

# Meeting Report

UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Diseases (TDR)



## Informal consultation on 4-drug Fixed-Dose Combinations (4FDCs) compliant with the WHO Model List of Essential Drugs

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Writing committee:

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**Bjørn Blomberg,**  
Centre for International Health,  
University of Bergen, Norway

**Peter Evans,**  
Management Sciences for Health (MSH),  
Geneva, Switzerland

**Souly Phanouvong,**  
WHO, Geneva, Switzerland

**Paul Nunn,**  
TDR/WHO, Geneva, Switzerland

UNDP/World Bank/WHO  
Special Programme for Research and Training in Tropical Diseases (TDR)



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# Abbreviations

API.....	<i>Active pharmaceutical ingredient</i>
BP.....	<i>British Pharmacopoeia</i>
CDC.....	<i>United States Centers for Disease Control and Prevention</i>
DOTS.....	<i>The WHO recommended strategy for TB control. The letters mean “Directly Observed Treatment, Short-Course” but the strategy includes many other elements (Table 2)</i>
DRA.....	<i>Drug regulatory authority</i>
E.....	<i>Ethambutol</i>
EDL.....	<i>WHO Model List of Essential Drugs</i>
EDM.....	<i>Essential Drugs and Medicines</i>
EP.....	<i>European Pharmacopoeia</i>
FDC.....	<i>Fixed-dose combination products</i>
GDF.....	<i>Global TB Drug Facility</i>
GMP.....	<i>Good manufacturing practice</i>
H.....	<i>Isoniazid</i>
HPLC.....	<i>High-performance liquid chromatography</i>
ICH.....	<i>International Conference on Harmonisation</i>
INN.....	<i>International non-proprietary name</i>
IUATLD.....	<i>International Union against Tuberculosis and Lung Disease</i>
IDA.....	<i>International Development Association</i>
JP.....	<i>Japanese Pharmacopoeia</i>
MDR-TB.....	<i>Multidrug resistant tuberculosis</i>
MEG.....	<i>The Medical Export Group</i>
NTP.....	<i>National Tuberculosis Control Programme</i>
OTC.....	<i>Over-the-counter</i>
QSM.....	<i>Quality Assurance and Safety</i>
R.....	<i>Rifampicin</i>
STOP-TB.....	<i>A partnership for global action to stop tuberculosis</i>
TB.....	<i>Tuberculosis</i>
TDR.....	<i>UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases</i>
TLC.....	<i>Thin layer chromatography</i>
UNDP.....	<i>United Nations Development Programme</i>
USP.....	<i>United States Pharmacopoeia</i>
WHO.....	<i>World Health Organization</i>
WHO recommended 4FDC.....	<i>4FDCs, which are compliant with the WHO Model List of Essential Drugs, i.e. tablets containing 150mg rifampicin (R), 75mg isoniazid (H), 400mg pyrazinamide (Z) and 275mg ethambutol (E)</i>
Z.....	<i>Pyrazinamide</i>

## Executive Summary

### Objective

The 3-day informal meeting gathered experts and researchers with particular knowledge of fixed-dose combination products (FDCs) and TB control. Representatives of pharmaceutical companies were included\*.

The main objective of the meeting was to define the research agenda necessary to accelerate the use of the WHO recommended 4-drug fixed-dose combinations (4FDCs) for TB control in both public and private health care sectors by:

- Addressing the remaining quality assurance issues regarding the 4FDCs
- Defining necessary actions to facilitate the registration and wider use of the 4FDCs
- Defining a research agenda aimed at expanding the knowledge base on the use of 4FDCs

The term "WHO recommended 4FDCs" refers exclusively to 4FDCs which are compliant with the WHO Model List of Essential Drugs, i.e. tablets containing 150mg rifampicin (R), 75mg isoniazid (H), 400mg pyrazinamide (Z) and 275mg ethambutol (E).

### Topic

WHO has recommended the use of 4FDCs with proven bioavailability since 1994,<sup>1</sup> based on available evidence, but they are so far little used. If their potential is realized, the 4FDCs can be a means of improving TB control and expanding the use of the WHO recommended DOTS (*Directly Observed Treatment, Short-course*) strategy for TB control. Ultimately, 4FDCs can help save the lives of TB patients. Issues regarding quality assurance of FDCs and registration issues remain to be solved, and there is a need to increase the evidence on which to continue recommending and implementing FDCs in TB control programmes and other settings.

### Meeting activities

The first one and a half days of the meeting focused on presentations to bring all meeting participants up to date with the current status and future issues of pharmacological and pharmacokinetic research, clinical trials, operational research issues and regulatory issues regarding 4FDCs. At the same time, the research priorities in each area were discussed and set. The remainder of the meeting was mainly dedicated to the development of generic protocols for studies in priority research areas (See Annex 1: Agenda).

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### Conclusions and recommendations

#### 1. Implementation of 4FDCs in TB control

### Current status

Four-drug FDCs have a number of self-evident advantages in preventing monotherapy and rationalizing drug supply management (simplification of the calculation of drug needs, ordering, procurement and distribution). Furthermore, 4FDCs carry potential or unproven benefits such as simplification of prescription and drug ingestion and prevention of drug resistance.<sup>2</sup> Given acceptable bioavailability of the constituent drugs,

\* (see Annex 2: List of participants).

the 4FDC has the same efficacy as the equivalent combination of single-drug formulations.<sup>3</sup> Four-drug FDCs, including rifampicin, of proven quality and bioavailability, and at WHO recommended strengths, are available on the market in many countries. Four-drug FDCs have been registered by some national regulatory authorities and are being used in a few national tuberculosis control programmes (NTPs). Wider use would likely realize significant operational advantages and have the added benefit of providing opportunities for further detailed assessment of those advantages, as well as any disadvantages.

## **Recommendations**

- 1a) WHO and other STOP TB partners should increase, as from today, support for the wider implementation of 4FDCs in TB control, including the introduction of the 4FDC in revised treatment guidelines.
- 1b) The global TB drug facility (GDF) should provide the WHO recommended 4FDC through their supply mechanism.

### 2) Improving the quality assurance and safety testing of 4FDCs

## **Current status**

Despite major advances in assuring the quality of FDCs, sub-standard and counterfeit FDC products circulate in the market.<sup>4</sup> Their use for TB treatment is dangerous, can lead to the death of patients and creation of drug resistance, and must therefore be prevented. Among the range of necessary procedures for comprehensive quality assurance of any pharmaceutical product,<sup>5,6</sup> bioavailability testing is essential for assessing the quality of 4FDCs. Proven bioavailability of rifampicin is an absolute requirement for the use of 4FDCs.<sup>7</sup> WHO and its partners have established a bioavailability testing network. However, current procedures for bioavailability testing need further development to simplify them, lower the cost and reduce the time taken. Currently, there is no official monograph for the 4FDC published in internationally recognized pharmacopoeias, such as United States Pharmacopeia (USP), British Pharmacopoeia (BP) and the International Pharmacopoeia, although a draft version of a 4FDC monograph from USP is circulating for review and comments.\*

## **Recommendations**

- 2a) TDR and WHO, in particular Essential Drugs and Medicines/Quality Assurance and Safety (EDM/QSM), should support further research to:
  - develop a more efficient algorithm for screening of the quality of 4FDCs.
  - establish whether dissolution testing at different agitation rates would be a good surrogate, or supplement, for bioavailability testing.
- 2b) WHO/EDM should continue the ongoing joint efforts with USP to produce a pharmacopoeial monograph for the 4FDC.

### 3) Facilitating registration of 4FDCs of proven quality

## **Current status**

4FDCs have only been registered in three countries (South Africa, India, Bangladesh). The public, including TB control managers and drug procurement officers, does not have satisfactory access to pharmacological data, in particular evidence of bioavailability.

\* An official monograph for the 4FDC has been now published in the USP (USP 25-NF 20, 2002. The Official Compendia of Standards. United States Pharmacopeia, 25th Revision - National Formulary, 20th Revision. 1st Supplement to USP 25-NF 20. Rockville, MD: The United States Pharmacopoeial Convention, Inc.; 2002.).

**Recommendations**

- 3a) WHO/EDM and TDR should make available a dossier of the key documents necessary to facilitate swift registration of 4FDCs. The dossier should be based on the WHO "Model application form for new marketing authorizations, periodic reviews and variations, with notes to the applicant" (Annex 3),<sup>8</sup> which outlines the required documents. As part of this dossier, WHO/EDM and TDR should make available an official WHO protocol for bioavailability testing of FDCs.
- 3b) Leading anti-TB agencies, including WHO and other STOP TB partners, should support the wider implementation of 4FDCs in TB control by facilitating the flow of information useful for the registration of 4FDCs in countries.
- 3c) WHO and TDR should publish on the TDR website a "white-list" of 4FDC products/manufacturers with proven quality,"including bioavailability, and supporting data. The legal implications of this should be investigated by WHO/EDM and TDR.
- 3d) In order to facilitate the registration of quality 4FDCs, industry should make the results of bioavailability testing publicly available.

4) Expanding the evidence base for the use of FDCs

**Current status**

The registration of 4FDCs and their use in TB control is recommended. Nevertheless, it was agreed that it is desirable to increase the evidence base on which to continue recommending and implementing 4FDCs in TB control in both public and private health care sectors by:

- Gathering more evidence of, and quantitative data on, the operational advantages and disadvantages of FDCs on treatment delivery, drug supply management and prevention of drug resistance.
- Collecting evidence from clinical trials and programmatic data of the efficacy and effectiveness, respectively, of the 4FDCs.

There is a need for more knowledge on pharmacological/ pharmacokinetic properties of TB drugs in special populations (e.g. HIV+, diabetic). This concern applies to TB drugs in general (including single drug formulations), and not specifically FDCs.

**Recommendations**

- Operational issues:
- 4a) WHO and TDR should support the development of protocols to study:
    - Operational advantages and disadvantages of FDCs on patients' and doctors' compliance.
    - Drug supply management issues.
    - 4FDCs' potential impact on drug resistance.
    - 4FDC use in the private sector, including the reasons why they are used or not used in various settings.
  - 4b) WHO, Stop TB and TDR should support NTPs to:
    - Collect and analyse data on treatment outcome from well-functioning DOTS-based NTPs using 4FDCs.
    - Facilitate the analysis and description of the extent, and management, of adverse reactions, including policy and supply issues.

## **Recommendations**

- Efficacy and effectiveness:
- 4c) Further research on the efficacy and safety of the 4FDCs in NTPs or other settings may be useful. The International Union Against Tuberculosis and Lung Disease (IUATLD) clinical trial C offers a high-quality example for a study protocol. WHO and TDR should support the development of a range of template study protocols, which can be used by NTPs, the pharmaceutical industry and others, in order to obtain prospective evidence of the effectiveness of 4FDCs in control programme settings.
- Pharmacokinetic studies:
- 4d) WHO and TDR should support the development of protocols for pharmacokinetic studies, including pharmacokinetic studies for special populations/situations (HIV, diabetes, etc). This could be most efficiently studied as part of a clinical trial or other study on 4FDCs.



## Introduction

The meeting was opened by Dr J. Kengeya-Kayondo, TDR, who emphasized the importance of maintaining a long-term perspective in the introduction of 4FDCs as a tool to improve TB control in high burden countries. The 3-day informal meeting gathered experts and researchers with particular knowledge of FDCs, including a programme manager, academics, representatives of pharmaceutical companies and WHO secretariat with both control and research experience (see *Annex 2: List of participants*).

The main objective of the meeting was to define the research agenda necessary to accelerate the use of 4FDCs for TB control in both public and private health care sectors by:

- Addressing the remaining quality assurance issues regarding 4FDC.
- Defining necessary actions to facilitate the registration and wider use of 4FDC.
- Defining a research agenda aimed at expanding the knowledge base on the use of 4FDCs.

Based on available evidence, WHO has recommended the use of 4FDCs of proven bioavailability since 1994,<sup>1</sup> but they are so far little used. If their potential is realized, the 4FDCs can be a means of improving TB control and expanding the use of the DOTS strategy.

