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OPERATIONAL GUIDE *for*

NATIONAL TUBERCULOSIS CONTROL PROGRAMMES

ON THE INTRODUCTION *and* USE OF FIXED-DOSE COMBINATION DRUGS

WORLD HEALTH ORGANIZATION

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OPERATIONAL GUIDE FOR NATIONAL TUBERCULOSIS CONTROL PROGRAMMES ON THE INTRODUCTION AND USE OF FIXED-DOSE COMBINATION DRUGS

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List of acronyms and abbreviations

AFB	Acid-fast baccili
AIDS	Acquired immunodeficiency syndrome
API	Active pharmaceutical ingredient
ARTI	Annual risk of tuberculosis infection
CMS	Central medical stores
DOT	Directly Observed Treatment
DOTS	Directly Observed Treatment, Short-course (the internationally recommended control strategy for tuberculosis)
DRA	Drug Regulatory Authority
E	Ethambutol
EDM	Essential Drugs and Medicines Policy Department (WHO)
FDC	Fixed-dose combination
FEFO	First-expired first-out
FIFO	First-in first-out
GDF	Global Drug Facility
GMP	Good Manufacturing Practices
H	Isoniazid
HIV	Human immunodeficiency virus
ICB	International competitive bidding
INN	International Nonproprietary Names
IUATLD	International Union Against Tuberculosis and Lung Disease
KNCV	Royal Netherlands Tuberculosis Association
LCB	Limited competitive bidding
MDR-TB	Multi-drug resistant tuberculosis
MSH	Management Sciences for Health
MOH	Ministry of Health
NGO	Nongovernmental organization
NTP	National tuberculosis programme
PTB	Pulmonary tuberculosis
QA	Quality assurance
R	Rifampicin
S	Streptomycin
SCC	Short-course chemotherapy
STB	WHO Stop Tuberculosis Department
TB	Tuberculosis
TB/HIV	TB and HIV co-infection
UNICEF	United Nations Children's Fund
WHO	World Health Organization
Z	Pyrazinamide

PREFACE

The World Health Organization (WHO) has promoted the DOTS strategy as the essential, most cost-effective package for tuberculosis control since 1994. Today, the 148 countries that have adopted DOTS are intensifying their efforts to achieve the targets set for 2005 by the World Health Assembly: to detect 70% of sputum smear-positive infectious cases and to cure at least 85% of such cases. One key element of the DOTS strategy is the use of short-course chemotherapy regimens, proven by clinical trials to be highly efficacious, under proper case management conditions. This includes direct observation of patients taking their drugs at the correct dosage and for the proper period of time.

Ensuring that people with TB complete a full course of treatment is one of the major challenges for TB control. Direct observation of treatment is essential to help patients stay on treatment, even after symptoms have subsided following the first few weeks of chemotherapy. The risk is that uninformed patients (as well as uninformed and careless doctors) may change the regimen, avoiding one or more of the drugs they believe are no longer necessary, leading to treatment failure or relapse. In so doing, some of these patients will develop antimicrobial resistance to one or more drugs. As a consequence, the spread of strains of mycobacteria resistant to drugs may then occur in a community. This is how the well known multidrug-resistant tuberculosis (MDR-TB) outbreaks have developed and spread in many parts of the world.

There are various strategies to prevent this from happening. The first is to have proper health care systems and services in place, in such a way that patients with TB are fully educated, nurtured and monitored throughout the 6-8 months of treatment required to cure their disease. However, there are additional tools to ensure that drugs are properly used. One approach is through fixed-dose combination (FDC) tablets. Recent advances in the field of pharmacology have made it possible to develop quality combinations of up to four anti-TB drugs. In a single tablet, we are now able to deliver the two, three or four essential first-line drugs in the proper dosages, thus guaranteeing easy adoption of the WHO-recommended regimens. Both WHO and the International Union against Tuberculosis and Lung Disease (IUATLD) recommend the use of FDCs as a means to prevent monotherapy and reduce the risk of drug resistance.

However, prevention of drug resistance is just one of the potential benefits of the use of FDCs. FDCs simplify administration of drugs by reducing the number of pills a patient takes each day and decreasing the risk of incorrect prescriptions. It is much simpler to explain to patients that they need to take four tablets of the same type and colour, rather than a mixture of tablets of different shapes, colours and sizes. FDCs are also simpler for care-givers as they minimize the risk of confusion. Finally, drug procurement, in all its components (stock management, shipping, distribution), is simplified by FDCs. For these reasons, WHO includes

FDCs for TB in its Model List of Essential Medicines and is recommending them to national TB programmes (NTPs).

Today, many NTPs are using 2-drug FDCs, some are using 3-drug FDCs, and a few have started using 4-drug FDCs. Some NTPs have hesitated to use FDCs because of concerns regarding cost and quality, particularly rifampicin bio-availability. In addition, registration and other regulatory obstacles have made it, at times, difficult for NTP managers to support introduction of FDCs in their programmes. These concerns have been addressed, and low cost, high quality 2-, 3- and 4-drug FDCs are now widely available. WHO has therefore developed this guide to facilitate the introduction of FDCs by NTPs. The guide is a tool that will help NTP managers to learn about the rationale behind FDCs, understand fully the need to ensure bio-availability of the products chosen, become acquainted with procurement mechanisms, familiarize themselves with regulatory requirements, and, finally, smoothly shift from regimens based on a single drug to those based on FDCs.

FDCs are important tools to further improve the quality of care for people with TB, and accelerate DOTS expansion to reach the global TB control targets for 2005. The guide has been requested by NTP managers and others involved in the treatment of people with TB, and will help ensure that FDC tools are used widely and effectively.

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KEY POINTS

This document is intended to promote the use of fixed-dose combination (FDC) anti-TB drugs in the treatment of tuberculosis (TB). It is directed to national TB programme (NTP) managers to assist them in the process of making policy decisions and planning for the introduction of 2-, 3-, and 4-drug FDCs.

For effective planning of the implementation of FDC drugs in a country's TB control programme, it is advisable that policy-developers and decision-makers, and the NTP managers in particular, study this guide before making any policy decision regarding programme and drug management. This is especially true if a country has never used 2-, 3- or 4-drug FDCs.

This publication provides easy-to-follow guidance on programmatic, managerial, quality and regulatory matters, with some practical approaches to facilitating the use of FDCs in a TB control programme. The guide contains minimum requirements and is not intended to replace existing requirements and practices in countries achieving high quality Directly Observed Treatment, Short-course (DOTS) implementation. Approaches other than those set out in this guide may be applicable and acceptable. It is the responsibility of the NTP manager and key stakeholders to choose the most suitable approach for their national and local settings to introduce FDCs. FDCs should be considered as part of the overall DOTS strategy implementation and should definitely not be seen as an alternative.

Policy-makers and national TB programme managers deciding to use FDCs should develop a clear strategy and detailed plan for replacing single drug formulations by FDCs. The implementation process should be carefully introduced and, if necessary, gradually expanded.

National drug regulatory authorities (DRAs) and NTP managers should ensure that all anti-TB drugs, including FDCs, meet acceptable standards of quality, safety and efficacy, and that they are accessible to the whole population. Anti-TB drugs should be used rationally in accordance with the current standardized treatment guidelines for effective treatment outcomes in both the public and private sectors. It is crucial for NTP managers to ensure that all TB patients have uninterrupted access to anti-TB drugs, and that the right drugs of the right quantity and in the right dosage form are delivered to the right patient at the right time.

Assuring the quality of both locally produced and imported FDCs may present a problem for many DRAs and NTP managers with limited technical capacity and resources. In that case, for imported FDCs, managers must rely on quality information from the DRA of the exporting country. For locally manufactured products, managers must establish their own quality assurance system and demand that suppliers provide the quality documents described in the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International

1 INTRODUCTION

1.1 Aim and objectives

The aim of this guide is to facilitate the implementation of the World Health Organization (WHO) DOTS strategy. The global TB control target, defined in 2000 by the World Health Assembly, is to detect 70% of all smear-positive cases and successfully cure 85% of these by 2005. The recommendation of WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) and their partners, for the introduction and use of FDC formulations of the essential anti-TB drugs, forms part of the expanded DOTS framework for effective TB control.

The main objective of this guide is to assist NTP managers and their personnel, including DOTS strategy implementers, drug procurement officers/personnel at different levels (national, regional, local), DOT providers, and drug regulatory authorities, in making policy decisions and planning to successfully introduce FDCs in their TB control programmes.

The specific objectives of this guide are to:

- explain the reasons and to advocate the rationale for using FDCs in DOTS expansion;
- promote the standardized FDCs recommended by WHO, especially the 4-drug FDC recently added to the WHO Model List of Essential Medicines, in order to facilitate the use of standardized treatment regimens recommended by WHO;
- raise awareness among NTP managers and drug regulatory authorities (DRAs) of the importance of bio-availability and quality control of rifampicin-containing FDCs in the course of their acquisition, i.e. of good drug management;
- provide guidance for adequate planning and smooth introduction of 4-drug FDCs/2-drug FDCs from a small scale to full implementation; and
- strengthen the interaction of NTP managers and DRAs to address the issues of registration of FDCs and other regulatory matters.

This guide is also intended for national TB control programme managers in all countries who are embarking on implementing DOTS strategy, which requires an effective drug supply management system. The entire TB control strategy can be hampered by use of poor quality anti-TB drugs, inappropriate drug need estimates, lack of adequate financing, late arrivals, mismanagement of drug distribution and storage, and misuse of anti-TB drugs.

1.2 What you can find in this guide

This guide consists of six main sections (see Box 1). The introductory part deals with the objectives of the guide and general considerations to be taken into account when introducing FDCs, and provides the background and rationale for

the use of anti-TB FDCs. The second section explains programmatic and managerial requirements, which ministries of health and NTP managers should

Box 1: Main sections

- Introduction: goal and objectives of the guide, background and rationale for using FDCs
- Programmatic and managerial requirements
- Drug supply management
- Quality bio-availability/bio-equivalence and regulatory requirements

consider before making certain policy decisions to introduce FDCs. This section reiterates the urgent need for accelerated expansion of DOTS strategy to combat the TB epidemic. It also describes the WHO-recommended FDCs for primary treatment of TB, the different treatment categories and respective regimens. The third section covers drug management issues, including the selection of dosage forms, quantification of drug needs, procurement, stock management and distribution. The fourth section provides useful information on regulatory requirements and proposes approaches for NTP managers and DRAs to address the quality control and bio-availability/bio-equivalence issues of FDCs, in particular FDCs containing rifampicin. The fifth section explains how to introduce and gradually change over to a regimen with 4-drug FDCs/2-drug FDCs. This involves planning, and offers a scenario for changing over to a regimen with 4-drug FDCs. The last section includes annexes of relevant materials and documents referred to in the main text.

1.3 Background and rationale

Every year, TB kills nearly two million people. With the poor access to adequate health services, including essential medicines, in many countries, the spread of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), and the emergence of multidrug-resistant tuberculosis (MDR-TB), greater efforts are urgently needed to combat the worsening impacts of TB. Estimates suggest that, in the absence of such efforts, every year between seven and eight million people will develop active TB. The economic costs of TB are tremendous and mostly affect the poor. The socioeconomic impact of the disease is greatest on adults in their most economically active years: three-quarters of the new cases of TB each year are among people aged between 15 and 54. The poor and marginalized in the developing world are the worst affected: 95% of all cases and 98% of deaths from TB occur in resource-poor countries.

Extending and maintaining regular access to effective TB treatment is clearly essential if patients are to be cured and drug resistance avoided. The expansion of DOTS strategy to control the TB epidemic has been identified as a high priority for

WHO's Stop TB Initiative. DOTS consists of a five-component policy package (see Box 2, and section 2) which is acknowledged internationally as the most effective intervention for preventing and controlling TB.

Within the DOTS strategy, standardized short-course chemotherapy, promptly delivered, can have a major impact on TB morbidity and mortality. Since 1994 and especially since 1998, WHO and IUATLD have advocated replacing single-drug regimens for treatment of primary TB with fixed-dose combinations. Use of WHO-recommended 3- and 4-drug FDC tablets has been promoted for the intensive phase of DOTS. The potential advantages of FDCs in treating TB include:

- simplicity of treatment with minimal prescription errors;
- increased patient acceptance and compliance with decreased likelihood of inadvertent medication errors;
- increased health worker compliance to standardized and correct treatment;
- improved drug management because ordering, procurement, distribution and dispensing/handling at different levels of the NTP are easier when there are fewer items with a single expiry date to deal with;
- lowered risk of misuse of single drugs and of emergence of drug-resistant TB due to reduced use of monotherapy.

This guide has been developed based on recommendations made at various meetings and consultations of experts in TB treatment, NTP managers, researchers, academics, drug regulatory authorities, and other concerned stakeholders.

2 PROGRAMMATIC AND MANAGERIAL REQUIREMENTS FOR FDCS

TB regimens and anti-TB drug formulations have changed regularly in the past in response to new insights and circumstances in TB control. The introduction of rifampicin in the 1970s shortened the regimen from 12-18 months to 6-8 months (short course chemotherapy: SCC). In the 1990s, SCC was expanded worldwide together with the expansion of DOTS strategy. More recently, the majority of countries using DOTS strategy have replaced rifampicin and isoniazid loose tablets with combination tablets (2-drug FDCs [RH]) as recommended by WHO and IUATLD since 1994. Since the early 1990s, many high HIV prevalence countries have replaced thioacetazone with ethambutol or rifampicin in the continuation phase and some countries have also changed from a daily to intermittent treatment regimen. The 1997 WHO Model List of Essential Medicines recommended the use of rifampicin 150 mg + isoniazid 75 mg (R150 mg + H75 mg) instead of the previously recommended rifampicin 150 mg + isoniazid 100 mg (R150 mg + H100 mg) and pyrazinamide 400 mg (Z400 mg) instead of pyrazinamide 500 mg (Z500 mg). All these changes were included in guidelines and training, and have been implemented at local level, resulting in increased DOTS efficiency.

Since 1999, 4-drug FDCs have been proposed for the initial phase of treatment of category 1 and 2 patients. Availability on the international market, quality and price no longer represent an obstacle. Considering the advantages, e.g. simpler prescription, decreased chance to select resistant strains, and increased patient and health worker acceptance, it is expected that 4-drug FDCs will become the standard formulation for TB regimens in the very near future.

