6. **Ensuring access to quality-assured anti-TB medicines**

This paper aims to promote (i) increased use of quality assured first-line fixed-dose combination anti-TB medicines (FDCs) as a means to help prevent the creation of drug resistant TB, (ii) increased demand for quality-assured SLDs to treat MDR-TB, (iii) widespread acceptance of international quality assurance standards for all anti-TB medicines, (iv) the acceleration of international prequalification of SLDs, (v) the strengthening of the capacity of national medicines regulatory authorities (NMRAs) to regulate the quality of anti-TB medicines produced in countries with the highest burden of MDR-TB.

6.1 **Increasing access to quality-assured first-line FDCs**

**The Problem**

An essential component of successful treatment of TB and the prevention of MDR-TB is the uninterrupted supply of quality assured medicines. The causes of MDR-TB include erratic medicine intake (particularly interruptions of treatment) and treatment with a single TB medicine. FDCs were developed primarily as a tool to mitigate the emergence of resistance by ensuring that all medicines were present in patients in effective concentrations at the same time. Use of FDCs significantly reduces the risk associated with monotherapy, i.e. the development of drug-resistant strains of *Mycobacterium tuberculosis*. Even though both WHO and the International Union against TB and Lung Disease recommend the use of FDCs, they are used in too few patients and their quality is not assured to WHO standards.

While many countries have adopted FDCs during the last decade, FDCs are still only used by approximately half of those reporting to WHO: out of 136 countries that reported to WHO in 2007, FDCs of 2, 3 or 4 medicines were used by 66 (50%) for the two-month intensive phase of treatment for new smear positive cases, while 61 countries (46%) used 2-medicine FDCs in the continuation phase of treatment. Globally, however, only about 15% of new patients receive FDCs.

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Secondly, treatment with poor quality medicines can result in insufficient concentration of the drug, selection of drug resistant bacilli, and thus the creation of a case with drug resistance, resulting in failure to cure. Yet, the quality of anti-TB FDCs is not always assured by NMRAs, even in countries that are using them. Furthermore, there are particular concerns regarding the bioavailability of rifampicin in FDCs which is easily compromised if strict manufacturing procedures are not followed, or poor quality raw materials are used. If the bioavailability of rifampicin is inadequate, treatment failures and emergence of rifampicin resistant TB is possible. Thus, national procurement and regulatory bodies should be strongly encouraged to insist on obtaining data proving the bioavailability of rifampicin, in addition to other quality assurance data when purchasing and distributing FDCs. Unfortunately, bioavailability testing is expensive, and although dissolution testing is much cheaper, adequate results in the dissolution tests are no guarantee of acceptable bioavailability of rifampicin.

WHO has established strategies for quality assurance of FDCs under its Prequalification Programme. A simplified protocol for testing of rifampicin bioavailability, moreover, has been developed and several laboratories now exist for quality assurance and rifampicin bioavailability testing for FDCs.

**The solution**

1. **National commitment to scale-up the introduction and/or use of FDCs**

Governments of high-burden MDR-TB countries could effectively increase their ability to prevent MDR-TB by committing to the introduction and/or scale up of use of quality assured FDCs (with proven rifampicin bioavailability), according to the WHO Stop TB Strategy. WHO has included FDCs in the Model List of Essential Medicines on the basis of the solid evidence that short-course chemotherapy is effective and the assumption that, as long as the constituents of FDCs provide the same bioavailability as the individual constituent medicines, FDCs will be as efficacious as single-medicine formulations.

While the precise impact of FDCs on reducing the development of drug resistance is still under study, FDCs have several practical advantages. The 4 and 3-medicine FDCs provide greater reliability in the delivery of short-course chemotherapy. Because of the

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large number of tablets that have to be taken every day, patients often default: use of FDCs reduces the number of pills that need to be taken. FDCs are therefore easier to dispense – fewer medicines are needed to be selected and counted. Prices of FDCs, especially the 4-drug FDC\textsuperscript{11} are the same as, or lower than, those of loose pills. Treatment is therefore easier to finance. FDCs are also easier to stock at all levels – just five medicines may be suitable for all categories and all patient weights; and they make it easier to assure quality - at the international level the few suppliers have been examined according to WHO standards and centrally monitored. Lastly, FDCs make it easier to adjust dosage by weight.