Ultimately, 4FDCs can help save lives of TB patients. Issues regarding quality assurance of FDCs and registration remain to be solved, and there is a need to increase the evidence on which to continue recommending and implementing FDCs in TB control programmes and other settings.

The agenda of the meeting is presented in Annex 1. The first one and a half days of the meeting were allocated to presentations and discussions to bring all meeting participants up to date with the current status and future issues of pharmacological and pharmacokinetic research, clinical trials, operational research issues and regulatory issues regarding 4FDCs. The presentations are available in *Annex 5*. For the remainder of the meeting, participants were allocated to working groups addressing the following main topics:

1. Regulatory issues
2. Quality issues
3. Efficacy issues
4. Operational issues

A number of generic protocols for proposed studies in priority research areas were prepared by the working groups and presented and discussed in plenum.

## Burden of TB and challenges of TB control

Every year, 8.5 million individuals get tuberculosis (TB) for the first time and 2 million die from it. The HIV epidemic has led to a huge increase in TB cases, particularly in sub-Saharan Africa. Multidrug-resistant TB (MDR -TB), i.e. TB resistant to the two most important TB drugs, isoniazid (H) and rifampicin (R), has emerged in all continents.<sup>9,10</sup> MDR-TB is extremely difficult and expensive to treat<sup>11,12</sup> and poses a serious challenge to the future of TB control.

The treatment of TB with short-course chemotherapy (four essential TB drugs for 2 months, followed by two essential TB drugs for 4-6 months) under proper supervision has been thoroughly documented as a highly-effective cure for TB. The recommended dose of each essential TB drug is shown in table 1.

**Table 1. Recommended Doses of Essential Tuberculosis Drugs**

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

The provision of short-course treatment to (at least) all smear-positive pulmonary TB cases is the backbone of any modern TB control programme as recommended by the International Union Against Tuberculosis and Lung Disease (IUATLD)<sup>13</sup> and WHO.<sup>14</sup> WHO has formulated a complete package for TB control called the DOTS strategy (Table 2).

**Table 2. The five main components of the WHO recommended DOTS (Directly Observed Treatment, Short-course) strategy for TB control**

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- 1) Government commitment to TB control
- 2) Diagnosis by smear microscopy mostly on self-reporting symptomatic patients
- 3) Provision of short-course chemotherapy under supervision at least during the first 2 months
- 4) An efficient and reliable system of supply of quality drugs
- 5) An efficient recording and reporting system with assessment of treatment results of individual patients

However, due to the length (6-8 months) and complexity (four drugs, up to 16 tablets a day) of the treatment, the delivery of short-course chemotherapy with single drug formulations is challenging and poses risks of prescription errors and lack of compliance with treatment. Drug supply management is complicated, since individual drugs must frequently be ordered from different sources, and there is a risk of out-of-stock situations, in which patients may be treated with too few drugs, or even only one drug in isolation. Subsequently, erratic drug intake may result in the selection of drug-resistant strains of the TB bacillus.

## Rationale for using FDCs in TB control

Since 1994, WHO and IUATLD have recommended the use of fixed-dose combination tablets for TB treatment.<sup>17</sup> In 1999, the WHO Model List of Essential Drugs (EDL) was updated to include a 4FDC, containing 150mg rifampicin (R), 75mg isoniazid (H), 400mg pyrazinamide (Z) and 275mg ethambutol (E), in addition to three paediatric FDCs,<sup>15,16</sup> bringing the total number of WHO recommended FDCs up to 12 as listed in Table 3.

**Table 3. The recommended strengths of fixed-dose combination formulations of essential anti-tuberculosis drugs (WHO Model List of Essential Drugs, 1999)**

For daily use		
Drugs	Form	Strengths
RHZE	Tablet	R 150mg + H 75mg + Z 400mg + E 275mg
RHZ	Tablet	R 150mg + H 75mg + Z 400mg
RHZ		R 60mg + H 30mg + Z 150mg (paediatric)*
RH	Tablet	R 300mg + H 150mg
RH		R 150mg + H 75mg
RH		R 60mg + H 30mg (paediatric) *
EH	Tablet	H 150 mg + E 400 mg
TH	Tablet	T 50mg + H 100mg
TH		T 150mg + H 300mg
For intermittent use 3 times weekly		
Drug	Forms	Strengths
RHZ	Tablet	R 150mg + H 150mg + Z 500mg
RH	Tablet	R 150mg + H 150mg
RH		R 60mg + H 60mg (paediatric) *

E=ethambutol, H=isoniazid, R=rifampicin, S=streptomycin, T=thioacetazone, Z=pyrazinamide\* (Dispersible form preferred)

For the first time, a fully FDC-based treatment could be given with formulations listed in the EDL, i.e. a 4FDC for the 2 months intensive phase followed by a 2FDC for the 4-6 months continuation phase. However, 4FDCs (RHZE) had in fact been available in the market since 1993, although not complying with the yet-to-come WHO recommended strengths. Other FDCs have a much longer history. Various 2FDCs have been used for approximately two decades, including TH, EH and RH. Currently, approximately a quarter of notified TB cases get treatment with the rifampicin-containing 2FDCs.<sup>17</sup> Later on, a 3FDC (RHZ) was introduced, but its market share has remained low, being used for less than 5% of notified TB cases.<sup>17</sup>

## FDCs simplify the delivery of treatment

FDCs have a number of obvious advantages over single drug formulations. In the WHO recommended FDCs, the strength of each constituent drug is carefully balanced in such a manner that adequate doses of all four drugs can be achieved for all patients by altering the number of tablets to be ingested per day according to bodyweight.<sup>2</sup> Table 4 and 5 show the easy-to-use dosage schedule for the rifampicin-containing FDCs for adults and children respectively. The FDC concept decreases both the risk of overdosing individual drugs, which theoretically may reduce the risk of dose-related adverse effects, and the risk of giving too low doses of individual drugs, which may help prevent selection of resistant strains of the TB bacillus. To further simplify the prescription, the number of tablets to be ingested per day remains the same in the continuation phase of the treatment if the 2-drug FDC with 150mg R and 75mg H is used. It is expected that this simplification of the treatment can reduce the risk of prescription errors and, thus, help ensure that the patient receives correct treatment.

**Table 4. Dosage schedule for FDCs of WHO recommended strengths for adults\***

Patient's body weight (kg)	Initial phase 2 months			Continuation phase		
	RHZE daily 150 mg+75 mg+ 400 mg+275 mg	RHZ daily 150 mg+75 mg +400 mg	RHZ 3x per week 150 mg+150 mg +500 mg	RH daily 150 mg+75 mg	RH 3x per week 150 mg+150 mg	HE daily 150 mg+400 mg
30-37	2	2	2	2	2	1.5
38-54†	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.

† The composition of the 4FDC also ensures adequate doses of the drugs when 50kg is chosen as cut-off point for changing between 3 and 4 tablets per day.

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**Table 5. Dosage schedule for FDCs of WHO recommended strengths for children\***

Patient's body weight (kg)	Initial phase 2 months	Continuation phase 4 months	
	RHZ daily 60 mg+30 mg+150 mg	RH daily 60 mg+30 mg	RH 3x per week 60 mg+60 mg
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

\* Referring to the use of paediatric formulations. R = rifampicin, H = isoniazid, Z = pyrazinamide.

As shown in table 6, the use of 4FDCs during the intensive phase of treatment may greatly reduce the number of tablets to be swallowed by the patient every day. In this way, treatment may become more agreeable to the patient, increasing the likelihood that she or he will comply with treatment. The relatively larger tablet size has been claimed as a possible disadvantage of the 4FDC. However, the newly developed 4FDCs from several manufacturers seem to be of acceptably modest size. Furthermore, there is evidence that patients feel more discomfort from the number of tablets to be swallowed, as compared to the size. In a study conducted in Hong Kong<sup>18</sup>, only 1% of 312 patients who received FDCs complained about the size or quantity to be ingested or difficulty with swallowing, as opposed to 5% of 308 patients receiving the single drug preparations. Treatment of TB in the private health sector is often of poor quality and usually without proper supervision from the health provider.<sup>19</sup> It has been argued that the FDC concept may improve the quality of treatment of TB in such settings as compared to giving single-drug formulations, due to the simplified prescription and ingestion of tablets.<sup>2</sup> However, erratic ingestion of FDCs may also lead to treatment failure and may promote the emergence of drug resistant TB.<sup>20</sup> Thus, whether FDCs or single-drug tablets are used, the other components of the WHO/IUATLD recommended strategy for tuberculosis control remain vital for successful tuberculosis control, including supervision of treatment. FDCs should be seen as a tool for reliable delivery of the short-course chemotherapy and promoted as an integrated part of a complete service package.

**Table 6. Simplification of treatment delivery by using FDCs. Examples of the number of tablets\* to be taken daily in the intensive phase of TB treatment according to body weight, either as single drugs or as FDCs†**

Body weight (kg)	Single-drug formulations					Total	4DFC†	
	R 150mg	H 300(100)‡ mg	Z 400mg	E 400 (100)‡ mg	Total			
35	2 [8.6]	1 [8.6]§	(2) ([5.7])	2 [22.9]§	2 [22.9]§	(6) ([17.1])	7-12	2
40	3 [11.3]	1 [7.5]§	(2) ([5.0])	2-3 [20-30]	2 [20.0]	(7) ([17.5])	8-14	3
50	3 [9.0]	1 [6.0]	(3) ([6.0])	3 [24]	2 [16]	(8) ([16.0])	9-17	3
60	4 [10.0]	1 [5.0]	(3) ([5.0])	4 [26.7]	3 [20.0]	(10) ([16.7])	12-21	4
75	5 [10.0]	1 [4.0]	(4) ([5.3])	4 [21.3]	4 [16.0]	(12)	13-25	5

\* Dosage per kg body weight is given in square brackets [...]

† R: 150mg+H: 75mg+Z: 400mg+E: 275mg

‡ Alternative strength formulations of isoniazid and ethambutol are given in brackets

§ Some formulations give slightly higher doses than recommended in the lower weight groups.

## FDCs simplify drug supply management

The use of FDCs limits the number of formulations to be procured and the number of manufacturers to consider, and may therefore simplify drug supply management issues such as calculation of drug needs, ordering, procurement, distribution and storage. There are currently 12 different anti-TB FDCs recommended by WHO, of which 9 contain rifampicin. These provide for different regimens with regard to dosage schedule (3 or 7 days per week) and different drug options in the continuation phase (RH, EH or TH). However, as shown in Table 7, the great majority of patients can be handled with only two main formulations (RHZE and RH). It has a severe effect on the TB treatment services when national tuberculosis programmes run out of stock of drugs. Out-of-stock situations can occur when too small supplies of drugs have been ordered, when buffer stocks are insufficient and when there are delays in receipt of orders from suppliers. Over-ordering drug supplies is also harmful, since large stocks of medicines may reach expiry dates before replacement stock has been made available. The use of FDC-based treatment may reduce the risk of out-of-stock situations, since there are fewer main drug formulations to consider and, thus, fewer manufacturers to deal with.

**Table 7. Formulations needed in TB control programmes using 4FDCs\***

Main formulations†	
RHZE	Intensive phase (adults, all categories)
RH (or EH or TH)	Continuation phase (adults)
Additional formulations‡	
Paediatric RHZ	Intensive phase (children)
Paediatric RH	Continuation phase (children)
Streptomycin	Intensive phase (re-treatment cases)
Ethambutol	Continuation phase (re-treatment cases)
Isoniazid	Prevention

\* This is only one of a number of possible alternative set-ups. † The great majority of patients can be handled with only two main formulations, including the sputum-smear positive pulmonary TB cases. ‡ In addition, single-drug tablets of the drugs R, H, Z and E need to be available at a limited number of central health facilities designated to the management of drug adverse reactions.