2.1 DOTS strategy

The essential government services needed to control tuberculosis, based on diagnosis and treatment of infectious cases and incorporating essential management tools, were developed and packaged as the DOTS strategy. Since the early 1990s, DOTS has been promoted as a global strategy (See Box 2).

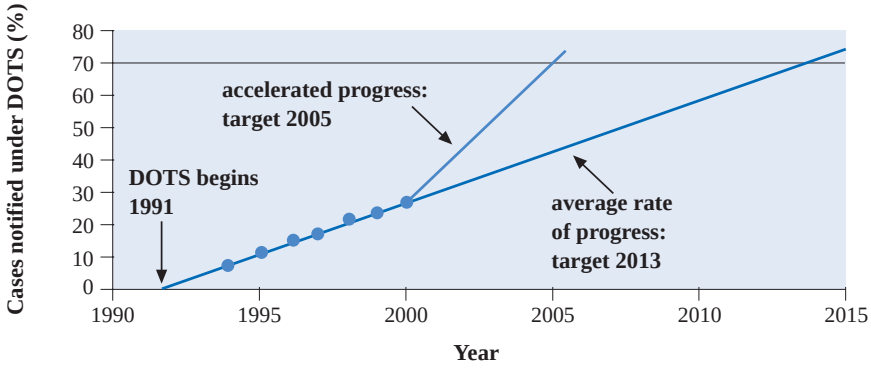
Box 2: DOTS strategy components

- Sustained political commitment
- Access to quality-assured TB sputum microscopy
- Standardized, short-course chemotherapy for all cases of TB under proper case management conditions including direct observation and treatment
- Uninterrupted supply of quality-assured drugs
- Recording and reporting system enabling outcome assessment

2.1.1 Challenges in TB control

Despite widespread acceptance of the principles of DOTS, many countries have not been able to expand DOTS as rapidly as needed and have failed to achieve the year 2000 global target of detecting 70% of the infectious cases and curing 85% of those detected. The main constraints to rapid expansion, as identified by an ad-hoc Committee on the Tuberculosis Epidemic held in London in 1998, were lack of political commitment, insufficient and ineffective use of financial resources, neglect of human resource development, poor health system organization and TB managerial capability, inadequate quality and irregular supply of anti-TB drugs, and lack of information. The number of countries adopting DOTS has, however, increased dramatically over the last decade, from 10 in 1990 to 148 (out of 192 WHO Member States) at present, but at the end of 2000 only 27% of people with infectious pulmonary TB were notified as being under DOTS programmes. With the current efforts to control TB, it is expected that the global target for detecting and treating efficiently 70% of the cases worldwide will be reached only by 2013 (see Figure 1). Accelerating DOTS expansion to achieve the target by 2005 – to which all countries recently committed themselves as part of the Amsterdam Declaration in March 2000 – will have profound health and socioeconomic impacts, saving 18 million lives by the year 2010, and preventing 48 million new cases by 2020 in the 22 high burden countries. This 'fast track' DOTS expansion plan will also mitigate the impact of HIV/AIDS and reduce the prevalence of drug resistance. The accelerated plan aims at increased access to drug treatment and care, mobilizing society, building capacity, and expanding DOTS population coverage.

Figure 1: Progress towards targets for TB control



Source: Global Tuberculosis Control. WHO Report 2002. WHO/CDS/TB/2002.295

2.1.2 Why switch to FDCs?

Use of 2-, 3- and 4-drug FDCs does not replace proper case management and directly observed treatment (DOT), which ensure adherence to treatment and ultimately the cure of a patient.

In some countries, the use of 4-drug FDC tablets might not (yet) be allowed by the DRAs for various reasons, e.g. they may not yet be registered or licensed for marketing.

Besides the potential advantages described above (section 1.3), FDC tablets will contribute tremendously to DOTS expansion in several ways:

- there will be no more monotherapy with one medicine or an insufficient number of different loose drugs, reducing the chance of development of resistant strains of TB;
- the 4-drug FDC regimen decreases the risk of treatment failure and relapse;
- patients will have fewer tablets to swallow, which will help improve compliance;
- having fewer tablets to handle, supervision of drug intake will be quicker, so greatly reducing the workload and potential prescription errors of health workers administering DOTS;
- drug ordering, storage and stock control will be simpler and time will be saved, while errors are less likely to occur (fewer items to handle with the same expiry date);
- from the programme management point of view, calculation of drug needs, procurement, distribution and stocking throughout the programme will become simpler and, in some instances, even cheaper (e.g. due to less volume and storage capacity needed); and
- it will be easier to adjust dosages by body weight (see Tables 4 and 5).

2.1.3 FDCs and adverse effects

Adverse reactions to drugs are not more common if FDCs are used. Nevertheless, whenever side-effects to one or more components in a FDC are suspected, there will be a need to switch to single-drug formulations. Reactions to FDCs which warrant withdrawal of drugs generally occur in only 3-6% of patients on TB treatment. These reactions may be more common in patients co-infected with HIV (e.g. when using thioacetazone); however FDCs are not contraindicated for these patients. A limited stock of single drugs should therefore be available in referral centres, where patients with severe adverse reactions, although very rare, can be managed under the supervision of a TB specialist.

FDCs can be used in some special situations:

- Renal failure - in normal dosage range, rifampicin, isoniazid and pyrazinamide are considered to be safe. Patients with impaired renal function may require a

reduced dosage of ethambutol as it is primarily excreted through the kidneys. Patients with severe renal failure should receive pyridoxine to prevent peripheral neuropathy.

- Liver disease – most anti-TB drugs can cause liver damage. Risk-benefit should be considered in patients experiencing severe side-effects (including symptoms of hepatitis and/or jaundice) or in patients who suffer from liver injuries. Jaundiced patients who develop TB should receive a treatment regimen adapted to their condition.

Further information on management of adverse drug reactions can be found in *Interventions for tuberculosis control and elimination*[1].

2.1.4 *Directly observed treatment and FDCs*

Directly observed treatment (DOT) means that a supervisor watches the patient swallowing the tablets. This ensures that a TB patient takes the right drugs, in the right doses, at the right intervals. DOT is applicable in outpatient settings. The supervisor may be a health worker or a trained and supervised member of the community.

DOT is recommended in the initial phase of treatment with FDCs, at least for all smear-positive cases, and in the continuation phase of rifampicin-containing (intermittent and daily) regimens. Patients' and health workers' compliance is a key factor in treatment success.

The use of FDCs will facilitate implementation of DOTS and must never be seen as a replacement for DOT.

2.2 FDC formulations in the WHO Model List of Essential Medicines

WHO is working toward standardized treatment regimens and effective monitoring of TB control programmes, and recommends the use of certain FDC dosage forms, as presented in Tables 1 and 2 below.

2.3 Treatment regimens using FDCs

The standardized treatment regimens for the different categories of TB cases, and dosage schedules (number of tablets) in relation to body weight, are presented in Tables 3, 4 and 5.

[1] Reider HL. *Interventions for Tuberculosis Control and Elimination*, Paris, International Union Against Tuberculosis and Lung Disease (IUATLD), 2002.

Table 1: The recommended dosage of essential first-line anti-TB drugs

Drug (abbreviation)	Mode of action	Recommended dose (dose range) in mg/kg body weight	
		Daily	Intermittent 3 times per week
rifampicin (R)	bactericidal	10 (8-12)	10 (8-12)
isoniazid (H)	bactericidal	5 (4-6)	10 (8-12)
pyrazinamide (Z)	bactericidal	25 (20-30)	35 (30-40)
streptomycin (S)	bactericidal	15 (12-18)	15 (12-18)
ethambutol (E)	bacteriostatic	15 (15-20)	30 (25-35)

Although used in some programmes, WHO does not recommend the use of thioacetazone (T) because of the risk of severe toxicity, particularly in HIV infected individuals. In general, thioacetazone should be replaced by ethambutol.

Table 2: Fixed-dose combinations from the WHO Model List of Essential Medicines *(revised April 2002)*

Drug	Dose form	Strength for Daily use	Strength for intermittent use 3 times per week
rifampicin + isoniazid [RH]	Tablet	150 mg + 75 mg 300 mg + 150 mg	150 mg + 150 mg
	Tablet or pack of granules*	60 mg + 30 mg	60 mg + 60 mg
ethambutol + isoniazid [EH]	Tablet	400 mg + 150 mg	-
isoniazid + thioacetazone [HT]**	Tablet	100 mg + 50 mg 300 mg + 150 mg	- -
rifampicin + isoniazid + pyrazinamide [RHZ]	Tablet Tablet or pack of granules*	150 mg + 75 mg + 400 mg 60 mg + 30 mg + 150 mg	150 mg + 150 mg + 500 mg -
rifampicin + isoniazid + pyrazinamide + ethambutol [RHZE]	Tablet	150 mg + 75 mg + 400 mg + 275 mg	- -

* For paediatric use
** Although used in some programmes, WHO does not recommend the use of thioacetazone (T) because of the risk of severe toxicity, particularly in HIV infected individuals. In general, thioacetazone should be replaced by ethambutol.

Table 3: Recommended treatment regimens for each treatment category

Tuberculosis diagnostic category	Tuberculosis patients	Tuberculosis treatment regimens	
		Initial phase (daily or 3 times per week*)	Continuation phase (daily or 3 times per week*)
I	New smear-positive patients; new smear-negative PTB with extensive parenchymal involvement; severe concomitant HIV disease or severe forms of extrapulmonary TB	2 RHZE**	4 RH***
II	Previously treated sputum smear-positive PTB: - relapse; - treatment after interruption; - treatment failure†	2 RHZES / 1 RHZE	5 RHE
III	New smear-negative PTB (other than in Category 1) and less severe forms of extrapulmonary TB.	2 RHZE††	4 RH***

* Direct observation of treatment intake is required for the initial phase in smear positive cases, and always when treatment includes rifampicin.
** Streptomycin may be used instead of ethambutol.
*** 4RH may be replaced by 6 EH daily when supervision of treatment is not possible. However, preliminary data from a recent clinical trial have shown that 6EH is much less effective than 4RH in terms of cure, with higher failure and relapse rates.
In meningitis: 2 RHZS/4 RH or 2 RHZS/4 (RH)3, replacing ethambutol with streptomycin.
† Whenever possible, drug sensitivity testing is recommended before prescribing category II treatment in failure cases. In patients with proven MDR-TB, it is recommended to use category IV regimens which are not described in this Guide (please refer to guidelines for management of failure and chronic cases in MDR-TB).
†† Ethambutol may be omitted for patients with non-cavitary, smear-negative pulmonary TB who are known to be HIV-negative, patients who are known to be infected with fully drug-susceptible bacilli. Young children with primary TB should be given 3 drugs combination only (without ethambutol).
R – rifampicin; H – isoniazid; Z – pyrazinamide; E – ethambutol; S – streptomycin; PTB – pulmonary tuberculosis.

Note: Standard code for TB treatment regimens. Each anti-TB drug has an abbreviation (shown in the Tables above). A regimen consists of 2 phases. The number before a phase is the duration of that phase in months. A number in subscript (e.g. $_3$) after a letter is the number of doses of that drug per week. If there is no number in subscript after a letter, then treatment with that drug is daily. For example: 2 RHZE/ 4 $(RH)_3$. The duration of the initial phase is 2 months and drug treatment is daily, with rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E). The continuation phase is 4 $(RH)_3$. The duration is 4 months, with rifampicin (R) and isoniazid (H) three times per week.

Table 4: Dosage schedules for adults: number of 4-, 3- and 2-drug FDC tablets

Patient body weight (kg)	Initial phase			Continuation phase		
	2 months			4 months		or 6 months*
	Daily	or Daily	or 3 times per week	Daily	or 3 times per week	Daily
	RHZE** 150 mg+75 mg+ 400 mg+275 mg	RHZ 150 mg+75 mg +400 mg	RHZ 150 mg +150 mg +500 mg	RH 150 mg+75 mg+	RH 150 mg+150 mg	EH 400 mg +150 mg
30-39	2	2	2	2	2	1.5
40-54	3	3	3	3	3	2
55-70	4	4	4	4	4	3
71 and more	5	5	5	5	5	3

R – rifampicin; H – isoniazid; Z – pyrazinamide; E - ethambutol
* 4RH may be replaced by 6 EH daily when supervision of treatment is not possible. However, preliminary data from a recent clinical trial have shown that 6EH is much less effective than 4RH in terms of cure, with higher failure and relapse rates.
** Maximum recommended daily dose of rifampicin in FDCs is 750 mg.

Table 5: Dosage schedules for smear-negative children: number of 3- and 2-drug FDC tablets

Patient body weight (kg)	Initial phase	Continuation phase	
	2 months	4 months	
	Daily	or Daily	or 3 times per week
	RHZ 60 mg+30 mg+150 mg	RH 60 mg+30 mg	RH 60 mg+60 mg
<7	1	1	1
8-9	1.5	1.5	1.5
10-14	2	2	2
15-19	3	3	3
20-24	4	4	4
25-29	5	5	5

R – rifampicin; H – isoniazid; Z – pyrazinamide

2.4 Justification for dosage forms and dosage schedules

The therapeutic range within which the 4-drug FDC (RHZE) recommended by WHO is effective and not toxic is illustrated in Figures 2-5 below. The charts demonstrate that, for the anti-TB drugs included in the FDC tablet, varying the dosage schedule according to body weight ensures that the dose remains within the therapeutic margin.

Figures 2-5: Dose distributions of the four FDC drugs

(rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg, ethambutol 275 mg) recommended by WHO (by body weight cut-off points of 30-37 kg, 38-54 kg, 55-70 kg, 71 kg and above).

