individual requirements for an adequate period of time at the lowest cost to them and their community.”⁸ Proper tuberculosis therapy requires appropriate prescription, supervision, and support. WHO has published guidelines on standardized TB treatment regimen and recommended DOTS—the heart of StopTB strategy—which has been implemented by several countries. Despite global and national TB treatment guidelines, in 2011, a report on 37 studies conducted on patients undergoing TB treatment showed that 67 percent received inappropriate treatment.⁹ Obtaining information on the patterns and practices among health workers and the general public is important for assessing medicines use in different regions and localities. This knowledge can be a guide to minimize financial loss, reduce waste of resources from drug expenditure, as well as improve the use of medicines and ultimately lower morbidity and mortality related to poor patient management and adverse drug reactions.

Several countries have implemented laws prohibiting the sale of anti-TB medicines in private pharmacies with prescriptions. However, this practice is not being enforced in most countries and some pharmacies and drug stores still sell these medicines without the required prescription.

To improve the rational medicine use, WHO recommends that countries implement national programs to promote rational medicines use through—

- Establishing a national body to coordinate and monitor the policies and its effect on the use of medicines
- Setting up a drug and therapeutic committees in districts and hospitals to monitor and implement interventions to improve the use of medicines
- Incorporating problem-based training in pharmacotherapy in undergraduate medical and paramedical training
- Continuing medical education (CME) as a licensure requirement. In developing countries, this can be supported by the governments and administered through universities and professional bodies. Most developed nations already require CME for licensure.
- Making medicine information publicly available that is independent and unbiased (in addition to that provided by pharmaceutical companies to health personnel and consumers)
- Supervising and auditing prescribers to allow comparison of prescribing practices to prescribing guidelines
- Educating the public on correct medicines usage, risk from improper use, and the importance of correct labeling and adherence to label contraindications and warnings

⁸ WHO. 2002. WHO Policy Perspectives on Medicines— Promoting rational use of medicines: core components. Geneva: WHO. <http://apps.who.int/medicinedocs>.

⁹ Langendam, M.W., M.J. van der Werf, E. Huitric, et al. 2012. Prevalence of inappropriate tuberculosis treatment regimens: a systematic review. *European Respiratory Journal*. 39(4): 1012–1020. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3342766/>

- Introducing standard prescribing and dispensing fees to avoid unreasonable financial motivation resulting in inappropriate prescribing practices
- Establishing a multidisciplinary national body that has permission to regulate and coordinate medicine policies
- Providing sufficient government expenditure/funding to ensure availability of medicines and health personnel¹⁰

The awareness of the global TB incidence and its relatedness to non-adherence as a result of side effects necessitates the need to improve on existing methods and develop a risk management plan with additional tools to promote the safe use of medicines used in TB management.

¹⁰ WHO. 2010. Medicines: rational use of medicines factsheet.
<http://www.who.int/mediacentre/factsheets/fs338/en/index.html>.

RISK MANAGEMENT PLAN

Despite the introduction of these strategies, there still exist persisting challenges regarding medicine safety particularly with reference to anti-TB medicines. An additional important necessary approach that is required to address these medicine safety concerns is the development of a risk management plan (RMP).

A risk is the probability that an unwanted or unexpected medical event could result from a medical procedure or the use of a medical product. The risk could be known or unknown—some may have already been identified from clinical studies and some may not have been identified prior to approval for public use. However, standard procedures such as a risk management plan are needed to identify and mitigate these safety issues.

Risk management is an iterative process of (a) assessing a product's risk-benefit balance; (b) developing and implementing tools to minimize its risks while preserving its benefits; (c) evaluating tool effectiveness and reassessing the risk-benefit balance; and (d) making adjustments, as appropriate, to the risk minimization tools to further improve the risk-benefit balance. A risk management plan (RMP) targets one or more safety-related health outcomes or goals and uses one or more tools to achieve those goals.

RMPs start with identifying the possible risks/benefits associated with a product or with the process used to develop, manufacture, and distribute a product. At each stage of a product's cycle, the following are taken into consideration: the safety risks, population at risk, predictability of risk, and cause of risk. Establishing the actual cause of each risk to determine the likelihood of its occurrence will provide guidance on interpreting the risk and direction on the path for the interventions.

The main aim of conducting a risk management activity is for—

- Early and better detection of ADR and characterization of risks in various patients and settings
- Development and harmonization of data standards and reports
- Better communication of known and unknown risks
- Minimization of morbidity and mortality —protecting the public health

RMP entails

- Identifying issues and putting into context
- Assessing risks/ benefits
- Identifying and analyzing options
- Selecting a strategy that may include restricted distribution, requirement for practitioner qualification or training, post marketing study requirements, market withdrawal, product labeling, risk information for patients, direct to consumer promotion- promotional materials that comply with regulation stating risks and benefits through media or print; outreach programs to ensure the widest distribution of risk information
- Implementing the strategy
- Evaluating results.

Before developing a RMP for any medicine, there should be a complete outline of the safety profile of the medicine and a pharmacovigilance plan. There are several processes by which risk can be identified and evaluated, such as active surveillance of medical records, patient or physician interviews, and spontaneous reports.

Risk Management Process

The entire process of a risk management plan involves risk assessment, (risk confrontation, and risk intervention.¹¹

- Risk assessment completely evaluates the risk associated with the product uses. During this process, the nature, frequency, and severity of the risk are identified and characterized. Risk assessments of medicinal products are performed during the pre- and postmarketing phases. Postmarketing assessment is dependent on spontaneous reports from health care workers, consumers, and the industry (e.g., manufacturers). This kind of assessment is designed to consistently monitor and the effectiveness and safety of a medicine throughout its life cycle. However, RMP requires continuous assessment of ADRs and studies for specific safety issues that may arise in a particular population.¹² Following an assessment, risk can be categorized into low, medium and high.
- Risk confrontation is an essential activity but is sometimes not included in the risk management process.¹³ It involves mobilizing and working with all stakeholders, health care personnel, advocacy groups, and communities in making decisions based on their analysis of the risk and benefits.
- Risk intervention is guided by risk assessment results and the review, selection, and implementation of alternative measures for control.

Risk Management System

A risk management system is a special medicine plan designed for medicines approval and maintaining the approval status for human use. A risk management system is defined as a set of pharmacovigilance activities and interventions that have been put in place to identify, characterize, prevent, or minimize unexpected or harmful effects (risks) associated with the use

¹¹ Sharrar, R. G. 2008. Interpreting the guidelines on risk management plans. American Pharmaceutical Outsourcing. <http://www.unitedbiosource.com/pdfs/in-the-news/interpreting-risk-management-plans.pdf>

¹² Graham, D. J., A. D. Moshoulder, K. Gelperin, et al. 2005. Pharmacoepidemiology and risk management. *Journal of The Association of Physicians of India* 7(8):556. www.japi.org/july_2008/corr_556.pdf

¹³ U.S. Food and Drug Administration (FDA). 1999. *Creating a risk management framework. Report from task force on risk management*. Washington, DC: US FDA. <http://www.fda.gov/downloads/Safety/SafetyofSpecificProducts/UCM180522.pdf>.

of any pharmaceutical product.¹⁴ It also assesses the effectiveness of communication and interventions on the harmful effects. This system is important for keeping consumers and health care professionals informed about possible harm from using these products and on intervention methods where required.

In 1990, the regulatory authorities of the European Union (EU), Japan, and the United States convened and established the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.¹⁵ The purpose of ICH was to address the safety, quality, and efficacy of medicines. ICH has developed several guidelines for medicine safety. ICH most current draft guideline (E2E) on pharmacovigilance planning is aimed at creating a more proactive approach towards identifying and quantifying safety issues that become evident after approval and marketing of a medicinal product in any of the three ICH regions.

The EU has developed a comprehensive guidance document on risk management plan (EU RMP) for medicines. The current EU risk minimization activities which are centered on medication use control methods apply to all medicines. The activities include—

- Summary of product characteristics
 - Labeling
 - Package leaflet
 - Pack size(s)
1. Product 's legal status¹⁶

Because of the global differences in health care systems and the nature, prevalence and severity of disease, risk management activities are tailored to match with systems in the particular country or regions. However, the principles guiding all risk management activities for medicinal products are uniform, i.e., to increase benefit and reduce risk.