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## WHO quality control network for FDCs provides easy access to quality testing, including bioavailability studies

Although we are probably only seeing the tip of the iceberg, there is growing evidence of the extent of substandard and plain counterfeit pharmaceutical products circulating in the international drug market, particularly in low-income countries,<sup>4,21-26</sup> and anti-TB drugs are not exempted from this dangerous trend.<sup>4,25</sup> With low budgets and priority, regulatory agencies seem unable to stop the distribution of substandard drugs,<sup>27</sup> leaving health professionals to contemplate the possible impact these products may have on morbidity, mortality and the development of drug resistance. The insistence on low prices by procurement officers may compel national tuberculosis programme managers to consider drug suppliers who cannot provide appropriate guarantees of quality. In its promotion of FDCs for TB treatment, WHO, IUATLD and other agencies have been very vocal about the paramount importance

of using only products of proven quality, including proven bioavailability of the constituent drugs.<sup>7</sup> A protocol for bioavailability testing of anti-TB FDCs<sup>28,29</sup> has been developed and a laboratory network for quality control of anti-TB FDCs has been established<sup>30,31</sup> and put into action.<sup>4</sup> Currently, two laboratories participate in the WHO laboratory network for quality control of FDCs, namely the National Tuberculosis Research Programme, Medical Research Council, Pretoria, South Africa and the Department of Pharmaceutics, National Institute of Pharmaceutical, Education and Research (NIPER), Punjab, India. In future, it may be desirable to expand this network to include more laboratories, and guidelines for ensuring laboratory proficiency have been published.<sup>31</sup> The network is intended to serve in a mechanism of pre-qualification of products and suppliers in order to help national tuberculosis programmes obtain FDCs of good quality. The network can assist drug industry as well as drug regulatory authorities and the buyers in the quality and bioavailability testing of rifampicin-containing anti-TB FDCs. As far as we know, there is no similar service for quality testing/pre-qualification of single-drug formulations, although the problem of poor quality may be as big or bigger than for FDCs.<sup>25</sup> Packing single drugs together in blister or combi packs may not solve any problems if different providers are responsible for the various drugs and/or the blister packing. The provider of each individual drug may not want to guarantee the drug quality if he/she has doubts about the quality of the blister-packing and, on the other hand, the provider of the blister-packing may blame any quality problem on the drugs themselves, and not on the packing process. The availability of the WHO laboratory network for quality control of FDCs reduces the inconvenience and dangers of dealing with suppliers of sub-standard or counterfeit products, and makes it easier for national TB programmes and others to obtain drugs of proven quality.

### **Management of adverse reactions**

The management of serious adverse reactions poses potential operational challenges, since it requires the use of single-drug formulations. However, adverse reactions serious enough to warrant withdrawal of treatment are relatively rare,<sup>32-36</sup> and all evidence to date suggests that 4FDCs do not produce more adverse reactions than equivalent combinations of single-drug formulations.<sup>18,37-40</sup> It has been proposed that drug adverse reactions should be managed at a limited number of central health facilities, where a limited stock of single-drug formulations must be available.

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### **FDCs may help prevent the emergence of drug resistance**

Development of drug resistant TB is thought mainly to arise from erratic drug intake, particularly multiple interruptions of treatment and effective treatment with a single anti-TB drug in isolation.<sup>20,41</sup> Since black-market rifampicin is often used against a variety of infections other than tuberculosis, it may be given as monotherapy to patients who unsuspectedly have active TB, and this may lead to selection of rifampicin-resistant strains of the TB bacillus. Similarly, out-of-stock situations, where too few drugs are, or a single drug is, continued in isolation, may promote rapid emergence of drug resistance.

By virtually eliminating the risk of monotherapy, 4FDCs may help prevent the emergence of drug-resistant TB. Indeed, there is some indirect evidence for the notion that FDCs reduce the emergence of drug resistance, since relatively low

prevalence of MDR-TB has been documented in Brazil and South Africa where good quality FDCs have been used for decades.<sup>9,10,42</sup>

### **Cost considerations**

Treatment costs have been raised as an argument against the use of fully FDC-based treatment. Drugs for 4FDC-based treatment vary in price, with some providers charging approximately US\$40 per patient. But quality products may be obtained through the GDF for under US\$10 per patient, which is the same cost or lower than the price for 2FDC treatments. This low cost also applies when the 4FDC is provided in blister packs. Furthermore, cost issues should be seen in a broader context. The focus is on how much it costs to deliver the complete treatment package to the patients, instead of only the cost of buying the drugs. One should also consider the potential future cost savings of potentially preventing the emergence of drug resistance. It was claimed in the meeting that companies providing quality products sometimes face stiff competition on price from less quality oriented companies to the degree that they perceive that "quality does not pay". As a response, some companies are now providing medication as part of a complete package, which, among other things, includes training of health workers. A summary of obvious and potential advantages of 4FDCs is provided in Table 8.

**Table 8. Summary of obvious and potential advantages of using 4FDCs in TB control**

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- 1) **Simplification of treatment**
    - Minimize prescription errors (to be justified)
    - Increase patient and health worker compliance (to be justified)
    - Enable reduction of supervision (to be justified)
  - 2) **Simplification of drug supply management**
    - Calculating drug needs (self-evident)
    - Ordering, procurement (self-evident)
    - Distribution, storage (self-evident)
    - Reduce out-of-stock situations (to be justified)
    - Ensure availability of high-quality drugs (self-evident)
    - Management of drug adverse reactions (obvious disadvantage – but not quantified)
  - 3) **Decrease emergence of drug resistance, by means of**
    - Ensuring delivery to the patient of the correct dose of all drugs (to be justified)
    - Preventing monotherapy (self-evident)
-

## Constraints and achievements in the introduction of 4FDCs in TB control

### Initial constraints

The main constraints in the implementation of 4FDCs in TB control have been related to three main aspects:

#### 1) *Quality issues*

Based on the work by Acocella, Ellard and others,<sup>43-51</sup> it became evident that some anti-TB FDCs did not have satisfactory bioavailability of rifampicin. Other FDC products had satisfactory rifampicin bioavailability and the bioavailability issue appeared to be related to deficiencies in the manufacturing process. An apparently satisfactory in vitro dissolution test did not, unfortunately, guarantee adequate rifampicin bioavailability. Although the studies focused on FDCs, it should be noted that single-drug formulations can also be subject to quality problems, which can result in unsatisfactory bioavailability. WHO and IUATLD recommended the use of only FDCs with proven bioavailability.<sup>1</sup> However, there was a lack of FDCs of proven quality on the market. This was only to be expected, since there was not even consensus on the necessary procedures to ensure the quality of FDC products.

#### 2) *Standardization of recommended strengths*

The advantages of FDCs originate from the concept that the relative strengths of the constituent drugs are standardized in such a way that they facilitate the delivery of the correct dose of each drug to the patient. However, WHO's 1998 survey of the global market for these formulations showed a lack of FDCs of WHO-recommended strengths, but wide availability of a variety of different, sometimes inappropriate, strengths of FDCs.<sup>52</sup>

#### 3) *Slow implementation of FDCs in TB control*

The 1998 market survey showed that, although recommended by both WHO and IUATLD, only a quarter of notified TB patients received treatment with the rifampicin-containing 2FDCs, and less than 5% received treatment with the 3FDC.<sup>17</sup> This slow implementation of FDCs in TB programmes may have a number of reasons, including concerns about quality, a general conservatism in changing treatment policies, and lack of advocacy from leading TB bodies. Cost may have been an issue previously, but, at least for the 2FDCs, the price fell to the same as, or lower than, that of single drugs by the mid 1990s.<sup>17</sup>

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### Milestones

- In 1994, WHO and IUATLD recommended that only FDCs with proven rifampicin bioavailability should be used for the treatment of TB.<sup>1</sup> However, initially there was no consensus on how to ensure the bioavailability.
- In the 1997 WHO guidelines for the treatment of TB,<sup>14</sup> a number of 2FDCs and 3FDCs were listed with the provision that only those of proven quality should be used.
- In 1997, WHO launched a FDC project to address quality assurance issues.
- In 1998, WHO provided recommendations for the strength of the 4FDC.
- By 1999, a protocol for bioavailability testing of FDCs had been developed and published<sup>28,29</sup> as part of a supplement of the International Journal of Tuberculosis and Lung Disease dedicated to quality assurance of FDCs.

- By 1999, the WHO laboratory quality control network had been established, and was being used to assess the quality of FDCs.<sup>4,30,31</sup>
- By the end of 1999, the 4FDC, along with three paediatric FDCs, were placed on the WHO Model List of Essential Drugs.<sup>15,1</sup>

## Achievements

### **The initial constraints outlined above have been partially addressed and the following achievements have been made:**

- There are now good quality 4FDCs of WHO recommended strengths available in the market. The Pharmaceutical industry responded swiftly to WHO recommendations in developing and manufacturing 4FDCs of WHO-recommended strengths.
- The WHO laboratory network for quality control is used for bioavailability testing of FDCs, mainly by industry for registration purposes.
- 4FDC products have been registered with national regulatory authorities in a number of countries, including South Africa, India and Bangladesh.
- 4FDCs have been introduced in a few TB control programmes.

## Remaining issues

### **The meeting identified four main areas to be addressed for successful further implementation of 4FDCs in TB control activities:**

- 1) Facilitating implementation of 4FDCs in TB control.
- 2) Improving quality assurance and safety testing of FDCs.
- 3) Facilitating registration of 4FDCs.
- 4) Increasing the evidence base in support of 4FDCs.

These four issues will be dealt with separately.

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## **Implementation of 4FDCs in TB control**

4FDCs have a number of self-evident advantages in preventing monotherapy and rationalizing drug supply management by means of simplification of the calculation of drug needs, ordering, procurement and distribution. Furthermore, 4FDCs have potential or unproven benefits such as simplification of prescription and drug ingestion and prevention of drug resistance.<sup>2</sup> Given acceptable bioavailability of the constituent drugs, the 4FDCs have the same efficacy as the equivalent combination of single-drug formulations, and consequently it is not required to undertake clinical trials for the purpose of registering and using this formulation.

In the WHO Technical Report "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability"<sup>3,5</sup>, fixed-dose combination products are on the list of products, which require in vivo equivalence studies for registration. It is clearly stated, "Where a drug produces meaningful concentrations in an accessible biological fluid, such as plasma, bioequivalence studies are preferred".

Thus, given the obvious, and some less obvious, advantages of 4FDCs in TB control, and provided proven bioavailability of the constituent drugs, these products can safely be registered and used in TB control activities. There is circumstantial evidence of the benefits of FDC-based treatment in that low rates of multidrug-resistant TB have been recorded in countries, such as Brazil<sup>9</sup> and South Africa,<sup>42</sup> where good quality FDCs have been used for a prolonged period.

Trials of 3FDCs<sup>18,37,40</sup> have shown that FDCs have as few or fewer side-effects than single-drug formulations. While studies in Algeria<sup>37</sup> and Hong Kong<sup>18,38</sup> found similar failure rates in the patients receiving 3FDCs and single-drug formulations, a Singapore study<sup>39,40</sup> showed a higher relapse rate on follow-up after five years in the group receiving 3FDCs, in spite of the good bioavailability of the preparation used.

However, it is difficult to draw conclusions from one study and it is uncertain whether this has any relevance for the 4FDCs, particularly since the 3FDC used had a different composition than the currently recommended FDCs. A clinical trial comparing the 4FDC to conventional formulations has been planned to be undertaken by the IUATLD clinical trials network, and this may provide valuable additional information (See - Expanding the evidence base for the use of FDCs, page 25).

Currently, a number of 4FDCs of proven quality and WHO recommended strengths are available in the market. These formulations have been tested in the WHO laboratory quality control network, and been found to have satisfactory quality, including rifampicin bioavailability. Dr Fourie reported that, out of 22 FDC products tested on request from pharmaceutical companies, only two failed rifampicin bioavailability testing. Some 4FDCs have been registered with national regulatory authorities, and 4FDCs are being used in a few TB control programmes.

