

Fixed-dose combination tablets for the treatment of tuberculosis

Report of
an informal
meeting
held in Geneva
Tuesday,
27 April 1999



World Health Organization
Communicable Diseases Cluster
1999



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EXECUTIVE SUMMARY

The World Health Organization (WHO) has continually emphasized that to confront the global tuberculosis emergency, all the elements of the framework of tuberculosis control as represented by the DOTS strategy, should function optimally. An essential component of the DOTS strategy is to have a reliable supply of quality drugs. Tuberculosis needs treatment with three to five different drugs simultaneously, depending on the patient category. These anti-tuberculosis drugs can be given as single-drug formulations or as fixed-dose combination formulations (FDCs) where two or more anti-tuberculosis drugs are present in fixed proportions in the same formulation. WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) advocate the replacement of single-drug preparations by FDC tablets as the primary treatment for tuberculosis. The justification for this recommendation is summarized below.

Background on FDCs

What is the recommended treatment approach for tuberculosis?

- Rifampicin (R), isoniazid (H), pyrazinamide (Z), and ethambutol (E) daily for 2 to 3 months
- R and H for further 4 months, either daily or 3 times per week, or E and H daily for 6 months
- FDC tablets are preferred
- 2- and 3-drug FDCs already are widely used, with 4-drug and pediatric FDCs to follow

Why fixed dose combination tablets?

- It provides a simple approach to delivering the correct number of drugs at the correct dosage as all the necessary drugs are combined in a single tablet
- By altering the number of pills according to the patient's body weight, complete treatment is delivered without the need for calculation of dose

What are the advantages of FDCs?

- Monotherapy is prevented, consequently the risk for selection of drug resistant bacilli is reduced. If given unsupervised, FDC tablets do not prevent patients from interrupting treatment repeatedly. Multiple interruptions of treatment can lead to emergence of drug resistance.¹ Therefore, FDC tablets must be given as directly observed treatment, at least during the intensive phase
- Prescription and administration is simplified; doctor/patient compliance with regimen improved
- Better drug stock management, shipping and distribution
- The risk of misuse of rifampicin for conditions other than tuberculosis is reduced

Do FDCs cost more than the component drugs separately?

- The cost of two-drug FDCs is already the same as that of the sum of the individual drugs. The same reduction in costs is expected for the four-drug FDC
- The high registration fees and/or importation taxes levied on drugs in many countries are cause for concern. Since such costs affect drug price significantly, reducing or canceling such levies on anti-tuberculosis FDCs need to be considered

Two and three-drug FDC tablets have been successfully used worldwide since the late 1980's and are registered in more than 40 countries. Indeed, approximately one fourth of the TB cases world-wide receive treatment with rifampicin-containing FDC tablets.² However, the many different strengths of FDCs available create confusion and the potential for incorrect dosing. Therefore, two and three-drug FDCs containing specified doses have been recorded in the WHO Model List of Essential Drugs of 1997 (See box below).³

In 1998 WHO and IUATLD agreed on the recommended strengths of a four-drug FDC tablet for daily use and three pediatric FDC formulations, and this revised list will be proposed for inclusion in the 1999 revision of the WHO Model List of Essential Drugs (See box below). Hoechst Marion Roussel (South Africa) has recently submitted for registration a four-drug FDC tablet, and Novartis (South Africa) has registered two pediatric FDCs, all according to the new WHO/IUATLD-recommended dosage formulations. Developments from other companies are also known to be underway. Four-drug FDCs, although different from WHO recommended strengths, are already used in countries such as India, Pakistan and South Africa. The companies that are known to produce such four-drug FDCs include Lupin Laboratories Limited (India), Wyeth-Lederle (Pakistan), and Hoechst Marion Roussel (South Africa).

The need for standardization

- Only FDCs of recommended strengths should ultimately be used by national programmes
- FDCs recommended in the 1997 WHO Model List of Essential Drugs:
 - RHZ (tablet): 150 mg + 75 mg + 400 mg for daily use
150 mg + 150 mg + 500 mg for intermittent use 3 times weekly
 - RH (tablet): 150 mg + 75 mg for daily use
300 mg + 150 mg for daily use
150 mg + 150 mg for intermittent use 3 times weekly
 - HE (tablet): 150 mg + 400 mg for daily use
- FDCs proposed to be included in the 1999 WHO Model List of Essential Drugs:
 - RHZE (tablet): 150 mg + 75 mg + 400 mg + 275 mg for daily use
 - RHZ (tablet): 60 mg + 30 mg + 150 mg for pediatric use (daily)
 - RH (tablet): 60 mg + 30 mg for pediatric use (daily)
60 mg + 60 mg for pediatric use (intermittent 3 times weekly)

The transition from single-drug formulations to FDC tablets has been in process for many years, and the introduction of a four-drug FDC tablet is just one further step towards ensuring adequate treatment of tuberculosis. However, there are concerns that must be addressed regarding the quality assurance of FDC preparations, problems regarding their registration, and barriers to their effective implementation into national programmes. Therefore, a joint meeting of representatives of WHO, the pharmaceutical industry, universities, and NGOs was called to formulate a response to these issues.

The major quality issue with FDC tablets is assuring the bioavailability of rifampicin. It is known that when rifampicin is combined with other drugs in the same formulation, its bioavailability is negatively affected if the manufacturing procedures are not strictly controlled. Consequently, a considerable number of FDCs are currently being marketed which are substandard as far as their rifampicin bioavailability is concerned. To address this problem, reference laboratories are being identified and an abbreviated protocol for bioavailability/-equivalence testing at reasonable cost has been developed. Two reference laboratories have been certified by WHO and a number of two-, three-, and four-drug formulations have been tested and found to be within the recommended specifications.

Quality of FDCs

- Bioavailability of FDCs point to the amount of drug, which gets absorbed into the blood. If inadequate, patients might fail on treatment. If produced according to GMP, FDCs have been shown to be bioequivalent to the single preparations in all their active components, including rifampicin
- A satisfactory dissolution test is no guarantee for adequate bioavailability. Recent studies show that many FDC preparations with poor rifampicin bioavailability exist in the marketplace
- WHO has embarked on a project which aims to provide guidelines to industry and to consumers on what constitutes good quality FDCs and how this quality can be monitored at country level

As mentioned above, industry representatives who attended the meeting reported progress in producing FDC tablets and registering or re-registering these products. However, manufacturers expressed frustration with the registration process in relation to the delay in having the WHO/IUATLD agreed formulations included in the WHO Model List of Essential Drugs, the variation in registration requirements by country and the high registration fees being charged in some circumstances. They also pointed out that some national drug regulatory agencies did not have the proficiency to perform their duties. Many developing countries' drug regulatory authorities prefer to register drug formulations that have already been registered in Europe or US. Therefore, concern was expressed that the European regulatory authorities require clinical efficacy trial for drug combinations containing more than two active substances. The four-drug FDC tablets consists of generic drugs whose efficiency and safety have been proven, and whose actions have been well-studied both for the individual drugs and when given together. The time constraints and costs of conducting further clinical trials would be strong disincentives for the manufacturers to produce FDC tablets.