Figure 2: Rifampicin dosage

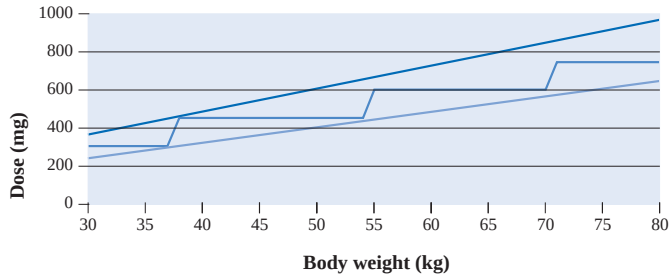
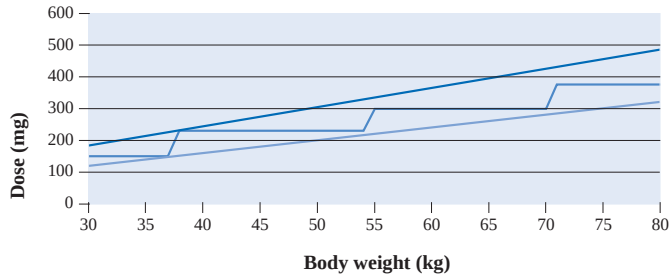


Figure 3: Isoniazid dosage



***Note**: The body weight range is adequately covered by all drugs in the 4-drug FDC formulation, i.e. the doses in mg per kg body weight do not breach the minimum or maximum cut-off points.*

Figure 4: Pyrazinamide dosage

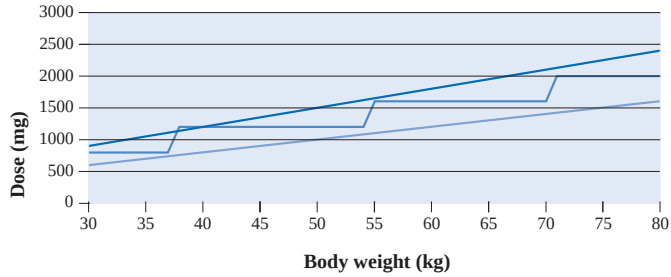
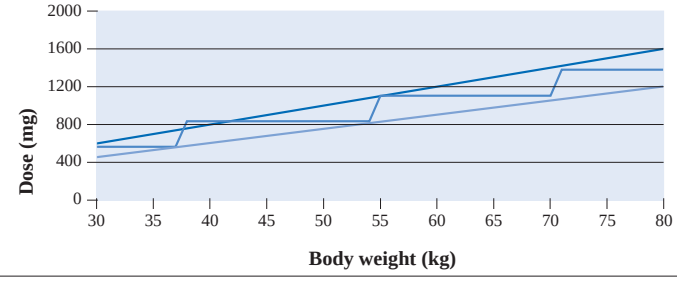


Figure 5: Ethambutol dosage

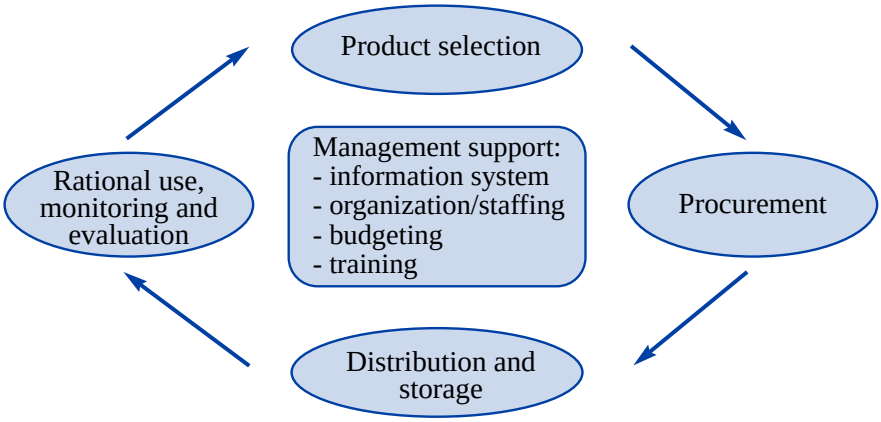


3

FDC DRUG MANAGEMENT

Taking a look at the TB drug management cycle (derived from *Managing Drug Supply*[2] and *Plan Supplies* in a WHO/TB training guide[3]) demonstrates how the different components of anti-TB drug management are linked (Figure 6 below).

Figure 6: Anti-TB drug management cycle



Management support is integral to each component of the drug management cycle: drug selection, procurement, storage and distribution, use and monitoring. Management support includes a variety of activities at all organizational levels, i.e. from the national programme level down to where drugs are dispensed to patients. The main activities include management of the information system, ensuring timely information flow between stakeholders at different levels, and securing the financial and other resources, including drugs, needed for the programme.

The NTP manager is responsible for developing and implementing the TB control policy and programme. Within this policy, drug supply management is one of the important elements – careful planning and implementation is required to ensure regular availability of high-quality anti-TB drugs for the programme. While the NTP manager usually does not have full responsibility for obtaining and supplying TB drugs, including FDCs, it is common for the NTP manager to be directly involved with selecting drug regimens and calculating drug needs prior to procurement. Additional drug management issues in which the NTP manager is likely to become involved, depending on

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2 Quick JD, Rankin JR, Laing RO, O'Connor RW, Hogerzeil HV, Dukes MNG, Garnett A. *Managing Drug Supply*, 2nd ed. West Hartford, Kumarian Press; 1997.

3 *Plan Supplies. Managing Tuberculosis at National Level.* A Training Course. 4th ed. Participant Guide. Global Tuberculosis Programme. Geneva, World Health Organization, 1996. WHO/TB/96.203.

resources and structure of the programme, include: training of staff in the use of FDCs, and the interrelationships of procurement, distribution, rational use and quality assurance for ensuring that FDCs are available when the patient needs them.

3.1 Product selection

Selection is the process of establishing a limited list of essential anti-TB drugs to be procured based on the most current acceptable clinical treatment guidelines while defining specifications (see Box 3 and section 3.2.4) and deciding which drugs will be available at different levels of TB facilities. In many national TB control programmes it is difficult to carry out TB drug selection activities independently and managers depend on the information researched and established by WHO with respect to FDCs and drug dosing. In these cases the standard treatment regimens will be the same as those discussed under DOTS strategy above, that is, the treatment regimens recommended by WHO and IUATLD.

Even where there are adequate human resources and experienced personnel to develop national standard treatment guidelines for TB, it is still recommended to use FDCs following the WHO guidelines.

Box 3: Specifications for each drug should include

- Drug description, generic name or INN
- A local trade name, if any
- Dosage form e.g. tablet, ampoule for injection
- Strength, e.g. rifampicin 150 mg + isoniazid 75 mg
- Package presentations, quantity of basic units

Once FDC treatment regimens have been selected, the TB programme should preferably use drug formulations which are included in the national essential medicines list and are registered. In case the relevant FDCs are not on this list, or are not registered, the NTP should enter into dialogue with the drug regulatory authority and request FDCs to be put on the list and registered. The advantage of using the essential medicines concept is to enable a health system to limit other more expensive or poor quality drugs from being purchased at local treatment levels in decentralized systems.

3.2 Procurement

Procurement is the process of acquiring anti-TB drugs through purchase or donation. The process includes quantifying drug needs, selecting methods for purchasing, selecting reliable suppliers, managing tenders, assuring quality, and ensuring compliance with contract terms. The procurement of FDCs, like other

drugs, also includes multiple activities. The activities take place over an extended period of time, often taking a year or more to complete a full procurement cycle in some countries. But even when the procurement cycle takes more than a year, there is a simple mechanism for assuring a constant supply of TB drugs – overlapping procurement cycles. Enough drugs for a year plus buffer stocks are procured, and then the next procurement cycle begins before the drugs arrive.

Box 4: NTP manager activities

- Accurate calculation of quantities needed
- Gain familiarity with other procurement activities

The NTP manager's contribution to procurement (Box 4) usually involves the first step of the process, estimating and calculating the quantities of each drug needed. For the other procurement activities (Box 6 – end of next section), the NTP can greatly support drug management by offering feedback to drug supply managers. For example, providing details of previous experience with FDCs and anti-TB products about a particular supplier's products to the procurement department will facilitate the tendering process when the procurement department begins to pre-qualify anti-TB drug suppliers. Other procurement activities are discussed later in this guide, but first, the estimation of FDC drug needs will be discussed.

3.2.1 *Quantification of drug needs*

The national TB programme manager must be sure that drugs and other supplies are correctly quantified before implementing the use of FDCs, so that every TB patient can begin treatment without delay and complete treatment without interruption. If the budget does not cover the cost of all drugs to be procured, the quantities of drugs must be decreased according to number of cases, since all drugs must be present when needed by the patient. Nevertheless, a NTP manager must find and secure the financial resources needed to buy enough drugs to guarantee an uninterrupted supply and to prevent stock-outs at all levels of TB care.

Box 5: Recommended approach to estimate drugs

- Expected number of cases to be treated as indicated by:
  - Previous diagnosis and notification of cases
  - Expected increase in case detection (according to the DOTS expansion plan)
- Drug requirements sufficient for complete treatment of patients in each category based on recommended standard chemotherapy regimens

There are two primary methods for quantifying TB drug needs (Box 5). Only the method based on *notification* data is discussed in this guide. The other method, based on drug use information, can also be used for calculating drug needs at national or central level, but this is not the method of choice. Consumption-based quantification is described in Annex 5.

Estimating the quantity of FDCs needed will obviously depend on the approved drug treatment regimens for each category of TB patient. The new 4-drug FDC is the most suitable formulation for the two-month intensive phase of treatment. Some countries now using 2-drug and 3-drug FDC tablets might want to switch over to 4-drug FDCs. For the continuation phase, the 2-drug FDC containing isoniazid and rifampicin is commonly used (see section 2.2).

Before estimating drug requirements, the length of time between placing an order and receiving the medicines at all levels must be known; this is commonly called *lead* time. If this is 6 months or less, the procurement plan should cover the drug needs for one year as well as the necessary reserve, or buffer, stock. However, if the lead time is likely to be more than 6 months, a procurement order of more than one year's supply should be prepared.

In countries with good management information systems, estimates of drug requirements should be based on the *number of notified cases* treated with the recommended standard chemotherapy regimens. In countries *without* a good management system, the information on expected TB case detection should be used to make the estimate.

The following example describes how to estimate drug needs when a country has recent case notification data:

1. Determine the amount of tablets or grams of each drug the programme needs to treat *one patient* in each treatment regimen for categories I, II and III (see Table 3 for categories).
2. Estimate the total amount of tablets or grams of each drug the programme needs to treat *all TB patients* during one year.
3. Specify the quantity of reserve/buffer stock needed at each level of the system.

Note:

- The coefficient/number should be assessed based on the: country's data, including notification data; expected increase in case detection; new cases of severe forms of extrapulmonary TB; number of re-treatment cases; percentage of child cases in Category III; body weight band.
- In the examples, figures are rounded up to the next nearest digit.
- In the examples, the body weight band is 38-54 kg. The quantities of drugs will need to be adjusted for other weight bands. Quantities of drugs for children in Category III are also provided as an example.
- Smear$^{(+)}$ = smear-positive; smear$^{(-)}$ = smear-negative.

Example: Category I regimen
Category I regimen is prescribed to new smear$^{(+)}$ patients; new smear$^{(-)}$ PTB patients with extensive parenchymal involvement; patients with severe concomitant HIV disease or severe forms of extrapulmonary TB.

In this example:

- the number of new smear$^{(+)}$ PTB (body weight band 38-54 kg) cases notified in the previous year was 7725.
- new smear$^{(-)}$ PTB cases - the expected increase in case detection according to the DOTS expansion plan – could be 30%, though this percentage increase will vary depending on TB prevalence and diagnostic practices. 7 725 x 0.30 = 2 318
- new cases of severe forms of extrapulmonary TB is 20% of new smear $^{(+)}$ cases. 7 725 x 0.20 = 1 545

Therefore total Category I cases to treat 7 725 + 2 318 + 1 545 = 11 588

Example: Category II regimen
The category II treatment regimen is prescribed to previously treated patients who are classified as relapses, failures, returning defaulters or re-treatment after premature interruption. In many instances, the number of re-treatment cases is equivalent to 10-40% of the new smear$^{(+)}$ cases.

In this example, 25% of the estimated number of new smear$^{(+)}$ cases is used. 7 725 x 0.25 = 1 932

Example: Category III regimen
The category III regimen is prescribed in cases of new smear $^{(-)}$ PTB (other than in Category I) and new less severe forms of extrapulmonary TB. In this example, the estimate is based on 15% of new smear $^{(+)}$ cases for adults and 8% for children.

7 725 x 0.15 = 1 159 (adults)
7 725 x 0.08 = 618 (children)

Therefore total Category III cases to treat. 1 159 + 618 = 1 777

Therefore total number of patients to treat for all three categories for one year. 11 588 + 1 932 + 1 777 = 15 297

Based on numbers calculated as in the example above, the quantities of each drug needed can be worked out in two steps:

1) determine the number of tablets of each drug needed to treat one patient for each TB category, then

2) multiply the number of tablets of each drug to treat one patient by the number of cases in each TB category. For example:

Note: All calculations below are based on 28 doses per month for a daily regimen and 12 doses per month for a 3 times per week regimen as follows:

For a daily regimen (one month = 28 doses)	**For a 3 times per week regimen** (one month = 12 doses)
2 months = 56 doses 3 months = 84 doses 5 months = 140 doses 6 months = 168 doses	4 months = 48 doses 5 months = 60 doses

*Example: Quantities needed for Cat. I **adult** patients (body weight band 38-54 kg): 2RHZE/4RH or 2RHZE/4(RH)$_3$:*

INTENSIVE PHASE:	DOSE	ONE CASE		ADULT CASES		TABLETS FOR ALL CASES
FDC tablet containing: R150 mg/H75 mg/Z400 mg/E275 mg	3 tablets daily for 56 doses	= 168	x	11 588	=	1 946 784

CONTINUATION PHASE (IF DAILY):	DOSE	ONE CASE		ADULT CASES		TABLETS FOR ALL CASES
FDC tablet containing: R150 mg/H75 mg	3 tablets daily for 112 doses	= 336	x	11 588	=	3 893 568
OR						
CONTINUATION PHASE (IF INTERMITTENT):	DOSE	ONE CASE		ADULT CASES		TABLETS FOR ALL CASES
FDC tablet containing: R150 mg/H150 mg	3 tablets at once, 3 times weekly for 48 doses	= 144	x	11 588	=	1 668 672

Note: in the example given below for Category II, the [RH] FDC is used for the continuation phase of treatment. WHO does not recommend use of rifampicin (R) as a single-drug tablet.