South Africa, a leading country in the use of 4FDCs, has followed WHO recommendations and available evidence, putting a 4FDC on the national EDL as the only option for intensive phase treatment of tuberculosis, but has differed from WHO recommendations in using a 4FDC with slightly different drug contents.

To the knowledge of the meeting participants, only three countries, South Africa, India and Bangladesh, have registered 4FDCs to date. And the use of 4FDCs as routine in national TB programmes is still very limited (South Africa and Congo Brazzaville).

Despite being on the WHO Model List of Essential Drugs, and despite their use being supported in principle by both WHO and IUATLD, there is a lack of emphasis and advocacy from leading TB agencies in actually promoting the implementation of 4FDCs at country level. In addition, as emphasized by Dr Blanc in his presentation, the majority of TB patients in the world are treated outside DOTS-based TB control programmes, and consequently erratic treatment is highly prevalent. The major constraint is that TB treatment is perceived as very complicated, because of the long treatment period, the many different drugs and the high numbers of tablets. While the emphasis on quality assurance has been very important and justified in the recommendation of FDCs, it has had the adverse effect of creating an impression of FDCs as being inferior to other anti-TB drug formulations as far as quality is concerned. Thus, it should be emphasized that quality is a concern of all TB drugs, not only FDCs. The emphasis on quality in the recommendation of 4FDCs has resulted in a situation where we now have a WHO laboratory network to ensure the quality of FDCs, while single-drug formulations are bought and used with much less awareness that they, also, can be subject to quality problems. The Chairperson, Dr Kibuga, confirmed the notion that many programme managers did not embrace the concept of FDCs because of concerns regarding their quality, and specifically their bioavailability. But he also said that, from a programme point of view, the 4FDC is not "unpopular", but that it is a new thing, which needs time to be adopted.

## **Supply issues**

Assuming that the efficacy and safety of the 4FDC is as good as, or better than, currently supplied TB drugs, the 4FDC should be introduced because it represents a chance to simplify many parts of the TB programme. Simplification generally improves the chances of success. While WHO/IUATLD have published standards, they allow for a wide range of solutions within the guidelines. This variability complicates all of the operational aspects of the programme. The variability of solutions occurs at all levels of the programme. Individual health centres are influenced by private practitioners and international STOP TB partners who make recommendations, which differ from one another. The 4FDC would allow for a simple common guideline capable of only one interpretation. Dispensing TB drugs at the health centre level is complicated and relies on a fail-proof forecasting and supply system. Errors result in one or more of the products being unavailable when needed, often making effective treatment impossible. The 4FDC will make forecasting, supply and dispensing measurably easier. Good surveillance can determine programme efficiency but it is difficult to determine if failure to succeed is due to bad practice, poor quality or stock-outs. In many health programmes, the off-take of products can be used as a rough indicator of programme activity. This is currently not possible for TB but could be if the 4FDC was introduced. Training to ensure acceptable practices in all aspects of TB control is undertaken to differing standards. Because the practices differ from country to country, each country must prepare its own training materials and undertake training to its own standards. The introduction of a standard regimen would allow for training materials to be universally applicable and lessons learned in one country to be transferable to other countries. Random surveys continue to show an unacceptable level of quality failures amongst TB drugs in widespread use. The quality assurance systems of the producing

and using countries leave a lot to be desired. International systems, to assure quality, have been created only to protect the interests of the purchasing agency and are insufficient to examine the large number of TB drug producers presently exporting drugs. Concentrated effort on a relatively few producers could ensure that only 4FDC of known good quality would be imported. The cost of the drugs for a full daily treatment with single-drug formulations, 2FDC-based or 4FDC-based treatment, is now approximately US\$10 per person. If supplied in packs of 1000, the cost of shipping should also be reduced by a few per cent, though savings would not be apparent if blister packs were supplied. The overall cost of delivering quality medication to the patients is expected to be similar or lower than present costs. A strong recommendation for the 4FDC will be followed by a limited number of countries (perhaps 10%) relying on international support. The majority of the countries will require a 2- to 3-year changeover period so they may debate the reasons for the proposed change, use up existing stock and exhaust contracts, prepare training materials and undertake training for the change. The 4FDC provides an excellent opportunity to rally the world around a new low-cost innovation for TB.

### **The Global TB Drug Facility**

Recently, the Global TB Drug Facility (GDF) has been established as a global mechanism to ensure universal uninterrupted access to quality TB drugs for DOTS implementation. The GDF is in collaboration with the Stop TB Partners and is managed by the Stop TB secretariat, which is housed in WHO. As presented by Peter Evans, the goal of the GDF is to use the best of available approaches to secure access to high-quality drugs and accelerate DOTS expansion. This is done by mobilizing funds for drug supply, reviewing drug needs from countries, supplying quality drugs via competitive bidding and ensuring monitoring and evaluation. The GDF uses technical assistance from the partners based on their "comparative strengths". GDF has created a menu of high-quality TB drugs, for which the technical specifications of drugs and packaging are in accordance with WHO guidelines. The GDF obtains drugs only from pre-qualified producers and uses a white list of producers drawn up from those being used by StopTB partners. The GDF has established the necessary procedures for efficient supply, online tracking of orders and monitoring, and has already finalized two application processes. A total of 25 countries applied for support, of which 12 countries were approved. Among the beneficial effects of this process are that costs of drugs purchased internationally have reduced, and that drugs are being produced to meet programme requests. Evans emphasized that when/if the 4FDC would be accepted as the first choice treatment, this would have impact on the supply mechanism. Firstly, a limited number of products will mean greater volume and lower production costs. Additionally, it would lead to greater predictability of demand, which in turn reduces the risk cost, and, furthermore, products can be stockpiled for rapid supply. The GDF provides a very timely opportunity to put emphasis on quality assurance, including the recommendation of standard testing and a standard quality assurance process. Fewer suppliers also mean easier auditing. Furthermore, the GDF provides a means of monitoring the use of 4FDCs, and it was suggested that supply could be used as an early indicator of progress. The requirements for successful implementation of 4FDC at programme

level would be training materials, which are transferable, one set of packaging of drugs, and the same advice given by all partners. The meeting saw the GDF as a very important vehicle to promote the use of 4FDCs at country level and, at the same time, ensure supplies of quality products. It would be a major support for the implementation of 4FDCs if the GDF would adopt a policy of recommending 4FDCs and approving applications for their use. If their potential is realized, the 4FDCs can be a valuable tool to improve TB control, ultimately helping save lives of TB patients. In the meeting it was agreed that the time has come to urge for a wider implementation of 4FDC-based TB treatment at country level. While the input of Stop TB partners is likely to be decisive in the further implementation of 4FDCs, the pharmaceutical industry also has an advocacy role to play.

**Recommendations**

- 1a) WHO and other Stop TB partners should increase, as from today, support for the wider implementation of 4FDCs in TB control, including the introduction of the 4FDC in revised treatment guidelines.
- 1b) The GDF should provide the WHO recommended 4FDCs through their supply mechanism.



## **Improving the quality assurance and safety testing of FDCs**

Despite major advances in assuring the quality of FDCs, sub-standard and counterfeit FDC products circulate in the market.<sup>4</sup> Tenders for TB drugs to national TB control programmes often have limited emphasis on quality, and sometimes the buyers don't even require proof of bioavailability. The use of poor-quality drugs for TB treatment is dangerous, can lead to the death of patients and the creation of drug resistance, and must therefore be prevented. Among the range of necessary procedures for comprehensive quality assurance of any pharmaceutical product,<sup>5,6</sup> bioavailability testing remains an important issue for assessing the quality of 4FDCs. However, quality assurance is a comprehensive process, and includes more than quality testing of the product. Mr de Goeje, International Development Association (IDA), advocated for inspection of good manufacturing practices (GMP) as another important requirement for approval of manufacturers.

Currently, two laboratories participate in the WHO laboratory network for quality control of FDCs, namely the National Tuberculosis Research Programme, Medical Research Council, Pretoria, South Africa, and the Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), Punjab, India. The two laboratories experience great demand for bioavailability testing of 4FDCs. Dr Fourie emphasized that, in his laboratory in South Africa, only one of the 23 products tested in the last three years has been tested for screening purposes.

The other 22 products were tested for licensing purposes on request from the pharmaceutical industry. It is encouraging that the industry uses the laboratory network to ensure the quality of their products. Nevertheless, it has been demonstrated that poor-quality FDC products circulates in the market,<sup>4</sup> and Dr Fourie raised the concern that there may be too little emphasis on testing products of unknown quality which are already available in the market.

### **An efficient algorithm for screening the quality of 4FDCs**

Proven bioavailability of rifampicin is an absolute requirement for the use of 4FDCs.<sup>7</sup> Every FDC product in clinical use should be tested, and only those which pass should be allowed to be used. HPLC-based determination of rifampicin serum/plasma concentrations in 24 healthy volunteers, in whom up to 15 blood samples are collected over a period of 24-48 hours, is regarded as the gold standard in assessing drug bioavailability. However, plasma-HPLC is expensive, cumbersome and time-consuming, because it requires hospitalization of study subjects, close observation to ensure 100% compliance with the study protocol, and a large team to carry out drug administration, blood taking and recording of each action at absolutely precise times. Also, the laboratory procedures are sophisticated and costly. To reduce costs, an abbreviated study protocol for bioavailability assessment of rifampicin was suggested, in which only six blood samples would be collected over an 8-hour period, and this abbreviated protocol showed closely similar results to those obtained using the extended protocol. However, even using the abbreviated protocol, serum/plasma-based bioavailability testing remains largely impractical as a screening tool in drug procurement, particularly due to cost considerations.

In the meeting, Dr Fourie proposed that an algorithm should be developed for the most cost-effective use of available tools for quality assurance of FDCs. Bioavailability testing would still be required as final proof of the quality of the formulations, but great cost savings could be achieved if less expensive tests could exclude poor quality

products at an earlier stage, limiting the number of final candidates for bioavailability testing. For additional procedures to be useful in such an algorithm, they must be:

- a) *Less expensive, and less cumbersome and/or time-consuming than plasma-bioavailability studies.*
- b) *Highly specific, i.e. no good products should be discarded based on the screening procedure.*

There are other, less expensive methods available for quality testing of anti-TB drugs, including urine-HPLC assays, colorimetric assessment of urinary excretion, thin layer chromatography (TLC), and dissolution testing. Dr Fourie showed data comparing the various test methods on a number of FDCs.

The urinary colorimetric method was the best predictor of plasma bioavailability.<sup>43,53</sup> A special TLC kit has been developed by the US Food and Drug Administration,<sup>54,55</sup> and has been used by the US Centers for Disease Control and Prevention (CDC) in a recent comprehensive study<sup>55</sup> of rifampicin - and isoniazid - containing formulations, both FDCs and single - drug products sampled from six countries.

TLC has special interest because of its very low cost compared to bioavailability studies. TLC has only 50% sensitivity in identifying good products, i.e. 50% of products which pass TLC will fail on bioavailability testing. Thus, TLC alone is not sufficient to determine the quality of products. However, it has great specificity in the sense that all products which fail on TLC will also fail on bioavailability testing. This high specificity makes TLC particularly useful as a screening tool to limit the number of products which need to be submitted for bioavailability testing.

The working group on quality issues came up with a draft protocol for development of an algorithm for a screening procedure which will reduce the number of investigations to be carried out by conventional bioavailability testing in human subjects.

### **Dissolution testing: potential surrogate for bioavailability**

Dissolution testing is one of the most widely used in vitro procedures in quality control of drugs. It is relatively cheaper and less labour-intensive than other procedures, but is not a reliable predictor of bioavailability.

Dr Panchagnula presented his recent work on dissolution testing, which showed that agitation rates and other factors influence the results. If agitation rates and other factors are adjusted, the dissolution results correspond much better to bioavailability results. It was proposed to look further into the feasibility of developing an inexpensive, faster and reliable surrogate marker for rifampicin bioavailability in 4 FDCs based on dissolution testing. Dr Panchagnula's working group developed a draft protocol for such studies, (see Annex 4).