Regulatory issues

- Rifampicin bioavailability must be a requirement for registration
- WHO simplified protocol for rifampicin bioavailability testing and other registration requirements are being finalized, which will include a supranational laboratory network for quality assurance of FDCs
- Proficiency of National Regulatory Authorities to deal with FDC applications should be strengthened

- Concerns of manufacturers over the regulatory process arise from the paradox that regulatory authorities require that the four-drug FDC must be included in WHO Model List of Essential Drugs before registration. However, the committee for the WHO Model List of Essential Drugs requires that the tablet be available and registered in at least one country before it is included in the list
- A master-file with justification for FDCs to replace single drug formulations must be prepared and made available to manufacturers and TB professionals

Implications for National Programmes

Changing from a policy of using single-drug formulations to one that is based on FDCs, will require appropriate planning and dissemination of information to service providers, procurement departments and local regulatory authorities. In this regard, the following points will need to be kept in mind:

- Personnel must be trained
- Manuals and teaching materials must be rewritten
- TB programmes will need to adjust their procurement plans
- Storage and distribution policies will need to be adapted
- Referral mechanisms for patients with drug reactions need to be created
- Recording and reporting system must be adjusted
- Sufficient time will need to be allowed for a transitional phase

Main recommendations from the meeting

- WHO should recommend to member countries that FDC tablets should replace single-drug formulations for the treatment of tuberculosis
- The WHO/IUATLD-recommended formulations should be proposed for inclusion in the 1999 revision of the WHO Model List of Essential Drugs
- The rifampicin bioavailability in FDC tablets must be assured according to standard protocols developed by WHO and IUATLD
- Training of regulatory staff to review applications for registration of FDC tablets may be required, and WHO should co-ordinate the partners in this project
- To minimize delays in registration of FDC tablets, a fast-track process is recommended
- To improve access to FDC tablets into the market, waiving or reduction of registration fees and import duties are proposed
- A system of pre-qualification of FDC suppliers by UNICEF and other agencies as has occurred with vaccines is recommended. Industry input into defining the criteria for this pre-qualification scheme is desirable
- Implementation of the change from single-drug formulations to FDC tablets will require substantial changes in the procurement systems of many countries, the

national TB control programmes, and the national essential drugs programmes. WHO should provide guidance to member countries to manage this transition

The meeting reaffirmed the importance of using FDC tablets as a component of the DOTS strategy to address the global tuberculosis emergency. Participants at the meeting confirmed their support for a partnership approach as exemplified in the meeting.

Background

WHO, IUATLD and partners recommend the use of fixed-dose combination (FDC) tablets for the treatment of tuberculosis (TB).⁴⁻⁶ The idea of using FDC tablets for the treatment of tuberculosis arose from the fact that tuberculosis always requires multi-drug therapy. For each of the anti-TB drugs there is a well-defined recommended dose per bodyweight. Because of minimum and maximum dose ranges, bodyweight ranges could be defined to which a specific number of FDC tablets would apply. Tablets could be made that contain the right strength of all the necessary drugs in a single preparation, all of the same size and colour, which would simplify the prescription process. It also implies that fewer tablets would need to be taken to receive an equal amount of drug as with the single-drug formulations.

The justification for recommending that FDC tablets replace single-drug tablets as the primary treatment for tuberculosis includes the following:

- FDCs prevent monotherapy, and it is expected that this will reduce the emergence of drug resistant tuberculosis
- FDCs simplify treatment, and thus minimize prescription error and increase patient and doctor compliance
- FDCs simplify drug stock management, shipping and distribution
- FDCs reduce the risk of misuse of rifampicin for conditions other than tuberculosis

Prevention of drug resistance

Emergence of drug resistance in high burden areas of the world presents a major threat to the future success of TB control. Drug resistance in most tuberculosis patients predominantly arises as a result of multiple interruptions of treatment.^{1,7} When using single-drug formulations, patients are more prone to interrupt their treatment on some drugs while not on others, thereby creating a risk of monotherapy and selection of drug-resistant mutants. Furthermore, out-of-stock or expiry situations in treatment facilities, which might lead to some drugs being continued in isolation while new stocks of others are being awaited, represent another potential source of monotherapy. Such problems are prevented more easily if FDCs are used.

Inadequate dose, especially of rifampicin, may also lead to treatment failure and drug resistance. FDC tablets of good quality ensure accurate dose delivery, and may thereby help to prevent anti-TB drug-resistance when given as directly observed treatment as recommended in the DOTS strategy.⁸ If FDC tablets are given unsupervised, patients can interrupt treatment repeatedly, and this may lead to emergence of drug resistance.¹ Thus, FDC tablets must be given as directly observed treatment, at least during the intensive phase to prevent drug resistance. If the bioavailability of rifampicin is inadequate, as might be the case in substandard

FDC tablets, treatment failures and emergence of drug resistant tuberculosis could follow. Thus, ensuring full bioavailability of rifampicin is an absolute requirement in the manufacturing of FDC tablets. Country procurement and regulatory bodies should be strongly encouraged to insist on the purchasing and distribution of products for which bioavailability data can be shown.

Simplifying treatment

Although little direct information exists to support the notion that the use of FDC tablets in the treatment of tuberculosis enhances the patient compliance with therapy, a study conducted in Hong Kong⁹ noted that only 1% of 312 patients who received FDCs complained about size, quantity to be ingested or difficulty with swallowing, as opposed to 5% of 308 patients receiving the single drug preparations. Complaints to adverse effects were similar in the two groups. Fewer pills to swallow per day no doubt will make treatment easier. (Table 1) In general, therefore, FDCs prevent indiscriminate selection of drugs and limit mistakes with the calculation of dosages.¹⁰ Combination drugs should be particularly useful in the private sector, where national guidelines may not be readily available, and use of inadequate regimens may be more common.¹¹

Table 1. Example of the number of tablets to be taken daily in the intensive phase of TB treatment by a 50kg patient either as single-drugs or as fixed-dose combination drug

Single-drug tablets	Number of tablets	FDC tablets	Number of tablets
Rifampicin (R) 150mg	3	RHZE	3
Isoniazid (H) 300mg (100mg)	1 (3)	(150 mg + 75 mg + 400 mg + 275 mg)	
Pyrazinamide (Z) 400mg	3		
Ethambutol (E) 400mg (100mg)	2 (7)		
Total	9 (16)	Total	3

* Figures in parentheses refer to alternative dose formulations and related number of tablets

Simplifying the drug supply management

FDC tablets simplify drug supply management. With single-drugs, out-of-stock situations occur for three main reasons: no buffer stock, delays in receipt of orders, and expiry date reached without replacement stock being available. With FDC tablets, there are fewer drug formulations to consider, thus making it easier to calculate the drug needs. Because of fewer drug formulations to order, ship and distribute, the result is less strain on staff in the national TB programmes. However, the issue of adverse effects complicates the management of drug treatment when using FDC tablets. Hepatitis is the main adverse effect in tuberculosis treatment, and can be caused by all the antituberculosis drugs (possibly with the exception of streptomycin). However, with currently recommended dosages in short-course regimens, hepatitis has been reported in only 3% or less of patients.¹² Also, adverse effects are not more commonly reported for FDC tablets than for single drug combinations.^{9,13} Nevertheless, whenever serious adverse effects or intolerance to one or more of the components in a FDC tablet are suspected there will be a need for single-drug formulations. Good and practical solutions to this problem must be found. Although it is recommended that FDCs replace single drug tablets, it is necessary to have a small stock of single drug tablets available. This stock should be kept only at higher-level health facilities that have competent TB specialists to handle patients with adverse effects.

