Difficulties in procurement of second-line anti-tuberculosis drugs

The experience of MSF in Abkhazia

MSF

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The experience of Médecins Sans Frontières in Abkhazia

This paper documents Médecins Sans Frontières' drug procurement experience in its program treating drug-resistant tuberculosis in the autonomous Georgian republic of Abkhazia. The objective is to highlight the difficulties inherent in the procurement of second-line anti-tuberculosis drugs through the Green Light Committee (GLC) mechanism.

The World Health Organization (WHO) estimates the number of new cases of multi-drug-resistant tuberculosis[1] at over half a million every year[2].

Any discussion of the international response to Multi-Drug Resistant TB (MDR-TB) must bear this alarming figure in mind.

The treatment of DR-TB is long and complex. This paper focuses on just one of the many management difficulties[3] in programs aiming to treat drug-resistant TB: ensuring sustained procurement of quality second-line anti-tuberculosis drugs.

Established in 2000 by the Stop TB Partnership, the Green Light Committee's mission is twofold:

- to maximise the number of DR-TB patients who have access to quality second-line drugs at negotiated prices.
- to simultaneously ensure their rational use thus minimising the risk of resistance emerging to Second Line Drugs (SLDs). The GLC also provides technical support to DOTS+ pilot programs.

In 2001 the WHO contracted a Dutch NGO, the International Dispensary Association (IDA), to ensure the "procurement, quality assurance, and distribution of second-line anti-tuberculosis drugs for the projects approved by the GLC. The purpose of this agreement is to ensure uninterrupted supply of high-quality products at the lowest price achievable."

Médecins Sans Frontières *(MSF) began treating patients with tuberculosis in Abkhazia in 1999. The first patients with drug-resistant forms of the disease were put on treatment in August 2001. In 2004, MSF successfully applied to the Green Light Committee. To date, 89 patients have been admitted into the MDR-TB program.*

There are significant problems in *"improving access to second-line anti-tuberculosis drugs at reduced prices"* despite the existence of the Green Light Committee mechanism.

MSF notes three serious challenges in the efficient procurement of second-line anti-tuberculosis drugs:

1. ***Rapidity***
2. ***Price***
3. ***Supply stability***

1- Drug-resistant (DR) strains of tuberculosis are resistant to one first-line anti-tuberculosis drug. Poly-drug-resistant (PDR) strains of tuberculosis are resistant to at least isoniazid or rifampicin and another drug. Multi-drug-resistant (MDR) strains of tuberculosis are resistant to at least both isoniazid and rifampicin.
2- Draft Strategic Plan 2006-2015, Stop TB Working Group on DOTS-Plus for MDR-TB, available at http://www.stoptb.org/gpstb., p1 and p5.
3- Others include adequate trained staff, in-patient facilities, ambulatory points, bio-safety measures, high-level laboratory facilities suitable for culture and drug sensitivity testing, adequate adherence support for medium-term treatments, and the adequate diagnosis, management, and follow-up of drug side effects. They are outside of the scope of this paper.
4- Procurement manual for the DOTS-Plus projects approved by the Green Light Committee, WHO and IDA, June 2004, p5.

1. *Rapidity*

▶ The WHO estimate of the average delay between the date of approval and the date of delivery as three months[5]

MSF waited 14,5 months from the time of application for GLC support until the arrival of a full second line regime in the MSF warehouse in France.

2004	**March 23rd**	MSF Paris sends GLC application
	April 21st	Oral confirmation that the application had been studied and that the GLC was preparing questions to be answered about the program
	June 2nd	2nd letter sent by MSF to GLC as no news
	July 19th	GLC questions received
	July 21st	Answers to questions sent
	Nov. 6th	GLC formal approval of the proposal
	Dec. 6th	WHO sends letter to IDA with required quantities of medications
2005	**April 14th**	Delivery of cycloserin and capreomycin
	May 23rd	Delivery of PAS
	June 1st	Delivery of kanamycin

It is important to note that there are then further delays to be taken into account before the drugs are actually available for use. These delays are due to shipment and customs clearance, the latter a particularly lengthy procedure in Georgia.

5- Increasing Transparency in Partnerships for Health – Introducing the Green Light Committee; published in Tropical Medicine and International Health, Vol. 7 No. 11, pp970-976, November 2002.

The delays involved were the following:

Delay in the preparation of the application

Given the complexity of the application to be filled out, **a medical TB specialist needed one month to write it.**

Delay between reception of the application and approval

▶ **The WHO announces "decisions by the Green Light Committee, in principle, will be taken rapidly after submission"[6].**

The Committee "reviews applications within the first four weeks after deadline. Decisions are taken by consensus and communicated to the applicant within the first week after the meeting.