### **Pharmacopoeial monograph for 4FDC**

A pharmacopoeial monograph for the 4FDCs has been called for<sup>56</sup> to facilitate the quality assurance of these products. A monograph for the WHO-recommended 3FDC is available from United States Pharmacopeia (USP). Currently, there is no official monograph for the 4FDC published in internationally recognized pharmacopoeias, such as USP, British Pharmacopoeia (BP) and the International Pharmacopoeia. However, a draft version of a 4FDC monograph from USP is circulating for review and comments\*. Dr Vanbel (Quality Assurance and Safety:

\* An official monograph for the 4FDC has been now published in the USP (USP 25-NF 20, 2002. The Official Compendia of Standards. United States Pharmacopeia, 25th Revision - National Formulary, 20th Revision. 1st Supplement to USP 25-NF 20. Rockville, MD: The United States Pharmacopoeial Convention, Inc.; 2002.).

Medicines, Essential Drugs and Medicines Policy - QSM, EDM, WHO) informed the meeting that WHO/EDM is formally collaborating with USP on the production of a 4FDC monograph, which eventually is expected to be presented as a joint publication between USP and WHO. In her presentation to the meeting, Dr Vanbel reviewed the WHO procedures for the preparation of drug quality control specifications. She emphasized that a pharmacopoeial monograph is a set of specifications with limits of acceptance. It provides specifications for one or more analytical procedures, which, in association with the limits of acceptance, define qualitative (identification) and quantitative (limits for impurities and content of active ingredient[s]) characteristics of the substance. In addition, the monograph should give general and specific requirements for dosage forms (e.g. disintegration test, dissolution test for tablets). The interpretation of a monograph must be in accordance with all general requirements and testing methods, texts or notices pertaining to it, and a pharmaceutical product has to comply with all the requirements stated in the monograph to be declared as of pharmacopoeial quality. In the International Pharmacopoeia, when complex methods such as HPLC are described, a classical method (e.g. TLC) is proposed as an alternative, if possible. There was great interest in the forthcoming USP/WHO monograph.

**Comparator products  
for bioavailability  
studies**

On various occasions, the need has been expressed for clear guidance on which comparator product (reference product) should be used for bioequivalence (comparative bioavailability) studies. This issue was clarified by Dr Vanbel, referring to an article in "WHO Drug Information",<sup>57</sup> which provides clear guidelines for comparator products. It is the responsibility of each country's national regulatory authority to determine which comparator products should be used. While many countries have established their lists of comparator products, other countries have not. WHO has produced a List of Comparator Products with reference to the WHO Model List of Essential Drugs. In general, it is recommended that the innovator product (the first form available of the drug in question) is used as comparator product, if it is available. If the innovator product is not readily identifiable or not available, the WHO List of Comparator Products may be consulted to identify a comparator product. If no innovator product can be obtained, a local market leader product may be used, provided quality, safety and efficacy are established. When no innovator product can be identified and there is no market leader product available, the proposed multisource pharmaceutical product should be manufactured in accordance with local, national or regional standards including, as applicable, *The International Pharmacopoeia* and *Multisource pharmaceutical products: WHO guidelines on registration requirements to establish interchangeability*.<sup>3</sup> There was consensus in the meeting that the guidelines regarding the issue of comparator products are sufficient.

**Recommendations**

- 2a) TDR and WHO, in particular EDM/QSM, should support further research to:
- develop a more efficient algorithm for screening of the quality of 4FDCs.
  - establish whether dissolution testing at different agitation rates would be a good surrogate, or supplement, for bioavailability testing.
- 2b) WHO/EDM should continue the ongoing joint efforts with USP to produce a pharmacopoeial monograph for the 4FDC.



## **Facilitating registration of FDCs of proven quality**

While 2FDCs (RH, EH, TH) and 3FDCs (RHZ) have been available on the market for a longer time than 4FDC, even the latter (RHZE) were in manufacture before WHO and IUATLD's milestone statement in 1994 recommending FDCs.<sup>1</sup> While 2FDCs account for approximately a quarter of all rifampicin used in the public health care sector,<sup>17</sup> the registration and use of 3FDCs and 4FDCs have been much more limited. This has partly been due to concerns regarding quality, stimulated by evidence that rifampicin bioavailability can be poor in FDCs.<sup>43-51</sup>

WHO is currently recommending the use of a 4FDC,<sup>15,16</sup> allowing for fully FDC-based treatment for TB. In the recommending of FDCs, WHO and IUATLD have been very focused on quality issues.<sup>1,7</sup> This has resulted in the development of a protocol for bioavailability testing of FDCs<sup>28,29</sup> and the establishment of a WHO laboratory quality control network for FDCs.<sup>4,30,31</sup> Currently, 4FDCs of high quality and WHO recommended strengths are available on the market, and, to the knowledge of the meeting participants, 4FDCs have been registered in three countries (South Africa, India, Bangladesh). South Africa, a forerunner in the implementation of 4FDCs, is already using a 4FDC in the national TB programme. Despite the availability of 4FDCs of proven quality, including rifampicin bioavailability, many TB professionals worldwide still have concerns about the quality of FDCs. This may be related to the fact that, as for single-drug formulations, poor-quality 4FDCs are available in the market. The public, including TB control managers and drug procurement officers, does not have satisfactory access to pharmacological data, in particular evidence of bioavailability. NTP managers and drug procurement officers clearly have a strong need for information on quality, including bioavailability of 4FDCs, in order to choose an appropriate product/supplier for their programme. There are two possible ways to achieve this. First of all, it is important that NTP managers and procurement officers insist on strong evidence of quality, including rifampicin bioavailability, as an absolute criterion for buying the products. Furthermore, the availability of a "white list" of products and suppliers with proven quality would help both the registration of products and their use in national TB programmes. A neutral organization, such as the WHO Global TB Drug Facility and TDR should be responsible for such a "white list", but there would also be a responsibility on industry to make available results on bioavailability testing and other quality assurance issues. In the meeting, on direct questioning from the co-chair, Mr Bumgarner, all representatives of pharmaceutical companies informally expressed either willingness to publish data on the bioavailability of their products, or said that the data were already available to the public.

An obstacle to swift registration of 4FDCs is that various regulatory authorities often insist on different sets of accompanying information. Thus, pharmaceutical companies cannot use the same dossier for the purpose of registration in different countries. There is a need for a standardized dossier outlining the key documents necessary for registration. Existing WHO documents<sup>8</sup> provide an outline of the necessary documentation and could thus be used as a template in the development of this dossier.

## **Recommendations**

- 3a) WHO/EDM and TDR should make available a dossier of the key documents necessary to facilitate swift registration of 4FDCs. The dossier should be based on the WHO "Model application form for new marketing authorizations, periodic reviews and variations, with notes to the applicant" (Annex 3),<sup>8</sup> which outlines the required documents. As part of this dossier, WHO/EDM and TDR should make available an official WHO protocol for bioavailability testing of FDCs.
- 3b) Leading anti-TB agencies, including WHO and other Stop TB partners, should support the wider implementation of 4FDCs in TB control by facilitating the flow of information useful for the registration of 4FDCs in countries.
- 3c) WHO and TDR should publish on the TDR website a "white-list" of 4FDC products/manufacturers, with proven quality, including bioavailability, and supporting data. The legal implications of this should be investigated by WHO/EDM and TDR.
- 3d) In order to facilitate the registration of quality 4FDCs, industry should make the results of bioavailability testing publicly available.



## **Expanding the evidence base for use of FDCs**

The registration of 4FDCs and their use in TB control is justified and recommended (see - Implementation of 4FDCs in TB Control (Page 15)). There was consensus in the meeting that there should be no need for further clinical trials for the purpose of registering and using 4FDCs in national TB programmes, provided the products are of WHO-recommended strengths and of good quality, including acceptable bioavailability of the constituent drugs. Although not necessary for registration and use of 4FDCs, it was agreed that it would be desirable to quantify any advantages and to increase the evidence base on which to continue recommending and implementing 4FDCs in TB control in both public and private health care sectors. This would, provided results are positive, provide an impetus for the wider implementation of 4FDCs.

Dr Chitsulo informed the meeting of the TDR activities in research capacity strengthening. TDR has advertised grants for the strengthening of research capacity in 40 TB high-burden countries. Seventy-nine initial applications have been condensed into a shortlist of the nine applications found most appropriate. Representatives for these nine institutions are to meet in September in a workshop in Ethiopia to further develop the protocols. A number of these applications vow to investigate the efficacy of 4FDCs under programme conditions. A positive effect of further studies on 4FDCs would be to enhance the capacity of developing countries' institutions to perform clinical trials.

Dr Jindani expressed the need for studies which cover all ethnic groups. Dr Ellard emphasized that bioavailability of rifampicin is the main quality issue and that available studies have not indicated any differences between races with respect to this.

Dr Laing underlined that treatment practice and policy are different in different settings and that it would be important to obtain data from studies in different geographical settings.

### **Operational issues**

The most obvious advantages of 4FDCs are operational in nature. 4FDCs would greatly simplify delivery of treatment, and they would be expected to have impact on both health workers' prescriptions and patients' compliance with treatment. Furthermore, drug supply management, including ordering, procurement, receipt of supplies, distribution and storage, is expected to become less complicated with the use of 4FDCs, except for the issue of drug adverse reactions. Possibly the most important advantage of the 4FDC would be its capability to prevent monotherapy, which potentially may safeguard against the development of drug resistance. It would thus be highly valuable to gather more evidence of, and quantitative data on, the operational advantages and disadvantages of FDCs.

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### **Efficacy and safety**

Dr Jindani presented the IUATLD network for clinical trials. The network will in the near future commence "Study C", which will compare the efficacy of the standard short-course chemotherapy regimen 2RHZE/4RH when given with 4FDCs and separate drugs in the initial phase of treatment. Although, as mentioned, the meeting did not see clinical trials as a "requirement" for registration or use of 4FDCs, there was broad consensus in the meeting that it would be highly valuable for this clinical trial to be conducted. The study has the potential to produce data which will either

support or conceivably discourage further implementation of 4FDCs in TB control. The meeting acknowledged IUATLD's "Study C" as a gold standard for other studies intended to study the efficacy and safety of FDCs. Furthermore, it would be valuable to collect evidence from clinical and programmatic data for the efficacy and effectiveness respectively of 4FDCs. This could be done in relatively short time and with low use of resources by collecting information from countries, such as South Africa, where large amounts of data may be available for patients on both 4FDC-based and alternative regimens.

### Pharmacokinetic issues

There is a need for more knowledge on pharmacological and pharmacokinetic properties of TB drugs in special populations. It was emphasized that this concern applies to TB drugs in general, including single drug formulations, and not specifically FDCs. Although there are many groups to consider, such as gender and persons with cystic fibrosis, asthma and other diseases, it was suggested that diabetics and, in particular, persons living with HIV/AIDS, would be the most important groups to study.

### Recommendations

- 4a) Operational issues  
WHO and TDR should support the development of protocols to study:
- Operational advantages and disadvantages of FDCs on patients' and doctors' compliance.
  - Drug supply management issues.
  - 4FDCs' potential impact on drug resistance.
  - 4FDC use in the private sector, including the reasons why they are used or not used in various settings.
- 4b) WHO, Stop TB and TDR should support NTPs to:
- Collect and analyse data on treatment outcome from well-functioning DOTS-based NTPs using 4FDCs.
  - Facilitate the analysis and description of the extent of, and the management of, adverse reactions, including policy and supply issues.
- 4c) Efficacy and effectiveness  
Further research on the efficacy and safety of the 4FDCs in national TB control programmes or other settings may be useful. In order to obtain synergistic effects of different research projects, the research should be planned and conducted in a careful, coordinated way, using the IUATLD clinical trial C as a gold standard for study protocols, but allowing for specific adaptation of the protocol according to study site, available budget and expertise, etc. WHO and TDR should support the development of a range of template study protocols which can be used both by NTPs, pharmaceutical industry and others.
- 4d) Pharmacokinetic studies  
WHO and TDR should support the development of protocols for pharmacokinetic studies, including pharmacokinetic studies for special populations/situations (HIV, diabetes, etc). Concern about pharmacokinetic issues is as much a topic for single drug formulations as for 4FDCs, but could nevertheless be studied as part of clinical trials or other studies on 4FDCs.