FDC tablets minimize the risk of theft and misuse of rifampicin for conditions other than tuberculosis

Besides tuberculosis, several other common infectious diseases can be treated successfully with rifampicin. Thus, theft and black-market sale of this drug is not uncommon. Using rifampicin on a wide scale for conditions other than tuberculosis may lead to rifampicin be given, as monotherapy, to patients who happen to have concomitant tuberculosis. Monotherapy with rifampicin in a TB patient rapidly leads to rifampicin resistance if given for short periods only. In combination drugs, the presence of isoniazid reduces the probability for the survival of rifampicin resistant mutants. FDC tablets are much less attractive for sale on the black-market, because they also contain other drugs than rifampicin. Thus, the use of FDC tablets helps to minimize the risk of theft and misuse of rifampicin for conditions other than tuberculosis.

The recommended strengths of FDC tablets

There has been somewhat conflicting advice concerning the recommended strength of each drug in the FDC tablets. Today, there is a great diversity of formulations of FDC tablets available in the market, and many differ from the WHO recommended strengths.¹⁴ In this setting, prescribing FDC tablets can be more

difficult than prescribing single-drug formulations. For rational use of FDC tablets, the tablets must be widely available in the recommended strengths. So far, only two- and three-drug FDC tablets appear in the WHO model list of essential drugs, though the four-drug FDC will be proposed to be included in the 1999 revision of the list.³ The Dispensary Information supplied by the United States Pharmacopoeia includes a monograph on the three-drug FDC tablet, referring to the WHO recommended strengths, although tablets of WHO recommended strengths are not available in the US market.¹⁵ The Technical Research and Advisory Committee (TRAC), held at WHO, Geneva, in August 1998, recommended the four-drug FDC tablet for adults, as well as three pediatric FDC tablets (Table 4) to be added to the WHO model list of essential drugs.¹⁶ These recommendations are based on the WHO dosage schedule (Table 2) with dose per tablet decided on the basis of a 55 kg breakpoint above and below which 4 or 3 tablets would be required to deliver the correct dose, within acceptable limits, to the patient (Figure 1).

Quality of FDC tablets

The major challenge in using FDC tablets is to ensure that only FDC tablets of good quality are used. In a symposium on quality control of anti-TB drugs, part of the scientific meeting of IUATLD in Dubrovnik, October 1988, Dr Acocella (University of Pavia, Italy) presented studies on bioavailability of rifampicin in two- and three-drug FDC tablets. His work showed that the bioavailability of rifampicin when given as FDC tablets, particularly the three-drug combination, could be poor. Furthermore, an apparently satisfactory *in vitro* dissolution test did not guarantee acceptable rifampicin bioavailability.¹⁷ The results of a series of studies have shown that while some FDC formulations had acceptable rifampicin bioavailability, others did not.¹⁷⁻²⁶ It appears that the bioavailability of rifampicin is easily put at risk if strict manufacturing procedures are not followed, or poor quality raw materials are used. Giving FDC tablets with poor rifampicin bioavailability means giving inadequate therapy, without even being aware of it. Consequently, using FDC tablets of poor rifampicin bioavailability could directly lead to poor treatment outcome and may create, and not prevent, drug resistance. Good quality FDC tablets with demonstrated bioavailability of rifampicin, is an absolute requirement for successful treatment outcomes in programmes utilizing FDC-based regimens. Against this background, WHO and IUATLD issued a joint statement in 1994 advising that only FDC tablets of good quality and proven bioavailability of rifampicin should be used in the treatment of tuberculosis.⁴ There are several forthcoming articles in a special supplement of the International Journal of Tuberculosis and Lung Disease devoted to the quality assurance of FDC tablets. These include a simplified protocol for assessing rifampicin bioavailability and its use in studies carried out in South Africa and India,²⁷⁻²⁹ high performance liquid chromatographic methods for assaying of rifampicin, isoniazid and pyrazinamide,³⁰ procedures for ensuring laboratory proficiency for rifampicin bioavailability studies,³¹ and a review of the pharmacology of rifampicin.³²

Registration of FDC tablets

Pharmaceutical products of good and poor quality circulate in international trade. The registration process and the institutions responsible for registration of drugs are fundamental elements to ensure that only drugs of good quality are purchased and used in any country. Registration of pharmaceutical products should ensure not only that the product itself is of good quality, but also that the manufacturer adheres to recognized good manufacturing practices (GMP) and that proper quality control is in place. Only in this way is it possible to ensure reliable supplies and availability of quality FDC tablets. WHO and partners are working to develop and strengthen mechanisms for prompt registration of FDC tablets. Other forthcoming articles in the *International Journal of Tuberculosis and Lung Disease* will discuss registration requirements³³ and tender requests³⁴ for anti-TB FDC tablets. In another anticipated publication, the WHO strategies for quality assurance of vaccines have been reviewed in order to provide input to the development of similar strategies for FDC tablets.³⁵ Other anticipated articles will address issues of policy recommendations, such as the roles and responsibilities in the use of FDC tablets in TB control³⁶ and responsibilities and required structures in the maintenance of a laboratory network for quality assurance of FDC tablets.³⁷

The market for FDC tablets

In the 11 years since Dr Acocella's presentation in Dubrovnik, FDC tablets are increasingly being used for the treatment of TB. A WHO survey of the global market for FDC tablets in 1998 estimated that approximately 50% of countries used FDC tablets.² While small countries often use FDC tablets, countries with large populations and high burdens of TB tend to use single-drug tablets. However, Dr Catalani demonstrated that the use of FDC tablets is widespread in India, accounting for 62% of the rifampicin used in the private health sector.³⁸ According to the 1998 WHO survey, an estimated 24% of TB cases worldwide are treated with rifampicin-containing FDC tablets. However, most patients receive only the two-drug combination. Currently, less than 5% of TB cases are given three or four-drug FDC tablets. With 75% of TB cases still being treated exclusively with single-drugs, it is still a major task to replace single tablets with FDC tablets as the primary treatment for TB.