Factors Contributing to Medicine-related Risk in Developing Countries

Several factors affect pharmaceutical products risk in developing countries. The lack of direct contact or access to a physician or healthcare facilities is a lingering problem that is adversely affecting medicine safety in most of these countries. Non-medically trained personnel who have little or no knowledge about the medicines being used or the expertise needed to manage diseases are the key means of obtaining medical help in some areas. The access of treatment and purchase of medicinal products from non-registered pharmacies or street vendors is associated with risk since the ability to identify and distinguish a medicine-induced adverse effect from a disease or medical condition is difficult or impossible. Even where there is access to a trained medical practitioner, other factors such as information on patients' nutritional status, eating habits, and other medicines being taken which influence patients' reactions/responses to

¹⁴ Sharrar, R. G. 2008. Interpreting the Guidelines on risk management plans.

<http://www.unitedbiosource.com/pdfs/in-the-news/interpreting-risk-management-plans.pdf>

¹⁵ International Conference on Harmonization 2012. ICH history. <http://www.ich.org/about/history.html>

¹⁶ Heads of Medicines Agencies (HMA). European Medicines Agency (EMA). 2012. Guideline on good pharmacovigilance practice (GVP). Module V – Risk management systems. EMA/838713/2011.

treatment may not be provided by the patients because provider did not ask patients or patients do not understand the need for such information. of lack of education of low literacy levels. With the lack of comprehensive training programs for health professionals in certain locations, some patients may be at risk of treatment error and possible adverse effects. This can be observed in the administration of contraindicated medications or inaccurate dose adjustment to pregnant women, infants, and the elderly. It may also occur when treatment is not in accordance with the national standard treatment guidelines. These can compromise treatment outcome as is evident in the case of tuberculosis with the development of resistant strains.

Another major problem requiring intervention is the issue of counterfeiting which is usually brought to light when a medicine that was not subjected to regulatory testing caused harm to large number of patients. An estimate from WHO suggest that counterfeit medicines account for about 30 percent of brand-name drug sales in developing countries.¹⁷ Oftentimes, the standard in these countries is to rely on either spontaneous reporting from providers or when public outrage arises after a harmful effect has been observed in a large number of people following the use of a medicine. Recently, samples of isoniazid and rifampicin (two commonly used anti-TB medicines) from private-sector pharmacies in 19 cities in Africa, Asia, South America, and Europe were collected for quality testing. Out of the 713 tested samples there was 16.6 percent failure rate for Africa, 10.1 percent for India, and 3.9 for the rest.¹⁸ Counterfeit medicines are known to have countered global efforts to improve health with disastrous effect on patient safety as in the case of development of anti-TB medicine resistance around the world which is largely related to fake anti-TB medicines.

There is also the problem of medicine theft or diversion from government facilities whereby medicines sometimes end up in private pharmacies and in some cases in other bordering countries. Increased donated and subsidized medicines through sources like Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) and the Stop TB/Global Drug Facility save countless lives but also increases probably of theft and diversion of those medicines. A study conducted by Roger Bates et al found that subsidized (affordable medicines for malaria) malaria medicines were diverted to non- participating private pharmacies in 11 of the 14 cities studied in the Africa region.¹⁹ This practice contributes to stock-out of medicines and can also lead to interruption in treatment and decreasing treatment outcomes. The Global Fund hosted a second meeting in 2011 (Addis Ababa) to coordinate action to prevent theft and illegal diversion of medicines. Meeting participants' identified recurring vulnerabilities and risks, shared best practices, and developed recommendations to inform the action plans that will be developed by implementers at country level. It was concluded that a sustainable reduction in drug theft can only be achieved when implementing countries take the lead in strengthening procedures and safety measures to ensure safe delivery of drugs.

¹⁷ United Nations Office on Drugs and Crime (UNODC). N.D. Counterfeit Products. http://www.unodc.org/documents/data-and-analysis/tocta/8.Counterfeit_products.pdf

¹⁸ Bate, R., P. Jensen, K. Hess, et al. 2013. Substandard and falsified anti-tuberculosis drugs: a preliminary field analysis. *International Journal of Tuberculosis and Lung Diseases e-publication*. <http://massetto.ingentaselect.co.uk/fstemp/a5829970064042ab6ec12023d514ef4f.pdf>

¹⁹ Bate, R., J. Milligan and L. Mooney. 2012. The AMFm and Medicine Diversion: Good intention enabling corrupt practices. *Malaria World Journal* 3, 2. http://www.aei.org/files/2012/02/23/-the-amfm-and-medicine-diversion-good-intent-enabling-corrupt-practices_104408750244.pdf

Improper storage of TB medicines can affect the quality of the medicine causing it to lose therapeutic effectiveness, prolongs the illness, be toxic to patients, and in some cases, cause death. It can also be toxic to the patients causing serious adverse effects. TB medicines that go bad because of improper storage wastes resources and can reduce the credibility of the public health system to the public population. It can ultimately results in development of resistant strains of TB infection. Countries should ensure facilities and systems preserve stability and purity of TB medicines during storage and distribution. Temperature sensitive medicines should be stored appropriately and monitored regularly. Risk minimization plans can be put in place to promote good storage.

The public awareness of the problem related to counterfeit drugs has grown since it was first raised at the WHO Conference of Experts on Rational Drug Use in 1985.²⁰ To ensure the good quality medicine internationally, the WHO prequalification programme was established.²¹ The initial focus of this program was on medicines used to treat HIV/AIDS, TB, and malaria but was later extended to cover some other diseases. By the end of 2012, the number of prequalified medicinal products for priority diseases contained in the list was 316.

The establishment of national pharmacovigilance centers and the adoption of WHO strategies for rational drug use are some additional measures being implemented by developing countries to address patient safety as these are important in detecting harmful effects from medicines and communicating new information. However these are not enough. Due to global concerns, some diseases such as TB do require risk management strategies and tools for effective management.

²⁰ WHO. N.D. *General Information on Counterfeit Medicines*.
<http://www.who.int/medicines/services/counterfeit/overview/en/index.html>

²¹ WHO. 2013. *Prequalification of Medicines*. Fact Sheet N.278.
<http://www.who.int/mediacentre/factsheets/fs278/en/index.html>

RISK ASSESSMENT

Risk assessment involves the identification and characterization of risks. All anti-TB medicines have inherent risk to the patients—some are avoidable while others are not. To identify the anti-TB medicines that may require risk minimization plans, different criteria were examined; but only the factors that are related to public health issues for TB were considered.

The risk factors considered in this document were adapted mostly from the FDA safe use initiative report which highlights different risk criteria such as medication error, intentional misuse or abuse of medicines, off label use, side effects such as drug-drug interactions, and drug quality defects.²² The European Medicines Agency guideline on good pharmacovigilance practices, module V risk management systems updated June 2012, was also examined and risk factors were adapted from the guideline.²³

Only risk factors with available data that are applicable in developing countries context were included in the risk score board used for determination of anti-TB medicine risks. The five main risk factor groups identified for consideration in this document include—

- Known serious or severe adverse effect
- Drug interactions
- Safe use indicators
- Drug integrity and supply chain
- Chronic medicine use risk

Each risk group consists of sub risk elements which have been defined. Please refer to the annex A for details on how each of these factors were considered for the context of this report and the risk analysis.

Data Collection and Analysis of TB Medicine Risk Factors

Data Collection

A tracer list of TB medicines was compiled from WHO treatment guidelines for susceptible and resistant TB treatment. Information for each medicine was collected through review of online literature, books, and medicine package inserts. The main source of drug information used to compile data was medicine package inserts obtained from Facts and Comparisons, LexiComp online access. For other information not available in this reference book, information was collected through literature search for articles, publications, documents, manufacturer websites, WHO website, and international regulatory authorities internet sites.

²² U.S. Food and Drug Administration (FDA). 2009. Collaborating to Reduce Preventable Harm from Medications. *FDA's Safe Use Initiative*. Available at <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM188961.pdf>.