*Example: Quantities needed for Cat. II **adult** patients (body weight band 38-54 kg): 2SRHZE/1HRZE/5RHE or 2SRHZE/1HRZE/5(RH)$_3$E$_3$:*

INTENSIVE PHASE:	DOSE	ONE CASE		ADULT CASES		TABLETS FOR ALL CASES
FDC tablet containing: R150 mg/H75 mg/Z400 mg/E275 mg	3 tablets daily for 84 doses	= 252	x	1 932	=	486 864
Streptomycin vials: S750 mg	1 vial daily for 56 doses	= 56	x	1 932	=	108 192
Water for injection vials: use with streptomycin	1 vial daily for 56 doses	= 56	x	1 932	=	108 192

CONTINUATION PHASE (IF DAILY):	DOSE	ONE CASE		ADULT CASES		TABLETS FOR ALL CASES
FDC tablet containing: R150 mg/H75 mg	3 tablets daily for 140 doses	= 420	x	1 932	=	811 440
Ethambutol tablet containing: E400 mg	3 tablets daily for 140 doses	= 420	x	1 932	=	811 440
OR						
CONTINUATION PHASE (IF INTERMITTENT):	DOSE	ONE CASE		ADULT CASES		TABLETS FOR ALL CASES
FDC tablet containing: R150 mg/H150 mg	3 tablets at once, 3 times weekly for 60 doses	= 180	x	1 932	=	347 760
Ethambutol tablet containing: E400 mg	3 tablets at once, 3 times weekly for 60 doses	= 180	x	1 932	=	347 760

*Example: Quantities needed for Cat. III **adult** patients (body weight band 38-54 kg): 2RHZE/4RH or 2RHZE/4(RH)$_3$:*

INTENSIVE PHASE:	DOSE	ONE CASE		ADULT CASES		TABLETS FOR ALL CASES
FDC tablet containing: R150 mg/H75 mg/Z400 mg/E275 mg	3 tablets daily for 56 doses	= 168	x	1 159	=	194 712

CONTINUATION PHASE (IF DAILY):	DOSE	ONE CASE		ADULT CASES		TABLETS FOR ALL CASES
FDC tablet containing: R150 mg/H75 mg	3 tablets daily for 112 doses	= 336	x	1 159	=	389 424
OR						
CONTINUATION PHASE (IF INTERMITTENT):	DOSE	ONE CASE		ADULT CASES		TABLETS FOR ALL CASES
FDC tablet containing: R150 mg/H150 mg	3 tablets at once, 3 times weekly for 48 doses	= 144	x	1 159	=	166 896

*Example: Quantities needed for **children** (body weight band 15-19 kg): 2RHZ/4RH or 2RHZ/4(RH)$_3$:*

INTENSIVE PHASE:	DOSE	ONE CASE		ADULT CASES		TABLETS FOR ALL CASES
FDC tablet containing: R60 mg/H30 mg/Z150 mg	3 tablets daily for 56 doses	= 168	x	618	=	103 824

CONTINUATION PHASE (IF DAILY):	DOSE	ONE CASE		ADULT CASES		TABLETS FOR ALL CASES
FDC tablet containing: R60 mg/H30 mg	3 tablets daily for 112 doses	= 336	x	618	=	207 648
OR						
CONTINUATION PHASE (IF INTERMITTENT):	DOSE	ONE CASE		ADULT CASES		TABLETS FOR ALL CASES
FDC tablet containing: R60 mg/H60 mg	3 tablets at once, 3 times weekly for 48 doses	= 144	x	618	=	88 992

Based on the above examples, Tables 6 and 7 show the drug requirements for the estimated total number of adult patients (body weight band 38-54 kg) and children (body weight band 15-19 kg) to be treated during the year.

Table 6: Summary of total drug needs based on the calculations above if the daily regimen is used for the continuation phase

Drug	Category I 2RHZE/ 4RH	Category II 2SRHZE 1RHZE/ 5RHE	Category III 2RHZE/ 4RH	Total quantity needed (T_Q)
R150 mg/H75 mg/Z400 mg/E275 mg (FDC)	1 946 784	486 864	194 717	2 628 360
R150 mg/H75 mg/Z400 mg (FDC)				
R150 mg/H150 mg/Z500 mg (FDC)*§				
R60 mg/H30 mg/Z150 mg (FDC)			103 824	103 824
R150 mg/ H150 mg (FDC)*				
R150 mg/ H75 mg (FDC)	3 893 568	811 440	389 424	5 094 432
R60 mg/ H30 mg (FDC)			207 648	207 648
R60 mg/ H60 mg (FDC)*				
E400 mg (FDC)		811 440		811 440
S750 mg (vial)		108 192		108 192
Syringes (3ml or 5ml)		108 192		108 192
Water for injection (vial)		108 192		108 192

* These formulations are for intermittent use.

§ To be used in cases where ethambutol is omitted for patients with non-cavitary, smear-negative pulmonary TB who are known to be HIV-negative, patients who are known to be infected with fully drug-susceptible bacilli.
Note: Loose tablets of rifampicin, isoniazid, ethambutol and pyrazinamide, which can be used in cases of side-effects, i.e. in 3-6% of new cases, may also need to be ordered and quantified for reference centres.

Table 7: Summary of total drug needs based on the calculations above if the intermittent (3 times per week) regimen is used for the continuation phase

Drug	Category I 2RHZE/ $4(RH)_3$	Category II 2SRHZE 1RHZE/ $5(RH)_3E_3$	Category III 2RHZE/ $4(RH)_3$	Total quantity needed (T_Q)
R150 mg/H75 mg/Z400 mg/E275 mg (FDC)	1 946 784	486 864	194 712	2 628 360
R150 mg/H75 mg/Z400 mg (FDC)				
R150 mg/H150 mg/Z500 mg (FDC)§				
R60 mg/H30 mg/Z150 mg (FDC)			103 824	103 824
R150 mg/ H150 mg (FDC)	1 668 672	347 760	166 896	2 183 328
R150 mg/ H75 mg (FDC)*				
R60 mg/ H30 mg (FDC)*				
R60 mg/ H60 mg (FDC)			88 992	88 992
E400 mg (FDC)		347 760		347 760
S750 mg (vial)		108 192		108 192
Syringes (3ml or 5ml)		108 192		108 192
Water for injection (vial)		108 192		108 192

§ To be used in cases where ethambutol is omitted for patients with non-cavitary, smear-negative pulmonary TB who are known to be HIV-negative, patients who are known to be infected with fully drug-susceptible bacilli.

* These formulations are for daily use.

Reserve or safety stock should be included in the quantification of drug requirements. To do this for the national programme, double the yearly total quantity (i.e. $2xT_Q$) in the above example. This will cover unexpected increases in TB cases, procurement lead time, delays in shipment and distribution, and drug loss due to damage, pilferage and poor quality. If quantifying for a district or health centre, then enough reserve stock should be added equal to the time it takes to replace stock (e.g. 1-3 months). Note that the full reserve stock needs to be procured only once; subsequent orders should take into account the expected remaining reserve stock at the date the new order becomes available.

Once quantification has been completed, the procurement plan should be prepared in collaboration with other stakeholders and partners, such as the essential medicines programme and DRA. It is important to consider the competitive prices of drugs and to compare NTP drug prices with those available internationally. This will allow the NTP to determine if their existing procurement practice is cost-effective. One of the sources of anti-TB drugs at very competitive prices is the new initiative of Stop TB, the Global TB Drug Facility (GDF).

Although the procurement processes are not the direct responsibility of the NTP manager (they are the direct responsibility of the procurement and QA managers), he/she should understand the entire process in order to be able to follow up on bottlenecks in supply of TB drugs. Preferably officially laid down procedures should be established with regular updates by the procurement manager and other stakeholders in the process.

The main activities of procurement managers are listed in Box 6. Procurement managers must have the skills to ensure that good quality TB drugs are procured and are available when the patient needs them in the treatment centre. FDCs and other TB drugs require special attention with respect to selection and monitoring of suppliers and QA of the products.

Box 6: Procurement manager activities

- Procure preferably FDCs of WHO-recommended forms and strengths
- Make sure drugs are registered in the exporting and importing countries
- Prequalify suppliers for quality and reliability
- Request tender bids only from prequalified suppliers
- Specify packaging requirements to suppliers before signing contract
- Monitor performance of FDC suppliers throughout the period of the contract
- Ensure that received FDCs are tested for quality

To be sure that the FDCs are effective and safe for patients, fixed-dose combination anti-TB drugs should be registered by the DRA before they are released for use in the country. This involves preparing a dossier of the required drug certificates from reputable sources, and laboratory testing by the regulatory authority (for more discussion, see section 4).

Another activity of the procurement manager is to specify, in the supplier's contract, the exact criteria for packaging of the FDCs, depending on the needs of the TB control programme. For example, FDCs might be required in blister packs, with all the doses of 4-drug FDCs required for a full day's or week's therapy packaged in the same blister, according to the patient's weight band. Blisters help health workers to identify the drugs easily and, when empty, can provide information of dispensing and drug-taking.

3.2.2 Procurement methods and selection of suppliers

Many procurement methods are used by governments and NGOs, including open tender, restricted tender, competitive negotiation, and direct procurement. National TB programmes may use one or a combination of these methods to procure anti-TB drugs. For more information on different procurement methods and selection and location of suppliers, please refer to *Managing Drug Supply*[4]. The overall goal is to identify good quality anti-TB drugs at competitive prices from quality assured suppliers. NTPs should strive to be self-sufficient in procuring drugs for their programmes. However, in countries without available resources and experience, it may be advantageous to obtain anti-TB drugs, including FDCs, through global initiatives such as the GDF.

The GDF is an initiative of the Global Partnership to Stop TB. The GDF provides a mechanism for expanding access to high-quality TB drugs to facilitate global DOTS expansion. The advantages of using the GDF include:

- competitive prices;
- procurement is done by others;
- timely deliveries are made to country port of entry;
- ongoing development of packaging, e.g. blisters, to promote patient compliance;
- appropriate linkage exists with the DOTS expansion programmes of WHO Member States and Stop TB partners for the benefit of drug use within the country;
- quality of products is controlled.

The GDF has a grants-in-kind mechanism to fill the gap in TB resources of DOTS countries, and in 2002, the GDF established a direct procurement mechanism. To use this direct procurement mechanism, countries must meet specific criteria that permit the sale of drugs only to those organizations and countries that follow DOTS guidelines and are committed to only using TB drugs procured through the GDF in DOTS patients. To continue purchasing from the GDF, countries must submit routine annual DOTS programme performance reports to WHO[5].

3.2.3 Procurement and quality assurance

Quality assurance is an important part of the drug procurement process, and national TB programme managers should ascertain the quality of anti-TB drugs being purchased. A comprehensive QA programme includes both technical and

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[4] Quick JD, Rankin JR, Laing RO, O'Connor RW, Hogerzeil HV, Dukes MNG, Garnett A. (editors) *Managing Drug Supply*, 2nd ed. West Hartford, Kumarian Press; 1997.

[5] See the Stop TB website for more information: http://www.stoptb.org/GDF/drugsupply/Direct_procurement_process.html.

managerial activities and ensures, among other things, that:

- Drugs are properly selected based on quality, safety and efficacy, are in the correct dosage form, and have the longest possible shelf-life.
- Suppliers selected have acceptable qualifications and quality standard products.
- Drugs received meet the specified quality requirements.

Proper pre-qualification and post-tender monitoring help to eliminate substandard suppliers. Pre-qualification[6] is the procedure of evaluating supplier capacity and reputation before bids are solicited for specific drug products. Post-tender monitoring evaluates the suppliers, after the bids have been received, for reliability in delivery of goods (e.g. lead time), product quality, and services including response to enquiries and provision of documents.

More detailed discussion on the quality of anti-TB drug products can be found in section 4.

3.2.4 Minimum product specifications, packaging and labelling requirements to be specified in the contract

In the contract document[7], or when placing an order, a NTP manager or his/her responsible staff should clearly state the product specifications as per the packaging and labelling requirements detailed below.

Product specifications:

- The International Nonproprietary Name(s) (INN) (or generic name) of the active ingredient(s);
- The designated name of the product if applicable;
- The pharmacopoeial standard that applies to each active ingredient;
- Requirements as to bio-availability/bio-equivalence for rifampicin-containing FDCs (see section 4.2);
- The strength of the active ingredient(s) per dosage unit (e.g. for the 4-drug FDCs, it is advised that the WHO-recommended dosage strength be used, i.e. R150 mg/H75 mg/Z400 mg/E275 mg per tablet);
- The dosage form and package details;
- The storage conditions and precautions, where applicable;
- The shelf-life.

6 Information on standard procedures for pre-qualification of suppliers and their products available at: http://www.who.int/medicines/organization/qsm/activities/pilotproc/ppdoc2.doc

7 An example of a bid document: *Standard Bidding Documents. Procurement of Goods.* Washington, The World Bank, 1995. Revised March 2002. Available at URL: http://www.worldbank.org/html/opr/biddocs/contents.html

Packaging and labelling requirements:

- The language to be used for all packaging and labelling;
- The name of the product;
- A description of its pharmaceutical form, strength and method of application;
- The pack size expressed in terms of the number, weight, or volume of the product per pack or container;
- Special storage conditions if goods are to be shipped in special containers, to ensure stability of the products;
- Preferred packaging, e.g. blister-packs, loose tablets, patient kit.

Labelling specifications:

- The INN or generic name;
- The designated name of the product, if applicable;
- The dosage form, e.g. tablet, ampoule, vial;
- The strength of the active ingredient(s) per dosage unit;
- The applicable pharmacopoeial standard;
- The content per pack;
- Instructions for use;
- The batch number;
- Special storage requirements;
- The date of manufacture and expiry date (in clear language, not code);
- The full name and address of the manufacturer.

3.3 Distribution and storage

Distribution is the process by which procured anti-TB drugs are received at the port of entry, cleared through customs, and transported from the central warehouse(s) to depots and health facilities where they are stored and dispensed to patients. In this process, attention is given to drug orders from the time they arrive in the country until they are distributed to TB treatment facilities. The process begins with rapid clearance through customs to avoid deterioration of the drugs while sitting in the port of entry or in inappropriate storage conditions.