A Global Drug Facility

The Stop TB Initiative, launched by the Director-General of WHO, identifies the availability of TB drugs of high quality as one of the weakest links in the chain of strategic elements to control the TB epidemic. Given this concern, the Stop TB Initiative has proposed a Global Drug Facility, which aims at identifying constraints and proposing solutions to facilitate global availability of high quality TB drugs. A key

component of the Global Drug Facility will be to promote FDC tablets as a replacement for single-drug tablets in tuberculosis control programmes and on the essential drugs lists of all countries.³⁹

Use of FDC tablets as part of the DOTS strategy

Concern has been expressed that FDC tablets might be seen as an opportunity to encourage self-supervision in TB treatment, thereby undermining the WHO-recommended DOTS strategy for TB control. This is certainly not WHO's intention. FDC tablets do not eliminate the need for supervision of treatment though they may simplify the process. Likewise, the other components of the DOTS strategy such as government commitment, case finding by sputum-smear microscopy and a monitoring system for evaluation and supervision, remain as important as previously. WHO recommend the use of FDC tablets as a new tool that will be promoted as an integral part of the DOTS strategy.

The objectives of the April 27th 1999 meeting

- To share ideas between representatives from the pharmaceutical industry, WHO and other organizations concerning the implementation of FDC tablets, in particular four-drug FDCs, as replacements for single-drug tablets as the primary treatment for tuberculosis.
- To identify the key constraints in the process of introducing the four-drug FDC tablet for treatment of TB.
- Propose recommendations and next steps to be taken to address identified constraints.

Opening of Meeting

Dr David Heymann, the Executive Director of the Communicable Diseases Cluster, opened the meeting. He spoke briefly of the importance of TB as a global health problem and suggested that FDC tablets would play a crucial part in effectively addressing this serious disease. Dr Paul Nunn echoed the welcome of Dr Heymann on behalf of the Stop TB Initiative and presented the concept of a Global Drug Facility. The final form of the facility had not yet been decided but it was very likely that the provision of FDC tablets would be a major concern of the facility.

Objectives of Meeting

Dr Sergio Spinaci introduced the objectives of the meeting. He suggested that the meeting should review the global situation for the provision of FDC tablets, to identify constraints to widespread introduction of FDC tablets, to share ideas with industry, other organizations and WHO, and to propose what should be done to overcome these constraints. He reviewed the many reasons justifying the **replacement** of single-drug tablets by FDC tablets. He suggested that based on past experience with two-drug FDC tablets, the price of the FDC tablets may become the same as for single-drug tablets over time. In addition, the benefits of improved treatment and reduced logistic costs, reduced losses and the prevention of MDR-TB would make the change to FDC tablets cost-effective. Adverse effects are NOT more common with FDC tablets.^{9,13} WHO and IUATLD have agreed on standard formulations and a dosage schedule related to weight for the four-drug FDC tablets and three pediatric FDC tablets.¹⁶ The major obstacle to using FDC tablets is concern about quality, specifically the rifampicin bioavailability in FDC tablets. Providing substandard FDC tablets would lead to treatment failures and to the emergence of drug resistance. WHO has been actively addressing the rifampicin quality issue, and over the past few years the organization has supported:

- The development of a protocol for assessing the rifampicin bioavailability of FDC tablets.
- The development of a protocol for assessing the proficiency of laboratories that would like to participate in an international network to determine FDC rifampicin bioavailabilities.
- Standardization of the strengths of FDC tablets.
- Review of the strategies for quality assurance and supply of vaccines as it applied to TB drugs.

WHO/IUATLD-recommended strengths and dosages of FDC tablets

Professor Pierre Chaulet reviewed the global situation as to dosage forms and treatment schedules for FDC tablets. He pointed out the important fact that the use of FDC tablets is not a new concept in TB control. In fact, FDC tablets have existed and been successfully used in TB control for more than 20 years. A wide range of different formulations has been produced by different companies and has been registered and marketed in different countries. The recommended dosages (mg/kg) for essential TB drugs (Table 2) were published in the 1997 WHO guidelines for treatment of tuberculosis.⁵ He stressed that combined preparations should be used for each of the three standard regimens recommended by WHO and IUATLD. In accordance with these guidelines, the 1995 and 1997 revisions of the WHO Model List of Essential Drugs included two and three-drug FDC tablets for the treatment of tuberculosis (Table 3).³

Based on detailed work presented at the meeting by Dr Bernard Fourie, an additional four-drug combination formulation would be proposed for adults, and two and three drug formulations for children (Table 4). These formulations would be combined with a simplified dosage schedule according to weight (Tables 5 and 6).

Table 2. Recommended doses (mg/kg) for essential TB drugs

Anti-TB drug (abbreviation)	Mode of action	Recommended dose (mg/kg)		
		Daily	Intermittent	
			3x per week	2x per week*
Isoniazid (H)	Bactericidal	5 (4-6)	10 (8-12)	15 (13-17)
Rifampicin (R)	Bactericidal	10 (8-12)	10 (8-12)	10 (8-12)
Pyrazinamide (P)	Bactericidal	25 (20-30)	35 (30-40)	50 (40-60)
Ethambutol (E)	Bacteriostatic	15 (15-20)	30 (25-35)	45 (40-50)
Streptomycin (S)	Bactericidal	15 (12-18)	15 (12-18)	15 (12-18)
Thioacetazone (T)	Bacteriostatic	2.5	Not applicable	

* WHO does not generally recommend twice weekly regimens. If a patient receiving a twice-weekly regimen misses a dose of tablets, this missed dose represents a bigger fraction of the total number of treatment doses than if the patient were receiving a thrice weekly or daily regimen. There is therefore a bigger risk of treatment failure.

Table 3. WHO Model List of Essential Drugs from December 1997

Drug	Forms	Strengths
Streptomycin	Powder for injection	S 1g (as sulfate) in vial
Rifampicin	Capsule or tablet	R 150 mg R 300 mg
Isoniazid	Tablet	H 100 mg H 300 mg
Pyrazinamide	Tablet	Z 400 mg
Ethambutol	Tablet	E 100 mg E 400 mg
Thioacetazone + isoniazid	Tablet	T 50 mg + H 100 mg T 150 mg + H 300 mg
Isoniazid + ethambutol	Tablet	H 150 mg + E 400 mg
Rifampicin + isoniazid	Tablet	R 150 mg + H 75 mg R 300 mg + H 150 mg R 150 mg + H 150 mg *
Rifampicin + isoniazid + pyrazinamide	Tablet	R 150 mg + H 75 mg + Z 400 mg R 150 mg + H 150 mg + Z 500 mg *

* For intermittent use three times weekly

E=ethambutol, H=isoniazid, R=rifampicin, S=streptomycin, T=thioacetazone, Z=pyrazinamide

Table 4. Recommended strengths of FDC tablets from the WHO Advisory Committee Meeting August 1998

Drug	Form	Strengths
Rifampicin + isoniazid (Pediatric)	Tablet **	R 60 mg + H 30 mg R 60 mg + H 60 mg *
Rifampicin + isoniazid+ pyrazinamide (Pediatric)	Tablet	R 60 mg + H 30 mg + Z 150 mg
Rifampicin + isoniazid + pyrazinamide + ethambutol (Adult)	Tablet	R 150 mg + H 75 mg + Z 400 mg + E 275 mg

* For intermittent use three times weekly

** Dispersible form preferred

E=ethambutol, H=isoniazid, R=rifampicin, Z=pyrazinamide

Table 5. Dosage schedule for adults (number of tablets)

Patient body weight (kg)	Initial phase		Continuation phase		
	2 months		4 months		6 months
	RHZE Daily	RHZ Daily	RH Daily	RH Thrice weekly	EH Daily
30-37*	2	2	2	2	1.5
38-54**	3	3	3	3	2
55-70**	4	4	4	4	3
71 and more*	5	5	5	5	3

*Only a small proportion of adult TB patients will fall into the categories with body-weights from 30 to 37kg or body-weights above 70kg. Therefore, in practice, most patients taking rifampicin-containing FDC tablets will receive either three or four tablets daily.

