



ROADMAP FOR MDR-TB SCALE UP: THE GLOBAL DRUG FACILITY (GDF) **INCREASING ACCESS TO MDR-TB DRUGS THROUGH INNOVATION AND ACTION**

The Past, Present and Future of GDF's activities to meet increased scale up demand

The need for Scale up:

The emergence of Multidrug-resistant tuberculosis (MDR-TB) presents a formidable challenge to TB control due to its more complex diagnosis and long treatment period. In 2008, the global number of MDR-TB cases newly emerging, was estimated to be 440,000 (range 390 000 - 510 000) with at least 150 000 deaths occurring due to MDR-TB. Countries, TB partners and donors have risen up together to meet this potential epidemic. Recognizing the threat that M/XDR (extremely drug resistant)-TB poses to public health, a Call for Action was issued by 27 member states at the Ministerial Meeting of High M/XDR-TB Burden Countries held in Beijing in April 2009. This led to the development of World Health Assembly resolution 62.15 endorsed in May 2009. The resolution urges WHO Members States:

"to achieve universal access to diagnose and treatment of M/XDR-TB and recognizes the need of "ensuring uninterrupted supply of first- and second-line medicines for tuberculosis treatment, which meet WHO prequalification standards or strict national regulatory authority standards, and that quality-assured fixed-dose combination medicines of proven bioavailability are prioritized within a system that promotes treatment adherence."

Increased country commitment and donor support, recent Stop-TB Partnership and WHO initiatives to increase case detection (TB REACH), improve diagnostic capacities in countries (EXPAND-TB) and introduce new rapid diagnostic technologies (GeneXpert), will result in an increased number of MDR-TB patients detected, diagnosed and requiring access to quality-assured MDR-TB medicines.

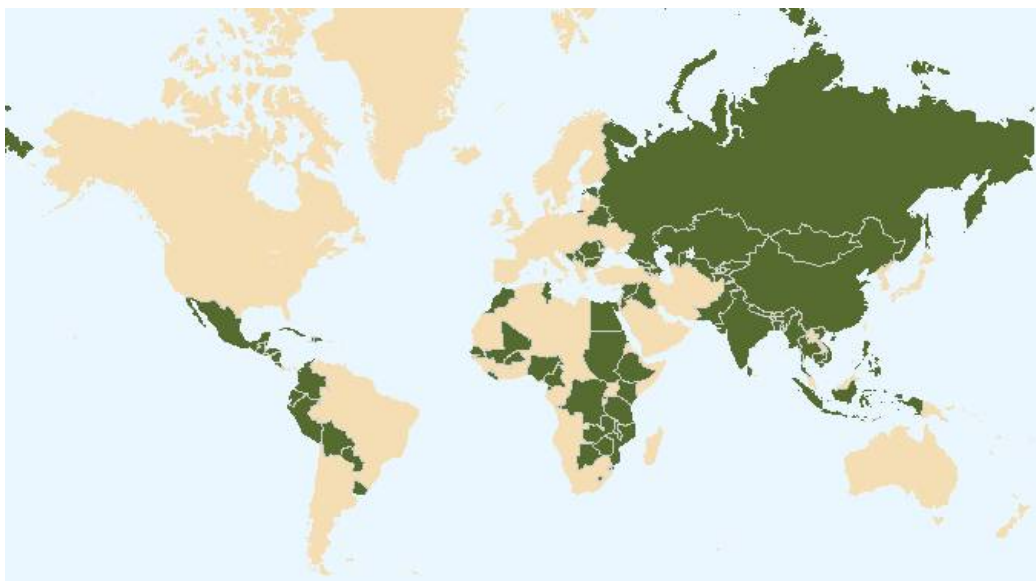
The Role of The Global Drug Facility (GDF):

The GDF is a procurement initiative of the Stop TB Partnership, which ensures access to high quality anti-TB drugs at an affordable price for countries in need. GDF's mandate is to ensure that increased detection and diagnosis of MDR-TB patients is met with an equal increase in the availability of quality-assured MDR-TB medicines.