Before the drugs can be distributed from the receiving warehouse, they must be inspected for quantity and quality. At least a visual inspection of random samples of each shipment should be done to check the labelling (language, dosage strengths, dosage form, and acceptable shelf-life or expiry date), quantities received, and condition of the drugs against the required specifications of the contract. Random samples should undergo laboratory testing, as should all suspect products e.g. those that appear damaged or are inappropriately labelled; this should include an identification test to determine the content of the active ingredient, and a dissolution test (see section 4.3).

Once the drug shipment has passed quality inspections and testing, the drugs can then be stored under normal storage conditions and distributed to local warehouses and TB treatment facilities. In order to provide TB drugs and supplies on time,

there needs to be a steady flow of information from health facilities concerning their current stocks of drugs and orders for additional drugs based on the notified (or estimated) number of TB cases. A transportation schedule needs to be established for timely delivery of orders, both for normal and emergency needs.

Accepted inventory control procedures must be used at all levels of the programme to avoid stock-outs and provide reliable data for estimating drug needs at the next procurement. See Box 7 for examples of good stock procedures. Supply managers may use a minimum (S_{min}) and maximum (S_{max}) stock level

Box 7: Good stock management

- Record the receipt and distribution of all shipments of FDCs and drugs to TB depots and health facilities
- Record the receipt and dispensing of all FDCs and drugs to inpatients and outpatients on a regular basis
- Store drugs in an appropriate way (no direct sunlight, dry environment, access security, easy to find)
- Rotate stocks, putting shortest expiry date in the front, to avoid loss due to expiry and possible dispensing of a deteriorated drug to a patient - the first-expired first-out (FEFO) and then the first-in first-out (FIFO) principles should apply
- Review the stock level for an item every time an issue is made. If the stock level is at, or has fallen below the set minimum, order enough stock to bring the level up to the maximum (see Box 8 for how to calculate stock levels)
- Maintain adequate buffer or reserve stocks at all levels of TB care facilities

formula to know when to place an order and the quantity (Q_o). This is based on the following parameters:

- C_A: Average monthly consumption, adjusted for stock-outs;
- C_T: Total consumption during review period, in basic units e.g. tablets;
- D_{OS}: Number of days an item was out of stock during the review period;
- R_M: Review period in months (number of months of data reviewed for forecasting);
- L_T: Supplier lead time in months;
- P_P: Procurement period (months) - time until the next order will be placed;
- S_S: Buffer (reserve or safety stock);
- S_1: Stock on hand in inventory; and
- S_o: Stock on order but not yet arrived.

Box 8: Maximum and minimum stock level formula and quantity to order

- $C_A = C_T \div [R_M - (D_{OS} \div 30.4)]$
- $S_{min} = (L_T \times C_A) + S_S$
- $S_{max} = S_{min} + (P_P \times C_A)$
- Quantity to order $(Q_o) = S_{max} - (S_o + S_1)$

3.4 Rational use of anti-TB medicines

Rational drug use is the process of correct diagnosis followed by correct prescribing of, labelling of, dispensing of, and ensuring that the patient adheres to, recommended treatment regimens. Anti-TB drug use by prescribers and patients is described in section 2. An important area of drug use is that of prescribing and dispensing the right drugs to the patient, and good prescribing and dispensing practices should not be overlooked. Fixed-dose combinations promote good practices and can contribute to fewer prescribing and dispensing errors because there are fewer tablets to handle at one time.

Some TB control programmes have instituted the use of patient kits, where all drugs for the intensive phase are placed in a box labelled with the patient's name. This assures the availability of drugs for that patient during this important phase of treatment. Fixed-dose combinations facilitate the preparation of patient kits. However, the use of patient kits does not replace DOT. Prescriber and patient compliance to drug regimens is a key factor in treatment success, and NTP managers must be sure that drug use practices are in accordance with the adopted standard treatment guidelines. Selected key indicators (e.g. percentage of new smear-positive patients with pulmonary TB who were prescribed correct drugs in correct dosages with correct duration, based on the standard treatment guidelines) should be developed and included in the TB programme monitoring system.

3.5 Drug problem reporting system

At central level, any FDC drug problem such as theft, recall by the supplier, poor quality, and adverse drug reactions in patients, should be recorded and reported to all involved parties. If such a system does not exist, the NTP manager may want to consider establishing one. It would involve developing problem-reporting forms, indicating to whom they should be sent, and what action should be taken (see also section 4).

3.6 Monitoring and evaluation

To be sure that the right quantities of FDCs and other anti-TB drugs are available when needed, the TB control programme can monitor drug management performance against planned activities by tracking routinely reported indicators. Suggested indicators are:

- Average percentage of time that each FDC drug is out of stock at different levels of Ministry of Health (MOH) health facilities;
- Average percentage of time that each unexpired FDC drug is available at different levels of MOH health facilities;
- Average time (days) required to clear anti-TB drugs from the port of entry;
- Number of anti-TB FDCs that fail quality control testing out of the total number of anti-TB drugs tested.

There are guidelines for developing appropriate indicators which could be adapted for TB programmes[8]. Currently the Stop TB partnership is facilitating the development and field testing of TB drug management indicators, such as the ones mentioned above. These should be formalized by the end of 2002, and will have input from many NTP and MOH drug managers.

3.7 Summary checklist for good anti-TB drug management

NTP managers are directly involved in a number of TB drug management components, e.g. selection and quantification of FDCs and other TB drugs. Although other aspects of drug management, such as procurement, distribution and monitoring, may not be the direct responsibility of the NTP manager, the manager can be the key player in promoting good drug management practices within the TB control programme. See Table 8 for a checklist of activities.

[8] *Indicators for Monitoring National Drug Policies*, 2nd ed. Geneva, World Health Organization, 1999. (WHO/EDM/PAR/99.3).

Table 8: NTP drug manager's checklist

Phase	Activity	Determination
Product planning	Selection of products	• DOTS strategy and existence of standard treatment protocols
	Estimation and quantification of TB drug requirements	• Notification of cases • Availability of locally produced TB drugs
Product procurement	Selection and location of suppliers	• Open and transparent communication with industry • Issue of Request for Expression of Interest to industry • Pre-qualified suppliers • Implementation of review mechanisms
	Assurance of quality of products and sources	• Criteria for manufacturer pre-qualification • Implementation of pre-qualification system • Use of WHO Certification Scheme, inspections and quality testing of samples • Pre-shipment physical inspection with random sampling for laboratory testing • Systems for records and supply monitoring
	Arrangements for purchasing	• Ongoing assessment of purchasing options, including national/regional purchasing • Need for special labelling and packing • Need for reserve/buffer stocks • Management of purchasing arrangements
Distribution, rational use and monitoring	Receipt in country	• Port clearance including availability of funds for payment of duties and taxes • Securing appropriate warehousing at all levels needed • Physical inspection on arrival of each consignment with random sampling for laboratory testing
	In-country distribution	• Logistics system for timely distribution to end users
	Rational use and monitoring	• Providers adequately trained • Systems for monitoring and reporting

4 ENSURING THE QUALITY OF FDC DRUGS

Treatment of TB with poor quality drugs will not only result in treatment failures but can lead to the development of drug resistance. This will have a deleterious effect on the health of the wider population. Ensuring the quality, safety and efficacy of all anti-TB drugs, including FDCs, used in a NTP, is therefore of utmost importance in combating the disease.

Safety, efficacy and quality are built into a product at the time of its design and production. This means that quality, safety and efficacy of FDC drugs are determined by the manufacturing process i.e. by compliance of the manufacturer with the requirements of good manufacturing practices (GMP) and pharmacopoeial specifications. However, a FDC product which has been produced in full compliance with GMP requirements and has passed all laboratory tests, may lose its quality and eventually become ineffective if the packaging, storage and transportation conditions are substandard. Consequently, in order to ensure that FDC products are safe, effective and of good quality, national TB programmes must establish a QA system addressing the following issues:

- Production of FDC products in accordance with GMP requirements;
- Storage, transport and distribution of FDC products under appropriate conditions (i.e. conditions stated by the manufacturer and appearing on the labels of the products).

4.1 Building a quality assurance system for the national TB programme

Generally, the complexity of the QA system to be developed and implemented will depend on whether a DRA exists and functions, and whether drug registration and inspection activities are operational and reliable or not.

4.1.1 *Quality assurance where there is an operational drug regulatory authority*

Where there is an operational DRA, the NTP has to follow the directives of the DRA and work closely with it. The programme has to procure and use only those FDC drugs approved by the DRA. In addition, the NTP has to:

- *Request the supplier to submit a copy of the marketing authorization* (certificate of registration) issued by the DRA to ensure that the product has been officially registered for use in the exporting country.
- *Check with DRA if product is registered in your own country.*
- *Request the supplier to submit a WHO-type batch certificate* (see Annex 3) issued by the manufacturer of the product. A WHO-type Batch Certificate

differs from the normal certificate of analysis in that it also provides information on: 1) the specification of the product at the time of batch release and the results of full analysis on the batch in question; 2) whether the product has been registered in the country of manufacturer; 3) the product licence number (registration number); 4) the name and address of the product licence holder etc.

- *Make a physical inspection on arrival of the shipment* - to verify adherence to contract specifications and spot any gross deficiencies. Also, random samples may be taken from each batch for laboratory testing to confirm the quality of the batch.

- *Conduct quality surveillance during distribution* - quality surveillance should be carried out once the FDC drugs are in the distribution chain. This involves ensuring that personnel involved are qualified, that storage facilities and transport conditions are appropriate, and that drugs have not expired. If necessary, samples should be taken and tested to confirm that product quality has been maintained.

- *Establish a product defects reporting system* - a product defects reporting system should be developed for prescribers/health workers, dispensers, store managers, etc., to report suspected or confirmed quality defects. There should be established written procedures and forms for reporting defective FDC drugs. All reports must be carefully reviewed using laboratory testing as required, and the appropriate action taken, including product recalls. The national drug regulatory authority should be informed about the situation.

- *Create a recall receiving system* - there should be a system to recall defective FDC products from health facilities and distribution outlets promptly. There should be written procedures. Distribution records should be kept complete and up to date to permit an effective recall. Recalls should be initiated promptly. All health facilities and distribution outlets to which FDC drugs have been distributed should be informed promptly of any intention to recall. Recalled products should be kept in a separate place. The quantities recalled should be reconciled with the quantities distributed and a report prepared for submission to the DRA.

4.1.2 *Quality assurance where there is no national drug regulatory authority or no operational drug registration system*

Where there is no DRA, or there is a DRA but no operational drug registration system, the responsibility to ensure that the FDC products used are manufactured in accordance with GMP requirements and that the products are safe, efficacious and of good quality, will be that of the national TB programme. To do this, the NTP has to create a QA system of its own. This will consist of recruiting a qualified pharmacist to be responsible for QA of procured drugs and for requesting from the supplier a WHO-

type certificate issued in accordance with the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, which provides licensure status of the product and inspection status of the manufacturer (see section 4.4). Two types of certificate are to be requested within the scheme[9]:

- A Certificate of a Pharmaceutical Product (product certificate) issued by the DRA in the exporting country. This certificate contains the name and dosage form of the product, the INN and amount of active ingredient(s) per unit dose, name and address of product holder and/or manufacturing facility, the product formula (complete composition including all excipients), and product information for health professionals and for the public as approved in the exporting country.
- A Batch Certificate of a Pharmaceutical Product to confirm that individual batches conform to quality and other specifications (normally issued by the manufacturer). This document is a vital instrument in drug procurement and usually a mandatory element of the tender document.

In addition to requesting the information above, the NTP QA officer should:

- Carry out physical inspections – post-shipment inspections - every time consignments arrive, to verify that the goods meet the specifications (i.e. compare the supplier's invoice with the original purchase order/contract).
- Conduct quality surveillance during distribution, e.g. make sure the drugs are appropriately stored.
- Establish a defects reporting system.
- Create a product recall system.

Where creating a QA system is not applicable, the NTP should procure anti-TB medicines from pre-qualified sources that guarantee quality, safety and efficacy of the products and comply with GMP. Wherever possible, the NTP and its qualified pharmacist should conduct a site inspection to ensure that the manufacturer complies with current GMP requirements. The WHO guidelines on GMP can be applied.

4.2 Bio-availability and bio-equivalence (interchangeability) data

A fixed-dose combination preparation that has met quality standards has also to conform to safety and efficacy standards to make sure it has the desired therapeutic effect when administered to a patient. A FDC preparation that has met quality requirements can sometimes fail to be bio-available when administered. The physical characteristics of the active ingredient, the composition of the dosage form and the manufacturing process used can affect the rate and extent of

9 Further information: *Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products. A Manual for a Drug Regulatory Authority.* Geneva, World Health Organization, 1998 (Regulatory Support Series, No.5, WHO/DMP/RGS/98.5). Also available at URL: http://www.who.int/medicines/library/qsm/manual-on-marketing/multisource-contents.html

absorption and resulting blood levels of the active ingredient. In order to ensure that such a problem does not arise, a bio-availability/bio-equivalence study needs to be conducted by the manufacturer as part of the product design process.

The problem of bio-availability is more apparent if a FDC drug that is usually purchased from one manufacturer is replaced with the same drug, in the same dosage form and in the same amount, from a different manufacturer. Even though the two products may contain the correct amount of active ingredients, the new preparation may not give the expected therapeutic result. In such a situation, a comparative bio-availability study is particularly important. Two pharmaceutical products are bio-equivalent if they are pharmaceutically equivalent and their bio-availability, after administration in the same dose, is similar to such a degree that their effects can be expected to be essentially the same.

In order to confirm that the FDC products being used by the TB programme can produce the expected therapeutic result, the suppliers should be requested to submit bio-availability/bio-equivalence data (refer to WHO guidelines on bio-equivalence studies)[10]. These data are crucial in the procurement process for rifampicin-containing FDCs. The NTP manager or procurement officer should request the following from the supplier(s):

- Bio-availability/bio-equivalence study details, including study design, procedures, calculation methods, results and assessment for all components of rifampicin-containing FDCs.
- Dissolution profile of the same batch used for bio-availability/bio-equivalence study of all components (rifampicin, isoniazid, pyrazinamide, ethambutol).
- Dissolution data for the specific batches shipped (requested with each delivery of FDCs).

