Submission to the Expert Committee on "Regulation of Newer TB drugs in India", Ministry of Health & Family Welfare, January 2014

Striking the right balance - Accessing new anti-tuberculosis drugs in India

In December 2012, the US Food and Drug Administration (USFDA) gave accelerated approval to bedaquiline (1). A second new chemical entity, delamanid, received approval from the European Medicines Agency in November 2013(2). These are the first new drugs active against sensitive and drug resistant forms of tuberculosis (TB) in decades (3).

In 2013, the Indian Ministry of Health (MoH) formed a high-level committee to discuss how to respond to this historic opportunity and to determine the way newer TB drugs will be used in India (4).

As a medical humanitarian organisation faced with the challenge of treating drug-resistant tuberculosis (DR-TB) in its Mumbai, Mon (Nagaland), Churachandpur (Manipur) and Chattisgarh medical projects, Médecins Sans Frontières (MSF) welcomes this important step. India faces major challenges with respect to TB, due to a large burden of cases and an increasingly recognised number of drug-resistant strains. DR-TB is becoming a serious public health challenge in India (5,6) and new treatment options for patients with strains having advanced resistance (e.g. extensively drug-resistant TB or XDR-TB) are desperately needed.

But accelerated access to these new treatment options comes with the challenge to prevent the irrational use or misuse of these drugs, a practice that had a role in the emergence of widespread resistance to older antibiotics and anti-TB drugs in the first place(7). MSF is therefore concerned that access to these new drugs be secured for patients diagnosed with XDR-TB, and at the same time, stricter regulation of these new drugs be implemented by the Drug Controller General of India (DCGI) and Ministry of Health in India. This briefing document outlines some of the issues that MSF would like the *Expert Committee on "Regulation of Newer TB drugs in India"* to consider.

1. Ensure timely regulatory approval of new TB drugs

India is a country with a high TB and DR-TB burden and patients with DR-TB strains are in desperate need for newer treatment options. Some patients have a very complex resistance profile that needs alternative treatment options in order to have any hope of achieving a cure (8). The need for these newer drugs is therefore acute. The DGCI should therefore consider the need to prioritise the approval of TB drugs (9), as new anti-microbacterial agents to treat patients with DR-TB represent an important public health need in India. Janssen Pharmaceuticals (a pharmaceutical company of Johnson & Johnson) submitted the registration dossier on bedaquiline to the DCGI in May 2013. The New Drug Advisory Committee (NDAC) of the Indian MoH is now in the process of reviewing this application. It is also common for originator companies to considerably delay registration of new drugs in developing countries. It is therefore

important that the pharmaceutical company Otsuka be also encouraged to submit its registration dossier on delamanid in India.

2. Include re-purposed drugs in the response to DR-TB

As well as new drugs, the role of "re-purposed" TB drugs needs to considered within the scope of the committee's deliberations and recommendations, as the evidence and use of these drugs both independently and as part of new regimens increases. In the treatment of MDR- and especially XDR-TB, the used WHO group 5 drugs such as linezolid and clofazamine may be required (10). There is increasing interest and observational evidence (11,12) on the role that linezolid and clofazamine could play in improving outcomes of XDR-TB patients as well as in developing new DR-TB regimens.

These drugs do not currently have an indication for use in TB and are often used "off-label". The World Health Organization (WHO) new drug taskforce is looking at releasing guidance for countries aiming to scale up the use of these drugs and regulatory advice regarding changing the indication for their use. This committee, the Central TB Division and the Indian MoH needs to consider how best to facilitate access to these drugs, the process of adding TB as an indication, as well as to regulate these drugs so that they are used in a rational manner.

3. Short-term pain, long-term gain: Restrict inappropriate sale and use of new drugs

WHO is currently working on a strategy plan for rational introduction of new TB drugs(13). India should also consider such a plan. As a first step, and until clinical trials determine optimal regimens for use of newly developed TB drugs, the government of India should restrict the use of these new drugs to the public sector and certain institutions (such as CMC Vellore, YRG Care, MSF) who apply for accreditation based on their expertise, capacity and experience of diagnosing and treating DR-TB. The ultimate goal would be to allow only those providers who are qualified and capable of dispensing TB regimens consistently and reliably with a constant supply of accompanying drugs and whose DR-TB treatment is documented to be of high quality.