In anticipation of the increased demand for quality-assured MDR-TB medicines, GDF accelerated its efforts to source and engage quality-assured suppliers to ensure that a sufficient quantity of medicine is available to countries.

This roadmap outlines the significant progress that GDF has made to date, identifies what is still needed and where high level advocacy could assist GDF to further scale up its activities.

From Past to Present - The Global Drug Facility's MDR-TB Scale Up activities 2007 until now...



Countries served through GDF's MDR-TB mechanism 2007-2010

GDF started providing MDR-TB medicines in 2007. Since then, GDF has:

- Procured medicines for a **total of 74** countries including **22 of the 27 High Burden MDR-TB countries**;
- Substantially increased the number of quality-assured MDR-TB second-line drugs (SLDs) available for procurement through GDF from **11** in 2008 to **25** in 2010;
- Tripled the number of suppliers of MDR-TB products from **5** in 2008 to **15** in 2010;
- ***Negotiated stable and sustainable prices valid from 12 to 24 months for all*** products without the conditionality of volume commitments. ***GDF has prevented treatment cost fluctuations despite the volatility of the market due to unstable economies, currency fluctuations and manufacturing cost increases;***
- Enabled programs to ***rapidly start treatment of patients and decrease the median delivery lead time for urgent orders¹ to 19 days,*** through the implementation of a Strategic Rotating Stockpile of 5,800 treatments funded by UNITAID. **39** countries/projects benefited from the stockpile in 2009. In 2010, the stockpile was accessed by **52** countries/projects served by GDF;
- Begun development of innovative mechanisms such as the ***Strategic Revolving Fund, a Market Allocation System and much needed forecasting tools*** to incentivize manufacturers and reduce countries constraints.

GDF has successfully met an increased demand for quality-assured MDR-TB medicines from supplying **19** countries in 2007 to **54** countries in 2010. GDF is confident that it can continue to meet the needs of the MDR-TB Scale Up programme.

Through its actions GDF will ensure that the ***future demand*** for drugs is met and a ***sustainable market*** is created.

¹ Urgent orders: deliveries to countries/projects under their specific request within 6-30 calendar days

GDF's Commitment to quality and sustainable markets

With 10 years of experience in procuring over **18 million treatments** for TB in over **115 countries** world-wide, GDF's approach to drug procurement has focused not only on the provision of quality medicines and support to countries, but also on building sustainable markets for increased access and improved affordability.

▪ **Commitment to Quality**

Recognizing the essentiality of quality-assured medicines in the treatment of MDR-TB and the prevention of further emergence of drug resistance leading to XDR-TB, **the quality of medicines is the pillar of GDF operations.** Today GDF supplies Second-line Drugs (SLDs) that are WHO prequalified, approved by Stringent Drug Regulatory Authorities² or, in exceptional cases, extensively assessed by an Expert Review Panel (convened by WHO/QSM).³

GDF continues to work closely with key stakeholders to increase the number of quality assured medicines from approved suppliers available for treatment:

- **Harmonization of a quality assurance policy** with major multilateral finance mechanisms and international organizations active in TB control, allowing for better cooperation and efficient use of resources;
- **Strong collaboration with the WHO (Essential Medicines Programme (EMP))** through regular communication on dossier assessment progress; prioritization of MDR-TB medicines dossiers and inspections; bio-waivers and requirements applicable to anti-TB medicines among others;
- **Collaboration with The United States Pharmacopoeia Promoting the Quality of Medicines Programme (USP PQM) since 2008**, to facilitate the prequalification of MDR-TB medicines. This is achieved through the provision of technical assistance (TA), free of charge, to manufacturers of second-line TB medicines world-wide seeking WHO prequalification. As of October 2010, USP PQM is and will continue providing TA for **17** dossiers, submitted by **7** manufacturers from **4** countries.