4.3 Laboratory testing

A well-functioning government drug control laboratory forms an important regulatory element of any QA system because it carries out the tests and assays required to establish whether drugs conform to the specifications claimed. In countries where such a laboratory exists, the NTP manager or his/her staff should take the lead in sending drug samples for quality testing. Samples of FDCs should be tested using accepted/adopted pharmacopoeial methods and techniques. Pharmacopoeial procedures usually involve:

- testing for uniformity of dosage units in terms of weight for tablets and volume for ampoules/vials;

[10] Further information: *Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products. A Manual for a Drug Regulatory Authority.* Geneva, World Health Organization, 1998 (Regulatory Support Series, No.5, WHO/DMP/RGS/98.5). Also available at URL: http://www.who.int/medicines/library/qsm/manual-on-marketing/multisource-contents.html

- identification of active pharmaceutical ingredients (API) (for 4-drug FDCs: rifampicin, isoniazid, pyrazinamide, ethambutol);
- a dissolution test;
- assay for the content of each active ingredient.

The United States Pharmacopeia and National Formulary (USP 25/NF 20) has recently released test methods and procedures for the 4-drug FDC preparations containing rifampicin, isoniazid, pyrazinamide and ethambutol.

After each analytical testing, the laboratory issues a certificate of analysis indicating the quality of the FDC tested based on the test results. The certificate should state clearly whether or not the FDC sample tested is in compliance with the required specifications.

4.4 The WHO Certification Scheme

The WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce has been in operation since 1975. This Scheme was developed by WHO to assist developing countries that have no national drug regulatory authorities, or where the DRAs are weak and cannot ensure the quality, safety and efficacy of imported drugs, to get some assurance from the DRAs of the exporting countries. The Scheme is not intended to replace national drug authorities of importing countries in their roles and responsibilities. Although WHO developed the Scheme, it does not issue certificates or provide assurance about the reliability of the DRAs which issue the certificates. The reliability of the information provided by the issuing authorities depends on their honesty and competence. Therefore, DRAs of importing countries, as well as programmes such as NTPs, have to make sure that the DRAs issuing certificates function well and are reliable. It should be understood that some countries which issue certificates have not officially accepted, in writing, to participate in the Scheme. The list of participating countries is published by WHO and is available on the WHO website at: http://www.who.int/medicines/organization/qsm/activities/drugregul/certification/certifsch-aplha.html. However, this list does not mean that those authorities appearing in the WHO publication or on the website have been certified by WHO. WHO has no such mandate. Despite these limitations, the Scheme has value if properly implemented, and exporters should always be requested to provide these certificates.

4.5 Facilitating the drug registration process

TB is one of the major health problems in many countries. In order to treat the disease, countries must ensure that FDC and other anti-TB drugs are of proven safety, efficacy and quality, and are available and affordable. In many countries, the time taken to assess and ensure the safety, efficacy and quality of drugs is unnecessarily long, thus affecting the timely availability of these badly needed

drugs. While ensuring safety, efficacy and quality of the drugs is critical, timely availability of the drugs is equally important from a public health perspective. Therefore, drug regulatory authorities must design mechanisms to facilitate timely availability of drugs, whilst not compromising the safety and quality of the drugs. A fast-track system is needed. Where possible and appropriate, DRAs should follow existing registration practices.

5 HOW TO INTRODUCE AND CHANGE OVER TO A REGIMEN WITH 4-DRUG FDCS/2-DRUG FDCS: PLANNING AND IMPLEMENTING A "SCENARIO"

5.1 The challenge

Once the decision to implement and change over to a treatment regimen with 4-drug FDCs is taken, several challenges have to be faced and a process of careful planning has to begin.

Firstly, it is essential that the change-over is flawless, i.e. without interruption in supply and treatment, so as not to endanger the health of patients due to long lead times for delivery of anti-TB drugs. The actual change-over cannot start unless the new drugs are in the country - due to the high cost of the medicines, no programme could afford to buy parallel stocks for the old and new FDC regimens in case the change-over was not successful. This implies that, once the process has started, there is practically no way back. The moment of ordering the new FDCs is the point of no return.

Even a pilot study in one district or dispensary does not have a grace period, since if the study proves a success, it is unthinkable to revert temporarily back to old dosage forms and regimens at the end of the study until the full order of new drugs arrives for the whole programme.

On the other hand, this does not mean that one should not start with one or two areas in order to gain experience, and to adjust the plans as necessary for full implementation throughout the programme.

Therefore it might be best to start in areas where the circumstances are most favourable (see Activity 13 in section 5.3.3). Also, one could start in two places, such as at a dispensary in a large city and another in a rural area.

To make the operation a success, it is essential to win the confidence and full cooperation of health staff at all levels of the programme. Also the support and cooperation of stakeholders outside the programme will have to be assured for the operation to be a success.

The second challenge in changing over to FDCs is to plan and execute two separate processes (see Section 5.4):

1) the process of preparing and introducing the new regimens within the programme, including logistics planning; and
2) the process of ordering and receiving the new drugs. These two processes are linked by bridge activities.

A third challenge is how to handle the stocks of old drugs whilst causing minimum waste of resources (further discussion in Activities 7 and 23 in section 5.3).

These three challenges form quite a unique situation in operational planning and thus proper preparation is essential.

Finally, it is good to bear in mind that the change-over to 4-drug FDC/2-drug FDC dosage forms can also be used as leverage to implement full DOTS coverage throughout the programme.

5.2 Planning

Careful planning (Box 9) and a well thought out scenario for the change-over is essential.

Box 9: The four main phases in the changeover process

- Decision-making
- Preparation phase
- Initial implementation
- Full implementation

One way to achieve this is through the use of a logical framework. Several computer programmes exist for setting up a logical framework. A project planning programme could also be used (but it should be remembered that learning to operate new computer programmes can take time and effort).

A simpler solution could be to use a spreadsheet, which in most cases will suffice.

On the inside back cover page, a sample of a planning process using a spreadsheet is given. The two main processes are called *Programme management* and *Drug management*, and the essential steps or activities of each are shown. Bridge activities, where the two processes are linked together and where the progress of one is dependent on the outcome of the other, are shown in bold.

Additional activities should be added according to local circumstances.

In the planning process it is essential to indicate, for every activity and sub-activity, the deadline and measurable criteria which determine if the activity has been completed successfully, and, above all, the name of the person responsible for each activity.

The process is divided into four main phases:

- Decision-making
- Preparation phase
- Initial implementation
- Full implementation

These phases will be discussed below in more detail.

5.3 The process

5.3.1 Decision-making phase

Before the decision can be taken, a number of activities have to be performed, and certain information has to be available. This information is crucial to making a well-founded decision, and to explaining to all parties concerned, both within and outside the programme, e.g. staff responsible for financing and planning, why it is desirable to make the change.

Programme management:

Activity 1 Find out what the cost per patient will be compared to the present cost.

Activity 2 Especially consider the use of 4-drug FDCs for the intensive phase of treatment and base calculations on loose tablets or blisters depending on which package you intend to use in the NTP. You may want to consider the opinion of staff at the dispensaries as well.

Activity 3 Reconsider the shape, colour embossment etc. for the tablets. When the drugs are purchased specially for the programme, this is possible and manufacturers may be willing to oblige, as long as they are informed of what is expected in good time. Also, the opinion of the staff handling the drugs could be sought in good time.

Activity 4 Calculate the value of the next drug order, and also what the change-over itself is going to cost.

Drug management:

Activity 1 Make an inventory of all the different dosage forms presently in use in the programme and whole country, including the private sector. Also, it is important to know which TB-drugs are actually registered for use by the DRA.

Once the FDCs have been selected, verify with the DRA their requirements for registration and whether exemptions and/or fast track registration is possible. Generally, it remains advisable to adhere as much as possible to normal registration policies so as not to create problems for the future.

Bridge activity 5

With the information from both ***programme management*** and ***drug management***, take a well-founded decision to switch over to 4-drug FDCs/2-drug FDCs.

5.3.2 Preparation

Preparation begins once the decision to switch over to a new regimen has been taken.

Programme management:

Activity 6 Arrange for the new NTP manuals on FDCs and reporting forms to be printed. Before the manuals are printed (this being a long process), provide a circular containing details of the new regimens and FDCs to all NTP staff. If possible, check and adjust, if necessary, the drug stock distribution and monitoring system, and verify if the current text in the manual is still valid.

Activity 7 Introducing the new dosage forms will mean that some old stocks will have to be recalled or re-distributed to specialized hospitals where the drugs can be used. A recall plan has to be made and additional storage space reserved. In general, it is easiest to recall all redundant drugs to one point, preferably the central stores, and to redistribute from there. At this stage, an estimate will have to be made of how many drugs are concerned and what can best be done with them. In some cases, NTP managers may negotiate with the supply companies to collect the old redundant stocks and replace them with FDCs, with or without extra charges. The outputs of activity 6 (the new NTP manual, the circular, the recall plan, data on old stock) will have to be verified with the central medical stores and other government bodies involved. [Note: In the transitional period it is better to be left with some additional stocks of single drug tablets than to run out of single drugs before the FDCs arrive].

Activity 8 Secure funds and print the new, adjusted manuals.

Activity 9 As soon as the manuals are ready, or when preliminary circulars have been issued, all stakeholders (including, in some cases, the private sector) can now be informed of the upcoming changes. Training and seminars for NTP staff, to introduce them to the new regimens and changes in the drug monitoring and distribution system, if any, can now be planned and can start once the necessary funds have been secured.

Activity 10 Determine the first possible arrival date of the new FDCs, and the actual starting date when the first patients will receive the new regimens. This can be calculated based on the expected stock-out date of present stocks, and the lead time for procurement of the new FDCs.

Activity 11 Calculate the amount of loose single medicines that need to be kept in referral centres for the treatment of patients with severe adverse drug reactions. These patients should be treated in specialist units only.

Drug management:

Activity 2 Hold an audit to determine the present stock of all TB drugs at all levels in the programme, the exact number of patients on register, and the size of the required buffer stocks.

Activity 3 Calculate the size and value of the first order of FDCs.

Activity 4 Re-examine the quality standards in use and/or set for FDCs. Special attention should be paid to bio-availability tests for the rifampicin in FDCs, and to the quality and source of the rifampicin raw material.

Activity 5 Set specifications for labelling and packing, according to the outcome of activity 3 of programme management.

Activity 6 Determine the procurement method according to the value of the order (usually LCB from pre-qualified suppliers), and secure the necessary funds.

The preparation phase now culminates in two scenarios, one for the programme management process and one for the drug management process:

Bridge activity 12
Programme management (set calendar and write change-over scenario which includes date of drug arrival, staff preparation seminars, starting date for DOTS with new FDCs).

Bridge activity 7
Drug management (set procurement calendar including dates for floating tender, tender opening, availability of funds, contract date, production duration, QA and shipment, delivery and payment).

Each of these scenarios can be summarized on a planning calendar.

5.3.3 Initial implementation

Programme management:

Activity 13 Determine the criteria which need to be fulfilled by an administrative unit before the introduction of the FDCs can be allowed, e.g. whether staff are trained, record keeping is reliable, the register is up to date. These criteria apply to each district that is going to start using new FDC regimens. It is important to train health workers in use of FDCs and the new dosages.

Activity 14 Set standards by which it can later be objectively determined if the introduction of the new regimen has been successful, i.e.:

- patient adherence
- patient acceptance
- health worker acceptance
- side-effects
- smear conversion after 2 months
- above all, set the date for completion and evaluation of the introduction period, i.e. 8 weeks after the start of the introduction of the FDCs. The whole exercise should show improvement in patient treatment outcomes.

Activity 15 Select site(s) for initial implementation. It is very important for the success of the total operation that the initial site is selected so as to offer the most favourable conditions to become a success itself.

Activity 16 Hold seminars to elicit the full support of all staff, once the initial sites have been chosen.

Drug management:

Activity 8 Start systematic monitoring of the procurement process.

Activities 9-11 Describe the main procurement steps, assuming that the programme manager only needs to monitor progress and is not actually doing the procurement (refer to section 3).

Bridge activity 17 - *Programme management;*
Bridge activity 12 - *Drug management*
Accept the FDCs on arrival in the country and subsequently release them to the initial site(s).

Programme management:

Activity 18 Begin the new regimens. Attention has already been paid to how the actual introduction will be done for all patients, old and new, and whether the FDCs will be implemented all at once, or gradually, for newly diagnosed patients only. This was decided during the decision-making process and introduction seminars.

Recall the remaining stocks of the old dosage forms as soon as possible once adequate stocks of the new drugs have arrived, according to the rules formulated under activity 7. This will also serve to emphasize to health staff in the pilot area that only the new FDCs are to be used from now on.

Activities 19 and 20 Monitor progress in order to discover what improvements can be made before introducing FDCs to the rest of the country.

Drug management:
The only steps which now remain are to pay the bills and to follow up eventual insurance or quality claims.

5.3.4 Full implementation

Activity 21 Before the change-over can be applied to other areas of the programme as previously planned, the results of the pilot introduction(s) should be used to adjust, as necessary, the scenario, selection of new areas, introduction calendar, and even the manual and drug ordering and distribution system.

Activities 22 – 28 These activities, in rolling out the new FDCs to the rest of the country according to the previously set and adjusted scenario and plans, are actually a repetition of what has been done in the pilot phase. From a programme management point of view this will be relatively easy, since the main job has been done and all conditions to make the change-over a success are already in place.

Annex 1 GLOSSARY AND USE OF TERMS

The terms listed below are defined specifically for the purposes of this manual. They may be defined differently in other documents, including annexes in this guide which were, in certain cases, published some years ago.

Active pharmaceutical ingredient (API): A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a therapeutically active compound (ingredient).

Batch (or lot): A defined quantity of a starting material, packaging material, or product processed in a single process or series of processes so that it can be expected to be homogeneous.

Batch certificate: A document containing information, as set out in Annex 3 of these guidelines, which will normally be issued for each batch by the manufacturer, or exceptionally will be validated or issued by the competent authority of the exporting country, particularly for vaccines, sera and other biological products. The batch certificate accompanies every major consignment.

Batch number: A distinctive combination of numbers and/or letters which specifically identifies a batch on the labels, the batch records, and the certificates of analysis, etc.

Bio-availability: The rate and extent of availability of an active drug ingredient from a dosage form as determined by its concentration/time curve in the systematic circulation or by its excretion in urine.

Bio-equivalence: Two pharmaceutical products are bio-equivalent if they are pharmaceutically equivalent and their bio-availabilities (rate and extent of availability), after administration in the same molar dose, are similar to such a degree that their effects can be expected to be essentially the same.