The Central TB division should consider a plan to restrict use of new drugs such as bedaquiline in the private sector, while ensuring appropriate access in the public sector. The MoH's directive on oseltamivir, for example, saw the government restrict companies (both originator and generic) from making the drug available in the open market through chemists and pharmacies that are either standalone or part of a private hospital (14).Companies and wholesalers were allowed to sell only to government hospitals or directly to the government. Already some developing countries like Brazil strictly regulate TB drugs and only allow TB drugs to be procured and distributed by the public sector, even for patients diagnosed by the private sector (15). Similarly the Indian MoH should consider a policy of ensuring that procurement, distribution and provision of new TB drugs are consolidated in the public sector. This will also enable the government to set up a system for tracking and monitoring patient outcomes and other variables.

4. Secure access to timely and accurate diagnosis

In order to promote rational use of new TB drugs and ensure that patients are rapidly put on correct and effective treatment with new TB drugs in combination with existing medicines, access to timely and accurate diagnosis will be key. To this end, strategies that implement new tools for rapid diagnosis of TB and DR-TB (e.g. DR-TB screenings with Xpert MTB/RIF[16]) should be promoted particularly in the public sector, in parallel with strengthening laboratory capacity to perform confirmatory tests (e.g. Line Probe Assay and phenotypic drug sensitivity testing, or DST). There is an urgent need to expand access to second-line DST (including for use at baseline) due to presence of very complex resistance profiles in India, and with present capacity within the country insufficient (only three labs are currently prequalified), access and use of new TB drugs will be difficult. Availability of the new drugs should be prioritised for centres that have access to these existing diagnostic tools.

5. Promote research initiatives on DR-TB

In order to develop a framework to devise and adopt new treatment regimens for drug-resistant TB within India, research initiatives by the Indian government and research establishment are needed. Research (including operational research and clinical trials) that study the use of new oral TB drugs such as bedaquiline and delamanid or PA-824 in combination with other drugs should be considered, particularly by the relevant government bodies. Research and development with the stated intention of developing fixed-dose combinations (FDCs) should also be prioritised. As a high-burden country with extraordinary research capacity and potential, India should lead clinical and operational research in TB. India along with Brazil, Russia, China & South Africa (BRICS countries) also committed in 2013 to work on innovation for new drugs and diagnostics and promotion of consortia of tuberculosis researchers to collaborate on clinical trials of drugs to reduce the burden of TB in their countries(17).

To determine optimal regimens that include newly developed and/or repurposed drugs for treatment of DR-TB under programmatic conditions, evidence and regulatory data from other countries who may be the first in conducting trials - like South Africa - could be equally important. This will help facilitate responsible use (appropriate indication for use, doses, drug combination(s), and treatment duration) of new TB drugs.

6. Establishing a TB registry for pharmacovigilance

Pharmacovigilance should be an important part of national policy for addressing the safety of current and new anti-TB drug regimens (18). TB treatment has always been plagued with adverse drug reactions (ADR) often resulting in treatment interruptions by patients and further contributing to avoidable morbidity, treatment failure, reduced quality of life, or death. New TB drugs such as bedaquiline that will be used in combination with existing anti-TB drugs have a potential of creating unrecognised drug interactions. Regular monitoring for adverse events and response should be performed.

As per the recently issued WHO guidelines, special measures need to be put in place to ensure the early detection and timely reporting of adverse events using active pharmacovigilance methods, such as 'cohort event monitoring' which is well suited to the post-marketing surveillance of new drugs (19). The Central TB Division -as a start- can develop a patient registry for bedaquiline-treated patients to assess incidence rates of serious adverse events, including death. This will provide an appropriate mechanism for treatment providers to report ADR.

7. Introduce rules on compassionate use to facilitate access to newer drugs

WHO defines compassionate use (CU) as a "programme that is intended to provide potentially life-saving experimental treatments to patients suffering from a disease for which no satisfactory authorised therapy exists and/or who cannot enter a clinical trial. For many patients, these programmes represent their last hope" (20). We know from experience that for some of the complex DR-TB patients who receive care and treatment at the MSF clinic in Mumbai, CU represents a 'last hope' of cure and would allow us to limit morbidity, mortality and transmission of DR-TB strains to others.