²³ European Medicines Agency (EMA) Heads of Medicines Agencies (HMA). 2012. *Guidelines on good pharmacovigilance practices (GVP), Module V-Risk management systems*. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf.

Data for each risk factor and for each anti-TB medicine was collected and put into Excel[®] spreadsheet. There was no data available for the following second-line medicines—gatifloxacin tablets, prothionamide, terizidone, and thioacetazone—because some of the medicines have been discontinued in the country regulatory authority resources reviewed or it is not widely used anymore. For first-line anti-TB medicines, there was no data available for the fixed-dose combination medicines used in most countries.

Data Analysis

A predefined scoring system was used to quantify the data collected for each medicine. Three categories of risk to patients were identified and defined—low, medium, and high risk. This overall assessment system was applied to each risk factor such as pregnancy or drug-drug interaction (table 1). Each TB medicine was then rated on the risk factors and the medicines. Risk scores were tallied to come up with a total score (tables 2 and 3). Based on this categorization, each TB medicine was labeled according to the total risk score determined by the analysis.

Table 1. Risk Factor Rating Base

Risk	Rating^d	Comments
Known serious or severe adverse event		
Known class effect	0 ^a (no) 1 ^b (yes)	
Known safety issues for renal impairment	0 ^a (no) 1 ^b (Yes)	
Known safety issues for hepatic impairment	0 ^a (no) 1 ^b (yes)	
Known safety issues for elderly	0 ^a (non-clinically significant) 1 ^b (clinically significant) 2 ^c (unknown)	
Pregnancy category ^d	0 ^a (category A to C) 1 ^b (category D) 2 ^c (category X)	
Potential risk during lactation	0 ^a (contraindicated or safe), 1 ^b (known effect but doctor decision) 2 ^c (unknown)	Discontinue drug or stop nursing considered as contraindicated.
Known safety issues for pediatrics	0 ^a (non-clinically significant or contraindicated) 1 ^b (clinically significant) 2 ^c (unknown)	Did not consider any medicine with whose safety profile was not established for anyone under the age of one, but did include those ages 1 to 12.
Experience with overdose	0 ^a (yes) 1 ^b (unknown)	

Interactions		
Drug-drug interactions	0 ^a (non-clinically significant interaction) 1 ^b (clinically significant)	All drugs have interactions with other drugs, difficult to determine which interaction to consider. All are clinically significant but may not relate to other anti-TB medicines
Drug food interactions (including ethanol and smoking)	0 ^a (none known) 1 ^b (yes)	
Drug disease interactions	0 ^a (none) 1 ^b (yes)	
Safe use indicators		
Potential for medication error-look alike, sound alike	0 ^a (no) 1 ^b (yes)	Some of the brand names for sound alike might not be available in all countries. For first-line drugs assumption is that none exists since TB clinic is separate and only TB medicines are held at these clinics.
Off-label use (besides for TB and leprosy treatment)	0 ^a (No or unknown) 1 ^b (yes)	
Potential for medication abuse (recreational abuse)	0 ^a (No) 2 ^c (yes)	No information was found for any TB medicine. This will vary by country.
Narrow therapeutic window	0 ^a (No) 2 ^c (yes)	
Action taken by regulatory authority or marketing authorization holder	0 ^a (withdrawal and no action), 1 (black box or REMS)	
New product	0 ^a (No) 2 ^c (Yes)	
Drug integrity and supply chain		
WHO prequalification	0 ^a (yes) 1 ^b (No)	Source MSF paper ²⁴
Total number of manufactures/suppliers prequalified	0 ^a (if greater or equals 4 suppliers) 1 ^b (if 2-3 suppliers) 2 ^c (if 1 or less)	Source MSF paper
Short-shelf life	0 ^a (greater than 36 months) 1 ^b (25- 36 months) 2 ^c (0- 24 months)	Shelf-life varies by manufacturer per WHO guideline. Donated products should not exceed 1 year shelf life.
Storage conditions	0 ^a (stored at room temperature) 1 ^b (store away from moisture or light) 2 ^c (needs refrigeration)	Did not consider stability after reconstitution; only stability of original package.
Counterfeit	0 ^a (no reports of counterfeiting) 1 ^b (counterfeit reported)	No data was found for TB medicines in the literature search.
Diversion	0 ^a (low pilferage item)	No data was found for TB medicines in the

²⁴ Medecins Sans Frontieres and International Union Against Tuberculosis and Lung Diseases, 2011. DR-TB Drugs Under the Microscope: Sources and Prices for Drug-Resistant Tuberculosis Medicines. http://www.msfacecess.org/sites/default/files/MSF_assets/TB/Docs/TB_report_UndertheMicro_ENG_2011.pdf

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	1 ^b (high pilferage item)	literature search. Any medicine can be pilfered. We need another parameter like cost to determine this; if not, it will vary from country to country.
Chronic medicine use risk		
Population exposed to the medicine	1 ^b (public health programs or part of top 20 medicines used in country) 2 ^c (other)	All second-line TB drugs are used for drug-resistant TB. Even some second-line medicines like pyrazinamide is also used for second-line treatment so it will be difficult to define this parameter.
Adverse drug reaction with prolonged use	0 ^a (acute use) 1 ^b (prolonged use)	This is difficult because sometimes regimens are changed. For MDR-TB, treatment for intensive phase is 8 months or 4 months past conversion; continuation phase is for at least 18 months past time of conversion.

^a Low Risk (score of 0)—this is defined in this context as acceptable risk; has minimal threat to the patient and does not require monitoring.

^b Medium Risk (score of 1)—this is also acceptable but the threat posed requires regular monitoring to ensure it does not increase. There may also be need to implement measure to reduce the risk.

^c High Risk (score of 2)—this is an unacceptable risk as it can lead to life-threatening conditions. In this context, unknown risk is also categorized as high risk because the risk has not been studied. This requires regular monitoring and interventions to reduce or eliminate the risk.

^d See annex 1 for description of pregnancy categories

Table 2. Summary Table of Risk Analysis for First-Line Anti-TB Medicines

	Isoniazid	Rifampicin	Ethambutol	Streptomycin	Pyrazinamide
Known serious or severe adverse effect	1	4	4	5	4
Interactions	3	3	2	2	1
Safe use indicator	1	1	1	2	0
Drug integrity and supply chain	1	2	0	4	0
Chronic medicine use risk	0	0	0	0	0
Total ^a	6	10	7	13	5

^a Interpretation of Risk Scores

- Score of 0 to 10 is categorized under low risk
- Score of 11 to 20 is categorized as medium risk
- Score of 21 and greater is categorized as high risk

Table 3. Summary Table of Risk Analysis for Second-Line Anti-TB Medicines

	Kanamycin	Amikacin	Capreomycin	Levofloxacin	Moxifloxacin	Gatifloxacin	Ofloxacin	Ethionamide	Prothionamide	Cycloserine	Terizidone	PAS	Clofazimine	Linezolid	Amoxicilline/Clavulante	Thioacetazone	Clarithromycin	Imipenem
Known serious or severe adverse effect	5	5	4	5	4	4	4	5	5	3	3	2	4	2	1	0	3	5
Interactions	2	2	2	3	3	2	3	3	3	3	3	1	0	3	1	0	3	1
Safe use	2	2	2	3	3	1	2	0	0	1	0	1	0	2	2	0	2	2
Drug integrity and supply chain	4	3	4	3	3	4	4	2	3	3	4	2	5	5	4	5	5	5
Medicine chronic use risk	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Total Score	15	14	14	17	16	14	16	13	14	13	13	9	12	15	11	8	16	16

Risk Characterization: Summary of Risk Analysis

The analysis showed that only one (PAS granules) out of the 14 second-line TB medicines reviewed for this exercise was found to be low risk—the rest have been categorized as medium risk. Gatifloxacin, prothionamide, terizidone, and thioacetazone were excluded from the analysis even though they are on the WHO list for second-line TB medicines because of incomplete data as some of these medicines have been discontinued due to severe adverse effects. Only one (streptomycin injection) out of the five first-line TB medicine analyzed was found to be medium risk to patients (table 4).