▪ **Sustainable Markets: Shaping the Market to meet the demand**

In the past years, the market for anti-TB medicines has been limited due to an uncertain demand and lack of volume procurement to justify a major investment of financial and human resources by manufacturers to produce more cost effective quality-assured medicines.

Since 2008, GDF has made increased efforts in market shaping, to ensure a sufficient supply of quality-assured products at the lowest sustainable price. This has changed its supplier landscape significantly.

² SRA are defined as an ICH member country, an ICH observer or any country whose regulatory authority is associated with an ICH member through a legally binding mutual recognition agreement, or be approved or subject to a positive opinion under the Canada S.C. 2004, c. 23 (Bill C-9) procedure, or Art. 58 of European Union Regulation (EC) No. 726/2004 or United States FDA tentative approval.

³ ERP is ad hoc risk comparative quality risk assessment review by a group of regulatory experts. The ERP reviews the medicine information provided and ERP comes up with an objection or no-objection conclusion as to the potential acceptability for procurement for a term-limited period (12 months). The FPPs must also meet the following eligibility criteria: a) the manufacturer of the FPP has submitted an application to the WHO PQP and has been accepted for assessment OR an application for marketing authorization to a SRA and has been accepted for assessment; b) the FPP is manufactured at a site that is compliant with the standards of GMP applicable to the FPP in question as verified after inspection by: 1) WHO PQP inspectors or 2) SRA inspectors or 3) A regulatory authority participating to the Pharmaceutical Inspection Cooperation Scheme (PIC/s).

New supplier landscape

Following a proactive supplier identification process, GDF has moved from having 11 single suppliers of MDR TB products in 2008, of which 6 products (63%) were from the same supplier, to the expanded supplier landscape as seen below in 2010:

4 medicines with 3 suppliers

- Cycloserine 250 mg, Levofloxacin 250 mg, Levofloxacin 500 mg, PAS

5 medicines with 2 suppliers

- Amikacin 500 mg/2ml, Kanamycin 1gr[#], Moxifloxacin 400 mg, Ofloxacin 400 mg, Prothionamide 250 mg

([#] = Second supplier will be available in Q1 2011)

4 medicines with 1 supplier

- Capreomycin 1g*, Ethionamide 250 mg*, Ofloxacin 200 mg*, Terizidone 250 mg

(* = at least one dossier submitted to PQ or SNRA)

Table 1. Comparison of available manufacturers at the 2008 and YTD 2010

Description	Manufacturer	Available in 2008	Available in 2010
Amikacin 500mg/2ml inj	Medochemie	YES	YES (SNRA)
Amikacin 500mg powder for injection	MYLAN S.A.S	NO	YES (SNRA)
Capreomycin 1gram powder for inj	Eli Lilly	YES	YES (SNRA)
Cycloserine 250mg	Aspen	NO	YES (WHO PQ TB 166)
Cycloserine 250mg	MacLeods Daman Plant	YES	YES (WHO PQ TB 154)
Cycloserine 250mg	The Chao Centre	NO	YES (SNRA)
Ethionamide 250mg	MacLeods Daman Plant	YES	YES (WHO PQ TB 133)
Kanamycin 1g/powder	Panpharma	YES	NO*
Kanamycin 1g/4ml inj	Meiji	NO	YES (SNRA)
Levofloxacin 250mg	Cipla	NO	YES (ERP)
Levofloxacin 250mg	MacLeods Daman Plant	YES	YES (ERP)
Levofloxacin 250mg	Micro labs Ltd	NO	YES (ERP)
Levofloxacin 500mg	Cipla	NO	YES (ERP)
Levofloxacin 500mg	MacLeods Daman Plant	YES	YES (ERP)
Levofloxacin 500mg	Micro labs Ltd	NO	YES (ERP)
Moxifloxacin 400 mg	Bayer	YES	YES (SNRA)
Moxifloxacin 400 mg	Cipla	NO	YES (WHO PQ TB 210)
Ofloxacin 200mg	MacLeods Daman Plant	YES	YES (ERP)
Ofloxacin 400mg	Macleods Daman Plant	YES	YES (ERP)
Ofloxacin 400mg	Micro labs Ltd	NO	YES (ERP)
PAS acid sachet eq. to 4 g aminosalicylic acid	Jacobus Inc.	YES	YES (SNRA)
PAS sodium granules 60% (p-aminosalicylate sodium)	MacLeods Daman Plant	NO	YES (WHO PQ TB 156)
PAS sodium undose sachets	Olainfarm	NO	YES (SNRA)
Prothionamide 250 mg	Fatol Arzneimittel	NO	YES (SNRA)
Prothionamide 250mg	Lupin	NO	YES (ERP)
Terizidone 250 mg	Fatol Arzneimittel	NO	YES (SNRA)
* available as from 2011		11	25