2. \textit{Commitment from high burden MDR-TB countries to buy and enforce the use of quality assured FDCs}

Beyond committing to introduce and/or scale-up use of FDCs, governments would also need to commit to purchasing only FDCs that are quality-assured. Such a commitment could take a number of forms in practice:

i. The Global Drug Facility (GDF), a supply mechanism set up by WHO and Stop TB partners, ensures that quality assured anti-TB medicines and diagnostics are available for implementation of the Stop TB Strategy. Its services fall into three areas: (i) grants of anti-TB medicines for eligible countries that are donor-dependent for some or all their medicine needs (ii) direct procurement services for countries that have sufficient finances but lack adequate procurement or quality assurance systems and (iii) a "white-list" of suppliers of medicines of known good quality for countries with sufficient finances and good procurement mechanisms but which lack a robust quality assurance system\textsuperscript{12}.

ii. For countries with cost effective local manufacturing capacity for FDCs, this commitment could mean accessing FDCs in the short-term via any of the service options listed above, while developing their capacity to produce quality-assured FDCs locally. In the medium term, support can be obtained through WHO, in collaboration with the government, or interested donors, to provide, or broker, technical support to improve the manufacturing practices of select manufacturers to produce FDCs that reach WHO standards.

6.2 Increasing access to quality-assured medicines to treat MDR-TB

The problem

\textit{Lack of demand for quality assured SLDs}


If countries are to rise to the challenge of treating all those in need, they will need access to sufficient supplies of affordable, SLDs produced to WHO standards. However, worldwide supply of such quality-assured SLDs is, as yet, small, and volumes are insufficient to treat the increasing numbers of patients being enrolled for care throughout the world. There are roughly three times as many MDR-TB patients being treated with medicines of uncertain quality than with quality-assured SLDs. There are robust sales of SLDs of uncertain quality in countries with high burdens of MDR-TB and they appear to be growing rapidly: the value of these SLDs sold last year, in China and Russia for example, was more than ten times higher than all the SLDs sold last year through the GDF.

**Lack of quality-assurance of SLDs**

Widespread use of SLDs of uncertain or sub-standard quality drives the production of XDR-TB, with its higher mortality and costs of treatment. Although international standards have been developed so that suppliers can ensure the quality of SLDs, these standards are not adhered to by most manufacturers involved in production. In fact, at present, only two SLDs have been successfully prequalified under the WHO Prequalification Programme.\(^\text{13}\) Even where national quality standards exist, these standards are not often enforced by NMRAs. As a result, the majority of patients being treated for MDR-TB around the world are receiving medicines of uncertain quality. Compared to the estimated global incidence of ~500,000 MDR-TB patients per year, only 14,000 patients per year are expected to be enrolled in GLC approved programmes (in 52 countries) and receive medicines that are quality-assured.

**Poor forecasting of demand**

A further major challenge to increased access to these medicines is that the global market for quality assured SLDs is fragmented and poorly-characterized. Moreover, demand is opaque, has always been difficult to forecast and is ineffectually communicated. Tapping this market will necessitate significantly improved forecasting of demand if manufacturers are going to be encouraged to invest in increased and improved quality of SLD production.

**The solution**

1. **National commitment to more rapid scale-up and enrolment of MDR-TB Patients**

If pharmaceutical suppliers are to produce adequate quantities of SLDs that are quality-assured, they must be able to see adequate market demand – from individual countries and at the global level. If countries make a commitment, in Beijing or thereafter, to significantly expand treatment of patients with MDR-TB and there is a significant expansion of government- or donor-sponsored purchase and procurement, this will help

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improve access to quality-assured SLDs. With relatively reliable and higher demand, governments and international purchasing facilities such as the GDF would be able to incentivize manufacturers via improved demand forecasting, to invest time and resources into improving the quality of their products. These changes in the market for quality assured anti-TB medicines will take some time to be understood by national and international market participants, but the sooner suppliers of SLDs understand the changing dynamics of the market, the more inclined they will be to incur the upfront expense of having their products quality-assured. And the more readily national governments and other purchasers of SLDs are able to access quality assured medicines, the more likely they will be to insist on them for their patients.