Table 4. TB Medicine Risk Classification

Low Risk	Medium Risk	High Risk
PAS	Kanamycin	None
Isoniazid	Amikacin	
Rifampicin	Capreomycin	
Pyrazinamide	Levofloxacin	
	Moxifloxacin	
	Ofloxacin	
	Ethionamide	
	Cycloserine	
	Clofazimine	
	Linezolid	
	Amoxicilline/Clavulanate	
	Clarithromycin	
	Imipenem	
	Streptomycin	

Risk Interventions and Tools

Risk intervention is a risk control action guided by the risk assessment results and involves identification, selection, and implementation of alternative approaches to minimize identified risk. These approaches should be targeted to the right audience to achieve favorable results. In this document, we have listed general examples of risk interventions and tools which may or may not apply in your setting. Once the medicines that pose serious risks to patients are identified, appropriate interventions should be selected which are feasible, cost effective, and sustainable for your setting. Following are examples of interventions targeting health care workers, patients, and other care givers that can be utilized to minimize risk posed to TB patients.

Interventions Targeting Health Care Workers

Communication interventions

There are various means medicine risks can be communicated to health care workers (HCWs) to educate and make them knowledgeable about the risks and how best to manage their patients on those medicines. Some common examples practiced widely in countries include—

- Letter to health care providers: “dear doctor letters” is a useful tool used to communicate important new information related to any medicinal product to health care providers to mitigate injury from the product use. The letter covers wmedicine warnings and recommendations on steps to take such as patient counseling, improving training programs on the medication use and where to report adverse reactions related to the

medicine if suspected. This is a risk mitigation strategy that is widely used by developed countries.

- Drug alerts or safety alerts: New potential safety risks are communicated to health care providers in a timely manner through this medium. Prescribers can subscribe to alerts to keep updated on important safety information related to individual medicines and key factors to consider during treatment.

Mandating Education and Certification for Product Prescribers

Mandatory certification and recertification requirement for TB care providers may be required for products where the risk has not been reduced by use of other approaches such as medication guides to patients and communications to health care providers. For this intervention, health care workers are required to undergo training (using the most cost effective and sustainable approach) and receive certification for the medicine in question. In this training, the HCW may be required to demonstrate knowledge and skills in appropriate methods of treatment and care of TB patients using that product. The HCW should be able to understand the risk and benefits of using the medicine and appropriate management of adverse effects to reduce the risk.

Certification of Treatment and Dispensing Facility

Depending on the product and the level of risk, certain facilities may be certified to treat patients with the product (example, MDR-TB treatment only done in certain facilities). The certification will require training the HCW about the risks and the requirements for treatment and dispensing of that particular medicine in his or her facility. Certain measures may be put in place to achieve this such as supplying medicines only to approved facilities, or requiring a preauthorization from a central, sub-district, or health facility committee that will approve use of the medicine for treatment. However, the latter approach will require additional monitoring to ensure that non-approved patients are not started on treatment without prior authorization. Examples of other approaches include dispensing medicines only from certain enrolled prescribers, or requirement of an additional documentation from prescribers prior to dispensing proving that the patient meets requirement for treatment with that medicine.

Routine Laboratory Monitoring

Laboratory monitoring for patients is required for some TB medicines to support proper management of adverse drug events. These monitoring requirements are sometimes required according to standard treatment guidelines and the HCWs receive training but this is not always done. As a risk intervention, trained dispensers may be required to see laboratory tests before dispensing particular medicines. They should have the knowledge to evaluate if the values fall within the safe range before dispensing the medicine to the patient.

Drug Toxicity Charting Tools

This can be manual charts or computerized monitoring systems for tracking incidences of toxicities. Drug toxicity charting tools are used to match side effects and adverse drug reactions

against offending medicines. An example is ototoxicity caused by aminoglycosides and ophthalmic toxicity by ethambutol. Additional information on steps to mitigate these toxicities may be described in a chart, e.g., Snellen's chart for visual acuity and color vision tests for severe reversible or irreversible damage to the eyes related to ethambutol; and a baseline audiometric test for aminoglycoside performed within 72 hours of treatment onset and then regularly throughout treatment.

Patient Adherence Interventions and Tools

Adherence to instructions on proper medicine use and effects is a key factor in ensuring treatment success and improved treatment outcomes. Some examples of approaches that can be used to improve adherence include—

- **Directly Observed Therapy (DOT):** This is an intervention recommended by WHO as parts of the DOTS strategy and widely implemented in many countries. In this approach, the patient is observed by the HCW or care giver when taking their medicines. This approach is implemented during the intensive phase of TB treatment. Studies show 86–90 percent success in patients completing treatment with DOT compared to 61 percent for those patients self-administering medicines.²⁵ This method has been shown to decrease the risk of drug-resistance associated with incomplete treatment and the chances of treatment failure and relapse.
- **Patient reminder tools:** The use of SMS (text message) messaging to alert patients on refilling and dispensing time to encourage patient adherence to treatment. Some existing examples which could be adapted are SIMpill and X out TB which have been effective in promoting patient adherence and preventing the development of drug resistance.

Templates and Information on Reporting Adverse Reaction

Documentation of an anti-TB medicine-related adverse reaction is only useful when used by health authorities to guide decision making related to patient safety. Prescribers should have standardized templates or forms and information on the process for reporting suspected adverse reactions when they occur.

Strengthening Quality Assurance Measures

The quality of medicines dispensed to patients is important as it can affect treatment outcomes. Poor quality medicines can lead to adverse reactions, treatment failures, drug resistance, and or even death. To assure the quality of medicines, WHO established a prequalification program for medicines; however, this process is not 100 percent efficient. Countries also procure TB medicines from non WHO prequalified suppliers and the integrity of medicines may be affected during storage and distribution in the country. They still need to perform quality control and quality assurance tests and equip their national testing laboratories where available to carry out this function. A post-marketing surveillance quality test is an example of an approach that can be undertaken to ensure that medicines in the supply chain are of good quality and safe to patients.

²⁵Minnesota Department of Health. N.D. *Directly Observed Therapy (DOT) for the Treatment of Tuberculosis, Factsheet describing how to use DOT with TB patient.*
<http://www.health.state.mn.us/divs/idepc/diseases/tb/dot.html>

The approach involves undertaking random testing of TB medicines samples and to determine where in the supply chain the integrity of the medicine was compromised. This approach can also help in the detection of counterfeited or substandard medicines particularly in the private sector.

Packaging and Labeling at Dispensing Facilities

The type of package and labels for dispensing medicines to patients can be useful in enhancing patient safety. Many medications are packaged in containers with similar shapes and sizes. Changing the medicine appearance such as the selection of different colors for labeling can help patients in distinguishing and identifying the appropriate medication thereby avoiding medicine mix-up. The packaging labels must include the written order exactly as prescribed to avoid errors in administration that may pose harm to patient and supplied in tamper resistant packages to minimize the risk of accidental use in children.

Medication Storage

It is necessary to store and stock medications in a manner that reduces unintended errors. Storage areas should be able to accommodate medication and they should be stored under appropriate conditions to maintain their quality. There should be a process for reviewing and separating expired, recalled, and short-dated products so that they are not dispensed to patients. A drug expiry monitoring tool could be kept to support regular monitoring of medicine drug expiry dates. This tool could be either manual or electronic.

Interventions Targeting Patients

A Medication Guide or Patient Package Insert (PPI):

These are used when the information on the drug label can affect ADRs and patient's decisions to use the medicine. The guides and PPIs can also be given when the effectiveness of the medicine depends on the directions for use as They contain written information on potential side effects to help patients make informed decisions about their treatment, instructions on the product use to improve use and effectiveness of treatment, and information that can help prevent serious adverse reactions. Both medication guides and PPIs are given to patients at the time of dispensing.

Patient Counseling

Patients should be counseled when they start treatment and every time their anti-TB treatment is refilled to give them important information about their medicines. Patient counseling should include information on the medicine's risks, benefits, and safe administration; the importance of continuing their medications and not skip doses; not sharing prescribed medications, steps to avoid overdosing, and importance of reviewing the medication guide provided. For effective outcomes, counseling communication should be tailored to the audience; language barrier and education levels should be considered when developing counseling messages.