*Buffer stock (*sometimes called *safety* or *reserve stock*): The stock that is kept on hand to protect against stock-outs caused by delayed deliveries or markedly increased demand. In theory, the safety stock is separate from the working stock, but in practice, there is no separation of the two.

Case of TB: A patient in whom TB has been bacteriologically confirmed, or has been diagnosed by a clinician. NB: any person given treatment for TB should be recorded.

Chronic (TB) case: A patient who is sputum positive at the end of a re-treatment regimen.

Container labelling: All information that appears on any part of a container, including that on any outer packaging, such as a carton.

Defaulter: A patient whose treatment was interrupted for 2 consecutive months or more.

Disintegration: The breaking up of a tablet or capsule into granules or aggregates in an aqueous fluid or solution.

Dissolution: The breaking down of fine particles into molecules or ions homogeneously dispersed in an aqueous fluid.

Dosage form: The form of the completed pharmaceutical product, e.g. tablet, capsule, injection, elixir, suppository.

Drug: Any substance or pharmaceutical product for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

Drug product: see pharmaceutical product.

Drug regulatory authority: A national body that administers the full spectrum of drug regulatory activities, including at least all of the following functions: marketing authorization of new products and variation of existing products; quality controlled laboratory testing; adverse drug reaction monitoring; provision of drug information and promotion of rational drug use; good manufacturing practice (GMP) inspections and licensing of manufacturers, wholesalers and distribution channels; enforcement of operations; monitoring of drug utilization.

Extrapulmonary TB case: A patient with TB of organs other than the lungs e.g. pleura, lymph nodes, abdomen, genito-urinary tract, skin, joints and bones, meninges. Diagnosis should be based on one culture-positive specimen, or histological or strong clinical evidence consistent with active extrapulmonary disease, followed by a decision by a clinician to treat with a full course of anti-TB chemotherapy. NB: a patient diagnosed with both pulmonary and extrapulmonary TB should be classified as a case of pulmonary TB.

Expiry (expiration) date: The expiry date placed on the container of a drug product established by the manufacturer designating the date up to which the product is expected to remain within specification, if stored correctly. It is established for every batch by adding the shelf-life period to the manufacturing date.

Failure (TB) case: Patient who, while on treatment, is sputum smear-positive at 5 months or later during the course of treatment.

Finished product: A product that has undergone all stages of production, including packaging in its final container and labelling.

Formulation: The composition of a dosage form, including the characteristics of its raw materials and the operations required to process it.

Generic products: The term *generic product* has somewhat different meanings in different jurisdictions. Use of this term is therefore avoided as much as possible, and the term *multisource pharmaceutical product* (see below) is used instead. Generic products may be marketed either under the approved nonproprietary name or under a brand (proprietary) name. They may be marketed in dosage forms and/or strengths different from those of the innovator products. Where the term *generic product* is used, it means a pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after expiry of the patent or other exclusivity rights. The term should not be confused with generic names for APIs.

GMP (good manufacturing practices): Performance standards for pharmaceutical manufacturers established by WHO and many national governments. They include criteria for personnel, facilities, equipment, materials, manufacturing operations, labelling, packaging, quality control, and in most cases, stability testing.

Interchangeability: An interchangeable pharmaceutical product is one that is therapeutically equivalent to a comparator (reference) product.

Labelling: See *container labelling* and *product information*.

Licence: see marketing authorization.

Lead time: The time interval needed to complete the procurement cycle. It begins at the time when new stock is ordered and ends when that stock is received and available for use. Lead time varies depending on the system, speed of deliveries, availability and reliability of transport, and sometimes, weather.

Logical framework: A logical framework approach is useful for planning in groups and is characterized by specific methods and tools; the requirement for a multidisciplinary team; use of visual tools; and specific steps, e.g. identification of the planning group, identification of stakeholders, problem analysis, objectives analysis, strategy analysis, project elements and monitoring, and follow-up.

Manufacture (manufacturing): All operations including purchase of materials and products, production, quality control, release, storage, shipment of finished products, and related controls.

Marketing authorization: An official document issued by a competent drug regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It must set out, *inter alia*, the name of the product, the pharmaceutical dosage form, the quantitative formula

(including excipients) per unit dose (using INN or national generic names where they exist), the shelf-life and storage conditions, and packaging characteristics. It specifies the information on which authorization is based (e.g. "The product(s) must conform with all the details provided in your application and as modified in subsequent correspondence"). It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization, and the period of validity of the authorization. Once a product has been given marketing authorization, it is included on a list of authorized products - the *register* - and is often said to be "registered" or to "have registration". Marketing authorization may occasionally also be referred to as a licence or product licence.

Multisource (generic) pharmaceutical product: Multisource pharmaceutical products are pharmaceutically equivalent products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

New (TB) case: Patient who has never had treatment for TB, or who has taken anti-TB drugs for less than one month.

Normal storage conditions: Storage in dry, well-ventilated premises at temperatures of 15-25 ˚C or, depending on climatic conditions, up to 30 ˚C. Extraneous odours, other indications of contamination, and intense light have to be excluded.

Pharmaceutical equivalence: Products are pharmaceutical equivalents if they contain the same amount of the same active ingredient(s) in the same dosage form; if they meet the same or comparable standards; and if they are intended to be administered by the same route. They may not be therapeutic equivalents due to differences in their excipients and/or manufacturing process.

Pharmaceutical product: Any medicine intended for human use or administered to food-producing animals, presented in its finished dosage form or as an active ingredient for use in such dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

Product certificate: A document, containing the information as set out in Annex 2 of these guidelines, that is validated and issued for a specific product by the competent authority of the exporting country and intended for use by the competent authority in the importing country or – in the absence of such an authority – by the drug procurement authority.

Product information: The product information normally consists of information for health professionals and the public (patient information leaflets), as approved in the exporting country and, when available, a data sheet or a summary of product characteristics approved by the regulatory authority.

Product licence: An official document issued by the competent drug regulatory authority for the purpose of the marketing or free distribution of a product. It must set out, *inter alia*, the name of the product, dosage form, the quantitative formula (including excipients) per unit dose (using INN or national generic names, where they exist), the shelf-life and storage conditions, and packaging characteristics. It also contains all the information approved for health professionals and the public (except promotional information), the sales category, the name and address of the licence holder, and the period of validity of the licence.

Provisional marketing authorization: Temporary authorization following the initial market inventory, pending full approval based on evaluation of quality, safety and efficacy.

Provisional registration: see provisional marketing authorization.

Quality assurance: A wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the objective of ensuring that pharmaceutical products are of the quality required for their intended use.

Quality control: Concerned with sampling, specifications and testing, and with the organization, documentation and acceptance/rejection procedures which ensure that the necessary and relevant tests are actually carried out and that starting materials, intermediates and finished products are not accepted for use, sale or supply until their quality has been judged to be satisfactory.

Reference product: A reference product is a pharmaceutical product with which the new product is intended to be interchangeable in clinical practice. The reference product will normally be the innovator product for which efficacy, safety and quality have been established. Where the innovator product is not available, the product which is the market leader may be used as a reference product, provided that it has been authorized for marketing and its efficacy, safety and quality have been established and documented.

Register: A list of all the pharmaceutical products authorized for marketing in a particular country. The register is maintained by the drug regulatory authority of the country in question.

Registered drug products: Pharmaceutical products that have a marketing authorization.

Registration: Any statutory system of approval required at national level as a precondition for introducing a pharmaceutical product on to the market. See also: *marketing authorization.* The terms *provisional registration* or *provisional marketing authorization* are preferred, but some countries do not have a separate category of provisional marketing authorization.

Relapse (TB) case: A patient previously declared cured but with a new episode of bacteriologically positive (sputum smear or culture) TB.

Retreatment (TB) case: A patient previously treated for TB whose treatment failed, who defaulted (treatment interrupted) or who relapsed.

Shelf-life: The period of time during which a drug product is expected, if stored correctly, to remain within specification as determined by stability studies on a number of batches of the product. The shelf-life is used to establish the expiry date of each batch.

Smear-negative pulmonary (TB) case: Pulmonary TB which does not meet the criteria for smear-positive disease. Diagnostic criteria should include: at least 3 sputum smear examinations negative for acid-fast baccilli (AFB); and radiographic abnormalities consistent with active pulmonary TB; and no response to a course of broad-spectrum antibiotics; and decision for a full course of anti-tuberculosis therapy; or positive culture but negative AFB sputum examinations.

Smear-positive pulmonary (TB) case: At least 2 initial sputum smear examinations (direct smear microscopy) AFB+; or one sputum examination AFB+ and radiographic abnormalities consistent with active pulmonary TB as determined by the treating medical officer; or one sputum specimen AFB+ and culture positive for *M. tuberculosis*.

Starting material: Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

Therapeutic equivalence: Two pharmaceutical products are therapeutically equivalent if they are pharmaceutically equivalent and, after administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same, as determined from appropriate bio-equivalence, pharmacodynamic, clinical or in vitro studies.

WHO-type certificate: A certificate of a pharmaceutical product of the type defined in the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (see Annexes 2 and 3).

Annex 2

WHO CERTIFICATION SCHEME - MODEL CERTIFICATE OF A PHARMACEUTICAL PRODUCT[1]

This certificate conforms to the format recommended by the World Health Organization. (general instructions and explanatory notes attached)

No. of Certificate: .....

Exporting (certifying) country: .....

Importing (requesting) country: .....

1. Name and dosage form of product:
.....
.....
.....

1.1 Active ingredient(s)[2] and amount(s) per unit dose[3]
.....
.....
.....
.....
.....

For complete composition including excipients see attached[4].

1.2 Is this product licensed to be placed on the market for use in the exporting country?[5]
yes/no *(key in as appropriate)*

1.3 Is this product actually on the market in the exporting country?
yes/no/unknown (*key in as appropriate)*

If the answer to 1.2 is yes, continue with section 2A and omit section 2B;
If the answer to 1.2 is no, omit section 2A and continue with section 2B.[6]

2A.1 Number of product licence[7] and date of issue:

2A.2 Product-licence holder (name and address):

2A.3 Status of product licence holder[8] :
a/ b/ c/ *(key in appropriate category as defined in note 8)*

2A.3.1 For categories (b) and (c) the name and address of the manufacturer producing the dosage form is:[9]

2A.4 Is summary basis of approval appended?[10]
yes/no (*key in as appropriate*)

2A.5 Is the attached, officially approved product information complete and consonant with the licence? [11]
yes/no/not provided *(key in as appropriate)*

2A.6 Applicant for certificate, if different from licence holder (name and address)[12]:

2B.1 Applicant for certificate (name and address): .....
.....
.....

2B.2 Status of applicant:
a/b/c/ *(key in appropriate category as defined in footnote 8)*

2B.2.1 For categories (b) and (c) the name and address of the manufacturer producing the dosage form is:[9] .....
.....

2B.3 Why is marketing authorization lacking?
not required/not requested/under consideration/refused
(key in as appropriate)

2B.4 Remarks[13] .....
.....

3. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced?
yes/no/not applicable[14] *(key in as appropriate)*

If no, or not applicable proceed to question 4

3.1 Periodicity of routine inspections (years): .....

3.2 Has the manufacture of this type of dosage form been inspected?
yes/no *(key in as appropriate)*

3.3. Do the facilities and operations conform to GMP as recommended by the World Health Organization?[15]
yes/no/not applicable[14] *(key in as appropriate)*

4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product[16].
yes/no *(key in as appropriate)*

If no, explain: .....
.....
.....

Address of certifying authority: .....
.....

Telephone no: ..... Fax no: .....

Name of authorized person: .....

Signature: .....

Stamp and date: .....

General instructions for Annex 2

Please refer to the guidelines for full instructions on how to complete this form and information on the implementation of the Scheme.

The forms are suitable for generation by computer. They should always be submitted as hard copy, with responses printed in type rather than hand-written.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes for Annex 2

1 This certificate, which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the certificate in the exporting country. It is for a single product only since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.
2 Use, whenever possible, International Nonproprietary Names (INN) or national non-proprietary names.
3 The formula (complete composition) of the dosage form should be given on the certificate or be appended.
4 Details of quantitative composition are preferred but their provision is subject to the agreement of the product-licence holder.
5 When applicable, append details of any restriction applied to the sale, distribution or administration of the product that is specified in the product licence.
6 Sections 2A and 2B are mutually exclusive.
7 Indicate, when applicable, if the licence is provisional or the product has not yet been approved.
8 Specify whether the person responsible for placing the product on the market:
  (a) manufactures the dosage form;
  (b) packages and/or labels a dosage form manufactured by an independent company; or
  (c) is involved in none of the above.
9 This information can only be provided with the consent of the product-licence holder or, in the case of non-registered products, the applicant. Non-completion of this section indicates that the party concerned has not agreed to inclusion of this information.

It should be noted that information concerning the site of production is part of the product licence.
If the production site is changed, the licence has to be updated or it is no longer valid.

10 This refers to the document, prepared by some national regulatory authorities, that summarizes the technical basis on which the product has been licensed.
11 This refers to product information approved by the competent national regulatory authority, such as summary product characteristics (SPC)
12 In this circumstance, permission for issuing the certificate is required from the product-licence holder. This permission has to be provided to the authority by the applicant.
13 Please indicate the reason the applicant has provided for not requesting registration:
  (a) the product has been developed exclusively for the treatment of

conditions — particularly tropical diseases — not endemic in the country of export;

(b) the product has been reformulated with a view to improving its stability under tropical conditions;

(c) the product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the country of import;

(d) the product has been reformulated to meet a different maximum dosage limit for an active ingredient;

(e) any other reason, please specify.

14 Not applicable means the manufacture is taking place in a country other than that issuing the product certificate and inspection is conducted under the aegis of the country of manufacture.

15 The requirements for good practices in the manufacture and quality control of drugs referred to in the certificate are those included in the thirty-second report of the *Expert Committee on Specifications for Pharmaceutical Preparations*, WHO Technical Report Series No. 823, 1992, Annex 1. Recommendations specifically applicable to biological products have been formulated by the *WHO Expert Committee on Biological Standardization* (WHO Technical Report Series, No. 822, 1992, Annex 1).

16 This section is to be completed when the product-licence holder or applicant conforms to status (b) or (c) as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and the extent and nature of any controls exercised over each of these parties.

