

## Summary of Activities in the Pharmaceutical Management of Tuberculosis Medicines Conducted in China, 2009–2012

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## **About SPS**

The Strengthening Pharmaceutical Systems (SPS) Program strives to build capacity within developing countries to effectively manage all aspects of pharmaceutical systems and services. SPS focuses on improving governance in the pharmaceutical sector, strengthening pharmaceutical management systems and financing mechanisms, containing antimicrobial resistance, and enhancing access to and appropriate use of medicines.

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## ACRONYMS AND ABBREVIATIONS

ADR	adverse drug reaction
DR	drug-resistant
FDC	fixed-dose combination
FHI 360	Family Health International 360
GLC	Green Light Committee [WHO]
MDR	multidrug-resistant
M&E	monitoring and evaluation
MIS	management information system
MSH	Management Sciences for Health
MTP	Monitoring-Training-Planning
NCTB	National Centre for Tuberculosis Control and Prevention
PAS	para-aminosalicylic acid
RDMA	Regional Development Mission Asia [USAID]
RPM Plus	Rational Pharmaceutical Management Plus [Program]
SLD	second-line drug
SOP	standard operating procedure
SPS	Strengthening Pharmaceutical Systems [Program]
TB	tuberculosis
TDF	Tropical Disease Foundation
TOT	training of trainers
USAID	US Agency for International Development
WHO	World Health Organization
XDR	extensively drug resistant

## EXECUTIVE SUMMARY

The Strengthening Pharmaceutical Systems (SPS) Program received funding from the US Agency for International Development (USAID) to help strengthen pharmaceutical management and systems in China. SPS provided technical assistance to the National Centre for Tuberculosis Control and Prevention (NCTB) from 2009 to 2012.

At the request of the NCTB, the technical assistance focused on standardizing and strengthening the pharmaceutical management practices for first- and second-line tuberculosis (TB) medicines to increase efficiency. SPS collaborated with the NCTB to provide technical support at the national and provincial levels.

The following four technical areas were the focus for strengthening pharmaceutical management:

- Standard operating procedure (SOP) implementation and use
- TB management information system (MIS)
- Quantification tool for fixed-dose combination (FDC) medicines
- Training workshop in the management of second-line drugs (SLDs)

For the SOP component, SPS conducted a monitoring and evaluation (M&E) visit in May 2009 to assess the implementation of SOPs for the management of first- and second-line TB medicines in Guangxi province. Findings revealed that the SOP for first-line TB medicines was not being implemented or followed in a standard manner, and that not all TB drug management functions were being carried out in accordance with SOP guidelines. The SOP for second-line TB medicines was implemented at the national level in a limited manner. Overall, even though the NCTB and provincial-level staff appreciated the SOP as a tool to standardize practice, its implementation was seen as imposing an increased workload, with too many forms to complete yet failing to bring about any immediate changes or positive outcomes. Consequently, the implementation of the SOPs was not enforced by the NCTB.

Also in 2009, SPS introduced the e-TB Manager® and provided technical assistance on assessing the NCTB's MIS. Priority areas were identified for strengthening the NCTB's MIS program; due to funding limitations, however, no activities progressed beyond the initial discussion phase.

In June 2010, SPS designed a quantification tool for FDCs of TB medicines, which was then presented at a training workshop and subsequently validated by the NCTB. Despite system compatibility challenges that emerged following the training, the NCTB expressed appreciation not only for SPS's expertise in pharmaceutical management and quantification but also for its knowledge of TB systems globally, which provided an international context and lessons learned—both beneficial to the national program.

