Republic of the Philippines
Department of Health 324-2
OFFICE OF THE SECRETARY
San Lazaro Compound, Rizal Avenue,
Sta. Cruz, Manila, Philippines
Tel. No. 711-95-02/711-95-03

July 30, 2003

DEPARTMENT CIRCULAR
No. 238 s., 2003

To: **All CHD Directors/NTP Coordinators and All other concerned.**

Subject: **Guidelines on the Use of *Fixed-Dose Combination (FDC)* Anti-TB Drugs under the National TB Program (NTP).**

In 1984, the National TB Program (NTP) has introduced the Shortcourse Chemotherapy (SCC) that highlighted the use of rifampicin as the potent drug for the treatment of tuberculosis. In 1987, when the TB Control Service was officially created, the Strengthened NTP has adopted the use of rifampicin nationwide. To ensure treatment compliance, the various anti-TB drugs were then contained in blister-packs that has become known as BP Type I (for the Intensive Phase) and BP Type II (for the Maintenance Phase). Up to present, with the D.O.T.S. strategy already in-place, the NTP still provides drugs that are singly prepared and come in blister packs.

Researches show that better compliance with anti-TB drugs, especially rifampicin, is achieved with the D.O.T.S. strategy, if patients take fewer tablets. Such tablets come in the form of *Fixed-Dose Combination (FDC)* drugs. Both the International Union against TB and Lung Diseases *(IUATLD)* and the World Health Organization *(WHO)* endorses the usage of FDCs in TB Programs since 1994. This is because of the simplification of treatment and the ease in management of drug supply accorded from these drug preparations. FDCs also prevent monotherapy or selective intake of drugs that create risk for multiple drug resistance or MDR.

The Philippines got an approved grant (1.5 million USD) from the Global Drug Facility (GDF) in the form of drugs, specifically, FDCs. With this huge provision, the NTP should initiate a shift from its current single drug formulation (SDF) to fix-dosed combination (FDC), considering its technical soundness and operational manageability. The shift is installed in two phases: 1) pilot period and 2) period of expansion.

In order to facilitate the implementation of FDCs by the field health workers, the guidelines hereby attached shall be adopted under the NTP. Both the Infectious Disease Office and the CHDs shall ensure the smooth transition from SDF to FDC until such time that nationwide coverage is achieved.

For information and guidance of all concerned.

MANUEL M. DAYRIT, MD, MSc
Secretary of Health

Signed DC
Received in the Records Section on 8-26-03

GUIDELINES ON THE USE OF FIXED DOSE COMBINATION ANTI-TB DRUGS IN THE ADVANCED IMPLEMENTATION SITES

National Tuberculosis Control Program
National Center for Disease Prevention and Control
Department of Health
Philippines
2003

1. Introduction

Why will the National TB Control Program (NTP) shift from single-drug formulation (SDF) Short Course Chemotherapy (SCC) to fixed dose combinations (FDCs)?

1. *It simplifies treatment of TB patients.* FDCs will enhance treatment compliance since the number of tablets that a TB patient will take will be reduced. For example, a patient under Regimen 1 with an average weight will only take three tablets of FDCs instead of six of single-drug formulation (1 Rifampicin, 2 PZA, 1 INH and 2 Ethambutol) currently being used in the Program. Also, it is easier to calculate the required dosage, hence, the risk of giving wrong dosage will be minimized.
2. *It simplifies management of drug supply.* This will facilitate the procurement and distribution process. Instead of ordering anti-TB drug preparation such as BP type I, BP type II and the loose preparation of INH, Ethambutol and PZA from various suppliers , the FDCs and others will be supplied by only one source. This also solves the chronic problem of mismatching of delivery of BP Type I and II.
3. *It prevents monotherapy or selective intake of anti-TB drugs.* This will help reduce the emergence of drug resistant TB.
4. *It reduces the risk of using Rifampicin for conditions other than TB.*

What is the situation that led to the shift to FDCs?