Ongoing efforts:

An Expression of Interest (EoI) for MDR-TB medicines evaluation by an Expert Review Panel was launched in July 2010, and 17 product dossiers were received. In addition, 3 medicines have been submitted to stringent regulatory authorities for evaluation. As a result, an increase of 1 or 2 suppliers for most of the medicines, particularly those that have a single source, is expected in 2011. Further EoIs will be launched every 6 months or as needed.

- **Price stabilization**

In 2009, GDF successfully concluded negotiations with major suppliers and **achieved stable and sustainable prices for all products for a period ranging from 12 to 24 months. Furthermore, stable prices have been achieved** without the conditionality of specific volume commitments. Considering the unstable global economic environment, including inflation and currency fluctuations, the location of manufacturers in different markets (India, Japan, EU and USA), resulting in increasing prime costs of the medicines produced, negotiating price stability is particularly important and will allow for better forward planning by country programs.

The Future - Innovation to meet increased demand

While GDF's actions to date have succeeded in achieving many market improvements, further incentivization is needed. Given that the MDR-TB medicine market is limited in size with high barriers of entry, GDF has engaged in key innovative approaches to render the market more attractive to suppliers. Among these are:

- a tiered market allocation system;
- improved forecasting;
- a rotating stockpile and;
- an advanced financing mechanism.

- **Market Allocation System**

A current challenge for GDF in the MDR-TB market landscape is to attract new suppliers while maintaining good collaboration with existing suppliers. GDF's approach has been to create incentivizing mechanisms in order to facilitate manufacturer entry and continuity in the market. The Market Allocation System is a tool that envisages a tiered system allocation of market share for eligible suppliers of the same medicines, based on a combination of price, quality and registration status criteria.

If provided with some market share, suppliers would be incentivized to enter the market and continue manufacturing drugs for MDR-TB treatment, thereby contributing to the scale-up, and to creating a healthier market of anti-MDR TB drugs. Furthermore, this would encourage competition between the suppliers, which is a natural market pre-condition for future price reductions.

Only after a competitive supply market is established, will it be possible to concentrate on the objective of price reduction.

- **Clear Demand Forecasting**

There is a need for accurate and regular forecasts to reliably predict volumes, reduce uncertainty and enable suppliers to make informed decisions on production planning, expected returns and gaining the economies of scale.

Originally designed as a tool for forecasting the GDF procurement needs, the Forecasting Tool, with relevant modification, can be effectively deployed for forecasting the global MDR-TB needs. Once fully developed, this tool will be able to resolve the issue of uncertainties and fluctuations in demand. The forecasts generated by the tool, together with the innovative solutions described below, will enable GDF

and TB partners to place commitments for purchase of specific volumes. This will create more favourable conditions for suppliers to plan their production and returns, and making this drug niche more attractive from a business perspective.