The final activity was conducted in March 2012, in collaboration with Family Health International 360 (FHI 360), at Regional Development Mission Asia (RDMA)/USAID's request for a training workshop on SLD management for TB. The objective was to enhance the capacity

of pharmaceutical managers at the provincial and prefecture levels to appropriately organize and operate pharmaceutical management at the service delivery points, and to further build the capacity of other health care workers in the supply and use of second-line TB medicines. At the conclusion of the workshop, all 30 participants had an improvement in their overall knowledge of multidrug-resistant (MDR) TB and pharmaceutical management of SLDs for TB. Key areas were also identified as in need of further attention, strengthening, and capacity building. Specifically, they are rational use, pharmacovigilance of SLDs for TB, consumption data and case reporting, and quantification of SLDs for TB.

## INTRODUCTION

The Management Sciences for Health's (MSH) Strengthening Pharmaceutical Systems (SPS) Program received funding from the US Agency for International Development's (USAID's) Regional Development Mission Asia (RDMA) to strengthen pharmaceutical management operations in China's tuberculosis (TB) program.

SPS is the follow-on program to the Rational Pharmaceutical Management (RPM) Plus Program. SPS partnered with the World Health Organization (WHO) and China's National Centre for Tuberculosis Control and Prevention (NCTB) to conduct pharmaceutical management operations for the country's TB medicines program. During RPM Plus, technical assistance focused on assessment of TB medicines management in treatment centers, and at the prefecture, provincial, and national levels. The end product for the series of assessments was standard operating procedures (SOPs) for TB pharmaceutical management of first- and second-line medicines.

Following the development of SOPs, one focus of the SPS Program was the implementation of the SOPs. In addition, SPS was involved in the following three areas: the management information system (MIS) for the TB program; quantification methodology and the introduction of a quantification tool for fixed-dose combination (FDC) medicines; and capacity building for pharmacy personnel in the supply and use of second-line TB medicines.

In 2009, SPS focused on providing technical guidance on implementing the SOP for first- and second-line TB medicines in the provinces, which emphasized standardized reporting, consumption, quantification, forecasting, and distribution for the facility, prefecture, and provincial levels in all provinces. In addition, monitoring and evaluation (M&E) visits were conducted to evaluate the implementation and use of the SOP in the provinces.

Also in 2009, two visits were dedicated to (1) defining the MIS needs of the NCTB relative to case and/or pharmaceutical management and (2) providing a technical basis for the development of an MIS for managing multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB cases and strengthening TB control activities within the country.

In 2010, a quantification workshop was conducted on the new quantification tool for FDCs of first-line TB medicines; the tool was subsequently validated and adopted by the NCTB to use in quantifying future FDC needs in the provinces. Despite system compatibility challenges that emerged after the training, the NCTB expressed appreciation for not only SPS's expertise in pharmaceutical management and quantification but also for the program's knowledge of global TB systems, which provided an international context and valuable lessons learned, both of which were beneficial.

In 2012, a training workshop was held in collaboration with Family Health International (FHI) 360. The objective was to enhance the capacity of pharmaceutical managers at the provincial and prefecture levels to appropriately organize and carry out pharmaceutical management at the service delivery points, and to further build the capacity of their fellow health care workers in the supply and use of second-line TB medicines.

## **PROGRAM ACTIVITIES AND RESULTS**

### **SOP Implementation and Use**

The SOPs for first- and second-line TB medicines were drafted and turned over to the NCTB by the RPM Plus Program. The focus of SPS was to provide technical assistance in implementing the SOPs in the provinces, prefectures, and facilities with the goal of standardizing pharmaceutical management of first- and second-line TB medicines.

Despite ongoing efforts to emphasize the importance of standardized practices in pharmaceutical management at each level, the NCTB and pharmacy staff did not fully recognize the importance of having such practices in place, and consequently, the drafted SOPs for first- and second-line TB medicines were implemented only in a limited manner.

During the May 2009 M&E visit for SOP implementation in Guangxi province, the NCTB director in charge of TB drug management indicated that all 31 provinces in China had now implemented the SOP for first-line TB medicines management. However, he mentioned that he was unsure how well SOPs had been implemented at all TB facilities and drug stores within China. Further findings revealed that the SOP was not being implemented or followed in a standardized manner, and that not all TB pharmaceutical management functions were being undertaken according to SOP guidelines. For example, interviewed staff indicated that orders were not being placed quarterly, and that order quantities were not worked out based on a maximum-stock-level formula.