The Philippines is one of the twenty-two countries with high TB burden. In response to this problem, the Directly Observed Treatment Short Course (DOTS) strategy was initiated in 1996. Within six years more than 90% of the population have access to this strategy. One of the major concerns of NTP in the past years is the availability of effective anti-drugs in the health centers. Hence, there is always a constant search for approaches to improve management of drug supply.

In 2002, the Philippines requested and was granted free anti-TB drugs from the Global Drug Facility (GDF). The preparation are in FDCs and these are expected to arrive in March, 2003. These will be initially distributed and used in selected areas and its use expanded later. This development will require a major change from the single drug formulation of SCC that NTP had used since 1987 to FDCs. This change will require careful planning and systematic implementation to be successful. Hence, these guidelines are prepared to guide the implementors in the advanced implementation sites (AIS) in adopting this change.

How will the change from SDF to FDC be implemented nationwide?

The change will be implemented in phases. On the first year, one province or big city per region will use the FDCs. These areas will be selected by the Centers for Health Development (CHD) in consultation with the Infectious Disease Office – National Center for Disease Prevention and Control (IDO-NCDPC) and with the agreement of the concerned Provincial Health Office (PHO) or City Health Office (CHO). There areas will be known as advanced implementation sites (AIS). After a year, the use of FDC will be expanded to other provinces and cities. This staggered implementation will give adequate time to assess the initial experiences and address whatever constraints will arise.

2. Facts about FDCs

What are FDCs?

The fixed dose combination (FDCs) are anti-TB drug preparations whereby two or more first line anti-TB drugs are combined in one tablet. There are 2-, 3-, or 4-drug fixed dose combination.

Are FDCs being used in other countries?

YES. Many countries are already using it.. The World Health Organization (WHO) and the International Union Against Tuberculosis (IUATLD) had endorsed the use of FDCs by the NTP since 1994. The 4-drug and 2-drug combination are included in the WHO Model List of Essential drugs since 1999.

What is the composition of FDCs that will be used in AIS?

There will be two types of FDCs – the 4-drug and the 2-drug combinations. The composition is as follows;

Drug	*Initial*	*FDC A 4 –drug(RHZE)*	*FDC B 2 – drug(RH)*
Rifampicin	(R)	150 mg	150 mg
INH	(H)	75 mg	75 mg
PZA	(Z)	400 mg	
Ethambutol	(E)	275 mg	

Aside from FDCs, single preparation drug such as Ethambutol, Pyrazinamide and Streptomycin will be used.

What is the preparation and packaging of FDCs and other drugs?

The FDCs and the single preparation of Ethambutol and Pyrazinamide are film-coated tablets and packaged in blister packs. The packaging is as follows;

Item (Composition)	Preparation	No. of drugs Per BP	No. of BP / box	Total no. of drugs per box
FDC A (RHZE)	Blister packs (BP) in Boxes	28	24	672
FDC B (RH)	Blister packs in Boxes	28	24	672
Ethambutol, 400 mg	Blister packs in Boxes	28	24	672

Pyrazinamide, 400 mg	Blister packs in Boxes	28	24	672
Streptomycin, .75 g	vials			56 vials

This is how FDC A, FDC B, Ethambutol and Pyrazinamide packaging look;

(Insert scanned pictures here)

FDC A blister pack

FDC B lister pack

Ethambutol blister pack

Pyrazinamide blister pack

How much is the cost of treatment using FDC per TB patient?

The cost of FDC in treating one TB patient belonging to 38 – 54 kg group under Regimen 1 is almost equal to the cost of the SDF currently being used by NTP (about $11). With simplified procurement and distribution process, FDC will be more cost-effective than the SDF.

How is the quality of FDCs assured?

One of the issues of FDCs is the bioavailability of Rifampicin. To ensure that the FDCs meet the quality requirements, FDCs will be provided through the Global Drug Facility which supplies FDCs of WHO-recommended strengths and of proven quality.

What will be the dosage schedule of FDCs?

The treatment regimens remain the same - only the vehicle changed. The dosage will follow the guidelines of WHO and IUATLD for individual anti-TB drugs as contained in p. 26 of the Manual of Procedures (MOP). The number of tablets of FDC per patient will depend on the body weight. Hence, all patients must be weighed (using kilogram as a unit) before treatment is started.