**Some countries traditionally use a cut-off point at 50kg, not 55kg as proposed here. The dosage schedule presented here can be used also with a cut-off point at 50kg, i.e. patients with bodyweights from 35 to 49kg receives three tablets, and those with bodyweights from 50 to 70kg receives 4 tablets.

Table 6. Dosage schedule for children (number of tablets)

Patient body weight (kg)	Initial phase	Continuation phase	
	2 months	4 months	
	RHZ Daily	RH Daily	RH Thrice weekly
Up to 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

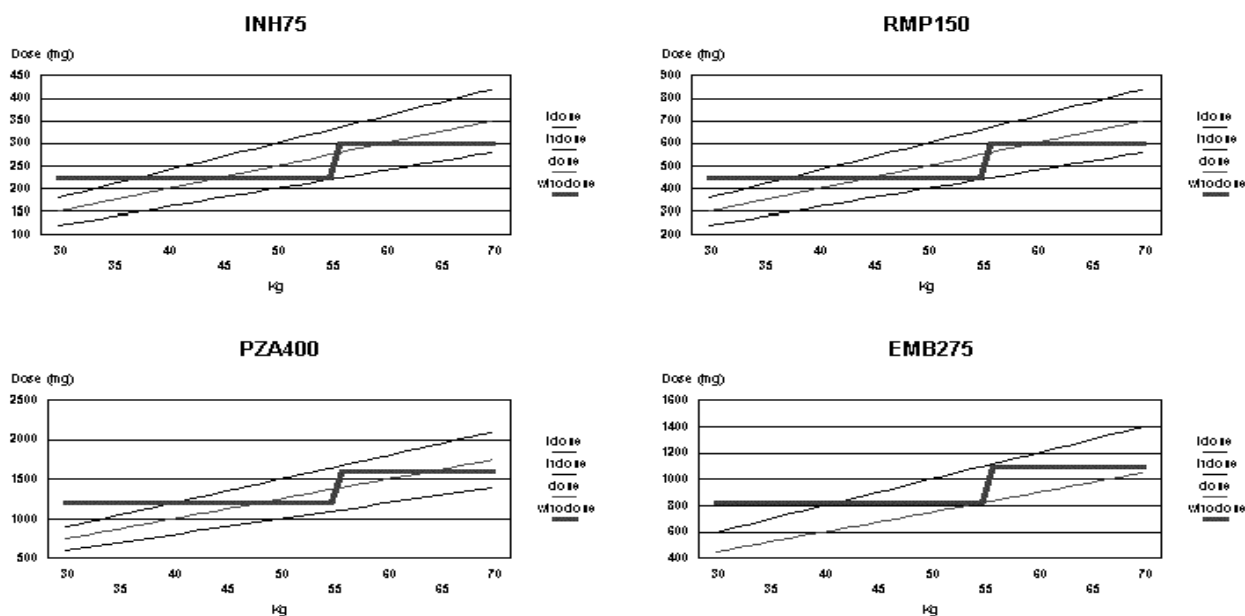
Justification for Dosage Forms and Dosage Schedules

Dr Bernard Fourie presented graphical data justifying these formulations and schedules. The effective therapeutic dosage for the different TB drugs in mg/kg is widely accepted and is recorded in Table 2 above. For any drug there is a therapeutic range within which the drug is effective and not toxic. He presented charts demonstrating that for the TB drugs included in FDC tablets, the simplified schedule according to weight ensured that doses remained within the therapeutic margins. Data showed that whether the cut-off point for changing from three tablets to four was at 50 kg or 55 kg, therapeutic efficacy would be maintained. Thus, for the vast majority of adults the number of tablets for both the intensive phase and the continuation phase would be the same. For those below 50 kg or 55 kg (depending on local NTP decision) the dosage would be three tablets, while for those over 55 kg the dose would be four tablets. For children of 10 kg and over, the dose would be one sachet of granules or dispersible tablet per 5 kg bodyweight. For lower bodyweights, the tablet dose would be halved and administered per 2.5 kg increments as appropriate. The chart below demonstrates the dose/weight relationship for adults where the change from three to four tablets occurs at 55 kg. Similar charts are available for children and for adults with a cut-off point for changing from three to four tablets at 50 kg. Figure 1. Justification of dosages of the four-drug FDC tablet



4 drug FDC for daily administration (R150/H75/Z400/E275)

WHO application: 3 tabs up to 55kg, then 4 tabs
(PB Fourie, MRC South Africa, 1998)



Quality Assurance of FDC tablets

Drs Gordon Ellard and Bernard Fourie jointly presented information on quality aspects of FDC tablets. They pointed out that different formulations of FDC tablets had been shown for many years to have differing bioavailability results for rifampicin; some acceptable, others not.¹⁷⁻²⁶ Bioavailability problems with the isoniazid, pyrazinamide and ethambutol components of FDC tablets have not been encountered, presumably because of their much greater water-solubilities. FDC tablets with unsatisfactory rifampicin bioavailability usually contain near to their stated rifampicin content as assessed by colorimetric methods. It is assumed that impaired bioavailability may result from changes in rifampicin's crystalline form during the tableting process.⁴⁰ Earlier studies have demonstrated the dose dependency of rifampicin's anti-tuberculosis activity.⁴¹ Recently, in studies of the early bactericidal activity of rifampicin, its therapeutic ratio was shown to be only approximately four as compared with sixteen for isoniazid.⁴² Its potency, therefore, will be severely compromised by using formulations with impaired rifampicin absorption. For this reason the bioequivalence of all rifampicin-containing FDC tablets must be established.^{4,23,43,44} While this is an expensive process, a simplified and effective protocol has been developed which is more convenient and cheaper. This utilizes six blood sample time points over an eight-hour period compared with the conventional requirement of about thirteen samples over a twenty-four hour period.²⁸ This has been shown to assess bioavailability with only a minimal loss of precision. At present, two laboratories have been approved to act as reference centers to assess the bioavailability of rifampicin-containing FDC tablets,³¹ and other laboratories will be recruited in due course.