The layout for this Model Certificate is available on the WHO/EDM website at: http://www.who.int/medicines/organization/qsm/activities/drugregul/certification/certifscheme.shtml

Annex 3

WHO Certification Scheme – Model Batch Certificate of a Pharmaceutical Product

Manufacturer's/Official[1] Batch Certificate of a Pharmaceutical Product
This certificate conforms to the format recommended by the World Health Organization *(general instructions and explanatory notes attached)*

1. No. of Certificate: . . . . . .

2. Importing (requesting) authority: . . . . . .
. . . . . .

3. Name of product: . . . . . .

3.1. Dosage form: . . . . . .

3.2 Active ingredient(s)[2] and amount(s) per unit dose: . . . . . .
. . . . . .
. . . . . .
. . . . . .
. . . . . .

3.2.1 Is the composition of the product identical to that registered in the country of export?
yes/no/not applicable[3] (*key in as appropriate*)

If no: please attach formula (including excipients) of both products.

4. Product-licence holder[4] (name and address): . . . . . .

4.1 Product-licence number[4]: . . . . . .
4.2 Date of issue[4]: . . . . . .
4.3 Product licence issued by[4]: . . . . . .
4.4 Product certificate number[4,5]: . . . . . .
5.1 Batch number: . . . . . .
5.2 Date of manufacture: . . . . . .
5.3 Shelf-life (years): . . . . . .
5.4 Contents of container: . . . . . .
5.5 Nature of primary container: . . . . . .
5.6 Nature of secondary container/wrapping: . . . . . .
5.7 Specific storage conditions: . . . . . .
5.8 Temperature range: . . . . . .
6 Remarks[6]: . . . . . .
7. Quality analysis: . . . . . .
7.1 What specifications apply to this dosage form. Either specify the pharmacopoeia or append company specifications.[7]

7.1.1 In the case of a product registered in the exporting country, have these company specifications[7] been accepted by the competent authority?
yes/no *(key in as appropriate)*

7.2 Does the batch comply with all parts of the above specifications?
yes/no *(key in as appropriate)*

7.3 Append certificate of analysis[8] . . . . . .

It is hereby certified that the above declarations are correct and that the results of the analyses and assays on which they are based will be provided on request to the competent authorities in both the importing and exporting countries.

Name and address of authorized person: . . . . . .

Telephone no: . . . . . .Fax no: . . . . . .

Signature of authorized person: . . . . . .

Stamp and date: . . . . . .

General instructions

Please refer to the guidelines for full instructions on how to complete this form and information on the implementation of the Scheme.

These forms are suitable for generation by computer. They should always be submitted as hard copy, with responses printed in type rather than hand-written.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes for Annex 3

Certification of individual batches of a pharmaceutical product is only undertaken exceptionally by the competent authority of the exporting country. Even then, it is rarely applied other than to vaccines, sera and biologicals. For other products, the responsibility for any requirement to provide batch certificates rests with the product-licence holder in the exporting country. The responsibility to forward certificates to the competent authority in the importing country is most conveniently assigned to the importing agent.

Any enquiries or complaints regarding a batch certificate should always be addressed to the competent authority in the exporting country. A copy should be sent to the product-licence holder.

1 Strike out whichever does not apply.
2 Use, whenever possible, International Nonproprietary Names (INN) or national non-proprietary names.
3 "Not applicable" means that the product is not registered in the country of export.
4 All items under 4 refer to the product licence or the Certificate of a Pharmaceutical Product issued in the exporting country.
5 This refers to the Certificate of a Pharmaceutical Product as recommended by the World Health Organization.
6 Indicate any special storage conditions recommended for the product as supplied.
7 For each of the parameters to be measured, specifications give the values that have been accepted for batch release at the time of product registration.
8 Identify and explain any discrepancies from specifications. Government batch release certificates issued by certain governmental authorities for specific biological products provide additional confirmation that a given batch has been released, without necessarily giving the results of testing. The latter are contained in the manufacturer's certificate of analysis.

The layout for this model certificate is available on the WHO/EDM website at: http://www.who.int/medicines/organization/qsm/activities/drugregul/certification/certifscheme.shtml

Example of an order form for anti-TB drugs for treatment facilities

Enter the number of cases enrolled in the previous three months (from quarterly report on case-finding).
Note: all calculations below are based on 28 doses per month for a daily regimen and 12 doses per month for a 3 times per week regimen using a standard body weight band of 37-54 kg body (dose = 3 tablets/day).
Note: Q = quantity

Item	Category I $2RHZE/4(RH)_3$			Category II $2SRHZE/1RHZE/5(RH)_3E_3$			Category III $2RHZE/4(RH)_3$			Total quarterly drug needs
	Cases	Factor**	Subtotal of tablets (Q_1)	Cases	Factor	Subtotal of tablets (Q_2)	Cases	Factor	Subtotal of tablets (Q_3)	$Q_4 = (Q_1 + Q_2 + Q_3)$
R150 mg/H75 mg/Z400 mg/E275 mg (FDC)		x 168 =			x 252 =					
R150 mg/H75 mg/Z400 mg (FDC)								x 168 =		
R60 mg/H30 mg/Z150 mg (FDC)								x 168 =		
R150 mg/ H150 mg (FDC)										
R150 mg/ H75 mg (FDC)*		x 336 =			x 420 =			x 336 =		
R60 mg/ H30 mg (FDC)*								x 336 =		
R60 mg/ H60 mg (FDC)										
E400 mg (FDC)*					x 420 =					
S750 mg (vials)					x 56 =					
Water for injection (vials)					x 56 =					

continued on page 72

Item	Quarterly drug needs (Q_4 from above table)	Reserve drugs Q_5 (=Q_4)	Drugs currently in stock Q_6	Total quantities to order $T_Q = (Q_4 + Q_5) - Q_6$
R150 mg/H75 mg/Z400 mg/E275 mg (FDC)				
R150 mg/H75 mg/Z400 mg (FDC)				
R60 mg/H30 mg/Z150 mg (FDC)				
R150 mg/ H150 mg (FDC)				
R150 mg/ H75 mg (FDC)*				
R60 mg/ H30 mg (FDC)*				
R60 mg/ H60 mg (FDC)				
E400 mg (FDC)*				
S750 mg (vials)				
Water for injection (vials)				
Syringes/Needles				

* These formulations are for daily use. If your programme is using daily treatment regimen for the continuous phase you must use the daily factors instead of the intermittent factors. Factor means the total number of tablets sufficient for a full course of treatment for one patient.

Note: Loose drug formulations of rifampicin, isoniazid, and pyrazinamide might be needed for management of side-effects.

Date: .....

Authorized Name and Signature: .....

Annex 5 Steps in the quantification of anti-TB drugs using consumption-based information

The consumption method uses data on drug consumption. The reliability of this method depends on a well-established and stable supply system with a relatively uninterrupted supply and full supply pipeline. Consumption data may or may not reflect rational prescribing and use of drugs. In this method, a list of anti-TB drugs is prepared using the most accurate inventory records of past consumption. Care should be taken that drug stock-outs and numbers of identified cases not treated are included in the consumption data. The following are the steps in quantifying anti-TB drugs using the consumption-based method:

1. Prepare a list of anti-TB drugs to be quantified.
2. Determine the period of time to be reviewed for consumption. If the procurement/order is to cover a 12-month period, consumption data for the past 12 months should be reviewed.
3. Enter consumption data for each drug, including total quantity used during the review period, number of days that each drug was out of stock in the review period, and the average lead time for the last several procurements.
4. Calculate the average monthly consumption which is the key variable in the quantification formula and should be as accurate as possible.
5. Calculate the safety/reserve/buffer stock needed for each drug.
6. Calculate the quantity of each drug required in the next purchasing period.
7. Adjust for expected changes in consumption pattern.
8. Adjust for losses.
9. Record the number of drugs currently in stock.
10. Record the number of drugs already on order but not yet received.
11. Compile decentralized quantifications i.e. at each facility or storage point.
12. Estimate costs for each drug and total costs.
13. Compare total costs with the budget and make adjustments.

Formula:

Average monthly consumption, adjusted for stock-outs (C_A) = $C_T \div [R_M - (D_{OS} \div 30.4)]$

Basic safety/reserve stock (B_S) = $C_A \times L_T$

Quantity to order (Q_O) = $C_A \times (L_T + P_P) + S_S - (S_1 + S_O)$

Where C_A = Average monthly consumption, adjusted for stock-outs.
C_T = Total consumption during review period, in basic units e.g. tablets.
D_{OS} = Number of days an item was out of stock during the review period.
L_T = Average lead time in months.
P_P = Procurement period (number of months to be covered by order).
Q_O = Quantity to order in basic units, before adjustment for losses or programme change.
R_M = Review period in months (number of months of data reviewed for forecasting).

S_O = Stock currently on order but not yet received, in basic units.
S_1 = Stock currently in inventory, in basic units.
S_S = Quantity needed for safety/reserve stock.
30.4 = Average number of days per month.

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Scenario for a change-over to a 4-drug FDC/2-drug FDC regimen

Phase		The 2 processes (programme management and drug management) to run concurrently until bridge activites have been finalized							
		Programme management				**Drug management**			
		Activity	**Sub-activity 1**	**Sub-activity 2**	**Sub-activity 3**		**Activity**	**Sub-activity 1**	**Sub-activity 2**
Decision-making	1	Consider use / introduction of 4-drug FDCs/2-drug FDCs	Calculate and compare costs per regimen per patient			1	Ascertain all dosage forms of drugs presently in use in NTP: regimens/loose/FDCs	Ascertain all dosage forms of drugs presently in use in the private sector	Verify with DRA which TB drugs are presently registered in the country
	2	Consider blister packs versus loose tablets	Consider feasibility in view of existing practices	Compare efficiency and cost of storage and distribution at all levels	Consult programme staff for suggestions, acceptability			Verify with DRA the existing registration requirements, enquire about fast track registration and exemptions	
	3	Set (new) regimens, INN and dosage forms of drugs (size, colour, shape, strength, embossment, loose / blisters) to be used in NTP	Decide how new regimens will be introduced, for all patients at once or gradually for new patients only	Consult programme staff for suggestions, acceptability					
	4	Estimate quantity and costs of next order including buffer stock	Estimate costs of introduction: seminars, printing forms and manuals	Inform and consult with government and external donors	Secure funds from government / external donors for drugs and introduction activities				
	Bridge Activity 5	**Take the decision to switch over to 4-drug FDCs/2-drug FDCs (or not)**							
Preparation	6	Re-examine/adjust present drug stocking, distribution and monitoring systems, including NTP drug ordering system	Consult/verify and confirm with CMS and other government bodies involved			2	Determine present stocks + no. of patients at all levels	Determine required size of buffer stocks at different levels	
	7	Make plan for recall of redundant drugs, possible re-distribution or disposal	Arrange extra storage space for recalled drugs	Consult/verify and confirm with CMS and other government bodies involved		3	Calculate size + value of first order of FDCs		
	8	Print (new) NTP manuals, ordering and distribution stationary	Secure funds for printing			4	Set quality assurance standards and verification methods. i.e.: special QA requirements for R; QA standards for raw materials		
	9	Inform all stakeholders of introduction of 4-drug FDCs/2-drug FDCs + new/revised systems for ordering, stocking, distribution and monitoring	Organize training and seminars for NTP staff at all levels on DOTS with 4-drug FDCs/2-drug FDCs + changes in drug monitoring and ordering system	Secure funds for training and seminars	Inform DRA of new dosage forms required from now on	5	Determine packing and labelling specifications		
	10	Calculate expected stock-out date at present consumption rate	Determine lead time for procurement process	Determine first possible arrival date of 4FDCs		6	Determine procurement method (ICB, LCB, direct purchase, donation)	Consult/verify and conform to CMS and other government bodies involved	Assure financing or donation for: goods, (overseas) transport, insurance, QA testing, clearing
	11	Calculate no. of loose drugs required for treatment of patients with side-effects							
	Bridge Activity 12	**Set calendar and write changeover scenario including dates of arrival of drugs, staff preparation seminars, starting date for DOTS with new FDCs**				Bridge Activity 7	**Set procurement calendar including dates for: floating tender, tender opening, availability of funds, contract, production, QA, shipment and delivery, and payments**		
Initial implementation	13	Set eligibility criteria for administrative unit to start using FDCs. For example:- adequate supervision, - a well trained staff, - a well functioning laboratory, - reliable record keeping, etc.				8	Start systematic monitoring of procurement process		
	14	Set date and standards to determine if introduction was successful: For example: - improved patient adherence, - reduced workload				9	Float tender/place order	Verify clearing/importation requirements, arrange timely exemptions	Consult / verify and conform to CMS and other government bodies involved
	15	Select pilot area(s). Consider possibility of using 2 pilot sites, one rural, one city. Note: Pilot area should comply with the starting criteria and be a good performer, near the central unit				10	Perform QA ex factory	Verify and conform to DRA requirements	Assess QA test costs and assure financing
	16	Hold introduction seminars				11	Check quantities, contents, packing on arrival	Determine discrepancies, inform manufacturer, insurance agent, verification bureau	Perform QA tests on arrival (when required)
	Bridge Activity 17	**Receive and store new drugs in pilot area(s)**				Bridge Activity 12	**Receive, stock new drugs at national stores and distribute to pilot areas**		
	18	Start treatment with 4-drug FDCs/2-drug FDCs	Recall old drugs except for small stock for side-effects			13	Pay invoices	Claim damages (if any)	
	19	Monitor data for success. Ask for and register reactions of staff and patients. For example: - cure rate; - treatment completed; - patient adherence; - patients' comments; - side effects							
	20	Make report of findings at end of introduction							
Full implementation	21	Adjust, scenario, calendar, manuals, seminar programmes, drug ordering and distribution system to findings from pilot areas				14	Distribute new drugs according to (adjusted) scenario and calendar		
	22	Inform and hold introduction seminars according to calendar				15	Receive and re-distribute old drugs according to scenario		
	23	Distribute and store new drugs in respective area							
	24	Recall old drugs except for small stock for side-effects							
	25	Start treatment with 4-drug FDCs/2-drug FDCs							
	26	Monitor data for success. Ask for and register reactions of staff and patients							
	27	Make report of findings at end of introduction per area							
	28	Make final report on introduction of FDCs for annual report, publication							

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