Regimen 1: 2 RHZE / 4RH

Body weight (kg)	No. of tablets per day Intensive Phase (2 months) RHZE	No. of tablets per day Continuation Phase (4 months) RH
30 - 37	2	2
38 - 54	3	3
55 - 70	4	4
>/ 71	5	5

Regimen 2: 2 RHZES / RHZE / 5 RHE

Body weight (kg)	Intensive Phase			Continuation Phase	
	First two months		Third month	RH	E 400 mg
	RHZE	Streptomycin	RHZE		
30 - 37	2	.75 g	2	2	1
38 - 54	3	.75 g	3	3	2
55 - 70	4	.75 g	4	4	3
>/ 71	5	.75g	5	5	3

Regimen 3: 2 RHZ / 4 RH

Body weight (kg)	No. of tablets per day Intensive Phase (2 months)		No. of tablets per day Continuation Phase (4 months)
	RH	Z (400mg)	RH
30 - 37	2	2	2
38 - 54	3	3	3
55 - 70	4	4	4
>/ 71	5	5	5

3. Steps in introducing FDCs in the advanced implementation sites (AIS)

How are the AIS selected?

The main criteria used for the selection of an AIS province or city are; (1) area is implementing DOTS for at least two years, (2) PHO or CHO agrees to be included in the AIS, and (3) provincial or city TB coordinator is available.

A letter from PHO / CHO expressing their agreement to being an AIS area will be submitted to NCDPC.

Who will participate in this initiative?

All health facilities in the AIS providing anti-TB drugs under the NTP and using the DOTS strategy such as Rural Health Units (RHU), Barangay Health Stations (BHS), hospitals and private clinics involved in the public-private mix DOTS initiative must participate.

How will the FDCs be introduced at AIS?

There will be three phases of implementation:

Phase 1: Preparation of areas

1. Orientation of all staff providing anti-TB treatment such as those from the Rural Health Units (RHU), hospital, PPM clinics.
2. Ordering and distribution FDCs

Phase 2: Implementation of new treatment guidelines on FDCs:

Introduction of FDCs

Phase 3: Monitoring, supervision and evaluation

It is estimated that the initial introduction of FDC in AIS and its evaluation will last for one year. However, this might vary from area to area.

Phase 1: Preparation of areas

Activity 1. Orientation of staff

Who will be oriented?

The approach will be like what was done with the DOTS strategy – a cascading approach The regional and provincial TB coordinators-trainers will orient the doctors and nurses of the RHUs, hospitals and clinics. They will in turn orient the midwives. The BHWs and other treatment partners will be oriented by the midwife. These guidelines will be used in the orientation.

Who will fund the orientation?

The Department of Health, both the IDO- NCDPC and CHD, will be responsible for ensuring that funds are available for the orientation of the regional and provincial/city coordinators and physicians and nurses of RHUs, hospitals and clinics. The LGUs will be requested to fund the orientation of midwives and treatment partners. To reduce the cost, orientation maybe done during the regular meeting of midwives and BHWs.

Activity 2: Initial ordering and distribution of drugs

How will the FDCs be distributed?

The IDO will directly send the six month – requirement plus a buffer stock of six months (total of 12 months) to the CHD. This will include the FDCs and SDF. The CHD will transfer all these drugs to the PHOse and CHOs of the participating provinces and cities. The provincial / city TB coordinator will then distribute to the health facilities their three-month requirement plus three month buffer stock for the initial order. Filling-up of the Order Form will be part of the orientation.

Will FDCs be included in the Contract Distribution Scheme?

For the AIS, the FDC will not be included in the CDS. The CDS is not yet fully implemented and the system does not yet allow inclusion of FDCs.

What will happen to the current supply of SDF?