## References

1. The promise and reality of fixed-dose combinations with rifampicin. A joint statement of the International Union Against Tuberculosis and Lung Disease and the Tuberculosis Programme of the World Health Organization. *Tubercle and Lung Disease*, 1994, 75:180-181.
2. Blomberg B et al.,(2001).The rationale for recommending fixed-dose combination tablets for treatment of tuberculosis. *Bulletin of the World Health Organization*, 79:61-68.
3. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996:65-79 (WHO Technical Report Series, No. 863).
4. Pillai G et al., (1999).Recent bioequivalence studies on fixed-dose combination anti-tuberculosis drug formulations available on the global market. *The International Journal of Tuberculosis and Lung Disease*, 3:S309-316; discussion S17-21.
5. World Health Organization. (1997). *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials*. Geneva, World Health Organization.
6. World Health Organization. (1999). *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2: Good manufacturing practices and inspection*. Geneva, World Health Organization,.
7. World Health Organization, International Union Against Tuberculosis and Lung Disease (1999). Assuring bioavailability of fixed-dose combinations of antituberculosis medication. A joint statement of the International Union Against Tuberculosis and Lung Disease and the World Health Organization. *The International Journal of Tuberculosis and Lung Disease*, 3:S282-S83.
8. World Health Organization (1998). *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products. A manual for a Drug Regulatory Authority*. Geneva, World Health Organization. (Regulatory Support Series, No. 5, WHO/DMP/RGS/98.5).
9. Pablos-Mendez A, et al. (1998). Global surveillance for antituberculosis-drug resistance. World Health Organization-International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. *The New England Journal of Medicine*, 338:1641-1649.
10. Espinal MA, et al.,(2001). Global trends in resistance to antituberculosis drugs. World Health Organization-International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. *The New England Journal of Medicine* , 344:1294-303.
11. Mahmoudi A, Iseman MD. (1993). Pitfalls in the care of patients with tuberculosis. Common errors and their association with the acquisition of drug resistance. *Journal of the American Medical Association*, 270:65-68.
12. Weyer K, Fourie PB, Nardell EA.,(1999). *The global impact of drug-resistant tuberculosis*. Chapter 5. A noxious synergy: tuberculosis and HIV in South Africa. Boston, Harvard Medical School and Open Society Institute.
13. Enarson DA, et al.: (1996) *Tuberculosis guide for low income countries*. Paris, International Union Against Tuberculosis and Lung Disease.

14. Maher D, et al., (1999). *Treatment of tuberculosis: Guidelines for National Programmes*. Geneva, World Health Organization, Communicable Diseases Cluster, 1997.
15. Essential drugs. WHO Model List (revised December 1999). *WHO Drug Information*, , 13:249-262.
16. *The use of essential drugs: ninth report of the WHO Expert Committee* (including the revised Model List of Essential Drugs). Geneva, World Health Organization, 2000 (WHO Technical Report Series, No. 895).
17. Norval PY, et al., (1999). Estimate of the global market for rifampicin-containing fixed-dose combination tablets. *The International Journal of Tuberculosis and Lung Disease*, 3:S292-300, discussion S17-21.
18. Hong Kong Chest Service/British Medical Research Council. Acceptability, compliance, and adverse reactions when isoniazid, rifampin, and pyrazinamide are given as a combined formulation or separately during three-times-weekly antituberculosis chemotherapy. *The American Review of Respiratory Disease*, 1989, 140:1618-22.
19. Uplekar MW, Shepard DS. (1991). Treatment of tuberculosis by private general practitioners in India. *Tubercle*, 72:284-90.
20. Mitchison DA. (1998). How drug resistance emerges as a result of poor compliance during short course chemotherapy for tuberculosis. *The International Journal of Tuberculosis and Lung Disease*, 2:10-5.
21. Taylor RB, Shakoor O, Behrens RH. (1995) Drug quality, a contributor to drug resistance? *Lancet*, 346:122.
22. Shakoor O, Taylor RB, Behrens RH. (1997). Assessment of the incidence of substandard drugs in developing countries. *Tropical medicine and international health*, , 2:839-45.
23. O'Brien KL, et al., (1998). Epidemic of pediatric deaths from acute renal failure caused by diethylene glycol poisoning. Acute Renal Failure Investigation Team. *Journal of the American Medical Association*, , 279:1175-80.
24. Schofield J. Counterfeit pharmaceuticals flood Russian market. *British Medical Journal*, 2001, 322:1564d.
25. Taylor RB, et al., (2001). Pharmacopoeial quality of drugs supplied by Nigerian pharmacies. *Lancet*, 357:1933-1936.
26. Newton P, et al., (2001). Fake artesunate in southeast Asia. *Lancet*, 2001, 357:1948-1950.
27. Chatterjee P. India's trade in fake drugs—bringing the counterfeiters to book. *Lancet*, , 357:1776.
28. Fourie PB, et al. (1999). *Model Protocol. Establishing the bioequivalence of rifampicin in fixed-dose formulations containing isoniazid with or without pyrazinamide and/or ethambutol compared to the single drug reference preparations administered in loose combination*. Geneva, World Health Organization, (unpublished document: WHO/CDS/TB/99.274).
29. Quality assurance: Protocol for assessing the rifampicin bioavailability of combined formulations in healthy volunteers. *The International Journal of Tuberculosis and Lung Disease*, 1999, 3:S284-s85.
30. Fourie PB, Spinaci S. (1999). Structures required, roles and responsibilities in maintaining laboratories for quality assurance of anti-tuberculosis fixed-dose combinations in accordance with the IUATLD/WHO statement.

- The International Journal of Tuberculosis and Lung Disease*, 3:S368-70, discussion S81-7.
31. Ellard GA. (1999). The evaluation of rifampicin bioavailabilities of fixed-dose combinations of anti-tuberculosis drugs: procedures for ensuring laboratory proficiency. *The International Journal of Tuberculosis and Lung Disease*, 3:S322-4, discussion S51-52.
32. Snider DE, et al. (1984). Supervised six-months treatment of newly diagnosed pulmonary tuberculosis using isoniazid, rifampin, and pyrazinamide with and without streptomycin. *The American Review of Respiratory Disease*, 130:1091-94.
33. Girling DJ. (1984). The role of pyrazinamide in primary chemotherapy for pulmonary tuberculosis. *Tubercle*, 65:1-4.
34. East African and British Medical Research Councils. Controlled clinical trial of five short-course (4-month) chemotherapy regimens in pulmonary tuberculosis. First report of 4th study. *Lancet*, 1978, 2:334-38.
35. Singapore Tuberculosis Service/British Medical Research Council. Clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. *The American Review of Respiratory Disease*, 1979, 119:579-85.
36. British Thoracic Association. A controlled trial of six months chemotherapy in pulmonary tuberculosis. First Report: results during chemotherapy. *British Journal of Diseases of the Chest*, 1981, 75:141-53.
37. Chaulet P, Boulahbal F. (1995). Essai clinique d'une combinaison en proportions fixes de trois médicaments dans le traitement de la tuberculose. [Clinical trial of a combination of three drugs in fixed proportions in the treatment of tuberculosis] Groupe de Travail sur la Chimiothérapie de la Tuberculose. *Tubercle and Lung Disease*, 76:407-12.
38. Hong Kong Chest Service/British Medical Research Council. Controlled trial of 2, 4, and 6 months of pyrazinamide in 6-month, three-times-weekly regimens for smear-positive pulmonary tuberculosis, including an assessment of a combined preparation of isoniazid, rifampin, and pyrazinamide. Results at 30 months. *The American Review of Respiratory Disease*, 1991, 143:700-06.
39. Singapore Tuberculosis Service/British Medical Research Council. Assessment of a daily combined preparation of isoniazid, rifampin, and pyrazinamide in a controlled trial of three 6-month regimens for smear-positive pulmonary tuberculosis. *The American Review of Respiratory Disease*, 1991, 143:707-12.
40. Teo S.K. (1999). Assessment of a combined preparation of isoniazid, rifampicin and pyrazinamide (Rifater) in the initial phase of chemotherapy in three 6-month regimens for smear-positive pulmonary tuberculosis: a five-year follow-up report [see comments]. *The International Journal of Tuberculosis and Lung Disease*, 3:126-32.
41. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: Recommendations 1998. *Thorax*, 1998, 53:536-548.
42. Weyer K, Groenewald P, Zwarenstein M, Lombard CJ. (1995). Tuberculosis drug resistance in the Western Cape. *South African Medical Journal*, 85:499-504.

43. Ellard GA, et al., (1986). The bioavailability of isoniazid, rifampin, and pyrazinamide in two commercially available combined formulations designed for use in the short-course treatment of tuberculosis. *The American Review of Respiratory Disease*, 133:1076-80.
44. Acocella G, et al., (1988). Comparative bioavailability of isoniazid, rifampin, and pyrazinamide administered in free combination and in a fixed triple formulation designed for daily use in antituberculosis chemotherapy. I. Single-dose study. *The American Review of Respiratory Disease*, 138:882-85.
45. Acocella G, et al., (1988). Comparative bioavailability of isoniazid, rifampin, and pyrazinamide administered in free combination and in a fixed triple formulation designed for daily use in antituberculosis chemotherapy. II. Two-month, daily administration study. *The American Review of Respiratory Disease*, 138:886-90.
46. Acocella G., (1989) Human bioavailability studies. *Bulletin of the International Union against Tuberculosis and Lung Disease*, 64:38-40.
47. Fox W. (1990). Tuberculosis in India, past, present and future. *Indian Journal of Tuberculosis*, 37:175-213.
48. Fox W. (1990) Drug combinations and the bioavailability of rifampicin. *Tubercle* 71:241-245.
49. Schall R, et al., (1995). Relative bioavailability of rifampicin, isoniazid and ethambutol from a combination tablet vs. concomitant administration of a capsule containing rifampicin and a tablet containing isoniazid and ethambutol. *Arzneimittelforschung*, 45:1236-239.
50. Zwolska Z, et al., (1998). Bioavailability of rifampicin, isoniazid and pyrazinamide from fixed- dose combination capsules. *The International Journal of Tuberculosis and Lung Disease*, 2:824-30.
51. Ellard GA, Fourie PB., (1999). Rifampicin bioavailability: a review of its pharmacology and the chemotherapeutic necessity for ensuring optimal absorption. *The International Journal of Tuberculosis and Lung Disease*, 3:S301-8, discussion S17-521.
52. Kitler ME., (1998). Report: *The fixed dose combination project*. Geneva, World Health Organization. (unpublished WHO document, Communicable Diseases Cluster).
53. Pillai G, et al., (2001). The potential use of urinary excretion data for assessing the relative bioavailability of rifampicin in fixed dose combination anti-tuberculosis formulations. *The International Journal of Tuberculosis and Lung Disease*, 5:691-5.
54. Kenyon TA, et al., (1999). Detection of substandard fixed-dose combination tuberculosis drugs using thin-layer chromatography. *The International Journal of Tuberculosis and Lung Disease*, 3:S347-50, discussion S51-52.
55. Laserson KF, et al., (2001). Substandard tuberculosis drugs on the global market and their simple detection. *The International Journal of Tuberculosis and Lung Disease*, 5:448-54.
56. Laing R, et al., (1999). World Health Organization. *Fixed dose combination tablets for the treatment of tuberculosis*. Report from an informal meeting held in Geneva, Tuesday, 27 April 1999. Geneva, World Health Organization.
57. International comparator products for bioequivalence testing. *WHO Drug Information*, 1999, 13:158-62.