It is important to highlight the fact that there are no specific written rules yet by the Central TB Division or the DCGI for CU of new experimental TB drugs (new chemical entities in clinical testing yet to be approved by any stringent regulatory authority) in India. No specific rules for CU could be found in the Indian Drugs & Cosmetics Act, but for individual use or for small numbers of patients, Indian physicians make use of the procedures defined by the Act for the importation of drugs as yet unregistered in India(21). In the case of TB, it would be of course safer for patients and caregivers to have rules available with clearer guidance on informed consent form collection, the required clearance from an Ethics Committee before implementing CU programmes, the required reporting of Serious Adverse Events and final treatment outcomes to health authorities. Guidance to develop a specific framework for CU of future experimental TB drug candidates

under development for XDR-TB patients is available in Annexure 5 of the Guidelines for the Programmatic Management of Drug-resistant Tuberculosis issued in 2008 by WHO (17).

8. Give guidance on overcoming patent barriers to secure access

The cost of new TB drugs will depend on a number of factors including the patent status in India that will affect the development of a generic version in the coming decade, the size of a market and the price at which originator companies price the medicine in developing countries like India.

Janssen Pharmaceuticals has suggested that a six-month treatment course of bedaquiline will cost $3,000 in countries in middle and upper middle-income bracket, $900 in least-developed and resource-limited countries. The $3,000 price is completely unaffordable for any developing country, and even the $900 price keeps over all regimen costs too high to facilitate urgently-needed treatment scale up. The company has not yet disclosed its pricing for India. Even assuming that Janssen will price bedaquiline at $900 for a six-month treatment course in India, the drug is priced at a level that sustains high prices for DR-TB regimens, and patents could further delay generic production of cheaper versions of this and other new TB drugs.

Patents on new TB drugs are starting to be granted in India and other middle-income countries under the TRIPS (22) patent regime. The Indian government can no longer depend on *automatic* generic production that was possible in the past to drive prices of essential medicines down to affordable levels. It is therefore important that the Indian government assess the patent barriers as they will pose a challenge to generic production, as well as the development of FDCs and paediatric formulations. (See Annexure 1 for the patent landscape of bedaquiline and delamanid).

The patent landscape on new TB drugs indicates that secondary patents—additional patents other than the patent on the basic compound and that cover new uses, formulations or combinations and serve to block generic competition even after the original patent expires—are a threat to future generic production.

The compound patents of bedaquiline, already granted in India expires in approximately 2023. The patent terms could be extended, however, through secondary patents (23). For example, secondary patents that have been filed for bedaquiline would extend the term of patent protection by at least four years until the end of 2027. Patent applications have also being filed on combination pills that include the new drugs in a fixed-dose combination together with existing medicines, which would be a serious barrier to the development of regimens combining new and repurposed TB drugs. Otsuka's patent applications on delamanid cover not only the compound but also its intermediate, isomer, salt, ester and combinations (24).

If India is unable to secure affordable access to newer TB medicines, it should consider exercising its rights under international trade rules to overcome patent barriers, for example by issuing compulsory licences to enable production, domestic supply and export of more affordable versions. In any case, secondary patents, where possible, should be examined strictly by the Indian patent office and challenged by civil society to ensure that generic competition is not unnecessarily delayed through abuse of the patent system.

To conclude, we request the Ministry of Health and RNTCP to hold a multi-stakeholder consultation with patients groups, civil society groups, treatment providers and other TB experts to discuss registration and regulation of new DR-TB drugs and provide recommendations that will inform guidelines for the roll-out and use of new TB drugs in the India.

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[3] A brief overview of the Global TB Drug Pipeline at Clinical Development Stage is available at http://www.newtbdrugs.org/pipeline.php

[4] 4 February 2013, Central TB Division (T-18020/1/2013-TB), DGHS, Ministry of Health & Family Welfare, Expert Committee on 'Regulation of newer TB drugs in India'.