This will depend on the available stocks and expiration dates of the SDF. Hence, all implementing units must conduct an inventory of their anti-TB drugs. They must retain adequate quantity of SDF for TB patients undergoing treatment. The excess must be returned to the PHO / CHO with proper documentation. The provincial TB coordinator will record all these returned drugs. A reserve stock of SDF must be maintained at the PHO / CHO for patients who may need them due to adverse reactions to any of the drug component of FDCs. Allocate

SDF for at least 5% of the expected total TB cases in a year. The excess SDF drugs must be returned to the CHD. The latter will distribute this to non-AIS areas.

How much drugs will be ordered?

To simplify the process of ordering, the number of drugs to be ordered will be based on the weight category where most of the patients would fall (38-54 kg group). The quantity per patient will be as follows;

	RHZE	RH	Z	E	Streptomycin
	No. of BP		No. of BP		No. of vials
Regimen 1	6	12			
Regimen 2	9	15		10	56
Regimen 3		18	6		

Priority for Regimen 3 are the new cases. For the initial order, the implementing health facilities will compute for one quarter requirement plus a one month buffer stock. Subsequent order will be for only one quarter. Use the attached form for ordering.

What will be the counterpart of the LGUs re: drug supply?

The LGUs are expected to share in the procurement of single formulation drug such as INH, PZA, Ethambutol and Rifampicin.

Phase 2. **Implementation of new treatment guidelines on FDCs**

When will the shift from SDF to FDCs start?

Start giving the FDCs to newly registered TB patients once the following conditions are met;

1. All the RHU / hospital /clinic staff and treatment partners who are involved in the treatment of TB patients had been oriented.
2. Adequate quantity of FDCs are already in the RHUs.
3. Records and reports are in place.

What will happen to the patients under SDF?

TB patients who had been initiated with the SDF must continue using these preparation until they complete the required duration.

Will the intake of FDCs be supervised?

YES. The time of drug intake will be agreed upon by the patient and the treatment partner. It must be two hours after a regular meal. .

What if there are side effects to FDCs?

On p. 32 of the Manual of Procedures, Table 6 lists the side effects of the individual anti-TB drugs and the probable responsible drug. If there are major side effects, the responsible drug must be discontinued. In this situation, shift from FDC to SDF. Studies showed that this may happen to about 5% of total cases. Hence, RHUs must have at least supply of SDF for two - patients. The PHO will also have a reserve of SDF for this situation.

Would there be new records and reports?

There will be no change in the format or content of treatment records and reports. However, to facilitate monitoring and evaluation, records of TB patients under FDCs must be marked. For the treatment cards, put a red bar (/) using a red ball pen or pentel pen at the right upper corner. For the NTP registry, put a red asterisk opposite the first entry of the first patient under FDC and also write under comments the "**start of FDC**". The patient number must be continuous.

Phase 3. Monitoring, supervision and evaluation of implementation

What will be the process of monitoring and evaluation?

It is important that the entire process be regularly monitored and assessed. Supervision is also critical in ensuring that the guidelines are properly implemented. Lessons gathered during this advanced implementation will be useful during the expansion to other areas.

Regional and provincial/city coordinators must monitor the implementing health facilities monthly during the first three months of implementation and quarterly thereafter. Provincial or city quarterly assessment must also be organized by the regional and provincial / city coordinators. The results must be sent to IDO-NCDPC. The latter will convene semi-annual evaluation workshop of the FDC implementation at AIS.

The physician and nurse of the RHUs, clinics and hospitals will then supervise their subordinates.

What will be supervised?

The supervisors must observe how the following activities are done by the staff:

- orientation of midwives and treatment partners
- giving instructions by health staff to TB patients
- dosage given to patients
- drug intake of TB patients
- management of side effects
- filling-up of treatment records such as treatment card and NTP registry

- preparing reports
- storage and distribution of drugs
- filling-up of Order Form

Feedback must be immediately provided to the supervisee and the next higher level.

What will be monitored and evaluated?

The following guide questions will help in the monitoring and evaluation of various program activities;

Orientation of staff

Were all the staff oriented? If not, why?
What is the duration of orientation per category of health workers?
What approaches were used in the orientation? (Ex. Modular, lecture type) Which is the most cost-effective approach?
Were funds available and adequate?
Were the guidelines useful? Are there things to be changed? Added? Deleted?
What were the common issues raised during the orientation? What issues need clarification?