UNDP/World Bank/WHO  
Special Programme for Research and Training in Tropical Diseases (TDR)

## Annex 1: Agenda

### Informal Consultation on 4-drug Fixed-Dose Combinations

*Geneva, Switzerland  
15-17 August 2001  
Chair: Dr Daniel Kibuga  
Co-chair: Dr Richard Bumgarner  
Rapporteur: Dr Bjørn Blomberg*

#### **Day 1: 15 August 2001**

09:00-09:05	: Welcome	J. Kengeya-Kayondo
09:05-09:15	: Introduction and Adoption of Agenda	R. Bumgarner (Co-chair)
09:15-09:30	: Objectives of Meeting	P. Nunn
09:30-09:50	: Current Status and Future Issues of Pharmacological and Pharmacokinetic Research and Clinical Trials	B. Fourie
09:50-10:00	: Discussion	
10:00-10:15	: Coffee	
10:15-10:35	: Health Policy Services & Systems Research in 4FDCs- Current Status And Future Issues	B. Blomberg
10:35-10:45	: Discussion	
10:45-11:30	: <u>Operational Issues:</u> 1) Control Programme Needs and DOTS Expansion 2) Procurement Issues and Global Drug Facility 3) Distribution, Storage, prescription and consumption issues 4) 4FDC study within NTP in Sulawesi, Indonesia: results so far	L.Blanc/D. Kibuga P. Evans R. Laing M. Becx-Bleuminck
11:30-12:10	: <u>Pharmacological Research and Clinical Trials Issues:</u> 1) Current status of WHO's bioavailability network 2) Clinical Trials of safety and efficacy- The IUATLD Clinical Trials Network	R. Panchagnula/ B. Fourie A. Jindani
12:10-12:30	: Summary of Research Issues	G. Roscigno
12:30-14:00	: Lunch	
14:00-15:00	: Current Status of 4FDCs in Industry	Wyeth-Lederle Novartis MEG-Svizzera Lupin IDA Aventis
15:15-15:30	: Discussion	
15:30-15:45	: Coffee	
15:45-17:30	: Moderated Discussion: Priority directions	Chair

<b>Day 2: 16 August 2001</b>		
09:00-09:10	National Regulatory Agencies and Standardization of Approaches to Registration	T. Kanyok
09:10-09:20	Preparation of an International Pharmacopoeia monograph on 4-FDC tablets and role of the Quality Assurance & Safety of Medicines Unit, WHO	P. Vanbel
09:20-09:30	Research Capacity Strengthening (RCS) Needs and TDR's plans	L. Chitsulo
09:30-09:50	RCS Discussion	
09:50-10:10	Definition of list of priorities for generic protocol development Formation of groups to work on each outline protocol	L. Geiter
10:10-10:30	Coffee	
10:30-12:30	Generic protocol development	
12:30-14:00	Lunch	
14:00-16:30	Generic protocol development	
16:30-17:30	Progress of individual groups, Dissemination of drafts, Discussion	
<b>Day 3: 17 August 2001</b>		
09:00-12:30	Generic protocol development	
12:30-14:00	Lunch	
14:00-16:30	Brief presentation of outline priority protocols. Next steps	

## Annex 2: List of participants

### Participants

Angela Bartacek .....	Int. Medical Manager, Novartis, Biochemiestr. 10 A-6250 Kundl, Austria. Tel: +43 5338/200 3548, Fax: +43 5338/200 407. Email: angela.bartacek@gx.novartis.com
Marijke Becx-Bleumink .....	P.O. Box 146, 2501CC The Hague, The Netherlands. Tel: + 31 70 4167222, Fax: +31 70 3584004. Email: becxm@kncvtbc.nl
Bjørn Blomberg .....	Research Fellow, Centre for International Health, University of Bergen, Norway, N-5021 Bergen, Norway. Dept of Microbiology and Immunology, Muhimbili University College of Health Sciences (MUCHS), P.O. Box 65001, Dar Es Salaam, Tanzania. Tel (Norway): +47-55974980, Tel (Tanzania): +255-744-281850. Email: bjorn.blomberg@cih.uib.no
Laszlo Borka .....	Vækerøvn 126-L, N - 0383 Oslo, Norway. Tel: +47 22 50 39 29. Email: lborka@frisurf.no
Richard Bumgarner .....	1715 Abbey Oak Drive. Vienna, VA 22182, USA. Tel: +1 703 242 6239 (residence), +1 703 622 8141 (mobile). Fax: +1 703 242 5795. Email: jrbumgarner@earthlink.net
Michiel de Goeje .....	Chief Pharmacist, International Dispensary Association, P.O. Box 37098, Amsterdam, 1030 AB, The Netherlands. Tel: +31 20 403-3051, Fax: +31 20-403-1854. Email: ga@ida.nl
Suzie Demmer .....	Wyeth Lederle Pharma GsmBH, Storchengasse 1, A-1150 Vienna Austria. Tel: +431-89-114-112, Fax: +431-89-114-209. Email: demmers@wai.wyeth.com
Gordon Ellard .....	12 Queens Walk, Ealing, W5 1TP – London, United Kingdom. Tel: +44 208 998 1034, Fax: +44 208 998 1034. Email: Gordon.Ellard@care4free.net
Peter Evans .....	MSH Consultant, Immeuble Keynes, 13, chemin du Levant, 01210 Ferney Voltaire, France. Tel: +33 450 40-6880 (home), Cell: +41 76 546-5228. Email: PETEREVANS43@yahoo.com
Bernard Fourie .....	Medical Research Council, Private Bag X385, Soutansberg Road, Pretoria, South Africa. Tel: +27 012 339-8547, Fax: +27 012 325-5970. Email: bfourie@mrc.ac.za

- Larry Geite  
.....  
Director, Clinical Studies, Sequella Global Tuberculosis Foundation  
9610 Medical Center Drive, Suite 220, Rockville, MD 20850, USA.  
Tel: +1 301-762-3100, Fax: +1 301-762-2122. Email:  
larrygeiter@sequellafoundation.org
- Amina Jindani  
.....  
Coordinator Clinical Trials, International Union Against Tuberculosis and Lung  
Disease, 68 Blvd. Saint-Michel, 75006 Paris France. Tel: +33 1 44 32 03 60,  
Fax: +33 1 43 29 90 87. Email: Alindani@iuatld.org
- Richard Laing  
.....  
Associate Director, Department of International Health, Boston University School of  
Public Health in the School of Medicine, 715 Albany St, Boston, MA 02118-2526,  
USA. Tel: +1 617-414-1444, Fax: +1 617 638-4476 or 414-1442.  
Email: Richardl@bu.edu
- Daniel Kibuga  
.....  
Head, National Leprosy Tuberculosis Programme (NTLP), Ministry of Health, Afya  
House, Cathedral Road, LG 05, P.O. Box 54335, Nairobi, Kenya.  
Tel: +254 733 610 320, Fax: +254 2 250 944. Email: dkibuga@insightkenya.com
- Lindie Marx  
.....  
Head, Development Centre, Rolab a sector of Novartis, Novartis South Africa (Pty)  
Ltd, Po Box 154 Isando 1600, 72 Steel Road, Spartan, Kempton Park, Gauteng, ZA-  
Isando, Johannesburg 1620, South Africa. Tel: +27 11 929 2208,  
Fax: +27 11 929 2454. Email: lindie.marx@gx.novartis.com
- Peter Mehlappe  
.....  
Aventis Pharma, 14 Appolo Street, East Village, Sunward Park, Boksburg 1459,  
South Africa. Tel: +27 - (0)11 - 256 37 81, Fax: +27 - (0) 11 -256 37 12.  
Email: peter.mehlappe@aventis.com
- Ramesh Panchagnula  
.....  
Head of Department, Department of Pharmaceutics, National Institute of  
Pharmaceutical, Education and Research, Sector-67, SAS Nagar, 160 062 Punjab, India.  
Tel: +91 172 214 700, Fax: +91 172 214 692. Email: panchagnula@yahoo.com
- Nadine Rohm  
.....  
Aventis Pharma, P.O. box 1869, Magalies View, 2067 Johannesburg  
South Africa. Tel: +27 - (0)11 - 256 37 81, Fax: +27 - (0) 11 -256 37 12.  
Email: nadine.rohm@aventis.com
- ...34  
Giorgio Roscigno  
.....  
Global Alliance for TB Drug Development, 59 John Street, Suite 800, New York,  
NY10038, USA. Tel: +1 212 227-7540, Fax: +1 212 227-7541.  
Email: giorgio.rosicigno@TBAlliance.org
- Himadri Sen  
.....  
Executive Vice President, Lupin Laboratories Ltd., A28/1, MIDC Area  
Chikalthana, Aurangabad 431 210, India. Fax: +91 0240 48 4121/484223.  
Email: himadrisen@lupinindia.com
- Trix Janet Tuin  
.....  
Quality Assurance Manager, The Medical Export Group of the Netherlands BV, P.O.  
Box 598, 4200 AN GORINCHEM, The Netherlands. Tel: +31 183 634 266,  
Fax: +31 183 634 650. Email: tuin@meg.nl
- Monica Vos  
.....  
Product Manager, The Medical Export Group of the Netherlands BV, P.O. Box 598,  
4200 AN GORINCHEM, The Netherlands. Tel: +31 183 634 266,  
Fax: +31 183 634 650. Email: vos@meg.nl

## **WHO Secretariat**

<u>Leopold Blanc</u>	World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. Tel: +41 22 791-4266, Fax: +41 22 791-4268. Email: blancl@who.int
<u>Lester Chitsulo</u>	TDR, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. Tel: +41 22 791-3862, Fax: +41 22 791-4854. Email: chitsulol@who.int
<u>Tom Kanyok</u>	TDR, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. Tel: +41 22 791-3684, Fax: +41 22 791-4854. Email: kanyokt@who.int
<u>Jane Kengeya-Kayondo</u>	TDR, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. Tel: +41 22 791-3737, Fax: +41 22 791-4774. Email: kengeya-kayondo@who.int
<u>Paul Nunn</u>	TDR, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. Tel: +41 22 791-2963, Fax: +41 22 791-4854. Email: nunnp@who.int
<u>Philip Onyebujoh</u>	World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. Tel: +41 22 791-4478, Fax: +41 22 791-4268. Email: onyebujohp@who.int
<u>Souly Phanouvong</u>	World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. Tel: +41 22 791-1328, Fax: +41 22 791-4167. Email: phanouvongs@who.int
<u>Mario Raviglione</u>	World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. Tel: +41 22 791-2663, Fax: +41 22 791-4268. Email: raviglionem@who.int
<u>Ian Smith</u>	World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. Tel: +41 22 791-2536, Fax: +41 22 791-4268. Email: smithi@who.int
<u>Kenichi Tamiya</u>	World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. Tel: +41 22 791-3717, Fax: +41 22 791-4730. Email: tamiyak@who.int
<u>Pascale Vanbel</u>	World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. Tel: +41 22 791-3669, Fax: +41 22 791-4730. Email: vanbelp@who.int
<u>Andre van Zyl</u>	World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. Tel: +41 22 791-3598, Fax: +41 22 791-4730. Email: vanzyla@who.int

## Annex 3: WHO Model application form for new marketing authorisation, periodic reviews and variations, with notes to the applicant

This annex is based on Annex 6 in the WHO publication *Model application form for new marketing authorizations, periodic reviews and variations, with notes to the applicant*.<sup>8</sup>

This page comprises details of the application and is followed by a certification form concerning the data set. The remaining pages contain an index to the complete data set. The form and index should be read in conjunction with the Notes to the Applicant that follow. The glossary, list of abbreviations and references are as those appearing in the main text.