Such expansion of demand will only come if the governments of high-burden MDR-TB countries take the necessary measures to build and/or strengthen National TB control Programmes so that they are able to enrol many more patients under proper programmatic management conditions for MDR-TB. Moreover, such measures would need to include accurate and regular monitoring and reporting of patients enrolled and treated to national and international agencies so as to enable reliable demand forecasts to be prepared and communicated to industry.

2. Commitment from high burden MDR-TB countries to buy and enforce the use of quality-assured SLDs

In order to effectively confront the MDR-TB epidemic, governments of high burden MDR-TB countries would need to commit to purchasing only SLDs that are quality-assured.

Such a commitment could take a number of forms in practice: (1) Working through the Green Light Committee (GLC) Initiative, countries unable to secure affordable, quality assured SLDs from their own national or regional markets or via their own procurement mechanisms, could do so via the GDF. The GDF uses consolidated pooled procurement, competitive international tendering mechanisms, strategic stockpiling and reliance on WHO’s Prequalification Programme or Stringent National Medicine Regulatory Authorities (SNRAs) to assure product quality. (2) Where governments have sufficient procurement capacity but are unable to identify sources of quality assured SLDs the GDF can assist them to identify these sources and share information on pricing.

These options, in order to be effective, would require: GDF and its partners to expand the number of sources of quality assured SLDs from its current baseline. (This is already under way through a tiered system of quality assurance involving WHO’s Prequalification Programme and SNRAs, which is also embraced by major financing mechanisms such as the Global Fund and UNITAID); GDF and its partners to establish stable benchmark prices for quality assured SLDs sourced by countries through the GLC mechanism or directly from suppliers of quality assured SLDs identified by the GDF; Governments to provide conditional approval of waivers or fast-track mechanisms for importation of
quality assured SLDs, even if only for an interim period while they develop their own capacity to produce and/or procure quality assured SLDs.

For some countries with comparative advantages for cost effective, local manufacturing of SLDs, this commitment could mean accessing quality assured SLDs in the short-term via options 1 or 2 above while developing their capacity to produce quality assured SLDs locally in the medium to long term.

Lastly, improving the capacity of NMRAs to ensure the production of anti-TB medicines of assured quality is a necessity. The responsibility for quality oversight ultimately lies with each country’s NMRA and alternative approaches through international prequalification mechanisms are costly and time-consuming. These alternative procedures, moreover, ignore the capabilities of existing NMRAs and do not take the actions necessary to build the NMRAs’ capacity to become stringent. This can undermine the authority that the NMRA currently has, increase dependence on external resources, and undermine the principle of sustainability at the national level. WHO, in collaboration with SNRAs and interested donors, could provide or broker technical support to high burden MDR-TB countries to strengthen the capacity of their NMRAs and, where appropriate, the capacity of their manufacturers.

Realistically, not all governments would be able to translate these commitments in the above areas into immediate practice. However, actions could certainly be taken in progressive phases accordingly to clear timelines and targets, with a willingness of governments to be monitored and report on their progress.

**Urgent actions needed**

- National commitment to increasingly (and in a phased manner if needed) buy quality assured FDCs.
- Willingness to accept targets for 1 and willingness to monitor and report on progress against targets.
- Provision of specific technical support and mechanisms to support WHO Prequalification of FDC suppliers in key priority countries (medium term) and/or to strengthen the capacity of NMRAs (long term).
- Commitment to expand the market for international sources of quality-assured FDCs and maintain low-cost benchmark prices.
- National commitment to rapidly enrol MDR-TB patients under proper programmatic conditions (as per realistic targets).
- National commitment to increasingly (and in a phased manner if needed) buy quality assured SLDs.
- National commitment to conditional approval of waivers or fast-track mechanisms for importation of quality assured SLDs, even if only for an interim period, while, where applicable, national capacities for production and/or procurement of quality assured SLDs are developed.