FDC ordering and distribution:

What was the ordering and distribution processes used? What were the constraints?
Is the ordering form appropriate? Properly filled-up
Did the FDCs come on time?
Were they adequate?
Were there problems in storage?
Were there buffer stock?
Were there SDF reserve stock at the province?

FDC distribution to patients

Was there any difficulty in explaining the treatment protocol? By doctors? Nurse? Midwife? Treatment partner?
Did the patient understand and follow the instructions? Any specific difficulty?
Were there instances that SDF need to be given for adverse reactions? What percentage of cases need the SDF? Are these available? At what level?
What are the feedback from TB patients? From treatment partners?
Is there a problem in recording?

Monitoring, supervision and evaluation

How frequent was the monitoring done by the provincial / regional coordinator?
How frequent was the supervision done by doctors / nurses?
What are the common issues / problems encountered?
Was feedback given to higher level and supervisee?
Is there a problem in reporting?
Were there quarterly assessment conducted? What were the results?

Treatment outcome:

How is the treatment outcome compared to the outcome before FDC implementation?

TO BE INCORPORATED IN THE MANUAL OF PROCEDURES OF THE NATIONAL TUBERCULOSIS CONTROL PROGRAM

Policies on the use of Fixed Dose Combination (FDCs) Anti-TB drugs

1. The Fixed Dose Combination (FDCs) Anti-TB drugs will gradually replace the Single Drug Formulation (SDF) for treatment of TB patients under the National Tuberculosis Control Program (NTP). The FDCs shall be initially introduced in one province or city per region which will known the advanced implementation sites (AIS). After a year of experience on FDCs at AIS, this will be expanded to other provinces and cities until all the regions are using the FDCs.
2. The dosage schedule will be in accordance to the internationally-prescribed dosage and intake must be supervised.
3. The Department of Health will provide the FDCs to the local government units and other health facilities for free. However, LGUs will be encouraged to procure a portion of the requirements for SDF for those with adverse reactions necessitating withdrawal of FDC.
4. Staff of health facilities such as Rural Health Units, hospitals, government and private clinics and treatment partners who involved in treatment of TB cases shall be properly trained on the use of FDCs and other new treatment guidelines.
5. Quality of FDCs must be ensured by ordering them from a source with track record of producing FDCs according to World Health Organization (WHO) prescribed strength and standards of quality.
6. The shift from SDF to FDC will be regularly monitored and assessed by the Infections Disease Office-National Center for Disease Prevention and Control, Center for Health Developments, Provincial Health Offices and the City Health Offices.

Facts about FDCs

The fixed dose combination (FDCs) are anti-TB drug preparations whereby two or more first line anti-TB drugs are combined in one tablet. The use of FDCs is recommended by the World Health Organization and the International Union Against Tuberculosis since 1994. They are also included in the WHO Model List of Essential Drugs.

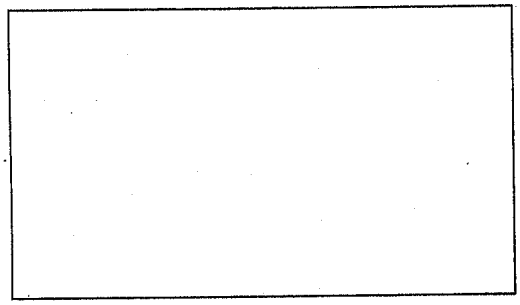
There will be two types of FDCs – the 4-drug and the 2-drug that will be used by NTP. The composition will be as follows;

Drug	*Initial*	*FDC A* *4 –drug(RHZE)*	*FDC B* *2 – drug(RH)*
Rifampicin	(R)	150 mg	150 mg
INH	(H)	75 mg	75 mg
PZA	(Z)	400 mg	
Ethambutol	(E)	275 mg	

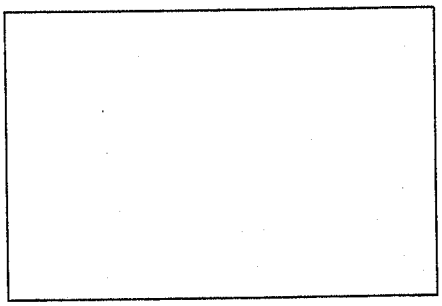
The initial supply will be provided through the Global Drug Facility – a project of the STOP TB Partnership.