- ***MDR-TB Strategic Rotating Stockpile (SRS)***

Since March 2009, the stockpile for 5,800 patient treatments has been fully operational. The stockpile has an estimated value of USD 11 million and is funded by UNITAID. It has enabled programs to rapidly start treatment of patients and has helped to decrease the delivery lead time, thereby aiding the MDR-TB Scale Up in countries in addition to providing a firm demand incentive to manufacturers.

Summary statistics on countries using the stockpile 2008 - 2010:

39 countries have benefited from the stockpile in 2009. As of mid November 2010, 52 out of 54 countries served by GDF have accessed the stockpile. Lead time for urgent orders has decreased from 50 days to an average of 29 days, with a median of 19 days.

To optimize its efficiency and effectiveness, GDF is exploring increasing the usefulness of the SRS as a drug supply market shaping tool and has submitted in September 2010 an expansion proposal to UNITAID to this effect.

New Tools to Come - More overarching innovative solutions

MDR-TB STRATEGIC REVOLVING FUND (SRF) - *IN FINAL STAGE OF DEVELOPMENT*

SRF is an innovative, collaborative project addressing MDR financing delay bottlenecks. The fund is a US \$22 million guarantee fund, supported by UNITAID. The objective of the fund is to enhance and accelerate the availability and delivery of second-line anti-TB drugs by providing eligible countries access to the SLDs by providing manufacturers with a financial guarantee to fulfil the order, while countries await fund disbursement.

The SRF is expected to be launched in Q2 2011.

MDR-TB ADVANCE PURCHASE COMMITMENT (APC) / MANUFACTURER INCENTIVIZATION PROGRAMS - *IN ANALYSIS STAGE*

As part of GDF efforts towards cost containment and long term market sustainability and development, GDF has embarked upon assessing the feasibility of advance market commitment and other manufacturer incentivization programs. These mechanisms would facilitate supplier production planning and optimize the economies of scale. Moreover, they would provide registration support, a known bottleneck due to the reluctance of suppliers to invest the financial cost and time resources required for an uncertain volume of sales. This would help the supplier to assess their return on investment, thereby making the SLD supply market more attractive, less uncertain and volatile. The second part of this work will assess the Active Pharmaceutical Ingredient (API) contingency planning for products where there are few quality-assured API suppliers.

NEW GDF MARKET DEVELOPMENT TEAM - *UNDER DEVELOPMENT*

In order to meet the increased complexities and changing needs within the TB landscape, GDF is performing a restructuring of its organization. This will enable increased focus on countries, market development and external stakeholders. Part of this restructuring will include the development of a Market Development Team focused on further developing the market for TB medicines while continuing to emphasize quality assurance. This team will be responsible for dynamic forecasting, supplier sourcing and vendor performance management. Facilitating the activities of this team will be the introduction of an innovative and user friendly business information and management application, which will enable ***improved data integration and standardization between partners*** in and outside of WHO. This tool is envisioned to improve GDF's data collection and coordination, as well as its performance management capacities.

Where GDF needs High Level Assistance to remove bottlenecks

GDF is strongly committed to continuing its efforts to widen availability of quality assured medicines and assist countries in need to have access to medicines. However, some of the challenges and bottlenecks remain beyond GDF's scope and capacity to address them. They require strong cooperation and high level assistance from WHO and Partners, and commitment from Member States. GDF's improvements and efforts will have limited impact if they are not endorsed and followed by global action and commitment.

The successful scale up of MDR-TB medicines will require high level support in different areas such as:

- Fast tracking and continued support through the WHO prequalification process to facilitate an increase in quality-assured manufacturers: both Active Pharmaceutical Ingredients (APIs) and FPP (Finished Pharmaceutical Products);
- Ensuring national commitment to the procurement of ***only*** quality-assured SRA or PQ MDR-TB medicines;
- Ensuring national commitment to conditional approval or fast-track mechanisms for importation of quality-assured medicines;
- Ensuring national commitment to rapidly enroll MDR-TB patients under proper programmatic conditions;
- Ensuring investment in country level capacity building to deliver a quality drug management system at national level for all anti-TB drugs.