Outreach/Advocacy Programs

Some patients who have successfully completed their TB treatment and are considered cured can be used as advocates to educate other patients suffering from TB. These advocates can provide the support group that other patients need to alleviate their concerns about the ADRs they are experiencing and the importance of adhering to their treatments.

Patient-Oriented Risk Communication

Promotional materials can educate patients on the risks and benefits of the medicines they are taking. Examples of approaches which have been implemented in countries include printed educational flyers; posters; media communication (TV, radio); outdoor placards, billboards and signs, and in some countries, the internet. These tools should be simplified for easy understanding by local population to increase the effectiveness of the message.

Incentives to Promote Adherence

Providing incentives to patients such as nutritional supplements, food, and acknowledgments are examples of approaches that can be used for improving adherence to treatment. A pilot study conducted by Jennifer Lorvick et al to test adherence to a six- months course of community-based directly observed preventative therapy showed 89 percent completion rate and adherence to therapy among study participants.²⁶

Risk Confrontation

Risk confrontation involves mobilizing and working with all stakeholders, health care personnel, advocacy groups, and communities in making decisions on the benefits and risks of medicines, and strategies to further reduce risks and maintain the benefits of the medicine. Under the leadership of the national TB program, efforts should be made to continue to reduce the risks of TB medicines. It is important to involve, coordinate, and mobilize a range of stakeholders; this may involve making serious efforts to build and maintain both formal and informal relationships within governments, communities, the private sector, and civil society. The stakeholders can be coordinated by the NTP using already existing committees or forums where TB medicines risk management is a standing item in the agenda. The group can be tasked with exploring feasible strategies to reduce the risks caused by identified medicines. The group would have to decide what intervention/tool will be used to reduce risk, how the tool will be developed, and who will implement it and how. When the TB program is looking for opportunities to reduce TB medicine risks, they have to involve the following people such as—

- Regulatory authorities
- Pharmacovigilance units

²⁶ Lorvick, J, S. Thompson, B. Edlin, et al. 1999. Incentives and accessibility: A pilot study to promote adherence to TB prophylaxis in a high-risk community. *Journal of Urban Health* 76(4): 461–467. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3456694/>

- National TB program
- TB clinical experts and other health care workers
- NGOs and TB implementing partners
- Community health workers for TB
- TB patients
- WHO
- Professional associations—doctors and pharmacists
- Academia

The composition of the team for initial decision making should be manageable (relatively small) and there may be need to form sub-committees to achieve varying tasks. Agreed on decisions by the committee can then be presented to a larger group for ratification. After ratification, recommendations should be forwarded to the appropriate offices for implementation.

Implementation and Evaluation of Interventions

As mentioned earlier, risk intervention can be educational or operational and can be targeted to improve systems that are associated with medicine risk problems. Appropriate risk minimization interventions that target the right audiences should be identified and agreed on for implementation by a group of key stakeholders under the leadership of the NTP.

Depending on the risk intervention identified, health workers have to be trained on how to implement the intervention. It is also important that monitoring and performance indicators are identified and incorporated in the intervention to evaluate how well the intervention is working to minimize risks. Data to monitor performance should be collected regularly and assessed after a period of time to decide if the problem has improved. It is also important to investigate the reasons why the intervention did not work; having this information will help in the redesign of the intervention. After the redesign of the risk intervention, it should be implemented and evaluated again to make sure the risk has been reduced.

When evaluating interventions to find out if risk has reduced, baseline and post-baseline data should be collected and compared to determine if the intervention is working. Examples of indicators that can be monitored over time to determine if the intervention is working include—

- Percentage reduction in the number of ADRs reported over a period of time
- Percentage increase in patient adherence to treatment
- Percentage reduction in use of contraindicated medicines by prescribers
- Percentage decrease in drug-drug interactions reported over a period of time
- Percentage increase in frequency of required laboratory testing for a set of tracer medicines
- Percentage increase in frequency of required clinical examination for a set of tracer medicines
- Percent of high risk medicines that require registers with those registers in place
- Percentage of physical stock counts that correspond to record counts for a set of tracer medicines
- Percentage of a set of tracer medicines stored appropriately

- Percentage of a set of tracer medicines reported to fail quality control tests
- Percentage of prescriptions in accordance with the national guidelines

Example 1

Problem: reduction in treatment success rate for DR-TB patients in certain regions of the country. Upon further investigation, the decrease was attributed to non-adherence to treatment due to rumors in the community that cycloserine causes mental health problems.

Interventions: (a) Monitor administration (DOT) of cycloserine during intensive phase of treatment; (b) during each patient visit to pick up medicines in continuation phase, use the adherence tool to record if patient has adhered to their treatment; (c) during each patient encounter, use the tool provided for accessing patient's mental state for each patient on cycloserine; (d) use appropriate media and posters and train health workers on how to counsel patients on cycloserine to demystify their fear of the medicine.

Monitoring and Evaluation: Monitor the following indicators quarterly; this should be incorporated into the regular quarterly monitoring visits.

- Total number of days DOTS was not done in intensive phase for MDR-TB patients—target 0 days
- Total number of days that patients did not adhere to their regimen during each monthly visit in continuation phase—target 0 days
- Total number of times patient's mental state was not assessed and documented during each patient encounter for cycloserine—target 0
- Percentage of patients counseled on side effects of cycloserine—target 100%
- Percentage increase in treatment success rate for MDR-TB patients—from baseline

If the indicators do not improve, review the process and make appropriate changes until the desired outcome is achieved.

Example 2

TB patients on a particular medicine that has a higher safety risk than other medicines will need intervention on the risks. Provide medication information either through a patient information guide (a one pager in lay language with main information about a drug and its risks and how to reduce it) or through use of pictures and counseling. The TB nurse or the pharmacists who dispense the medicine to the patient will have to be trained so that a standardized approach either through the written guide or pictures and counseling will be taken to provide the medication information.

First explain the content, then give the patient the guide, preferably in local language; or the pictorial information and counseling. The nurses or pharmacists should monitor if the patient is following instructions as counseled upon each visit. The patient should also be evaluated to find out if the risk occurred or has reduced depending on their individual situations. They should also document why the problem did not improve. This should be reported through the formal reporting channels and information will be used for redesign of the intervention. The whole process should be repeated—implementation, monitoring, and evaluation of intervention.

CONCLUSIONS

All medicines cause an unwanted effect in patients in addition to treating what it was prescribed to treat. The level of this effect differs across medicines. The goal of good patient management is to ensure that the benefit of using the medicine outweighs its risk; and that measures are put in place to further reduce the risks. TB medicines, particularly second-line medicines, are associated with high risks of intolerance and serious toxic effects and this affects treatment outcomes. Ensuring that TB medicines are safe to patients requires systematic planning and approaches.

Through extensive review of the risk contributory factors, this document addresses some measures that can be implemented to prevent harmful medicine-related effects to patients undergoing TB treatment. It also emphasizes the need for appropriate management and treatment to promote rational use. The risk factors identified in this document can be used as a guide for health workers to identify and focus on the products with the most risk and potential for harm to patients. In addition, some tools have been identified and developed to assist health workers, patients, and others administering care to TB patients to reduce or prevent the occurrence of these risks. The responsibility will fall on the national TB program to coordinate with key stakeholders and reach consensus on the most feasible and cost effective approaches required to minimize the risks caused by TB medicines. This process requires constant review and evaluation and use of targeted tools to ensure that the risks to patients are reduced.

GLOSSARY

Antimicrobial: Any substance (medicine, solution) that destroys or prevents the growth and or multiplication of microorganisms, e.g., bacteria

Adherence: Also sometimes called compliance, refers to the extent to which patients correctly take their medicines as prescribed or follow the right instructions/procedure on taking their medicines.

Adverse event: Any untoward medical occurrence in a subject that results after the use of a medical or investigational product which may or may not be related to the product.

Adverse drug reaction : An unintended or unexpected reaction to a medicine at the normal recommended dose for human use.