The FDCs and single drug formulation of Ethambutol and Pyrazinamide are film-coated tablets and packaged in blister packs. There are 28 tablets per blister pack as shown below;

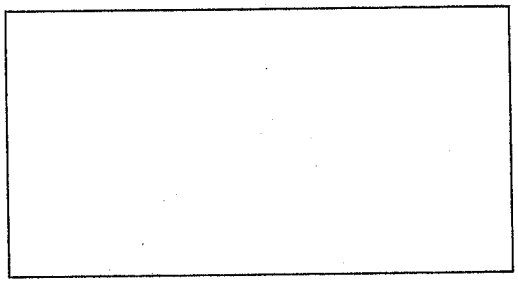
FDC – A



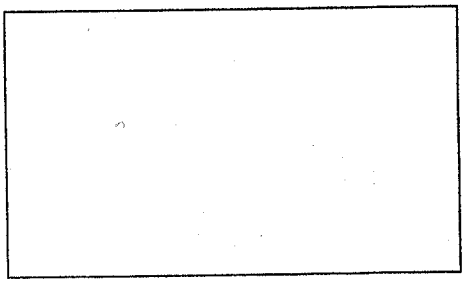
FDC - B



Ethambutol



Pyrazinamide



Dosage per treatment regimen

The dosage will follow the guidelines of WHO for individual anti-TB drugs as contained in p.26 of this Manual of Procedures (MOP). The number of tablets of FDCs per patient will therefore depend on the body weight. Hence, all patients must be weighed (using kilogram as a unit) before treatment is started.

Regimen 1: 2 RHZE / 4 RH

Body weight (kg)	No. of tablets per day Intensive Phase (2 months) RZHE	No. of tablets per day Continuation Phase (4 months) RH
30 - 37	2	2
38 - 54	3	3
55 - 70	4	4
>/ 71	5	5

Regimen 2: 2 RHZES / RHZE / 5 RHE

Body weight (kg)	Intensive Phase			Continuation Phase	
	First two months		Third month	HR	E 400 mg
	RHZE	Streptomycin	RHZE		
30 - 37	2	.75 g	2	2	1
38 - 54	3	.75 g	3	3	2
55 - 70	4	.75 g	4	4	3
>/ 71	5	.75g	5	5	3

Regimen 3: 2 RHZ / 4 RH

Body weight (kg)	No. of tablets per day Intensive Phase (2 months)		No. of tablets per day Continuation Phase (4 months)
	RH	Z (400mg)	RH
30 - 37	2	2	2
38 - 54	3	3	3
55 - 70	4	4	4
>/ 71	5	5	5

include the buffer stock of three months. Use the form below for ordering;

	Est. no. of cases	FDC A RHZE (BP)	FDC B RH (BP)	PZA (BP)	Ethambutol (BP)	Streptomycin (vial)
Regimen 1		X 6	X 12			
Regimen 2		X 9	X 15		X 280	X 56
Regimen 3			X 18	X 168	X 268	
Total	xxxxxx xxxxxxx					
Total x 2	xxxxxx xxxxxxx					
Stock on hand	xxxxxx xxxxxx					
Quantity to be ordered	xxxxxx xxxxxx					

Management of side effects of FDCs

Table 6 on p.36 of the MOP lists the side effects of the individual anti-TB drugs and the probable responsible drug. There are major side effects that necessitate withdrawal of the responsible drug. In this case, FDC must be changed to SDF.

NOTE:

Policies and guidelines of other program components such as case finding, case-holding, sputum follow-up, health education, recording and reporting and others shall still be based on the 2001 Manual of Procedures.