Registration of FDC tablets

Dr Bernard Fourie reported that two four-drug combination preparations were already registered in South Africa, though at present these do not conform to the WHO recommended strengths (Table 7). They do, however, conform to WHO recommended mg/kg dose delivery requirements. Two pediatric formulations (two and three-drug FDC tablets) which also conform to WHO recommendations have recently been registered. Three adult formulations (two and four-drug FDC tablets) and two further pediatric formulations (two and three-drug FDC tablets) which fully conform to the WHO recommended dosages per tablet have been submitted for registration. All of these preparations have passed the bioavailability tests for rifampicin and other actives. For registration purposes, it is generally required that bioavailability testing is performed for all four components of the FDC tablet, not only for rifampicin. However, the WHO's recommendation will be that only rifampicin bioavailability needs to be established, whilst data on dissolution would be sufficient for other actives.

Table 7. Preparations recently assayed for registration purposes in South Africa and shown to be fully bioavailable/equivalent*

Reference Centre for the Chemotherapy of Mycobacterial Diseases, National Tuberculosis Research Programme, Medical Research Council, South Africa (PB Fourie, 1999)

Formulation	Form	For	Manufacturer	Status in S. Africa
**R120 + H60 + Z300 + E225	Tablet	Adults	Wyeth-Lederle, Pakistan	Registered
**R120 + H60 + Z300 + E200	Tablet	Adults	Hoechst Marion Roussel, South Africa	Registered
*** R60 + H30 + Z150	Dispersible tablet	Pediatric	Novartis, South Africa	Registered
*** R60 + H60	Dispersible tablet	Pediatric	Novartis, South Africa	Registered
*** R150 + H75 + Z400 + E275	Tablet	Adults	Hoechst Marion Roussel, South Africa	Submitted for registration
*** R150 + H75	Tablet	Adults	Hoechst Marion Roussel, South Africa	Submitted for registration
*** R150 + H150	Granular sachet	Adults	Hoechst Marion Roussel, South Africa	Submitted for registration
*** R60 + H30 + Z150	Granular sachet	Pediatric	Hoechst Marion Roussel, South Africa	Submitted for registration
*** R60 + H30	Granular sachet	Pediatric	Hoechst Marion Roussel, South Africa	Submitted for registration

* Bioequivalence: 90% confidence interval of the Test/Reference ratio lies completely within the range 80% to 125%.

** These tablets conform to WHO-recommended dose/bodyweight (mg/kg) delivery requirements, but do not conform to the WHO-recommended dosage strengths (Table 3 and 4).

*** Formulated according to WHO recommended dosage strengths per tablet (Table 3 and 4).

In summary

Dr Bernard Fourie and Dr Gordon Ellard concluded that:

- Only rifampicin-containing formulations with proven rifampicin bioavailability should be used.
- These bioavailability studies should be carried out by an independent WHO-certified laboratory using previously validated HPLC methods and according to an accepted, standardized protocol.
- Such combined formulations should be bio-equivalent to accepted rifampicin single-drug reference preparations using standard methods.

Proposed minimum requirements for registration of FDC tablets

The aim of the proposed strategy presented by Dr Bernard Fourie, was to reduce development time and cost, to simplify regulatory requirements, to achieve standardization, to ensure bioavailability of the rifampicin component and to demonstrate consistency in quality. These could be achieved at the level of registration, submission of tenders and following allocation of the tenders. Many developing countries' drug regulatory authorities prefer to register drug formulations that have already been registered in Europe or US. Therefore, concern was expressed that the European regulatory authorities require clinical efficacy trial for drug combinations containing more than two active substances. The four-drug FDC tablets consists of generic drugs whose efficiency and safety have been proven, and whose actions have been well-studied both for the individual drugs and when given together. The time constraints and costs of conducting further clinical trials would be strong disincentives for the manufacturers to produce FDC tablets.³³ Other criteria for registration were suggested to be demonstrated rifampicin bioavailability, with the principal parameters of interest being peak serum levels (C_{max}) and Area under the Curve (AUC) for the time period zero to eight hours with six time point measurements. At this stage, most countries require bioavailability testing of all component drugs in the tablet.

For submission of tenders the following should be required from the manufacturer:

- Comparative bioavailability results for rifampicin with dissolution data for the other components.
- A declaration by the manufacturer of consistency between the starting and subsequent batches.
- A correlation over time between dissolution tests of different batches.
- A statement that the raw materials are in accordance with reference specifications.

Following the allocation of the tender, new dissolution, disintegration and chemical analytic data should be provided for each batch supplied. Simple screening by colorimetric, physical and disintegration methods after delivery can be used. The client should be able to request new assessments at the supplier's cost. All procedures to define product quality should be in accordance with WHO protocols and performed in accredited laboratories.

Expansion of the use of FDC tablets

Assuming that quality and regulatory issues are resolved, much work still needs be done in the delivery, monitoring and expansion of the use of FDC tablets in National Tuberculosis Programmes.

NTP Perspective

Dr Jacob Kumaresan from WHO's Department on Communicable Diseases Prevention and Control (CPC) gave a brief presentation on the future expansion of the use of FDC tablets and the changes that must occur. At the central level, the NTP must estimate the demand and adjust their procurement plan accordingly. Storage and distribution issues must be identified and resolved (i.e., packaging requirements at central level versus periphery). Post-marketing surveillance and quality assurance schemes must be established for monitoring and evaluation. Wide-scale training of health care workers must occur. Field staff must adjust their drug-ordering schedule, modify recording practices, ensure that storage conditions are adequate and develop a referral plan for treatment failures and cases of adverse reactions to drugs. All of these are certainly surmountable obstacles. However, a preparatory phase with a lead-time of at least six to nine months would make the transition easier. National guidelines must be changed; staff retrained; recording and reporting systems adjusted. In larger countries, a phased implementation may be more feasible.

Practical implications of introducing and promoting FDCs

Dr Hans Hogerzeil from WHO's Department on Essential Drugs and Other Medicines (EDM) presented the following indicative "checklist" of necessary steps for wide acceptance and use of FDC tablets in national programmes. This list should be considered as a guideline, not as mandatory. The WHO Health Technology and Pharmaceutical Cluster (HTP) will be working toward identifying intermediate steps before full implementation. He stressed that:

The science must be right

- Pharmacology, toxicology, bioavailability
- Clear treatment recommendation from expert committee based upon clinical evidence and cost-effectiveness
- Inclusion in international reference manuals and training materials

The legal/regulatory status must be right

- Inclusion on WHO Model of Essential Drugs (November 1999)
- Registration in country of production, in ICH countries and in country of use

National clinical status must be right

- Accepted by national TB programmes and professional associations
- Accepted by national Drugs and Therapeutic Committees
- Included in national Standard Treatment Guidelines
- Included on national essential drugs list (per level of care)
- Included in national supply system or reimbursement scheme

Supply system must be right

- Sufficient suppliers (international, national)
- Estimation of national requirements, minimum stock level, reorder level
- Funding identified and available (public, development loan, cost sharing, reimbursement, private)
- Inclusion in central medical stores catalogue and tender documents
- Distribution system (vertical, integrated with public sector, (semi-) private)

Training and supervision must be in place

- Adaptation in national treatment guidelines
- Inclusion in national reference manuals on drug treatment
- Inclusion in national training programme and supervision systems
- Training in private sector training such as CME (Continuing Medical Education) and professional associations

Surveillance system must be in place

- Post-marketing surveillance of FDC tablets
- Protocol to measure impact on relapse rates and MDR-TB

Issues raised in the discussions

In any change, there are obstacles that might be difficult to overcome. In this case, the local manufacturers might find it difficult to meet the pre-qualification criteria. Such a situation may pose a significant threat to successful implementation of FDC tablets. Special attention needs to be paid to a system which will be simple, low cost and rapid in order to ensure that pre-qualification criteria do not act as a deterrent to manufacturers in producing anti-TB FDCs.