The SOP for second-line TB medicines was found to be implemented at the national level in only a limited manner. The NCTB had adapted the quantification tools in the second-line SOP to forecast and quantify needs under the Global Fund MDR-TB program. The 2009 Green Light Committee (GLC) visit revealed that implementation of the second-line TB medicines SOP was lacking in the two provinces visited, Zhejiang and Guangdong.

It was determined that implementation of the SOPs was perceived as creating an increased workload, with too many forms to complete. Specifically, regarding first-line agents, medicines can be conveniently procured on a local basis and stock-outs or shortages are a minimal occurrence. As a result, the SOP was perceived as somewhat unnecessary. As for the Global Fund MDR-TB program, significant delays during procurement and importation resulted in frequent stock shortages for the second-line agents. However, management personnel attributed these delays and stock-outs to the problems of the GLC and the Global Fund. Therefore, implementing an SOP was seen as a low-priority intervention.

### **TB Management Information Systems and e-TB Manager®**

SPS helped NCTB to define its MIS needs relative to case and/or pharmaceutical management and to collect information to form a technical basis for the development and adoption of an MIS

for managing TB and MDR/XDR-TB cases as well as strengthening TB control activities throughout the country.

During the initial visit, SPS introduced e-TB Manager®, a comprehensive, Web-based tool for programmatic management of TB, including drug-resistant TB (DR-TB), to the NCTB. SPS presented the functions of this Web-based program, helped to identify the specific needs of the NCTB, given existing data collection and management tools and SOPs, and discussed how to adapt the e-TB Manager® to meet local requirements.

A follow-up visit involved needs assessment, encompassing case management and treatment guidelines, pharmaceutical management practices, information flows at all levels, required system layout, required collection and presentation of data, and required system functionalities to be incorporated into the generic version of e-TB Manager®.

Although NCTB appreciated the comprehensive functions of the e-TB Manager®, the program decided that it would be more efficient to improve its own “home-grown,” existing MIS. In support, SPS would provide technical assistance in priority areas defined by the NCTB: (1) assessing information-tracking needs for pharmaceutical management of MDR-TB at the prefecture level, since this is the focal point for managing MDR-TB cases; (2) assisting in analysis and design of a TB MIS; and (3) accomplishing the system improvements needed for incorporating the MDR-TB MIS into the TB MIS. By the end of the project period, these activities had not progressed beyond the initial discussion phase. This is primarily due to limited funding, as well as to a significant amount of time spent on establishing a common understanding of the type of technical assistance SPS could provide for TB MIS.

### **Quantification Tool for Fixed-Dose Combinations**

Following an operational pilot study of FDC use in selected provinces, the NCTB requested SPS’s assistance to facilitate the expanded procurement of TB FDCs throughout the country by developing a tool to quantify FDC medicines (figure 1). As a companion to the tool, the SPS team visited Beijing to conduct a validation and training workshop for NCTB staff. The training focused on tailoring the tool to best suit the program’s needs.

Despite system compatibility challenges following the training, the NCTB expressed appreciation not only for SPS’s expertise in pharmaceutical management and quantification but also for its knowledge of TB systems globally, which provided an international context and lessons learned, both beneficial to the national program.