Clinical study: A research study that evaluates new medical approaches on human. These studies could involve new inventions on screening, prevention, diagnosis, or treatment of a disease. This is sometimes referred to as a clinical trial.

Combination therapy: Using more than one medical product to treat a condition.

Concomitant medications: Using two or more medicines given during the same time period.

Counterfeit medicines: Medicines that are fraudulently manufactured and sold with falsely labeled ingredients and source.

Drugs and medicine: These two words are used interchangeably in this protocol. They both refer to substances used to diagnosis, treatment, or prevent a disease.

Drug exposure registries: These are documents containing uniform information about registered patient drug usage for scientific, clinical, and health policy decision purposes.

Drug and therapeutic committees: A committee that is set up to promote and ensure the safe, rational, and cost-effective within their jurisdiction.

Drug efficacy: The ability and maximum effective level that a drug at any dose.

Drug regimen: This is a decision on administration of a medicine with respect to the schedule, formulation, route, and dose, interval of dosing and treatment that is expected to produce a beneficial effect.

Drug-resistant tuberculosis: This is when there is resistance to any standard form of tuberculosis treatment due to the ability of the causative organism (mycobacterium tuberculosis) to develop.

Epidemiology: The section in medical science that studies the patterns (incidence, distribution), causes, and control of a disease in a population.

Extensively drug-resistant TB: This form of tuberculosis is resistance to at least isoniazid and rifampin among the first-line anti-TB drugs and is resistant to any fluoroquinolone and at least one of the three second-line injectable drugs.

Health care provider letters: These are information dispersed to health care providers/physicians on important new information about a medicinal product or device.

International Conference on Harmonization of Technical Requirement for Registration of a Pharmaceuticals for Human Use: This is a forum where regulatory authorities of the United States, Europe, and Japan; and experts from the pharmaceutical industries in the three regions come together to discuss scientific and technical issues related to the registration of pharmaceutical products for human use.

Multidrug-resistant tuberculosis: Tuberculosis that is resistant to two or more of the anti-tuberculosis medications that are primarily used for treatment.

Off-label use: This is a situation prescription medicines are legally used for treatment of a condition that has not been approved by medicine regulatory authorities, e.g., FDA.

Pharmacoepidemiology: This is a process that studies how medicines are used while assessing the health risk to the population.

Pharmacovigilance: This is a process where medicines are assessed and monitored for safety both in the development and post-marketing stages. It also involves the planning of actions to reduce harm and increase the benefits to humans.

Post-marketing surveillance: This is a process where already approved and on market pharmaceutical products (devices, medicines) are monitored for safety

Prospective studies: This is a study that is designed to ascertain the relationship between a condition and a characteristic shared by some members of a group and then followed forward in time.

Retrospective studies: Studies study that compares two groups of people, i.e., those with the disease—case group, and those without the disease or condition—control group. Also called a case-control study.

ANNEX A. IDENTIFICATION OF RISK FACTORS FOR ANTI-TB MEDICINE

The following factors listed below will be used for risk identification to determine which anti-TB medicines require risk management interventions based on the level of risk.

Known Serious or Severe Adverse Event

A serious adverse event or reaction is defined as any untoward medical occurrence which at any dose may—

- Result in death
- Is life threatening (patient was at risk of death at the time of the event)
- Require inpatient hospitalization or prolongation of existing hospitalization
- Result in persistent or significant disability/incapacity
- Cause a congenital anomaly/birth defect²⁷

A severe event is a clinical term for describing the most grave or dangerous state of a clinical condition.²⁸ The term severe is used to describe the intensity of a specific event which may be of a minor medical significance while serious usually based on an event outcome is used when an event poses a threat to the functioning or to a patient's life. For these criteria, the following factors were considered:

An expected or known adverse event or reaction is an event that is noted in the labeling package insert for the medicine.

Under these criteria, the following factors were considered—

1. Known pharmacological class effect: These are identified or potential risks from clinical development and post-authorization experience which are believed to be common to a drug class.²⁹ For example, the aminoglycoside class of antibiotics such as amikacin and kanamycin used for MDR-TB treatment cause ototoxicity (damage to the auditory nerve). This means that taking two medicines in this pharmacologic class can increase the risk and effect of ototoxicity in patients. Only anti-TB medicines with known class effect from the tracer list of anti-TB medicines were considered in the medicine risk scoreboard.
2. Known safety issues for renal impairment: These medicines are identified or potential risks of causing renal impairment or kidney damage when administered at a normal therapeutic dose. The level of risk of a medicine that causes renal impairment is increased if the TB patient already has a kidney disease. For examples, anti-TB medicines like capreomycin should be avoided in patients with mild to severe kidney problems because of the increased risk of damage to the kidneys. Only anti-TB medicines with known safety issues for renal impairment in normal patients at normal dose of medicine and for patients with kidney disease were considered in the medicine risk scoreboard.

²⁷ Cobert, B.. 2012. *Cobert's Manual of Drug Safety and Pharmacovigilance 2nd ed.* Massachusetts, USA: Jones and Bartlett Learning.

²⁸ Cobert, B. and P. Biron. 2002. *Pharmacovigilance from A to Z.* Oxford, UK: Blackwell.

²⁹ European Medicines Agency (EMA) Heads of Medicines Agencies (HMA). 2012. *Guidelines on Good Pharmacovigilance Practices (GVP), Module V-Risk Management Systems.*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf

3. Known safety issues for hepatic impairment: These are medicines with identified or potential risks of causing hepatic impairment or liver damage when administered at a normal therapeutic dose. Anti-TB medicines like isoniazid and pyrazinamide can cause liver damage when taken at normal therapeutic dose, and the risk level increases if the patient already has a liver condition. Only anti-TB medicines with known safety issues for hepatic impairment³⁰ in normal patients at normal dose of medicine and for patients with hepatic disease were considered in the medicine risk scoreboard.
4. Known safety issues for elderly: these are medicines with identified or potential risks of causing harm to elderly patients. The elderly represent a special group in pharmacology because they tend to have more diseases than younger people and therefore consume more medicines that can increase risk of drug interactions. Also, the rate and extent of absorption, distribution, metabolism and elimination of medicines in the elderly may be change, producing different effects from what will occur in younger population. Safety information available for elderly during time of approval is limited thereby increasing the risk potential. Anti-TB medicines with known clinically significant safety effects in elderly and medicines with unknown effects (no clinical information available) were considered in the medicine risk scoreboard. Clinical significance is defined by Kraemer et al as a change to normal functioning due to therapy.³¹ It is based on external standards provided by clinicians, patients, or researchers. It is when the effect of the drug makes enough difference to the provider and patient to justify changing it.
5. Known safety issues for pediatrics: these are medicines with identified or potential risks of causing harm to pediatric patients. Pediatrics is different from adults in having still-developing body systems so additional considerations may be involved. There is also very limited safety information on pediatric populations during approval of medicines increasing potential for risks. Information obtained online following the examination of more than 60,000 research trials from 2005 to 2010 using data entered into the US clinicaltrials.gov registry, showed that only about 8 percent of trails were designed for children younger than 18 years.³² Key safety issues like drug-drug, drug-food, and other safety related issues in children are largely unknown and most recommendations are based on extrapolations from adult data. Anti-TB medicines with known clinically significant safety effects in pediatric patients and medicines with unknown effects (no clinical information available) were considered in the medicine risk scoreboard.
6. Pregnancy risk category: These are medicines that cause harm to the fetus when taken by pregnant women at the normal recommended doses. The pregnancy categories considered in this document taken from FDA website are:

³⁰ Kraemer, H. C., Morgan, G. A., Leech, N. L., et al. 2003. Measures of Clinical Significance. Clinicians Guide to Research Methods and Statistics. *Journal of the American Academy of Child & Adolescent Psychiatry*, 42:12. <http://psy6023.alliant.wikispaces.net/file/view/Kraemer2003.pdf>

³¹ Duke Medicine News and Communications. 2012. *Children Underrepresented in Drug Studies*. DukeHealth.org.