A switch to the four-drug FDC requires government commitment and investment to ensure that an adequate supply of these drugs will be available.

Official communication from WHO to World Bank and other large procurement agencies should clearly delineate the WHO recommendation in an unequivocal statement.

Fair competition can be ensured despite a potential decrease in the number of manufacturers by an ordered market. In addition, rather than awarding the full tenders to a single manufacturer, an alternative system could be established in which the lowest bid (of pre-qualified manufacturers) receives 50% of the award, next lowest 30%, etc.

The overwhelming quality issue regarding FDC tablets is the potential inadequate bioavailability of rifampicin when used in fixed-dose combinations. Unfortunately, this can only be detected through bioavailability testing. Manufacturers, however, supported a system of strict quality assurance on rifampicin-containing FDCs.

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Industry Presentations

Representatives from several manufacturers gave brief presentations on their involvement with the production of FDC tablets. The presentations showed a tradition of production of FDC tablets in a variety of combinations over the past decade, consistent with GMP standards. Currently, FDC tablets are registered in a large number of countries, and most of the tablets have strengths in compliance with the 1997 WHO Model List of Essential Drugs. Dr Giorgio Roscigno, representing the pharmaceutical company Hoechst Marion Roussel, reported that their two and three-drug FDC tablets have already been registered in forty countries. Other presentations from pharmaceutical companies were given by Dr Georg Ingram, representative of Biochemie GmbH/Novartis, Dr Anup Banerjee, representative of Lyka Labs Limited, Ms Suzie Demmer, representative of Wyeth-Lederle, and Dr Richard Urbanczik, representative of Fatol Arzneimittel GmbH. Regrets were expressed that representatives from manufacturers in India and other countries were unable to attend the meeting (See Annex 3). The presentations unveiled that manufacturers are in varying stages of production of the recommended four-drug FDC, from market analysis to registration. Pricing of the four-drug FDC is not expected to be a major issue. The ultimate price, following recovery of higher initial costs (dedicated machinery, etc.), tends to be comparable to the price of treatment with single-drug tablets. One manufacturer that was unable to attend the meeting, Dr Dhananjay S Bakhle, representative of Lupin Labs Ltd, communicated that their four-drug FDC tablet costs less than the sum of the individual single-drug tablets. In addition, as expected, economies of scale are realized and cost decreases as volume increases.

Manufacturers expressed the following frustration with the registration process.

- To register a drug formulation, many countries require that the formulation appears on the WHO Model List of Essential Drugs. However, for the formulation to be included in the Model List of Essential Drugs, WHO requires that the formulation is already available and registered in at least one country. This apparent paradox hinders the prompt registration of the four-drug FDC tablet.
- Registration requirements vary across countries. Some do not require bioequivalence testing for registration of FDC tablets.
- The European regulatory authorities requires clinical efficacy trials for combinations of three or more generic drugs; regulatory authorities in many non-European countries consider European registration a prerequisite.
- Competence of National Regulatory agencies is sometimes low yet the WHO certification scheme is dependent upon the adequacy of regulators.

- High registration fees are charged in some countries and pose a high barrier to entry.

Specific concerns were expressed

- Dr Urbanczik, representative of Fatol Arzneimittel GmbH, expressed the concern that their market analysis showed that there was no real market for three and four-drug FDC tablets in Europe. The fact that data from clinical efficacy trials are required for registration of combination drugs containing more than two active components in Europe, has led to only two-drug combinations being available. Until this situation changes, nothing would be able to be done to promote a four-drug combination tablet in the region.
- Not many FDC tablets are registered in Russia, as authorities are reluctant to register them. However policies are being set now in Russia and there is the opportunity to influence new policies.

Industry expectations

- Global alignment of National Tuberculosis Programmes with the WHO recommendations.
- Quick introduction of the new four-drug FDC tablet into the WHO Model List of Essential Drugs (1999).
- More proactive role of WHO and other international organizations in promoting implementation of the quality assurance strategy with national regulatory authorities.
- Creation of a task force of WHO and industry representatives to standardize regulatory requirements for FDC.

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Working Groups

Participants broke into two working groups. One focused on regulatory issues, the other on quality assurance issues. The following are the conclusions made by each group.

Working group on regulatory issues

All FDC tablets used for treatment of tuberculosis must be registered by the National Regulatory Authority. In addition to general registration requirements for pharmaceutical products, registration of FDC tablets must also include an assessment of the bioavailability of rifampicin performed according to the WHO-recommended protocol. The issue of stability testing of FDCs was raised in the discussions. WHO and partners should further investigate the necessity of including data on stability in the registration for anti-TB FDC tablets.

There were concerns for the European regulatory authorities' requirements of clinical trials for registration of combination preparations. The working group was of the opinion that the four-drug FDC tablets should be registered without any further clinical trial, as FDC tablets are combinations of generic pharmaceutical products whose efficiency and safety have been proven, and whose actions have been well-studied both for the individual drugs and when given together. To promote proficiency of regulatory authorities, training for regulatory personnel in the issues related to FDC tablets should be addressed by a global training facility similar to the Global Training Network established by WHO Department for Vaccines and other Biologicals. Given the emergency of the global tuberculosis situation, National Regulatory Authorities should consider a fast track process for approval of the four-drug FDC tablets for treatment of tuberculosis. The high registration fees for anti-TB drugs were identified as a major disincentive for manufacturers to submit their formulations for registration. National Regulatory Authorities should consider reducing or cancelling these registration fees, in particular for the four-drug FDC tablets. In addition, governments should consider reducing importation taxes on anti-TB drugs, in particular FDC tablets.

WHO should promptly assess the feasibility of establishing a system of pre-qualification of manufacturers of anti-TB FDCs led by UNICEF or other UN agencies, or as a shared responsibility between WHO and other UN agencies. The four-drug FDC tablet should be proposed to be included in the WHO Model List of Essential Drugs in the next meeting of the Expert Committee on the Use of Essential Drugs in November 1999. To facilitate this process, WHO and partners should produce a document justifying the introduction of the four-drug FDC tablet in the WHO Model List of Essential Drugs, and compile a file of all relevant

publications to support this action. This documentation should also be made available for National Regulatory Authorities and pharmaceutical manufacturers and suppliers to promote the prompt registration of the four-drug FDC in countries. WHO should release a statement recommending FDC tablets to replace single-drug tablets as the primary drugs for TB treatment.