Marketing authorization No.:  
 (only to be completed when a change to or review of the marketing authorization is required)

<p>A. Type of application (check the box applicable)</p> <p>New marketing authorization for a pharmaceutical product</p> <p>Periodic review of an existing marketing authorization</p> <p>Variation to an existing marketing authorization</p>	<p>B. Identity of the product</p> <p>Proprietary name (trade name)</p> <p>Approved generic name(s) (use the INN, if any)</p> <p>Strength(s) per dosage unit</p> <p>Dosage form</p> <p>Route of administration</p> <p>Anatomical therapeutic classification</p>
<p>C. Applicant</p> <p>Name</p> <p>Business address</p> <p>Postal address</p> <p>Telephone number .....</p> <p>Fax number.....</p> <p>Email ..</p>	<p>D. Contact person in applicant company</p> <p>Name:</p> <p>Position in company: .</p> <p>Postal address</p> <p>Telephone number.....</p> <p>Fax number</p> <p>Email address. .</p>

**Certification by a responsible person in the applicant company**

I, the undersigned, certify that all the information in the accompanying documentation concerning an application for a marketing authorization for:

- Proprietary name (trade name)
- Approved generic name(s) (use the INN, if any)
- Strength(s) per dosage unit
- Dosage form
- Applicant company

is correct and true, and reflects the total information available. I further certify that I have examined the following statements and I attest to their accuracy.

1. The current edition of the WHO guideline on "Good manufacturing practices for pharmaceutical products" Guideline 1 below, or an equivalent national guideline, is applied in full in all premises involved in the manufacture of this product.
2. The formulation per dosage form correlates with the master formula and with the batch manufacturing record forms.
3. The manufacturing procedure is exactly as specified in the master formula and batch manufacturing record forms.
4. Each batch of all starting materials is either tested or certified (in an accompanying certificate of analysis for that batch) against the full specifications in the accompanying documentation and must comply fully with those specifications *before it is released for manufacturing purposes*.
5. All batches of active pharmaceutical ingredient(s) are obtained from the source(s) specified in the accompanying documentation.
6. No batch of active pharmaceutical ingredient will be used unless a copy of the batch certificate established by the active ingredient manufacturer is available.
7. Each batch of the container/closure system is tested or certified against the full specifications in the accompanying documentation and complies fully with those specifications *before it is released for manufacturing purposes*.
8. Each batch of the finished product is either tested, or certified (in an accompanying certificate of analysis for that batch), against the full specifications in the accompanying

documentation and complies fully with the release specifications *before it is released for sale.*

9. The person releasing the product for sale is an authorized person as defined by the WHO guideline "Good manufacturing practices: Authorized person - the role, functions and training" (Guideline 10 below).
10. The procedures for control of the finished product have been validated for this formulation. The assay method has been validated for accuracy, precision, specificity and linearity.
11. The following WHO-type certificates are attached:  
All aspects of the product which is the subject of this application are identical to that marketed in *(the country or countries issuing the WHO-type certificate[s])*, including formulation, method and sites of manufacture, sources of active and excipient starting materials, quality control of the product and starting materials, packaging, shelf-life and product information (apart from language), except as follows:  
*(Append additional pages if necessary).*
12. The market authorization holder has a standard operating procedure for handling adverse reaction reports on its products.
13. The market authorization holder has a standard operating procedure for handling batch recalls of its products (Guideline 1 below, Part 7).
14. All the documentation referred to in this certificate is available for review during a GMP inspection.
15. Any clinical trials were conducted according to WHO's "Guidelines for good clinical practice (GCP) for trials on pharmaceutical products" (Guideline 11 on page 55).

Signature

Name (print or type)  
Position in company (print or type) .

Date:

- Notes to the applicant**
1. The application form is suitable for applications for a new marketing authorization for a pharmaceutical product, to review an existing marketing authorization, or to vary an existing marketing authorization.
  2. For definitions of terms, see the glossary.
  3. Note that a number of WHO guideline documents exist and should be followed. A list of the guidelines follows these notes.
  4. **New marketing authorizations.** For a new marketing authorization, provide all the data mentioned in the "Index to the complete data set" above.
  5. **Variations.** To vary an existing marketing authorization, not all of the data mentioned in the "Index to the complete data set" are necessarily required. Provide:
    - A full description of the proposed change. Compare the product before and after the change, e.g. the nature of a changed component of the container and its nature before the change.
    - Validation data as necessary (stability data, comparative dissolution data for a change to formulation, etc.).Include this statement in the letter of application:

"I provide assurance that no changes have been made to this product other than (1) those which are the subject of this application and (2) changes described by (name of DRA) as not needing prior approval."
  6. **Periodic reviews.** The intention of a periodic review is to consolidate the information held by the DRA. Any pharmaceutical (manufacturing, quality control, shelf-life, container labelling, etc.) variations/changes made to the product since the first marketing authorization or the last review should be either those for which prior approval has been obtained or those not requiring prior approval.

Any safety updates should have been made when the relevant safety information became sufficiently well established as defined by CIOMS (Guideline 7, p.39). GMP practices should have been maintained and, as necessary, improved at all sites of manufacture. For the periodic review of an existing marketing authorization, submit the following information:

    - (a) An updated WHO-type product certificate for each foreign site of manufacture of the finished product (Guideline 2, section 3.5). When the draft WHO guidelines for certification of APIs have been finalized (Guideline 3), it may also be necessary to supply WHO-type API certificates for sites of manufacture of APIs.
    - (b) Updated certificates of GMP for domestic manufacturing sites.
    - (c) A chronological list of all approved pharmaceutical variations of any type, and all amendments made to product information since the first marketing authorization or the last periodic review. Provide the dates of approval and file reference for each change.

(d) A set of current specifications for the API(s) and finished product, including test methods in sufficient detail for them to be replicated by another laboratory. The periodic review should not be used as an opportunity to seek authorization for new variations. These should be the subject of separate applications. Nor should it be a means of regularizing unauthorized changes to pharmaceutical or product information.

7. In product information, promotional activities and applications, always use an INN name for the generic name when one exists (Guideline 8).
8. "ATC classification" means the WHO Anatomic Therapeutic Chemical classification and "DDD" means the WHO Defined Daily Dose (Guideline 9).
9. Where an applicant is asked to "justify" or "provide a justification", it is intended that scientific information and/or logical argument be provided.
10. The following pharmacopoeias are recognized for the purposes of this application form.
  - .....
  - .....
  - .....
11. References to a pharmacopoeia should normally be to the current edition. An applicant must justify citing an edition other than the latest. If there is no monograph in the current edition, the year of the most recent monograph should be cited.
12. The European Pharmacopoeia Commission will, upon submission of a full drug master file (No.20 on page 55) concerning production of an API by a particular synthetic route at a particular site, determine whether or not the relevant EP monograph is suitable to control the material fully. If the monograph is suitable, the Commission will issue a "certificate of suitability" (Nos.12 and 13 on page 55). Some certificates of suitability have appendices, and these must be attached. The accompanying "Report A" is available to the manufacturer on request.

**Guidelines and other relevant materials applicants should consult**

- Guideline 1:** Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report.* Geneva, World Health Organization, 1992:14-79 (WHO Technical Report Series, No. 823).
- Guideline 2:\*** Guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report.* Geneva, World Health Organization, 1996:155-177 (WHO Technical Report Series, No. 863).
- Guideline 3:** *WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce: Proposed guidelines for the certification of active pharmaceutical ingredients.* Geneva, World Health Organization, 1997 (document WHO/PHARM/96.586 Rev.1).
- Guideline 4:\*** Agreement Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report.* Geneva, World Health Organization, 1996:65-79 (WHO Technical Report Series, No. 863).
- Guideline 5:\*** Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report.* Geneva, World Health Organization, 1996:114-154 (WHO Technical Report Series, No. 863).
- Guideline 6:** *Ethical criteria for medicinal drug promotion.* Geneva, World Health Organization, 1988.
- Guideline 7:** *Guidelines for preparing core clinical-safety information on drugs.* Report by the Council for International Organizations of Medical Sciences (CIOMS). Geneva, World Health Organization, 1995.
- Guideline 8:** *Guidelines on the use of international nonproprietary names (INNs) for pharmaceutical substances.* Geneva, World Health Organization, 1997 (document: WHO/PHARMS/NOM 1570).
- Guideline 9:** *Guidelines for ATC classification and DDD assignment.* Oslo, WHO Collaborating Centre for Drug Statistics and Methodology, 1996.
- Guideline 10:** Good manufacturing practices: authorized person - the role, functions and training. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report.* Geneva, World Health Organization, 1998: (WHO Technical Report Series, No.885).
- Guideline 11:** Guidelines for good clinical practice for trials on pharmaceutical products. In: *The use of essential drugs. Sixth report of the WHO Expert Committee.* Geneva, World Health Organization, 1995, 97-137 (WHO Technical Report Series No. 850).

- Artigos A. Certification of suitability of monographs of the European Pharmacopoeia. *Pharmeuropa*, 1994, 6(2):199.
- *Certification of suitability to the monographs of the European Pharmacopoeia* (revised version, March 1998). Council of Europe Public Health Committee, Resolution AP-CSP (98)2.
- *Validation of analytical procedures*, Geneva, International Conference on Harmonisation, 1994.
- *Stability testing of new drug substances and products*. International Conference on Harmonisation, 1993.
- *List of permitted food colours*. Official journal of the European Communities, 1994, L237 (European Commission Directive 94/36/EC).
- *Specific purity criteria concerning colours for use in foodstuffs*. Official journal of the European Communities, 1995, No. L226.
- *Inactive ingredient guide*. Rockville, MD, United States Food and Drug Administration, Division of Drug Information and Research, 1996.
- *Japanese pharmaceutical excipients*. Tokyo, Pharmaceutical and Cosmetics Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare (updated annually or biennially).
- European drug master file procedure for active substances. In: *The rule governing medicinal products in the European Union*, 3A:47-56. Brussels, European Commission, 1996.

*Guidelines marked with an asterisk are also available as part of a compendium entitled "Quality assurance of pharmaceuticals: a compendium of guidelines and related materials, Volume 1" (Geneva, World Health Organization, 1997).*



## **Annex 4: Generic protocols**

**On day 2 and 3 of the meeting, participants were allocated to the following working groups:**

- 1) Working group on quality issues
- 2) Working group on regulatory issues
- 3) Working group on operational issues
- 4) Working group on safety and efficacy issues

Each working group developed one or more draft generic protocols for the prioritized research areas within their respective fields. These protocols may be obtained from TDR upon request.



## Annex 5: Presentations

### The presentations of the meeting covered the following topics:

- Objectives of the meeting (*P. Nunn*)
- Current status and future issues of pharmacological and pharmacokinetic research and clinical trials (*B. Fourie*)
- Health policy services and research in 4FDCs-current status and future issues (*B. Blomberg*)
- Control programme needs and DOTS expansion (*D. Kibuga, L. Blanc*)
- Procurement issues and the Global Drug Facility (*P. Evans*)
- Distribution, storage, prescription and consumption issues (*R. Laing*)
- 4FDC study within the NTP in Sulawesi, Indonesia: preliminary results (*M. Becx-Bleumink*)
- Current status of WHO's bioavailability network (*R. Panchagnula*)
- Clinical trials of safety and efficacy – The IUATLD Clinical Trials Network (*A. Jindani*)
- Current status of 4FDCs in the pharmaceutical industry
  - Wyeth Lederle (*S. Demmers*)
  - Lupin (*H. Sen*)
  - Novartis (*A. Bartacek*)
  - MEG Svizzera (*T. Tuin*)
  - IDA (*M. de Goeje*)
  - Aventis (*N. Rohm*)
- National regulatory agencies and standardization of approaches to registration (*T. Kanyok*)
- Preparation of international pharmacopoeia and role of Quality & Safety of Medicines Unit, WHO (*P. Vanbel*)
- Research Capacity Strengthening (*L. Chitsulo*)







**Mailing Address:**

TDR  
World Health Organization  
Avenue Appia 20  
1211 Geneva 27  
Switzerland

**Street Address:**

TDR  
Centre Casai  
Avenue Louis-Casai 53  
1216 Geneva  
Switzerland

Tel: (+41) 22-791-3725  
Fax: (+41) 22-791-4854  
E-mail: [tdrnews@who.int](mailto:tdrnews@who.int)  
Web: [www.who.int/tdr](http://www.who.int/tdr)