Treatment Category	TB Treatment Regimens		Medicines	# of Tablet(s) / Capsule(s) / Blister Pack / Vial required per day [F]	# of Doses per Month [G]	Months of Treatment [H]	# of Doses per Treatment Phase (F x G x H)	Number of Expected Patients	Total Quantity Required (# Tablets / Capsules / Blister Pack / Vial, etc.)	CALCULATE
	Dosage Form	Regimen								
New Sputum Smear Positive & Negative	FDC, Adult	2[HRZE]/4[HR]					0		0	
	Blister Pack, Adult	2[HRZE] <sub>1</sub> /4[HR] <sub>1</sub>					0		0	
	Loose Drugs, Adult	2HRZE/4HR					0		0	
	FDC, Adult	2[HRZE]S/6[HR]					0		0	
	Blister Pack, Adult	2[HRZE]S <sub>1</sub> /6[HR] <sub>1</sub>					0		0	
	Loose Drugs, Adult	2HRZE/6HR					0		0	
Retreatment Sputum Smear Positive Cases	FDC, Adult	2[HRZE]/10[HR]E					0		0	
	Blister Pack, Adult	2[HRZE] <sub>1</sub> /10[HR]E <sub>1</sub>					0		0	
	Loose Drugs, Adult	2HRZE/10HRE					0		0	
							0		0	
Pulmonary Pleurisy							0		0	
							0		0	
							0		0	
							0		0	
							0		0	
							0		0	

Figure 1. MS-Excel FDC quantification tool

### Management of Second-Line TB Medicines Training Workshop

Based on a request from USAID/RDMA, in collaboration with FHI 360, SPS conducted a training of trainers (TOT) workshop on the pharmaceutical management of second-line TB medicines and MDR-TB. The workshop was held in Kunming City, Yunnan province, on March 28–31, 2012 (figure 2).

The objective was to enhance the capacity of pharmaceutical managers at the provincial and prefecture levels to appropriately organize and carry out pharmaceutical management at the service delivery points, and to further build the capacity of their fellow health care workers in the supply and use of second-line TB medicines. The purpose of this training was to support FHI 360 and the provincial TB and pharmaceutical managers in implementing future interventions of TB services. The training focused on (1) advocating the prevention of MDR-TB through the improvement of pharmaceutical supply management and rational use of TB medicines; (2) updating knowledge of pharmaceutical supply chain management and rational use of second-line TB medicines; and (3) building the capacity in training, supervision, and implementation of the provincial- and prefecture-level pharmaceutical managers and TB program managers. Two second-line drug (SLD) quantification tools—GLC’s tool for national-level quantification and the Tropical Disease Foundation’s (TDF) tool for treatment, inventory, and quantification at the facility level—were introduced and the participants practiced using them. A Monitoring-Training-Planning (MTP) method was introduced as a TOT approach. Thirty participants from 12 provinces participated in the workshop.

At the conclusion of this training, there was a 12-point percentage increase in participants' knowledge of the subject matter. A majority (94 percent) of participants rated the training sessions as good and helpful.



**Figure 2. TOT workshop for the management of MDR-TB and second-line TB medicines in Kunming City, Yunnan province, March 2012**

Several key areas were identified as in need of further attention, strengthening, and capacity building: rational selection of treatment regimens; availability of para-aminosalicylic acid (PAS) sachet in place of PAS tablets and injectables; availability of cycloserine; pharmacovigilance and adverse drug reaction (ADR) reporting for second-line TB medicines; case reporting and consumption data; quantification of second-line TB medicines; and improved case detection for MDR-TB.

### ***Key Challenges in TB Medicines Pharmaceutical Management***

The SPS team noted several areas that presented challenges or barriers to success.

#### ***Leadership and Management***

- Despite the NCTB's endorsement of the SOPs for pharmaceutical management of first- and second-line TB medicines, implementation of the SOPs at the provincial level has been limited. Even where the SOPs are used, variations in the outlined procedures exist.
- Although the NCTB leadership recognized the need for SOPs to improve efficiency and minimize stock-outs, implementation of the SOPs was not enforced, leaving the sites to determine their own needs and process in managing TB medicines.
- Additionally, leaders had not communicated a strong message regarding the importance of having a standardized practice to the lower levels.

### *Human Resources Availability and Training*

- A lack of designated staff hampers the ability to adopt and implement SOPs because pharmaceutical management staff often have multiple responsibilities.
- Medical staff have limited knowledge and expertise in detecting and treating DR-TB, as well as limited experience in identifying treatment-related ADRs.