In general, the WHO will communicate the GLC's initial assessment to the project director within four weeks of the meeting date"[7]. In November 2002, the average delay for reviewing a project was estimated at three and a half months[8].

7 1/2 months went by between the MSF Abkhazia application and definitive approval

Delay in the transmission of approval to IDA

One month was required for the WHO to inform IDA that the project had been approved and the drug order accepted

Delays between drug orders and delivery

▶ **WHO estimates the average delay between the date of approval and the date of delivery as three months[9].**

6 months passed between the sending of the Abkhazia order and the arrival of the drugs in the MSF warehouse.

These delays are due to:

- The absence of stocks at the level of the distributor (IDA) who waits to receive an order before ordering from the supplying drug company
- The absence of stocks at the level of the supplying drug company. Some produce drug only on demand
- Limited production capacities, notably for PAS
- The distributor not respecting delivery delays, the kanamycin was delivered two months later than announced

6- DOTS-Plus and the Green Light Committee, World Health Organization, Geneva, 2000. p7
7- Instructions for Applying to the Green Light Committee for Access to Second-line Anti-tuberculosis Drugs, World Health Organization, Geneva, 2002. p8
8- Increasing Transparency in Partnerships for Health – Introducing the Green Light Committee; published in Tropical Medicine and International Health, Vol. 7 No. 11, pp970-976, November 2002.
9- Increasing Transparency in Partnerships for Health – Introducing the Green Light Committee; published in Tropical Medicine and International Health, Vol. 7 No. 11, pp970-976, November 2002.

2. Prices

According to WHO, one of the advantages for the projects approved by GLC is to have access to "low-cost drugs"[10]

The drug prices are still very high

GLC prices for DR-TB regimens are still over 300 times more expensive than a first-line treatment. Thus the cost of SLD remains a considerable barrier to increasing the numbers of patients receiving treatment or reducing the number condemned to death. A second-line treatment course including PAS costs at least 4,300 US$ and up to 6,000 US$ depending on the choice and availability of medication sources.

	Lowest price available through GLC mechanism	Highest price available through GLC mechanism	Price available outside of GLC mechanism
A Regimen[11]	4,424 US$	6,020 US$	13,761 US$
B Regimen[12]	4,323 US$	5,441 US$	8,896 US$
C Regimen[13]	994 US$	2,590 US$	6,546 US$

The drug prices paid through the GLC and to the general public - Figures from 2005.

GLC: prices have been reduced up to 99% compared with the prices in the open market"[14]

Such announcements are no longer helpful nor are they accurate, despite having been potentially useful as advertising for the GLC mechanism in its earlier years. As shown in the table **the regimen prices are only 2 to 3 times cheaper.**

The prices of second-line drugs announced by the World Health Organization should reflect the reality – that high prices act as a barrier preventing greater access to SLD, and that this barrier has not yet been removed by the Green Light Committee mechanism.

Greater transparency on this issue will not only serve to raise awareness of the problem, it will enable realistic comparisons on the price reductions obtained through the GLC, and may serve to galvanise further price reductions which are still needed.

Local supply problems add to the cost of treatment

The GLC supplied Brown and Burk (Microlabs) ofloxacin preparation is not commercially registered in Georgia. To circumvent lengthy Georgian registration processes, MSF was compelled to purchase the Ranbaxy preparation, as it was the only formulation registered in Georgia, despite it costing 5 1/2 times more.

This factor contributed in making the actual cost of the Abkhazia DR-TB drug order 18% higher than the nominal cost obtained through the GLC mechanism.

This difference increases the difficulty in correctly forecasting the DR-TB drug budget in a TB program. It should be noted that ordering and budgeting are already very complex affairs.

Even with individual patient drug sensitivity testing for all admitted to the program, changes in drug regimens, side effects, deaths and defaulters all make drug requirement predictions hazardous. Ordering the correct amount of expensive drugs with short shelf lives is very, very difficult.