Annex 1: Key risks and how GDF can have a mitigating impact to contribute towards a successful scale up:

(1) Availability of quality-assured medicines.

Risk:

The current availability of most quality-assured medicines is sufficient to cover the predicted demand. However, some of the key medicines (Capreomycin 1g, Ethionamide 250 mg) remain supplied by a single source (Eli Lilly and Macleods). The challenge remains to accelerate and support suppliers through WHO Prequalification and Stringent Drug Regulatory Authority.

Risk Mitigation:

- Ongoing proactive supplier sourcing for these products, including:
 - launch of Expressions of Interest for manufacturers;
 - proactively finding, evaluating and engaging manufacturers;
 - collecting information from the healthcare market;
 - encouraging the submission of medicines dossiers for quality assessment;
 - liaising with WHO/EMP and the IPC (International Pharmaceutical Coordination) Group to define strategies and collaborative activities for sourcing anti-TB medicines in short supply.
- Currently, there are 17 second-line anti-TB medicines dossiers from 5 manufacturers from 2 countries under assessment by the WHO Pre-Qualification Programme (PQP). These include dossiers for 3 of the 4 single source products. Three additional dossiers have been submitted to stringent regulatory authorities for evaluation.
- Collaboration with WHO country office, WHO/EMP and the Global Fund to support and encourage TB manufacturers to improve and implement the new national GMP standards (both APIs, FPPs) in China, as part of the health systems strengthening component of the Global Fund grant for three years. Advocate and work with other countries with pharmaceutical production capacity, particularly Russia, India and Brazil, to develop similar project requests to be covered by grants from the Global Fund.

(2) Small market with uncertain demand

Risk:

The market for MDR-TB drugs, roughly 30,000 treatments a year at the moment, with a maximum foreseeable expansion to around 250,000 treatments annually if all TB cases detected were tested for drug susceptibility is small compared to other diseases. For instance, the global demand for ARVs is estimated at 8 million treatments a year by 2012.⁴ Artemisinin compound combination therapies (ACT) could reach about 500 million⁵ annually. Additionally the uncertain demand that has previously been exhibited will discourage manufacturers from entering into the MDR-TB drug market.

Risk Mitigation:

- GDF, in cooperation with the Clinton Health Access Initiative (CHAI), has embarked upon development of a forecasting system to estimate the demand with an acceptable degree of accuracy, which will contribute to the reduction of production and delivery lead times and the reduction of product costs. Forecasting will be based on a dual approach: one system for the short-term (years 1 and 2), and one system outlining trends for the longer term (years 3-5). Forecasting will be used for GDF's

⁴ www.who.int/hiv/amds/chai_challenges_scaleup_art_obrien_singh.pdf

⁵ www.york.ac.uk/org/cnap/artemisiaproject/fact_sheets_amt.htm

market shaping activities as well as to evaluate global MDR-TB product needs. In the rollout phase of the initial drug forecasting system, 5-6 pilot countries are expected to be engaged by the end of 2010 and early 2011. The 2nd phase will include a larger number of countries, based on available funding allocated for this project.

(3) Sustainability of the current project due to time limited donor funding

Risk

The Strategic Rotating Stockpile (SRS) is a donor (UNITAID) funded initiative. According to the current agreement, the fund will end in December 2011. Another donor (UNITAID) funded initiative, the Strategic Revolving Fund (SRF) project is still in the phase of revision by the parties for finalization and has not yet been launched.

Risk Mitigation:

- GDF has submitted a request for extension and expansion for 10,725 patient treatments of the Strategic Rotating Stockpile Initiative up to 2015 to continue serving the health needs of the countries. This will also assist GDF to develop the other innovative mechanisms, which will incentivize growth of the market.
- The Strategic Revolving Fund Project Plan will hopefully be launched in Q2 2011. Approval of the plan by the donor and finalization of the project technical documentation is of critical importance if GDF is to meet this target.