### *Capacity Development for Pharmaceutical Management of TB Medicines*

- *Quantification of TB Medicines.* Knowledge of quantification for first-line FDCs is limited. For second-line TB medicine quantification, the morbidity method is the primary method used. The consumption method is not used to cross-check the forecast quantity. As a result, fluctuations in consumption are not accounted for. This is a problem, especially when the first-line MDR-TB regimen is not standardized. In certain patient populations, one or two agents are eliminated from the regimen due to the contraindication of age or co-morbid disease states. In addition, currently the quantification of DR-TB medicines provided by the Global Fund is done at the national level. Provincial-level staff have limited exposure and experience in the quantification of second-line TB medicines.
- *Planning, Recording, and Reporting.* There was a change of one agent in the first-line MDR-TB regimen, from levofloxacin to moxifloxacin, during the middle of a procurement cycle. However, this change was not incorporated in the planning stage, resulting in the overstock of one agent and shortage of the other. In addition, because of the limited adoption of SOPs and the lack of promotion from the provincial level, the record keeping and reporting requirements were minimally performed.
- *Monitoring and Supervision.* Pharmaceutical management was not integrated into the routine monitoring and supervision visit.

### *Rational Use of TB Medicines*

- *Rational Prescribing.* In addition to the standard four-drug, six-month rifampicin-based regimen, patients on the first-line TB regimen may also be prescribed short-term fluoroquinolone. Since fluoroquinolone is also one of the crucial antibiotics used in the MDR-TB regimen, with cross-resistance commonly occurring among the fluoroquinolone agents, this can potentially result in the ineffectiveness of a fluoroquinolone when used in the MDR regimen. There is disparity between provinces in the regulation and enforcement of rational prescribing and use of antibiotics.

## RECOMMENDATIONS

### Immediate Recommendations

#### *National Level*

- Integrate consumption data and cohort data to track rational prescribing and use of TB medicines.
- Integrate ADRs of TB medicines into the national pharmacovigilance database.
- Regulate antibiotic prescribing in the provinces, specifically the fluoroquinolones, to prevent cross-resistance, which can potentially lead to DR-TB treatment failure.
- Ensure the availability of PAS sachet and cycloserine by registering both agents with the State Food and Drug Administration (SFDA).
- Improve the clinical competency of medical staff, including laboratory technicians, especially in the areas of diagnostics, case detection, and treatment.
- Develop or adopt existing TB SOPs to standardize basic essential practices and support the further implementation of province-specific SOPs for TB medicines management.
- Strengthen management and leadership practices in TB drug management by—
  - Establishing a functional communication channel between the leadership at the national and provincial levels.
  - Conducting regular supportive monitoring and supervision visits to provide on-the-job training to new staff and refresher training to existing staff and to evaluate incremental changes in the management of TB medicines and any subsequent effects on patient outcomes.

#### *Provincial Level*

- Implement SOPs, establish a mechanism to monitor progress, and establish enforcement measures and indicators to ensure compliance.
- Improve the clinical competency of medical staff, including laboratory technicians, especially in the areas of diagnostics, case detection, treatment, and ADR detection.
- Improve staff members' understanding of the general principles of pharmaceutical management, particularly quantification concepts and methods for quantifying FDCs and second-line TB medicines; establish a refresher course and standardized training materials to

assure uniformity and consistency in TB medicines management practices for the Global Fund and provincial TB programs.

- Ensure that pharmaceutical management is included as part of the routine monitoring and supervision visit to track appropriate use of SOPs.
- Have leaders at each level commit to facilitate the implementation of the SOPs, including allocating adequate human resources, establishing an action plan and time line, developing a mechanism to track progress, and introducing enforcement measures to ensure compliance.