Actual cost for Abkhazia order	GLC nominal cost for Abkhazia order
93,760 US$	79,481 US$

10- Meet the Expert" session, 33rd IUATLD World Conference, Oct 2002
11- A Regimen: 6 months capreomycin, ofloxacin, ethionamide, cycloserin, PAS; 18 months ofloxacin, ethionamide, cycloserin, PAS.
12- B Regimen: 6 months kanamycin, ofloxacin, ethionamide, cycloserin, PAS; 18 months ofloxacin, ethionamide, cycloserin, PAS.
13- C Regimen: 6 months capreomycin, ofloxacin, ethionamide, cycloserin; 18 months ofloxacin, ethionamide, cycloserin.
14- http://www.who.int/tb/dots/dotsplus/management/en/index.html

3. *Supply stability*

Availability

Supplying a DR-TB program is complicated by the fact that for certain medications there is only one acceptable source.
Such a situation inevitably leads to supply bottlenecks, delays and running out of DR-TB drug stock, the latter potentially catastrophic for patients. The procurement of PAS capreomycin and cycloserin are particularly problematic in this respect.

Only one source of PAS complies with MSF quality assurance requirements and the production capacity of this manufacturer is extremely limited. Earlier this year the quality-assured manufacturer's production capacity was effectively monopolised by the allocation of all PAS to a Peruvian program. This bottleneck led to a considerable delay in supplying the PAS to Abkhazia, and this delay would have been longer had the GLC not intervened to divert some of the PAS earmarked for Peru.

Capreomycin and cycloserin production is also severely limited. Eli Lilly does not produce either drug on a routine basis but only upon reception of orders. MSF experienced considerable difficulties in purchasing these drugs for its Abkhazia program in 2003.

Capreomycin and cycloserin also have particularly **short shelf lives** of 18 to 24 months depending on the labelling language. One of the practical implications is that sometimes when the drugs arrive they can no longer be sent to some countries such as Georgia where the importation any batch of drugs within six months to expiry is illegal. Eli Lilly has been helpful in supplying MSF in certain cases to avoid shortages and treatment interruptions.

Certain products currently recommended for the treatment of drug-resistant TB are **not available** through the GLC mechanism. Levofloxacin, for example, is included on the list of GLC drugs, but no sources have yet been identified by the dispensary agent.

GLC mechanism does not include drugs that are needed in DR-TB programmes to treat the side-effects of second-line anti-tuberculosis drugs.

Conversely, clofazimin is not available *outside* of the GLC mechanism. Until recently the WHO restricted the drug's use in leprosy programs. Although the product, which is no longer marketed, is now available for GLC approved DR-TB programs, it remains impossible to procure it outside of the mechanism

Non-commercially registered drugs

MSF's experience in Abkhazia provides a practical example of how registration issues can act as a serious impediment to the procurement of SLDs. Drug importation is possible in Georgia as long as the product is registered, but second-line drug manufacturers are not interested in marketing their product in this country amongst others due to the lack of financial incentive, and do not apply for commercial registration.

To overcome this barrier, the Georgian government authorises international organisations to apply for drug registration on humanitarian grounds. In Georgia, the registration of DR-TB drugs was handled not by the manufacturer but by MSF, and proved to be a tedious, labour-intensive and time consuming process for an organisation.

A further constraint is the reluctance of some manufacturers to share sensitive information necessary for registration with external bodies, effectively making registration impossible for those products.

Furthermore, some DR-TB drugs, such as Eli Lilly's cycloserin and capreomycin, Panpharma's kanamycin, and clofazimin registration permits expire in 2006.

▶ Non pre qualified drugs

To date, no sources of anti-tuberculosis SLDs have completed the WHO prequalification process.[15]
MSF therefore selected sources from IDA's product catalogue that comply with MSF's quality assurance procedures when placing orders with IDA for Abkhazia. A number of the SLD generics proposed by IDA do not display proof of their equivalence with the original products and do not yet comply fully with WHO prequalification recommendations in terms of quality.

This applies to sources of cycloserin, PAS, ofloxacin, and ethionamide. A recent recall by the IDA of a generic PAS formulation due to instability problems serves as an illustration of possible consequences of this shortfall.

CONCLUSION

If the World Health Organization wants the Green Light Committee to attain its mandate, it must address the above issues relating to the efficiency of the mechanism and the availability and prices of drugs. The World Health Organization has an important role to play here, in linking manufacturers, the GLC distributor, and GLC applicants, in order to:

- Simplify application procedures
- Establish a more responsive mechanism to reduce delays in application processing and in drug supply
- Ensure lower second-line drug prices
- Provide greater transparency on real costs
- Identify more production sources
- Secure buffer stocks at distributor and manufacturer levels
- Work locally at a country level to promote permanent DR-TB drug registration and to facilitate customs clearance
- Improve the availability of drugs such as levofloxacin
- Improve forecasting at WHO, producers and distributors levels.

15- http://mednet3.who.int/prequal/. Although originator products manufactured by Eli Lilly and Jacobus are registered with the US FDA