³² The American Heritage Medical Dictionary. 2007, 2004 by Houghton Mifflin Company. <http://medical-dictionary.thefreedictionary.com/drug+interaction>

- Category C: human data is lacking or not done but animal studies are positive for causing fetal harm
 - Category D: Human data show risk to fetus, benefits may outweigh risks
 - Category X: animal and human data are positive to cause harm to the fetus
7. Potential risk during lactation: these are medicines that affect lactating mothers, or can pass through breast milk to the baby, causing harm. Many medicines pass through the breast milk but the decision whether to take the drug or not should be determined by a risk benefit analysis. Anti-TB medicines that produce the following effects were considered in the medicine risk scoreboard.
- Medicines contraindicated during lactation
 - Medicines that need risk benefit analysis
 - Medicines where effect on lactation is unknown
8. Experience with drug overdose or toxic levels: these are described as medicines where specific methodology or approaches for management of toxic effects or overdose in patients were defined. Overdose is a lethal or toxic amount of a drug. In the medicine risk scoreboard, medicines with defined approaches to handle overdose were considered as lower risk than medicines without any defined approach to control overdose.

Interactions

Interactions discussed and considered as risk criteria in this document include—

1. Potential for clinically significant drug-drug interactions: Drug interaction is the pharmacological result, either desirable or undesirable, of drugs interacting with themselves or with other drugs, with endogenous chemical agents, or with chemicals used in or resulting from diagnostic tests.³³ When the combined effect of two drugs equals the sum of each drug given alone, it is called an additive effect. An example is the use of cycloserine and isoniazid at the same time can cause an additive effect to increase the toxicity and side effects of isoniazid. Interaction called a synergistic effect occurs when the combined effect exceeds the sum of the effect of each medicine given alone by a drug interaction is described as a potentiation effect when the medicine in the presence of another medicine creates a toxic effect. An antagonistic effect is the interference of one medicine with the action of another. Drug-drug interactions considered in the medicine risk scoreboard are interactions that have been documented to be clinically significant for example, drug interaction that either stimulate or inhibit the liver enzymes which can result in overdosing or underdoing of one of the medicines administered. Only drug-drug interactions with clinical significance were considered in the anti-TB medicine risk scoreboard.
2. Drug-food interactions: The National Consumers League and the FDA define drug-food interactions as “changes in the bioavailability and/or pharmacokinetics (absorption, distribution, metabolism, elimination) of an agent as a result of its interaction with the

³³ U.S FDA. Avoid Food-Drug Interactions. *A Guide from National Consumers League and the FDA*. Publication no. (FDA) cder 10-1933.
<http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/EnsuringSafeUseofMedicine/GeneralUseofMedicine/UCM229033.pdf>.

nutritional or chemical components of food.³⁴ A food-drug interaction can cause changes in the efficacy and safety profile of an agent by altering its therapeutic effects and/or side effects.” Simply described as the effect produced when some drugs and certain foods or beverages are taken at the same time. For example, mixing alcohol with some drugs may cause you to feel tired or slow your reactions. A specific example is taking cycloserine with alcohol which increases the risk of convulsion in chronic alcoholics. In the medicine risk scoreboard, all anti- TB medicines that interact with any food or beverage were considered.

3. Drug-disease interactions: According to Lindblad et al, this is exacerbations of preexisting diseases, conditions, or syndromes due to the use of multiple medications.³⁵ Examples include a person with high blood pressure could experience an unwanted reaction (increased heart rate) from also using a nasal decongestant or Another example is patients with diabetic mellitus using levofloxacin which causes some disturbances of blood glucose including hyper and hypoglycemia. All diseases that interact with a TB medicine were considered in the medicine risk scoreboard.

Safe Medicine Use indicators

A safe medical product is one that has reasonable risk given the magnitude of benefits expected and the alternatives available.⁴⁰ The FDA notes that reasonable risk to individual research participants is defined as (1) requiring the least amount of intrusion into interests of participants that is necessary to facilitate sound scientific inquiry, and (2) are consistent with an equal regard for the basic interest of study participants and the members of larger community whose interest that research is intended to serve.³⁶

The elements of safe use examined in this document include—

1. Potential for medication error: a medication error is any incorrect or wrongful administration of a medication, such as a mistake in dosage or route of administration, failure to prescribe or administer the correct drug or formulation for a particular disease or condition, use of outdated drugs, failure to observe the correct time for administration of the drug, or lack of awareness of adverse effects of certain drug combinations. Causes of medication error may include difficulty in reading handwritten orders, and confusion about different drugs with similar names amongst other reasons.³⁷ For this document, only medication error due to look alike and sound alike was considered in the medicine risk scoreboard. Please note that these criteria will need to be adapted according to country relevance. Medicine brand names may

³⁴ Lindblad, C., J. Hanlon, C. R. Gross, et al. 2006. *Consensus Statement- Clinically Important Drug Diseases Interactions and their Prevalence in Older Adults. Clinical Therapeutics* 28 (8).

³⁵ U.S. Department of health and Human Services (DHHS). 1999. *Managing the risk from medical products use: Creating a risk management framework. FDA Report to the FDA Commissioner from the task force on risk management.* <http://www.fda.gov/Safety/SafetyofSpecificProducts/ucm180325.htm>.

³⁶ London, A. J. 2006. Reasonable risks in clinical research: A critique and a proposal for the Integrative Approach. *Statistics in Medicine.* <http://www.hss.cmu.edu/philosophy/london/London%20Integrative%20Approach%20StatMed%20unpaginated.pdf>

³⁷ Medication error. Mosby's Medical Dictionary, 8th edition. © 2009, Elsevier.

<http://medical-dictionary.thefreedictionary.com/medication+error>

differ by country. Information analyzed in the scoreboard was derived from the FDA website.

2. Off-label use of medicines: This is when marketed medicines are used to treat conditions that were not studied during clinical development of the product.³⁸ For example when a particular medicine is not approved for pediatric use but used off label in pediatrics. There is usually uncertainty about benefits and risks because less information about the safety and efficacy information of the medicine are available. However, if the medicine is approved for use in the particular country in question (not in the US or EU for example) then it is not off label use. For this document, only anti- TB medicines that have known off label use (except for the treatment of TB as an off-label use) was considered in the medicine risk scoreboard. Off label data used for the analysis is based on the United States FDA approvals of medicines. This indicator should be adjusted according to country context.
3. Potential for medication abuse: Medication abuse is defined in this context as habitual use of the medicine to alter one's mood, emotion or state of consciousness.³⁹ Review of literature did not show any information about any anti-TB medicine that has been used recreationally or abused.
4. Narrow therapeutic window: Maureen burns article defines narrow therapeutic index to be those medicines that have less than a twofold difference in median lethal dose (LD50) and median effective dose (ED50), or those that have less than a twofold difference in minimum toxic concentration (MTC) and minimum effective concentration (MEC). Simply described, a narrow therapeutic window is usually a short time interval (after a precipitating event) during which a particular therapy can be given safely and effectively. A narrow therapeutic effect may go from therapeutic to toxic with an increase of just 10 micrograms per milliliter in blood concentration.⁴⁰ No anti-TB medicines were found to have a narrow therapeutic index in the medicine risk scoreboard.
5. Action taken by regulatory authority or marketing authorization holder: This includes any significant regulatory action in any market imposed due to safety concerns. Significant regulatory action include: a new or strengthened warning such as a black box warning or action to suspend or revoke a marketing authorization.⁴¹ The regulatory authority considered

³⁸ Cobert, B. 2012. *The Theory and Definitions of Drug Safety (Pharmacovigilance)*. 2nd ed. Massachusetts, Jones and Bartlett Learning,

³⁹ The American Heritage Stedman's Medical Dictionary. 2002. Boston: Houghton Mifflin Company. <http://dictionary.reference.com/browse/drug+abuse>.

⁴⁰ Burns, M.. 1999. Management of Narrow Therapeutic Index Drugs. *Journal of Thrombolysis* 7(2):137-43. <http://www.ncbi.nlm.nih.gov/pubmed/10364779>

⁴¹ Merriam Webster Dictionary. Accessed June 4, 2012. <http://www.merriam-webster.com/medical/therapeutic%20window>.

