Improving the Supply of and Demand for Quality-Assured 2nd-line TB Drugs

Background Paper for Stop TB Coordinating Board
October 2008

At its October 2007 meeting, the Stop TB Coordinating Board decided that access to quality-assured second-line TB drugs (QA SLDs) was a "critical and complex issue." The Board:

1. Asked for further analysis of the issue from the Global Drug Facility (GDF) and the MDR Working Group's Drug Management Sub-committee (DMSC);
2. Asked for clear language about the issue for country delegations;
3. Sent a letter to the WHO Director General calling for prioritization of SLDs for pre-qualification;
4. Requested a mapping analysis on expected shortfalls of particular SLDs;
5. Requested clarification (and, if need be, recommended resolutions) if differing donor standards were a significant problem.

This Background Paper responds to the Board's request for further analysis of SLD shortages and of the risks this critical and complex issue presents. It hopes to provide clear language by separating the issue into three components: a Supply Problem, Delivery Obstacles, and a Demand Problem.

Lastly, the paper summarizes recommendations as to how to engage countries to expand demand for SLDs that are quality-assured, and to encourage and catalyze new supply of these drugs, particularly from producers in India, Russia and China. These recommendations have been endorsed, in part and with reservations, by the GLC and will be acted upon by the DMSC and the MDR-TB Working group later this month. They will then be recommended to the WHO, as presented here or with amendment.

The mapping analysis on shortfalls will be presented at the Coordinating Board meeting, along with clarification about the impact of donor standards and some specific requests for assistance.

The MDR-TB Working Group expressed alarm in Tbilisi last year about the inability of countries scaling up MDR-TB programs to access adequate supplies of quality-assured SLDs. In the past year, there has been good progress quantifying the current shortage of SLDs, clarifying the reasons for it and communicating the need for additional suppliers. There are now increased expressions of interest from suppliers seeking approval of their products from WHO Pre-Qualification and two firms (Lupin and Cipla) have made firm commitments to submit 4 dossiers to Pre-Qualification by the end of the year. The GDF and the DMSC have enlisted assistance from USPDQI (United States Pharmacopeia Drug Quality and Information Program) (with financial support from USAID) to assist interested suppliers with understanding and initiating the process of pre-qualifying their products. Progress on all these fronts will provide benefits in future years. There have also been encouraging increases in supplies of some SLDs as a result of IDA evaluation and approval of 5 new products[1] and the approval of one new product by WHO Pre-Qualification.[2] But the challenges are still significant.

Supply Problem:

- There is still only 1 QA supplier for all but one important SLD.
- There have been three dossiers submitted to WHO PQ, which is encouraging. But there are only 3 SLD dossiers that are complete and active; a fourth is now under review.

---

[1] New products approved by IDA, and, thereby, provisionally by GDF, are Amikacin (Medochemie), Lovofloxacin (Macleods); Moxifloxacin (Bayer), Capreomycin (Macleods) and Pas Sodium (Macleods)

[2] Macleods' Ethionomide was approved by WHO PQ in December 2007.

- There are still shortages of Capreomycin and PAS, which are key QA SLDs, while orders from GLC projects continue to rise; There is no evidence of capacity to supply large new projects with QA SLDs, at least until demand for QA 2nd-line drugs increases considerably.
- Persistent shortages of QA drugs and suppliers will frustrate the expansion of programmatic MDR-TB management. Erratic use of non-QA SLDs is already happening in many high burden MDR-TB countries and this will result in further development of drug resistance.

Delivery Obstacles

There has been solid progress documenting and resolving the SLD delivery obstacles. Staffing has increased at the GDF and has improved oversight of the Procurement Agent; communication with the GLC-project customers has increased. The GDF began accumulating its UNITAID-funded buffer stock early this year and supplies from that stock have been used to speed and facilitate deliveries to 23 countries. Nearly $500k worth of Capreomycin from the buffer stock, by way of example, was shipped in the first 8 months of this year. The GDF has recently begun to use a new Order Management System (OMS) for SLDs. When fully operational, OMS will give real-time information on orders, specific procurement problems, and delivery schedules. Nonetheless, SLD needs forecasting, communication, order processing, payment and delivery mechanisms still need improvement, and there are still serious delivery obstacles in important countries (registration, packaging and customs barriers and delays).

- There is still a sole procurement agent (IDA) for all GLC-approved SLD purchases, although action is underway to provide an additional agent(s).
- Supply shortages and delays are regularly exacerbated by registration bottlenecks and customs delays for imports to important large countries.

Demand Problem for Quality-Assured Second-line Drugs

A Strategic Options paper, submitted last month to the GLC and to the MDR-TB Core Group, identifies potential solutions to a longer-term Demand Problem for quality-assured second-line TB drugs - ensuring that, as MDR-TB scale-up occurs, increasingly more and more patients will be treated with quality-assured medications. There has been encouraging support and assistance on this front from the Stop TB Partnership, the GDF, WHO, USAID, UNITAID and others. But the Demand Problem is more serious than the Supply and Delivery issues discussed above.