Working group on quality assurance issues

Pre-qualification of manufacturers is widely accepted to be highly desirable and will require clear specifications, high quality product testing, and adequate monitoring. The procedures established by the WHO Department for Vaccines and Other Biologicals were considered as a model that might be useful in the establishment of a pre-qualification scheme for anti-tuberculosis drugs. Once a pre-qualification scheme for anti-tuberculosis drug manufacturers has been established and implemented, procurement agencies should purchase exclusively from pre-qualified manufacturers to ensure quality.

Bioavailability of rifampicin should always be demonstrated. No suitable correlates of bioavailability are known which do not involve the use of human subjects in assessing drug kinetics, and therefore, the assessment of drug absorption and uptake can only be done through appropriate clinical studies. Although dissolution tests can be useful to evaluate lot to lot consistency, it cannot replace bioavailability studies. International criteria in quality assurance should apply. Different expert committees dealing with similar issues (i.e. expert committees on pharmaceuticals and those dealing with tuberculosis) should interact and communicate regularly in order to ensure that guidelines on the production and quality assurance of anti-tuberculosis FDC tablets are in accordance with globally agreed criteria.

Thin layer chromatography (TLC) should not be used as a tool for specifying drug quality, i.e. to seek regulatory approval for registration and/or distribution. TLC does not test bioavailability but may be a useful screen to detect gross quality defects especially where no other testing occurs.

In the treatment of tuberculosis, a constant and steady supply of drugs is an essential prerequisite. Manufacturers, in order to guarantee steady production, should have a minimum of two high-quality suppliers; should one be unable to meet demand for whatever reason, another can fill the order. This raises an additional question of whether separate rifampicin bioavailability studies must be done when there is a change in supplier of rifampicin raw material. As long as the production process remains unchanged and the new supplier delivers rifampicin of the same crystalline form and of proven quality, new bioavailability testing may not be necessary.

Raw material regulation should be kept to a minimum but should be strictly based upon pharmacopoeia specifications. The manufacturer is ultimately responsible for the quality of the drugs they produce, and therefore, excessively rigid regulation of the sources and crystalline form of rifampicin used in the manufacture of FDC tablets would be unhelpful since it would result in decreased competition and increased prices. Rifampicin crystalline forms 1 and 2 are currently both used in the production of rifampicin-containing FDC tablets. The US Pharmacopoeia specifies that crystalline form 2 be used in all rifampicin preparations.

Specification requirements should include not only convincing evidence for stated drug content, and rapid and complete release of the active components (dissolution profile), but need also to include a 24-month demonstrated stability for products appropriately stored under typically tropical conditions (high temperature, high humidity). This would be beyond the ICH (International Conference on Harmonization) specifications.

National capacity of GMP monitoring should be expanded. Expertise found within the drug industry and the vaccine network could be utilized as potential sources of training.

Continuous post marketing surveillance of FDC quality should be undertaken. The nature, location, logistics and frequency of post-marketing surveillance need to be considered to ensure that registered manufacturers of FDC tablets maintain the quality of their products. However, it is unclear who would pay.

The possibility of standardization of the physical properties and presentation of FDC tablets should be further pursued. More discussion is needed concerning the relative advantages and disadvantages of increased standardization of both the physical properties of FDC tablets (colour, shape and size) and their packaging. Scoring of FDC tablets is acceptable for pediatric but not for adult preparations. To be able to easily halve tablets will defeat the purpose of FDC tablets, namely to provide appropriate drug delivery which is simple and standardized. In-between dosing will encourage individualization of treatment and the possibility of mistakes in dose calculation. In young children, under 10kg-body weight, dividing dose as per WHO dosage schedule would be necessary.

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Next Steps / Commitments

WHO will:

- Produce a concise, action-oriented meeting report incorporating comments from the participants.
- Produce a justification paper regarding the use of FDC.
- Produce a SCRIP one-pager with WHO recommendations.
- Work on monograph for selected pharmacopoeia.
- Work to expand the laboratory network.
- Promote collaboration within WHO, particularly between the Communicable Diseases Cluster (CDS) and the Health Technologies and Pharmaceuticals Cluster (HTP), on procurement and pre-qualification issues, taking lessons learned from vaccines.
- Investigate possible operational projects that provide a solid evidence base to the benefits of FDC and their link to the prevention of MDR-TB.
- Convene a meeting with ICH and developing country regulatory authorities to determine what will be necessary to facilitate the prompt registration of FDC tablets in various countries.

WHO and the pharmaceutical industry together will:

- Work on a “master file” of technical documents (including efficacy trials, etc.) that will facilitate the inclusion of the recommended four-drug FDC in the 1999 WHO Model List of Essential Drugs.
- Look for ways to work with regulatory agencies regarding the possibility of fast-track registration.

The manufacturers will:

- In addition, maintain open lines of communication through notification of future developments.

The United States Centers for Disease Control and Prevention (CDC) are encouraged to continue their work on post-marketing surveillance, including the possible publication of a manual.

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Annex 1: Agenda

WHO, Conference Room B

Chair-person: Dr Richard Laing

8.15-9.00	Registration. Distribution of meeting material.	
9.00-9.05	Welcome: Dr David Heymann, Executive Director of Communicable Diseases Cluster, WHO	
9.05-9.10	Introduction of participants	All
9.10-9.25	Objectives, expected outcome, agenda. Brief review of the justification for FDC tablets to replace single-drug tablets for treatment of TB	Dr S. Spinaci
9.25-9.40	The WHO/IUATLD recommended strengths of FDC tablets	Dr P. Chaulet
9.40-9.55	Assessing the rifampicin bioavailability of FDC tablets	Dr G. Ellard
9.55-10.15	Registration of FDC tablets. The quality of FDC tablets available on the market.	Dr B. Fourie
10.15-10.30	Questions to the presenters	All
10.30-11.00	Coffee break	
11.00-11.30	Discussion	All
11.30-12.30	Presentations from manufacturers explaining briefly what is being done on FDC tablets, particularly the four-drug FDC, in the company, including quality assurance, regulatory issues and what strengths of FDC tablets are produced.	Representatives of the manufacturers
12.30-14.00	Lunch	

14.00-15.30	Working groups to discuss the four-drug FDC tablets: How can WHO and the industry collaborate to establish mechanisms for <ol style="list-style-type: none">1. Regulatory issues (Group 1. Location: Room E-110)2. Quality assurance (Group 2. Location: Conference Room B)	
15.30-16.00	Coffee break	
16.00-16.15	Presentation of group 1	Group 1
16.15-16.30	Presentation of group 2	Group 2
16.30-17.30	Discussion, recommendations: How can the manufacturers, WHO and partners work together to: <ul style="list-style-type: none">• Promote quality of FDC tablets?• Ensure prompt registration of FDC tablets (the four-drug combination)?• Ensure supply and availability of quality FDC tablets in the countries? What are the implications of a change to FDC tablets as the primary drugs for TB treatment?	Discussions chaired by: Dr Kumaresan Dr Hogerzeil
17.30-17.50	Summary of meeting and recommendations	Dr R. Laing
17.50-18.00	Closing of meeting	Dr S. Spinaci Dr P. Nunn
18.30	Reception in the WHO restaurant	

Annex 2: List of participants

Invited participants

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