European Medicines Agency (EMA) Heads of Medicines Agencies (HMA). 2012. Guidelines on good pharmacovigilance practices (GVP), Module V-Risk management systems. Available at U.S FDA. Center for Veterinary Medicine (CVM). 2008. Guidance for Industry. Drug Stability Guidelines. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf. <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm051556.pdf>.

in this analysis is the US FDA for actions taken after marketing authorization was issued to the manufacture. This section may need to be adapted by the country as needed.

6. New product: A new product can be referred to as a new preparation and presentation (new dose, generic formulation, and route of administration), new indication, and new population approved for use (pediatric, geriatric, or others).⁴² Usually, the drug safety profile conducted by the manufacturer prior to pre-approval of the medicines do not cover all special populations such as pediatric, elderly, and pregnant women, and populations with racial or genetic predispositions. Also, because the drug is new, it may require more prolonged use in a larger population size before some of its side effects will be detected. A new product in the context of this document is one that meets above three criteria for TB medicines within the last three years.

Drug Integrity and Supply Chain

Availability of good quality anti-TB medicines is important to ensuring patients' safety and to also ensure that the medicine can manage the condition effectively. Consequences of use of poor quality medicine include lack of therapeutic effect which can prolong the illness or even cause death; induce adverse reactions that can be harmful to the patient; and a waste of scarce resources.

A stable drug product is described as one that can retain its properties within specified limits in order to be useful.⁴³ Stability is defined by World Bank as "capabilities of a particular formulation of a pharmaceutical in a specified container/closure system to remain within specified physical, chemical, microbiological, therapeutic and toxicological specifications."⁴⁴ The time period that a medicine can be stable is established by the manufacturer or sometimes by a country's drug regulatory authority; this period ends with the expiration date of the medicine.

The elements considered in these criteria include—

1. WHO prequalification of medicines: This is a service provided by WHO to ensure that medicines supplied by procurement agencies meet acceptable standards of quality, safety, and efficacy. This service is specifically for TB, HIV/AIDS, malaria, reproductive health products medicines, and zinc. This service is used by international procurement agencies and increasing by countries to guide bulk purchasing of medicines. In the context of this document, the WHO prequalification is considered as to first step of quality control for countries with weak regulatory systems to ensure safety of medicines. Medicines that are prequalified are categorized as having a lower risk than medicines that are not.
2. Total number of manufactures or suppliers prequalified: Even though the WHO prequalification is considered as a first step to quality control for countries with weak

⁴² European Medicines Agency (EMA) Heads of Medicines Agencies (HMA). 2012. *Guidelines on Good Pharmacovigilance Practices (GVP), Module V-Risk Management Systems*. EMA/838713/2011. European Medicines Agency.

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf

⁴³ Cobert, B. and P. Biron 2002. *Pharmacovigilance from A to Z*. Oxford, UK:Blackwell Publishing Company.

⁴⁴ MSH/WHO.1997. *Managing Drug Supply*. 2nd ed. West Hartford, CT: Kumarian Press.

regulatory systems, not all TB medicines have been prequalified. For the prequalified medicines, there are very few quality assured sources available which can lead to a global stock out for those medicines making countries to procure from non-quality assured sources. Because of weak and non-functional regulatory systems to assure medicine quality, procuring from suppliers whose products and manufacturing plants have not been certified or prequalified by a strong regulatory authority increases the risk of the possibility that the medicine could be substandard. Also, if there are fewer suppliers for a medicine, there is a higher risk of stock-outs from the manufacturer if there is a problem with the manufacturing plant or if demand was not well quantified. The assumption made in this document and considered in the risk management score board is that the fewer the suppliers available for a prequalified medicine, the higher the risk of procuring substandard medicines from non-prequalified suppliers.

3. **Short shelf life:** The FDA defines shelf life of medicines as the time period from the date of manufacture of the product until it is administered to the patient.⁴⁵ It is the length of time that a medicine can be stored and still remains safe and effective for use by patients. Shelf-life is sometime used interchangeably with expiry date which is defined by WHO as the date given on the individual container of a drug product up to and including which the product is expected to remain within specifications if stored correctly.⁴⁶ The main difference is that a medicine still within the expiry date period can be unstable if not properly stored. In this document, products with a shorter shelf-life are considered a higher risk than products with long shelf-life. Regular inventory monitoring is required for medicines with short shelf-life to ensure they are utilized before expiry and to dispose after expiry. Anecdotal evidence shows that some patients are sometimes given expired medicines due to lack of inventory monitoring. Expired products are less effective due to decreased potency. Countries may also be forced to make emergency procurements and sometimes these products may not be quality assured increasing the risk to patients. In the context of this document, short shelf life is defined as time period from 0 to 24 months.
4. **Storage conditions:** These are determined by the manufacture after stability testing and it is the condition at which a medicine should be stored to still remain stable. In the developing country context, medicines that require refrigeration will be at a higher risk of been unstable because of irregular power supply. Medicines that require reconstitution also have slightly higher risk than other medicines that do not because of risk of contamination during reconstitution. Medicines that also need to be stored away from light and away from moisture have a higher risk of been unstable if not properly stored.
5. **Counterfeit Medicines:** Counterfeit medicine is fake medicine which may be contaminated or which does not contain the right active ingredient or which has no active ingredient at all. It may also have the right active ingredient but at the wrong dose. In a draft document by WHO

⁴⁵ Botwe, B. 2005. *World Bank Training Program on HIV/AIDS Drugs, Training Module 4: Quality Assurance*. http://www.who.int/hiv/amds/capacity/tza4_quality_assurance.pdf.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm051556.pdf.

⁴⁶ US Department of Health and Human Services, FDA, Center for Veterinary Medicine. 2008. *Guidance to Industry Drug Stability Guidelines*. Rockville, MD:FDA. <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm051556.pdf>.

in 2005, counterfeit medicine was defined as a medicine which⁴⁷ is deliberately and fraudulently mislabeled with respect to identity or source.⁴⁸ Counterfeit medicines are illegal and may be harmful to patient health, medicines with high cost and medicines used by widely are usually targeted as well as countries with weak regulatory enforcements for medicines. Medicines that have been reported to be counterfeited are allotted a higher risk score in this risk scoreboard.

6. Diversion of medicines: Medicines may be diverted from legal and medically necessary uses towards uses that are illegal and typically not medically authorized or necessary. In the context of this document, drug diversion is defined as losses due to pilferage. Due to the economic situation in many developing countries, expensive medicines are sometimes lost or diverted either during transport to health facilities or from the health facility store and usually traded for personal gain. Medicines that have a high potential for diversion are allotted a higher risk profile than other medicines because medicine quality may be compromised during diversion causing high toxic levels; the country will also be quick to run out of stock of the medicine and they may be forced to procure emergency stock from non-prequalified sources compromising on medicine quality.

Chronic Medicine Use Risk

1. Population exposed to the medicine: The target audience and size of its population is a risk determinant which has been considered in this study. The larger the population that is exposed to the medicine, the higher the number of casualties from an associated risk event. In this document, a higher risk score is associated with medicines which are used for treatment in larger populations. In the context of this document, we are considering all medicines used for management of public health diseases (of which TB is a public health disease) to constitute a higher risk than medicines used for treatment of nonpublic health diseases. This document also considered that medicines in the top 20 list of most used medicines in the country constitute a higher risk than other medicines.
2. Adverse drug event at prolonged use: As the length of time that a particular medicine is taken for the treatment of TB is increased, patients are at a higher risk of developing adverse drug events that may be toxic to the body. In this document, a higher risk is allotted to resistant TB medicines since they are used for a longer period of time than for medicines used for susceptible TB treatment.

⁴⁷ WHO. 2003. *Guide to Good Storage Practices for Pharmaceuticals*. WHO Technical Report Series, No 908. Annex 9. <http://apps.who.int/medicinedocs/documents/s18675en/s18675en.pdf>

⁴⁸ Forzley, M. 2005. Draft: Combating counterfeit drugs: a concept paper for effective international collaboration World Health Organization. http://www.who.int/medicines/services/counterfeit/CombatingCounterfeitDrugs_Conceptpaper.pdf.