## **Long-Term Recommendations**

### ***National Level***

- Identify the essential components needed to standardize TB management, and encourage experience sharing among the provinces on adoption and implementation of SOPs that are level-specific to the provinces, prefectures, and facilities.
- Facilitate the provinces in developing and fully implementing SOPs for management of both first- and second-line TB medicines.
- Integrate the pharmaceutical management of the provincial and Global Fund MDR-TB programs to streamline operations at all levels.
- Improve supervision skills at all levels by adding leadership and management training to pharmaceutical management training.

### ***Provincial Level***

- Establish a follow-up mechanism to allow for review and updating of the tools, forms, and SOPs to reflect current practices.
- Ensure that sufficient human resources are allocated to pharmaceutical management, with adequate compensation to minimize staff turnover.
- Make standardized training and materials available so that all staff have the same level of understanding of the basic pharmaceutical management principles.

## LIST OF DELIVERABLES

### Reports

Dias, V. 2008. *Review of First-Line SOP Implementation Progress in Guangxi Province, China, May 11–15, 2009: Trip Report*. Submitted to the US Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Sciences for Health (MSH).

Dias, V. 2009. *The Global Drug Facility MDR-TB Mission Checklist and Report, China*. September 17–25. Arlington, VA: MSH.

Hollist, S., V. Dias, and J. Keravec. 2009. *Workshop to Introduce e-TB Manager, China, January 14–16, 2009: Trip Report*. Submitted to the US Agency for International Development by the SPS Program. Arlington, VA: MSH.

Hollist, S., T. Moore, and M. Leinhaas. 2009. *Technical Consultation to Chinese National Center for TB Control and Prevention, July 7–10, 2009, Beijing, China: Trip Report*. Submitted to the US Agency for International Development by the SPS Program. Arlington, VA: MSH.

Wang, S., N. Munez, L. Li, and F. Cheng. 2012. *Training Workshop for the Management of MDR-TB and Second-Line TB Medicines in Kunming, China*. March 28–31. Submitted to the US Agency for International Development by the SPS Program and TB-CAP Program. Arlington, VA: MSH/Family Health International (FHI) 360.

Wong, A., and V. Dias. 2010. *Conduct TB FDC Quantification Workshop and Assessment on Technical Support Needed for Pharmaceutical Management of MDR-TB Program, Beijing, China, June 15–24, 2010: Trip Report*. Submitted to the US Agency for International Development by the SPS Program. Arlington, VA: MSH.

Wong, A., J. Keravec, and V. Dias. 2009. *SPS Symposium on Pharmaceutical Management at the International Union Against Tuberculosis and Lung Disease Conference, Asia Pacific Region, and Participation in GLC Mission on MDR-TB, September 7–25, 2009, Beijing and JiangSu Province, China: Trip Report*. Arlington, VA: MSH.

### SOP Manuals

Dias, V. 2006. *Standard Operating Procedures Manual for Managing Tuberculosis Drugs and Medical Supplies at Provincial TB Drug Warehouse in Henan Province*. Arlington, VA: MSH.

Dias, V., and S. Hollist. 2008. *Standard Operating Procedures for Managing Second-Line Tuberculosis Medicines through the Chinese National Center for Tuberculosis Control and Prevention*. Arlington, VA: MSH.

## **Tools**

Bhattarai, H. R. 2010. Fixed-Dose Quantification Excel Tool. Arlington, VA: MSH.

## **Training Materials**

Green Light Committee second-line drugs quantification tool, Tropical Disease Foundation second-line drugs quantification tool, and Monitoring-Training-Planning site visit data collection tool and action plan form.

Moore, T. 2009. *Standard Operating Procedures for Tuberculosis Drug Administration: Participants' Guide*. Arlington, VA: MSH.

Moore, T. 2009. *Standard Operating Procedures for Tuberculosis Drug Administration: Training of Trainers Guide*. Arlington, VA: MSH.

SPS Program and FHI 360. 2012. Training materials for MDR-TB prevention and second-line drugs pharmaceutical management. 19 modules.