- Estimates are that there are roughly three times as many MDR-TB patients being treated with drugs of uncertain quality than with QA SLDs.
- There are robust sales of SLDs of uncertain quality in countries with high burdens of MDR and they appear to be growing rapidly; the value of these SLDs sold last year, in China and Russia[3] for example, were more than 10 times higher than all the QA SLDs sold last year through the GDF.
- There are increasing signs that large countries with significant MDR-TB burdens (India, Russia and China) are inclined to bypass the GLC (even while following WHO guidelines) and treat the majority of their patients in non-GLC projects, with SLDs of uncertain quality. There are, simultaneously, important indications of their interest in GLC engagement and in following WHO Guidelines. Yet, because there is little evidence that large countries can procure significant quantities of QA SLDs, they are likely to treat most MDR-TB patients with SLDs from domestic suppliers, of uncertain quality. Short-term national and political reasons will incline them to do so, even though the long term consequences – failed treatment and worsening drug resistance – could be dire. Absent availability of QA SLDs and concerted international advocacy for their use, governments of large countries will not insist on purchasing them, particularly if they are only available from foreign suppliers and if their domestic drug manufacturers have no prospect of becoming approved as QA suppliers.

The market(s) for SLD will grow significantly in the next several years. This is the conclusion reached by *Pathway to Patients*, a 2007 publication of the TB Alliance. The study concludes that there is now only a limited commercial

[3] *Pathway to Patients*, available at http://www.tballiance.org/newscenter/publications.php

market for SLDs.[4] The study notes, though, that TB drug market dynamics are in significant flux, being affected by increased levels of drug-resistant TB, by increases in the number of countries that include MDR-TB treatment in their national programs, by changes in policies and by increased funding being made available for treatment of MDR-TB. All these factors point towards a growing market for SLDs. Yet, the authors argue, there is significant variability in the dynamics of national markets in different countries, markets are fragmented and likely to remain so, and they have a multitude of suppliers. Although increasing treatment of MDR- and XDR-TB offer more attractive markets for suppliers, "tapping this market would require a significant expansion of public sector treatment programs, as well as government- or donor-sponsored purchase and procurement."

A Strategic Options paper presented to the GLC and the MDR-TB Core Group recommends, to the WHO, the Stop TB Partnership, the GLC and the GDF, changes in operating procedures that will make this [5]"significant expansion of public sector treatment programs" more likely to occur under the auspices of the GLC. It identifies 4 "Streams" of engagement with the WHO and GLC for countries scaling up MDR-TB treatment - following WHO guidelines and using QA drugs. Streams A and B would require minor modifications of existing GLC and GDF procedures, but projects in these streams would still be "GLC-approved". Countries unwilling or unable to pursue Streams A or B, but still intent on treating MDR-TB patients, could still undertake to follow WHO guidelines, and commit to the use of QA SLDs, even if they were not yet prepared to only purchase drugs from the GDF-approved supplier list. Stream C countries would submit to GLC monitoring and reporting, but would not be GLC-approved, until they came into full compliance on QA SLDs. But, importantly, these countries would make a public commitment to quality-assured drugs and to resolving the disagreement regarding quality standards. Stream D projects and countries would be those as yet unwilling to commit to using QA SLDs, but who nonetheless seek monitoring by the WHO/GLC and who commit to regular reporting and evaluation.

Changes such as these, along with international advocacy for commitment to quality-assured drugs will facilitate expansion of public sector treatment programs in high burden MDR countries. But these alone may not be sufficient to provide significant "government- or donor-sponsored purchase and procurement," necessary to jumpstart production of QA drugs in significant quantities. Addressing this problem requires a decisive intervention in the market dynamics for SLDs, to create an international market for QA drugs that would supersede fragmented national markets, for drugs of uncertain quality, that are dominant today.

A 5-year, international donor commitment to pay the cost of QA SLDs for all MDR-TB treatment projects approved by, and in good standing, with the GLC would be a market changing event. It would be a huge financial commitment and a significant change in funding practice for donors. But, treatment with drugs of uncertain quality is now widespread, and is likely to increase, and it generates further MDR- and XDR-TB. Under these circumstances, less decisive commitments are likely to fall short of what is needed.

Lastly, it will be important for the Partnership and WHO support efforts in countries to restrict (not ban) the availability of non-QA SLDs, and to monitor sales and rationalize use of these drugs.

It is important to emphasize that this paper does not recommend changes in GLC standards or WHO policy regarding the use of QA SLDs. It does recommend mechanisms to encourage new commitment from countries now using SLDs of uncertain quality. It offers a means of engaging them with the GLC, and of boosting the demand for QA SLDs. The Global MDR-TB & XDR-TB Response Plan has a goal of 100,000 patients enrolled on treatment by the end of 2008. We will reach that goal in years to come. But it is far from certain that the majority of these patients will be treated quality-assured second-line drugs, unless act today to make that likely.

---

[4] The authors emphasize the difficulty in assessing the market for SLDs, but they estimate the SLD markets in ten countries studied to be worth $54 million, more than half of which comes from China ($25m), India ($8m) and South Africa ($2.5m). However, the authors also provide a case study for Russia and estimate the SLD market in that country to be worth $56m. For more on what is summarized here see *Pathway to Patients,* available at http://www.tballiance.org/newscenter/publications.php