[5] BRICS Health Ministers' Meeting Declaration signed in Delhi on 12 January 2013 "multi-drug resistant tuberculosis is a major public health problem for the BRICS countries due to its high prevalence and incidence mostly in the marginalized and vulnerable sections of society." http://pib.nic.in/newsite/erelease.aspx?relid=91533

[6] WHO estimates that in 2012 around 64,000 people had MDR-TB (among notified new and retreatment pulmonary TB cases) in India, of which only 14143 were put on treatment. WHO Global Tuberculosis Report 2013: Country Profiles, Annex 2 http://www.who.int/tb/publications/global_report/gtbr13_annex_2_country_profiles.pdf

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[8] MSF in its Mumbai Clinic has diagnosed 43 Pre XDR, 16 XDR and 4 XXDR(extra XDR) patients till date. Out of these, treatment has been started for 13 pre XDR, 11 XDR and 4 XXDR patients.

[9] Janssen submitted bedaquiline to the DCGI in May 2013. The New Drug Advisory Committee (NDAC) of the Indian MoH which oversees the review of the registration dossier files submitted by the companies and give approval is still to meet to discuss registration of this drug in India.

[10] Guidelines for the programmatic management of drug-resistant TB, 2011 update. WHO 2011, Geneva. http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf

[11] Systematic review of clofazimine for the treatment of drug-resistant tuberculosis Gopal M, Padayatchi N, Metcalfe JZ, O'Donnell MR. Int J Tuberc Lung Dis. 2013 Aug;17(8):1001-7. doi: 10.5588/ijtld.12.0144. Epub 2013 Mar 25.

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[13] In 2012, WHO set up the Task Force for New Drug Policies, which will issue a toolkit in October 2012 to help guide national TB programmes in the roll-out of new drugs and regimens for TB treatment at the country level. Key contents will include a checklist for country preparedness, requirements for monitoring & evaluation, and pharmacovigilance. http://www.who.int/tb/advisory_bodies/newdrugs_taskforce/en/index.html

[14] Times of India, Govt retains ban on sale of anti-flu drug, 9 May 2009, http://articles.timesofindia.indiatimes.com/2009-05-09/india/28173073_1_anti-flu-drug-oseltamivir-hetero-drugs

[15] Except for quinolones and aminoglycosides, TB drugs are not available in private pharmacies; they are exclusively distributed in the public health system. Treatment of TB is based on national recommendations and guidelines edited jointly by the MoH and professional associations. There is no private market for TB drugs or TB treatment. As a consequence, the rate of multidrug-resistant TB in the country has remained low (1.4%, personal communication by Brazilian National TB Control Program (NTP), based on national survey conducted in 2008–2009). See http://www.biomedcentral.com/1471-2458/13/279 and http://www.iom.edu/~/media/Files/Activity%20Files/Research/DrugForum/2012-JUL-31-AUG-01/731%20%20Session%20II%20%20Keravec%20Joel.pdf

[16] Priority should also be given to rapid adoption of imminent new WHO guidance on the use of Xpert.

[17] BRICS Health Ministers' Meeting Delhi Declaration, 12 January 2013 http://pib.nic.in/newsite/erelease.aspx?relid=91533

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[20] Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008, WHO/HTM/TB/2008.402 http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf

[21] See: Rules 33A-36, Drugs & Cosmetics Act-1940 India
Form 12A, Form 12AA and Form 12B, Drugs & Cosmetics Act-1940 India

[22] Trade Related Aspects of Intellectual Property Rights (TRIPS) was signed by India in 1995 and in 2005, **India** changed its patent law to become fully **TRIPS** compliant.

[23] The compound patents of both Bedaquiline (BDQ) and Delamanid if granted in developing countries expire in approximately 2023 and 2024 respectively (based on 20 years from PCT filing date) unless the market exclusivity is extended by secondary patents. BDQ compound patent, PCT /EP2003/050322, has been granted in India and is expected to expire in 2023. On BDQ, Janssen has filed secondary patents covering the fumarate salt (PCT/EP2007/063186, expiring 2027), its use in TB (PCT/EP2005/052371, expiring in 2025) and the process (PCT/EP2006/062502, expiring 2026).

[24] Delamanid compound patents PCT /JP2003/013070 and PCT/JP2004/016492 are pending before the Kolkata patent office. On Delamanid, Otsuka has applied for secondary patents on the isomer/salt and composition (PCT/JP2006/314708), expiring approximate 2006), its ester (PCT/JP/2006/321954, expiring approximately 2026), its combination with other TB drugs (PCT/JP2006/320239, expiring approximately 2026), and the intermediate (PCT/JP2011/052307, expiring approximately in 2031)